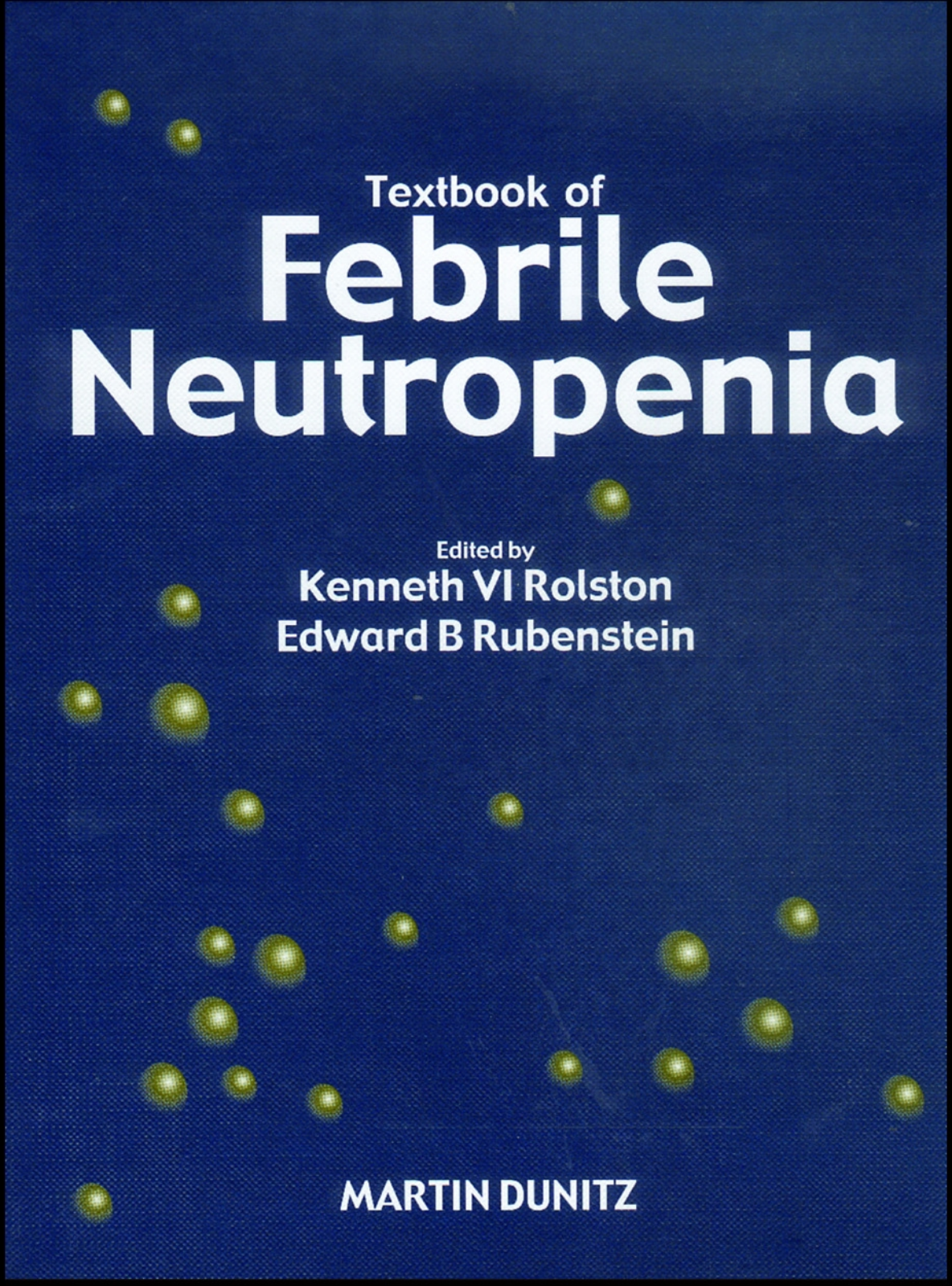
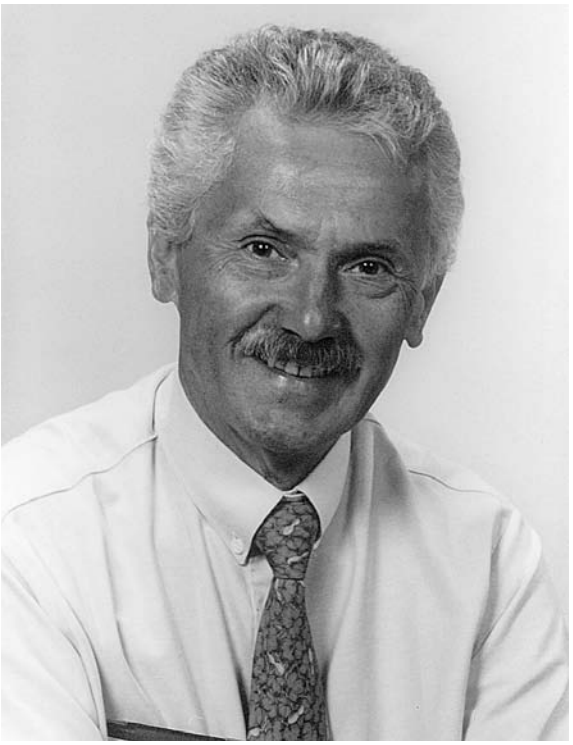


Textbook of

Febrile Neutropenia

This book is dedicated to Gerald P Bodey, MD and Jean Klastersky, MD in recognition of their pioneering observations, pivotal contributions towards the management of infections in cancer patients, and their enthusiastic efforts to disseminate this knowledge.

Gerald P Bodey, MD



Jean Klastersky, MD

Textbook of
Febrile Neutropenia

Edited by

Kenneth VI Rolston, MD, FACP
Section of Infectious Diseases
UTMD Anderson Cancer Center
Houston, Texas, USA

Edward B Rubenstein, MD, FACP
Section of Medical Supportive Care
UTMD Anderson Cancer Center
Houston, Texas, USA

MARTIN DUNITZ

First published in the United Kingdom in 2001
by Martin Dunitz Ltd, The Livery House, 7–9 Pratt Street, London
NW1 0AE

Tel: +44-(0)20-7482-2202
Fax: +44-(0)20-7267-0159
E-mail: info.dunitz@tandf.co.uk
Website: http://www.dunitz.co.uk

This edition published in the Taylor & Francis e-Library, 2004.

A CIP catalogue record for this book is available from the British Library

ISBN 0-203-21527-3 Master e-book ISBN

ISBN 0-203-27170-X (Adobe eReader Format)
ISBN 1-84184-033-5 (Print Edition)

Contents

Preface

Following the introduction of myelosuppressive combination chemotherapy, infection and bleeding were the two leading causes of death in patients with acute leukemia. The widespread use of chemotherapy for patients with solid tumors and the expanding indications for stem cell transplantation have resulted in a substantial increase in the population at risk for developing serious infections. The introduction of potent broad-spectrum antimicrobial agents and the acceptance of the concept of empiric therapy has led to a substantial decrease in infection-related mortality. Over the past four decades, improvements in supportive care, including: transfusion medicine, antimicrobial therapy and prophylaxis, antineoplastic therapy, and the development of hematopoietic growth factors, have enabled clinical investigators to evaluate endpoints other than response rates to antimicrobial agents, adverse events, and mortality. As a result of these advances, issues such as routes of antibiotic administration, time to clinical response, site and cost of care and quality of life have become important considerations for our investigations.

In this textbook, we have assembled a group of international experts, many of whom have led the way in this complex and ever-changing field, to provide a comprehensive overview of the historical aspects and recent developments in the care of cancer patients with fever and neutropenia. In addition to providing their unique experiences and insights regarding traditional evaluation and management of such patients, newer concepts have been included, for example, the pharmacokinetic/pharmacodynamic interaction of antimicrobial agents, clinical trials methodology and design, risk assessment, and risk-based treatment strategies. We are extremely grateful to our colleagues who have gladly contributed their time and their expertise towards this endeavor. For us, it has been an immensely rewarding experience, and we consider ourselves privileged and fortunate to have had the opportunity to work with and be mentored by Professors Bodey and Klastersky.

Kenneth VI Rolston
Edward B Rubenstein

Acknowledgment

The Editors (KVIR and EBR) are grateful to Ms Belinda DeBose for her administrative and secretarial expertise, which were essential in the preparation of this book.

Contributors

Claude Afif, MD
Department of Infectious Diseases & Infection Control
UTMD Anderson Cancer Center
1515 Holcombe Blvd
Houston, TX 77030
USA

Sarah W Alexander, MD
Department of Hematology/Oncology
The Dana Farber Cancer Institute
44 Binney Street
Boston, MA 02115
USA

Ben E De Pauw, MD, PhD
Supportive Care in Oncology
Clinical Division of Hematology and Blood Transfusion Service
University Medical Center St Radboud
Geert Grootplein Zuid 8
6500 HB Nijmegen
The Netherlands

J Peter Donnelly, FIBMS, MIBiol, PhD
Studies in Supportive Care
Department of Hematology
University Medical Center St Radboud
Geert Grootplein Zuid 8
6500 HB Nijmegen
The Netherlands

Linda S Elting, DrPH
Department of Health Services Research
UTMD Anderson Cancer Center
1515 Holcombe Blvd
Houston, TX 77030
USA

Ronald Feld, MD
Department of Medical Oncology and Hematology
The Ontario Cancer Institute
Princess Margaret Hospital
610 University Avenue
Toronto, Ontario M5G 2M9
Canada

Katarzyna J Finiewicz, MD
Division of Hematology/Oncology
University of Florida College of Medicine
JHMHC, 1600 SW Archer Road
Gainesville, FL 32610-0277
USA

Winfried V Kern, MD
Medizinische Universitätsklinik und Poliklinik
Robert-Koch-Strasse 8
D-89081 Ulm
Germany

Natasha Leighl, MD
Department of Medical Oncology and Hematology
The Ontario Cancer Institute
Princess Margaret Hospital
610 University Avenue
Toronto, Ontario, M5G 2M9
Canada

Russell E Lewis, PharmD
University of Houston College of Pharmacy and
Section of Infectious Diseases
UTMD Anderson Cancer Center
1515 Holcombe Blvd
Houston, TX 77030
USA

Marianne Paesmans, MSc
Unité de Biostatistique
Institut Jules Bordet
Centre des Tumeurs de l'Université de
Bruxelles
Rue Heger-Bordet, 1
B-1000 Bruxelles
Belgium

Philip A Pizzo, MD
Dean
Standford University School of Medicine
300 Pasteur Drive
Standford, CA 94305
USA

Randall A Prince, PharmD
University of Houston College of Pharmacy and
Section of Infectious Diseases
UTMD Anderson Cancer Center
1515 Holcombe Blvd
Houston, TX 77030
USA

Issam Raad, MD
Department of Infectious Diseases & Infection
Control
UTMD Anderson Cancer Center
1515 Holcombe Blvd
Houston, TX 77030
USA

Kenneth VI Rolston, MD, FACP
Section of Infectious Diseases
UTMD Anderson Cancer Center
1515 Holcombe Blvd
Houston, TX 77030
USA

Edward B Rubenstein, MD, FACP
Section of Medical Supportive Care
UTMD Anderson Cancer Center
1515 Holcombe Blvd
Houston, TX 77030
USA

Stephen C Schimpff, MD
Chief Executive Officer
University of Maryland Medical Center
22 South Greene Street
Baltimore, MD 21201
USA

Thomas D Szucs, MD
Department of Medical Economics
Zurich University Hospitals
Rämistrasse 100
CH-8091 Zurich
Switzerland

James A Talcott, MD, SM
Center for Outcomes Research
Massachusetts General Hospital
55 Fruit Street, B75 230
Boston, MA 02114
USA

James C Wade, MD, MPH
Clinical Research Division
Fred Hutchinson Cancer Research Center
1100 Fairview Avenue N, D5-280
Seattle, WA 98109
USA

John R Wingard, MD
Bone Marrow Transplant Program
Department of Medicine
Division of Hematology/Oncology
University of Florida College of Medicine
JHMHC, 1600 SW Archer Road
Gainesville, FL 32610-0277
USA

1

Fever and neutropenia: An historical perspective

Stephen C Schimpff

INTRODUCTION

Many serious cancers can now be treated effectively. Infectious complications, however, continue to be a frequent cause of morbidity, and often a leading cause of death, despite the remarkable progress that has been made in their recognition, prevention, and therapy. This dichotomy stems from the intensification of present-day drug and irradiation treatment regimens that have, in actuality, only been possible because of refinements in supportive care. Although survival has improved, the price has been a continued and even increased predisposition to infection.

This situation is not unlike that which faced oncologists in the late 1960s and early 1970s, as chemotherapy became more effective and more commonly utilized. Infections that were unusual, hard to diagnose, and often rapidly fatal had become common, yet the principles of management that are taken as standard practice today were still being developed.

FACTORS PREDISPOSING TO INFECTION

The following are some of the most important factors that predispose to infection in cancer patients:

- neutropenia and other defects in phagocytic defenses;
- cellular immune dysfunction;
- humoral immune dysfunction;
- anatomic-barrier (mucosal or integumentary) damage;
- obstructive phenomena;
- central nervous system dysfunction;
- various iatrogenic procedures.

Additional considerations are the alterations in microbial flora and the acquisition of new organisms in the hospital environment.

NEUTROPENIA

Neutropenia is common in patients with acute leukemia, following bone marrow transplantation, and following intensive myelosuppressive drug therapy for other malignancies, or as a result of aplastic anemia. The incidence and severity of infection is inversely proportional to the absolute neutrophil count. Figure 1.1[1] graphically displays the incidence of all infections among 64 consecutive patients with acute non-lymphocytic leukemia admitted for their initial remission induction therapy. The incidence of infection began to rise as the neutrophil count fell below 500/μl, with a very

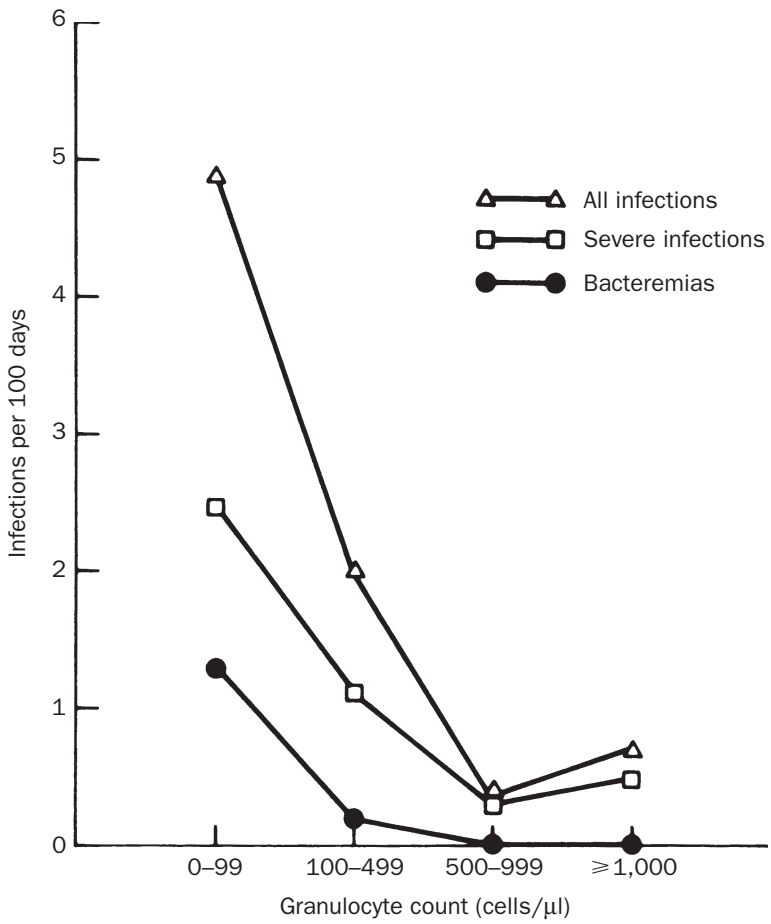


Figure 1.1 Incidence of infection in acute non-lymphocytic leukemia during induction therapy. Reprinted from Joshi JH, Schimpff SC, Infections in the compromised host. In: *Principles and Practice of Infectious Diseases*, 2nd edn (Mandel GL, Douglas RG Jr, Bennett JE, eds), Copyright © 1985, John Wiley & Sons, Inc. Reprinted by permission of John Wiley & Sons, Inc.

substantial rise when the neutrophil count was between 0 and 100/μl. It is obvious from the figure that most severe infections and nearly all bacteremias occurred when the neutrophil count was less than 100/μl. An additional factor, not indicated by the figure, is the effect of the rate of fall of the neutrophil count; rapid declines were more often associated with infection. These observations are directly comparable to those first described by Bodey et al[2] in 1966 in a landmark article that definitively related neutropenia to infection incidence and severity.

Not only does the level and rapidity in decline of the neutrophil count correlate with infection – so too does the duration of the aplastic phase. The current approach to remission induction therapy of acute myelocytic leukemia, for example, is such that patients will become and remain neutropenic for 20–40 days, with about one-half of that time spent with an absolute level of circulating neutrophils of less than 100/μl. Likewise, patients who receive allogeneic bone marrow transplants will have a period of approximately 3 weeks with essentially no circulating neutrophils, and are at an exceedingly high risk of infection during that time.

Although neutropenia clearly predisposes to infection, the occurrence of infection in the setting of neutropenia is dependent upon the presence or absence of some other associated predisposing factors, which act in concert with the absence of neutrophils. When cancer chemotherapy damages mucosal membranes, the opportunity for development of pharyngitis or esophagitis, typhilitis, or perianal lesions is accentuated. Damage to the integument by venipuncture, indwelling vascular catheters, or axillary shaving may lead to infection. Damage to the mucosa of the trachea and bronchi, along with damage to ciliary function due to cancer chemotherapy, may offer the opportunity for pneumonia to develop. Any form of obstructive phenomenon can interact with neutropenia to encourage infection, such as the development of a urinary tract infection in a patient with tumor infiltration of the prostate, otitis media following an enlargement of adenoid tissue in patients with lymphocytic leukemia, or the development of axillary lesions in patients who use occlusive antiperspirants.

SITES OF INFECTION

The most common sites (Figure 1.2) of infection in neutropenic patients are the oropharynx, the

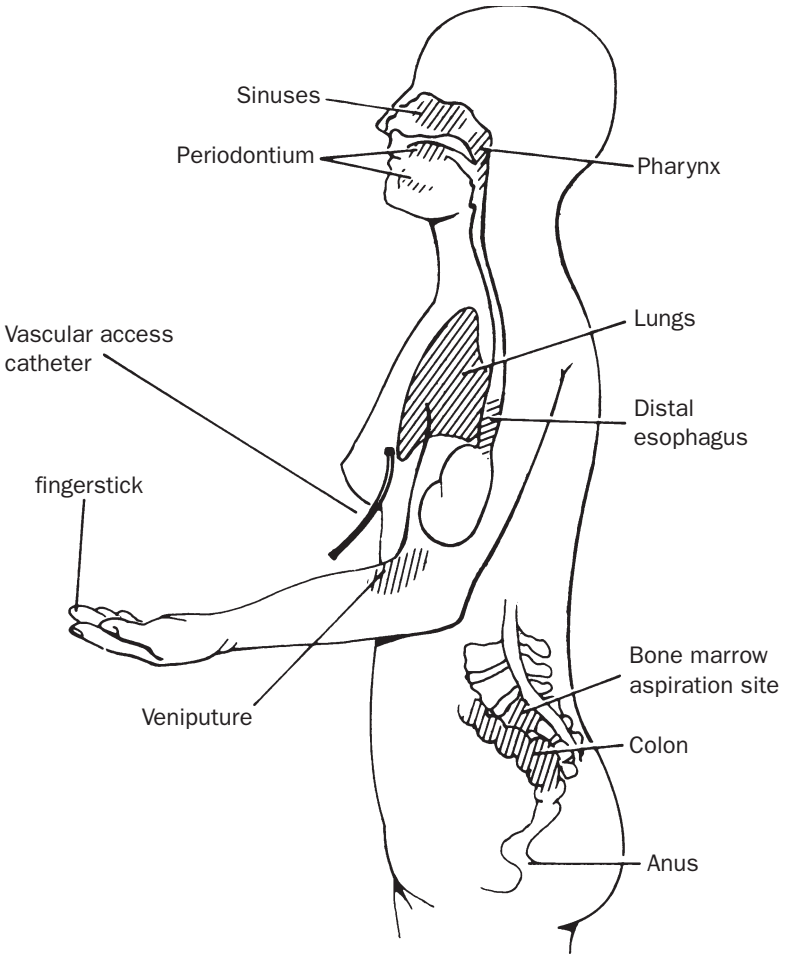


Figure 1.2 Sites of infection among granulocytopenic cancer patients. Reprinted with permission from Schimpff SC, Infection in patients with cancer: overview and epidemiology. In: *Comprehensive Textbook of Oncology*, 2nd edn (Moossa AR, Schimpff SC, Robson MC, eds). Copyright Williams & Wilkins, 1991.

Table 1.1 Infections in neutropenic patients[a],[3]

Sites	Pathogens
Alimentary canal:	Gram-negative bacilli:
Periodontitis	*Escherichia coli*
Pharyngitis	*Pseudomonas aeruginosa*
Esophagitis	*Klebsiella pneumoniae*
Colitis	
Perianal lesions	Gram-positive cocci:
Respiratory tract:	*Streptococcus* spp.
Sinusitis	*Staphylococcus aureus*
Pneumonitis	*Staphylococcus epidermidis*
Skin:	
Local trauma	Yeasts/fungi:
Vascular access	*Candida* spp.
	Aspergillus fumigatus/flavus

[a] These patients can become infected at any site and by any potential pathogen, but the sites and pathogens listed here represent more than 85% of acute infections.

lung, the perianal area, and the skin, especially at sites of damage/invasion. As a general rule, the organisms that cause infection (Table 1.1) at any given site are usually organisms that have colonized (not being just transiently present in) that area or a nearby area.[3] In the presence of a damaged mucosal barrier, ciliary dysfunction, or obstruction, and in the absence of normal numbers of granulocytes, it becomes possible for such an organism of otherwise low pathogenicity to cause infection. Thus, pneumonias are usually caused by organisms that have been colonizing the patient's oronasopharynx, and perianal lesions are caused by one or more of the organisms colonizing the lower intestinal tract.[3,4] In addition, there are bacteremias of unknown origin, some of which are presumed to relate to bacterial translocation along the intestinal wall. It is important to recognize that, although most infections are caused by organisms already colonizing the patient, these may well have been acquired by the patient subsequent to admission to the hospital. These acquired organisms may prove to be more virulent or more resistant to commonly utilized antibiotics, or both.[5]

These predominating infection sites are readily explainable: acute periodontitis occurs as a result of acute exacerbation of previously unrecognized chronic periodontal disease. Esophagitis occurs in the distal esophagus because of mucosal damage due to chemotherapeutic agents exacerbated by acid reflux from the stomach, which is secondary to chemotherapy-induced vomiting. A not uncommon progression is infection first with herpes simplex, followed by a mixed bacterial infection, followed by invasive infection by *Candida*. Perianal lesions occur particularly in patients with acute monocytic or myelomonocytic leukemia, and can reach an incidence of 33%. Patients with a history of hemorrhoids are most frequently affected because of the development of small mucosal tears at the base of the hemorrhoid at the anal opening.[6] The high pressures developed in the process of defecation exacerbate this process. Sinusitis seems to develop in patients with a previous history of sinus infections, perhaps suggesting a tendency toward obstruction to the ostia. Pneumonia results from damaged ciliary function, with reduced tracheobronchial clearance of mucus. These alterations in normal clearance mechanisms allow the organisms normally aspirated during sleep to establish local infection, which is then unchecked by either neutrophils or pulmonary macrophages. The axillae are common sites of infection because of the warm, moist environment that allows for the growth of organisms in an area that has been damaged by shaving or in an area where hair follicles have been occluded by antiperspirants. Infection at areas of direct damage to the skin, such as bone marrow aspiration sites and fingersticks, occurs because healing is slow after chemotherapy and because

the number of organisms necessary to induce infection in the individual who is neutropenic is substantially less than in the normal host.

'Bacterial translocation' is a term used to define the movement of bacteria across the intact intestinal epithelium into the mesenteric lymph nodes and possibly beyond to cause systemic infection. This process is well recognized with *Salmonella typhi* in the production of typhoid fever. However, animal experimentation shows that certain aerobic Gram-negative organisms, principally *Escherichia coli*, *Klebsiella pneumoniae*, and *Pseudomonas aeruginosa*, can also translocate across the normal alimentary canal mucosa under conditions of suppression of the anaerobic flora of the intestinal tract or suppression of cellular immune function. It is therefore possible that many episodes of so-called bacteremia of unknown origin have their origin in the intestinal tract as a result of bacterial translocation in the absence of specific mucosal epithelial damage.

PATHOGENS CAUSING INFECTION

The most common (i.e. approximately 85%) causes of bacterial infection in the neutropenic patient are the aerobic Gram-positive cocci *Staphylococcus epidermidis* (i.e. coagulase-negative staphylococci), α (viridans) *Streptococcus* spp. and *Staphylococcus aureus*, and the aerobic Gram-negative rods, especially *E. coli*, *K. pneumoniae*, and *Ps. aeruginosa*. Despite colonization with other aerobic Gram-positive and Gram-negative organisms, patients who are neutropenic generally do not develop infection or bacteremia other than with those noted above. *Bacteroides fragilis*, an anaerobic Gram-negative rod that is known to cause infection in many other settings, and other anaerobes are also uncommon causes of infection during neutropenia. The principal yeasts and fungi to cause infection during neutropenia are *Candida* spp. (especially *C. albicans* and *C. tropicalis*), and *Aspergillus* spp. (especially *A. flavus* and *A. fumigatus*).[7]

ALTERATIONS IN MICROBIAL FLORA/ACQUISITION OF NEW ORGANISMS

Various exogenous influences can affect the host's normal microbial flora. The general debilitation that occurs as a consequence of any severe or chronic illness will perturb indigenous flora. Shifts of the normal oropharyngeal flora toward a predominance of Gram-negative bacilli occur with acute illness, and the prevalence of colonization by Gram-negative bacilli correlates directly with the severity of illness.[8] Most bacterial pneumonias result from aspiration of oropharyngeal contents. Colonization of the oropharynx by potential Gram-negative pathogens in the compromised host with diminished pulmonary defense mechanisms can, therefore, lead to aspiration and pneumonia. Once an infection has become established in the neutropenic patient, it can rapidly progress and easily disseminate.

Antimicrobial agents have the most dramatic effect on indigenous flora, and cause both rapid and radical changes. Broad-spectrum antibiotics can suppress the non-invasive and potentially beneficial normal flora that may provide a degree of protection against colonization or infection, or both, by more pathogenic microorganisms. Suppression of alimentary canal anaerobes may destroy a means of endogenous microbial protection termed 'colonization resistance'.[9] In neutropenic hosts, the loss of this, yet another normal host defense barrier to infection can be substantially detrimental and increase the high infection risk. The occurrence of resistant organisms and infections in those receiving broad-spectrum antimicrobial therapy is another serious liability. The role of antibiotics in predisposing to fungal infections is clear.[10] Table 1.2, from the first of the European Organisation for Research and Treatment of Cancer (EORTC) studies, demonstrates the increasing incidence of further infections as antibiotic therapy is continued over time.[11]

The cancer patient may spend substantial time in the hospital or clinic, and, as a result, is given an opportunity to acquire potential

Table 1.2 Relation between incidence of further infection and neutrophil count and duration of antibiotic therapy for infection in neutropenic patients with cancer (EORTC Trial I)[a]

	Patients with further infection/ patients with stable neutrophil count[b]		Patients with further infection/ patients with increased neutrophil count[b]	
Duration of antibiotic therapy (days)	Number	Percentage	Number	Percentage
<5	17/87	20[c]	1/52	2[d]
6–10	17/96	17	8/115	7
11–15	16/39	41	6/34	18
>15	8/27	30[c]	5/20	25[d]
Total	58/249	23[e]	20/221	9[e]

[a] Modified with permission from EORTC International Antimicrobial Therapy Cooperative Group, *J Infect Dis* 1978; **137:** 14–29.[11]
[b] Patients with a stable neutrophil count had persistent neutropenia, and the neutrophil count of patients with an increase rose by 100/μl or more during therapy.
[c] $p = 0.20$ for the difference between these two values (not significant); [d] $p = 0.005$ for the difference between these two values; [e] $p = 0.001$ for the difference between these two values.

pathogens from this environment.[3,10] The organisms colonizing a patient at the time of infection may have been acquired only subsequent to patient admission. This is of considerable importance, because the organisms that a patient is likely to acquire in the hospital are more likely to be resistant to various antibiotics. Approximately one-half of all infections are caused by organisms that have been acquired by the patient during hospitalization in the setting of neutropenia.[3]

INFLAMMATORY RESPONSE

The absence or near absence of neutrophils substantially limits the inflammatory response, which in turn affects both diagnosis and prognosis. There are very few early signs and symptoms except for fever.[12] It is this ability of an otherwise minor-appearing and localized infection to progress rapidly to a systemic bacteremia that makes the need for early diagnosis and prompt empiric therapy critical. The patient with a Gram-negative bacteremia who is not treated promptly will usually die within 24–48 hours unless antimicrobial therapy is initiated within the first few hours.

Despite the presence of few of the classic manifestations of localized infection, the vast majority of these febrile episodes occurring during the period of neutropenia are due to infection.[12] Approximately 20% of febrile episodes have an associated bacteremia, another 20% have a microbiologically documented infection without bacteremia, and another 20% have clear-cut evidence of the site of infection but an etiologic agent cannot be defined. This leaves 20% with fever caused by a non-infectious etiology (infection doubted) and the remaining 20% in whom infection is highly suspected but is never proved. Overall then, at

least 60% of new febrile episodes are associated with infection.[11]

GRAM-POSITIVE INFECTION

Viridans and α-hemolytic streptococci have become frequent pathogens in febrile neutropenic patients. These streptococcal infections may be severe and present with septic shock or acute respiratory distress syndrome. Since viridans streptococci are normal inhabitants of the mouth and pharynx, it has been hypothesized that these infections arise from the oral cavity. These streptococcal infections may be secondary to the development of severe mucositis following radiation therapy or chemotherapy, particularly in patients treated with high-dose cytosine arabinoside, but may also be secondary to oral ulcerations due to herpesvirus infections. Another factor predisposing patients to these streptococcal infections may be the use of quinolone antibiotics for the prevention of bacterial infection.[13–15]

GRAM-NEGATIVE INFECTIONS

Gram-negative bacteremia is essentially a disease of modern times, with fewer than 100 reported cases prior to 1920. Over the last 40 years, a number of studies have looked at the incidence of Gram-negative bacteremia and have noted a continuing increase.[16] Although mortality rates in various reports range widely, a case fatality rate of about 50% is common. The fatality rate depends fairly dramatically on host factors, along with the approach to treatment, the occurrence of complications, and, to some degree, the specific pathogen. McCabe and Jackson[17] were the first to emphasize the importance of the host's underlying disease by dividing patients into those with rapidly fatal disease (i.e. those expected to die within the course of the next year), those with ultimately fatal disease (i.e. those who would die within about 4 years), and those with non-fatal underlying disease. They found the fatality rates to be 91%, 66%, and 11%, respectively.

EMPIRIC THERAPY

At the Baltimore Cancer Research Center of the National Cancer Institute in 1969, a review of the microbiology records from the previous year indicated that there were 22 episodes of *Ps. aeruginosa* bacteremia. Of these 22 patients, 11 died within 72 hours from the time the first positive blood culture was drawn; all but one patient eventually died of the infection.[18] The site of infection was never identified in the vast majority. Antibiotic therapy usually included a combination of cephalothin plus kanamycin (neither drug being active against *Ps. aeruginosa*), and was usually not started until after a report of a positive blood culture for a Gram-negative rod had returned from the laboratory or until the patient developed signs of septic shock. Polymixin B or E tended to be added to the regimen only when laboratory identification had been achieved.

In the 1960s and early 1970s, the accepted approach was not to institute antibiotic therapy until there was some definitive proof of infection – fever alone was not considered enough. But it was clear from review of the 22 patients with *Pseudomonas* bacteremia that one could not wait for laboratory results to return, because half of the patients had died within 72 hours. Further, it seemed that, apart from fever, documentation of infection was uncommon except for the culture report, which generally returned too late to be of value. Therefore, it only seemed appropriate to treat all neutropenic patients who developed new fever with an antibiotic regimen empirically. Carbenicillin and gentamicin (both still investigational in 1969) seemed to be a logical regimen because of the broad Gram-negative and Gram-positive activity of gentamicin, including against *Ps. aeruginosa*, and the antipseudomonal activity of carbenicillin. Further, there were laboratory data which indicated that carbenicillin and gentamicin were synergistic in

vitro against *Ps. aeruginosa*, and there were some data to suggest that resistance might develop less rapidly when a combination was utilized. We then treated 75 febrile neutropenic patients with this regimen: 48 had a microbiologically documented infection, another 12 had a clinically documented infection, 12 had a possible infection, and 3, in retrospect, were felt not to have been infected. Thus, the empiric approach to therapy was appropriate in all but either 3 or 15 of 75 patients. Among the 48 patients with a microbiologically documented infection were 13 with a *Pseudomonas* bacteremia, of whom 8 improved and 3 improved temporarily, plus an additional 8 patients with a non-bacteremic *Ps. aeruginosa* infection, of whom 6 improved. This was a fairly striking difference from the results of the prior year, noted above; however, it could not be ascertained whether the critical factor here was the early empiric institution of antibiotics, the effectiveness of the new investigational combination of agents, or both. It is noteworthy, however, that during this same time frame, an additional 8 patients with neutropenia and fever, who proved to have a *Ps. aeruginosa* bacteremia, were treated with gentamicin alone shortly after fever developed. Each patient had a strain susceptible to gentamicin, yet 7 patients had persistently positive blood cultures while receiving this drug, whereas 1 patient rapidly improved with this single-agent therapy. This suggested that gentamicin alone was not adequate therapy for *Pseudomonas* bacteremia in neutropenic patients.[19]

EARLY INITIATION OF THERAPY

The studies by Greisman et al[20] are relevant to the observation that prompt therapy is important. They studied non-neutropenic mice, each of which received a lethal intraperitoneal dose of a Gram-negative rod such as *E. coli* or *K. pneumoniae*. They then utilized an antibiotic to which the organism was susceptible, in a dose and schedule that would assure a blood level above the minimal inhibitory concentration on a continuing basis. The only variable in the experiment was the time of initiation of the first dose of antibiotic. It was found that if the first dose of the antibiotic was administered concurrently with the intraperitoneal injection, none of the mice died. However, the longer the first dose was delayed, the greater was the likelihood that death would occur. Even though the animal might survive for a few days, death was inevitable if the first dose was more than just a few hours delayed from the onset of infection (Table 1.3). Thus, it was demonstrated that there is a 'window of opportunity' within which therapy must begin if death is not to ensue.

This was demonstrated nicely in two studies by Bodey et al from the University of Texas MD Anderson Cancer Center. In reviewing *Pseudomonas* bacteremia, they found that about 15% of neutropenic patients died if the first dose of therapy was given within 12 hours of the onset of fever, yet 55–75% died if the first dose

Table 1.3 Mouse mortality after Gram-negative infection[20]

Time (hours) since antibiotic begun	% mortality
0	0
1	15
1.5	45
2	70
3	95
4	100

Mice were injected intraperitoneally with a lethal dose (1×10^8) of *E. coli* 018, then treated with a bactericidal antibiotic at a dose and schedule to maintain an effective serum concentration, i.e. constantly above the minimum bactericidal concentration of the challenge organism. Note the 'window of opportunity', i.e. mice treated quickly with first dose all survive, but die if treated for first time only a few hours after innoculum of bacteria injected intraperitoneally.

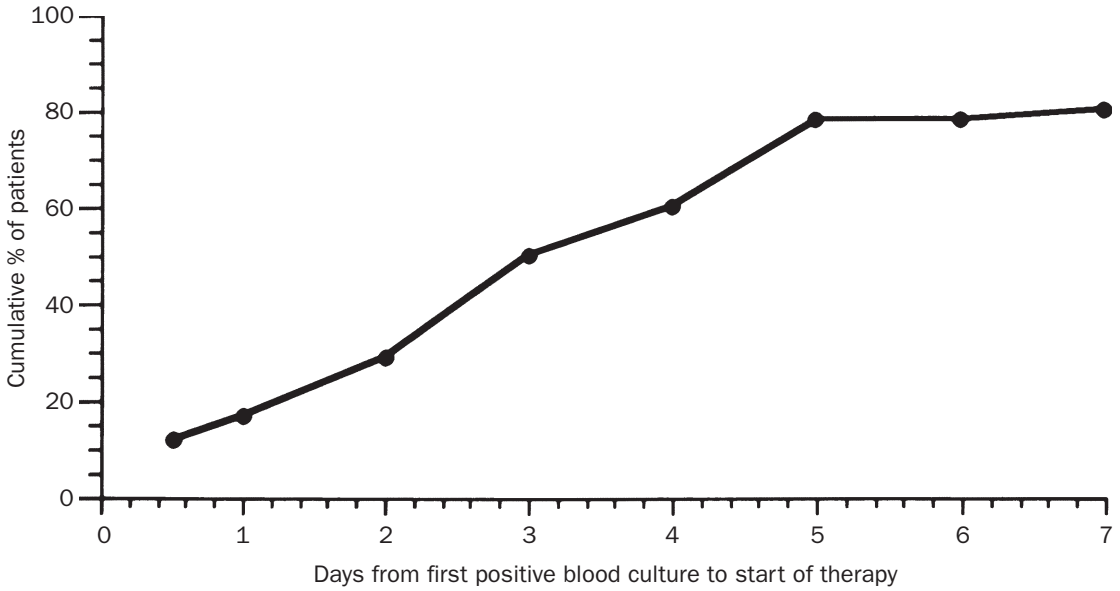


Figure 1.3 *E. coli* bacteremia. Mortality is related to time of onset of bacteremia after the first positive blood culture and institution of appropriate therapy. Reprinted from *Am J Med*, Vol 81 (Suppl 1A), Bodey GP, Elting L, Kassameli H, Lim BP, *Escherichia coli* bacteremia in cancer patients, pp 85–95. Copyright 1986, with permission from Excerpta Medica Inc.

of antibiotic was delayed.[21] For *E. coli* bacteremia, including neutropenic and non-neutropenic patients, about 12% of patients died (Figure 1.3) if antibiotics were started within the first 12 hours, compared with 18% when they were started between 12 hours and 24 hours, and 30% when they were started between 24 hours and 48 hours after the collection of the first blood culture that proved to be positive. The mortality rate continued to rise to 80% if appropriate therapy had not been instituted promptly.[22] A similar observation was made with *Ps. aeruginosa* bacteremia (Figure 1.4).[21]

Many published reports indicate that the site of Gram-negative bacteremia in the neutropenic cancer patient is frequently never identified. This has not been my experience when each patient has been studiously examined on a daily basis.[3] Perhaps what is most important is the recognition that the signs and symptoms of inflammation are markedly diminished and therefore evidence of infection may be subtle. It is particularly helpful to have seen the patient on a regular basis prior to the onset of infection, so that one can compare the prefebrile examination with any changes that may have occurred. If one knows the common sites of origin of infection in these patients, then it is possible to give particular attention to those sites and look for subtle changes. For example, infection arising from pharyngitis may be represented only by complaints of an intense sore throat and some erythema, but little other physical evidence. Bacteremia due to a perianal lesion may be detected by the patient noting pain with defecation, and an examination that shows only minimal erythema but intensive tenderness over the site of a minor-appearing fissure, often at the base of a hemmorrhoid, which serves as the nidus and origin for the bacteremia.

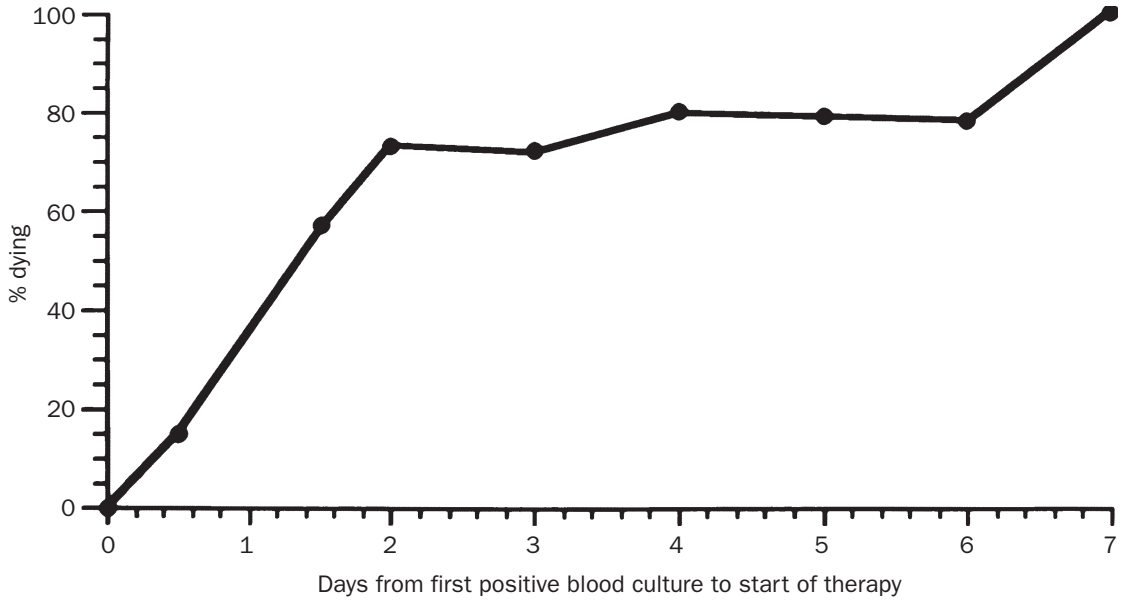


Figure 1.4 *Ps. aeruginosa* bacteremia. Mortality is related to time of onset of therapy after the first positive blood culture. Reprinted with permission from Bodey GP, Jadeja L, Elting L, *Pseudomonas* bacteremia: retrospective analysis of 410 episodes. *Arch Intern Med* 1985; **145:** 1621–9. Copyright 1985, American Medical Association.

Some organisms, notably *Ps. aeruginosa*, are exceptionally invasive during profound neutropenia (i.e., if colonized, the patient frequently becomes infected). Colonization with other organisms such as *E. coli* and *K. pneumoniae* occasionally leads to bacteremia, and colonization with still other organisms such as non-aeruginosa *Pseudomonas* spp. very rarely proceed to infection, even during profound neutropenia. Thus, there is a clear difference in invasive potential among Gram-negative bacilli in this highly vulnerable population of patients.

CHOICE OF DRUGS AND LEVEL OF NEUTROPENIA: IMPLICATIONS FOR SURVIVAL

Bodey et al have reviewed the common causes of Gram-negative bacteremia in cancer patients, such as *E. coli*,[22] *Ps. aeruginosa*,[21] and some of the less common organisms, such as *Serratia marcescens* and *Enterobacter* spp. Consistently, the rate per 1000 admissions is higher for patients with acute leukemia than for patients with other hematologic malignancies, and much higher than for patients with solid tumors. Bodey and his colleagues have noted that for patients who become bacteremic, the blood culture may be positive 50% or more of the time when fever is first documented (Figure 1.5). Another consistent finding has been the importance of the neutrophil count with regard to the ultimate response; when the initial neutrophil count was below 100/μl and remained unchanged, the response rate for *E. coli* bacteremia was 48%, whereas if the neutrophil count increased, the response rate was 83%. When the initial neutrophil count was above 100/μl yet less than 1000/μl and remained unchanged, the response rate was 47%, but if the neutrophil count increased further, the

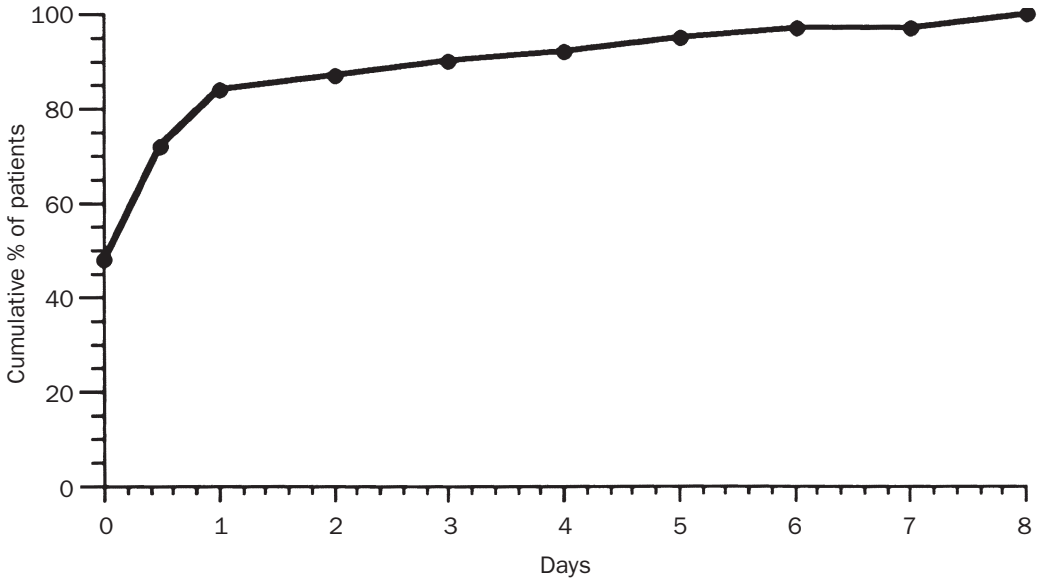


Figure 1.5 *E. coli* bacteremia. Time of first positive blood culture relative to onset of fever. Nearly 50% of patients were bacteremic when fever first developed. Reprinted from *Am J Med*, Vol 81 (Suppl 1A), Bodey GP, Elting L, Kassameli H, Lim BP, *Escherichia coli* bacteremia in cancer patients, pp 85–95. Copyright 1986, with permission from Excerpta Medica Inc.

response rate was 95%. In addition, and not surprisingly, there was a marked difference in survival depending upon whether the patient received appropriate therapy (i.e. antibiotics to which the organism was susceptible) or inappropriate therapy. For *E. coli* bacteremia, the survival rates were about 75% for those who received appropriate therapy and 38% for those who received inappropriate therapy initially (Figure 1.6).

THERAPY OF FEBRILE NEUTROPENIA

Given all of these factors, empiric therapy for the febrile, neutropenic patient must be:

- prompt;
- empiric;
- bactericidal;
- broad-spectrum.

The need for prompt institution of therapy is due to the rapid and high mortality rate of patients with Gram-negative bacteremia and, occasionally, the bacteremias caused by *Streptococcus* spp. Recall from above that the risk of dying was closely related to the interval between the onset of bacteremia and the institution of appropriate antibiotic therapy (Table 1.3 and Figures 1.3 and 1.4).[21,22] The need for prompt therapy makes the use of empiric antibacterial regimens obvious. It should be emphasized that an antibiotic regimen must be chosen that is most appropriate for the specific patient in a specific institution. It is necessary to know what organisms are, or are likely to be, colonizing the patient and what the likely susceptibility patterns will be. It is critical to have continually updated information on the susceptibility patterns of organisms frequently recovered from the hospital and the area of the

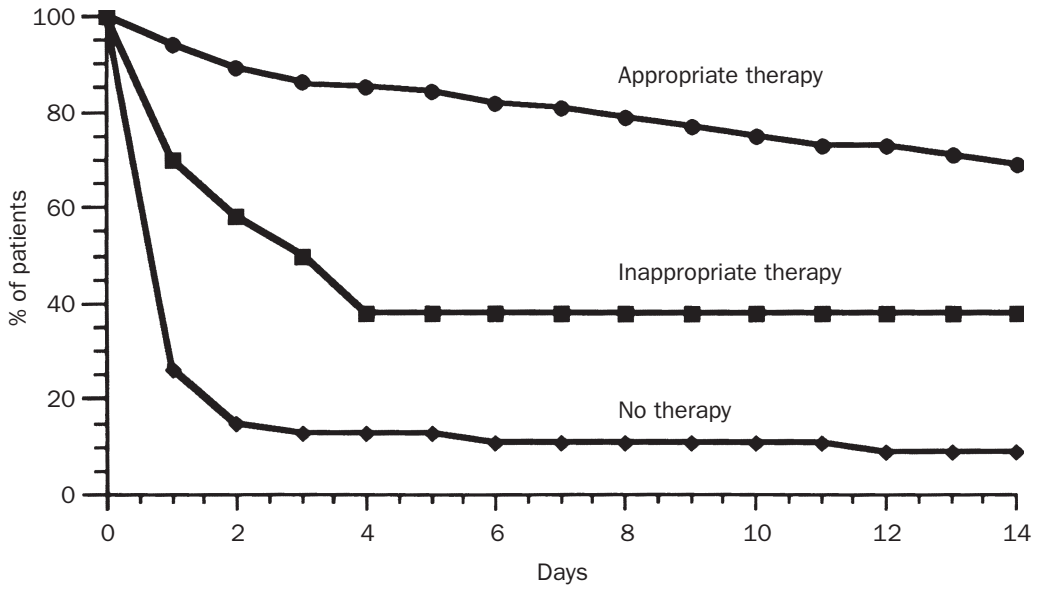


Figure 1.6 *E. coli* bacteremia. Mortality is related to whether or not initial therapy was appropriate, i.e. whether the organism was susceptible by in vitro testing. Reprinted from *Am J Med*, Vol 81 (Suppl 1A), Bodey GP, Elting L, Kassameli H, Lim BP, *Escherichia coli* bacteremia in cancer patients, pp 85–95. Copyright 1986, with permission from Excerpta Medica Inc.

hospital where the patient is being treated. Bactericidal rather than bacteriostatic antibiotics are essential, since, in the absence of neutrophils, this is a battle of 'bugs versus drugs'. The agents should have a broad spectrum so as to 'cover' the great majority of the relatively limited number of potential pathogens.

Combination empiric therapy

The options for choices of antibiotics are wide (Table 1.4). For many years, the most common approach was the use of β-lactam plus an aminoglycoside. These combinations have withstood the test of time, they have been found to be broadly effective, the newer β-lactams offer 'coverage' for most of the Gram-negative and Gram-positive bacteria that invade these patients, there is synergistic activity against many Gram-negative bacilli, and there are data to suggest that the development of resistance to the β-lactam is less likely with the added aminoglycoside. Among the penicillins, those with the broadest spectrum include piperacillin (especially when combined with tazobactam) and ticarcillin (especially when they are combined with the β-lactamase inhibitor clavulanic acid). The antipseudomonal cephalosporins such as ceftazidime and cefepime likewise offer broad Gram-negative coverage, as do the carbapenems imipenem and meropenem. The monobactam azetreonam has excellent Gram-negative activity, but incorporates no Gram-positive activity. The cephalosporins and carbapenems have activity against *S. aureus* and the streptococci. None of these agents are effective for *S. epidermidis* (even if susceptibility results suggest activity). The penicillins, some of the cephalosporins, and imipenem have activity against anaerobes (which rarely cause bacteremia but which are

Table 1.4 Available antibiotics for initial empiric therapy of the febrile neutropenic patient

β-lactams	Aminoglycosides
Penicillins	Gentamicin
Piperacillin ± tazobactam	Tobramycin
Ticarcillin + clavulanic acid	Amikacin
Cephalosporins	
Ceftazidime	
Cefepime	
Ceftriaxone	
Monobactam	
Aztreonam	
Carbapenems	
Imipenem	
Meropenem	

important along the alimentary canal to preserve colonization resistance), whereas ceftazidime has no activity against anaerobes. The choice of the β-lactam agent should be based largely on institutional antimicrobial susceptibility patterns and, preferably, knowledge of susceptibility patterns for recent infections within the oncology unit.

The commonly utilized aminoglycosides include gentamicin, tobramycin, and amikacin. For susceptible organisms, each of these aminoglycosides probably has equivalent efficacy. Aminoglycosides are both ototoxic and nephrotoxic, and it is generally advisable to measure serum levels to be sure that one is within the therapeutic, yet below the toxic, range. If one approaches the aminoglycoside primarily for its value in adding synergy, then it is probably not necessary to push toward the higher, more toxic side of the accepted therapeutic range, and thereby lessen the opportunity for undesirable side-effects. There are no data to demonstrate that higher peak and trough levels of aminoglycosides, when given in combination with a β-lactam for this type of patient, are more efficacious than a somewhat lower dose. There is sufficient data to demonstrate that aminoglycosides alone are not adequate in the setting of profound neutropenia (i.e. <100/μl).

Monotherapy

With the advent of the very broad-spectrum β-lactams, such as ceftazidime, imipenem, and ticarcillin plus clavulanic acid, and given the inherent toxicities of the aminoglycosides, it seemed reasonable to attempt to use single-agent therapy for initial empiric treatment. The classic study was completed by Pizzo et al,[23] who randomly allocated patients to a combination of carbenicillin, cephalothin plus gentamicin or to ceftazidime at the onset of fever during neutropenia. Ceftazidime alone was as efficacious as the combination. A large number of patients required alteration in therapy, such as the addition of vancomycin, an antifungal, or an antiviral agent to each of the two initial regimens. However, the ultimate responses were equivalent, and the mortality rate was extremely small in both groups. Ceftazidime, imipenem, meropenem, and cefepime have been used effectively for many patients as initial empiric therapy for fever during neutropenia.

I do not believe that there is adequate data to assess whether monotherapy with one of these agents is sufficient for the patient who has profound, persistent neutropenia and a Gram-negative rod bacteremia. Only about 10% of patients in most large studies have proven to have a Gram-negative rod bacteremia, and only about half of these patients tend to fall into the category of those with profound, persistent neutropenia. For example, in the study by Pizzo et al,[23] there were only 13 Gram-negative rod

Table 1.5 EORTC IV trial[24]

Entries	**1074**
Exclusions	**202**
Protocol violation	52
Doubted infection	135
Viral/fungal infection	15
Evaluable episodes	**872**
Possible infection	342
Clinically documented	225
Microbiologically documented	305
Without bacteremia	53
With bacteremia	252
Polymicrobial	33
Single-organism	219
Gram-positive	90
Gram-negative	129
Persistent profound neutropenia	53

bacteremias out of more than 500 patient entries. In an EORTC trial,[24] there were only 129 Gram-negative bacteremias out of 1074 patients entered (Table 1.5), and of the 129, only 53 had profound, persistent neutropenia. It is this latter group of patients, however, that concern me. In study after study, they tend to do poorly regardless of the agent(s) used, but do less well with single-agent therapy (see below). In this EORTC trial, for example, the response rates for patients with Gram-negative rod bacteremia and a neutrophil count of less than 100/μl throughout therapy were 6% with ceftazidime and short-course amikacin, compared with 50% with ceftazidime and long-course amikacin ($p = 0.03$) (Table 1.6 and Figure 1.7). This was further evidence to suggest the value of the aminoglycoside in combination with the β-lactam in this particular subgroup of patients.

Synergy

At our institution, de Jongh et al[25] looked at a series of 75 consecutive Gram-negative rod bacteremias that occurred among patients who had a neutrophil count of less than 100/μl; each received prompt empiric antibiotic therapy using a combination. The critical observations were as follows. First, there was a dramatic difference in response rate between patients who remained profoundly neutropenic and those whose neutrophil count began to rise during the next few days (Figure 1.8). Indeed, the response rate for those who were profoundly neutropenic was substantially and disturbingly poorer. Dissecting further, the patients with persisting, profound neutropenia had a response rate that was significantly better if they had received two drugs to which the Gram-negative bacillus proved to be suscepti-

Table 1.6 Response to treatment in the presence and absence of persistent profound neutropenia[24]

Condition of patients	Patients with response/patients with bacteremia			
	Azlocillin + amikacin	Ceftazidime + short amikacin	Ceftazidime + long amikacin	Total
Persistent profound neutropenia:				
Present[a]	5/25 (20%)	1/16 (6%)	6/12 (50%)	12/53 (23%)[b]
Absent[c]	11/15 (73%)	19/26 (73%)	32/35 (91%)	62/76 (82%)[b]

Reprinted with permission from EORTC International Antimicrobial Therapy Cooperative Group, *N Engl J Med* 1987; **317**: 1692–8. Copyright © 1987 Massachusetts Medical Society. All rights reserved.
[a] The *p* values for comparison of treatment regimens were as follows: global, 0.02; azlocillin + amikacin versus ceftazidime + short amikacin, 0.45; azlocillin + amikacin versus ceftazidime + long amikacin, 0.14; and ceftazidime + short amikacin versus ceftazidime + long amikacin, 0.03.
[b] $p < 0.001$.
[c] Global p value = 0.12.

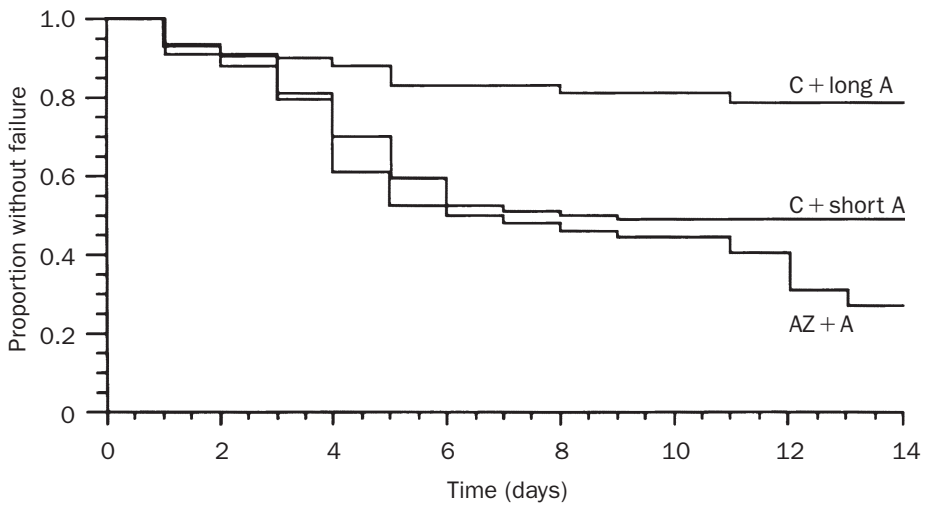


Figure 1.7 Time to treatment failure according to treatment regimen (C, ceftazidime; A, amikacin; AZ, azlocillin). Continued use of the aminoglycoside with ceftazidime led to better response rates for Gram-negative bacteria. Reprinted with permission from EORTC International Antimicrobial Therapy Cooperative Group, Ceftazidime combined with a short or long course of amikacin for empirical therapy of Gram-negative bacteremia in cancer patients with granulocytopenia. *N Engl J Med* 1987; **317:** 1692–8. Copyright © 1987 Massachusetts Medical Society. All rights reserved.

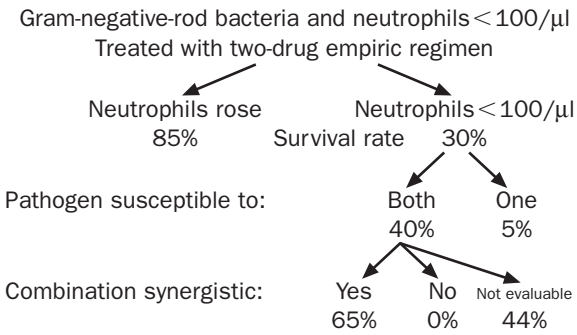


Figure 1.8 Treatment of infection in cancer patients with granulocytopenia.[25] Reprinted from Schimpff SC, Gram-negative bacteremia. *Support Care Cancer* 1993; **1:** 5–18. Copyright 1993 Springer-Verlag.

Table 1.7 Summary of the results of 12 controlled clinical trials of therapy with single versus multiple antibiotics and with synergistic versus non-synergistic combinations of antibiotics in neutropenic patients infected with Gram-negative bacilli[a]

Type of therapy	Number of patients with a favorable clinical response
Single antibiotic (195 patients)	119 (61%)
Multiple antibiotics (170 patients)	138 (81%)
Nonsynergistic combinations (179 patients)	77 (43%)
Synergistic combinations (208 patients)	158 (76%)

[a] Reproduced with permission from Klastersky J, Empiric treatment of infections in neutropenic patients with cancer. *Rev Infect Dis* 1983; **5**(Suppl): S21–31.

ble; the response rate when the organism was susceptible to only one drug was particularly poor. Further analysis demonstrated that if the combination of two drugs was synergistic in vitro against the invading organism, then these patients did better than if the combination was not synergistic.

The study demonstrates that among persistently neutropenic patients who are treated with two effective bactericidal antibiotics, combination with in vitro synergism is associated with a more favorable clinical outcome than are similar combinations that are not synergistic in vitro even when both agents are quite active against the pathogen. Such synergism is of no prognostic importance among patients with rising neutrophil counts; only those patients with Gram-negative bacteremia who are profoundly and persistently neutropenic benefit from the presence of the two-drug synergistic combination.

Serum bactericidal activity

Klastersky and colleagues[26,27] and Anderson et al[28] demonstrated that synergistic combinations of agents were more effective for Gram-negative bacteremia than single agents (Table 1.7). Klastersky[29] reported that synergistic combinations also elicited a serum bactericidal activity that was significantly greater (1 : 16 versus 1 : 4 at peak and 1 : 8 versus 1 : 2 at trough) (Table 1.8). However, with the advent of newer β-lactams such as ceftazidime and imipenem, good bactericidal activity could be obtained with the single agent. For example, Standiford et al[30] gave ticarcillin and amikacin or ceftazidime to volunteers and measured serum bactericidal activity at 1 hour and 6 hours. Ceftazidime had a notably better serum cidal profile for *Ps. aeruginosa*, *E. coli*, and *K. pneumoniae* than did the combination (Table 1.9 and Figure 1.9).[30]

In a later study, imipenem was compared

Table 1.8 Clinical responses and serum bactericidal activity in patients with cancer and Gram-negative bacillary infections who received synergistic or non-synergistic combinations of antibiotics (the studies were performed at the Institut Jules Bordet, Brussels, Belgium)[29]

Type of combination	Number of patients with a favorable clinical response	Median titer of serum bactericidal activity	
		Maximum	Minimum
Synergistic (100 patients)	80 (80%)[a]	1 : 16	1 : 8
Non-synergistic (105 patients)	52 (50%)[a]	1 : 4	1 : 2

Reproduced with permission from Klastersky J, *Eur J Cancer* 1979; **15**: 3–13.[29]
[a] $p < 0.01$

Table 1.9 Reciprocal geometric mean bactericidal titers generated at 1 and 6 hours by each regimen[30]

Test organism	Titer obtained with			
	Ceftazidime		Ticarcillin–amikacin	
	1 h	6 h	1 h	6 h
Ps. aeruginosa (31 strains)	40.7	4.7	12.2	2.1
S. aureus (7 strains)	3.6	NA[a]	24.3	3.0
E. coli (7 strains)	256.0	128.0	125.5	8.2
K. pneumoniae (7 strains)	236.5	97.0	86.1	8.0

Reproduced from Standiford HC et al, *Antimicrob Agents Chemother* 1984; **26**: 339–42.[30]
[a] No activity assayable.

with ticarcillin plus amikacin.[31] At 1 hour, the geometric mean bactericidal titers were 13 and 12, respectively, while at $5\frac{1}{2}$ hours, they were 3 and 2, respectively. An animal model demonstrated that severely neutropenic rats given a lethal intraperitoneal challenge of *Ps. aeruginosa* responded as well to imipenem alone as to the combination of moxalactam and amikacin. However, the rat survival was substantially better still when amikacin was added to the imipenem (Figure 1.10).[32]

Alternatively, it may be that two antibiotics can effectively eliminate a Gram-negative bacillus during profound neutropenia only if

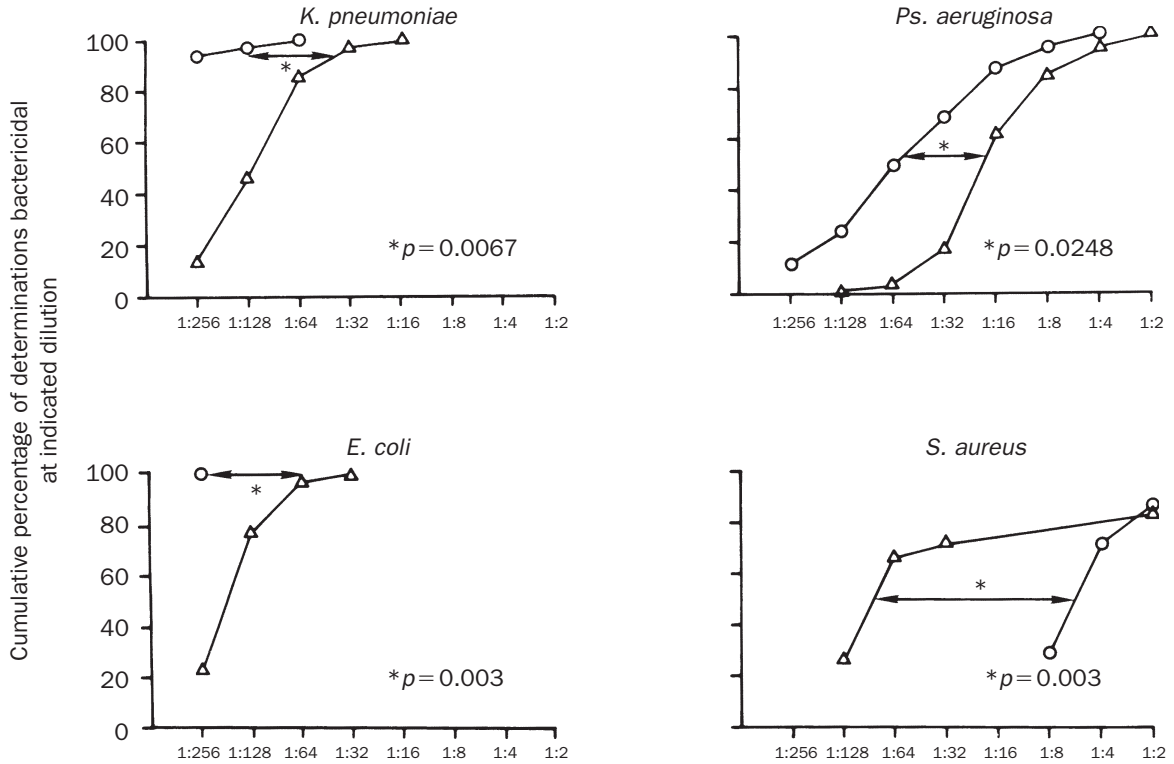


Figure 1.9 Cumulative percentage of determinations bactericidal against pathogens commonly bacteremic in neutropenic cancer patients. Serum was obtained from volunteers 1 hour after the end of the infusion. The *p* value represents the level of significance between geometric mean bactericidal titers produced by the two regimens. *Symbols:* ○, ceftazidime; △, ticarcillin plus amikacin. Reprinted with permission of the American Society for Microbiology from Standiford HC, Drusano GL, Fitzgerald B et al, Bactericidal activity of ceftazidine in serum compared with that of ticarcillin combined with amikacin. *Antimicrob Agents Chemother* 1984; **26:** 339–42.

they attack by different mechanisms. Using an in vitro system that exposed *Ps. aeruginosa* to fluctuating levels of gentamicin, Gerber et al[33] noted the development of small colonies of gentamicin-resistant variants. Although these variants were less pathogenic in normal and moderately neutropenic mice than were susceptible colonies, they invariably killed severely neutropenic mice challenged intraperitoneally. The development of these gentamicin-resistant variants could be prevented by the addition of ticarcillin.[34,35] Thus, two agents killing by separate mechanisms and preventing the emergence of resistant organisms may be important.

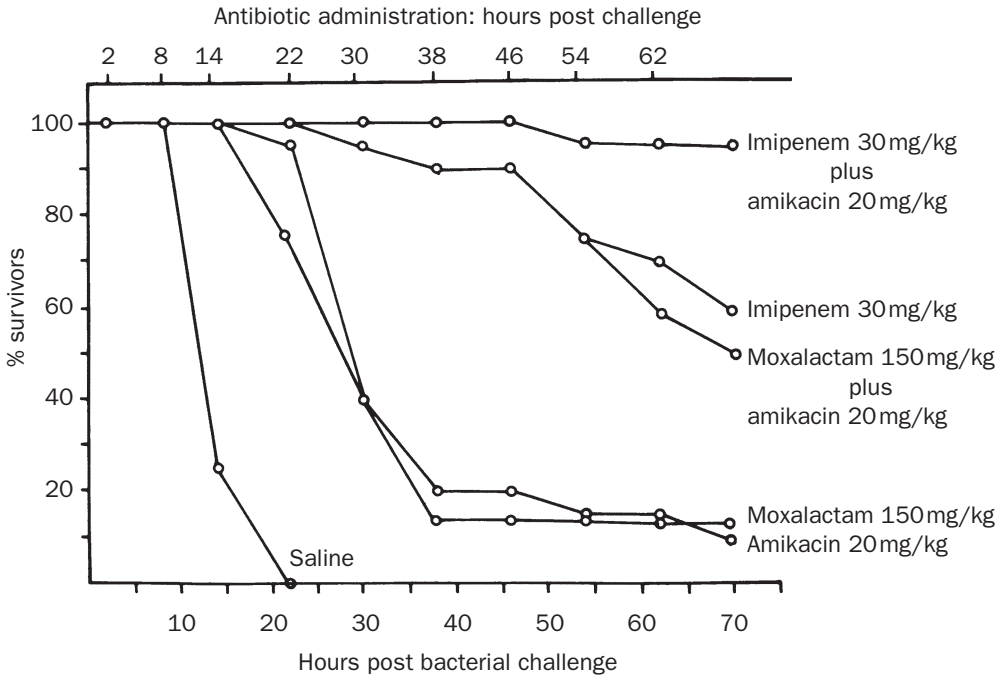


Figure 1.10 Antibiotic therapy in neutropenic rats challenged with 250 LD_{50} (2.2×10^9) of *Ps. aeruginosa* strain number 228. Reprinted with permission from Johnson DE, Calia FM, Snyder MJ et al, Imipenem therapy of *Pseudomonas aeruginosa* bacteremia in neutropenic rats. *J Antimicrob Chemother* 1983; **12:** 89–96. Copyright 1983 Oxford University Press.

Therapy of persistent fever and persistent neutropenia

A major concern for the clinician dealing with the febrile neutropenic patient is what to do with the patient who has persistence of fever following the administration of empiric antibiotic therapy. The questions relate to whether the initial antibiotic should be continued or discontinued, whether an additional antibacterial antibiotic should be added, and whether an antifungal agent such as amphotericin B or an antiviral agent such as acyclovir should be added. There is no single correct answer. The first step should be to carefully repeat the history, physical examination, and chest X-ray, and to review the results of the original cultures. More often than not, such a review will reveal an infection site, if one exists. However, other causes of fever must be considered: blood product transfusions, a history of fever with the underlying tumor, and drug fever from compounds such as cytosine arabinoside or from the empiric antibiotics themselves. Pizzo et al[36,37] showed that continued therapy prevented new/recurrent bacterial infection for patients with persistent neutropenia; however, fungal infections became common yet could be prevented/treated by instituting amphotericin B on day 7 of continued fever.

The EORTC found that the addition of empiric amphotericin B after four days of broad-spectrum antibiotics and persistent fever and neutropenia had some benefit. Of the

patients with added amphotericin B, 69% had resolution of fever, compared with 53% in the control group. There was one fungemia (1 of 68 patients) compared with six (6 of 64 patients), and there was one death due to fungal infection compared with four. Of note, those who had fungal infections usually had some clinical evidence to suggest that it might be present, i.e. this was not entirely 'empiric' therapy.[38]

Therapy of persistent neutropenia with febrile response

There are some patients with persistent neutropenia and no specific evidence of infection on repeated history and physical examination who have a 'febrile response', i.e. the fever abates promptly after institution of antibiotics. This raises the question as to whether the patient was infected and whether the antibiotic(s) should be continued? The critical step is to repeat the history and physical examination, review all cultural data, and repeat the chest X-ray. If no specific evidence of infection can be determined, yet it appears that the patient has had a febrile response secondary to antibiotic therapy, then it would seem reasonable to continue the antibiotics for a total of about 10 days. If at that time the neutrophil count remains very low, one would have to decide whether to continue antibiotic therapy for a longer period. I usually discontinue antibiotics at this time, but there is evidence to suggest that continuing antibiotic therapy is appropriate.[36] However, continuation must be balanced against the potential risk of predisposing toward fungal infection, which may require the addition of amphotericin B or other antifungal agents.[38]

SHIFT FROM GRAM-NEGATIVE TO GRAM-POSITIVE PREDOMINANCE

In the 1960s and 1970s, the predominant pathogens of febrile neutropenic episodes were Gram-negative bacilli along with some *S. aureus*. Over the past 25 years, a change toward fewer Gram-negatives and a predominance of certain Gram-positives, especially coagulase-negative staphylococci and viridans streptococci, has occurred (Figure 1.11).[39]

The reasons for this shift are not totally clear, but some hypotheses are as follows. Prevention techniques such as attention to handwashing may have reduced *S. aureus* transmission. Attention to water sources (e.g. faucet aerators and tamperproof ice machines) and the use of lower-microbial-content foods (e.g. avoiding salads and uncooked tomatoes, and using freshly ground pepper) may have reduced the acquisition of Gram-negative bacilli.[40] The use of alimentary canal microbial suppression (e.g. oral quinolones) may have reduced Gram-negative bacillary invasion of the damaged mucosa.[41]

Concurrently, the commonplace use of indwelling vascular access catheters has increased the opportunity for *S. epidermidis* infections (entry-site infections, tunnel infections, and especially internal colonization of the catheter, with bloodstream seeding).[42] Streptococcal infections may be related to intensive oral-mucosal-damaging chemotherapy, specific agents such as high-dose cytosine arabinoside, and the use of quinolones as prophylaxis.

This shift in pathogen frequency has led to consideration of changes in the choice of empiric antibiotics.[43] Some have suggested that a combination including vancomycin should be used in the initial regimen. Others have indicated that *S. epidermidis*, unlike Gram-negative bacilli, tends to cause a more indolent infection and hence there is time to substitute or add vancomycin once culture reports are available[44–46] (Figure 1.12). This avoids the inherent nephrotoxicity of vancomycin, especially when it is used in conjunction with an aminoglycoside, amphotericin B, or both. The increasing problem of vancomycin-resistant enterococci (VRE) and hence the need to restrict vancomycin to situations where it is truly needed

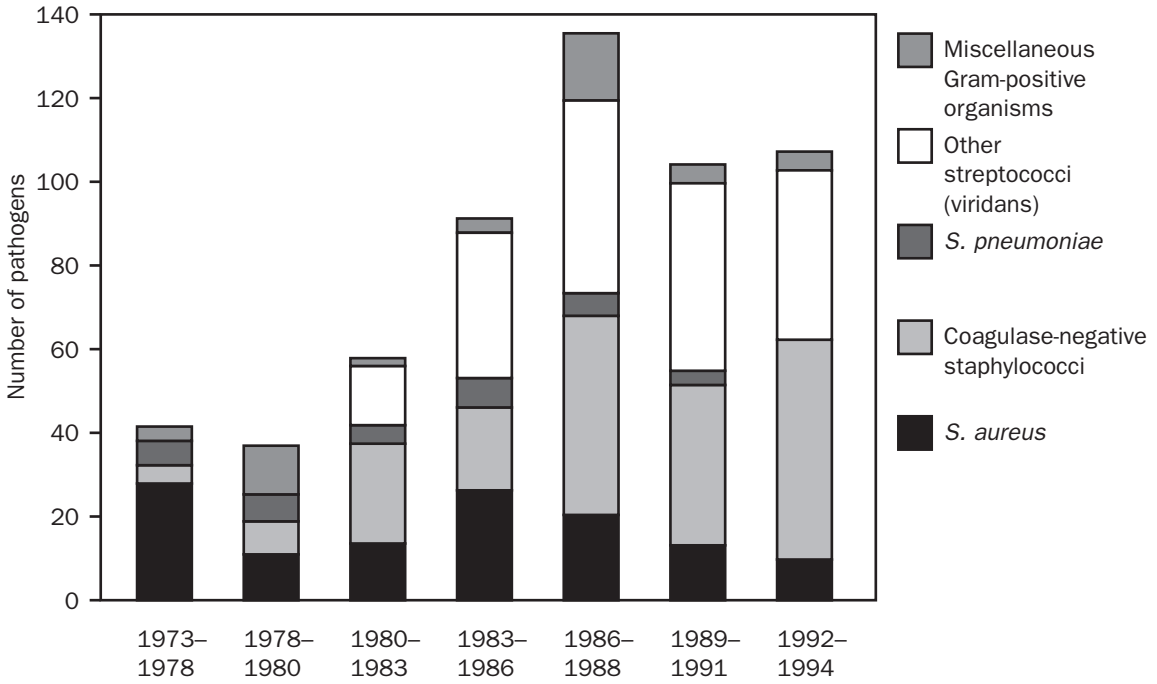


Figure 1.11 Changing pattern of infectious organisms in febrile neutropenia. Reprinted from Maschmeyer G, Noskin GA, Ribaud P, Sepkowitz KA, Changing patterns of infections and antimicrobial sensitivities. *Oncology* 2000; **14**(Suppl 6): 9–16. With permission of *ONCOLOGY*, Melville, NY.

strengthens the case for withholding vancomycin as part of the initial empiric regimen.

The streptococci are generally quite susceptible to the various β-lactams in use, although resistance to penicillins is definitely on the rise.[47] Prompt initiation of therapy is key, because these organisms are capable of causing very serious infection with shock over a short time frame.

ORAL THERAPY INSTEAD OF INTRAVENOUS THERAPY

The initial concepts in treating the febrile neutropenic patient empirically included:

- use of broad-spectrum antibiotics to assure coverage for most of the common pathogens;
- intravenous therapy to assure rapid achievement of adequate serum levels;
- close monitoring because of the concern for progression to septic shock with Gram-negative bacteremia or possibly the development of respiratory failure with pneumonia.

Today, Gram-negative bacteremia is much less common, and it is possible to establish the patient's relative risk for an adverse outcome of febrile neutropenia. Hence, it would seem logical to utilize oral agents that have an

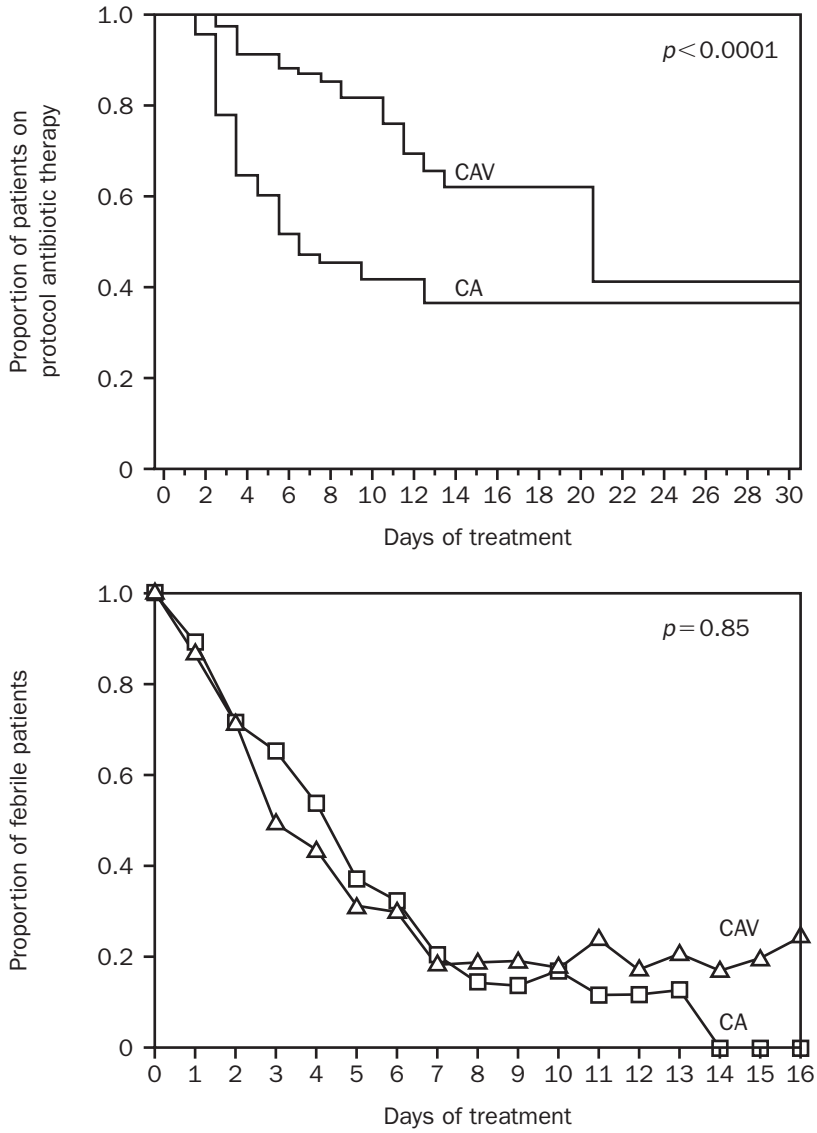


Figure 1.12 Gram-positive bacteremia: proportion of febrile patients at each treatment day in the two treatment regimens. No discrepancy was noted between the two groups in the proportion of febrile patients ($p = 0.85$).[44] CA (□), ceftazidime and amikacin; CAV (△), ceftazidime, amikacin and vancomycin. Reprinted with permission from EORTC International Antimicrobial Therapy Cooperative Group and the National Cancer Institute of Canada – Clinical Trials Group, Vancomycin added to empirical combination antibiotic therapy for fever in granulocytopenic cancer patients. *J Infect Dis* 1991; **163:** 951–8. Copyright 1991 University of Chicago Press.

adequate spectrum and are well absorbed, especially in low-risk patients. Data supporting this approach have recently been published.[48–51] See Chapter 9.

SUMMARY

Much progress has been made over the past 30–35 years regarding the treatment of neutropenic patients who develop fever.

- It has become accepted that empiric therapy is appropriate when fever develops.
- It has been recognized that the inflammatory response is muted, so that signs and symptoms are limited, making site identification difficult. Repeated examinations focusing on the common sites will often define the site over the course of a few days.
- Some pathogens can cause sepsis and death quickly – notably Gram-negative bacilli and streptococci – necessitating prompt initiation of therapy with a regimen designed to 'cover' the most likely organisms.
- Selection of a regimen should take into account the current antibiotic susceptibility pattern at the hospital/oncology center.
- Monotherapy with a variety of β-lactams is effective for most patients.
- Subgroups of patients with lower risk can be identified, thus allowing consideration of outpatient/home therapy and/or oral therapy.
- Oral therapy can be effective, but some patients will be intolerant owing to nausea, vomiting, or possibly diarrhea; close follow-up is required to be certain that the oral therapy is being ingested adequately.
- The spectrum of pathogens has shifted increasingly toward Gram-positive cocci, especially coagulase-negative staphylococci and viridans streptococci. In general, vancomycin is required for *S. epidermidis* infections, but can be withheld until culture reports confirm staphylococcal presence.
- The most important factor in response, other than the immediate initiation of the proper regimen, is return of circulating neutrophils. Neutrophil transfusions for aplastic patients can be useful, but it is difficult to obtain adequate numbers, and those at greatest need are often alloimmunized. Colony-stimulating factors (e.g. granulocyte or granulocyte–macrophage colony-stimulating factors: G-CSF and GM-CSF) may be helpful in assisting a more rapid return of bone marrow function.

These improvements mean that most patients will have rapid resolution of fever and infection. Unfortunately, one subgroup continues to have a dismal prognosis – namely, those patients with an aplastic marrow and a Gram-negative bacteremia. Response rates to highly active antibiotic(s) are poor at best. In large studies, these patients represent about 5% of the total that develop fever during neutropenia. The absolute numbers of patients are low – but so is their survival.

CURRENT RECOMMENDATIONS

Monotherapy with drugs such as ceftazidime, cefepime, and imipenem is probably adequate for most patients who develop fever yet have only moderate degrees of neutropenia. These patients rarely have Gram-negative-rod bacteremia, and their prognosis is generally good. For those patients who have profound neutropenia (<100/μl) and an aplastic bone marrow, one might consider a combination of drugs such as a β-lactam along with an aminoglycoside. Neutrophil transfusions are rarely utilized today. G-CSF or GM-CSF is an appropriate adjunct for those patients with profound, persistent neutropenia in whom Gram-negative bacteremia is either proven or highly suspected.

REFERENCES

1. Joshi JH, Schimpff SC, Infections in the compromised host. In: *Principles and Practice of Infectious Diseases*, 2nd edn (Mandel GL, Douglas RG Jr, Bennett JE, eds). New York: Wiley, 1985: 1644–9.
2. Bodey GP, Buckley M, Sathe YS et al, Quantitative relationships between circulating leukocytes and infection in patients with acute leukemia. *Ann Intern Med* 1966; **64:** 328–40.
3. Schimpff SC, Young VM, Greene WH et al, Origin of infection in acute nonlymphocytic leukemia: significance of hospital acquisition of potential pathogens. *Ann Intern Med* 1972; **77:** 707–14.
4. Williams DM, Krick JA, Remington JS, Pulmonary infection in the compromised host. *Am Rev Respir Dis* 1976; **114:** 359.
5. Schimpff SC, Infection in patients with cancer: overview and epidemiology. In: *Comprehensive Textbook of Oncology*, 2nd edn (Moossa AR, Schimpff SC, Robson MC, eds). Baltimore: Williams & Wilkins, 1991: 1720–32.
6. Schimpff SC, Wiernik PH, Block JB, Rectal abscesses in cancer patients. *Lancet* 1972; **ii:** 844–7.
7. Young LS, Nosocomial infections in the immunocompromised adult. *Am J Med* 1981; **70:** 394.
8. Johanson WG, Pierce AK, Sanford JP, Changing pharyngeal bacterial flora of hospitalized patients: emergence of Gram-negative bacilli. *N Engl J Med* 1969; **281:** 1137.
9. van der Waaij D, Berghuis-de Vries JM, Lekkerkerk JEC, Colonization resistance of the digestive tract of mice during systemic antibiotic treatment. *J Hyg* 1972; **70:** 605.
10. Aisner J, Murillo J, Schimpff SC, Steere AC, Invasive aspergillosis in acute leukemia: correlation with nose cultures and antibiotic usage. *Ann Intern Med* 1979; **90:** 4–9.
11. EORTC International Antimicrobial Therapy Cooperative Group, Three antibiotic regimens in the treatment of infection in febrile granulocytopenic patients with cancer. *J Infect Dis* 1978; **137:** 14–29.
12. Sickles EA, Greene WH, Wiernik PH, Clinical presentation in granulocytopenic patients. *Arch Intern Med* 1975; **135:** 715–19.
13. Pizzo PA, Ladisch S, Witebsky FG, α-hemolytic streptococci: clinical significance in the cancer patient. *Med Pediatr Oncol* 1978; **4:** 367–70.
14. Kern W, Kurrle E, Vanek E, High risk of streptococcal septicemia after high dose cytosine arabinoside treatment for acute myelogenous leukemia. *Klin Wochenschr* 1987; **65:** 773–80.
15. Sotiropoulos SV, Jackson MA, Woods GM et al, α-streptococcal septicemia in leukemic children treated with continuous or large dosage intermittent cytosine arabinoside. *Pediatr Infect Dis* 1989; **8:** 755–8.
16. DuPont HL, Spink WW, Infections due to Gram-negative organisms: an analysis of 860 patients with bacteremia at the University of Minnesota Medical Center, 1958–1966. *Medicine* 1969; **48:** 307–32.
17. McCabe WR, Jackson GG, Gram-negative bacteremia. I. Etiology and ecology. *Arch Intern Med* 1962; **110:** 847–55.
18. Schimpff SC, Greene WH, Young VM, Wiernik PH, Significance of *Pseudomonas aeruginosa* in the patient with leukemia or lymphoma. *J Infect Dis* 1974; **130**(Suppl): S24–31.
19. Schimpff SC, Satterlee W, Young VM, Serpick A, Empiric therapy with carbenicillin and gentamicin for febrile patients with cancer and granulocytopenia. *N Engl J Med* 1971; **284:** 1061–5.
20. Greisman SE, DuBuy JB, Woodward CL, Experimental Gram-negative bacterial sepsis: prevention of mortality not preventable by antibiotics alone. *Infect Immun* 1979; **25:** 538–57.
21. Bodey GP, Jadeja L, Elting L, *Pseudomonas* bacteremia: retrospective analysis of 410 episodes. *Arch Intern Med* 1985; **145:** 1621–9.
22. Bodey GP, Elting L, Kassamali H, Lim BP, *Escherichia coli* bacteremia in cancer patients. *Am J Med* 1986; **81** (Suppl 1A): 85–95.
23. Pizzo P, Hathorn J, Hiemenz J et al, A randomized trial comparing ceftazidime alone with combination antibiotic therapy in cancer patients with fever and neutropenia. *N Engl J Med* 1986; **315:** 552–8.
24 EORTC International Antimicrobial Therapy Cooperative Group, Ceftazidime combined with a short or long course of amikacin for empirical therapy of Gram-negative bacteremia in cancer patients with granulocytopenia. *N Engl J Med* 1987; **317:** 1692–8.
25. de Jongh CA, Joshi JH, Newman KA et al, Antibiotic synergism and response in Gram-negative bacteremia in granulocytopenic cancer patients. *Am J Med* 1986; **80:** 96–100.
26. Sculier JP, Klastersky J, Significance of serum

bactericidal activity in Gram-negative bacillary bacteremia in patients with and without granulocytopenia. *Am J Med* 1984; **76:** 429–35.
27. Klastersky J, Daneau D, Swings G, Weerts D, Antibacterial activity in serum and urine as a therapeutic guide in bacterial infections. *J Infect Dis* 1974; **129:** 187–93.
28. Anderson ET, Young LS, Hewitt WL, Antimicrobial synergism in the therapy of Gram-negative rod bacteremia. *Chemotherapy* 1978; **24:** 45.
29. Klastersky J, Combinations of antibiotics for therapy of severe infections in cancer patients. *Eur J Cancer* 1979; **15:** 3–13.
30. Standiford HC, Drusano GL, Fitzgerald B et al, Bactericidal activity of ceftazidime in serum compared with that of ticarcillin combined with amikacin. *Antimicrob Agents Chemother* 1984; **26:** 339–42.
31. Wade JC, Standiford HC, Drusano GL et al, Potential of imipenem as single-agent empiric antibiotic therapy of febrile neutropenic patients with cancer. *Am J Med* 1985; **78**(Suppl A): 54–64.
32. Johnson DE, Calia FM, Snyder MJ et al, Imipenem therapy of *Pseudomonas aeruginosa* bacteremia in neutropenic rats. *J Antimicrob Chemother* 1983; **12:** 89–96.
33. Gerber AU, Wiprachtiger P, Stettler-Spichiger U, Lebek G, Constant infusions versus intermittent doses of gentamicin against *Pseudomonas aeruginosa* in vitro. *J Infect Dis* 1982; **145:** 554–60.
34. Gerber AU, Vastola AP, Brandel J, Craig WA, Selection of aminoglycoside-resistant variants of *Pseudomonas aeruginosa* in an in vivo model. *J Infect Dis* 1982; **146:** 691–7.
35. Gerber AU, Craig WA, Aminoglycoside-selected subpopulations of *Pseudomonas aeruginosa*. *J Lab Clin Med* 1982; **100:** 671–81.
36. Pizzo PA, Robichaud KJ, Wesley R et al, Fever in the pediatric and young adult patient with cancer. A prospective study of 1001 episodes. *Medicine* 1982; **61:** 153.
37. Pizzo PA, Robichaud KJ, Gill FA et al, Duration of empiric antibiotic therapy in granulocytopenic patients with cancer. *Am J Med* 1979; **67:** 194–200.
38. EORTC International Antimicrobial Therapy Cooperative Group, Empiric antifungal therapy in febrile granulocytopenic patients. *Am J Med* 1989; **86:** 668–72.
39. Maschmeyer G, Noskin GA, Ribaud P, Sepkowitz KA, Changing patterns of infections and antimicrobial susceptibilities. *Oncology* 2000; **14**(Suppl 6): 9–16.
40. Remington JS, Schimpff SC, Please don't eat the salads. *N Engl J Med* 1981; **304:** 433–5.
41. Schimpff SC, Prevention of infection in cancer patients. In: *Supportive Care in Cancer. A Handbook for Oncologists*, 2nd edn (Klastersky J, Schimpff SC, Senn HJ, eds). New York: Marcel Dekker, 1999: 129–54.
42. Tenney JH, Moody MR, Newman KA et al, Adherent microorganisms on lumenal surfaces of long-term intravenous catheters: importance of *Staphylococcus epidermidis* in patients with cancer. *Arch Intern Med* 1986; **146:** 1949–54.
43. Shenep JL, Hughes WT, Roberson PK et al, Vancomycin, ticarcillin, and amikacin compared with ticarcillin–clavulanate and amikacin in the empirical treatment of febrile, neutropenic children with cancer. *N Engl J Med* 1988; **319:** 1053–8.
44. European Organization for Research and Treatment of Cancer (EORTC) International Antimicrobial Therapy Cooperative Group and the National Cancer Institute of Canada – Clinical Trials Group, Vancomycin added to empirical combination antibiotic therapy for fever in granulocytopenic cancer patients. *J Infect Dis* 1991; **163:** 951–8.
45. Ramphal R, Bolger M, Oblon DJ et al, Vancomycin is not an essential component of the initial empiric treatment regimen for febrile neutropenic patients receiving ceftazidime: a randomized prospective study. *Antimicrob Agents Chemother* 1992; **36:** 1062–7.
46. Dompeling EC, Donnelly JP, Deresinksi SC et al, Early identification of neutropenic patients at high risk of Gram-positive bacteraemia and the impact of empirical administration of vancomycin. *Eur J Cancer* 1996; **32A:** 1332–9.
47. Carratalá J, Alcaide F, Fernandez-Sevilla A et al, Bacteremia due to viridans streptococci that are highly resistant to penicillin: increase among neutropenic patients with cancer. *Clin Infect Dis* 1995; **20:** 1169–73.
48. Rubenstein EB, Rolston K, Benjamin RS et al, Outpatient treatment of febrile episodes in low-risk neutropenic patients with cancer. *Cancer* 1993; **71:** 3640–6.
49. Kern WV, Cometta A, de Bock R et al, Oral versus intravenous empirical antimicrobial therapy for fever in patients with granulocytopenia who

are receiving cancer chemotherapy. *N Engl J Med* 1999; **341:** 312–18.

50. Lucas KG, Brown AE, Armstrong D et al, The identification of febrile, neutropenic children with neoplastic disease at low risk for bacteremia and complications of sepsis. *Cancer* 1996; **77:** 791–8.
51. Freifeld A, Marchigiani D, Walsh T et al, A double-blind comparison of empirical oral and intravenous antibiotic therapy for low-risk febrile patients with neutropenia during cancer chemotherapy. *N Engl J Med* 1999; **341:** 305–11.

2

Overview of pharmacokinetic and pharmacodynamic principles of anti-infective dosing in the neutropenic patient

Russell E Lewis, Randall A Prince

INTRODUCTION

Effective antimicrobial therapy is dependent upon a number of factors, many of which are beyond the direct control of the clinician (see Figure 2.1). Antimicrobial selection and dosing, however, are two variables of drug therapy that can be controlled. Since anti-infective therapy plays such a critical role in successful outcomes for the neutropenic patient, optimization of drug regimen design is essential. This chapter will focus on pharmacokinetic and pharmacodynamic principles of antimicrobial dosing in the neutropenic host. Special attention will be devoted to describing differences between various classes of antimicrobials, as well as special pharmacokinetic issues in the care of neutropenic patients.

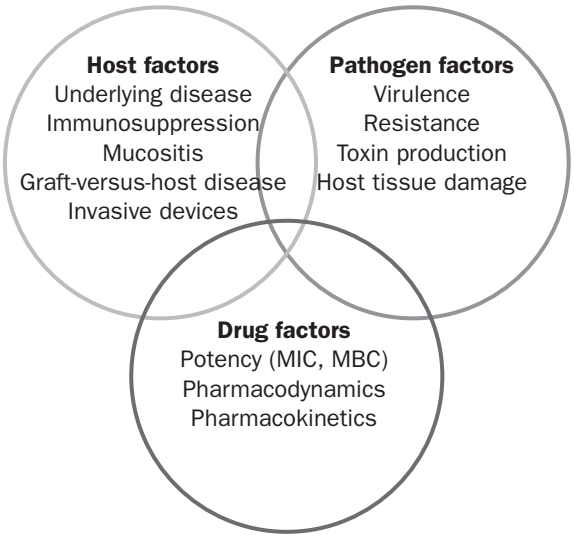


Figure 2.1 Interrelationship of host, pathogen, and drug factors that influence outcome in anti-infective therapy.

RATIONALE OF ANTIMICROBIAL DOSING

Three components of antimicrobial pharmacology are of special interest in developing effective dosage regimens:

(i) the potency of the antimicrobial against the pathogen(s) in question;
(ii) the concentration achieved by the antimicrobial in the serum and at the site of infection (pharmacokinetics);
(iii) the relationship of drug concentrations to the rate and extent of pathogen killing (pharmacodynamics).

Antimicrobial potency is typically defined by susceptibility-testing endpoints such as the minimum inhibitory concentration (MIC) and the minimum bactericidal concentration (MBC). Despite its many limitations, MIC testing provides a reasonable measurement of drug activity that can be easily related to the drug concentrations achieved in the body. Historically, the goal of most antimicrobial dosing strategies has been to maintain drug concentrations above the MICs of common pathogens in serum/tissues for the extent of the dosing interval. Although this dosing strategy may produce acceptable antibacterial efficacy with some compounds, it does not take into account fundamental pharmacodynamic differences between various antimicrobial classes.

The study of antimicrobial pharmacodynamics has provided new insight into the relationship of drug concentrations to bacterial or fungal killing.[1] Antimicrobial concentration–killing relationships generally follow one of two patterns (see Figure 2.2). The first pattern is characterized by concentration-dependent killing over a broad range of clinically achievable concentrations (drug B). That is, the higher the drug concentration, the greater the rate and extent of bacterial or fungal killing. The second pattern, however, is characterized by minimal concentration-dependent killing over the range of clinically achievable levels (drug A). Generally, drug concentrations greater than four times the MIC do not enhance the rate or extent of activity.[2–4] Since the extent of killing noted with this second pattern is largely dependent on how long drug concentrations remain near the MIC, it is also termed time-dependent killing pharmacodynamics.

Some antimicrobial agents may produce persistent or prolonged inhibitory effects even as drug concentrations fall below the MIC.[5] The phenomena related to the sub-MIC concentrations, including the post-antibiotic effect (PAE), sub-MIC effect (SME), and the post-antibiotic leukocyte enhancement (PALE), are increasingly incorporated into the development of dosing regimen strategies. Some investigators have

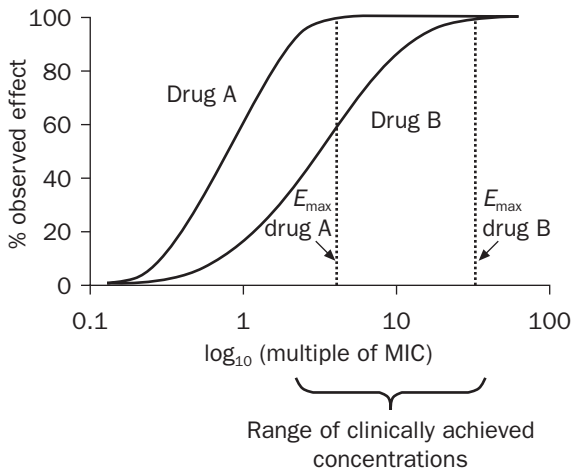


Figure 2.2 Comparison of concentration-dependent and concentration-independent pharmacodynamics.

even recommended that the dosing interval of an antibiotic should be equal to the time for which drug concentrations remain above the MIC plus the duration of the PAE.[6] Of the three aforementioned mechanisms, the PAE has been studied the most. The PAE is thought to be due to a lag time in the disassociation of the antimicrobial from the cellular receptors in the organism or the recovery of the organism from cellular injury.[1] The significance of these phenomena in the neutropenic population, however, remains to be determined. With certain antimicrobials, the PAE is often more prolonged the higher the concentration of antibiotic exposure or the greater the duration of exposure.[5] This has led some investigators to propose a third pattern of pharmacodynamic activity where concentration-independent killing predominates initially, but persistent effects or the PAE are concentration-dependent.[1,6,7] This 'combination' pharmacodynamic picture may be seen with newer macrolides such as azithromycin.[8]

Defining the killing characteristics of an antibiotic or antifungal is essential for optimizing dosing. For agents that exhibit concentration-dependent pharmacodynamics, dosing regi-

mens should maximize peak concentrations (C_{max}) or overall exposure to the drug (area under the curve, AUC). In some cases, larger infrequently administered doses may be necessary to achieve sufficient peak concentrations. For example, in extended-interval dosing of aminoglycosides, high peak concentrations (>8–10 times the MIC) have been shown to result in more rapid and extensive bacterial killing, and may reduce the probability of resistance.[9–11] In neutropenic patients, the benefits of increasing antibiotic dosages for concentration-dependent agents generally outweigh the increased risk of adverse drug effects. For antimicrobials with concentration-independent killing pharmacodynamics, dosing regimens should optimize the time for which concentrations remain above the MIC. Escalating antimicrobial dosages for these antibiotics per se does not significantly improve antimicrobial killing.

Increasingly, pharmacokinetic/pharmacodynamic relationships are being used to compare the activity of antimicrobial agents (see Table 2.1 and Figure 2.3). This approach has several inherent advantages over comparing drugs on the basis of MIC data alone. First, by dividing

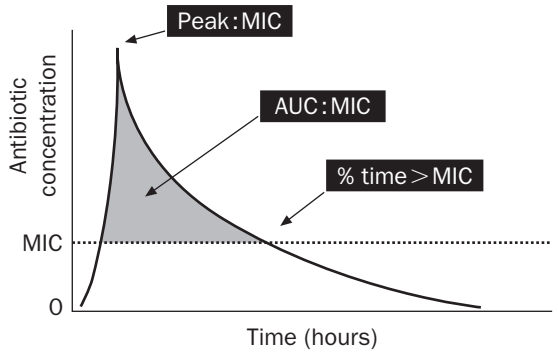


Figure 2.3 Pharmacokinetic : Pharmacodynamic parameters of interest in antimicrobial therapy.

Table 2.1 Pharmacokinetic and pharmacodynamic parameters correlating with efficacy of antimicrobial therapy for various anti-infective classes

	Pharmacokinetic : pharmacodynamic parameters	Refs
Concentration-dependent killing agents		
Aminoglycosides	Peak : MIC, $AUC_{0–24}$: MIC	9–11, 13
Fluoroquinolones	Peak : MIC, $AUC_{0–24}$: MIC	14–16
Metronidazole	Peak : MIC	56, 57
Amphotericin B	Peak : MIC	58–60
Time-dependent killing agents		
β-lactams	Time > MIC	17–21
Macrolides	Time > MIC, AUC_{0-24} : MIC	1, 7, 8
Vancomycin	$AUC_{0–24}$: MIC	1
Lincosamides	Time > MIC	1
Tetracyclines	$AUC_{0–24}$: MIC	1
Azoles	Time > MIC, $AUG_{0–24}$: MIC	58–61
Oxazolidinones	$AUC_{0–24}$: MIC	62–64
Streptogramins	$AUC_{0–24}$: MIC	8, 65, 66

the serum pharmacokinetic parameter value by the MIC, drugs with dissimilar potency and pharmacokinetics can be directly compared. For example, if a new fluoroquinolone that was fourfold more potent against *Pseudomonas aeruginosa* than an older and established fluoroquinolone were introduced on the market, it would appear by comparing MICs alone to be a superior drug for *Pseudomonas* infections. However, if the drug concentrations achieved with the new agent were one-sixth that achieved with ciprofloxacin, it may actually be a less effective agent. By creating a ratio of the pharmacokinetic and pharmacodynamic parameters, disparities in potency and pharmacokinetics are normalized, thus allowing a more direct comparison of the agents.[12]

Pharmacokinetic : pharmacodynamic (PK : PD) ratios are very useful as markers or 'breakpoints' of drug activity.[12] It has been shown for aminoglycosides, for example, that a C_{max} : MIC > 8–10 is associated with maximal clinical efficacy against Gram-negative organisms.[9,13] For quinolones, such as ciprofloxacin, a serum C_{max} : MIC > 12 or a serum AUC_{0-24} : MIC > 125 (put another way, averaging concentrations 4–6 times the MIC over the dosing interval) have been associated with maximal bacteriological and clinical outcomes for Gram-negative infections.[14–16] For drugs with more concentration-independent killing characteristics such as β-lactams, maintenance of drug concentrations above the MIC for at least 50% of the dosing interval has been associated with bacteriological efficacy.[17–21]

Once PK : PD breakpoints have been described for an antimicrobial class, it is often possible to compare agents with disparate potency, pharmacokinetics, and pharmacodynamics. Table 2.2 shows PK : PD breakpoints achieved with various agents that often constitute empiric therapy to treat *Pseudomonas* spp. For most anti-pseudomonal β-lactams presented in the table, the critical breakpoint of surpassing the MIC for greater than 50% of the dosing interval is easily achieved at standard dosages. However, if agents are compared on the basis of the more conservative measurement of the MIC (MIC_{90}), one sees that many of the drugs fall on the borderline of meeting the PK : PD threshold of 50%. For some β-lactams (e.g. cefepime and piperacillin/tazobactam), activity can be improved by using higher dosages and shorter dosing intervals.

Similarly, those agents with concentration-dependent killing activity can be compared in the same fashion. Quinolones such as ciproflaxacin and levofloxacin both achieve a serum C_{max} : MIC > 12 if MIC_{50} data are considered. If the MIC_{90} data are assessed, however, both agents fall well below the C_{max} : MIC threshold of 12 and AUC : MIC of 125, despite ciprofloxacin appearing initially to be the more effective agent. This same strategy of comparing antibiotics on the basis of PK : PD parameters can be individualized using institutional MIC data and dosing practices to develop specific PK : PD antibiograms. Clinicians can then identify both antimicrobial agents and dosing strategies that would be more effective for empiric therapy.

It is important to recognize, however, that PK : PD ratios serve only as *general* markers of antimicrobial activity and have many inherent limitations. The vast majority of PK : PD data derived for antibacterial and antifungal agents have come from in vitro pharmacodynamic models and animal studies – not from human trials. Although these PK : PD breakpoints are generally conserved among animal species (e.g. a quinolone C_{max} : MIC ratio that results in maximal bacteriologic efficacy is generally the same in mice and humans), PK : PD data from animal models may not be completely applicable to humans. Also, it must be emphasized that the vast majority of PK : PD experiments are based on serum/plasma data, which may not always reflect the conditions at the site of infection. It is known, for example, that tissue concentrations achieved with fluoroquinolones are often higher than concurrent serum concentrations. Therefore, the PK : PD data in Table 2.2 may underestimate activity at the site of infection. Most studies to date, however, have noted that

Table 2.2 Comparison of anti-pseudomonal PK : PD data for various antimicrobials used in empiric therapy[a]

Drug and dose	MIC_{50} : MIC_{90} (μg/ml)	Serum % time > MIC_{50}/MIC_{90}	Serum C_{max} : MIC_{50}/MIC_{90}	Serum AUC_{0-24} : MIC_{50}/MIC_{90}
Imipenem	2/>8			
500 mg q6h		90/⩽50	NA	NA
1000 mg q6h		90/⩽60		
Meropenem	0.25/2			
1000 mg q8h		100/<60	NA	NA
Cefepime	2/16			
1 g q12h		73/35	NA	NA
2 g q8h		100/75		
Ceftazidime	2/16			
1 g q8h		100/35	NA	NA
2 g q8h		100/35		
Piperacillin/tazobactam	4/64			
3.375 g q6h		75/<25	NA	NA
4.5 g q4h		100/40		
Ciprofloxacin	0.12/2.0			
400 mg q12h		NA	38/2.4	106/6.35
400 mg q8h			38/2.4	275/16.5
Levofloxacin	0.5/>4.0			
500 mg q24h		NA	12.4/1.5	110/3

[a] All PK data have been extracted from represented package insets; MIC data have been generated from reference 68. NA, not applicable.

serum/plasma drug concentrations (including quinolone data) correlate best with clinical response/efficacy. Finally, it is important to remember there is a paucity of data that have validated PK : PD 'breakpoints' with clinical outcome in the neutropenic patient.

SPECIAL PHARMACOKINETIC CONSIDERATIONS IN THE NEUTROPENIC HOST

Tissue penetration

Besides the spectrum and potency of an antimicrobial agent, the penetration of an agent into infected tissue is perhaps the most important determinant of antimicrobial efficacy.[22–24] Numerous factors can affect the distribution of the drug from the bloodstream to the tissue, including the ionic charge of the drug molecule, lipophilicity, plasma protein binding, tissue binding, and permeability barriers (e.g. central nervous system (CNS) and aqueous humor). The elimination rate of the drug from the body can also affect the distribution/penetration of the drug into infected tissues. For most drugs, however, distribution occurs more rapidly than elimination. One method used to estimate distribution of different drugs is to calculate the apparent volume of distribution (V_d) of the agent. As can be seen in Table 2.3, virtually all antimicrobials have 'volume' values that suggest a distribution outside of plasma (volume approximately 3 l or 0.04 l/kg) and into tissues. In fact, many agents have a volume of distribution value similar or greater than the total body water (0.65 l/kg). One must be cautious, however, in trying to utilize the V_d term to predict and/or relate to specific anatomic sites and sites of drug accumulation/penetration in the body.

For antimicrobials that are commonly utilized as empiric regimens for patients with febrile neutropenia, general categorizations of drug penetration can be made (see Tables 2.3 and 2.4). Aminoglycosides have poor-to-moderate penetration in tissues, including the lung and CNS. These agents are likely to be most effective for infections in the bloodstream and urinary tract, and generally should not be employed as monotherapy, particularly in the neutropenic patient.[25,26] Anti-pseudomonal penicillins, carbapenems, and cephalosporins achieve moderate-to-good concentrations in the lung, tissues, and CNS (high dose), with the exception of the so-called first-generation cephalosporins (poor penetration in CNS). In most cases, the use of a β-lactam provides good baseline coverage into tissues throughout the body. Vancomycin achieves moderate-to-good concentrations in the lung and tissues; however, higher dosages may be necessary to achieve even moderate CNS penetration. In general, fluoroquinolones and trimethoprim/sulfamethoxazole reach high concentrations in tissues, and both agents exhibit good penetration into the CNS. Amphotericin B and its lipid formulations exhibit moderate-to-good tissue penetration, particularly in the lungs, spleen, kidney, and liver. However, CNS penetration of amphotericin B is poor.[27,28] Flucytosine, which possesses excellent CNS penetration, should be used in combination with amphotericin B during initial induction therapy for cryptococcal meningitis and other CNS fungal infections.[29] Interestingly, liposomal amphotericin B (AmBisome) may exhibit higher CNS concentrations than conventional amphotericin B.[30–32] The azole, fluconazole, distributes widely to most tissues and the CNS.[33] Similarly, itraconazole distributes to the lung and other tissues, but does not penetrate the CNS as well as fluconazole.[27,34] Lastly, most antivirals distribute widely throughout the body; however, only acyclovir and ganciclovir achieve clinically useful concentrations in the CNS.[35–37]

Renal and liver dysfunction

The kidney serves as the primary route of elimination for the majority of antimicrobial agents

Table 2.3 Selected pharmacokinetic features of anti-infective agents[a]

Drug	Pharmacokinetic properties						Maintenance regimen in renal failure[b] Glomerular filtration rate		
	Oral dose	Bioavailability (%)	Intravenous dose	Major excretion pathway	V_d (l/kg)	Half-life (h)	50–80 ml/min	10–50 ml/min	<10 ml/min
Antibacterials									
Aminoglycosides									
Amikacin			0.25–0.5 g q8h	Renal	0.34	2	TDM	TDM	TDM
Gentamicin			1.5 mg/kg q8h	Renal	0.24	2	TDM	TDM	TDM
Tobramycin			1.5 mg/kg q8h	Renal	0.25	2.5	TDM	TDM	TDM
inhalation (TOBI)	0.3 g q12h						unnecessary	unnecessary	unnecessary
β-lactams									
Amoxicillin/clavulanate	0.25–0.5 g q8h	75		Renal	0.26–0.31	1.2	Usual	q12–24h	q12–24h
Ampicillin/sulbactam			1–2 g q6h	Renal	0.26–0.31	1	Usual	Usual	Usual
Aztreonam			1–2 g q6h	Renal	0.18–0.2	1.7–2	1–2 g q8h 1–2 g q8–12h	1–2 g q12h 1–2 g q12–18h	1–2 g q24h
Cefepime			0.5–2 g q8–12h	Renal	0.18	2.0	0.5–2.0 g q12h	0.5–1 g q24h	0.25–0.5 g q24h
Cefotaxime			1–2 g q4–8 h	Renal	0.28	1.5	Usual	1–2 g q6–12h	1–2 g q12h
Ceftazidime			1–2 g q8–12h	Renal	0.21	1.8	1–2 g q48h	1 g q12–24h	0.5 g q24–48h
Ceftriaxone			0.5–2 g q12–24h	Renal, Gut	0.15	8	Usual	Usual	Usual
Imipenem/cilastatin			0.5–1 g q6h	Renal	0.34–0.45	1.0	0.5 g q6–8h	0.5 g q8–12h	0.25–0.5 g q12h
Meropenem			1 g q8h	Renal	0.27	1.0	Usual	0.5 g q12h	0.5 g q24h
Nafcillin			0.5–2 g q4–6h	Hepatic	0.18	0.5	Usual	Usual	Usual
Oxacillin	0.5–1 g q6h	30	1–3 g q6h	Renal		0.5	Usual	Usual	Usual
Penicillin G, crystalline penicillin V	0.4–0.8 MU q6h	60–70	12–18 MU qd	Renal	0.5–0.67 0.67	0.5	Usual	Usual	½ usual dose

[a] All data have been extracted from representative package inserts and reference 67.
[b] TDM, therapeutic drug monitoring.

Contd

Table 2.3 Selected pharmacokinetic features of anti-infective agents[a] – *contd*

Drug	Pharmacokinetic properties						Maintenance regimen in renal failure[b] Glomerular filtration rate		
	Oral dose	Bioavailability (%)	Intravenous dose	Major excretion pathway	V_d (l/kg)	Half-life (h)	50–80 ml/min	10–50 ml/min	<10 ml/min
Piperacillin/tazobactam			3/0.375 g q4–6h	Renal	0.14	1.0	Usual	2/0.25 g q6h	2/0.25 g q8h
Ticarcillin/clavulanate			3 g q4–6h	Renal	0.16	1.2	Usual	2–3 g q6–8h	2 g q12h
Fluoroquinolones									
Ciprofloxacin	0.25–0.75 g q8–12h	70	0.4 g q8–12h	Renal	1.24	4	Usual	0.25–0.5 g q12h	0.25–0.5 g q24h
Gatifloxacin	0.4 g q24h	96	0.4 g q24h	Renal	1.36	7–8	Usual	0.4 g q24–48h	0.4 g q48h
Levofloxacin	0.5 g q24h	98	0.5 g q24h	Renal	1.20	7	Usual	250 mg q24h	250 mg q48h
Moxifloxacin	0.4 g q24h	89		Hepatic	1.26	10–14	Usual	Usual	Usual
Ofloxacin	0.2–0.4 g q12h	98	0.2–0.4 g q12h	Renal	1.14	7	Usual	0.2–0.4 g q24h	0.1–0.2 g q24h
Lincosamides									
Clindamycin	0.15–0.3 g q12h	0.90	0.3–0.9 g q6–8h	Hepatic	0.85	2.4	Usual	Usual	Usual
Macrolides									
Azithromycin	0.25 g q24h	37	0.5 g q24h	Hepatic	6.6	12/68 h	Usual	No data	No data
Clarithromycin	0.25–0.5 g q12h	50		Hepatic/renal	1.78	5–7	Usual	Usual	0.25–0.5 g q24h
Erythromycin(s)	0.25–0.5 g q6h	18–45	0.5–1 g q6h	Hepatic	0.7–1.5	2–4	Usual	Usual	Usual
Oxazolidonones									
Linezolid	0.3–0.6 g bid	100	0.6 g q12h	Hepatic	0.570.6 2	6	Usual	Usual	Usual
Streptogramins									
Quinupristin/dalfopristin			7.5 mg/kg q8–12h	Hepatic	1.5	1.5	Usual	Usual	Usual
Vancomycin	0.125–0.25 g q8h	<1	0.5–1 g q12h	Renal	0.45	6–8	1 g q24h	1 g q3–10d TDM	1 g q3–10d TDM

Drug	Pharmacokinetic properties						Maintenance regimen in renal failure[b] Glomerular filtration rate		
	Oral dose	Bioavailability (%)	Intravenous dose	Major excretion pathway	V_d (l/kg)	Half-life (h)	50–80 ml/min	10–50 ml/min	<10 ml/min
Sulfonamides									
Sulfisoxazole	2–4 g q6h	70–80		Renal	2.14	3–7	Usual	1 g q8–12h	1 g q12–24h
Trimethoprim/ sulfamethoxazole	2–4 tabs q24h or 1–2 DS tabs q24h	90–100	3–5 mg/kg q6–12h	Renal	S: 0.22 T: 2.28	S: 7–12 T: 24	Usual	0.1 g q24h	Avoid
Trimethoprim	0.1 g q12h	90		Renal	2.28	24	Usual	0.1 q24h	Avoid
Tetracyclines									
Doxycycline	0.1 g q12h	93	0.1 g q12h	Renal/gut	0.7	14–25	Usual	Usual	Usual
Minocycline	0.1–0.2 g q12h	95	0.1 g q12h	Hepatic	1.42	16	Usual	Usual	Usual
Tetracycline	0.25–0.5 g q6h	80		Renal	1.78	8	Usual	Use doxycycline	
Others									
Atovaquone	0.75 g q12h	25–50		Gut	0.6	70	Usual	Usual	No data
Dapsone	0.05–0.1 g q24h	>85		Hepatic	1.5	30	Usual	Usual	No data
Metronidazole	0.25–0.75 g q8h	90	0.5 g q6–8h	Hepatic	0.35	6–12	Usual	Usual	Usual
Pentamidine	4 mg/kg q24h		4 mg/kg q24h	Non-renal	0.5	6–8	Usual	4 mg/kg q24–36h	4 mg/kg q48h
Polymyxin B			7500–12 500 U/ kg/day q12h	Renal		6	7500–12 500 U/ kg/day q12h	5625–12 500 U/ kg/day q12h	3750–6250 U/ kg/day q12h
Pyrimethamine	25–75 mg q24h	>70		Hepatic	3	100	Usual	Usual	Usual
Rifabutin	0.3 g q24h	53		Hepatic/feces		45	Usual	Usual	Usual
Rifampin	0.6 g/day	100	0.6 g/day	Hepatic	1.25	2–5	Usual	Usual	Usual
Trimetrexate			45 mg/m^2 q24h	Hepatic/gut	0.5–2	11			
Antifungals									
Amphotericin B deoxycholate	100 mg q6h	<1	0.5–1.5 mg/kg q24h	Non-renal	4	Serum: 24;	Usual	Usual	Usual
Amphotericin B liposomal (AmBisome)			3—5 mg/kg q24h	Non-renal	0.22	Serum: 8.6;	Usual	Usual	Usual

Contd

Table 2.3 Selected pharmacokinetic features of anti-infective agents[a] – *contd*

Drug	Pharmacokinetic properties						Maintenance regimen in renal failure[b] Glomerular filtration rate		
	Oral dose	Bioavailability (%)	Intravenous dose	Major excretion pathway	V_d (l/kg)	Half-life (h)	50–80 ml/min	10–50 ml/min	<10 ml/min
Amphotericin B lipid (ABLC)			5 mg/kg 24h	Non-renal	131	Serum: 10;	Usual	Usual	Usual
Amphotericin B lipid (ABCD)			5 mg/kg q24h	Non-renal	4.1	Serum: 28.2;	Usual	Usual	Usual
Fluconazole	0.15–0.8 g q24h	0.90	0.4–0.8 g q24h	Renal	0.25	24	Usual	½ dose	½ dose
Flucytosine	37 mg/kg q24h	>0.90		Renal	0.68	2.5–6	Usual	37 mg/kg q12–24h	TDM
Itraconazole			0.2 g q12–24h	Hepatic	11	30–40	Usual	Avoid i.v.	Avoid i.v.
Capsules	0.1–0.4 g q24h	10–45							
Solution	0.2 g q12–24h	60–85							
Ketoconazole	0.2–0.4 g q12–24h	40–70 (pH-dependent)	0.2–0.4 g q12–24h	Hepatic	2	8	Usual	Usual	Usual
Nystatin		0	0.4–1 MU q6h				Usual	Usual	Usual
Terbinafine	0.25 g q12–24h	>70			2.85	36	Usual	No data, consider ½ dose	No data
Antivirals									
Acyclovir	200–800 mg 5× day	0.15–0.3	5–10 mg/kg q8h	Renal	0.5–0.8	2–2.5	Usual	Usual	200 mg q12h
Amantadine	0.1 g bid	0.80		Renal	3–8	15–20	0.1–0.15 g q24h	0.1–0.2 g 2–3× week	0.1–0.2 g qweek
Cidofovir			5 mg/kg q2week	Renal	0.4–0.5	17–65	Usual	Avoid	Avoid
Famciclovir	0.125 g bid	0.77		Renal	1–2	2.5	Usual	0.125 g q24h	0.125 g q48h
	500 mg tid							0.5 g q12–24h	0.25 g q48h
Foscarnet				Renal	0.4–0.5	3	40–50 mg/kg q8h	20–30 mg/kg q8h	Avoid
Induction			60 mg/kg q8h						
Maintenance			90–120 mg/kg qd						

Drug	Pharmacokinetic properties						Maintenance regimen in renal failure[b] Glomerular filtration rate		
	Oral dose	Bioavailability (%)	Intravenous dose	Major excretion pathway	V_d (l/kg)	Half-life (h)	50–80 ml/min	10–50 ml/min	<10 ml/min
Ganciclovir					0.74				
Induction			5 mg/kg bid	i.v.: Renal		i.v.: 3	2.5 mg/kg q12h	2.5 mg/kg q24h	1.25 mg/kg q24h
Maintenance	1000 mg tid	0.05		Oral: GI		Oral: 2–7	500 mg q8h	500 mg q24h	500 μg 3× week
Oseltamivir	75 mg bid	0.75	75 mg bid	Renal	0.35	6–10	Usual	75 mg q24h	Avoid
Ribavirin	600–1800 mg/day (aerosol)	0.64		Hepatic		300	Usual	? Dose reduction	Avoid
Rimantadine	0.1 g bid	0.96		Hepatic	24–30	Usual	Usual	0.1 g q24h	
Valacyclovir	1 g tid			Renal		3	Usual	1 g q12–24h	0.5 g q24h
Zanamivir	10 mg bid (inhalation)	0.04–0.17		Renal	0.30	2.5–5	Usual	No data	No data

(see Table 2.3). Therefore, decreases in kidney function secondary to drug therapy (aminoglycosides, amphotericin B, cyclosporin, antineoplastic agents) or underlying disease states (sepsis, hypotension) can have a profound influence on the overall clearance of antimicrobial agents. In particular, the neutropenic population is affected since they are often receiving higher dosages of anti-infectives and are at greater risk for the development of nephrotoxicity. For most antibacterial agents, dosing adjustments are not necessary until the creatinine clearance is below 50 ml/min/70 kg (see Table 2.3). However, for antibiotics that are predominantly eliminated renally, major dose regimen adjustments (e.g. one-half reductions) may be necessary when the renal function is equal to or greater than half-normal. Specifically, in patients with a creatinine clearance of less than 30 ml/min/70 kg, patients should be dosed according to specific guidelines for the drug or, in the case of aminoglycosides, vancomycin, and flucytosine, on the basis of serum drug concentration monitoring (see Table 2.3).

Dosage adjustments in patients with clinically significant hepatic dysfunction are less clear, because liver disease is associated with changes in multiple factors that can affect drug clearance (e.g. protein binding and V_d).[38] Additionally, no clear clinical marker has been correlated with changes in drug clearance in hepatic dysfunction. The absence of a useful marker precludes specific dosage adjustment calculations. Generally, dosage adjustments are approached on an individualized basis. Dosages should be decreased in patients with significant hepatic impairment (increases in clotting factors) or with patients receiving drugs with a narrow therapeutic index (e.g. chloramphenicol).

Mucositis and graft-versus-host disease

Both mucositis and graft-versus-host disease (GVHD) are complications of bone marrow transplantation and intensive chemotherapy that may have an effect on the pharmacokinetics of antimicrobial agents. It is difficult to describe, however, any consistent effect that these conditions will have on drug absorption, distribution, and elimination, partly owing to institution-specific differences in chemotherapy, infectious complications, and supportive care. Although neutropenia itself does not appear to markedly alter the pharmacokinetics of β-lactams, aminoglycosides, quinolones, or azole antifungal agents,[39–49] antibiotic body clearance may be increased in hyperdynamic states such as sepsis or during periods of severe stress.[49] Moreover, fluid shifts and decreases in serum albumin may affect the V_d, drug clearance, and penetration of antibiotics into some tissues and fluids.[22]

Mucositis/stomatitis may either increase or decrease the rate and extent of antibiotic absorption. If significant gut edema or achlorhydria is present, absorption may be delayed or decreased for some antibiotics.[49,50] In patients with grade II or grade III mucositis, absorption is unpredictable. Several studies examining the ability of oral non-absorbable antimicrobial agents to decontaminate the gastrointestinal tract have documented significant drug concentrations in the bloodstream in patients with grade II–III mucositis.[51–53]

Oral antibiotic therapy is increasingly recognized as a simpler and more cost-effective option in the treatment of some low-risk patients with neutropenic fever.[54,55] Mucositis and GVHD, however, should be considered relative contraindications towards the use of oral antimicrobial therapy.[26] The majority of studies examining the use of oral therapy in the management of febrile neutropenia have excluded patients with any evidence of mucositis or GVHD. Moreover, these patients are at higher risk for breakthrough infections on oral therapy caused by streptococcal species, anaerobes, and *Candida* species. Further studies are required to document the effects of mucositis and GVHD on antimicrobial pharmacokinetics.

Table 2.4 CNS penetration and protein binding of antimicrobial agents in febrile neutropenia[a]

Drug	Biliary concentration (% serum)	CNS concentration (% serum)	% protein binding
Antibacterials			
Aminoglycosides			
Amikacin	30	10–30	0–10
Gentamicin	10–60	10–30	0–10
Tobramycin Inhalation (TOBI)	10–60	10–30	0–10
β-lactams			
Amoxicillin/clavulanate	100–3000	12	20–30
Ampicillin/sulbactam	100–3000	13–15	18–22
Aztreonam	114–405	2–5	56
Cefepime	5	10	20
Cefotaxime	15–75	10	30–51
Ceftazidime		20–40	<10
Ceftriaxone	200–500	8–16	85–95
Imipenem/cilastatin	<2	8.5	15–25
Meropenem	3–300	21	
Nafcillin	6	9–20	90
Oxacillin		5–10	94
Penicillin G, crystalline	500	5–10 (HD)[b]	65
penicillin V			
Piperacillin/tazobactam	100—6000	30	16—48
Ticarcillin/clavulanate		40	45/30
Fluoroquinolones			
Ciprofloxacin	2–4	26	20–40
Gatifloxacin	4	36	20
Levofloxacin	5–6	30–50	24–40
Moxifloxacin	4–5	20–40	50
Ofloxacin	4–7	30–50	24–40
Lincosamides			
Clindamycin	250–300	<1	85–94

Contd

[a] All data have been extracted from representative package inserts and reference 67.
[b] HD, high dose.

Table 2.4 CNS penetration and protein binding of antimicrobial agents in febrile neutropenia[a] – *contd*

Drug	Biliary concentration (% serum)	CNS concentration (% serum)	% protein binding
Macrolides			
Azithromycin	Very high	2–13	12–50
Clarithromycin	7000	2–13	65–70
Erythromycin(s)	High	2–13	70–74
Oxazolidinones			
Linezolid	<6		31
Streptogramins			
Quinupristin/Dalfopristin	8–60		40–60
Vancomycin	50	7–14 (HD)[b]	10–55
Sulfonamides			
Sulfisoxazole	40–70	80	40–60
Trimethoprim/sulfamethoxazole	100–200	40–50	40–70
Trimethoprim	100	40	40–70
Tetracyclines			
Doxycycline	200–3200		93
Minocycline	200–3200		76
Tetracycline	200–3200		20–67
Others			
Atovaquone			99
Metronidazole	100	30–100	20
Pyrimethamine			85
Rifabutin		7–56	
Rifampin	10 000	7–56	80
Trimetrexate			95
Antifungals			
Amphotericin B deoxycholate		3	90
Amphotericin B liposomal (AmBisome)		5–15	
Amphotericin B lipid (ABLC)		0–3	

Table 2.4 CNS penetration and protein binding of antimicrobial agents in febrile neutropenia[a] – *contd*

Drug	Biliary concentration (% serum)	CNS concentration (% serum)	% protein binding
Amphotericin B		0–3	
lipid (ABCD)			
Fluconazole		50–94	11–12
Flucytosine		60–100	2–4
Itraconazole	3–18	5	99
Capsules			
Solution			
Antivirals			
Acyclovir	1–2	0.5	9–33
Amantadine		0.5	67
Cidofovir		<0.05	<6
Famciclovir	>1		<25
Foscarnet		0.69	17
Induction			
Maintenance			
Ganciclovir		0.25–0.7	1–2
Induction			
Maintenance			
Oseltamivir			
Ribavirin	100–1000	0.7	0
Rimantadine	>1	0.4–0.6	
Valacyclovir			9–33

SUMMARY

Antimicrobial therapy remains the most important medical intervention affecting survival in the febrile neutropenic patient. With the growing armamentarium of new agents, it is important that clinicians consider the pharmacokinetic and pharmacodynamic properties of drug therapy in addition to the individual antibiotic/pathogen MIC profile. PK : PD ratios not only aid in the comparison of anti-infective regimens with different potencies, but also provide a useful method for developing institution-specific dosing strategies for empiric therapy. There are significant differences among currently available antimicrobial agents with respect to distribution and penetration into various tissues and bodily fluids. For agents with low-to-moderate concentrations in the lung tissue and CNS, higher dosages or

combination therapy should be considered for empiric regimens. Finally, neutropenia itself has not been shown to alter the pharmacokinetic behavior of antibiotics in patients, but is often associated with other conditions that may preclude the use of oral therapy in low-risk patients.

REFERENCES

1. Craig WA, Pharmacokinetic/pharmacodynamic parameters: rationale for antibacterial dosing of mice and men. *Clin Infect Dis* 1998; **26:** 1–10; quiz 11–2.
2. Craig WA, Interrelationship between pharmacokinetics and pharmacodynamics in determining dosage regimens for broad-spectrum cephalosporins. *Diagn Microbiol Infect Dis* 1995; **22:** 89–96.
3. Leggett J, Fantin B, Ebert S et al, Comparative antibiotic dose–effect relations at several dosing intervals in murine pneumonitis and thigh-infection models. *J Infect Dis* 1989; **159:** 281–92.
4. Vogelman B, Gudmundsson S, Leggett J et al, Correlation of antimicrobial pharmacokinetic parameters with therapeutic efficacy in an animal model. *J Infect Dis* 1988; **158:** 831–47.
5. Craig WA, Gudmundson S, In *Antibiotics in Laboratory Medicine* (Lorain V, ed). Baltimore: Williams & Wilkins, 1996.
6. Turnidge JD, Prediction of antibiotic dosing intervals from in vitro susceptibility, pharmacokinetics and post-antibiotic effect: theoretical considerations. *Scand J Infect Dis Suppl* 1990; **74:** 137–41.
7. Ramadan MA, Tawfik AF, Shibl AM, Gemmell CG, Post-antibiotic effect of azithromycin and erythromycin on streptococcal susceptibility to phagocytosis. *J Med Microbiol* 1995; **42:** 362–6.
8. Carbon C, Pharmacodynamics of macrolides, azalides, and streptogramins: effect on extracellular pathogens. *Clin Infect Dis* 1998; **27:** 28–32.
9. Moore RD, Lietman PS, Smith CR, Clinical response to aminoglycoside therapy: importance of the ratio of peak concentration to minimal inhibitory concentration. *J Infect Dis* 1987; **155:** 93–9.
10. Blaser J, Stone BB, Groner MC, Zinner SH, Comparative study with enoxacin and netilmicin in a pharmacodynamic model to determine importance of ratio of antibiotic peak concentration to MIC for bactericidal activity and emergence of resistance. *Antimicrob Agents Chemother* 1987; **31:** 1054–60.
11. Craig WA, Once-daily versus multiple-daily dosing of aminoglycosides. *J Chemother* 1995; **7**(Suppl 2): 47–52.
12. Li RC, Zhu M, Schentag JJ, Achieving an optimal outcome in the treatment of infections. The role of clinical pharmacokinetics and pharmacodynamics of antimicrobials. *Clin Pharmacokinet* 1999; **37:** 1–16.
13. Kashuba AD, Nafziger AN, Drusano GL, Bertino JS Jr, Optimizing aminoglycoside therapy for nosocomial pneumonia caused by Gram-negative bacteria. *Antimicrob Agents Chemother* 1999; **43:** 623–9.
14. Preston SL, Drusano GL, Berman AL et al, Pharmacodynamics of levofloxacin: a new paradigm for early clinical trials. *JAMA* 1998; **279:** 125–9.
15. Forrest A et al, Pharmacodynamics of intravenous ciprofloxacin in seriously ill patients. *Antimicrob Agents Chemother* 1993; **37:** 1073–81.
16. Fantin B, Leggett J, Ebert S, Craig WA, Correlation between in vitro and in vivo activity of antimicrobial agents against Gram-negative bacilli in a murine infection model. *Antimicrob Agents Chemother* 1991; **35:** 1413–22.
17. Turnidge JD, The pharmacodynamics of beta-lactams. *Clin Infect Dis* 1998; **27:** 10–22.
18. Roosendaal R, Bakker-Woudenberg IA, van den Berg JC, Michel MF, Therapeutic efficacy of continuous versus intermittent administration of ceftazidime in an experimental *Klebsiella pneumoniae* pneumonia in rats. *J Infect Dis* 1985; **152:** 373–8.
19. Roosendaal R, Bakker-Woudenberg IA, van den Berghe-van Raffe M, Michel MF, Continuous versus intermittent administration of ceftazidime in experimental *Klebsiella pneumoniae* pneumonia in normal and leukopenic rats. *Antimicrob Agents Chemother* 1986; **30:** 403–8.
20. Craig WA, Ebert SC, Continuous infusion of beta-lactam antibiotics. *Antimicrob Agents Chemother* 1992; **36:** 2577–83.
21. Craig WA, Andes D, Pharmacokinetics and pharmacodynamics of antibiotics in otitis media. *Pediatr Infect Dis J* 1996; **15:** 255–9.
22. Drusano GL, Role of pharmacokinetics in the outcome of infections. *Antimicrob Agents*

Chemother 1988; **32:** 289–97.
23. Bergeron MG, Tissue penetration of antibiotics. *Clin Biochem* 1986; **19:** 90–100.
24. Nix DE, Goodwin SD, Peloquin CA et al, Antibiotic tissue penetration and its relevance: impact of tissue penetration on infection response. *Antimicrob Agents Chemother* 1991; **35:** 1953–9.
25. Klastersky J, Science and pragmatism in the treatment and prevention of neutropenic infection. *J Antimicrob Chemother* 1998; **41**(Suppl D): 13–24.
26. Hughes WT, Armstrong D, Bodey GP et al, 1997 guidelines for the use of antimicrobial agents in neutropenic patients with unexplained fever. Infectious Diseases Society of America. *Clin Infect Dis* 1997; **25:** 551–73.
27. Groll AH, Piscitelli SC, Walsh TJ, Clinical pharmacology of systemic antifungal agents: a comprehensive review of agents in clinical use, current investigational compounds, and putative targets for antifungal drug development. *Adv Pharmacol* 1998; **44:** 343–500.
28. Nagata MP, Gentry CA, Hampton EM, Is there a therapeutic or pharmacokinetic rationale for amphotericin B dosing in systemic *Candida* infections? *Ann Pharmacother* 1996; **30:** 811–18.
29. Saag MS, Graybill RJ, Larsen RA et al, Practice guidelines for the management of cryptococcal disease. Infectious Diseases Society of America. *Clin Infect Dis* 2000; **30:** 710–18.
30. Wong-Beringer A, Jacobs RA, Guglielmo BJ, Lipid formulations of amphotericin B: clinical efficacy and toxicities. *Clin Infect Dis* 1998; **27:** 603–18.
31. Janknegt R, de Marie S, Bakker-Woudenberg IA, Crommelin DJ, Liposomal and lipid formulations of amphotericin B. Clinical pharmacokinetics. *Clin Pharmacokinet* 1992; **23:** 279–91.
32. Groll AH, Giri N, Petraitis V et al, Comparative efficacy and distribution of lipid formulations of amphotericin B in experimental *Candida albicans* infection of the central nervous system. *J Infect Dis* 2000; **182:** 274–82.
33. Grant SM, Clissold SP, Fluconazole. A review of its pharmacodynamic and pharmacokinetic properties, and therapeutic potential in superficial and systemic mycoses. *Drugs* 1990; **39:** 877–916.
34. Dupont B, Drouhet E, Early experience with itraconazole in vitro and in patients: pharmacokinetic studies and clinical results. *Rev Infect Dis* 1987; **9**(Suppl 1): S71–6.
35. Fletcher C, Sawchuk R, Chinnock B et al, Human pharmacokinetics of the antiviral drug DHPG. *Clin Pharmacol Ther* 1986; **40:** 281–6.
36. Brigden D, Bye A, Fowle AS, Rogers H, Human pharmacokinetics of acyclovir (an antiviral agent) following rapid intravenous injection. *J Antimicrob Chemother* 1981; **7:** 399–404.
37. Whitley RJ, Blum MR, Barton N, de Miranda P, Pharmacokinetics of acyclovir in humans following intravenous administration. A model for the development of parenteral antivirals. *Am J Med* 1982; **73:** 165–71.
38. Ritschel WA, Thompson GA, The one-point method in predicting dosage regimen in case of hepatic and/or renal failure in presence or absence of change in volume of distribution. *J Clin Pharmacol* 1979; **19:** 350–6.
39. Bianco TM, Dwyer PN, Bertino JS Jr, Gentamicin pharmacokinetics, nephrotoxicity, and prediction of mortality in febrile neutropenic patients. *Antimicrob Agents Chemother* 1989; **33:** 1890–5.
40. Daenen S, Erjavec Z, Uges DR et al, Continuous infusion of ceftazidime in febrile neutropenic patients with acute myeloid leukemia. *Eur J Clin Microbiol Infect Dis* 1995; **14:** 188–92.
41. Davis RL, Lehmann D, Stidley CA, Neidhart J, Amikacin pharmacokinetics in patients receiving high-dose cancer chemotherapy. *Antimicrob Agents Chemother* 1991; **35:** 944–7.
42. Davis R, Markham A, Balfour JA, Ciprofloxacin. An updated review of its pharmacology, therapeutic efficacy and tolerability. *Drugs* 1996; **51:** 1019–74.
43. Drusano GL, de Jongh C, Newman K et al, Moxalactam and piperacillin: a study of in vitro characteristics and pharmacokinetics in cancer patients. *Infection* 1985; **13:** 20–6.
44. Drusano GL, Plaisance KI, Forrest A et al, Steady-state pharmacokinetics of imipenem in febrile neutropenic cancer patients. *Antimicrob Agents Chemother* 1987; **31:** 1420–2.
45. Janmohamed RM, Leyland MJ, Kelly J, Farrell I, Pharmacokinetics of imipenem/cilastatin in neutropenic patients with haematological malignancies. *J Antimicrob Chemother* 1990; **25:** 407–12.
46. Lortholary O, Tod M, Rizzo N et al, Population pharmacokinetic study of teicoplanin in severely neutropenic patients. *Antimicrob Agents Chemother* 1996; **40:** 1242–7.

47. MacGowan AP, Bedford KA, Blundell E et al, The pharmacokinetics of once daily gentamicin in neutropenic adults with haematological malignancy. *J Antimicrob Chemother* 1994; **34:** 809–12.
48. Nyhlen A, Ljungberg B, Nilsson-Ehle I, Pharmacokinetics of meropenem in febrile neutropenic patients. Swedish Study Group. *Eur J Clin Microbiol Infect Dis* 1997; **16:** 797–802.
49. Fry DE, The importance of antibiotic pharmacokinetics in critical illness. *Am J Surg* 1996; **172:** 20S–25S.
50. Schafer-Korting M, Pharmacokinetic optimisation of oral antifungal therapy. *Clin Pharmacokinet* 1993; **25:** 329–41.
51. Okuno SH, Foote RL, Loprinzi Cl et al, A randomized trial of a nonabsorbable antibiotic lozenge given to alleviate radiation-induced mucositis. *Cancer* 1997; **79:** 2193–9.
52. Rohrbaugh TM, Anolik R, August CS et al, Absorption of oral aminoglycosides following bone marrow transplantation. *Cancer* 1984; **53:** 1502–6.
53. Samaranayake LP, Robertson AG, McFarlane TW et al, The effect of chlorhexidine and benzydamine mouthwashes on mucositis induced by therapeutic irradiation. *Clin Radiol* 1988; **39:** 291–4.
54. Rolston KV, New trends in patient management: risk-based therapy for febrile patients with neutropenia. *Clin Infect Dis* 1999; **29:** 515–21.
55. Rubenstein EB et al, Outpatient treatment of febrile episodes in low-risk neutropenic patients with cancer. *Cancer* 1993; **71:** 3640–6.
56. Lewis RE, Klepser ME, Ernst EJ et al, Comparison of oral immediate-release (IR) and extended-release (ER) metronidazole bactericidal activity against *Bacteroides* spp. using an in vitro model of infection. *Diagn Microbiol Infect Dis* 2000; **37:** 51–5.
57. Nix DE, Tyrrell R, Muller M, Pharmacodynamics of metronidazole determined by a time–kill assay for *Trichomonas vaginalis*. *Antimicrob Agents Chemother* 1995; **39:** 1848–52.
58. Klepser ME, Wolfe EJ, Pfaller MA, Antifungal pharmacodynamic characteristics of fluconazole and amphotericin B against *Cryptococcus neoformans*. *J Antimicrob Chemother* 1998; **41:** 397–401.
59. Lewis RE, Lund BC, Klepser ME et al, Assessment of antifungal activities of fluconazole and amphotericin B administered alone and in combination against *Candida albicans* by using a dynamic in vitro mycotic infection model. *Antimicrob Agents Chemother* 1998; **42:** 1382–6.
60. Andes D, In vivo pharmacodynamics of amphotericin B against *C. albicans*. In: *Abstracts of the 39th Interscience Conference on Antimicrobial Agents and Chemotherapy*. Washington, DC: American Society for Microbiology, 1999: 79.
61. Andes D, van Ogtrop M, Characterization and quantitation of the pharmacodynamics of fluconazole in a neutropenic murine disseminated candidiasis infection model. *Antimicrob Agents Chemother* 1999; **43:** 2116–20.
62. Schulin T, Thauvin-Eliopoulos C, Moellering RC Jr, Eliopoulos GM, Activities of the oxazolidinones linezolid and eperezolid in experimental intra-abdominal abscess due to *Enterococcus faecalis* or vancomycin-resistant *Enterococcus faecium*. *Antimicrob Agents Chemother* 1999; **43:** 2873–6.
63. Dresser LD, Rybak MJ, The pharmacologic and bacteriologic properties of oxazoladinones, a new class of synthetic antimicrobials. *Pharmacotherapy* 1998; **18:** 456–62.
64. Diekema DI, Jones RN, Oxazolidinones: a review. *Drugs* 2000; **59:** 7–16.
65. Aeschlimann JR, Zervos MJ, Rybak MJ, Treatment of vancomycin-resistant *Enterococcus faecium* with RP 59500 (quinupristin–dalfopristin) administered by intermittent or continuous infusion, alone or in combination with doxycycline, in an in vitro pharmacodynamic infection model with simulated endocardial vegetations. *Antimicrob Agents Chemother* 1998; **42:** 2710–17.
66. Hershberger E, Aeschlimann JR, Moldovan T, Rybak MJ, Evaluation of bactericidal activities of LY333328, vancomycin, teicoplanin, ampicillin–sulbactam, trovafloxacin, and RP59500 alone or in combination with rifampin or gentamicin against different strains of vancomycin-intermediate *Staphylococcus aureus* by time–kill curve methods. *Antimicrob Agents Chemother* 1999; **43:** 717–21.
67. ASHP, *American Hospital Formulary Service.* Bethesda, MD: American System of Health System Pharmacists, 2000.
68. Diekema DJ, Pfaller MA, Jones RN et al, Survey or bloodstream infections due to Gram-negative bacilli: frequency of occurrence and antimicrobial susceptibility of isolates collected in the United States, Canada, and Latin America for the SENTRY Antimicrobial Surveillance Program, 1997. *Clin Infect Dis* 1999; **29:** 595–607.

3

Controversies and quandaries: The design of clinical trials in fever and neutropenia

Linda S Elting, Marianne Paesmans

INTRODUCTION

The evolution of clinical trial design in febrile neutropenia has paralleled the evolution of the antibiotic armamentarium. The initial study establishing the relationship between neutrophil count and infection focused on mortality, a common event in the 1960s before modern antibiotics were available.[1] An early trial of carbenicillin, which documented the need for empiric therapy at the onset of infection, was a 'before-and-after' design.[2] Results from the introduction of empiric therapy with an anti-pseudomonal penicillin were compared with historical data. In this case, the mortality rate was so high prior to empiric and specific anti-pseudomonal therapy, and the clinical experience so consistent from one institution to the next, that a randomized trial was not required to demonstrate efficacy. As the options for antibiotic therapy have increased, increasingly stronger evidence from rigorously designed clinical trials has been required to change practice. Currently, clinical trialists are challenged to design within-antibiotic-class comparisons examining subtle differences among very similar agents.[3] Despite over four decades of experience in clinical trials in febrile neutropenia, many issues remain unresolved, and new controversies have arisen with advances in medicine and healthcare policy. In this chapter, we describe the current state of the art in design of clinical trials of febrile neutropenia, and discuss the controversies that challenge us in the field today.

THE STATE OF THE ART

Although controversies and challenges remain, there is consensus on many methodological criteria for clinical trials in febrile neutropenia.[4] We discuss these in the following section. Clinical trials designed to establish the usefulness of a new agent are divided into four phases.[5] Phase I trials examine the maximum tolerated dose of the agent. Phase II trials roughly estimate its efficacy and toxicity to determine if it is worthwhile to proceed with further research. Even when randomized, phase II trials, are not conducted for comparison purposes. Phase III trials compare promising agents with the best known standard of care or with placebo if no standard exists. Phase IV trials examine the effectiveness in large unselected populations. In this chapter, we focus on methodological standards for phase II and III trials of the efficacy of empiric antimicrobial therapy for febrile neutropenia.

Trial design

Clinical trials are conducted for the purpose of generalizing their results to the treatment of future patients.[6] They should therefore be designed to maximize the generalizability of the results and to minimize random error, which has no preferred direction, and systematic error, called bias. In the absence of bias, the distribution of the values of the estimated treatment effect (in the case of repeated trials) is centered around the true value. In the presence of bias, estimates of treatment effect are not centered around the true value.

The trial design should be described in a master document (protocol) that includes the following features.

- *Description of the trial objectives* The primary objective should be clearly described. This objective will be used to determine the sample size. Secondary objectives, which will be analyzed descriptively for future hypothesis generation, should also be included.
- *Design* In the description of the design, the phase (II or III) should be stated. The standard for phase III trials is the randomized design. This design, which was first used in clinical research about 50 years ago,[7] is the only design that reliably eliminates selection bias. In large samples, it also results in comparability of the study groups.[6] Random assignment is analogous to random sampling, which is an assumption basic to statistical inference. It is the only accepted design when comparing the efficacy of two (or more) treatments.
- *Description of the targeted patient population* This description should include a list of the eligibility criteria both for inclusion and for exclusion from the trial, along with operational definitions of these criteria. At a minimum, definitions of fever and neutropenia should be included. (Guidelines for these definitions have been provided by the Immunocompromised Host Society.[8]) Other factors that influence outcome may be used for inclusion or exclusion of patients, depending on the objectives of the study. These include the underlying neoplasm, age, risk class as defined by validated risk models,[9,10] and severity of illness. These also should be clearly defined in the protocol. Some investigators have suggested the use of expected duration of neutropenia as an eligibility criterion. However, predictions of the duration of neutropenia at trial entry are generally inaccurate. To avoid bias, all eligible patients should be included in the trial. If not, the number of patients rejected should be recorded, along with the reason for rejection.
- *Description of the treatment plan* A clear description of dosing and administration schedules should be included, as well as instructions for duration of therapy, and conditions for modification or discontinuation of therapy. Descriptions of the number and timing of clinical, laboratory, and microbiological examinations should also be specified.
- *Description of the outcomes* The most commonly reported outcome in trials of febrile neutropenia is the response to the empiric regimen. Although opinions vary on the specific definition of this outcome, whatever the definition used, it should be specified a priori, because different measures may yield different results.[11] Other outcomes, such as mortality, incidence of adverse events or toxicities, and time to defervescence, may also be useful. Timing of the assessments of outcome should be clearly delineated.
- *Statistical design* The objective of a clinical trial is formally addressed by a statistical test of one or more hypotheses. The null hypothesis of no difference is typically tested against an alternative hypothesis. The observed results of the trial lead to rejection of the null hypothesis or to acceptance of the null hypothesis. The decision is

based on reasoning with probability distributions. Two types of random error may occur. The null hypothesis may be rejected when it is, in fact, true (type I error) or the null hypothesis may be accepted when it is actually false (type II error). The probability of making a type I error is controlled in each statistical test, and is reported as the '*p* value'. Classically, but often too dogmatically, a *p* value of less than 0.05 results in rejection of the null hypothesis. It should be interpreted, case by case, considering the other characteristics of the trial, particularly the number of hypothesis tests performed. The probability of a type II error is controlled only by an adequate sample size, which is achieved by using realistic estimates of the expected response rates and the difference that would be considered clinically significant. This should be considered when interpreting a *p* value of greater than 0.05, which does not necessarily mean that the null hypothesis is true, but only that there is insufficient evidence that it is false.[12]

In phase II trials, the primary outcome of interest is usually dichotomous – that is, it has only two possible values, such as success and failure. The objective is to estimate the success rate and to determine whether further study will be worthwhile by comparing the observed success rate with a threshold rate specified a priori. In order to limit exposure of patients to an ineffective treatment, most designs use two (or more) stages. After accrual of an initial series of patients, the trial is terminated if the study drug is clearly inferior. Otherwise, a second series of patients is recruited to permit precise estimation of the success rate and to inform the decision to proceed to phase III studies. The most commonly accepted two-stage designs are those proposed by Gehan,[13] Fleming,[14] and Simon.[15] There are two versions of the Simon design, one minimizing the sample size for treatments of low activity and one minimizing the maximum sample size.[15] Recently developed alternatives include three-stage designs,[16] designs that evaluate efficacy and toxicity jointly,[17] and Bayesian designs, which incorporate a priori estimates of the probability of outcomes.[18]

We recommend a randomized design for all phase III trials. In order to eliminate investigator bias, randomization should be organized so that the investigator cannot know which treatment will be received before an individual patient is registered on the trial. In multicenter studies, randomization should be centralized in one coordinating center. The minimization technique for treatment allocation results in a minimal value of the global imbalance function, and is a recommended choice.[19]

Most commonly, two treatments are compared, with the intention of detecting a previously specified, clinically significant difference,[20] using either a fixed sample size or a planned interim analysis with early trial termination possible in the case of a treatment difference greater than expected.[21] In some cases, the goal is to show equivalence between the studied treatments.[22] For the primary comparison, the probability of type I error is set to 5% and the probability of type II error to 10–20%. The decision between an equivalence trial and a superiority trial must be made early in the design phase, because it has a major impact on both sample size and on the hypothesis tested. During the design phase, the sample size is calculated and a plan of the statistical analysis is prepared. This plan includes the statistical tests that will be used and the subsets that will be analyzed separately (intention to treat and per protocol).

Trial monitoring

Monitoring the progress of the trial is as important as monitoring the progress of individual patients. Patient accrual, investigator compliance with the protocol, and safety monitoring should be done systematically. This is particularly important for multicenter trials,

and clear procedures for timely communication of key monitoring information between investigators and the central data monitoring center should be specified as part of the protocol. No preliminary analyses of the primary outcome are conducted unless planned a priori, with appropriate statistical adjustment for the multiple statistical tests. If interim analyses are planned, the results are not communicated to the investigators or to the scientific community prior to completion of recruitment. Ideally, interim analyses are performed and interpreted by an independent data monitoring board, which advises the principal investigator on early termination or continuation of the trial.[23]

Outcome assessment

The assessment of outcomes should be as consistent as possible. In multicenter trials, the data review committee determines the eligibility and outcome of each case. The reviewers are blinded to the treatment received. The data review committee will also conduct site visits to verify protocol compliance and data against the source documents.

Trial analysis and reporting

Standards for analyzing and reporting the results of clinical trials have been described previously.[8,24–26] Briefly, the analysis should begin with a description of the number of patients registered in the trial, the number of ineligible patients, with a description of the reasons for ineligibility, and the number of inevaluable patients (and reason for inevaluability). In randomized trials, these results should be reported separately for each treatment group. This analysis is followed by a description of the patients' characteristics, including, at least, demographic characteristics, sites of infection, and documentation of infection, pathogens and susceptibilities. The type and dosage of chemotherapy should be specified for descriptive purposes, although, at the present time, there are no simple means to predict the occurrence and course of febrile neutropenia on the basis of the type of chemotherapy that has been given.

In the case of randomized trials, the comparability of the treatment groups for important prognostic factors should be examined. If imbalances are discovered for important prognostic factors, statistical comparisons of the treatment groups should be adjusted retrospectively. If the outcome is dichotomous, the logistic regression model can be used for this purpose.[27] Time-to-event distributions can be estimated using the Kaplan–Meier technique and compared using the logrank test. Examination of time-to-event outcomes with adjustment for covariates can be accomplished using Cox proportional hazards regression.[28] Reports of the results of hypothesis testing should be accompanied by reports of parameter estimates with confidence intervals (a confidence level of 95% is generally adequate). Ideally, interpretation of the data will include examination of both p values and confidence intervals to permit assessment of clinical and statistical significance.[29]

CONTROVERSIES AND QUANDARIES

Despite the sophistication of current trial designs, there are still a number of controversial and challenging issues to be resolved. The perennial problem of ensuring comparability of the study groups and generality of results plagues studies of febrile neutropenia as it does other studies. Blinding of trials, although theoretically optimal, is clinically and operationally challenging. In addition to these longstanding issues, methodological advances and changes in the healthcare marketplace have introduced new challenges in clinical trial design. These include the use of alternatives to classical fixed-sample-size designs and conducting cost–effectiveness analyses alongside clinical trials. Among the more controversial issues are the choice of outcomes to measure and the hand-

ling of multiple entries and withdrawals. We discuss each of these below.

How can the generality of results be ensured?

The sole reason for conducting clinical trials is to apply the observed outcomes of subjects in trials more broadly, to a larger population. Therefore, it is essential that the study sample and the larger population be similar with respect to factors that affect clinically important outcomes of the condition. Factors affecting the outcomes of febrile neutropenia have been well described.[1,8,30] They include host factors, infection-related factors, and factors related to antineoplastic therapy (Table 3.1). Depending on the purpose of the study, any or all of these may be clinically important.

Table 3.1 Prognostic factors in febrile neutropenia

Host factors

Severity of illness
Comorbid conditions
Stage of disease
Age

Infection factors

Site of infection, especially complex tissue infections
Pathogen and susceptibility
Shock

Treatment factors

Depth of neutropenia
Duration of neutropenia
High-dose chemotherapy
Bone marrow transplantation
Presence of catheters
Prophylactic antibiotics

The prevalence of these factors varies significantly, depending on practice patterns, referral patterns, and the local microbiological flora. To the extent that the prevalence in the study sample does not match that in the overall or reference population, the results of the study will not be useful. In order to ensure that the results of trials are useful outside the study sample, stratified analyses accounting for those factors present at baseline are appropriate. (Subset analyses of factors that occur during the course of therapy should be avoided, since their occurrence may be affected by the study drugs. This will almost certainly bias the results of the study.[31]) Univariate subset analyses by a few variables of relevance to the specific population (specified a priori) and multiple-variable modeling of overall response rates are recommended. However, numerous subset analyses should be avoided, because of the risk of observing chance occurrences of statistically significant differences. To compensate for this problem, a lower threshold for statistical significance should be used.

By what method is comparability of groups ensured?

In comparative trials, it is also essential that the study groups be comparable *at baseline* with respect to the prognostic factors mentioned above. However, in studies of febrile neutropenia, there are substantial within-study heterogeneities in prognostic and complicating factors. Randomization does not guarantee comparability with respect to important prognostic factors – it leaves comparability to chance. As illustrated in Table 3.2, in some randomized trials, imbalance of important prognostic factors occurs. Stratification is used prior to randomization to ensure comparability for a few prognostic factors known at baseline.[32–39] Depending on the hypotheses and population being studied, these may include age, risk

Table 3.2 Comparability of treatment groups in two randomized studies

Ref	Regimen 1 % pneumonia (95% CI)	Regimen 2 % pneumonia (95% CI)	Regimen 3 % pneumonia (95% CI)	*p* value
60	4 (2, 8)	4 (2, 8)	—	0.66
61	21 (15, 29)	10 (6, 16)	11 (6, 17)	0.009

CI, confidence interval.

group, severity of illness or comorbidity score, and study site (in multicenter studies).

Unfortunately, the most significant predictors of outcome of febrile neutropenia are not known prior to randomization. In some cases, surrogates can be used. For example, growth factor use, high-dose chemotherapy use, and bone marrow transplantation are reasonably good surrogates for the depth and duration of neutropenia. The presence of shock is a fair surrogate for the presence of systemic infection. However, none of these are perfect surrogates. Therefore, it is generally necessary to construct multiple-variable models of outcome to account for prognostic factors present at baseline, but not yet known.

Which outcomes should be measured and reported?

The outcomes of interest in clinical trials of febrile neutropenia have evolved as antibiotic agents have become more effective and effective agents have become more numerous. Most agree that the primary outcome of interest is response to antibiotic therapy, but opinions differ widely on the timing of its measurement.[4] Some measure response at the end of initial therapy, and others measure it after therapy has been modified.[40,41] In the absence of a standard definition for the primary outcome, meta-analyses and informal comparisons across trials are virtually impossible. In the absence of consensus, we favor reporting both outcomes. Infection-related mortality is an important outcome, but, in trials of modern antibiotic regimens, it is usually too rare an event to be practical in clinical trials. All-cause mortality is too non-specific to be useful in a cancer population. The incidence of toxicity or superinfection may be useful in discriminating between antibiotic regimens of similar efficacy. A recent study suggests that time to response also shows promise in this regard, but its usefulness in practice remains to be demonstrated.[42]

Outcomes in clinical trials also reflect recent therapeutic developments and trends in the healthcare industry. In trials of outpatient therapy of febrile neutropenia, response in the outpatient setting is as important as response to antibiotic therapy. Trends in quality of life and tools for measuring quality of life during febrile neutropenia are currently being studied. Finally, in today's world, economic outcomes, such as duration of antibiotics, duration of hospitalization, and cost of care, are also important.

Is there a more efficient alternative to the traditional fixed-sample-size randomized design?

The fixed-sample-size randomized controlled clinical trial (RCCT) is the gold standard for comparisons of therapies for febrile neutropenia and for all other conditions. However, these trials can be prohibitively difficult for uncom-

mon problems, and they are costly for the most common of problems. Designs requiring smaller sample sizes would be preferable. Furthermore, fixed-sample-size RCCTs possess the undesirable characteristic of exposing as many subjects to an inferior therapy as the superior therapy.[43] Ethicists and statisticians have argued that in trials addressing uncommon or life-threatening conditions, the weight of the individual's interests exceeds the collective (research) interest of society.[43] Therefore, exposure of individual subjects to an inferior therapy should be minimized. For ethical and practical reasons, alternative, data-dependent randomized designs have been studied for decades.[43–49] These are used only rarely, but trials of febrile neutropenia present a promising venue for such designs.

Data-dependent randomized designs are of three basic types. 'Adaptive' designs incorporate accumulating outcome data to amend probabilities of treatment allocation in order to give patients a better chance of receiving the superior treatment. This is a randomized, play-the-winner design. 'Bayesian' designs test prior estimates of probabilities against implied posterior probabilities, which are updated as evidence accumulates. It is generally unnecessary to continue such trials to the prespecified accrual. 'Sequential' designs involve interim monitoring for predetermined threshold values of outcomes, which, when crossed, lead to termination of the trial. Each interim test affects type I error ('spends alpha'), and therefore adjustment of the overall significance level is required for the final analysis. These designs are only practical when individual subjects' outcomes are known rapidly (before recruitment of the remainder of the subjects). Bayesian designs are only practical when other phase III or pilot study data are available on which to base prior estimates of probabilities.[43]

Should clinical trials be 'blinded'?

If the RCCT is the gold standard in clinical research, a blinded RCCT is the platinum standard, and a double-blinded RCCT is the jewel in the crown. Blinding is a mechanism by which investigators and/or subjects are kept ignorant of which of the alternative therapies (investigational or control) is received.[32] It is achieved by 'packaging' the investigational and control therapies so that they appear identical to the subjects and caregivers. The study report forms are also 'packaged' so that study drug assignment is unknown to those assessing response.

Blinding minimizes the risk that actions or judgements on the part of investigators or subjects will bias the results of the trial. Blinding of study subjects is essential when the outcomes that will be measured are subjective, such as symptom severity, wellbeing, or quality of life. Investigator blinding is essential to allow unbiased assessment of outcomes. Even assessment of mortality, which appears to be a straightforward clinical event, can be biased in unblinded studies if knowledge of the treatment assignment influences attribution of cause of death. It is also important in studies that permit amendment of treatment plans based on clinical judgement. Although blinding adds to the complexity and cost of studies, the primary objection is usually a clinical one. Sometimes, management of the treatment or its complications requires knowledge of the specific treatment to which the subject has been assigned. On the basis of this clinical objection, blinding is commonly rejected as an option. However, in such cases, it is often possible for a physician external to the study to decide on the proper course of action, without compromising the care of subjects. Although it is occasionally in the best interest of an individual subject to break the blinding, this rare event should not preclude the use of blinding in clinical trials.

How should multiple episodes in the same patient be handled?

Entry of multiple episodes of febrile neutropenia in a single patient violates the assumptions of independence required by most statistical

tests. Practically speaking, multiple entries per patient may introduce bias due to within-patient correlation for important prognostic factors and for outcomes. The risk of this problem in febrile neutropenia is not trivial. When multiple episodes are closely related in time, it is likely that severity of illness, use of growth factors, high-dose chemotherapy and BMT, and depth and duration of neutropenia will be virtually identical. Nevertheless, most infectious disease experts agree that inclusion of multiple entries is desirable, provided that sufficient time (usually 14 days) has elapsed between episodes to ensure that a new episode *has* occurred. Thus, multiple entry of individual patients is commonplace in published trials of febrile neutropenia, and is endorsed by expert panels.[8] Two techniques may be used to account for the violation of assumptions introduced by this practice:

1. When multiple entries occur, a separate analysis, using only one episode per patient (either the first episode or a randomly chosen episode) should be reported. If differences between study drugs change in a clinically or statistically meaningful way, confounding due to multiple entries is likely and the results should be interpreted in that light.
2. A second option is to include all episodes for all patients in a mixed, multiple-variable model, with patients nested within febrile episodes. This is effectively a repeated-measures analysis, which accounts for within-patient correlation for prognostic factors. Such analyses can now be computed with standard statistical packages such as SAS.

How should withdrawals be handled?

Studies of febrile neutropenia vary in the frequency with which subjects, once randomized, fail to receive the entire course of therapy specified by the protocol. Two clinical phenomena – 'early deaths' and adverse reactions that require discontinuation of the study drug – account for the majority of such cases. Studies also vary in the frequency with which subjects, initially considered eligible for the study, are proven to be ineligible, after more complete diagnostic evaluation. Most studies of empiric therapy of febrile neutropenia include at least a few patients whose specific infections render them ineligible after the results of baseline cultures become available. Most studies also include a few patients whose fever is proven to be due to problems other than infection. These patients are typically considered inevaluable. Although removal of inevaluable and ineligible cases from the analysis of eligible subjects who complete an entire course of therapy is intuitively appealing, their removal can introduce bias of unknown magnitude and direction.[50]

Several methods of handling withdrawals have been suggested, from retaining all such cases in the analysis to removing them. Based on what is known about febrile neutropenia and patients' responses to antibiotic therapy, we favor retention of patients who receive inadequate trials because of early deaths or adverse events and classification of such cases as failures to antibiotic therapy. Elimination of such cases removes failures from the analysis; a truly inferior antibiotic regimen presumably would have more such cases than an optimal regimen. Thus, the results of a comparison would be biased in favor of an inferior regimen.

The case of ineligible subjects is less straightforward. Inclusion of patients with proven fungal infections in the analysis of a trial of antibacterial antibiotics is counterintuitive. However, removal of subjects whose fungal infections are documented late in the course of antibiotic therapy biases the results in favour of regimens that predispose to fungal superinfection. Given the necessity of treating febrile neutropenia empirically, we recommend enrollment of patients presumed to be eligible and subsequent withdrawal of ineligible patients *based only on the results of diagnostic tests obtained at baseline*. We further recommend

removal of patients considered inevaluable for other reasons, such as fever due to other causes. In such cases, two analyses should be presented – one an intention-to-treat analysis, with inevaluable subjects included, and a second with such subjects removed (per protocol analysis).[50]

Should cost–effectiveness analyses be conducted alongside clinical trials?

Cost–effectiveness analyses alongside clinical trials are controversial.[51–59] Such analyses provide high internal validity because of the extensive clinical information obtained for the trial. Piggybacking cost–effectiveness studies on to clinical trials also may be a more efficient and less costly way of collecting such data. However, these analyses involve significant tradeoffs. High internal validity is obtained at the cost of very questionable external validity. To what extent do patients enrolled on a clinical trial resemble all patients with febrile neutropenia? How generalizeable are costs and resource utilization derived from protocol-driven care in academic centers? In our view, the argument that tips the balance toward conducting such trials is that decisions about reimbursement for new agents are made at the time products are licensed. If cost–effectiveness analyses are delayed until phase IV or prospective community-based data are available, then many patients may be denied access to new agents.

For these reasons, we recommend that cost–effectiveness analyses be conducted alongside phase III clinical trials in febrile neutropenia. From a methodological standpoint, there are two important issues in such trials. First, there is the problem of sample size. Because the ratio of the effect size to the variance is typically smaller than that for clinical outcomes, sample sizes for phase III studies may need to be increased to provide sufficient power.[55,58] We recommend that cost-of-therapy studies be conducted alongside phase II studies in order to obtain preliminary estimates of the magnitude and variance of cost in order to inform decisions about sample size for phase III studies.

The second major methodological problem is outcome measurement. Cost–effectiveness is generally expressed as the incremental cost per quality-adjusted life-year. Episodes of febrile neutropenia are short-term health states; therefore, the results of such analyses are measured in life-months or days. An incremental advantage in quality-adjusted life-months could potentially be realized from (i) a lower mortality rate, or (ii) higher quality because of more rapid response to therapy. As previously noted, mortality is extremely uncommon, and is unlikely to be useful in discriminating between antibiotic regimens. Thus, the challenge in cost–effectiveness is to measure quality of life during the short duration of febrile neutropenia. Although this issue is being studied, there are currently no widely accepted tools for measuring quality of life during febrile neutropenia.

SUMMARY

Clinical trial methodology in febrile neutropenia has developed significantly since the initial trials were conducted in the 1960s. However, important controversies still remain, and new developments in the healthcare marketplace demand innovative methodological solutions. Data-driven designs, methods for cost–effectiveness, and measurement tools for quality of life during febrile neutropenia are particularly fruitful topics for methodological research. Such research is critical to the success of future trials in febrile neutropenia.

REFERENCES

1. Bodey GP, Buckley M, Sathe YS, Freireich EJ, Quantitative relationships between circulating leukocytes and infection in patients with acute leukemia. *Ann Intern Med* 1966; **64:** 328–40.

2. Schimpff S, Satterlee W, Young V et al, Empiric therapy with carbenicillin and gentamicin for febrile patients with cancer and granulocytopenia. *N Engl J Med* 1971; **284:** 1061–5.
3. Klastersky J, Zinner SH, Calandra T et al, Empiric antimicrobial therapy for febrile granulocytopenic cancer patients: lessons from four EORTC trials. *Eur J Cancer* 1988; **24**(Suppl 1): S35–45.
4. Feld R, Methodology for clinical trials in cancer patients with febrile neutropenia. *Support Care Cancer* 1998; **6:** 423–4.
5. Pocock SJ, *Clinical Trials: A Practical Approach.* Chichester: Wiley, 1990.
6. Piantadosi S, *Clinical Trials: A Methodologic Perspective*. New York: Wiley, 1997.
7. Medical Research Council, Streptomycin treatment of pulmonary tuberculosis. *BMJ* 1948; **ii:** 769–82.
8. Immunocompromised Host Society, The design, analysis and reporting of clinical trials on the empiric management of the neutropenic patient. *J Infect Dis* 1990; **161:** 397–401.
9. Talcott JA, Siegel RD, Finberg R et al, Risk assessment in cancer patients with fever and neutropenia: a prospective, two-center validation of a prediction rule. *J Clin Oncol* 1992; **10:** 316–22.
10. Klastersky J, Paesmans M, Rubenstein EB et al for the Study Section on Infections of the Multinational Association for Supportive Care in Cancer, The Multinational Association for Supportive Care in Cancer Risk Index: a multinational scoring system for identifying low-risk febrile neutropenic cancer patients. *J Clin Oncol* 2000; **18:** 3038–51.
11. Elliott C, Pater JL, The effect of different measures of outcome on the results of studies of empiric antibiotic therapy in febrile neutropenic patients. *Clin Invest Med* 1988; **11:** 327–30.
12. Altman DG, Bland MJ, Statistics notes. Absence of evidence is not evidence of absence. *BMJ* 1995; **311:** 485.
13. Gehan EA, The determination of the number of patients required for a follow-up trial of a new chemotherapy agent. *J Chron Dis* 1961; **13:** 346–53.
14. Fleming TR, One-sample multiple testing procedure for phase II clinical trials. *Biometrics* 1982; **38:** 143–51.
15. Simon R, Optimal two-stage designs for phase II clinical trials. *Control Clin Trials* 1989; **10:** 1–10.
16. Chen TT, Optimal three-stage designs for phase II cancer clinical trials. *Stat Med* 1997; **16:** 2701–11.
17. Bryant J, Day R, Incorporating toxicity considerations into the design of two-stage phase II clinical trials. *Biometrics* 1995; **51:** 1372–83.
18. Stallard N, Sample size determination for phase II clinical trials based on Bayesian decision theory. *Biometrics* 1998; **54:** 279–94.
19. Pocock SJ, Simon R, Sequential assignment with balancing for prognostic factors in the controlled clinical trial. *Biometrics* 1975; **31:** 103–15.
20. Armitage P, *Statistical Methods in Medical Research.* Oxford: Blackwell Scientific, 1971.
21. Jennison C, Turnbull BW, *Group Sequential Methods with Applications to Clinical Trials.* Boca Raton, FL: Chapman and Hall/CRC, 2000.
22. Blackwelder WC, Proving the null hypothesis in clinical trials. *Control Clin Trials* 1982; **3:** 345–53.
23. Wittes J, Behind closed doors: the Data Monitoring Board in randomized clinical trials. *Stat Med* 1993; **12:** 419–24.
24. Chalmers TC, Smith H, Blackburn B et al, A method for assessing the quality of a randomized control trial. *Control Clin Trials* 1981; **1:** 31–49.
25. Pater JL, Weir L, Reporting the results of randomized trials of empiric antibiotics in febrile neutropenic patients – a critical survey. *J Clin Oncol* 1986; **4:** 346–52.
26. Paesmans M, Statistical considerations in clinical trials testing empiric antibiotic regimens in patients with febrile neutropenia. *Support Care Cancer* 1998; **6:** 438–43.
27. Hosmer DW, Lemeshow S, *Applied Logistic Regression.* New York: Wiley, 1989.
28. Marubini E, Valsecchi MG, *Analysing Survival Data from Clinical Trials and Observational Studies.* Chichester: Wiley, 1995.
29. Braitman LE, Confidence intervals assess both clinical significance and statistical significance. *Ann Intern Med* 1991; **114:** 515–17.
30. Elting L, Rubenstein E, Rolston K et al, Outcomes of bacteremia in neutropenic cancer patients: observations from two decades of epidemiologic and clinical trials. *Clin Infect Dis* 1997; **25:** 247–59.
31. Byar DB, Simon RM, Friedewald WT et al, Randomized clinical trials. *N Engl J Med* 1976; **295:** 74–80.

32. Friedman LM, Furberg CD, DeMets DL, *Fundamentals of Clinical Trials*, 2nd edn. Littelton, MA: PSC, 1985.
33. Grizzle JE, A note on stratifying versus complete random assignment in clinical trials. *Control Clin Trials* 1982; **3:** 365–8.
34. Hill AB, The clinical trial. *Br Med Bull* 1951; **7:** 278–82.
35. Meier P, Stratification in the design of a clinical trial. *Control Clin Trials* 1981; **1:** 355–61.
36. Peto R, Pike MC, Armitage P et al, Design and analysis of randomized clinical trials requiring prolonged observation of each patient. *Br J Cancer* 1976; **34:** 585–612.
37. Pocock SJ, Simon R, Sequential treatment assignment with balancing for prognostic factors in the controlled clinical trial. *Biometrics* 1975; **31:** 103–15.
38. Pocock SJ, Allocation of patients to treatments in clinical trials. *Biometrics* 1979; **35:** 183–97.
39. Elting LS, Stratification in clinical trials of febrile neutropenia. *Support Care Cancer* 1998; **6:** 457–61.
40. Pizzo PA, Hathorn JW, Hiemen ZJ et al, A randomized trial comparing ceftazidime alone with combination antibiotic therapy in cancer patients with fever and neutropenia. *N Engl J Med* 1986; **315:** 552–8.
41. Kern WV, Cometta A, De Bock R et al, Oral intravenous empiric therapy for fever in patients with granulocytopenia who are receiving cancer chemotherapy. *N Engl J Med* 1999; **341:** 305–11.
42. Elting LS, Rubenstein EB, Rolston KVI et al, Time to clinical response: an outcome of antibiotic therapy of febrile neutropenia with implications for quality and cost of care. *J Clin Oncol* 2000; **18:** 3699–706.
43. Palmer CR, Rosenberger WF, Ethics and practice: alternative designs for phase III randomized clinical trials. *Control Clin Trials* 1999; **20:** 172–86.
44. Simon R, Adaptive treatment assignment methods and clinical trials. *Biometrics* 1977; **33:** 743–9.
45. Rosenberger WF, Lachim JM, The use of response-adaptive designs in clinical trials. *Control Clin Trials* 1993; **14:** 471–84.
46. Brophy JM, Lawrence J, Placing trials in context using Bayesian analysis: GUSTO revisited by Reverend Bayes. *JAMA* 1995; **273:** 871–5.
47. Lilford RJ, Thornton JG, Braunholtz D, Clinical trials and rare diseases: a way out of a conundrum. *BMJ* 1995; **311:** 1621–5.
48. Lilford RJ, Braunholtz D, For debate: The statistical basis of public policy: a paradigm shift is overdue. *BMJ* 1996; **313:** 603–7.
49. Brophy JM, Joseph L, Bayesian interim statistical analysis of randomized trials. *Lancet* 1997; **349:** 1166–8.
50. Tsiatis A, Analysis and interpretation of trial results: intent-to-treat analysis. *J Acquir Immune Defic Syndr* 1990; **3:** S120–3.
51. Drummond MF, O'Brien B, Stoddart GL, Torrance GW, *Methods for the Economic Evaluation of Health Care Programmes*, 2nd edn. Oxford: Oxford University Press, 1997.
52. Drummond M, Economic analysis alongside clinical trials: problems and potential. *J Rheumatol* 1995; **22:** 1403–7.
53. Bennett CL, Westerman IL, Economic analysis during phase III clinical trials: Who, what, when, where, and why. *Oncology* 1995; **9**(Suppl): 169–75.
54. Donaldson C, Hundley V, McIntosh E, Using economics alongside clinical trials: why we cannot choose the evaluation technique in advance. *Health Econ* 1996; **5:** 267–9.
55. Schulman KA, Llana T, Yabroff KR, Economic assessment within the clinical development program. *Med Care* 1996; **34:** DS89–95.
56. Bennett CL, Waters TM, Economic analyses in clinical trials for cooperative groups: operational considerations. *Cancer Invest* 1997; **15:** 448–53.
57. Fayers PM, Hand DJ, Generalization from phase III clinical trials: survival, quality of life, and health economics. *Lancet* 1997; **350:** 1025–7.
58. Schulman KA, Ohishi A, Park J et al, Clinical economics in clinical trials: the measurement of cost and outcomes in the assessment of clinical services through clinical trials. *Keio J Med* 1999; **48:** 1–11.
59. Van Enckevort PJ, TenVergert EM, Kingma J et al, Factors to consider when designing phase III clinical trials involving economic evaluations. *Perceptual and Motor Skills* 1999; **89:** 1059–72.
60. Freifeld AG, Walsh T, Marshall D et al, Monotherapy for fever and neutropenia in cancer patients: a randomized comparison of ceftazidime versus imipenem. *J Clin Oncol* 1995; **13:** 165–76.
61. Jones PG, Rolston KVI, Fainstein V et al, Aztreonam therapy in neutropenic patients with cancer. *Am J Med* 1986; **81:** 243–8.

4

Current epidemiology of infections in neutropenic cancer patients

Winfried V Kern

INTRODUCTION

Fever is the most frequent – sometimes the only – sign of infection subsequent to neutropenia. Most epidemiologic studies have focused on fever episodes and have evaluated their causes and outcome. A rough approximation of fever incidence rates according to the duration of neutropenia is shown in Figure 4.1. Severe infections may sometimes develop without fever. Conversely, fever may not always result from infection, and may remain unexplained.

In addition to the depth and duration of neutropenia, other variables may impact on the frequency and causes of infectious complications in neutropenic patients. These include age, comorbidities, activity and site of the underlying disease ('obstruction leads to infection'), preceding type of therapy (type and doses of chemotherapeutic agents; radiation), variables related to exposure to pathogens (including hospital hygiene, intravenous catheter use and care, diet, air filtration, etc.), use of antimicrobial chemoprophylaxis (Figure 4.1), and others. Although fever in a severely neutropenic host requires prompt diagnostic work-up and initial empiric therapy, there is considerable heterogeneity in causative pathogens, sites of infection, clinical evolution, and risk of severe complications.

The outcome of febrile neutropenia has improved after the adoption of the concept of empiric antimicrobial therapy and with the availability of broad-spectrum β-lactams for initial therapy.[1–3] Deaths from primary infection, however, continue to be observed. Complicated secondary infections due to drug-resistant microorganisms have now become more

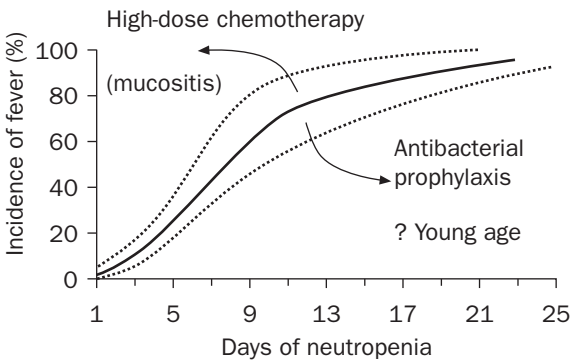


Figure 4.1 Schematic diagram estimating the incidence of fever according to the duration of neutropenia (neutrophils < 500/μl). Mucositis and antibacterial prophylaxis among other variables may impact on the fever incidence, as indicated by the arrows and the dashed lines.

common in patients with a long duration of neutropenia, and reduce the likelihood of survival.[4,5] In an analysis of 3080 febrile neutropenic patients selected to participate in clinical trials of the European Organization for Research and Treatment of Cancer (EORTC) International Antimicrobial Therapy Cooperative Group, the acute mortality rate was 3.2%, while the mortality rate at the end of the febrile neutropenic episode was 8.7%.[6]

EPIDEMIOLOGY

Acute leukemia

Bone marrow involvement and intensive chemotherapy render the patient with acute leukemia highly vulnerable to infection.[7] Often, neutropenia lasts 3 weeks or longer, and patients with early onset of fever and prolonged periods of broad-spectrum antibiotics are at increased risks of developing fungal superinfections. In a retrospective study at the University Hospital of Zürich, the incidence of febrile neutropenia among acute leukemia patients (139 patients; 230 neutropenic episodes) was 86%.[8] In a retrospective analysis at Ulm University Hospital and Medical Center, the overall incidence of febrile neutropenia in hospitalized adult patients with acute leukemia (period 1990–1993, 221 patients, 539 neutropenic episodes) was 71%. This rate had been similar in an earlier analysis, and did not change substantially in more recent years (Figure 4.2). Fever was best predicted by the duration of severe neutropenia (<100 cells/μl) and the type of leukemia (lymphoblastic, ALL, versus myeloid, AML) (Figure 4.2), while age, sex, and type of chemotherapy were not predictive, and the status (relapsed/refractory versus de novo) was marginally significant (unpublished observations).

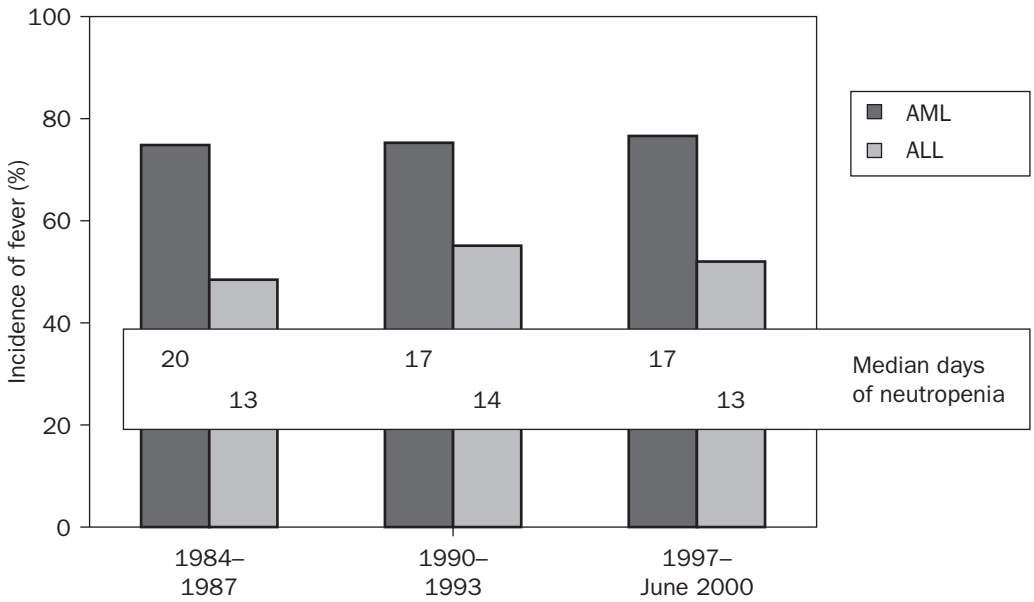


Figure 4.2 Incidence of febrile neutropenia in adult patients with acute leukemia during neutropenic episodes. Data are from retrospective studies at Ulm University Hospital and Medical Center during three different periods.

Intensive consolidation with high-dose cytosine arabinoside (HDAC) has been associated with a high incidence of fever.[9] Streptococcal bacteremia, sometimes associated with respiratory distress syndrome, has been reported as a complication. Complications of HDAC with daunorubicin and with idarubicin respectively may lead to differing complications in the course of fever. HDAC–idarubicin combinations may be associated with greater gastrointestinal damage, resulting in more cases with diarrhea or typhlitis/enterocolitis.[10] These observations illustrate the impact of chemotherapeutic regimens on fever and infection. Patients with ALL (compared with AML) develop fever less often during remission induction, partly because the antileukemic regimens frequently contain steroids. This may increase the risk of fungal infections. These patients also develop infections after neutrophil recovery.[11,12] The type of steroids (dexamethasone or prednisone) may have an influence on infectious complications.[13] The incidence of febrile neutropenia in childhood leukemias is lower than in adult acute leukemia patients, and the outcome better.[14]

Other hematologic malignancies

Not all chemotherapy regimens for Hodgkin´s disease or non-Hodgkin´s lymphoma (NHL) produce profound neutropenia. Also, depending on marrow reserves, neutropenia after commonly used lymphoma regimens seldom lasts longer than 5–6 days. Accordingly, the incidence of febrile neutropenia may be quite low.[15] Lymphoma patients may have other defects in host defense in addition to neutropenia. Examples are multiple myeloma and chronic lymphocytic leukemia patients with functional hypogammaglobulinemia. Hodgkin´s disease is associated with T-cell defects, increasing the susceptibility to opportunistic infections such as listeriosis, cryptococcosis, and toxoplasmosis. Enhanced susceptibility to opportunistic infections in Hodgkin´s disease and some NHL patients may also be related to the wider use of immunosuppressive drugs such as steroids and purine analogs. Agents such as fludarabine and 2-chlorodeoxyadenosine (cladribine) enhance the risk of opportunistic infections by inducing a long-lasting T-cell defect that can be measured by enumerating $CD4^+$ T cells in the peripheral blood.[16,17]

Chemotherapy for solid tumors

The incidence of febrile neutropenia in solid tumor patients receiving chemotherapy depends on the dose intensity of the cytotoxic regimens. Many regimens do not produce profound neutropenia. Accordingly, febrile neutropenia may be quite uncommon. Fever incidences in small cell lung cancer are usually less than 50%.[15] Fever was reported in 15 of 45 ovarian cancer patients (33%) receiving 177 cycles of paclitaxel with or without platinum.[18] Fever after chemotherapy for testicular cancer was also relatively uncommon (<20%).[19,20] The initial cycle is more likely to put patients at risk of developing fever than are subsequent cycles. The reasons for this are manifold, and include high tumor burden leading to obstruction and/or reduced general status or even cachexia. Also, patients are often in hospital and have undergone recent surgery and/or other invasive procedures when they are receiving their initial chemotherapy, while subsequent cycles are given on an outpatient basis. Less exposure to nosocomial flora and a better general status then contribute to a better tolerance of cytotoxic drugs.

Blood stem cell and bone marrow transplantation

Numerous reports have assessed the frequency and outcome of infectious complications after high-dose chemotherapy with autologous peripheral blood stem cell reinfusion (autoPBSCT).[21–26] The duration of neutropenia is

usually about 7–10 days, depending on marrow reserves, pretreatment with cytotoxic drugs, prior radiation, and the number of reinfused $CD34^+$ cells. Many centers that offer this comparatively new approach use prophylactic antimicrobial regimens similar to those used for allogeneic peripheral blood or bone marrow transplant (alloBMT) recipients. Nevertheless, reported fever incidence rates in many centers appear to be high: greater than 60%, and often approaching 100%. Death rates, however, appear to be lower than those reported in acute leukemia patients, most likely because of the much shorter duration of neutropenia. Experience has been obtained with autoPBSCT patients in ambulatory care settings.[27–29] There is no indication that fever is more or less frequent in ambulatory patients compared with hospitalized patients. Based on the available literature, however, one should expect that roughly half of the patients, if not more, require readmission – most because of febrile neutropenia that is not manageable on an outpatient basis. A significant problem in these patients may be severe mucosal damage, leading to stomatitis, abdominal pain, and diarrhea. Bacterial translocation or endotoxinemia leading to fever may thus be facilitated.

Although the use of allogeneic peripheral blood stem cells instead of bone marrow has reduced the time to engraftment, fever incidence rates and infection rates during the early neutropenic phase have remained high in this setting. Depending on the use of chemoprophylaxis and on environmental exposure, documented infections, including secondary infections, may be more common in alloBMT patients than in autoPBSCT patients.[30–32] (See Chapter 7.)

Neutropenia due to other causes

Limited epidemiologic data are available on the incidence of fever in patients with neutropenia due to myelodysplastic syndromes (MDS) and aplastic anemia, and in patients with non-malignant chronic neutropenia.[33–36] Case–control studies in the setting of HIV-related neutropenia have estimated an adjusted risk of greater than 20-fold for Gram-negative bacteremia in patients with a neutrophil count of below 250 cells/μl compared with patients with levels above 1000 cells/μl.[37,38] Some of the infectious complications among such patients are due to complex host defense deficits, such as hypocomplementemia, T-cell deficiencies, or qualitative defects in phagocyte function in addition to neutropenia. It is important to recognize that chronic neutropenia preceding intensive chemotherapy (as is often the case in MDS) or immunosuppressive therapy (as in aplastic anemia) predisposes the patient to substantially increased risks of infection due to increased colonization with fungi and/or antibiotic-resistant bacteria.

IMPACT OF ANTIMICROBIAL PROPHYLAXIS ON FEVER IN PATIENTS RECEIVING CANCER CHEMOTHERAPY

Some studies of antibacterial prophylaxis have shown a significant reduction in the incidence of fever during neutropenia.[39,40] One explanation may be that it is inherently difficult to show effects on fever incidence rates on the extreme sides of neutropenia, i.e. in short-duration and very long-duration neutropenia. It is more likely to be able to show an effect, if it exists, in patients with intermediate duration of neutropenia (Figure 4.1). Few studies have evaluated the time to onset of fever. Delayed fever onset and reduced fever duration might well be acceptable endpoints of effective prophylaxis.[41–44] Prophylactic regimens targeting Gram-positive bacteria (such as addition of rifampin, macrolides, or penicillins) have not been more effective than regimens that primarily target Gram-negative bacteria (single-drug fluoroquinolone prophylaxis).[39,45,46] In studies of antifungal prophylaxis, fever has not commonly been used as endpoint.

UNEXPLAINED FEVER VERSUS INFECTION, PRIMARY INFECTION VERSUS SUPERINFECTION

Unexplained fever (or fever of unknown origin, FUO) – i.e. negative cultures and no localizing signs and symptoms – is common in neutropenic patients. The pathophysiology of unexplained fever is poorly understood. Some investigators believe that such episodes are infections with a low microbial load, which in the absence of empiric therapy would eventually develop into overt infection. Careful examination may reveal mild localizing symptoms, or viral infection. Using eubacterial rRNA polymerase chain reaction (PCR), one can find evidence of DNAemia (bacteremia with non-viable organisms or below the threshold of conventional cultures) in approximately 25% of febrile neutropenic patients without culture-proven bacteremia.[47] In unexplained fever episodes, there is usually a moderate cytokine response measurable in the plasma that is not very different from that with non-bacteremic documented infections.[48,49] Fungal DNAemia has also been found in patients with FUO who later developed documented invasive fungal infection.[50–52] The inability in some studies of prophylaxis to reduce the incidence of fever despite a reduction in the incidence of documented infection may be due to the drug's effect of rendering cultures negative, i.e. suppressing viable organisms to counts below the limit of detection. Blood culture studies using resin media to inactivate residual drug activity in blood samples support this view.[53,54] Thus FUO or fever with non-specific mild localizing signs and symptoms often represents an early phase of infection that cannot be documented by routine clinical examination and laboratory tests. It is plausible that the shorter the neutropenia, the more frequent is FUO, while documented infections tend to become more common as neutropenia persists (Figure 4.3). Two recent studies among low-risk neutropenic patients (median duration of neutropenia less than 5 days) reported a relative frequency of unexplained fever of about 60–70%.[55,56] Among patients with acute leukemia and alloBMT recipients (median duration of neutropenia longer than 10 days) this proportion is usually less than 50%. The prognosis of FUO is excellent, both in terms of time to defervescence with initial empiric therapy and in terms of survival (Figure 4.4). However, while many patients at initial presentation have unexplained fever, FUO is a diagnosis that can be established only at the end of neutropenia.

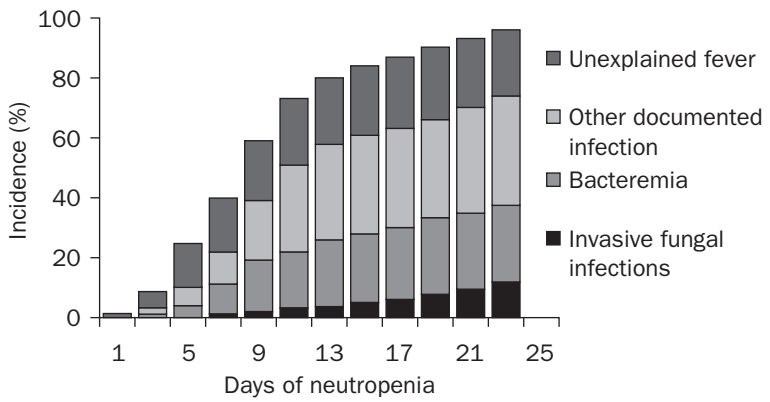
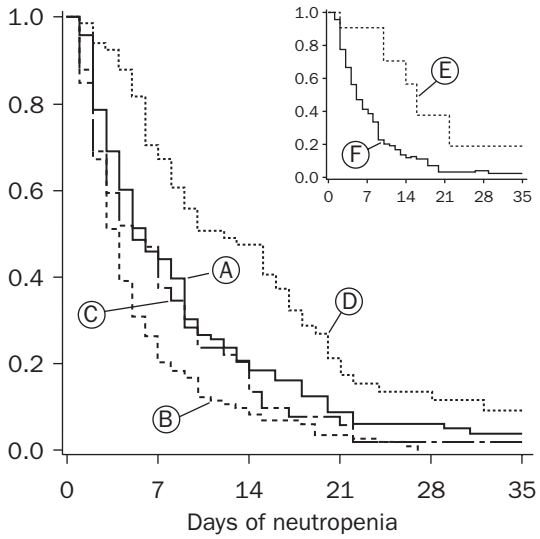


Figure 4.3 Schematic diagram estimating the incidence of unexplained fever and documented infections (bacteremia, non-bacteremic focal infections, invasive fungal infections) according to the duration of neutropenia (neutrophils < 500/μl).



Key: A, bacteremia; B, FUO; C, non-bacteremic non-pulmonary focal infection; D, pneumonia.

Figure 4.4 Time to defervescence (in days) according to type of infection. Data are from a retrospective study at Ulm University Hospital and Medical Center evaluating the outcome of febrile neutropenic episodes among adult patients with acute leukemia (period 1990–1993). The insert shows the time to defervescence for the subgroups of patients with bacteremia with (E) and without (F) pulmonary infiltrates.

DOCUMENTED INFECTIONS

A commonly used classification differentiates microbiologically documented infections (with or without bacteremia) from clinically documented infections. Widely used in studies of initial empiric therapy,[57] this classification has limited prognostic implications – primarily because it does not recognize the focus of infection. Review of a number of studies suggests that among non-bacteremic infections, pulmonary infection differs most in prognostic characteristics from infections at other sites. Also, the prognosis of bacteremic infection differs substantially between cases with or without a clinical focus; and among the cases with a clinical focus, bacteremia with pneumonia may be the most critical infection (Figure 4.2). Conversely, urinary tract infections (without bacteremia) or cases of mild tonsillopharyngitis (clinically documented infection) do not significantly differ in their prognosis from FUO.

Bacteremia

Bacteremia is one of the most frequent complications of neutropenia. Classically, enteric Gram-negative rods have been the most frequent pathogens of bloodstream infections. Over the past three decades, considerable changes have occurred in the types of bacteria causing infection.[58–65] As a consequence of long-dwelling intravascular devices, fluoroquinolone prophylaxis, and high-dose chemotherapy-induced mucositis, there has been a shift towards bacteremia due to Gram-positive cocci (Table 4.1).

Organisms enter the bloodstream via mucosal sites, skin, or intravascular catheters. Entry via the gastrointestinal tract is probably a common event, and a number of unexplained fevers may represent portal bacteremias. The more aggressive the chemotherapy and resulting mucosal damage, the more likely is bacteremia with saprophytic organisms from the oropharyngeal microflora (which do not need to pass the liver). The quantity of the pathogen that entered the bloodstream may make a difference.[66] Numerous, unusual blood culture isolates from neutropenic patients represent oral microflora constituents. Examples include *Micrococcus*, *Gemella*, *Stomatococcus*, various streptococci, *Leptotrichia*, *Actinomyces*, and *Fusobacterium*.

Incidence

The proportion of bacteremic infections among febrile neutropenic episodes ranges between 10% and 40%. Occasionally, higher rates have been reported.[30] The overall incidence of bacteremia per neutropenic episode ranges

Table 4.1 Bacteremia in clinical trials of the EORTC International Antimicrobial Therapy Cooperative Group

			Single-organism bacteremia	
Trial	**Period**	**No. of patients**	**% Gram-negative**	**% Gram-positive**
I	1973–1976	145	71	29
II	1977–1980	111	67	23
III	1980–1983	141	59	41
IV	1983–1985	219	59	41
V	1986–1988	213	37	63
VIII	1989–1991	151	31	69
IX	1991–1993	161	33	67
XI	1994–1996	199	31	69
XII (low-risk)	1995–1997	39	59	41
XIV (high-risk)[a]	1997–2000	186	47	53

[a] Prelimary data.

between less than 3% and 30% (Figure 4.3). Without effective chemoprophylaxis, more than half of the isolates are Gram-negative rods. In patients with acute leukemia and in BMT recipients, the expected incidence of Gram-negative bacteremia per neutropenic episode is about 15–20%; in lymphoma patients receiving CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisone) chemotherapy, it is about 3% per neutropenic episode. Strategies for chemoprophylaxis and initial empiric therapy need to consider these figures when – as is often the case – Gram-negative aerobes are the primary target organisms.

Risk factors for the development of bacteremia have been poorly defined.[67,68] In one study, systemic antifungal prophylaxis was identified and later confirmed as a risk factor.[69,70] Rackoff and others have identified an absolute monocyte count (<100/μl) plus high fever as predicting bacteremia.[71,72] Procalcitonin serum levels may discriminate between bacteremia and other documented infections and FUO.[73–75] Measurement at fever onset of interleukin (IL)-6 or IL-8 plasma or serum levels may be useful to predict the absence of Gram-negative bacteremia.[48,76,77] None of these factors can predict bacteremia accurately.

Prognosis

The prognosis of bacteremia is worse than that of unexplained fevers. Polymicrobial bacteremia is associated with a worse prognosis than single-organism bacteremia. A study from Spain examined prognostic factors influencing mortality in cancer patients with neutropenia and bacteremia.[78] The overall mortality rate within 30 days of the onset of bacteremia was 24%. Shock at onset, pneumonia, uncontrolled cancer, and absence of quinolone prophylaxis were independently associated with increased mortality. Early evolution into septic shock is clearly related to Gram-negative bacteremia, whereas it is less frequent in Gram-positive bacteremia, and particularly unusual in bacteremia due to coagulase-negative staphylococci.[11,69,70,78,79]

A rough estimate for the overall case-fatality rate in Gram-negative bacteremia is 10–15%; the estimated rate in viridans streptococcal bacteremia is about 10%, depending on host factors.[80] Elting and colleagues[81] have shown that major organ and tissue infection (such as pneumonia) in neutropenic patients with bacteremia severely compromises response to initial therapy as well as the ultimate outcome – experience that is consistent with that of other investigators.[78,82,83] In the same study, shock, *Pseudomonas aeruginosa* as the organism, and in vitro resistance to the therapeutic agent(s) were other prognostic factors. Among neutropenic children with bacteremia, the overall mortality rate was reported to be 15%.[84]

Bacteremia: selected organisms and associated syndromes

Viridans streptococci

These organisms have been reported to cause bacteremic infection among leukemia patients and BMT recipients.[85] The frequency of streptococcal infection appears to be dependant on the cumulative dose of the cytotoxic agent cytosine arabinoside or the use of anthracyclines in BMT patients, in association with mucosal damage.[9,80,86–93] Fluoroquinolone prophylaxis may be another risk factor. Incidence rates vary widely, being as high as 48% in adults and 36% in children with high-dose cytosine arabinoside therapy, and 46% in BMT patients. [87] Serious complications, including encephalopathy, respiratory distress syndrome (ARDS), and septic shock have been reported in association with these organisms. The pathogenesis of these complications is unknown. Polymicrobial infection with an as yet unidentified anaerobe has been one speculation about pathogenic events in this so-called 'α-streptococcal shock syndrome'. Other possible mechanisms are direct toxicity from cytotoxic agents and/or from streptococcal products such as toxins, superantigens, or cell wall components, probably via effects on host immune cells.[94] Penicillin resistance has become a problem in some centers.[93,95,96] Death rates may be as high as 38% in adults and 24% in children, and occur most often in association with ARDS.

In contrast to the increased incidence of viridans streptococci, pneumococcal bacteremia is surprisingly rare in neutropenia. In trials of the EORTC International Antimicrobial Therapy Cooperative Group, less then 25 cases were documented in more than 3000 patients (unpublished observations). Similarly, a Spanish study found only 17 episodes of pneumococcal bacteremia among 340 neutropenic cancer patients with bacteremia.[97]

Coagulase-negative staphylococci

The relative proportion of coagulase-negative staphylococci (CNS) among blood culture isolates has been increasing since the late 1980s. In a study from Spain, bacteremia caused by CNS among neutropenic cancer patients increased between 1988 and 1993 from 3 episodes per 1000 admissions to 19 episodes per 1000 admissions.[61] CNS are the classical vascular access device-related pathogens.[98,99] Although most cases of bacteremia due to CNS are catheter-related, the reverse is not necessarily true. There are several studies reporting a large proportion (40–50%) of catheter-related infections due to organisms other than CNS.[100–103] Device-related sepsis may frequently be caused by *Acinetobacter* spp. and other non-fermenters, *Enterobacter* and *Citrobacter* spp., *Bacillus* spp., *Corynebacterium* spp., *Micrococcus*, and others. Mucosal sites can be the origin of CNS bacteremia in the neutropenic host.[104,105] In the individual patient, clonal diversity of CNS colonizing the skin and mucosal surfaces is being reduced after hospital admission and in response to administration of antimicrobial drugs.[106,107] Catheters are rapidly colonized via skin or hub, and organisms survive in biofilms spread over the internal and external catheter surfaces. Even in a given hematology–oncology service, there may be only a limited number of clones of *Staphylococcus epidermidis* causing catheter-related infections over extended peri-

ods of time. Consequently, infection due to relatively virulent and usually multiresistant isolates of CNS among hospitalized patients has become very difficult to control. Most hematology–oncology departments report endemic oxacillin resistance in CNS isolates,[108] resulting in the frequent use of glycopeptide antibiotics.[108,109]

Most often, the course of bacteremia due to CNS is uncomplicated even when the catheter has not been removed. Also, despite resistance to oxacillin, patients with CNS bacteremia receiving delayed glycopeptide therapy defervesce as rapidly as those receiving upfront glycopeptides. This may be related to low-grade bacteremia, or to contamination rather than true bacteremia. Complications of CNS bacteremia include catheter tunnel infections, cellulitis, septic thrombophlebitis, endocarditis, osteitis/osteomyelitis, and foreign body infections at distant sites (e.g. joint prosthesis infection). CNS are a group of more than 10 species potentially pathogenic for man. The most frequent isolates from febrile neutropenic patients are *S. epidermidis*, *S. haemolyticus*, *S. warneri*, and *S. hominis*. Many laboratories no longer differentiate CNS to species level. Since susceptibility patterns differ among species, such differentiation might be important in cases of relapsing bacteremia.

Staphylococcus aureus bacteremia is much less common than CNS bacteremia.[110] It is infrequently reported in neutropenic patients, with notable exceptions.[59,60,111,112] The reason is unclear. It is likely that patients with solid tumors are at higher risk of *S. aureus* infection than patients with hematologic malignancies (who experience neutropenia more often) owing to increased age, less intensive antimicrobial pretreatments, or more postoperative infections.[113]

Pseudomonas aeruginosa *and other non-fermenters*

Bacteremic infections due to *Ps. aeruginosa* have been a common, difficult-to-treat complication in neutropenic patients.[114] More than three decades ago, reported case-fatality rates in neutropenic patients were over 50%. In the 1970s, the outcome improved with the use of combination therapy consisting of carbenicillin (or other β-lactam antibiotics with antipseudomonal activity) plus gentamicin. More recently, cure rates of about 80% have been reported.[115,116] Currently, the relative frequency among blood culture isolates from neutropenic patients is about 5%, and the overall incidence of *Ps. aeruginosa* bacteremia among febrile neutropenic episodes, accordingly, is only about 1%. At the University of Texas MD Andersen Cancer Center, an incidence in acute leukemia patients of 55 per 1000 registrations has been reported (including non-neutropenic episodes). At that center, no major changes in incidence were noted over the last 30 years, except that in more recent years there were more community-acquired infections.[115] In a large multicenter study of bloodstream infections among cancer patients, infection due to *Ps. aeruginosa* was identified as an independent risk factor of death.[117]

Initial clinical sites of infection are frequently observed, with pneumonia being the most common site (about 40%), and skin and soft tissue including the perianal/perirectal area the second most common site.[115] Skin and soft tissue infections can be extensive and severe, and can extend from the perirectal area to include the perineum and scrotum as a rapidly spreading necrotizing infection.[118] Ecthyma gangrenosum occurs in less than 5% of patients. The frequency of development of shock may be as high as 20–30%, depending on the clinical site, evolution of neutrophil counts, and adequate therapy.

Glucose-non-fermenting Gram-negative rods other than *Ps. aeruginosa* are a heterogenous group of organisms comprising *Pseudomonas* spp. (*fluorescens*, *putida*, *stutzeri*, and others), related genera (for example *Burkholderia*, *Stenotrophomonas*, *Flavimonas*, *Chryseomonas*, *Comamonas*, *Shewanella*, and *Methylobacterium*), and the genera *Acinetobacter*, *Achromobacter*, *Alcaligenes*, *Ochrobactrum*, *Agrobacterium*,

Flavobacterium, *Sphingobacterium*, and *Moraxella*. With the exception of the latter genus, these organisms have been increasingly prevalent among blood culture isolates from immunocompromised patients over the last two decades.[119–123] The most common isolate in this group is probably *Stenotrophomonas maltophilia*. Many of the organisms are widely distributed in the environment such as soil, water, organic material. Some (e.g. *Ps. fluorescens*, *Burkholderia pickettii* and *Ps. paucimobilis*) are well known for their property to contaminate wet hospital equipment, antiseptics, intravenous fluids, and cosmetics. Infections often follow instrumentation, are associated with intravascular catheters, or follow administration of contaminated intravenous fluids or blood products (including bone marrow or stem cells).[124–135] A complication may be right-sided endocarditis. Rarely, other sites of infection can be observed, notably the lung in the case of *S. maltophilia* and *Chryseobacterium meningosepticum.*[124,136,137] The infections have sometimes occurred in small clusters of true infection or of pseudobacteremia, presumably because of common sources in the hospital and often unusual antimicrobial resistance patterns with associated selection and transmission advantages.[137–145] Examples of the unusual resistance patterns of the organisms are the intrinsic resistance of *S. maltophilia* to carbapenems, the unpredictable resistance to aminoglycosides (often gentamicin-susceptible but tobramycin- and/or amikacin-resistant) in *Comamonas*, *Alcaligenes*, *Agrobacterium*, and others, and the unusually frequent susceptibility of many nonfermenters to trimethoprim–sulfamethoxazole and tetracyclines. Since susceptibilities vary greatly between and within species, detailed testing is mandatory. Unfortunately, disk diffusion tests have often been unreliable.

Unusual organisms

Many rare microorganisms have been reported to cause infection in neutropenic patients.[146] Examples are nutritionally variant streptococci or *Gemella* among streptococci, rare species of CNS, and rare species of Enterobacteriaceae such as *Kluyvera*, *Hafnia*, and *Rahnella*.[147] Many of these cause catheter-related infections: *Bacillus* spp.,[148–151] diphtheroids, some of the aerobic actinomycetes, and *Mycobacterium fortuitum* and other non-tuberculous mycobacteria.[152–157] Most others (*Fusobacterium* and other gram-negative anaerobes,[158–160] *Lactobacillus* spp.,[161,162] clostridia,[163] anaerobic actinomycetes, *Capnocytophaga* spp. group DF-1,[164,165] and *Stomatococcus* spp.[166–168]) have been implicated in causing bacteremia in association with oral or intestinal mucositis.

Antibiotic-resistant Enterobacteriaceae

Recent reports have emphasized the risk of the emergence of fluoroquinolone- and broad-spectrum β-lactam-resistant Enterobacteriaceae.[169] Fluoroquinolone resistance appears to be the result of the extensive use of fluoroquinolones for prophylaxis in cancer patients.[170–172] The prevalence of resistance in the cancer patient population, however, is also highly dependant on the resistance rates among isolates from the community.[173] A study from Spain, for example, described a 20% rate of colonization with fluoroquinolone-resistant *Escherichia coli* among cancer patients on admission. This rate increased after admission to more than 40%.[174] In the Netherlands and Germany, colonization rates are much lower, although fluoroquinolones are continuously used for prevention of Gram-negative sepsis in high-risk neutropenic cancer patients.[170,175] The incidence of bacteremia due to fluoroquinolone-resistant *E. coli* among patients given prophylaxis therefore ranges widely between less than 3% and more than 10%.[173–176] The latter rate indicates that the prophylactic trend towards reduction of Gram-negative sepsis has been lost. Based on data from two recent EORTC International Antimicrobial Therapy Cooperative Group trials, the proportion of patients with Gram-negative bacteremia during fluoroquinolone prophylaxis increased between the periods 1993–1994 and 1998–2000; an increase in the incidence of Gram-negative bacteremia,

however, was also observed among patients without fluoroquinolone prophylaxis (unpublished observations) (Table 4.2). Some hospitals where fluoroquinolone prophylaxis has been discontinued have experienced an increasing incidence of Gram-negative bacteremia, along with a reduction of fluoroquinolone resistance among the isolates.[177,178]

According to reports of large numbers of Gram-negative isolates from patients with neutropenia, β-lactam resistance rarely exceeds 10%.[179,180] Resistance rates are higher for aztreonam and ceftazidime than for carbapenems, and appear to increase slowly in those centers that use these drugs for empiric therapy. Extended-spectrum β-lactamase can be found in common Gram-negative bacilli, notably in *E. coli* and *Klebsiella pneumoniae.*[181] Small epidemics have been reported.[182] There is a well-documented risk of development of β-lactam resistance in *Enterobacter.*[180,183] The recent increase in Gram-negative bacteremia in neutropenic patients treated within EORTC International Antimicrobial Therapy Cooperative Group trials is in part a result of more frequent infections due to *Klebsiella* and *Enterobacter*.

Vancomycin-resistant enterococci

Vancomycin-resistant *Enterococcus faecium* (VRE) have been surprisingly common in many hematology–oncology units. The organism is known for its intrinsically decreased susceptibility to ampicillin. Endemic situations as well as small outbreaks of bacteremic infection in oncology units have been reported.[184–187] Outbreaks in cancer hospitals in association with antibiotic formulary changes have been described.[187] These outbreaks may initially be polyclonal. New patients may become colonized with VRE within two weeks after admission, and shed the organism over extended periods of time.[185,188] In a given unit, the genetic diversity of VRE becomes limited, and cross-contamination and cross-infection are frequent.[189] An endemic situation follows. The use of third-generation cephalosporins together with glycopeptides appears to be associated with the emergence of vancomycin-resistant enterococci. A study from the UK showed that about 50% of the patients became colonized with VRE during a period in which ceftazidime was used as initial empiric regimen.[186] After changes to piperacillin–tazobactam as empiric

Table 4.2 Gram-negative bacteremia and fluoroquinolone prophylaxis in clinical trials of the EORTC International Antimicrobial Therapy Cooperative Group

	Trial XI[a] (1994–1996)	Trial XIV[a,b] (1997–2000)
Number of patients	386	332
Fluoroquinolone prophylaxis	212 (55%)	125 (38%)
Gram-negative bacteremia		
Patients with fluoroquinolone prophylaxis	13/212 (6.1%)	12/125 (9.6%)
Patients without fluoroquinolone prophylaxis	16/174 (9.2%)	30/207 (14.5%)

[a] The analysis includes only those 14 centers that participated in both trials.
[b] Preliminary data.

β-lactam, colonization rates first fell to less than 20%, increasing to 36% upon reintroduction of the cephalosporin. The incidence of clinical infection can be low (about 10%), despite common intestinal colonization.[184,185] A recent study described a 33% risk of bacteremia in colonized cancer patients.[188] The case-fatality rate ranges from 10% to more than 70%, but the attributable mortality is probably much lower. VRE may sometimes be a surrogate marker for poor-prognosis cancer. Vancomycin-dependant enterococci are mutants of VRE. A small outbreak involving five BMT patients has recently been described.[190] Infection control measures and revision of antibiotic policies (less use of empiric vancomycin) were able to control the situation.

Pneumonia

Pneumonia is one of the most critical infections in patients with neutropenia. Response to initial empiric therapy is often poor, and reported case-fatality rates range between 20% and more than 60%.[83,191–193] Patient age, etiology, presence of bacteremia, severity of lung infection, and persistent neutropenia have a major impact on survival. Patients who develop respiratory insufficiency have a very poor prognosis; only 20% or less survive. The relative frequency of pneumonia among febrile neutropenic episodes ranges between 10% and 30%.[8,23,83] In children, the infection is less frequent. Pneumonia often develops after several days of empiric therapy[83,191] and sometimes it is difficult to say whether it is the primary infection or a superinfection.

Based on culture and histology, the etiology of lung infections in the neutropenic host can be defined in only 10–45% of cases,[191–195] partly because patients have often been given empiric therapy before invasive diagnostic procedures such as bronchoscopy. The most common bacterial pathogens have been *Ps. aeruginosa*, *Klebsiella*, pneumococci, and *S. aureus*. Pneumococcal, staphylococcal, and polymicrobial infections may be more common in solid tumor patients, but there is limited epidemiologic data on this issue. Isolates from initial blood cultures are not necessarily the cause of evolving pneumonia, even among patients with documented pulmonary infiltrates at the time of bacteremia. Thus, using results of blood cultures overestimates the bacterial etiology of pneumonia in the febrile neutropenic patient. In particular, cases of bacteremia due to enterococci, viridans streptococci, CNS, diphtheroids, and non-fermenters other than *Ps. aeruginosa* with subsequent pulmonary infiltrates remain suspicious of a non-bacterial superinfection of the lung, toxic lung injury, or pulmonary hemorrhage. Among the most important organisms causing severe lung infection in neutropenia in present times are filamentous fungi, notably *Aspergillus* spp., *Legionella*, mycobacteria, *Pneumocystis carinii*, protozoa, and viruses are infrequent.[191–193,196,197] Recently, cases of *Chlamydia pneumoniae* respiratory infection in acute leukemia patients have been described.[198] Like many other pneumonias, they occurred later during febrile neutropenia. A viral etiology outside the BMT setting is rare. Chest computed tomography (CT) scans have substantially improved the diagnostic sensitivity and specificity, while there is increasing debate about the role of routine chest radiography within 24 hours after the onset of fever in the absence of localizing signs and symptoms.[199,200]

Selected focal infections

Many sites of infection have been described in febrile neutropenia. The most frequent outside the lungs are oropharynx, skin/soft tissue and intravascular catheters, paranasal sinuses, gastrointestinal tract/perianal area, and urinary tract. Unusual sites are the central nervous system/meninges, bones and joints, eyes and ears, heart, liver, biliary tract/pancreas, endocrine organs, and lymph nodes. These unusual sites when involved are very often secondary sites after hematogenous dissemination.

Strict consensus definitions are not available for all of these focal infections, and a detailed comparative epidemiologic analysis is therefore not possible. An example is oropharyngeal mucositis. Although there has been much progress in clinical grading of oral lesions,[201] the question remains unanswered as to whether mucositis at any stage or only at more severe stages should be considered an infection. Clinically, oral lesions in the neutropenic patient with fever are diverse. They include oropharyngeal candidiasis, buccal ulcers and necrotizing ulcerative gingivitis (both suggestive of being caused by herpes simplex virus), soft palate ulcers, and necrotizing tonsillitis. Such lesions are common. In AML patients, for example, their incidence approaches 100%, and different entities often coexist. In the individual patient, the grading of the lesions correlates inversely with the neutrophil count. The incidence of urinary tract infections, in contrast, rarely exceeds 10%. Often, the diagnosis is based solely on documentation of significant bacteriuria. Pyuria is not a reliable marker in the neutropenic patient, and dysuria is rare. Individually, it is difficult to ascertain that the fever is, in fact, related to the bacteriuria.

Catheter-related infection

Intravascular catheter-related infection may remain localized or may generalize after hematogeous dissemination. Some epidemiologic studies of catheter-related infection in neutropenic patients have analyzed only the frequency and outcomes of bacteremic infections related to central venous catheters. The epidemiology of non-bacteremic catheter-related infections during neutropenia has been less well studied. Definitions vary, even for catheter-related bacteremia, and often a definite diagnosis cannot be established without microbiologic examination of the explanted catheter. In a recent study, approximately half of the catheter-related infections were non-bacteremic, including insertion site and tunnel infections.[202] Up to 20% of all central venous catheters will be the source of infection, depending on many factors such as intensity of catheter usage, infection control measures during insertion and manipulations, catheter type, and duration and degree of neutropenia. Totally implanted catheters are associated with fewer infections than tunnelled catheters or non-tunnelled central venous catheters.[203,204] For tunnelled catheters, incidence rates range between 1 or less[205,206] and about 5–7 per 1000 catheter days.[102,202,207,208] A large study of non-tunelled silastic catheters found an infection rate of 1.3 per 1000 catheter days.[209] In children with ALL, the adjusted risk for infection (any type) was two- to fourfold higher when a central venous catheter was in place.[210]

Neutropenic enterocolitis and antibiotic-associated colitis

Acute abdomen is the clinical presentation of acute neutropenic enterocolitis.[211] This complication typically begins 7–10 days after chemotherapy, with fever, right lower quadrant or diffuse abdominal pain, and rebound tenderness, sometimes with diarrhea or bloody diarrhea. Patients without preceding chemotherapy are rarely involved. An incidence of about 1% was reported in autoPBSCT recipients.[23] Among acute leukemia patients, an incidence of 5–6% was reported;[212,213] following taxane-based chemotherapy, the incidence was 0.1%.[214] Complications are pneumatosis intestinalis, bowel necrosis, perforation, peritonitis, and septic shock. In a report from the 1980s, the case-fatality rate appears to have been very high (64%).[215] More recently, rates of 45%[213] or less[212,214,216–218] were reported.

Neutropenic enterocolitis is a non-infectious transmural inflammatory lesion following cytotoxic chemotherapy, with secondary tissue invasion, spread, and translocation of bacteria. In some cases, necrotizing infection due to clostridia has been implicated in the pathogenesis;[219] in others, necrotizing leukemic infiltrates in the bowel wall have been documented, and pseudomembranes or only mild mucosal inflammation have been found. Most frequently, the terminal ileum, the caecum

('typhilitis'), and ascending colon are involved. The cause of death is usually septic shock, with or without bacteremia. Occasionally, there is bowel perforation.

Clostridium difficile has become recognized as the most frequent cause of antibiotic-associated colitis. This disease is characterized by acute inflammation of the colonic mucosa, with formation of macroscopic or microscopic pseudomembranes. Atypical presentations are abdominal distention, ascites, and hyperbilirubinemia without diarrhea. Asymptomatic carriage of the organism has been described. Critical illness leading to intensive care unit admission or death caused by the disease occur with a relative frequency of less than 5%. Although toxigenic *C. difficile* is the most frequent cause, occasionally other pathogens have been implicated, notably other clostridia, salmonellae, *S. aureus*, and *Klebsiella oxytoca*. The relative risks of specific antibacterial drugs inducing antibiotic-associated colitis are not precisely known. Pretreatment with several cytotoxic drugs, such as methotrexate or 5-fluorouracil, can also predispose to development of the disease. Unlike neutropenic enterocolitis, antibiotic-associated colitis most often affects the distal bowel. More than 80% of cases are nosocomially acquired. The clostridial spores can persist on fomites and surfaces for several months. Nosocomial transmission via the hands of personnel or contaminated environments is common. Among cancer patients with diarrhea, 10–45% will have a positive toxin test result and/or a positive culture of the organism.[220–224] Fluoroquinolone prophylaxis during neutropenia may lower the risk of developing *C. difficile* colitis.[225] The overall incidence among autoPBSCT patients in one recent study was 7%.[220] The outcome was good in all patients. Interestingly, there is an epidemiologic link between *C. difficile* colitis and the emergence of bacteremia due to VRE.[226] A policy of initial reisolation after readmission of known carriers is able to reduce endemicity.[227] Hospitalization, parenteral vancomycin in the last 2 months, and high-dose chemotherapy predicts an increased risk of *C. difficile* colitis.[228]

Perianal/perirectal cellulitis

Perianal or perirectal cellulitis is rare. According to a recent observational study, the incidence among patients with acute leukemia was 7%, and the case-fatality rate was 20%.[229] The reported incidence among autoPBSCT patients and alloBMT patients is much smaller (<1%).[23,230] In the acute leukemia patients cohort of Ulm University Hospital, perianal cellulitis was observed in 2% of febrile neutropenic episodes (unpublished observations). Initially, the inflammation is characterized by painful induration and redness perianally. Progression into deeper tissue with involvement of the perirectal area and development of necrotic lesions and fistula indicates a critical stage. Some patients may become bacteremic. *E. coli* and *Ps. aeruginosa* are the most common organisms involved, sometimes associated with anaerobes, enterococci, and CNS.

Invasive fungal infections

Based on several comparative trials evaluating the impact of prophylactic antifungals, the incidence of documented deep fungal infections among patients with hematologic malignancies given no systemic antifungal prophylaxis is about 4–10% (Table 4.3).[231–237] The rate is higher among BMT patients. For example, 18% proven systemic fungal infections were reported among placebo recipients in a study conducted at the Fred Hutchinson Cancer Research Center in Seattle.[235] However, a significant proportion of invasive fungal infections in this patient population occurred after engraftment (Figure 4.5). The incidence of deep fungal infection during neutropenia usually does not exceed 10% even in this patient population. This contrasts with the frequent use of therapeutic amphotericin B and other antifungals, which is on the order of about 20–25%, and 50% or more in BMT recipients. Reasons for the frequent use of empiric or preemptive therapy are the poor prognosis of invasive fungal infections with current therapeutic protocols and the inherent

Table 4.3 Incidence of and mortality related to proven invasive fungal infections in patients with neutropenia. Data are from placebo arms of large, controlled clinical trials evaluating antifungal chemoprophylaxis

Authors	Underlying disease	Proven invasive fungal infection		
		Incidence (%)	No. of yeast/ other fungal infections	Related mortality rate (%)
Goodman et al (1992)[236]	48% alloBMT 52% autoBMT	16	27/3	6
Slavin et al (1995)[235]	12% autoBMT 88% alloBMT	18	29/3	21[a]
Rotstein et al (1999)[237]	60% acute leukemia 44% autoBMT	17	22/1	5
Winston et al (1993)[234]	100% acute leukemia	8	7/4	0
Nucci et al (2000)[233]	80% acute leukemia	9	6/3	1
Menichetti et al (1999)[232,b]	76% acute leukemia	9	8/1	3
Harousseau et al (2000)[231,b]	70% acute leukemia	5	3/10	2

[a]Mortality until day 110 after BMT.
[b]Patients in the placebo arms received oral non-absorbable polyene antifungals.

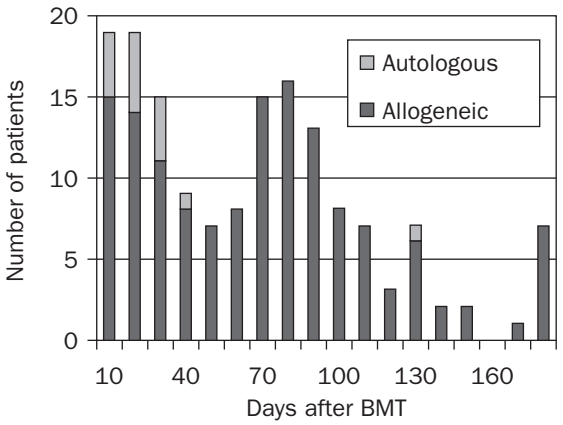


Figure 4.5 Time course of invasive aspergillosis in autologous and allogeneic BMT patients. Data are from Wald et al.[276]

difficulties in firmly establishing the diagnosis.

One-half to two-thirds of the documented infections among patients given no systemic prophylaxis are *Candida* infections; the others are mould infections (Table 4.3). The latter are very often termed 'invasive aspergillosis'. However, many of these cases are not culture-confirmed, and *Aspergillus* cannot be differentiated histopathologically from most other hyalohyphomycetes. Therefore, the term 'invasive hyalohyphomycosis' is preferable (Table 4.4). The introduction of fluconazole into clinical practice has reduced the incidence of systemic *Candida* infections, and has shifted the spectrum of yeasts from *C. albicans* and *C. tropicalis* to *C. glabrata* and *C. krusei*. As with bacterial

Table 4.4 Selected agents of aspergillosis and of other hyalohyphomycoses causing invasive fungal infection with similar histologic appearance in patients with neutropenia

Aspergillus spp.	*Fusarium* spp.	*Penicillium* spp.
A. flavus	*F. chlamydosporum*	*P. citrinum*
A. fumigatus	*F. moniliforme*	*Scedosporium* spp.
A. nidulans	*F. oxysporum*	*S. apiospermum*
A. niger	*F. solani*	*S. prolificans*
A. ochraceus	*Neosartorya fischeri*	*Scopulariopsis* spp.
A. terreus	*Paecilomyces* spp.	*S. brevicaulis*
A. ustus	*P. lilacinus*	*Scytalidium* spp.
Acremonium spp.	*P. variotii*	*S. dimidiatum*
Emmonsia spp.		*Hormographiella* spp.
E. parva		*H. aspergillata*

infections, the spectrum of fungi causing significant infections in the neutropenic patient has broadened to include rare and unusual organisms that are often resistant to currently used antimicrobial drugs. Yeasts other than the more common *Candida* spp. listed above and moulds other than *Aspergillus*, *Fusarium* (the most prevalent plant fungus worldwide),[238,239] and zygomycetes (Figure 4.6) (*Mucor* spp. and related genera),[240,241] however, are still rare in neutropenic patients. Rare and unusual fungi most recently reported include *Trichosporon/Blastoschizomyces* spp.,[242–244] *Candida dubliniensis*,[245] *Candida inconspicua*,[246] *Paecilomyces lilacinus* (coming from contaminated skin lotions),[247] *Metarrhizium anisopliae* (used commercially for the biocontrol of insects),[248] *Acremonium* spp.,[249] *Scedosporium prolificans*,[250] *Cunninghamella bertholletiae*,[251] *Trichoderma longibrachiatum*,[252] *Hormographiella aspergillata*,[253] *Penicillium citrinum*,[254] *Malassezia* (associated with hyperalimentation with intravenous lipids), dematiaceous (darkly pigmented) fungi causing phaeohyphomycoses (which are exceptional in the setting of neutropenia), and some others. The list of unusual fungal pathogens is enlarging much more rapidly in patients with chronic immunodeficient states, including transplant patients, than in patients with chemotherapy-induced (transient) neutropenia. The reason for this is obvious – it is simply a result of increased exposure of the usually ambulatory, chronic immunosuppressed patient to particular environments that may be specific habitats of rare fungi.

Fungemia

Fungemia, most often candidemia, may originate from gastrointestinal lesions, but also often develops as an initial catheter-related infection.[255] *C. parapsilosis* and *C. lusitaniae* appear to be overrepresented in catheter-related fungemias. A risk factor for the development of candidemia is prior colonization at multiple mucosal sites.[256] The risk of developing fungemia is much higher in patients colonized by *C. tropicalis* than in those colonized by *C. albicans*. Another possible risk factor for fungemia is prior glycopeptide therapy and/or bacteremia.[257–259] The case-fatality rate in many series of neutropenic patients exceeds 20%.[258,260–263] Tissue invasion and dissemination markedly decreases survival. Decreased survival has also been observed in infection due to *C. glabrata* and *C. krusei* when compared with other non-albicans species or *C. albicans*. The infection usually

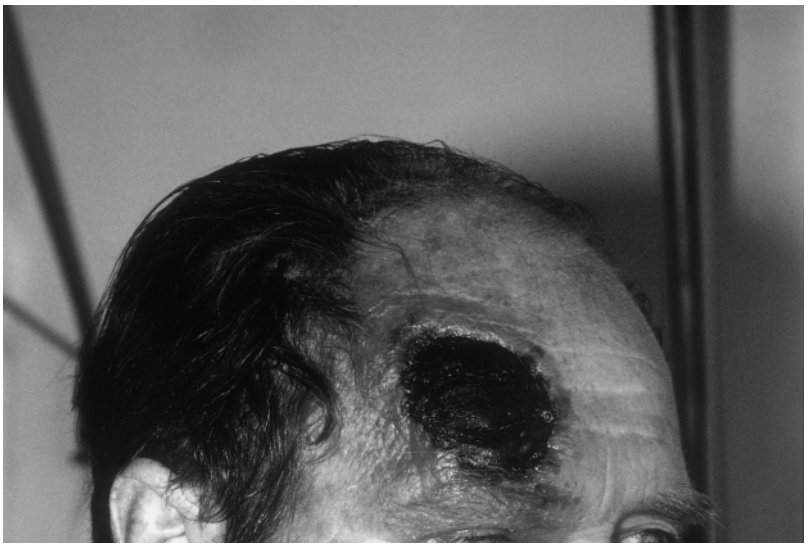


Figure 4.6 Zygomycosis in a neutropenic patient. Necrotizing skin and soft tissue infection extending into the tabula externa of the skull in a patient with non-Hodgkin's lymphoma, who was initially treated as an outpatient. *Absidia corymbifera* was isolated in pure culture from necrotic tissue.

develops late after onset of neutropenia. It is sometimes accompanied by non-specific respiratory symptoms, myalgias, and characteristic skin and chorioretinal lesions.[264] Some use the term 'acute disseminated candidiasis' in such cases of tissue invasion. Severe sepsis and shock occurs with a similar frequency as in Gram-negative bacteremia.

Rare cases of fungemia are caused by *Trichosporon*, *Rhodotorula*, *Fusarium*, *Malassezia*, and others. *Fusarium* infections are exceptional in that the organism is a filamentous fungus relatively often growing in blood culture when causing disseminated infection. Hematogenous dissemination of *Fusarium* involves multiple sites and organs, including sinuses, lungs, skin, brain, bone, and joints. In contrast to aspergillosis, blood cultures are positive in 50% or more of all cases. Fungemia due to other organisms is often catheter-related, and may have a rather benign evolution after catheter removal.

Disseminated candidiasis

Subacute or chronic disseminated candidiasis, formerly called 'hepatosplenic candidiasis', was increasingly diagnosed in the late 1980s and early 1990s.[265–268] In a Finnish center, incidence rates increased from about 2% (1980–84) to about 10% (1989–93) among patients with acute leukemia.[266] This can be explained partly by improved imaging techniques; improved survival of candidemia may be another reason. Strictly speaking, subacute or chronic disease is not an infection of the neutropenic patient, but rather an infection after neutrophil recovery. The infection begins with fever during neutropenia, and the fever persists for weeks despite empiric therapy (including antifungals) and neutrophil recovery. The host reaction is granuloma formation, with a paucity of microorganisms, and the organs predominantly involved are liver and spleen. These chronic infections are being seen much less frequently since the introduction of fluconazole into clinical practice.

Aspergillosis

Moulds of the genus *Aspergillus* are widespread in the environment, being found in the air, soil, and water, and on plants, certain food, and decomposing organic matter. Fungal spore counts in outdoor air may be as high as 100–1000 CFU per cubic meter of air. Pathogenic *Aspergillus* spp. represent about

1–10% of these spores. Inhalation of spores is the major source of invasive infection. The level of environmental contamination and host factors determine the incidence of invasive infection.[269–271] Critical host factors are neutropenia of long duration, graft-versus-host disease, and intensive immunosuppressive therapy. Macrophages and cellular immune response play an important role in controlling the infection.[272] AlloBMT patients are therefore at high risk.[273] Prior or concomitant bacteremia or Gram-negative bacterial infection and cytomegalovirus disease increase the risk of aspergillosis in these patients and/or worsen the outcome.[274,275] Among BMT patients, the onset of infection is bimodal. Peaks at 16 and 96 days after transplant have been observed (Figure 4.5).[276] For patients with early infection, underlying disease, donor type, season, and transplant outside of air-filtered rooms were associated with significant risk for invasive aspergillosis. The cumulative incidence among alloBMT patients exceeds 10%. *A. fumigatus* remains the most frequent species, and accounts for more than 50% of cases, *A. flavus* is the second most frequent species. *A. niger* and *A. terreus* are isolated with increased frequency.[277] The incubation time is unknown, and it is an open question how many cases becoming manifest during admission are in fact community-acquired. Molecular typing of pathogenic isolates and isolates from hospital environments suggest that half or more of the infections may not be nosocomial.[278–280] The impression of many physicians is that during the last decade, the incidence of invasive aspergillosis has been increasing as a result of less use of protected environments/reverse isolation for leukemia treatment, and of much more frequent discharges to home care. Nosocomial outbreaks have been described in association with environmental disturbances: hospital construction or construction in adjacent areas; contaminated fireproofing materials, or air filters in the hospital ventilation system; contaminated carpeting.[269,270,281–284] High-efficiency particulate air (HEPA) filtration in sealed rooms with positive air pressure is protective in such situations, leading to undetectable fungal spore counts (i.e. <0.1 CFU per cubic meter of air).[283] The potential for tap water and water from shower heads to aerosolize molds needs to be studied in more detail.[285,286]

Clinical disease associated with invasive aspergillosis in neutropenic patients includes sinusitis, pulmonary infection, and disseminated infection. Brain involvement is frequent (about 40–50% among alloBMT patients), and carries a poor prognosis.[287–290] Rare manifestations include necrotizing cellulitis, necrotizing mucosal lesions, hematogenous osteitis (often spondylodiscitis), nephritis, and thyroiditis. The outcome is poor. Invasive infection limited to the lungs responds to antifungal therapy in about 30–50% of cases. The infection often becomes chronic, and the patient remains at high risk of relapse during subsequent neutropenic episodes or periods of increased immunosuppression.[291,292] Among allogeneic transplant patients with an earlier invasive aspergillosis, relapse rates of 40% have been reported. Extensive granulomatous tissue reactions can be seen in chronic disease. A major step towards improved prognosis of patients with invasive aspergillosis has been earlier presumptive diagnosis by chest CT scan, while screening by serologic assays and nucleic acid amplification-based laboratory tests still await a thorough evaluation of their cost–effectiveness against clinical and radiological assessment.[293,294] A major diagnostic problem remains the difficulty in establishing a culture-confirmed diagnosis. Bronchoalveolar lavage cultures in cases of pulmonary involvement are positive in only 10–40% of cases. The paucity of culture-confirmed cases with a majority of presumptive cases or histologically diagnosed non-*Aspergillus*-specific hyalohyphomycoses may be a good reason for a more intense use of PCR and serological tests.

Viral infections during febrile neutropenia

Reactivation of latent herpesviruses, more specifically of herpes simplex virus (HSV), is by far the most common viral infection in adult patients with neutropenia.[295] Outside the blood and marrow transplant setting, infections due to varicella zoster virus (VZV), cytomegalovirus (CMV), Epstein–Barr virus (EBV), and other herpesviruses (human herpesvirus (HHV)-6, HHV-7, and HHV-8) are uncommon, and the risk of reactivation of one of these is much smaller in autoPBSCT patients than in alloBMT patients. Patients treated with fludarabine or other purine analogs, however, may form a specific subgroup with a different risk profile. In a recent case report, for example, an AML patient developed EBV-associated lymphoproliferative disease after fludarabine/cytosine arabinoside/granulocyte colony-stimulating factor chemotherapy, which is a very unusual complication outside the alloBMT setting. The patient´s leukemia was in remission, and the patient was no longer neutropenic at that time.[296] Also, in the autoPBSCT setting, patients with $CD34^+$ cell-selected transplants (which are associated with more pronounced CD4 lymphopenia compared with unselected products) may have a significantly higher risk of viral infection, specifically CMV infection.[297]

Primary infections with other viruses, such as adenovirus, influenza and parainfluenza viruses, respiratory syncytial virus (RSV), and others, do occur. They usually reflect the general epidemiologic situation and exposure characteristics, rather than indicating a particular risk specific to neutropenia (season, crowding, etc.). It appears plausible that the severity of these infections among neutropenic patients outside the BMT setting is substantially different from that seen in the general population. The data supporting this view, however, are conflicting. Active untreated RSV infections, for example, need not consistently lead to severe complications during neutropenia, even among autoPBSCT recipients.[298] On the other hand, there are reports of outbreaks of severe infections among neutropenic patients, and neutropenic patients with RSV infection may be at increased risk of developing pneumonia (as opposed to tracheobronchitis and upper respiratory tract infection) and of death.[299–302] In the MD Anderson Cancer Center study, not all deaths, however, were definitely related to the RSV infection.[301]

HSV reactivation during neutropenia is common. Studies in acute leukemia patients have shown that among seropositive subjects, about 25–50% will have shedding of the virus in the mouth, associated with herpes labialis and/or ulcerative gingivostomatitis.[42,303,304] The incidence is higher among alloBMT patients (about 70% or more), reflecting the more severe mucosal damage in this setting and additional immunosuppression. HSV lesions in neutropenic patients may be severe and long-lasting. There has been some discussion of the role of HSV lesions in facilitating entry of bacterial and fungal mircoorganisms into the bloodstream. Esophagitis is a significant complication, but has become rare because of prompt therapy of oropharyngeal lesions. Other organs are very rarely involved, although there have been reports of HSV pneumonitis.

Complications due to other herpesviruses are unusual during neutropenia, and often occur after neutrophil recovery in auto PBSCT or alloBMT patients. The most frequent have been VZV infections, and the most problematic has been CMV disease. CMV viremia or antigenemia has been documented in about 3% of autoPBSCT recipients versus about 60% of alloBMT recipients. In one report, the incidence of fatal CMV interstitial pneumonia in autoPBSCT patients was 0.8%.[24] CMV disease in alloBMT patients before engraftment has been documented in a few cases.[305] Most often, the lung has been the primary site of infection, but, in some cases, the histopathologic appearance of the lesions was atypical and/or significant copathogens could be identified. Only occasionally, patients with hematologic malignancy or solid tumors develop CMV disease during neutropenia – most often pneumonia and colitis.[306,307]

VZV infections have been surprisingly common (10–25%) in several series of autoPBSCT patients.[24,308] Clinical disease from reactivation during neutropenia was probably suppressed by prophylactically administered acyclovir, and overt infection was not observed until after neutrophil recovery (and discontinuation of acyclovir). In children with ALL, the risk of having chickenpox or herpes zoster is clearly increased.[309] Severe cases with minimal skin and extensive extracutaneous involvement (lungs, liver, spleen, or central nervous system) have been reported.[310] HHV-6 and HHV-7 are recently discovered β-herpesviruses. DNA can be detected in blood or bone marrow from healthy subjects.[311,312] Infection with HHV-6 is very common, approaching 100% in seroprevalence. The virus appears to persist in low levels in cells and tissues, and can reactivate during cytotoxic chemotherapy and/or immunosuppressive therapy. It has been associated with lymphopenia, exanthema, and hepatopathy in children with cancer.[313] In BMT patients, bone marrow suppression, interstitial pneumonitis, and encephalitis have been reported as complications of HHV-6 reactivation.[314–316] Primary infections with self-limited clinical symptoms and asymptomatic reactivation have also been well documented in alloBMT recipients.[317]

SUMMARY

The epidemiology of infections in neutropenic cancer patients is complex and undergoes periodic changes. A number of factors influence the spectrum and severity of infection, including the underlying malignancy and associated immunologic deficits, geographic and local factors, the use of strategies such as chemoprophylaxis, the increasing use of catheters and other foreign objects, and the widening applications of hematopoietic stem cell transplantation. Newer, opportunistic pathogens will continue to emerge, and widespread resistance among bacterial, fungal, and viral pathogens will continue to be a significant problem. Constant vigilance, in order to detect epidemiologic shifts early, is essential. Rapid and more specific diagnostic methods need to be developed, along with less immunosuppressive and myelosuppressive antineoplastic treatment modalities. Until this happens, infections will continue to be a challenge in this unique group of patients.

REFERENCES

1. Zembower T, Epidemiology of infectious complications in cancer patients. *Cancer Treat Res* 1998; **96:** 33–75.
2. Pizzo PA, Management of fever in patients with cancer and treatment-induced neutropenia. *N Engl J Med* 1993; **328:** 1323–31.
3. Klastersky J, Science and pragmatism in the treatment and prevention of neutropenic infection. *J Antimicrob Chemother* 1998; **41**(Suppl D): 13–24.
4. Nucci M, Spector N, Bueno AP et al, Risk factors and attributable mortality associated with superinfections in neutropenic patients with cancer. *Clin Infect Dis* 1997; **24:** 575–9.
5. Engels EA, Ellis CA, Supran SE et al, Early infection in bone marrow transplantation: quantitative study of clinical factors that affect risk. *Clin Infect Dis* 1999; **28:** 256–66.
6. Paesmans M, Factors predicting mortality among febrile neutropenic cancer patients treated within a clinical trial: ten years experience by the EORTC International Antimicrobial Therapy Cooperative Group. In: *Proceedings of 3rd International Symposium on Febrile Neutropenia, Brussels, Belgium*, 1997: Abst 97.
7. Chanock SJ, Pizzo PA, Infectious complications of patients undergoing therapy for acute leukemia: current status and future prospects. *Semin Oncol* 1997; **24:** 132–40.
8. Jud B, Gmür J, Follath F, Art und Häufigkeit schwerer Infektkomplikationen bei der Behandlung akuter Leukämien. *Schweiz Med Wochenschr* 1994; **124:** 2060–3.
9. Gamis AS, Howells WB, de Swarte-Wallace J et al, Alpha-hemolytic streptococcal infection during intensive treatment for acute myeloid leukemia: a report from the children´s cancer

group study CCG-2891. *J Clin Oncol* 2000; **18:** 1845–55.
10. Seipelt G, Hofmann WK, Martin H et al, Comparison of toxicity and outcome in patients with acute myeloid leukemia treated with high-dose cytosine-arabinoside consolidation after induction with a regimen containing idarubicin or daunorubicin. *Ann Hematol* 1998; **76:** 145–51.
11. Auletta JJ, O'Riordan MA, Nieder ML, Infections in children with cancer: a continued need for the comprehensive physical examination. *J Pediatr Hematol Oncol* 1999; **21:** 501–8.
12. Rahiala J, Perkkio M, Riikonen P, Infections occurring during the courses of anticancer chemotherapy in children with ALL: a retrospective analysis of 59 patients. *Pediatr Hematol Oncol* 1998; **15:** 165–74.
13. Hurwitz CA, Silverman LB, Schorin MA et al, Substituting dexamethasone for prednisone complicates remission induction in children with acute lymphoblastic leukemia. *Cancer* 2000; **88:** 1964–9.
14. Hann I, Viscoli C, Paesmans M et al, A comparison of outcome from febrile neutropenic episodes in children compared with adults. Results from four EORTC studies. *Br J Haematol* 1997; **99:** 580–8.
15. Bow EJ, Infection risk and cancer chemotherapy: the impact of the chemotherapeutic regimen in patients with lymphoma and solid tissue malignancies. *J Antimicrob Chemother* 1998; **41**(Suppl D): 1–5.
16. Potter M, New anti-cancer therapies, new opportunities for infection. *Curr Opin Infect Dis* 1999; **12:** 359–63.
17. Morra E, Nosari A, Montillo M, Infectious complications in chronic lymphocytic leukaemia. *Hematol Cell Ther* 1999; **41:** 145–51.
18. Carlson JW, Fowler JM, Mitchell SK et al, Chemoprophylaxis with ciprofloxacin in ovarian cancer patients receiving paclitaxel: a randomized trial. *Gynecol Oncol* 1997; **65:** 325–9.
19. Hartlapp JH, Antimicrobial prophylaxis in immunocompromised patients. *Drugs* 1987; **34**(Suppl 1): 131–3.
20. Counsell R, Pratt J, Williams MV, Chemotherapy for germ cell tumors: prophylactic ciprofloxacin reduces the incidence of neutropenic fever. *Clin Oncol R Coll Radiol* 1994; **6:** 232–6.
21. Holland HK, Dix SP, Geller RB et al, Minimal toxicity and mortality in high-risk breast cancer patients receiving high-dose cyclophosphamide, thiotepa, and carboplatin plus autologous marrow/stem-cell transplantation and comprehensive supportive care. *J Clin Oncol* 1996; **14:** 1156–64.
22. Mossad SB, Longworth DL, Goormastic M et al, Early infectious complications in autologous bone marrow transplantation: a review of 219 patients. *Bone Marrow Transplant* 1996; **18:** 265–71.
23. Salazar R, Sola C, Maroto P et al, Infectious complications in 126 patients treated with high-dose chemotherapy and autologous peripheral blood stem cell transplantation. *Bone Marrow Transplant* 1999; **23:** 27–33.
24. Offidani M, Corvatta L, Olivieri A et al, Infectious complications after autologous peripheral blood progenitor cell transplantation followed by G-CSF. *Bone Marrow Transplant* 1999; **24:** 1079–87.
25. Seropian S, Nadkarni R, Jillela AP et al, Neutropenic infections in 100 patients with non-Hodgkin lymphoma or Hodgkin´s disease treated with high-dose BEAM chemotherapy and peripheral blood progenitor cell transplant: outpatient treatment is a viable option. *Bone Marrow Transplant* 1999; **23:** 599–605.
26. Eucker J, Sezer O, Metzner B et al, Factors influencing the rate of infectious complications in high-dose chemotherapy with autologous peripheral stem cell transplantation. *Support Care Cancer* 2000; **8:** 160 (Abst 61).
27. Herrmann RP, Trent M, Cooney J, Cannell PK, Infections in patients managed at home during autologous stem cell transplantation for lymphoma and multiple myeloma. *Bone Marrow Transplant* 1999; **24:** 1213–17.
28. Meisenberg B, Gollard R, Brehm T et al, Prophylactic antibiotics eliminate bacteremia and allow safe outpatient management following high-dose chemotherapy and autologous stem cell rescue. *Support Care Cancer* 1996; **4:** 364–9.
29. Westermann AM, Holtkamp MM, Linthorst GA et al, At home management of aplastic phase following high-dose chemotherapy with stem-cell rescue for hematological and non-hematological malignancies. *Ann Oncol* 1999; **10:** 511–17.
30. Mullen CA, Nair J, Sandesh S, Chan KW, Fever and neutropenia in pediatric hematopoietic

stem cell transplant patients. *Bone Marrow Transplant* 2000; **25:** 59–65.
31. Busca A, Saroglia EM, Giacchino M et al, Analysis of early infectious complications in pediatric patients undergoing bone marrow transplantation. *Support Care Cancer* 1999; **7:** 253–9.
32. van Burik JA, Weisdorf DJ, Infections in recipients of blood and marrow transplantation. *Hematol Oncol Clin North Am* 1999; **13:** 1065–89.
33. Oguma S, Yoshida Y, Uchino H et al, Infection in myelodysplastic syndromes before evolution into acute non-lymphoblastic leukemia. *Int J Hematol* 1994; **60:** 129–36.
34. Cunningham I, MacCallum SJ, Nicholls MD et al, The myelodysplastic syndromes: an analysis of prognostic factors in 226 cases from a single institution. *Br J Haematol* 1995; **90:** 602–6.
35. Higuchi T, Mori H, Niikura H et al, Prognostic implications in myelodysplastic syndromes: a review of 62 cases. *Leuk Lymphoma* 1996; **21:** 479–84.
36. Sievers EL, Dale DC, Non-malignant neutropenia. *Blood Rev* 1996; **10:** 95–100.
37. Hermans P, Sommereijns B, van Cutsem N, Clumeck N, Neutropenia in patients with HIV infection: a case control study in a cohort of 1403 patients between 1982 and 1993. *J Hematother Stem Cell Res* 1999; **8**(Suppl 1): S23–32.
38. Caperna J, Barber RE, Toerner JG, Mathews WC, Estimation of the effect of neutropenia on rates of clinical bacteremia in HIV-infected patients. *Epidemiol Infect* 1998; **120:** 71–80.
39. Cruciani M, Rampazzo R, Malena M et al, Prophylaxis with fluoroquinolones for bacterial infections in neutropenic patients: a meta-analysis. *Clin Infect Dis* 1996; **23:** 795–805.
40. Engels E, Lau J, Barza M, Efficacy of quinolone prophylaxis in neutropenic cancer patients: a meta-analysis. *J Clin Oncol* 1998; **16:** 1179–87.
41. International Antimicrobial Therapy Cooperative Group of the EORTC, Reduction of fever and streptococcal bacteremia in granulocytopenic patients with cancer. A trial of oral penicillin V or placebo combined with pefloxacin. *JAMA* 1994; **272:** 1183–9.
42. Bergmann OJ, Mogensen SC, Ellermann-Eriksen S, Ellegaard J, Acyclovir prophylaxis and fever during remission induction therapy of patients with acute myeloid leukemia: a randomized, double-blind, placebo-controlled trial. *J Clin Oncol* 1997; **15:** 2269–74.
43. Lopez A, Soler JA, Julia A et al, Prophylaxis with ciprofloxacin in postchemotherapy neutropenia in acute myeloid leukemia. *Med Clin Barc* 1994; **102:** 81–5.
44. Kern W, Kurrle E, Ofloxacin versus trimethoprim-sulfamethoxazole for infection prevention in acute leukemia. *Infection* 1991; **19:** 73–80.
45. Hidalgo M, Hornedo J, Lumbreras C et al, Lack of ability of ciprofloxacin–rifampin prophylaxis to decrease infection related morbidity in neutropenic patients given cytotoxic therapy and peripheral blood stem cell transplants. *Antimicrob Agents Chemother* 1997; **41:** 1175–7.
46. Gomez-Martin C, Sola C, Hornedo J et al, Rifampin does not improve the efficacy of quinolone antibacterial prophylaxis in neutropenic cancer patients: results of a randomized trial. *J Clin Oncol* 2000; **18:** 2126–34.
47. Ley BE, Linton CJ, Bennett DM et al, Detection of bacteremia in patients with fever and neutropenia using 16S rRNA gene amplification by polymerase reaction. *Eur J Clin Microbiol Infect Dis* 1998; **17:** 247–53.
48. De Bont ES, Vellenga E, Swaanenburg JC et al, Plasma IL-8 and IL-6 levels can be used to define a group with low risk of septicemia among cancer patients with fever and neutropenia. *Br J Haematol* 1999; **107:** 375–80.
49. Engel A, Mack E, Kern P, Kern WV, An analysis of interleukin-6, interleukin-8 and C-reactive protein serum concentrations to predict fever, gram-negative bacteremia and complicated infection in neutropenic cancer patients. *Infection* 1998; **26:** 213–19.
50. Yamakami Y, Hashimoto A, Yamagata E et al, Evaluation of PCR for detection of DNA specific for *Aspergillus* species in sera of patients with various forms of pulmonary aspergillosis. *J Clin Microbiol* 1998; **36:** 3619–23.
51. Hebart H, Löffler J, Meisner C et al, Early detection of *Aspergillus* infection after allogeneic stem cell transplantation by polymerase chain reaction screening. *J Infect Dis* 2000; **181:** 1713–19.
52. Skladny H, Buchheidt D, Baust C et al, Specific detection of *Aspergillus* species in blood and bronchoalveolar lavage samples of immunocompromised patients by two step PCR. *J Clin Microbiol* 1999; **37:** 1846–51.
53. Kern W, Kirchner S, Vanek E, Resin versus

standard blood culture medium used with the new BACTEC automated infrared system. An evaluation in febrile granulocytopenic patients. *Zentralbl Bakteriol* 1990; **273:** 156–63.

54. Rozdzinski E, Feldkamp M, Schmeiser T, Kern W, Evaluation of the BACTEC high volume resin blood culture media in febrile neutropenic patients. *Med Microbiol Lett* 1992; **1:** 213–19.
55. Freifeld A, Marchigiani D, Walsh T et al, A double-blind comparison of empirical oral and intravenous antibiotic therapy for low-risk febrile patients with neutropenia during cancer chemotherapy. *N Engl J Med* 1999; **341:** 305–11.
56. Kern WV, Cometta A, de Bock R et al, Oral versus intravenous empiric therapy for fever in patients with granulocytopenia who are receiving cancer chemotherapy. *N Engl J Med* 1999; **341:** 312–18.
57. Immunocompromised Host Society, The design, analysis and reporting of clinical trials on the empirical antibiotic management of the neutropenic patient. *J Infect Dis* 1990; **161:** 397–401.
58. Kiehn TE, Armstrong D, Changes in the spectrum of organisms causing bacteremia and fungemia in immunocompromised patients due to venous access devices. *Eur J Clin Microbiol Infect Dis* 1990; **9:** 869-872.
59. Gunther G, Bjorkholm M, Bjorklind A et al, Septicemia in patients with hematological disorders and neutropenia. A retrospective study of causative agents and their resistance profile. *Scand J Infect Dis* 1991; **23:** 589–98.
60. Zinner SH, Changing epidemiology of infections in patients with neutropenia and cancer: emphasis on Gram-positive and resistant bacteria. *Clin Infect Dis* 1999; **29:** 490–4.
61. Gonzalez-Barca E, Fernandez-Sevilla A, Carratala J et al, Prospective study of 288 episodes of bacteremia in neutropenic cancer patients in a single institution. *Eur J Clin Microbiol Infect Dis* 1996; **15:** 291–6.
62. Funada H, Matsuda T, Changes in the incidence and etiological patterns of bacteremia associated with acute leukemia over a 25-year period. *Intern Med* 1998; **37:** 1014–18.
63. Marie JP, Vekhoff A, Pico JL et al, Neutropenic infections: a review of the French Febrile Aplasia Study Group trials in 608 febrile neutropenuic patients. *J Antimicrob Chemother* 1998; **41**(Suppl D): 57–64.
64. Paganini H, Bologna R, Debbag R et al, Fever and neutropenia in children with cancer in one pediatric hospital in Argentina. *Pediatr Hematol Oncol* 1998; **15:** 405–13.
65. Wehl G, Allerberger F, Heitger A et al, Trends in infection morbidity in a pediatric oncology ward, 1986–1995. *Med Pediatr Oncol* 1999; **32:** 336–43.
66. Rolston KVI, Balakrishnan M, Elting L, Tarrand JJ, Is quantitative variation in cancer patients with bacteremic infections linked to severity of infection? In: *Proceedings of 40th Interscience Conference on Antimicrobial Agents and Chemotherapy*. Washington, DC: American Society for Microbiology, 2000: 473 (Abst 729).
67. Yuen KY, Woo PC, Hui CH, Unique risk factors for bacteraemia in allogeneic bone marrow transplant recipients before and after engraftment. *Bone Marrow Transplant* 1998; **21:** 1137–43.
68. Pagano L, Tacconelli E, Tumbarello M et al, Bacteremia in patients with hematological malignancies. Analysis of risk factors, etiological agents and prognostic indicators. *Haematologica* 1997; **82:** 415–19.
69. Viscoli C, Bruzzi P, Castagnola E, Factors associated with bacteremia in febrile granulocytopenic cancer patients. *Eur J Cancer* 1994; **30A:** 430–7.
70. Viscoli C, Paesmans M, Langenaeken J et al, Association between antifungal prophylaxis and occurrence of bacteremia in febrile netropenic cancer patients. In: *Proceedings of 37th Interscience Conference on Antimcrobial Agents and Chemotherapy*. Washington, DC: American Society for Microbiology, 1997; 380 (Abst LM-83).
71. Rackoff WR, Gonin R, Robinson C et al, Predicting the risk of bacteremia in children with fever and neutropenia. *J Clin Oncol* 1996; **14:** 919–24.
72. Klaassen RJ, Goodman TR, Pham B, Doyle JJ, Low-risk prediction rule for pediatric oncology patients presenting with fever and neutropenia. *J Clin Oncol* 2000; **18:** 1012–19.
73. Bernard L, Ferriere F, Casassus P et al, Procalcitonin as an early marker of bacterial infection in severely neutropenic febrile adults. *Clin Infect Dis* 1998; **27:** 914–15.
74. Engel A, Steinbach G, Kern P, Kern WV, Diagnostic value of procalcitonin serum levels in neutropenic patients with fever: comparison

with interleukin-8. *Scand J Infect Dis* 1999; **31:** 185–9.
75. Ruokonen E, Nousianen T, Pulkki K, Takala J, Procalcitonin concentrations in patients with neutropenic fever. *Eur J Clin Microbiol Infect Dis* 1999; **18:** 283–5.
76. Lehrnbecher T, Venzon D, de Haas M et al, Assessment of measuring circulating levels of interleukin-6, interleukin-8, C-reactive protein, soluble Fc-gamma receptor type III, and mannose-binding protein in febrile children with cancer and neutropenia. *Clin Infect Dis* 1999; **29:** 414–19.
77. Kern WV, Heiss M, Steinbach G, Prediction of gram-negative bacteremia in patients with cancer and febrile neutropenia by means of interleukin-8 levels in serum: targeting empirical monotherapy versus combination therapy. *Clin Infect Dis* 2001; **32:** 832–5.
78. Gonzalez-Barca E, Fernandez-Sevilla A, Carratala J et al, Prognostic factors influencing mortality in cancer patients with neutropenia and bacteremia. *Eur J Clin Microbiol Infect Dis* 1999; **18:** 539–44.
79. Aledo A, Heller G, Ren L et al, Septicemia and septic shock in pediatric patients: 140 consecutive cases on a pediatric hematology-oncology service. *J Pediatr Hematol Oncol* 1998; **20:** 215–21.
80. Kern W, Kurrle E, Schmeiser T, Streptococcal bacteremia in adult patients with leukemia undergoing aggressive chemotherapy. A review of 55 cases. *Infection* 1990; **18:** 138–45.
81. Elting LS, Rubenstein EB, Rolston KV, Bodey GP, Outcomes of bacteremia in patients with cancer and neutropenia: observations from two decades of epidemiological and clinical trials. *Clin Infect Dis* 1997; **25:** 247–59.
82. Carratala J, Roson B, Fernandez-Sevilla A et al, Bacteremic pneumonia in neutropenic patients with cancer: causes, empirical antibiotic therapy, and outcome. *Arch Intern Med* 1998; **158:** 868–72.
83. Link H, Maschmeyer G, Meyer P et al, Interventional antimicrobial therapy in febrile neutropenic patients. Study Group of the Paul Ehrlich Society for Chemotherapy. *Ann Hematol* 1994; **69:** 231–43.
84. Viscoli C, Castagnola E, Giacchino M et al, Bloodstream infections in children with cancer: a multicentre surveillance study of the Italian Association of Paediatric Haematology and Oncology. Supportive Therapy Group – Infectious Diseases Section. *Eur J Cancer* 1999; **35:** 770–4.
85. Bochud PY, Calandra T, Francioli P, Bacteremia due to viridans streptococci in neutropenic patients: a review. *Am J Med* 1994; **97:** 256–64.
86. Van der Lelie H, van Ketel RJ, von dem Borne AEGK et al, Incidence and clinical epidemiology of streptococcal septicemia during treatment of acute myeloid leukemia. *Scand J Infect Dis* 1991; **23:** 163–8.
87. Donnelly JP, Dompeling EC, Meis JF, de Pauw BE, Bacteremia due to oral viridans streptococci in neutropenic patients with cancer: cytostatics are a more important risk factor than antibacterial prophylaxis. *Clin Infect Dis* 1995; **20:** 469–70.
88. Richard P, Amador Del Valle G, Moreau P et al, Viridans streptococcal bacteraemia in patients with neutropenia. *Lancet* 1995: **345:** 1607–9.
89. Villablanca JG, Steiner M, Kersey J et al, The clinical spectrum of infections with viridans streptococci in bone marrow transplant patients. *Bone Marrow Transplant* 1990; **6:** 387–93.
90. Martino R, Subira M, Manteiga R et al, Viridans streptococcal bacteremia and viridans streptococcal shock syndrome in neutropenic patients: comparison between children and adults receiving chemotherapy or undergoing bone transplantation. *Clin Infect Dis* 1995; **20:** 476–7.
91. Martino R, Manteiga R, Sanchez I et al, Viridans streptococcal shock syndrome during bone marrow transplantation. *Acta Haematol* 1995; **94:** 69–73.
92. Ruescher T, Sodeifi A, Scrivani SJ et al, The impact of mucositis on alpha-hemolytic streptococcal infection in patients undergoing autologous bone marrow transplantation for hematologic malignancies. *Cancer* 1998; **82:** 2275–81
93. Bilgrami S, Feingold JM, Dorsky D et al, Streptococcus viridans bacteremia following autologous peripheral blood stem cell transplantation. *Bone Marrow Transplant* 1998; **21:** 591–5.
94. Engel A, Kern P, Kern WV, Cytokines and cytokine inhibitors in the neutropenic patient with α-streptococcal shock syndrome. *Clin Infect Dis* 1996; **23:** 785–9.
95. Carratala J, Alcaide F, Fernandez-Sevilla A et al, Bacteremia due to viridans streptococci that are

highly resistant to penicillin: increase among neutropenic patients with cancer. *Clin Infect Dis* 1995; **20:** 1169–73.
96. Bochud PY, Eggiman P, Calandra T et al, Bacteremia due to viridans streptococcus in neutropenic patients with cancer: clinical spectrum and risk factors. *Clin Infect Dis* 1994; **18:** 25–31.
97. Carratala J, Marron A, Fernandez-Sevilla A et al, Treatment of penicillin-resistant pneumococcal bacteremia in neutropenic patients with cancer. *Clin Infect Dis* 1997; **24:** 148–52.
98. Raad II, Bodey GP, Infectious complications of indwelling vascular catheters. *Clin Infect Dis* 1992; **15:** 197–210.
99. Raad I, Alrahwan A, Rolston K. *Staphylococcus epidermidis*. *Clin Infect Dis* 1998; **26:** 1182–7.
100. Nouwen JL, Wielenga JJ, van Overhagen H et al, Hickman catheter-related infections in neutropenic patients: insertion in the operating theater versus insertion in the radiology suite. *J Clin Oncol* 1999; **17:** 1304.
101. Castagnola E, Garaventa A, Viscoli C et al, Changing pattern of pathogens causing broviac catheter-related bacteraemias in children with cancer. *J Hosp Infect* 1995; **29:** 129–33.
102. Elishoov H, Or R, Strauss N, Engelhard D, Nosocomial colonization, septicemia and Hickman/Broviac catheter-realted infections in bone marrow transplant recipients. *Medicine* 1998; **77:** 83–101.
103. Groeger JS, Lucas AB, Thaler HAT et al, Infectious morbidity associated with long-term use of venous access devices in patients with cancer. *Ann Intern Med* 1993; **119:** 1168–74.
104. Lina B, Forey F, Troncy J et al, Oral source of *Staphylococcus epidermidis* septicemia in a neutropenic patient. *Eur J Clin Microbiol Infect Dis* 1994; **13:** 773–5.
105. Kennedy HF, Morrison D, Kaufmann ME et al, Origins of *Staphylococcus epidermidis* and *Streptococcus oralis* causing bacteraemia in a bone marrow transplant patient. *J Med Microbiol* 2000; **49:** 367–70.
106. Nouwen JL, van Belkum A, de Marie S et al, Clonal expansion of *Staphylococcus epidermidis* strains causing Hickman catheter-related infections in a hemato-oncologic department. *J Clin Microbiol* 1998; **36:** 2696–702.
107. Lyytikainen O, Valtonen V, Sivonen A et al, Molecular epidemiology of *Staphylococcus epidermidis* isolates in a hematological unit during a 4-month survey. *Scand J Infect Dis* 1995; **27:** 575–80.
108. Jones RN, Contemporary antimicrobial susceptibility patterns of bacterial pathogens commonly associated with febrile patients with neutropenia. *Clin Infect Dis* 1999; **29:** 495–502.
109. Feld R. Vancomycin as part of initial empirical antibiotic therapy for febrile neutropenia in patients with cancer: pros and cons. *Clin Infect Dis* 1999; **29:** 503–7.
110. Morrison VA, Peterson BA, Bloomfield CD, Nosocomial septicemia in the cancer patient: the influence of central venous access devices, neutropenia, and type of malignancy. *Med Pediatr Oncol* 1990; **18:** 209–16.
111. Escande MC, Herbrecht R, Prospective study of bacteraemia in cancer patients. Results of a French multicentre study. *Support Care Cancer* 1998; **6:** 273–80.
112. Rubio M, Palau L, Vivas JR et al, Predominance of Gram-positive microorganisms as a cause of septicemia in patients with hematological malignancies. *Infect Control Hosp Epidemiol* 1994; **15:** 101–4.
113. Gopal AK, Fowler VGJr, Shah M et al, Prospective analysis of *Staphylococcus aureus* bacteremia in nonneutropenic adults with malignancy. *J Clin Oncol* 2000; **18:** 1110–15.
114. Rolston KV, Tarrand JJ. *Pseudomonas aeruginosa* – still a frequent pathogen in patients with cancer: 11-year experience at a comprehensive cancer center. *Clin Infect Dis* 1999; **26:** 463–4.
115. Chatzinikolaou I, Abi-Said D, Bodey GP et al, Recent experience with *Pseudomonas aeruginosa* bacteremia in patients with cancer: Retrospective analysis of 245 episodes. *Arch Intern Med* 2000; **160:** 501–9.
116. Todeschini G, Franchini M, Tecchio C et al, Improved prognosis of *Pseudomonas aeruginosa* bacteremia in 127 consecutive neutropenic patients with hematologic malignancies. *Int J Infect Dis* 1998–99; **3:** 99–104.
117. Coullioud D, van der Auwera P, Viot M, Lasset C, Prospective multicentric study of the etiology of 1051 bacteremic episodes in 782 cancer patients. CEMIC (French–Belgian Study Club of Infectious Diseases in Cancer). *Support Care Cancer* 1993; **1:** 34–46.
118. Martinelli G, Alessandrino EP, Bernasconi P et al, Fournier´s gangrene: a clinical presentation

of necrotizing fasciitis after bone marrow transplantation. *Bone Marrow Transplant* 1998; **22:** 1023–6.

119. Kern W, Rozdzinski E, Schmeiser T et al, Emerging bacterial pathogens in patients with acute leukemia: viridans streptococci and non-fermentative gram-negative bacilli. In: *Acute Leukemias IV – Prognostic Factors and Treatment Strategies* (Büchner T, Hiddemann W, Wörmann B et al, eds). Berlin: Springer-Verlag, 1994: 795–8.
120. Martino R, Martinez C, Pericas R et al, Bacteremia due to glucose non-fermenting gram-negative bacilli in patients with hematological neoplasias and solid tumors. *Eur J Clin Microbiol Infect Dis* 1996; **15:** 610–15.
121. Martino R, Santamaria A, Munoz L et al, Bacteremia by Gram-negative bacilli in patients with hematologic malignancies. Comparison of the clinical presentation and outcome on infections by enterobacteria and non-glucose-fermenting Gram-negative bacilli. *Acta Haematol* 1999; **102:** 7–11.
122. Castagnola E, Conte M, Venzano P et al, Broviac catheter-related bacteraemias due to unusual pathogens in children with cancer: case reports with literature review. *J Infect* 1997; **34:** 215–18.
123. Williamson EC, Millar MR, Steward CG et al, Infections in adults undergoing unrelated donor bone marrow transplantation. *Br J Haematol* 1999; **104:** 560–8.
124. Micozzi A, Venditti M, Monaco M et al, Bacteremia due to *Stenotrophomonas maltophilia* in patients with hematologic malignancies. *Clin Infect Dis* 2000; **31:** 705–11.
125. Edmond MB, Riddler SA, Baxter CM et al, *Agrobacterium radiobacter*: a recently recognized opportunistic pathogen. *Clin Infect Dis* 1993; **16:** 388–91.
126. Hernandez JA, Martino R, Pericas R et al, *Achromobacter xylosoxidans* bacteremia in patients with hematologic malignancies. *Haematologica* 1998; **83:** 284–5.
127. Sader HS, Jones RN, Pfaller MA. Relapse of catheter-related *Flavobacterium meningosepticum* bacteremia demonstrated by DNA macrorestriction analysis. *Clin Infect Dis* 1995; **21:** 997–1000.
128. Hornei B, Luneberg E, Schmidt-Rotte H et al, Systemic infection of an immunocompromised patient with *Methylobacterium zatmanii*. *J Clin Microbiol* 1999; **37:** 248–50.
129. Fernandez M, Dreyer Z, Hockenberry-Eaton M, Baker CJ, *Methylobacterium mesophilica* as a cause of persistent bacteremia in a child with lymphoma. *Pediatr Infect Dis J* 1997; **16:** 1007–8.
130. Brown MA, Greene JN, Sandin RL et al, *Methylobacterium* bacteremia after infusion of contaminated autologous bone marrow. *Clin Infect Dis* 1996; **23:** 1191–2.
131. Duggan JM, Goldstein SJ, Chenoweth CE et al, *Achromobacter xylosoxidans* bacteremia: report of four cases and review of the literature. *Clin Infect Dis* 1996; **23:** 569–76.
132. Knippschild M, Schmid EN, Uppenkamp M et al, Infection by *Alcaligenes xylosoxidans* subsp. *xylosoxidans* in neutropenic patients. *Oncology* 1996; **53:** 258–62.
133. Kern WV, Oethinger M, Kaufhold A et al, *Ochrobactrum anthropi* bacteremia: report of four cases and short review. *Infection* 1993; **21:** 306–10.
134. Yu WL, Wang DY, Lin CW, Tsou MF, Endemic *Burkholderia cepacia* bacteraemia: clinical features and antimicrobial susceptibilities of isolates. *Scand J Infect Dis* 1999; **31:** 293–8.
135. Salazar R, Martino R, Sureda A et al, Catheter-related bacteremia due to *Pseudomonas paucimobilis* in neutropenic cancer patients: report of two cases. *Clin Infect Dis* 1995; **20:** 1573–4.
136. Bloch KC, Nadarajah R, Jacobs R, *Chryseobacterium meningosepticum*: an emerging pathogen among immunocompromised adults. Report of 6 cases and literature review. *Medicine* 1997; **76:** 30–41.
137. Labarca JA, Leber AL, Kern VL et al, Outbreak of *Stenotrophomonas maltophilia* bacteremia in allogenic bone marrow transplant patients: role of severe neutropenia and mucositis. *Clin Infect Dis* 2000; **30:** 195–7.
138. Klausner JD, Zukerman C, Limaye AP, Corey L, Outbreak of *Stenotrophomonas maltophilia* bacteremia among patients undergoing bone marrow transplantation: association with faulty replacement of handwashing soap. *Infect Control Hosp Epidemiol* 1999; **20:** 756–8.
139. Rogues AM, Sarlangue J, de Barbeyrac B et al, *Agrobacterium radiobacter* as a cause of pseudobacteremia. *Infect Control Hosp Epidemiol* 1999; **20:** 345–7.
140. Ezzedine H, Mourad M, van Ossel C et al, An

outbreak of *Ochrobactrum anthropi* bacteraemia in five organ transplant patients. *J Hosp Infect* 1994; **27:** 35–42.
141. Kappstein I, Grundmann H, Hauer T, Niemeyer C, Aerators as a reservoir of *Acinetobacter junii*: an outbreak of bacteraemia in paediatric oncology patients. *J Hosp Infect* 2000; **44:** 27–30.
142. Namnyak S, Hussain S, Davalle J et al, Contaminated lithium heparin bottles as a source of pseudobacteraemia due to *Pseudomonas fluorescens*. *J Hosp Infect* 1999; **41:** 23–8.
143. Hsueh PR, Teng LJ, Pan HJ et al, Outbreak of *Pseudomonas fluorescens* bacteremia among oncology patients. *J Clin Microbiol* 1998; **36:** 2914–17.
144. Chetoui H, Melin P, Struelens MJ et al, Common-source outbreak of *Burkholderia pickettii* bacteremia. *J Clin Microbiol* 1997; **35:** 1398–403.
145. Luk WK, An outbreak of pseudobacteraemia caused by *Burkholderia pickettii*: the critical role of an epidemiological link. *J Hosp Infect* 1996; **34:** 59–69.
146. Beebe JL, Koneman EK, Recovery of uncommon bacteria from blood: association with neoplastic disease. *Clin Microbiol Rev* 1995; **8:** 336–56.
147. Hoppe JE, Herter M, Aleksic S et al, Catheter-related *Rahnella aquatilis* bacteremia in a pediatric bone marrow transplant recipient. *J Clin Microbiol* 1993; **31:** 1911–12.
148. Thuler LC, Velasco E, de Souza-Martins CA et al, An outbreak of *Bacillus* species in a cancer hospital. *Infect Control Hosp Epidemiol* 1998; **19:** 856–8.
149. Christenson JC, Byington C, Korgenski EK et al, *Bacillus cereus* infections among oncology patients at a children's hospital. *Am J Infect Control* 1999; **27:** 543–6.
150. Musa MO, Al-Douri M, Khan S et al, Fulminant septicaemic syndrome of *Bacillus cereus*: three case reports. *J Infect* 1999; **39:** 154–6.
151. Arnaout MK, Tamburro RF, Bodner SM et al, *Bacillus cereus* causing fulminant sepsis and hemolysis in two patients with acute leukemia. *J Pediatr Hematol Oncol* 1999; **21:** 431–5.
152. Skiest DJ, Levi ME, Catheter-related bacteremia due to *Mycobacterium smegmatis*. *South Med J* 1998; **91:** 36–7.
153. Esteban J, Fernandez-Roblas R, Roman A et al, Catheter-related bacteremia due to *Mycobacterium aurum* in an immunocompromised host. *Clin Infect Dis* 1998; **26:** 496–7.
154. Moreno A, Llanos M, Gonzalez A, Batista N, *Mycobacterium fortuitum* bacteremia in an immunocompromised patient with a long-term venous catheter. *Eur J Clin Microbiol Infect Dis* 1996; **15:** 423–4.
155. Rodgers GL, Mortensen JE, Blecker-Shelly D et al, Two case reports and review of vascular catheter-associated bacteremia caused by nontuberculous *Mycobacterium* species. *Pediatr Infect Dis J* 1996; **15:** 260–4.
156. Holland DJ, Chen SC, Chew WW, Gilbert GL, *Mycobacterium neoaurum* infection of a Hickman catheter in an immunosuppressed patient. *Clin Infect Dis* 1994; **18:** 1002–3.
157. Levendoglu-Tugal O, Munoz J, Brudnicki A et al, Infections die to nontuberculous mycobacteria in children with leukemia. *Clin Infect Dis* 1998; **27:** 1227–30.
158. Vidal AM, Sarria JC, Kimbrough RC 3rd, Keung YK, Anaerobic bacteremia in a neutropenic patient with oral mucositis. *Am J Med Sci* 2000; **319:** 189–90.
159. Patel JB, Clarridge J, Schuster MS et al, Bacteremia caused by a novel isolate resembling *Leptotrichia* species in a neutropenic patient. *J Clin Microbiol* 1999; **37:** 2064–7.
160. Landsaat PM, van der Lelie H, Bongaerts G, Kuijper EJ, *Fusobacterium nucleatum*, a new invasive pathogen in neutropenic patients? *Scand J Infect Dis* 1995; **27:** 83–4.
161. Fruchart C, Salah A, Gray C et al, *Lactobacillus* species as emerging pathogens in neutropenic patients. *Eur J Clin Microbiol Infect Dis* 1997; **16:** 681–4.
162. Cooper CD, Vincent A, Greene JN et al, *Lactobacillus* bacteremia in febrile neutropenic patients. *Clin Infect Dis* 1998; **26:** 1247–8.
163. Valentine EG, Nontraumatic gas gangrene. *Ann Emerg Med* 1997; **30:** 109–111.
164. Maury S, Leblanc T, Rousselot P et al, Bacteremia due to *Capnocytophaga* species in patients with neutropenia: high frequency of beta-lactamase-producing strains. *Clin Infect Dis* 1999; **28:** 1172–4.
165. Kristensen B, Schonheyder HC, Peterslund NA et al, *Capnocytophaga* (*Capnocytophaga ochracea* group) bacteremia in hematological patients with profound granulocytopenia. *Scand J Infect Dis* 1995; **27:** 153–5.
166. Gruson D, Hilbert G, Pigneux A et al, Severe

infection caused by *Stomatococcus mucilaginosus* in a neutropenic patient: case report and review of the literature. *Hematol Cell Ther* 1998; **40:** 167–9.

167. Henwick S, Koehler M, Patrick CC, Complications of bacteremia due to *Stomatococcus mucilaginosus* in neutropenic children. *Clin Infect Dis* 1993; **17:** 667–71.
168. Goldman M, Chaudhary UB, Greist A, Fausel CA, Central nervous system infections due to *Stomatococcus mucilaginosus* in immunocompromised hosts. *Clin Infect Dis* 1998; **27:** 1241–6
169. Zinner SH, Changing epidemiology of infections in patients with neutropenia and cancer: emphasis on Gram-positive and resistant bacteria. *Clin Infect Dis* 1999; **29:** 490–4.
170. Kern WV, Andriof E, Oethinger M et al, Emergence of fluoroquinolone-resistant *Escherichia coli* at a cancer center. *Antimicrob Agents Chemother* 1994; **38:** 681–7.
171. Carratala J, Fernandez-Sevilla A, Tubau F et al, Emergence of quinolone-resistant *Escherichia coli* bacteremia in neutropenic patients with cancer who have received prophylactic norfloxacin. *Clin Infect Dis* 1995; **20:** 557–60.
172. Yeh SP, Hsueh EJ, Yu MS et al, Oral ciprofloxacin as antibacterial prophylaxis after allogeneic bone marrow transplantation: a reappraisal. *Bone Marrow Transplant* 1999; **24:** 1207–11.
173. Kern WV, Epidemiology of fluoroquinolone-resistant *Escherichia coli* among neutropenic cancer patients. *Clin Infect Dis* 1998; **27:** 235–7.
174. Carratala J, Fernandez-Sevilla A, Tubau F et al, Emergence of fluoroquinolone-resistant *Escherichia coli* in fecal flora of cancer patients receiving norfloxacin prophylaxis. *Antimicrob Agents Chemother* 1996; **40:** 503–5.
175. Van Kraaij MG, Dekker AW, Peters E et al, Emergence and infectious complications of ciprofloxacin-resistant *Escherichia coli* in haematological cancer patients. *Eur J Clin Microbiol Infect Dis* 1998; **17:** 591–2.
176. Perea S, Hidalgo M, Arcediano A et al, Incidence and clinical impact of fluoroquinolone-resistant *Escherichia coli* in the faecal flora of cancer patients treated with high dose chemotherapy and ciprofloxacin prophylaxis. *J Antimicrob Chemother* 1999; **44:** 117–20.
177. Martino R, Subira M, Altes A et al, Effect of discontinuing prophylaxis with norfloxacin in patients with hematologic malignancies and severe neutropenia. A matched case–control study of the effect on infectious morbidity. *Acta Haematol* 1998; **99:** 206–11.
178. Guerrini G, Calmaggi A, Sallaber S et al, Impact of different strategies to control antibiotic resistance in a oncohematological unit. *Clin Infect Dis* 2000; **31:** 283 (Abst 413).
179. Rolston KV, Elting L, Waguespack S et al, Survey of antibiotic susceptibility among Gram-negative bacilli at a cancer center. *Chemotherapy* 1996; **42:** 348–53.
180. Jacobson K, Rolston K, Elting L et al, Susceptibility surveillance among Gram-negative bacilli at a cancer center. *Chemotherapy* 1999; **45:** 325–34.
181. Ariffin H, Navaratnam P, Mohamed M et al, Ceftazidime-resistant *Klebsiella pneumoniae* bloodstream infection in children with febrile neutropenia. *Int J Infect Dis* 2000; **4:** 21–25.
182. Knowles S, Herra C, Devitt E et al, An outbreak of multiply resistant *Serratia marcescens*: the importance of persistent carriage. *Bone Marrow Transplant* 2000; **25:** 873–7.
183. Johnson MP, Ramphal R. β-lactam resistant *Enterobacter* bacteremia in febrile neutropenic patients receiving monotherapy. *J Infect Dis* 1990; **162:** 981–3.
184. Kapur D, Dorsky D, Feingold JM et al, Incidence and outcome of vancomycin-resistant enterococcal bacteremia following autologos peripheral blood stem cell transplantation. *Bone Marrow Transplant* 2000; **25:** 147–52.
185. Henning KJ, Delencastre H, Eagan J et al, Vancomycin-resistant *Enterococcus faecium* on a pediatric oncology ward: duration of stoll shedding and incidence of clinical infection. *Pediatr Infect Dis J* 1996; **15:** 848–54.
186. Bradley SJ, Wilson ALT, Allen MC et al, The control of hyperendemic glycopeptide-resistant *Enterococcus* spp. on a haematology unit by changing antibiotic usage. *J Antimicrob Chemother* 1999; **43:** 261–6.
187. Lisgaris MV, Hoyen C, Salata RA et al, An outbreak of vancomycin-resistant enterococcus colonization and bacteremia after a formulary change on an adults oncology unit. *Clin Infect Dis* 2000; **31:** 215 (Abst 20).
188. Zaas AK, Song X, Perl TM, Tucker PC, Nosocomial vancomycin-resistant enterococcal blood stream infection: development in oncol-

ogy patients colonized with vancomycin-resistant enterococci. *Clin Infect Dis* 2000; **31:** 278 (Abst 382).
189. Mannan G, Fuchs A, Molavi A et al, Vancomycin-resistant *Enterococcus faecium* bacteremia on an oncology unit from 1995–1999. *Clin Infect Dis* 2000; **31:** 278 (Abst 383).
190. Kirkpatrick BD, Harrington SM, Smith D et al, An outbreak of vancomycin-dependent *Enterococcus faecium* in a bone marrow transplant unit. *Clin Infect Dis* 1999; **29:** 1268–73.
191. Maschmeyer G, Link H, Hiddemann W et al, Pulmonary infiltrations in febrile patients with neutropenia. Risk factors and outcome under empirical antimicrobial therapy in a randomized multicenter study. *Cancer* 1994; **73:** 2296–304.
192. Ewig S, Glasmacher A, Ulrich B et al, Pulmonary infiltrates in neutropenic patients with acute leukemia during chemotherapy: outcome and prognostic factors. *Chest* 1998; **114:** 444–51.
193. Fernandez-Aviles F, Batlle M, Ribera JM et al, Pneumonias in patients with malignant hemopathies. Their etiology, response to treatment and prognostic factors in 69 patients (88 episodes). *Med Clin Barc* 1999; **112:** 321–5.
194. Gruson D, Hilbert G, Valentino R et al, Utility of fiberoptic bronchoscopy in neutropenic patients admitted to the intensive care unit with pulmonary infiltrates. *Crit Care Med* 2000; **28:** 2224–30.
195. Gruson D, Hilpert G, Portel L et al, Severe respiratory failure requiring ICU admission in bone marrow transplant recipients. *Eur Respir J* 1999; **13:** 883–7.
196. Sepkowitz KA, Brown AE, Telzak EE et al, *Pseumocystis carinii* pneumonia among patients without AIDS at a cancer hospital. *JAMA* 1992; **267:** 832–7.
197. Kulke MH, Vance EA, *Pneumocystis carinii* pneumonia in patients receiving chemotherapy for breast cancer. *Clin Infect Dis* 1997; **25:** 215–18.
198. Heinemann M, Kern WV, Bunjes D et al, Severe *Chlamydia pneumoniae* infection in patients with neutropenia: case reports and literature review. *Clin Infect Dis* 2000; **31:** 181–4.
199. Heussel CP, Kauczor HU, Heussel G et al, Early detection of pneumonia in febrile neutropenic patients: use of thin-section CT. *AJR* 1997; **169:** 1347–53.
200. Korones DN, Hussong MR, Gullace MA, Routine chest radiography of children with cancer hospitalized for fever and neutropenia: Is it really necessary? *Cancer* 1997; **80:** 1160–4.
201. Peterson DE, Research advances in oral mucositis. *Curr Opin Oncol* 1999; **11:** 261–6.
202. Nouwen JL, Wielenga JJ, van Overhagen H et al, Hickman catheter-related infections in neutropenic patients: insertion in the operating theater versus insertion in the radiology suite. *J Clin Oncol* 1999; **17:** 1304.
203. Stone S, Abdelmalak S, Laquaglia M et al, Central venous catheter infections among children with cancer. *Clin Infect Dis* 1999; **29:** 1045 (Abst 473).
204. Biffi R, de Braud F, Orsi F et al, Totally implantable central venous access ports for long-term chemotherapy. A prospective study analyzing complications and costs of 333 devices with a minimum follow-up of 180 days. *Ann Oncol* 1998; **9:** 767–73.
205. Astagneau P, Maugat S, Tran-Minh T et al, Long-term central venous catheter infection in HIV-infected and cancer patients: a multicenter cohort study. *Infect Control Hosp Epidemiol* 1999; **20:** 494–8.
206. Howell PB, Walters PE, Donowitz GR, Farr BM. Risk factors for infection of adult patients with cancer who have tunnelled central venous catheters. *Cancer* 1995; **75:** 1367–75.
207. Newman, KA, Reed WP, Schimpff SC et al, Hickman catheters in association with intensive cancer chemotherapy. *Support Care Cancer* 1993; **1:** 92–7.
208. Rotstein C, Brock L, Roberts RS, The incidence of first Hickman catheter-related infection and predictors of catheter removal in cancer patients. *Infect Control Hosp Epidemiol* 1995; **16:** 451–8.
209. Raad I, Davis S, Becker M et al, Low infection rate and long durability of nontunneled silastic catheters. A safe and cost-effective alternative for long-term venous access. *Arch Intern Med* 1993; **153:** 1791–6.
210. Rackoff WR, Ge J, Sather HN et al, Central venous catheter use and the risk of infection in children with acute lymphoblastic leukemia: a report from the Children´s Cancer Group. *J Pediatr Hematol Oncol* 1999; **21:** 260–7.
211. Sayfan J, Shoavi O, Koltun L, Benyamin N, Acute abdomen caused by neutropenic entero-

colitis: surgeon's dilemma. *Eur J Surg* 1999; **165:** 502–4.
212. Buyukasik Y, Ozcebe OI, Haznedaroglu IC et al, Neutropenic enterocolitis in adult leukemias. *Int J Hematol* 1997; **66:** 47–55.
213. Jain Y, Arya LS, Kataria R, Neutropenic enterocolitis in children with acute lymphoblastic leukemia. *Pediatr Hematol Oncol* 2000; **17:** 99–103.
214. Kouroussis C, Samonis G, Androulakis N et al, Successful conservative treatment of neutropenic enterocolitis complicating taxane-based chemotherapy: a report of five cases. *Am J Clin Oncol* 2000; **23:** 309–13.
215. Wade DS, Nava HR, Douglass HO Jr, Neutropenic enterocolitis. Clinical diagnosis and treatment. *Cancer* 1992; **69:** 17–23.
216. Song HK, Kreisel D, Canter R et al, Changing presentation and management of neutropenic enterocolitis. *Arch Surg* 1998; **133:** 979–82.
217. Baerg J, Murphy JJ, Anderson R, Magee JF, Neutropenic enteropathy: a 10-year review. *J Pediatr Surg* 1999; **34:** 1068–71.
218. Gomez L, Martino R, Rolston KV, Neutropenic enterocolitis. *Clin Infect Dis* 1998; **27:** 695–9.
219. Coleman N, Speirs G, Khan J et al, Neutropenic enterocolitis associated with *Clostridium tertium*. *J Clin Pathol* 1993; **46:** 180–3.
220. Bilgrami S, Feingold JM, Dorsky D et al, Incidence and outcome *of Clostridium difficile* infection following autologous peripheral blood stem cell transplantation. *Bone Marrow Transplant* 1999; **23:** 1039–42.
221. Schuller I, Saha V, Lin L et al, Investigation and management of *Clostridium difficile* colonisation in a paediatric oncology unit. *Arch Dis Child* 1995; **72:** 219–22.
222. Husain A, Aptaker L, Spriggs DR, Barakat RR, Gastrointestinal toxicity and *Clostridium difficile* diarrhea in patients treated with paclitaxel-containing chemotherapy regimens. *Gynecol Oncol* 1998; **71:** 104–7.
223. Gorschlüter M, Glasmacher A, Hahn C et al, *Clostridium difficile* infections in neutropenic patients. *Onkologie* 2000; **23**(Suppl 7): 165 (Abst 629).
224. Alangaden GJ, Jamma K, Chandrasekar PH et al, *Clostridium difficile* associated diarrhea during hemopoietic stem cell transplantation. *Clin Infect Dis* 2000; **31:** 280.
225. Lew MA, Kehoe K, Ritz J et al, Ciprofloxacin versus trimethoprim/sulfamethoxazole for prophylaxis of bacterial infections in bone marrow transplant recipients: a randomized, controlled trial. *J Clin Oncol* 1995; **13:** 239–50.
226. Roghmann MC, McCarter RJ Jr, Brewrink J et al, *Clostridium difficile* infection is a risk factor for bacteremia due to vancomycin-resistant enterococci (VRE) in VRE-colonized patients with acute leukemia. *Clin Infect Dis* 1997; **25:** 1056–9.
227. Boone N, Eagan JA, Gillern P et al, Evaluation of an interdisciplinary re-isolation policy for patients with previous *Clostridium difficile* diarrhea. *Am J Infect Control* 1998; **26:** 584–7.
228. Hornbuckle K, Chak A, Lazarus HM et al, Determination and validation of a predictive model for *Clostridium difficile* diarrhea in hospitalized oncology patients. *Ann Oncol* 1998; **9:** 307–11.
229. Buyukasik Y, Ozcebe OI, Sayinalp N et al, Perianal infections in patients with leukemia: importance of the course of neutrophil count. *Dis Colon Rectum* 1998; **41:** 81–5.
230. Cohen JS, Paz IB, O'Donnell MR, Ellenhorn JD, Treatment of perianal infection following bone marrow transplantation. *Dis Colon Rectum* 1996; **39:** 981–5.
231. Harousseau JL, Dekker AW, Stamatoullas-Bastard A et al, Itraconazole oral solution for primary prophylaxis of fungal infections in patients with hematological malignancy and profound neutropenia: a randomized, double-blind, double-placebo, multicenter trial comparing itraconazole and amphotericin B. *Antimicrob Agents Chemother* 2000; **44:** 1887–93.
232. Menichetti F, Del Favero A, Martino P et al, Itraconazole oral solution as prophylaxis for fungal infections in neutropenic patients with hematologic malignancies: a double-blind, multicenter trial. *Clin Infect Dis* 1999; **28:** 250–5.
233. Nucci M, Biasoli I, Akiti T et al, A double-blind, randomized, placebo-controlled trial of itraconazole capsules as antifungal prophylaxis for neutropenic patients. *Clin Infect Dis* 2000; **30:** 300–5.
234. Winston DJ, Chandrasekar PH, Lazarus HM et al, Fluconazole prophylaxis of fungal infections in patients with acute leukemia. Results of a randomized placebo-controlled, double-blind, multicenter trial. *Ann Intern Med* 1993; **118:** 495–503.
235. Slavin M, Osborne B, Adams R et al, Efficacy

and safety of fluconazole prophylaxis for fungal infections after marrow transplantation – a prospective, randomized, double-blind study. *J Infect Dis* 1995; **171:** 1545–52.

236. Goodman JL, Winston DJ, Greenfield RA et al, A controlled trial of fluconazole to prevent fungal infections in patients undergoing bone marrow transplantation. *N Engl J Med* 1992; **326:** 845–51.
237. Rotstein C, Bow EJ, Laverdiere M et al, Randomized placebo-controlled trial of fluconazole prophylaxis for neutropenic cancer patients: benefit based on purpose and intensity of cytotoxic therapy. The Canadian Fluconazole Prophylaxis Study Group. *Clin Infect Dis* 1999; **28:** 331–40.
238. Musa MO, Aleisa, A, Halim M et al, the spectrum of *Fusarium* infection in immunocompromised patients with haematological malignancies and in non-immunocompromised patients: a single institution experience over 10 years. *Br J Haematol* 2000; **108:** 544–8.
239. Krcmery VJr, Jesenska Z, Spanik S et al, Fungemia due to *Fusarium* spp. in cancer patients. *J Hosp Infect* 1997; **36:** 223–8.
240. Kontoyiannis DP, Wessel VC, Bodey GP, Rolston KVI, Zygomycosis in the 1990s in a tertiary-care cancer center. *Clin Infect Dis* 2000; **30:** 851–6.
241. Ribes JA, Vanover-Sams CL, Baker DJ, Zygomycetes in human disease. *Clin Microbiol Rev* 2000; **13:** 236–301.
242. Kwon-Chung KL, Bennett JE, *Medical Mycology: Infections Due to* Trichosporon *and Other Miscellaneous Yeast-Like Fungi*. Philadelphia: Lee & Febiger, 1992.
243. Tashiro T, Nagai H, Nagaoka H et al, *Trichosporon beigelii* pneumonia in patients with hematologic malignancies. *Chest* 1995; **108:** 190–5.
244. Krcmery VJr, Mateicka F, Kunova A et al, Hematogenous trichsporonosis in cancer patients: report of 12 cases including 5 during prophlyaxis with itraconazole. *Support Care Cancer* 1999; **7:** 39–43.
245. Meis JF, Ruhnke M, de Pauw BE et al, *Candida dubliniensis* candidemia in patients with chemotherapy-induced neutropenia and bone marrow transplantation. *Emerg Infect Dis* 1999; **5:** 150–3.
246. D´Antonio D, Violante B, Mazzoni A et al, A nosocomial cluster of *Candida inconspicua* infections in patients with hematological malignancies. *J Clin Microbiol* 1998; **36:** 792–5.
247. Orth B, Frei R, Itin PH et al, Outbreak of inavsive mycoses caused by *Paecilomyces lilacinus* from a contaminated skin lotion. *Ann Intern Med* 1996; **125:** 799–806.
248. Burgner D, Eagles G, Burgess M et al, Disseminated infection due to *Metarrhizium anisopliae* in an immunocompromised child. *J Clin Microbiol* 1998; **36:** 1146–50.
249. Brown NM, Blundell EL, Chown SR et al, *Acremonium* infection in a neutropenic patient. *J Infect* 1992; **25:** 73–6.
250. De Batlle J, Motje M, Balanza R et al, Disseminated infection caused by *Scedosporium prolificans* in a patient with acute multilineal leukemia. *J Clin Microbiol* 2000; **38:** 1694–5.
251. Kontoyianis DP, Vartivarian S, Anaissie EJ et al, Infections due to *Cunninghamella bertholletiae* in patients with cancer: report of three cases and review. *Clin Infect Dis* 1994; **18:** 925–8.
252. Richter S, Cormican MG, Pfaller MA et al, Fatal disseminated *Trichoderma longibrachiatum* infection in an adult bone marrow transplant patient: species identification and review of the literature. *J Clin Microbiol* 1999; **37:** 1154–60.
253. Verweij PE, van Kasteren M, van de Nes J et al, Fatal pulmonary infection caused by the basidiomycete *Hormographiella aspergillata*. *J Clin Microbiol* 1997; **35:** 2675–8.
254. Mok T, Koehler AP, Yu MY et al, Fatal *Penicillium citrinum* pneumonia with pericarditis in a patient with acute leukemia. *J Clin Microbiol* 1997; **35:** 2654–6.
255. Abi-Said D, Anaissie E, Uzon O et al, The epidemiology of hematogenous candidiasis caused by different Candida species. *Clin Infect Dis* 1997; **24:** 1122–8.
256. Guiot HF, Fibbe WE, van 't Wout JW. Risk factors for fungal infection in patients with malignant hematologic disorders: implications for empirical therapy and prophylaxis. *Clin Infect Dis* 1994; **18:** 525–32.
257. Richet HM, Andremont A, Tancrede C et al, Risk factors for candidemia in patients with acute lymphocytic leukemia. *Rev Infect Dis* 1991; **13:** 211–15.
258. Pagano L, Antinori A, Ammassari A et al, Retrospective study of candidemia in patients with hematological malignancies. Clinical fea-

tures, risk factors and outcome of 76 episodes. *Eur J Haematol* 1999; **63:** 77–85.
259. Marr KA, Seidel K, White TC et al, Candidemia in allogeneic blood and marrow transplant recipients: evolution of risk factors after the adoption of prophylactic fluconazole. *J Infect Dis* 2000; **181:** 309–16.
260. Viscoli C, Girmenia C, Marinus A et al, Candidemia in cancer patients: a prospective, multicenter surveillance study by the Invasive Fungal Infection Group of the European Organization for Research and Treatment of Cancer (EORTC). *Clin Infect Dis* 1999; **28:** 1071–9.
261. Anaissie EJ, Rex JH, Uzun O, Vartivarian S, Predictors of adverse outcome in cancer patients with candidemia. *Am J Med* 1998; **104:** 238–45.
262. Meunier F, Aoun M, Bitar N, Candidemia in immunocompromised patients. *Clin Infect Dis* 1991; **14**(Suppl 1): S120–5.
263. Goodrich JM, Reed EC, Mori M et al, Clinical features and analysis of risk factors for invasive candidal infection after marrow transplantation. *J Infect Dis* 1991; **164:** 731–40.
264. Ribeiro S, Sousa AB, Nunes O et al, Candidemia in acute leukemia patients. *Support Care Cancer* 1997; **5:** 249–51.
265. Bodey GP, Anaissie EJ, Chronic systemic candidiasis. *Eur J Clin Microbiol Infect Dis* 1989; **8:** 855–7.
266. Anttila VJ, Elonen E, Nordling S et al, Hepatosplenic candidiasis in patients with acute leukemia: incidence and prognostic implications. *Clin Infect Dis* 1997; **24:** 375–80.
267. Martino R, Sureda A, Brunet S, Disseminated candidiasis in patients with acute leukemia. *Clin Infect Dis* 1998; **26:** 245–6.
268. Bodey GP, Luna MA, Disseminated candidiasis in patients with acute leukemia: two diseases. *Clin Infect Dis* 1998; **27:** 238.
269. Fridkin SK & Jarvis WR, Epidemiology of nosocomial fungal infections. *Clin Microbiol Rev* 1996; **9:** 499–511.
270. Vandenbergh MFG, Verweij PE, Voss A, Epidemiology of nosocomial fungal infections: invasive aspergillosis and the environment. *Diagn Microbiol Infect Dis* 1999 ; **34:** 221–7.
271. Warnock DW, Fungal infection in neutropenia: current problem and chemotherapeutic control. *J Antimicrob Chemother* 1998; **41:** 95–105
272. Latgé JP, *Aspergillus fumigatus* and aspergillosis. *Clin Microbiol Rev* 1999; **12:** 310–50.
273. O'Donnell MR, Schmidt GM, Tegtmeier BR et al, Prediction of systemic fungal infection in allogeneic marrow recipients. Impact of amphotericin prophylaxis in high risk patients. *J Clin Oncol* 1994; **12:** 827–34.
274. Sparrelid E, Hagglund H, Remberger M et al, Bacteraemia during the aplastic phase after allogeneic bone marrow transplantation is associated with early death from invasive fungal infection. *Bone Marrow Transplant* 1998; **22:** 795–800.
275. Wahiduzzaman M, Chandrasekar PH, Alangaden GJ, High frequency of Gram-negative bacterial pneumonia in bone marrow/stem cell transplant recipients with graft-versus-host disease and pulmonary aspergillosis. *Clin Infect Dis* 1999; **29:** 1014 (Abst 296).
276. Wald A, Leisenring W, van Burik JA, Bowden RA, Epidemiology of *Aspergillus* infections in a large cohort of patients undergoing bone marrow transplantation. *J Infect Dis* 1997; **175:** 1459–66.
277. Denning DA, Invasive aspergillosis. *Clin Infect Dis* 1998; **26:** 781–805.
278. Girardin H, Sarfati J, Traore F et al, Molecular epidemiology of nosocomial invasive aspergillosis. *J Clin Microbiol* 1994; **32:** 684–90.
279. Chazalet V, Debeaupuis JP, Sarfati J et al, Molecular typing of environmental and patient isolates of *Aspergillus fumigatus* from various hospital settings. *J Clin Microbiol* 1998; **36:** 1494–500.
280. Leenders ACAP, van Belkum A, Behrendt M et al, Density and molecular epidemiology of *Aspergillus* in air and relationship to outbreaks of aspergillus infection. *J Clin Microbiol* 1999; **37:** 1752–7
281. Arnow PM, Sadigh M, Costas C et al, Endemic and epidemic aspergillosis associated with in-hospital replication of *Aspergillus* organisms. *J Infect Dis* 1991; **164:** 998–1002.
282. Thio CL, Smith D, Merz WG et al, Refinements of environmental assessments during an outbreak investigation of invasive aspergillosis in a leukemia and bone marrow transplant unit. *Infect Control Hosp Epidemiol* 2000; **21:** 18–23.
283. Withington S, Chambers ST, Beard ME et al, Invasive aspergillosis in severely neutropenic patients over 18 years: impact of intranasal

amphotericin B and HEPA filtration. *J Hosp Infect* 1998; **38:** 11–18.
284. Manuel RJ, Kibbler CC, The epidemiology and prevention of invasive aspergillosis. *J Hosp Infect* 1998; **39:** 95–109.
285. Anaissie EJ, Stratton SL, Summerbell RC et al, *Aspergillus* species aerosols in hospitals: showering as a potential mode of exposure. In: *Proceedings of 39th Interscience Conference on Antimicrobial Agents and Chemotherapy, San Francisco.* Washington, DC: American Society for Microbiology, 1999: 579 (abst).
286. Warris A, Gaustad P, Meis J et al, Water as a source of filamentous fungi in a childhood bone marrow transplantation unit. In: *Proceedings of 39th Interscience Conference on Antimicrobial Agents and Chemotherapy, San Francisco.* Washington DC: American Society for Microbiology, 1999: 579 (abst).
287. Abbasi S, Shenep JL, Hughes WT et al, Aspergillosis in children with cancer: a 34-year experience. *Clin Infect Dis* 1999; **29:** 1210–19.
288. Denning DW, Marinus A, Cohen J et al, An EORTC multicentre prospective survey of invasive aspergillosis in haematological patients: diagnosis and therapeutic outcome. *J Infect* 1998; **37:** 173–80.
289. Pagano L, Ricci P, Montillo M et al, Localization of aspergillosis to the central nervous system among patients with acute leukemia: report of 14 cases. Gruppo Italiano Malattie Ematologiche dell'Adulto Infection Program. *Clin Infect Dis* 1996; **23:** 628–30.
290. Ribaud P, Chastang C, Latge JP et al, Survival and prognostic factors of invasive aspergillosis after allogeneic bone marrow transplantation. *Clin Infect Dis* 1999; **28:** 322–30.
291. Martino R, Nomededéu J, Altés A et al, Successful bone marrow transplantation in patients with previous invasive fungal infections: report of four cases. *Bone Marrow Transplant* 1994; **13:** 265–9.
292. Offner F, Cordonnier C, Ljungman P et al, Impact of previous aspergillosis on the outcome of bone marrow transplantation. *Clin Infect Dis* 1998; **26:** 1098–103.
293. Caillot D, Casasnovas O, Bernard A et al, Improved management of invasive pulmonary aspergillosis in neutropenic patients using early thoracic computed tomographic scan and surgery. *J Clin Oncol* 1997; **15:** 139–47.
294. Blum U, Windfuhr M, Buitrago-Tellez C et al, Invasive pulmonary aspergillosis. MRI, CT, and plain radiographic findings and their contribution for early diagnosis. *Chest* 1994; **106:** 1156–61.
295. Wood MJ, Viral infections in neutropenia – current problems and chemotherapeutic control. *J Antimicrob Chemother* 1998; **41**(Suppl D): 81–93.
296. Tinchon C, Auner H, Linkesch W, EBV-associated lymphoproliferative disease after therapy with fludarabine in AML. *Onkologie* 2000; **23**(Suppl 7): 163 (Abst 623).
297. Holmberg LA, Boeckh M, Hooper H et al, Increased incidence of cytomegalovirus disease after autologous CD34-selected peripheral blood stem cell transplantation. *Blood* 1999; **94:** 4029–35.
298. Aslan T, Fassas AB, Desikan R et al, Patients with multiple myeloma may safely undergo autologous transplantation despite ongoing RSV infection and no ribavirin therapy. *Bone Marrow Transplant* 1999; **24:** 505–9.
299. Fouillard L, Mouthon L, Laporte JP et al, Severe respiratory syncytial virus pneumonia after autologous bone marrow transplantation: a report of three cases and review. *Bone Marrow Transplant* 192; **9:** 97–100.
300. Harrington RD, Hooton TM, Hackman RC et al, An outbreak of respiratory syncytial virus in a bone marrow transplant center. *J Infect Dis* 1992; **165:** 987–93.
301. Whimbey E, Couch RB, Englund JA et al, Respiratory syncytial virus pneumonia in hospitalized adult patients with leukemia. *Clin Infect Dis* 1995; **21:** 376–9.
302. Vettenranta K, Ukkonen P, Saarinen UM, RSV infection complicating the therapy of pediatric malignancies: report of six cases. *Med Pediatr Oncol* 1996; **26:** 261–3.
303. Bergmann OJ, Ellermann-Eriksen S, Mogensen SC, Ellegaard J, Acyclovir given as prophylaxis against oral ulcers in acute myeloid leukaemia: randomised, double blind, placebo controlled trial. *BMJ* 1995; **310:** 1169–72.
304. Lönnqvist B, Palmblad J, Ljungman P et al, Oral acyclovir as prophylaxis for bacterial infections during induction therapy for acute leukaemia in adults. *Support Care Cancer* 1993; **1:** 139–44.
305. Limaye AP, Bowden RA, Myerson D, Boeckh M, Cytomegalovirus disease occurring before engraftment in marrow transplant recipients. *Clin Infect Dis* 1997; **24:** 830–5.

306. Van den Brande J, Schrijvers D, Colpaert C, Vermorken JB, Cytomegalovirus colitis after administration of docetaxel–5-fluorouracil–cisplatin chemotherapy for locally advanced hypopharyngeal cancer. *Ann Oncol* 1999; **10:** 1369–72.
307. Nagafuji K, Eto T, Hayashi S et al, Fatal cytomegalovirus interstitial pneumonia following autologous peripheral blood stem cell transplantation. *Bone Marrow Transplant* 1998; **21:** 301–3.
308. Peters WP, Ross M, Vredenburgh JJ et al, High-dose chemotherapy and autologous bone marrow support as consolidation after standard-dose adjuvant therapy for high-risk primary breast cancer. *J Clin Oncol* 1993; **11:** 1132–43.
309. Poulsen A, Schmiegelow K, Yssing M. Veraicella zoster infections in children with acute lymphoblastic leukemia. *Pediatr Hematol Oncol* 1996; **13:** 231–8.
310. Rowland P, Wald ER, Mirro JR Jr et al, Progressive varicella presenting with pain and minimal skin involvement in children with acute lymphonblastic leukemia. *J Clin Oncol* 1995; **13:** 1697–703.
311. Ohyashiki JH, Abe K, Ojima T et al, Quantification of human herpesvirus-6 in healthy volunteers and patients with lymphoproliferative disorders by PCR–ELISA. *Leuk Res* 1999; **23:** 625–30.
312. Gautheret-Dejean A, Dejean O, Vastel L et al, Human herpesvirus-6 and human herpesvirus-7 in the bone marrow from healthy subjects. *Transplantation* 2000; **69:** 1722–3.
313. Michalek J, Horvath R, Benedik J, Hrstkova H, Human herspesvirus-6 infection in children with cancer. *Pediatr Hematol Oncol* 1999; **16:** 423–30.
314. Johnston RE, Geretti AM, Prentice HG et al, HHV-6-related secondary graft failure following allogeneic bone marrow transplantation. *Br J Haematol* 1999; **105:** 1041–5.
315. Wang FZ, Linde A, Hagglund H et al, Human herpesvirus-6 DANN in cerebrospinal fluid specimens from allogeneic bona marrow transplant patients: Does it have clinical significance? *Clin Infect Dis* 1999; **28:** 562–8.
316. Singh N, Paterson DL, Encephalitis caused by human herpesvirus-6 in transplant recipients: relevance of a novel neurotropic virus. *Transplantation* 2000; **69:** 2474–9.
317. Cone RW, Huang ML, Corey L et al, Human herpesvirus-6 infections after bone marrow transplantation: clinical and virologic manifestations. *J Infect Dis* 1999; **179:** 311–18.

5

Infections in patients with solid tumors

Kenneth VI Rolston

INTRODUCTION

Patients with cancer develop infection far more often than individuals without cancer.[1] The function of the immune system is a major factor in determining the frequency and nature of infection, and the overall response to therapy, once an infection has developed. Patients with hematologic malignancies or aplastic anemia and those receiving immunosuppressive therapy following bone marrow transplantation often have prolonged periods of neutropenia, defects in phagocytosis, and impaired cellular and/or humoral immunity – each associated with an increased frequency and a distinct spectrum of infection. In contrast, most patients with solid tumors are not significantly immunosuppressed, but are predisposed towards infection as a result of damage to normal anatomic barriers such as the skin and mucosal surfaces, obstructive phenomena (e.g. lung carcinoma and biliary and pancreatic tumors), procedures such as surgery and radiation, central nervous system dysfunction, and the use of medical devices such as shunts, catheters, and prostheses. Although chemotherapy-induced neutropenia does occur in patients with solid tumors, it is often short-lived, does not have the same impact as it does in patients with hematologic malignancies, and is associated with a lower frequency or risk of developing infection.

Infections in patients with hematologic malignancies and in bone marrow transplant recipients have been studied in great detail, and many of the principles for the management of infections in cancer patients have been developed in this patient population.[2] However, solid tumors account for the vast majority of cancers in adults. Data published by the American Cancer Society indicate that approximately 1.14 million new cases of solid tumors are diagnosed each year in the USA.[3] The spectrum, clinical features, diagnosis, and management of infection in these patients is substantially different, and treatment strategies specific for these patients need to be developed. This chapter will review various aspects of infections that occur commonly in, or are unique to, patients with solid tumors.

RISK FACTORS FOR INFECTION

Several factors contribute to the risk of infection in patients with solid tumors. The presence of multiple risk factors in the same patient is not uncommon, and contributes towards increased risk. These factors are summarized in Table 5.1 and include neutropenia, disruption of normal

Table 5.1 Risk factors predisposing towards infection in patients with solid tumors[a]

Risk factor(s)	Additional comments
Neutropenia	Antineoplastic chemotherapy, radiation therapy, infiltration of bone marrow with tumor, other agents (ganciclovir)
Disruption of normal anatomic barriers	Chemotherapy (mucositis), radiation therapy, diagnostic or therapeutic surgical procedures, catheters and other devices
Obstruction	Primary or metastatic tumor
Airways	Post-obstructive pneumonia/lung abscess/empyema
Biliary tract	Ascending cholangitis
Urinary tract	Urinary tract infection/prostatitis
Bowel	Bowel obstruction/perforation, peritonitis/hemorrhage
Procedures and devices	
Vascular access catheters	Catheter-related infection
Shunts	Shunt infection
Prosthetic devices	Infected prosthesis
Diagnostic/therapeutic surgery	Local/disseminated infection
Miscellaneous factors	
Loss of gag reflex/cord compression	Central nervous system, tumors → aspiration, impaired micturition → urinary tract infections
Age, malnutrition, antibiotic usage	Increased risk and severity of infection, selection of resistant pathogens

[a] Multiple factors in the same patient increase the risk of infection.

anatomic barriers, obstruction, procedures and devices employed in therapy of the tumor, as well as a number of other factors.

Neutropenia

Neutropenia is induced most often by antineoplastic chemotherapy. Varying degrees of neutropenia are also seen after radiation therapy, after the administration of agents such as ganciclovir, and occasionally after extensive infiltration of the marrow by tumor. Unlike patients with hematologic malignancies, patients with solid tumors usually have normally functioning neutrophils, and conventional chemotherapy rarely produces severe neutropenia that lasts for more than 7–10 days.[4] Thus the 'at-risk' period is generally short, and many solid tumor patients who develop a febrile episode while

they are neutropenic are considered 'low-risk' (see Chapter 8).

Disruption of normal anatomic barriers

Normal anatomic barriers, which include intact skin, oropharyngeal, respiratory, gastrointestinal, and genitourinary mucosal surfaces, provide an important defense mechanism against invasion by microorganisms. Cancer chemotherapy often damages mucosal surfaces, increasing the risk of infections caused by organisms that colonize these surfaces. Agents that are particularly prone to causing mucositis include chlorambucil, cisplatin, cytarabine (cytosine arabinoside, Ara-C), doxorubicin (Adriamycin), 5-fluorouracil (5-FU), and methotrexate. Damage to mucosal barriers can also be caused by radiation therapy, surgical procedures, and the use of medical devices. When such patients are hospitalized, the risk of acquiring serious nosocomial infections (often caused by multidrug-resistant microorganisms) increases. (See Chapter 1.)

Obstruction

Obstruction caused by rapidly expanding primary or metastatic lesions is fairly common in patients with solid tumors. Bronchogenic carcinomas (or metastatic pulmonary lesions) often cause partial airway obstruction, leading to the development of post-obstructive pneumonia. Empyema may occasionally complicate post-obstructive pneumonia. Biliary tract obstruction in patients with hepatobiliary pancreatic tumors results in ascending cholangitis. Ureteral obstruction resulting in urinary tract infection is seen in patients with carcinoma of the cervix, whereas ureteral obstruction causing urinary tract infection and/or prostatitis is seen in patients with carcinoma of the prostate. In all these situations, mixed or polymicrobial infections are common, and the etiologic agents are generally those that colonize the site of obstruction.

Procedures and devices

Surgery, medical procedures, radiation therapy, and the widespread use of catheters and other devices (shunts, stents, prostheses) are often associated with the development of infection. The use of multiple-lumen vascular access catheters (e.g. Hickman or Broviac catheters) has become commonplace, and greatly facilitates the drawing and/or administration of blood or blood products, and the administration of chemotherapy or antimicrobial agents and other supportive medications. Infection is the major complication associated with these catheters. The organisms causing catheter-related infections are listed below in Table 5.3 (see Chapter 10). Approximately 80% are Gram-positive, with *Staphylococcus* spp. being predominant. Urinary catheters are used frequently when obstruction or urinary incontinence is present. Local involvement of the bladder or ureters with the malignancy often requires the creation of surgical diversions into ileal or colonic segments. Bacteremia progressing to acute or chronic pyelonephritis with intestinal microorganisms is not uncommon. Many patients with central nervous system (CNS) tumors require the placement of cerebrospinal fluid shunts. When infected, the CNS end of the shunt produces symptoms such as headache, mental status changes, and meningismus, whereas the distal ends of such shunts, which are generally located in the pleural or peritoneal cavities, give rise to symptoms of pleuritis or peritonitis. Surgically implanted prosthetic devices are used frequently in patients with osteosarcoma and other bone tumors. Infection is the most common complication associated with these devices, and is caused most often by organisms colonizing the skin.

Miscellaneous factors

Patients with primary CNS tumors or metastatic brain lesions often develop partial loss of the

gag reflex, predisposing towards aspiration. Neurologic abnormalities resulting in impaired micturition also occur. Damage to ciliary function in the respiratory tract, most often the result of radiation, increases the likelihood of developing pneumonia. Many solid tumors occur in the elderly, in whom immunologic deficits caused by ageing, malnutrition, and cancer cachexia may all influence the frequency and severity of infection, and the ultimate response to therapy. Previous and concurrent antibiotic usage can influence the spectrum of infection by selecting resistant organisms. For example, excessive vancomycin (oral and parenteral) usage has been associated with increased isolation rates of glycopeptide-resistant organisms such as vancomycin-resistant enterococci (VRE), *Leuconostoc* and *Pediococcus* spp.[5] The primary drawback of quinolone prophylaxis is the development of resistant Gram-negative bacilli (*Escherichia coli*, *Pseudomonas aeruginosa*, etc.).[6] Prophylactic and empiric antimicrobial regimens are used less often and for shorter durations in patients with solid tumors than in other, more immunosuppressed, patients. However, practice patterns vary, and must be taken into consideration along with local susceptibility/resistance patterns when evaluating patients for infection.

PREDOMINANT SITES OF INFECTION

Predominant sites of infection depend upon the location and size of the primary tumor or metastatic lesions, and the site and nature of medical devices and surgical procedures. These are summarized in Table 5.2.

As indicated previously, patients with CNS tumors often have partial or complete loss of the gag reflex, predisposing them to aspiration pneumonia. Impaired micturition and urinary retention as a result of neurological impairment leads to urinary tract infection. Following surgery for tumor resection and/or the placement of shunts, surgical wound infections, epidermal and subdural infections, cerebral abscesses, meningitis, and shunt infection can develop. Infections of the upper respiratory tract – including sinusitis, pneumonia (including aspiration and ventilator-associated pneumonia), and local cellulitis or necrotizing infections following surgical excision and reconstruction – are the most common sites in patients with head and neck tumors. Infected masses extending along the soft tissues in the neck can give rise to airway obstruction.

Patients with carcinoma of the lung develop pulmonary infections such as post-obstructive and/or necrotizing pneumonia, lung abscess, empyema, and surgical wound infections. Localized infections may lead to the development of bacteremia or disseminated infections. Cellulitis following axillary lymph node dissection is the most common site in patients with breast cancer. Mastitis and breast abscesses are less common.[7] Cholangitis with or without bacteremia, solitary or multiple hepatic abscesses, and peritonitis are not infrequent in patients who have hepatobiliary–pancreatic tumors.[8] Abscesses in the pancreatic bed and subdiaphragmatic abscesses can occur following extensive surgical resection. Patients receiving intra-arterial chemotherapy for hepatic tumors are also at risk for such infections. Patients with colonic or gynecologic tumors develop abdominal or pelvic abscesses, occasionally after fistula formation or perforation of a viscus. Ureteral obstruction resulting in urinary tract infection is relatively common in patients with carcinoma of the cervix, and is caused most often by local extension of tumor, and occasionally by radiation damage. Osteomyelitis, osteoradionecrosis, and infected prosthetic devices – with adjacent bone, joint, or soft tissue infections – predominate in patients with osteosarcoma and other bone neoplasms.

SPECTRUM OF INFECTION

Most infections in patients with solid tumors are caused by the patients' own resident microflora. The acquisition of nosocomial

Table 5.2 Predominant sites of infection in cancer patients with solid tumors

Tumor	Common sites of infection
Brain (CNS)	Wound infection; epidural and/or subdural infection; brain abscess; meningitis/ventriculitis; shunt-related infection; urinary tract infection; pneumonia (aspiration)
Head and neck	Cellulitis/wound infection; deep facial space infection; mastoiditis; sinusitis; aspiration/nosocomial pneumonia; cavernous (or other) sinus thrombosis; meningitis; brain abscess; retropharyngeal and paravertebral abscesses; osteomyelitis
Upper gastrointestinal	Mediastinitis; tracheo-esophageal fistula with pneumonitis; gastric perforation and abscess; feeding-tube-related infections
Breast	Surgical wound infection; cellulitis/lymphangitis following axillary node dissection; mastitis; breast abscess
Hepatobiliary–pancreatic	Surgical wound infection; peritonitis; ascending cholangitis ± bacteremia; hepatic, pancreatic, or subdiaphragmatic abscess
Lower gastrointestinal and pelvic	Wound infection, peritonitis; intra-abdominal or pelvic abscess; acute or chronic urinary tract infection; necrotizing fasciitis; typhlitis; enterocolitis (radiation-induced); perianal/perirectal infection; sacral/coccygeal osteomyelitis
Genitourinary and prostate	Acute and chronic pyelonephritis ± bacteremia; prostatitis; catheter-related complicated urinary tract infection; wound infection
Bone, joints, cartilage	Surgical wound infection; skin and skin structure infection; bursitis; synovitis; septic arthritis; osteomyelitis; infected prosthesis

pathogens occurs after hospitalization, particularly following prolonged or multiple antibiotic exposure(s). The distribution of causative organisms, therefore, generally mirrors the normal flora at a particular site of infection, or the nosocomial flora of a particular unit or institution. For example, surgical wound infections and catheter-related infections are caused most often by organisms colonizing the skin (coagulase-negative staphylococci, *Staphylococcus aureus*, *Streptococcus* spp., *Bacillus* spp., *Corynebacteria*), although certain opportunistic pathogens such as *Acinetobacter* spp., the Enterobacteriaceae, *Ps. aeruginosa,* and *Candida*

spp. are significant pathogens in the nosocomial setting. Similarly, most respiratory infections are caused by the resident oropharyngeal flora (*Streptococcus pneumoniae*, *Haemophilus influenzae*, mouth anaerobes, etc.), with *Staphylococcus* spp. and Gram-negative bacilli gaining predominance in the hospital. Enteric Gram-negative bacilli, intestinal anaerobes, and the enterococci dominate abdominal and pelvic sites of infection. Polymicrobial infections occur commonly when there is tissue involvement.[9] Examples include pneumonia, complicated or extensive wound infections, neutropenic enterocolitis (typhlitis), perirectal infections, and other skin and skin structure infections. Catheter-associated infections may also be polymicrobial in nature. Gram-positive cocci, Gram-negative bacilli, anaerobes, and yeast (*Candida* spp.) are commonly isolated, depending upon the site of infection. Occasionally, bacterial, fungal, and/or viral infections may coexist. *Candida* spp. frequently colonize debilitated hospitalized patients, particularly those who have received multiple or prolonged courses of broad-spectrum antibacterial therapy. Candiduria and candidemia are not uncommon in this setting, although disseminated candidiasis is distinctly uncommon in solid tumor patients. Colonization with *Candida* spp., therefore, is not sufficient reason for antifungal therapy in such patients. However, colonization at multiple sites in the same patient does increase the likelihood of disseminated infection and pre-emptive therapy might be indicated in some patients who are heavily colonized. The emergence of resistant *Candida* spp. such as *C. krusei*, *C. glabrata*, and *C. tropicalis* is of great concern.

Localized fungal infections such as primary cutaneous aspergillosis (associated with vascular catheters) or nailbed infection by *Fusarium* and other fungi are rare, and seldom progress to more invasive/disseminated infections. Invasive mold infections are rare. Local debridement and a short course of antifungal therapy usually produces satisfactory response rates. Viral infections (cytomegalovirus (CMV), varicella zoster virus (VZV), Epstein–Barr virus (EBV), respiratory syncytial virus (RSV), respiratory viruses) and parasitic infections (toxoplasmosis, *Strongyloidiasis*) are also quite rare in solid tumor patients. There are increasing reports of the occurrence of *Pneumocystis carinii* pneumonia (PCP) in patients with breast cancer, and other solid tumor patients receiving corticosteroid or other immunosuppressive therapies.[10–12] A breakdown of predominant pathogens according to site of infection is provided in Table 5.3.

CLINICAL FEATURES AND DIAGNOSIS

The predominant clinical features encountered with specific infections depend largely on the site and nature of the infection. As a general rule, patients who are severely neutropenic or are receiving corticosteroid or other type of immunotherapy have a blunted inflammatory response, leading to a paucity of clinical signs and symptoms.[13] In contrast, most patients with solid tumors who develop an infection have a normal, vigorous inflammatory response, making clinical evaluation and diagnosis a little easier to accomplish.

There is no substitute for a careful and detailed history and a thorough physical examination as part of the initial evaluation. Since the institution of broad-spectrum empiric therapy is generally not as critical as in neutropenic patients with hematologic malignancies, time spent on obtaining pertinent historical information and conducting a physical examination can often lead to the identification of a specific focus. For example, a history of travel to or residence in areas endemic for specific infections (tuberculosis, endemic mycoses, parasitic diseases) is important, and might help draw attention to them as the patient is being evaluated. Knowledge of prior surgical procedures and implanted prosthetic devices is also an important historical factor in such patients, since it may help identify a specific focus of infection. The use of prior antibiotics and over-the-

Table 5.3 Predominant organisms by site of infection

Site	Predominant organisms
Bloodstream	Coagulase-negative staphylococci, *Staphylococcus aureus*, *Enterococcus* spp., *Streptococcus* spp., *Enterobacteriaceae*, *Ps. aeruginosa*, *Candida* spp.
Central nervous system (including shunt-related and post-surgical infections)	Coagulase-negative staphylococci, *S. aureus*, enteric Gram-negative bacilli, *Streptococcus pneumoniae*, *Haemophilus influenzae*, mouth anaerobes, *Listeria monocytogenes*, *Cryptococcus neoformans*
Respiratory tract (upper respiratory infections, lower respiratory tract infections, lung abscess, empyema)	*S. pneumoniae*, *H. influenzae*, *Moraxella catarrhalis*, *Enterobacteriaceae*, *Ps. aeruginosa*, coagulase-negative staphylococci, *S. aureus*, mouth anaerobes (*Peptococcus*, *Peptostreptococcus*, *Fusobacterium*, etc.)
Biliary tract	Enteric Gram-negative bacilli, *Enterococcus* spp., enteric anaerobes, *Candida* spp.
Intra-abdominal/pelvic	Enteric Gram-negative bacilli, *Enterococcus* spp., enteric anaerobes (*Bacteroides* spp., *Clostridium* spp.), *Candida* spp.
Catheter-related	Coagulase-negative staphylococci, *S. aureus*, *Bacillus* spp., *Corynebacterium jeikeium*, *Ps. aeruginosa*, *Acinetobacter* spp., *Stenotrophomonas maltophilia*, enteric Gram-negative bacilli, mycobacteria (rapid growers), *Candida* spp.
Skin/skin structure	*S. aureus*, *Streptococcus* spp., *Ps. aeruginosa*, enteric Gram-negative bacilli, anaerobes

counter medications can alter the nature and spectrum of subsequent infection, and should be determined when interviewing the patient. An immunization history (e.g. pneumococcal vaccine) might also be useful. Seizure activity might suggest an intracranial process and/or aspiration pneumonia. A persistent cough, productive of large amounts of foul-smelling sputum, is consistent with the presence of a lung abscess or post-obstructive pneumonitis. The

expression of urine or fecal material through the vagina indicates the presence of a vesicovaginal or recto-vaginal fistula. During physical examination, close attention needs to be focused on the oropharyngeal cavities, the groin and perirectal region, sites where obstruction might occur, surgical wounds, prosthetic devices, irradiated areas, the skin (including the nail beds), catheter insertion sites, and the paranasal sinuses.

There is nothing unique about the initial laboratory evaluation of patients with solid tumors. A basic evaluation that includes chemical analysis of the blood and urine, a complete and differential blood count, tests for hepatic and renal function, and all appropriate microbiological cultures should be conducted on all patients. In patients with diarrhea, testing for *Clostridium difficile* toxin is often recommended as the first step. If this is negative and the diarrhea is suspected to be of infectious etiology, the stools should be tested for specific bacteria (e.g. *Aeromonas*, *Campylobacter*, *Plesiomonas*, *Salmonella*, *Shigella*, and *Yersinia*), protozoa (amoeba, *Cryptospordium*, *Giardia*, etc.), viruses (rotavirus, CMV), and also mycobacteria (*Mycobacterium avium* complex: MAC). Urine cultures are indicated if the patient is symptomatic, the urinalysis is abnormal, a urinary catheter is in place, or surgery involving the urinary tract has been performed. Examination of the cerebrospinal, pleural, and ascitic fluids should be performed when clinically indicated, and the specimens should be sent for bacterial, fungal, and other appropriate cultures. Radiographic evaluation of the chest is not useful on a routine basis, but is indicated when primary or metastatic lung disease or pulmonary symptoms (cough, sputum, dyspnea, chest pain, or hemoptysis) are present. Radiographic imaging studies (computed tomography, magnetic resonance imaging) may be particularly useful in evaluating the CNS, paranasal sinuses, pulmonary, abdominal, and pelvic foci. Indium-labeled leukocyte scans, bone scans, and gallium scans are often done, but provide useful diagnostic information infrequently. Doppler or venous flow studies are useful for the evaluation of deep venous thrombophlebitis that is often not clinically apparent. Serologic studies are generally not very useful unless a specific pathogen that elicits a serologic response is suspected.

Cutaneous lesions should be biopsied for Gram staining, staining for other pathogens (fungi, mycobacteria, and protozoa), culture, and cytologic examination. Other invasive procedures, such as biopsies of the lung, liver, bone, brain, lymph nodes, and bone marrow, should be performed expeditiously when clinically indicated, and handled in a similar fashion. In general, such procedures are easier to perform in patients with solid tumors than in patients with hematologic malignancies, since most patients are not thrombocytopenic, and hemostasis is not a significant problem.

The role of serial microbiological surveillance cultures in patients with solid tumors has not been established. They can occasionally provide useful information; however, the predictive yield of such cultures is low. Knowledge of local microflora, however, is an important factor when considering the use of surveillance cultures. In institutions where resistant organisms such as VRE, methicillin-resistant *S. aureus* (MRSA), *Ps. aeruginosa*, *Stenotrophomonas maltophilia*, *C. krusei*, etc. are relatively common, prior knowledge of colonization with such organisms can help in the choice of appropriate therapy when infection develops, and in the prevention of nosocomial transmission of these organisms from patient to patient.

THERAPY

Experience from the National Cancer Institute (Bethesda, MD) and from institutions that participate in the IATCG/EORTC trials indicates that the frequency of bacteremias is lower in neutropenic patients with solid tumors than in those with hematologic malignancies (12% versus 25%), whereas episodes of unexplained fever are more common (65% versus 40–50%).

In contrast, at the University of Texas MD Anderson Cancer Center, clinically and microbiologically documented infections are encountered more often in patients with solid tumors (50–60% versus 40%) and episodes of unexplained fever are less common in these patients (40% versus 60%).[4,14] Therapeutic strategies, therefore, are largely institution-dependant, and will be discussed under two broad categories: treatment of unexplained fever, and treatment of specific infections.

TREATMENT OF UNEXPLAINED FEVER

The principles of the management of unexplained fever in solid tumor patients with neutropenia are similar to those for patients with hematologic malignancies.[4,15,16] Empiric therapy generally consists of the administration of parenteral broad-spectrum antibiotics, while the patient is monitored in the hospital. Several choices for initial therapy are available, but specific regimens need to be tailored to local microflora and susceptibility patterns. These choices include the following:

combination regimens
- aminoglycoside plus β-lactam;
- glycopeptide plus β-lactam;
- glycopeptide plus quinolone;
- aminoglycoside plus quinolone.

monotherapy
- extended-spectrum anti-pseudomonal cephalosporin;
- carbapenem.

Initial usage of glycopeptides should be considered only when the likelihood of infection with resistant Gram-positive organisms is high (MRSA, viridans streptococci, coagulase-negative staphylococci, and *Corynebacterium jeikeium*). The routine use of these agents should be avoided, since this has been associated with the emergence of VRE and other glycopeptide-resistant microorganisms.[17,18] Of concern is the increasing level of glycopeptide resistance among organisms such as *Bacillus* spp. and *Rhodococcus* spp.[19] If used empirically, glycopeptide therapy should be discontinued promptly when relevant microbiological cultures are negative for resistant Gram-positive organisms. Various combination regimens and broad-spectrum agents used as monotherapy have been associated with overall response rates of 65–95%.[15]

Changes or alternations of the initial regimen are indicated for failure to respond and/or progressive infection, new clinical developments, or microbiological data and susceptibility information that indicate the need for a change. Frequent alternations or modifications include the following:

- addition of a glycopeptide if not used initially, when Gram-positive coverage needs to be strengthened;
- addition of a second drug with potent Gram-negative activity (if only one was included in the initial regimen), especially if a documented Gram-negative infection is not responding adequately;
- additional anaerobic coverage (clindamycin, metronidazole) for infections such as necrotizing gingivitis, neutropenic enterocolitis, perirectal abscesses, or other intra-abdominal pelvic sites;
- addition of empiric antifungal agents (fluconazole, itraconazole, amphotericin B or its lipid formulations);
- surgical intervention (e.g. drainage of an abscess or debridement for suspected/documented fungal infections of devitalized tissue) or removal of foreign bodies such as an infected catheter is occasionally necessary.

Standard therapy for febrile neutropenia in patients with solid tumors does not differ much from that in patients with hematologic malignancies, except that the duration of treatment is generally shorter owing to the shorter 'at-risk' period. Recently, clinical and statistically derived risk-prediction models have enabled

clinicians to simplify the treatment of 'low-risk' neutropenic patients (most of whom are patients with solid tumors receiving conventional chemotherapy), with the use of parenteral, sequential (intravenous → oral), or oral regimens that enable early discharge from the hospital, or outpatient therapy for the entire duration of the febrile episode.[20–23] This 'risk-based' approach to therapy might be more cost-effective, and might result in improved quality of life for patients and their care-givers, than the standard approach of hospital-based therapy. Early discharge from hospital or outpatient therapy also decreases the frequency of 'healthcare-associated' infections (many of which are caused by multidrug-resistant organisms), and reduces other hazards of hospital-based care.[24–26] (See Chapter 9.)

THERAPY OF SPECIFIC INFECTIONS

Gram-positive infections

Response to standard antibacterial therapy in solid tumor patients who develop Gram-positive infections exceeds 95%.[27] Agents other than glycopeptides (vancomycin, teicoplanin) to which the specific pathogen isolated is susceptible are generally appropriate. These include anti-staphylococcal penicillins (nafcillin, oxacillin), other β-lactams, trimethoprim/sulfamethoxazole (TMP/SMX), the tetracyclines, the macrolides, clindamycin, and some newer quinolones (gatifloxacin, moxifloxacin).[28,29] Glycopeptides are indicated when an organism resistant to other antimicrobial agents is isolated, or in patients who are allergic to β-lactams or other antimicrobial agents, but should not be used solely for the sake of convenience of administration. Occasionally, combination regimens that interact synergistically are preferable. Examples include an aminoglycoside plus a β-lactam, and vancomycin plus an aminoglycoside or rifampin.

New agents have recently become available for the treatment of glycopeptide-resistant organisms, particularly VRE. These include the oxazolidinone linezolid, and the quinipristin/dalfopristin combination Synercid.[30,31] Although these agents are active against a wide spectrum of organisms, they should not be used indiscriminately, since resistance to them is already being encountered.

Many Gram-positive bacteremic infections are related to the presence of an indwelling catheter. Many of these infections, especially those caused by coagulase-negative staphylococci, can be treated with antimicrobial agents alone, without removal of the catheter. However, persistent bacteremia or fever, significant infection at the catheter entry site, or the isolation of certain microorganisms (*Bacillus* spp., *S. aureus*, *C. jeikeium*) might necessitate catheter removal. The duration of therapy is 10–14 days unless evidence of endocarditis, septic thrombophlebitis, or other signs of dissemination is present.

Gram-negative infections

A large number of antimicrobial agents with potent activity against commonly isolated Gram-negative bacilli are currently available. The most commonly used are the extended-spectrum cephalosporins (ceftazidime, cefepime), anti-pseudomonal penicillin/β-lactamase combinations (ticarcillin/clavulanate, piperacillin/tazobactam), the carbapenems (imipenem, meropenem), the monobactam (aztreonam), the aminoglycosides (gentamicin, tobramycin, amikacin), and the quinolones (ciprofloxacin, gatifloxacin). Agents such as TMP/SMX and rifampin also have useful activity against many Gram-negative pathogens, although they are seldom used as 'first-line' agents. The aminoglycosides are not appropriate for the monotherapy of Gram-negative infections in neutropenic patients, even if in vitro susceptibility of the causative pathogen is demonstrated. They are best utilized in combination with other classes of antimicrobial agents, particularly if such combinations are synergistic.

The appropriate management of infections caused by *Ps. aeruginosa* continues to be debated. Some authorities recommend the use of combination regimens (preferably synergistic) without exception, particularly in patients with severe neutropenia. However, in a large review of *Ps. aeruginosa* bacteremia in cancer patients from the MD Anderson Cancer Center, the most critical factors for a favorable response were the timing of therapy (i.e. any delay adversely affected outcome), and susceptibility of the organism to the non-aminoglycoside component of the therapeutic regimen.[32] This experience has been confirmed in a follow-up study from the same institution.[33] Although combination therapy may not always be necessary, *Ps. aeruginosa* is known to be an aggressive pathogen, and is associated with considerable morbidity and mortality. In light of recent data indicating that major organ and/or tissue involvement is associated with poorer outcomes, particularly in patients with *Ps. aeruginosa* bacteremia, it might be prudent to administer combination regimens to patients with such complicated infections.[34]

Unlike Gram-positive bacteremias, most Gram-negative bacteremias are not catheter-related. However, *Acinetobacter* spp., *Pseudomonas* spp., and *S. maltophilia* are more likely to cause catheter-related infections than other Gram-negatives, and catheter removal, in addition to appropriate antimicrobial therapy, might occasionally be necessary.

Anaerobic infections

Many empiric regimens contain adequate anaerobic coverage, since they include agents such as the carbapenems and piperacillin/tazobactam. However, monotherapy with extended-spectrum cephalosporins or combination therapy with cephalosporin/aminoglycoside does not provide adequate anaerobic coverage. In patients receiving such regimens, the addition of agents such as clindamycin or metronidazole or a change to a broad-spectrum agent with anaerobic activity is indicated when anaerobes are isolated or strongly suspected to be present. Surgical intervention may be life-saving in some infections involving anaerobes, and surgical consultants should be involved in the management of necrotizing anaerobic infections from the onset.

Fungal and viral infections

Fluconazole is effective for the treatment of candidemia caused by susceptible species (i.e. most *Candida* spp. except *C. krusei*.[35] Species other than *C. albicans* might require high-dose fluconazole therapy (800–1200 mg/day) for adequate response to occur, owing to 'dose-dependent susceptibility' of these isolates.[36] Removal or exchange of infected catheters shortens the duration of candidemia, and hastens response.[37] Amphotericin B is also effective, but its use is limited by substantial toxicity. The lipid formulations of amphotericin B are much less toxic, but far more expensive, and are indicated when toxicity or refractory infections make the use of amphotericin B deoxycholate unrealistic or impractical.[38] Fluconazole is also effective for more localized infections (thrush, esophagitis, vaginitis, candiduria). Cryptococcal meningitis is seen occasionally – particularly in patients receiving prolonged corticosteroid therapy. Other, disseminated fungal infections are rare in solid tumor patients, and their treatment is standard.

Patients with solid tumors are not at particular risk of developing disseminated viral infections, and there is nothing unique about their management, when documented in this patient population. Acyclovir remains the agent of choice for the treatment of infections caused by herpes simplex virus (HSV) and VZV. For localized lesions or where parenteral therapy is no longer necessary, the newer oral agents (valaciclovir, famciclovir) provide greater bioavailability than oral acyclovir. CMV, EBV, and human herpesvirus-6 (HHV-6) are rarely encountered in solid tumor patients.

Community respiratory viruses (influenza, parainfluenza, RSV) have recently been shown to be important causes of morbidity and mortality in recipients of bone marrow transplants and patients with hematologic malignancies. They have not been studied extensively in patients with solid tumors, and, in all likelihood, do not have the same impact in this setting. Management according to currently established standards is adequate.

Many solid tumor patients develop elevation of aminotransferase (transaminase) levels, indicating hepatic injury, but it is often difficult to determine whether the disease is viral or drug-induced. The presence of hepatitis may result in considerable delays in the administration of antineoplastic therapy, since it is hazardous to administer hepatotoxic drugs to patients whose liver functions are already impaired. Several reports have focused on the phenomenon of reactivation of quiescent liver disease due to hepatitis B virus following cytotoxic or immunosuppressive therapy.[39,40] The clinical picture is that of fulminant hepatitis, which has led to the requirement for liver transplantation in some patients.

Parasitic infections (toxoplasmosis, cryptosporidosis, etc.) are uncommon in solid tumor patients. Standard therapeutic measures are indicated.

Mycobacterial infections

Mycobacterial infections occur more frequently in patients with cancers than in the general population. In a review of 201 cases of tuberculosis from the Memorial Sloan-Kettering Cancer Center, patients with lung cancers had the highest prevalence of tuberculosis (920 per 100 000) among solid tumor patients.[41] Lung cancer and head and neck cancer patients presented more often with tuberculosis at the time of cancer diagnosis, whereas patients with other malignancies developed tuberculosis more often while receiving cancer chemotherapy. More recent data from the MD Anderson Cancer Center indicate that tuberculosis remains particularly common in patients with head and neck cancers[42] (Figure 5.1). Fifty percent of patients were receiving antineoplastic therapy and 14.2% were, or had recently been, on corticosteroids. The various manifestations of tuberculosis described in this report include pulmonary tuberculosis, adenitis, chest wall and psoas abscess, pleuritis, meningitis, and widely disseminated infection. No multidrug-resistant isolates were encountered. Despite this, the mortality rate was 25%.

Two mechanisms of tuberculosis reactivation have been postulated in this setting. Tumor necrosis can cause the breakdown of pre-existing granulomas, liberating sequestered mycobacteria. Alternatively, chemotherapy-induced immunosuppression, corticosteroids, or malignancy-associated cachexia can impair cell-mediated immunity to such a degree that reactivation of tuberculosis occurs. Since therapy for many solid tumors has increasingly become more intensive, the possibility of an increase in the incidence of tuberculosis reactivation exists. Consequently, a high index of suspicion for tuberculosis needs to be maintained, particularly if a patient's history or epidemiologic background suggests prior exposure to or active treatment of tuberculosis. In such patients, the development of pulmonary symptoms and/or radiographic findings should prompt an evaluation for the presence of tuberculosis (tuberculin skin test; sputum, bronchoalveolar lavage, or lung biopsy samples for acid-fast bacillus (AFB) smears and cultures). Prophylaxis with daily isoniazid is indicated for a period of 6–12 months in patients with a positive tuberculin test and no evidence of active tuberculosis. Newer prophylactic regimens (rifampin plus pyrazinamide) that can be administered for a shorter period have recently been evaluated – primarily in patients with AIDS – but have not been well studied in patients with neoplastic diseases.[43] Whenever AFBs are identified in smears or cultures of respiratory specimens or on histopathology or cytology, therapy for presumed

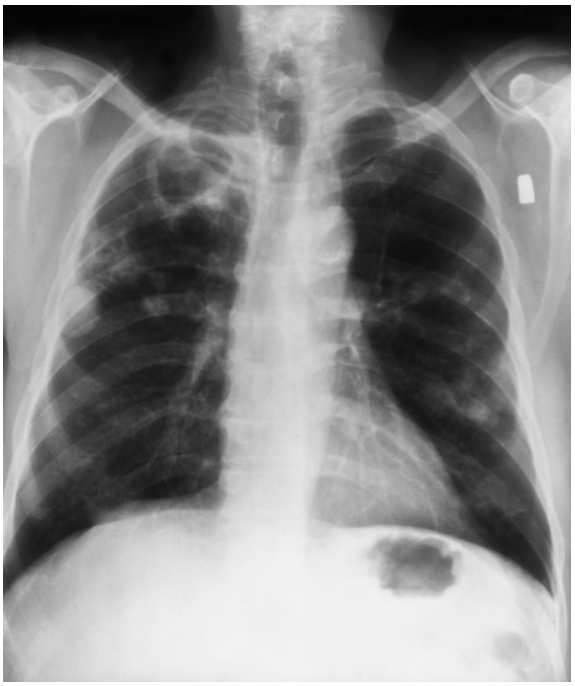


Figure 5.1 Right upper lobe cavitary tuberculosis in a Latin American male with primary nasopharyngeal carcinoma. The patient responded to standard antitubercular chemotherapy.

active pulmonary tuberculosis should be instituted. Upon final identification of the organisms, therapy should be continued (if tuberculosis is confirmed), modified (if other pathogenic mycobacteria such as *M. kansasii* or MAC are identified), or discontinued (if contaminants such as *M. gordonae* are identified).

Mycobacterium kansasii has traditionally been considered to be the most virulent nontuberculous mycobacterium, and infections caused by *M. kansasii* have also been described with increased frequency in cancer patients. In a recently published report from the MD Anderson Cancer Center, the incidence of *M. kansasii* infection was 25 cases per 100 000 cancer patient registrations.[44] The infection was actually more common in patients with leukemia than in solid tumor patients (115 versus 14 cases per 100 000), and pleuropulmonary disease was predominant. Two patients (8%) had disseminated infection. Most patients were treated with rifampin-based regimens. Although 60% died within 20 months of *M. kansasii* isolation, death was attributed to the primary neoplasm and not to *M. kansasii* in most instances.

Rapidly growing mycobacteria have also been reported to cause pulmonary, catheter-related, and disseminated infections in cancer patients.[45–48] These organisms are isolated less frequently than *M. tuberculosis* and *M. kansasii*, and are encountered predominantly in patients with solid tumors.[45] They are resistant to standard antitubercular drugs, but are susceptible to agents such as TMP/SMX, the quinolones, and the macrolides. As in the case of other mycobacterial infections, combination regimens are recommended.

Similarly, MAC bacteria cause pulmonary, or disseminated infections in cancer patients, predominantly in solid tumor patients.[49] These organisms are also resistant to standard antitubercular agents, and require combination therapy with agents to which they are susceptible.[50]

SPECIAL CONSIDERATIONS

Post-obstructive pulmonary infections

Lung cancer patients often develop focal pulmonary infections. In most instances, this is due to partial obstruction of the bronchial tree leading to atelectasis and post-obstructive pneumonitis. Occasionally, the infection may progress to abscess formation and even empyema (Figure 5.2). In a small number of cases, infection occurs within an area of tumor necrosis, rather than as a result of airway obstruction. These infections are predominantly polymicrobial (staphylococci, Gram-negative bacilli, anaerobes), and, in addition to prolonged broad-spectrum antibiotic therapy, methods to overcome the obstruction (antineoplastic therapy, radiation, endobronchial

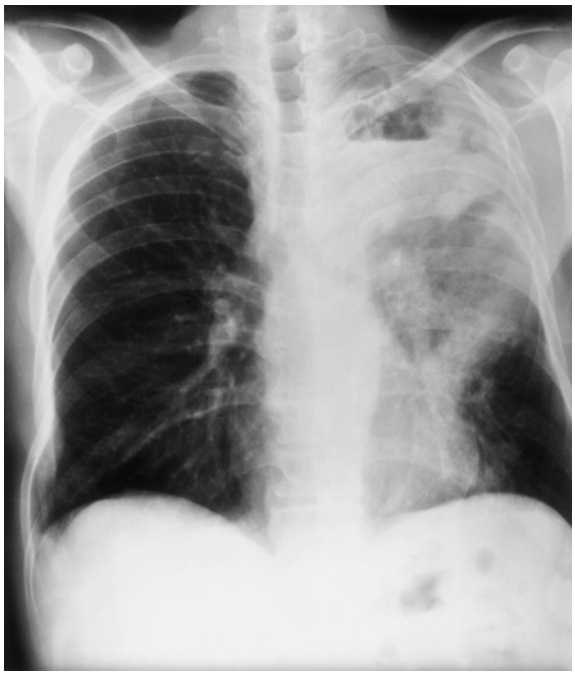


Figure 5.2 This 48-year-old man with primary adenocarcinoma of the lung presented with fever, chills, and a cough productive of foul-smelling sputum. Chest radiograph revealed extensive infiltration in the left lung, post-obstructive pneumonia, progressing to lung abscess formation. Note the air–fluid level in the abscess.

brachytherapy stent placement) are usually necessary to ensure adequate drainage of the infected lung.

Infections associated with breast cancer surgery

Breast cancer is the most commonly diagnosed malignancy in women in the USA, accounting for 182 800 of 600 400 new cancer cases in women in 2000.[51] Most of these patients undergo some surgical procedure of the involved breast, along with resection of ipsilateral lymph nodes, and radiation, which predisposes them to poor wound healing and various infectious complications (both early and late), primarily involving the skin and soft tissue.[52–54] These range from post-operative wound-infection, post-operative hematoma or seroma formation followed by secondary infection, breast cellulitis, lymphedema and lymphangitis, mastitis, and breast abscess formation (Figure 5.3). In a matched case–control study designed to identify risk factors for the development of breast cellulitis after breast conservation therapy, the following six factors were significant:[55]

- drainage of a hematoma;
- postoperative ecchymosis
- presence of lymphedema;
- volume of resected breast tissue;
- previous number of biopsies;
- number of breast seroma aspiration procedures.

Patients with these risk factors may be at lifelong risk for developing infections that are slow to respond and are often recurrent. Even minor trauma in patients with lymph node dissection can lead to cellulitis or more invasive infections. Patients should be instructed to minimize such events by avoiding phlebotomy, vascular access catheters, blood pressure monitoring or other routine procedures on the involved extremity. Early and aggressive therapy at the earliest sign of infection can prevent local skin breakdown and invasion. A selected group of patients with recurrent infections might benefit from chronic suppressive antimicrobial therapy.

Ommaya-reservoir-related infections

The treatment of diffuse leptomeningeal disease or neoplastic meningitis includes chemotherapy delivered through an Ommaya reservoir, since placing an Ommaya reservoir allows direct access to the ventricular system for both fluid analysis and drug delivery. These reservoirs, however, can act as a focus of infection, particularly in patients in whom frequent

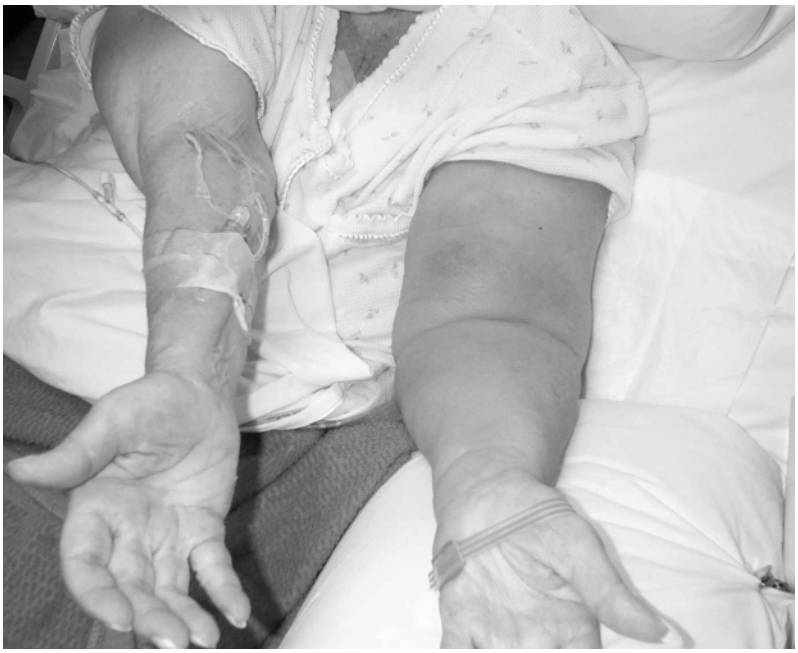


Figure 5.3 This 60-year-old woman underwent surgery for left breast carcinoma, including the removal of 16 lymph nodes. She developed massive edema, pain, and cellulitis in her left upper extremity following chemotherapy. Note the difference between the normal and infected extremity.

ventricular access is required. Coagulase-negative staphylococci, and other common inhabitants of the skin, are the most frequent pathogens in this setting. Systemic and intraventricular installation of antimicrobial agents to which the offending pathogens are susceptible usually produces a satisfactory response. In some cases, removal of the infected Ommaya reservoir is necessary, in addition to antimicrobial therapy.

Hepatobiliary infection

Obstruction of the biliary tract as a result of hepatobiliary and/or pancreatic tumors results in the development of ascending cholangitis.[8] On rare occasions, single or multiple hepatic abscesses might also develop. Ascending cholangitis might also be the initial manifestation of local malignancy, and may lead to this diagnosis during evaluation. Finally, hepatic abscesses have been reported after invasive procedures for hepatocellular carcinoma, including the administration of intra-arterial chemotherapy. Most of these infections are polymicrobial in nature, with enteric Gram-negative bacilli, anaerobes and *Enterococcus* spp. predominating. Broad-spectrum antimicrobial therapy and percutaneous drainage are often necessary in order to achieve an adequate response and prevent recurrent infection.

Gynecologic-cancer-associated infections

Local obstruction caused by tumor, tumor necrosis, and therapeutic modalities (including chemotherapy, surgery, and radiation) all contribute to infections in patients with gynecologic malignancy. Tumor-related infections depend on the site and size of the tumor. For example, infections complicating stage I cervical cancer generally involve the surfaces of the tumor and are usually limited to the vagina.[56] As tumors enlarge, obstruction to various organs results in the development of urinary tract infections, tubo-ovarian abscesses, and

pyometra. Rupture of tubo-ovarian abscesses or pyometra can lead to the development of acute peritonitis.[57,58] These complications are rare, since most gynecologic cancers are detected and treated at an earlier stage.

Infections related to the treatment modalities used in patients with gynecologic cancers depend on the mode of treatment. The general principles relating to the management of febrile neutropenic patients also apply to patients with gynecologic cancers when they receive chemotherapy and become neutropenic. However, documented intrapelvic/abdominal sites are more common than in patients with other cancers, and empiric antimicrobial coverage needs to include potent Gram-negative and anaerobic activity. In addition to routine post-surgical infections (e.g. wound infections), the removal of pelvic organs and tissue results in the creation of spaces that are filled by blood and serum, with a high potential for infection. Complications of radiation include bowel obstruction or perforation, and fistula formation. All these complications are life-threatening, and require prompt and aggressive antimicrobial therapy in conjunction with appropriate surgical intervention.

Infections mimicking cancer

Certain infections can occasionally produce clinical manifestations and radiographic images that are indistinguishable from those produced by neoplasms. The most common site of such lesions is the lung. Some patients may be totally asymptomatic, and pulmonary lesions may be identified on routine yearly physician visits, or during medical evaluations required by new employers or insurance companies. Most lesions identified in this manner do turn out to be neoplastic. However, in a large study conducted at the MD Anderson Cancer Center, 37 of 2908 patients (1.3%) with pulmonary lesions who were referred to 'rule out' lung cancer had an infection instead.[59] In none of these patients was an infection strongly suspected during the primary evaluation. Fungal infections (histoplasmosis, coccidioidomycosis, and cryptococcosis) accounted for 46% of these infections, and mycobacterial infections for 27%. Bacterial and parasitic infections were uncommon.

Lesions in other parts of the body (liver, bone, thyroid, lymph nodes, breast, etc.) can also simulate cancer and create diagnostic and therapeutic challenges.[60–63] A recent report highlights a series of patients with actinomycosis, who presented with mandibular and pelvic lesions that were thought to be neoplastic on initial presentation and evaluation.[64] Documentation of a specific diagnosis by microbiological and/or histologic techniques is mandatory for the proper management of these patients.

Many of these infections can also present diagnostic challenges in patients with cancer who have been effectively treated. When new lesions are detected in such patients, the most common suspicion is that of metastatic or recurrent neoplastic disease. These lesions also need to be evaluated carefully, and a specific diagnosis made, since the management of recurrent neoplastic disease is totally different from that of infection.

SUMMARY

Patients who have hematologic malignancies often develop life-threatening infections, especially when they are severely neutropenic. Since this is a relatively homogeneous group, it has been the subject of intense study, and a large number of well-designed trials have been instrumental in developing general and specific principles for the management of such patients. In contrast, patients with solid tumors are extremely heterogeneous, and infections in such patients have been less well studied. They do, however, represent the majority of new cases of cancer diagnosed each year, and develop a large number of infectious complications. Some are related to the tumor itself, and some to local phenomena such as obstruction or

disruption of normal anatomic barriers. Others are related to various treatment modalities (chemotherapy, surgery, or radiation) and the nature of these infections depends on the treatment modality and the type and site of tumor being treated. Since most tumors are diagnosed earlier than they used to be owing to improvements in screening programs and diagnostic techniques, infections related to the tumor itself are becoming less common. In contrast, patients with solid tumors are receiving increasingly intensive antineoplastic therapy (often employing multiple modalities in the same patient) in order to achieve better antitumor responses. Consequently, infections related to these treatment modalities have become more frequent. In order to better understand the diversity of infections seen and to develop management strategies specifically for the different solid tumor groups (CNS tumors, breast cancer, lung cancer, etc.), carefully designed studies focusing on the predisposing factors, epidemiology, manifestations, diagnosis, and treatment of these infections need to be conducted. Such studies will provide the information needed to appropriately manage patients with solid tumors who develop infections, rather than applying management strategies that have been developed for, and are more pertinent in, patients with hematologic malignancies.

REFERENCES

1. Bodey GP, Infection in cancer patients: a continuing association. *Am J Med* 1986; **81**(Suppl A-1): 11–26.
2. Pizzo PA, Management of fever in patients with cancer and treatment induced neutropenia. *N Engl J Med* 1993; **328:** 1323–32.
3. Greenlee RT, Murray T, Bolden S, Wingo PA, Cancer statistics, 2000. *CA Cancer J Clinicians* 2000; **50:** 7–33.
4. Rolston KVI, Infections in patients with solid tumors. In: *Management of Infections in Immunocompromised Patients.* (Pizzo P, Glauser MP, eds). London: WB Saunders Company Ltd, 2000; 117–40.
5. Rolston KVI, Raad I, Whimbey E, Bodey GP, The changing spectrum of bacterial infections in febrile neutropenic patients. In: *Febrile Neutropenia* (Klastersky JA, ed). Berlin: Springer-Verlag, 1998: 53–6.
6. Rolston KVI, Commentary: Chemoprophylaxis and bacterial resistance in neutropenic patients. *Infect Dis Clin Pract* 1998; **7:** 202–4.
7. Keidan Rd, Hoffman JP, Weese JL et al, Delayed breast abscesses after lumpectomy and radiation therapy. *Am Surg* 1990; **56:** 440–4.
8. Rolston KVI, Dholakia N, Rodriguez S, Rubenstein EB, Nature and outcome of febrile episodes in patients with pancreatic and hepatobiliary cancer. *Support Care Cancer* 1995; **3:** 414–17.
9. Elting LS, Bodey GP, Fainstein V, Polymicrobial septicemia in the cancer patient. *Medicine* 1986; **65:** 218–22.
10. Kulke MH, Vance EA, *Pneumocystis carinii* pneumonia in patients receiving chemotherapy for breast cancer. *Clin Infect Dis* 1997; **25:** 215–18.
11. Sepkowitz KA, Brown AE, Talzak EE et al, *Pneumocystis carinii* pneumonia among patients without AIDS at a cancer hospital. *JAMA* 1992; **267:** 832–7.
12. Koibuchi Y, Iino Y, Yokoe T et al, *Pneumocystis carinii* pneumonia during treatment for recurrent breast cancer. A case report. *Jpn J Clin Oncol* 1995; **25:** 218–21.
13. Sickles EA, Greene WH, Wiernik PH, Clinical presentation of infection in granulocytopenic patients. *Arch Intern Med* 1975; **135:** 715.
14. Rodriguez SJ, Rolston KVI, Infections in cancer patients with solid tumors. In: *Proceedings of 37th Annual Meeting of the Infectious Diseases Society of America, Philadelphia, PA, November 18–21, 1999*: Abst 456.
15. Hughes WT, Armstrong D, Bodey GP et al, 1997 guidelines for the use of antimicrobial agents in neutropenic patients with unexplained fever. *Clin Infect Dis* 1997; **25:** 551–73.
16. NCCN Practice Guidelines for Fever and Neutropenia, *Oncology* 1999; **13:** 197–257.
17. Murray BE, Vancomycin-resistant enterococcal infections. *N Engl J Med* 2000; **342:** 710–21.
18. Van der Auweera P, Pensart N, Korten V et al, Influence of oral glycopeptides on the fecal flora of human volunteers: selection of highly glycopeptide-resistant enterococci. *J Infect Dis* 1996; **173:** 1129–36.

19. Diekema DJ, Coffman SL, Marshall SA et al, Comparison of activities of broad spectrum β-lactam compounds against 1128 Gram-positive cocci recently isolated in cancer-treatment centers. *Antimicrob Agents Chemother* 1999; **43:** 940–3.
20. Talcott JA, Finberg R, Mayer RJ et al, The medical course of cancer patients with fever and neutropenia. *Arch Intern Med* 1988; **148:** 2501–68.
21. Talcott JA, Whalen A, Clark J et al, Home antibiotic therapy for low risk cancer patients with fever and neutropenia: a pilot study of 30 patients based on validated prediction rule. *J Clin Oncol* 1994; **12:** 107–14.
22. Klastersky J, Paesman M, Rubenstein EB et al, The Multinational Association for Supportive Care in Cancer Risk Index: a multinational scoring system for identifying low-risk febrile neutropenic cancer patients. *J Clin Oncol* 2000; **18:** 3038–51.
23. Rolston K, New trends in patient management: risk-based therapy for febrile patients with neutropenia. *Clin Infect Dis* 1999; **29:** 515–21.
24. Rubenstein EB, Rolston K, Benjamin RS et al, Outpatient treatment of febrile episodes in low risk neutropenic cancer patients. *Cancer* 1993; **71:** 3640–6.
25. Gerberding JL, Preventing antimicrobial-resistant healthcare infections: beyond 2000. *Clinical Updates in Infectious Diseases*, Vol V, Issue 2, National Foundation for Infectious Diseases, Bethesda, MD, 2000.
26. Kohn L, Corrigan J, Donaldson M (eds), *To Err is Human: Building a Safer Health System*. Committee on Quality of Health Care in America. Institute of Medicine Report. National Academy Press: Washington, DC, 2000.
27. Rubin M, Hathorn JW, Marshall D et al, Gram-positive infections and the use of vancomycin in 550 episodes of fever and neutropenia. *Ann Intern Med* 1988; **108:** 30–5.
28. Rolston KVI, LeBlanc B, Ho DH, In vitro activity of gatifloxacin against Gram-positive isolates from cancer patients. In: *Proceedings of 39th Annual Interscience Conference on Antimicrobial Agents and Chemotherapy, San Francisco, September 26–29, 1999*: Abst 360.
29. Rolston KVI, Streeter HD, LeBlanc BM, In-vitro activity of a new carbapenem (MK-0826) against Gram-positive organisms (GPO) from hospitalized cancer patients. In: *Proceedings of 1st International Symposium – Resistant Gram-Positive Infections, San Antonio, TX, December 3–5, 2000* (abst).
30. Mollering Rec, Linden PK, Reinhardt J et al, The efficacy and safety of quinupristin/dalfopristin for the treatment of infections caused by vancomycin-resistant *Enterococcus faecium*. *J Antimicrob Chemother* 1999; **44:** 251–61.
31. Noskin GA, Siddiqui F, Stosor V, Successful treatment of persistent vancomycin-resistant *Enterococcus faecium* bacteremia with linezolid and gentamicin. *Clin Infect Dis* 1999; **28:** 689–90.
32. Bodey GP, Jadeja L, Elting L, *Pseudomonas* bacteremia: retrospective analysis of 410 episodes. *Arch Intern Med* 1985; **145:** 1621–9.
33. Chatzinikolaou I, Abi-Said D, Bodey GP et al, Recent experience with *Pseudomonas aeruginosa* bacteremia in patients with cancer. Retrospective analysis of 245 episodes. *Arch Intern Med* 2000; **160:** 501–9.
34. Elting LS, Rubenstein EB, Rolston KVI, Bodey GP, Outcomes of bacteremia in patients with cancer and neutropenia: observations from two decades of epidemiological and clinical trials. *Clin Infect Dis* 1997; **25:** 247–59.
35. Rex JH, Walsh TJ, Sobel JC et al, Practice guidelines for the treatment of candidiasis. *Clin Infect Dis* 2000; **30:** 662–78.
36. Rex JH, Pfaller MA, Galgiani NJ et al, Development of interpretive breakpoints for antifungal susceptibility testing: conceptual framework and analysis of in vitro–in vivo correlation data for fluconazole, itraconazole, and *Candida* infections. *Clin Infect Dis* 1997; **24:** 235–47.
37. Rex JH, Bennett JE, Sugar AM et al, Intravascular catheter exchanges and the duration of candidemia. *Clin Infect Dis* 1995; **21:** 994–6.
38. Wong-Beringer A, Jacobs RA, Guglielmo BJ, Lipid formulations of amphotericin B: clinical efficacy and toxicities. *Clin Infect Dis* 1998; **27:** 603–18.
39. Rolston KVI, Bodey GP, Infections in patients with cancer. In: *Cancer Medicine*, 5th edn (Holland JF, Frei E, eds). Hamilton, Ontario: BC Decker, 2000: 2407–32.
40. Galbraith RM, Eddleston AL, Williams R, Zuckerman AJ, Fulminant hepatic failure in leukemia and choriocarcinoma related to withdrawal of cytotoxic drug therapy. *Lancet* 1975; **ii:** 528.
41. Kaplan MH, Armstrong D, Rosen P, Tuberculosis complicating neoplastic disease: a

review of 201 cases. *Cancer* 1974; **33:** 850–8.
42. DeLaRosa G, Jacobson K, Whimbey E, Kontoyiannis D, Tuberculosis in the '90s in a tertiary cancer center. In: *Proceedings of the 38th Annual Meeting of the Infectious Diseases Society of America, New Orleans, LA, September 7–10, 2000*: Abst 552.
43. Gordin F, Chaisson RE, Matts JP et al, Rifampin and pyrazinamide vs. isoniazid for prevention of tuberculosis in HIV-infected persons. *JAMA* 2000; **283:** 1445–50.
44. Jacobson K, Teira R, Libshitz H et al, *Mycobacterium kansasii* infections in patients with cancer. *Clin Infect Dis* 2000; **30:** 965–9.
45. Jacobson K, Garcia R, Libshitz H, Clinical and radiological features of pulmonary disease caused by rapidly growing mycobacteria in cancer patients. *Eur J Clin Microbiol Infect Dis* 1998; **17:** 615–21.
46. Rolston KVI, Jones PG, Fainstein V, Bodey GP, Pulmonary disease caused by rapidly growing mycobacteria in patients with cancer. *Chest* 1985; **4:** 503–6.
47. Raad II, Vartivarian S, Khan A, Bodey G, Catheter-related infections caused by the *Mycobacterium fortuitum* complex: 15 cases and review. *Rev Infect Dis* 1991; **13:** 1120–5.
48. Hoy JF, Rolston KVI, Hopfer L, Bodey GP, *Mycobacterium fortuitum* bacteremia in patients with cancer and long-term venous catheters. *Am J Med* 1987; **83:** 213–17.
49. Bhamani A, Elting L, Tarrand J, Rolston K, *Mycobacterium avium-complex* (MAC) infection in cancer patients. In: *Proceedings of the 35th Annual Meeting of the Infectious Diseases Society of America, San Francisco, CA, September 13–16, 1997*: Abst 708.
50. Dunne M, Fessel J, Kumar P et al, A randomized, double-blind trial comparing azithromycin and clarithromycin in the treatment of disseminated *Mycobacterium avium* infection in patients with human immunodeficiency virus. *Clin Infect Dis* 2000; **31:** 1245–52.
51. Simon MS, Cody RL, Cellulitis after axillary lymph node dissection for carcinoma of the breast. *Am J Med* 1992; **93:** 543–8.
52. Rescigno J, McCormick B, Brown AE, Myskowski PL, Breast cellulitis after conservative surgery and radiotherapy. *Int J Radiat Oncol Biol Phys* 1994; **29:** 163–8.
53. Dixon JM, Breast infection. *BMJ* 1994; **309:** 946–9.
54. Brewer VH, Hahn KA, Rohrbach BW et al, Risk factor analysis for breast cellulitis complicating breast conservation therapy. *Clin Infect Dis* 2000; **31:** 654–9.
55. Brooker DC, Savage JE, Twiggs LB et al, Infectious morbidity in gynecologic cancer. *Am J Obstet Gynecol* 1987; **156:** 515–20.
56. Barton DPJ, Fiorica JV, Hoffman MS et al, Cervical cancer and tubo-ovarian abscesses: a report of three cases. *J Reprod Med* 1993; **38:** 561–4.
57. Imachi M, Tanaka S, Ishikawa S, Matsuo K, Spontaneous perforation of pyometra presenting as generalized peritonitis in a patient with cervical cancer. *Gynecol Oncol* 1993; **50:** 384–8.
58. Rolston KVI, Rodriguez S, Dholakia N et al, Pulmonary infections mimicking cancer: a retrospective, three year review. *Support Care Cancer* 1997; **5:** 90–3.
59. Chandrasoma PT, Intramedullary cord tuberculosis resembling glioma. *Neurol India* 1976; **24:** 164–6.
60. Cleaton-Jones P, Oral tuberculosis – its similarity to oral carcinoma. *J Can Dent Assoc* 1971; **37:** 388–9.
61. Kumar S, Chandrasekar D, Rao MS, Banerjee CK, Solitary paravesical tuberculosis masquerading as bladder carcinoma. *Tubercle* 1981; **62:** 143–4.
62. Matthews JI, Matarese SL, Carpenter JL, Endobronchial tuberculosis simulating lung cancer. *Chest* 1984; **86:** 642–4.
63. Shindy SR, Chandawarkar RY, Deshmukh SP, Tuberculosis of the breast masquerading as carcinoma: a study of 100 patients. *World J Surg* 1995; **19:** 379–81.
64. LaRosa AM, Weigand M, Rolston KVI, Actinomycosis: an unusual infection presenting as or complicating malignancy. *Infect Dis Clin Pract* 2000; **9:** 331–3.

6

Infections in patients with hematologic malignancies

Ben E De Pauw

INTRODUCTION

An intact defense system offers protection against infections through a complex interrelationship of protecting surfaces, cells, and soluble factors. A good general condition, optimal nutritional status, and normal organ function, together with all components of the cellular and humoral immune system, provide adequate protection against pathogenic microorganisms. There are fundamental differences between hematologic malignancies and solid tumors which affect the incidence as well as the severity of infectious complications concerned. Leukemias and lymphomas reside by definition within the immune system itself, exerting a dual deleterious effect. The malignant population interferes with and supplants the immunocompetent elements at their original location. Hemorrhages, inevitable during the course of acute leukemia, may impede organ function and facilitate the growth of microorganisms that may be present. The effects of the various noxious events that occur while treating a hematologic malignancy differ in severity and in primary targets. Moreover, such hazardous events exercise their impact dynamically as the degree of disturbance varies with time during or after a course of treatment. There is, in fact, a reciprocity: better supportive care allows more aggressive therapy to achieve better cure rates at the price of peculiar, hitherto rare, infectious complications. Therefore, the survival of patients with a hematologic malignancy depends heavily on the quality of supportive care. Neutropenia is the most important risk factor, there being an inverse correlation between the number of circulating neutrophils and the frequency of infection. All patients with a neutrophil count of less than 100/µl for more than three weeks will develop fever, whereas only one-fifth of patients who are not neutropenic become febrile.[1]

The signs and symptoms of infection are muted owing to the absence of neutrophils, and diagnostic procedures may be very problematic in immunocompromised hosts.[2] No microbiological explanation for the fever will be found in about 60% of patients who become febrile while neutropenic, but the fact that more than three-quarters of them will improve clinically after treatment with broad-spectrum antibacterials suggests an occult bacterial source as the cause of fever.[3,4] A small inoculum, enough to cause symptoms of infection in a patient with a defective defense mechanism, might stay below the detection limit of standard blood culture techniques, particularly if marginal samples for cultures are taken. Ideally, close cooperation ought to be established between all disciplines

involved in the care of the patient: nurses, hematologists or oncologists, microbiologists, radiologists, pulmonologists, pathologists, and specialists in infectious diseases.

A vast majority of the organisms responsible for infection during chemotherapy-induced neutropenia arise from the patient's endogenous microbial flora, particularly from the gastrointestinal tract and cutaneous surfaces.[3] Interestingly, potentially pathogenic organisms that belong to the patient's flora on admission are unlikely to cause serious infections. Conversely, Fainstein et al[5] showed that the oropharyngeal and fecal flora are altered during hospital visits, and this change in colonization has clinical consequences. These acquired organisms show a greater propensity to invade the body, and are frequently responsible for life-threatening, disseminated infections. But worldwide, there is presently no predominant causative pathogen. Prior to 1960, *Staphylococcus aureus* was most commonly involved in fatal infections, whereas during the 1960s and 1970s, Gram-negative rods prevailed.[6] The spectrum of organisms responsible for infections in the neutropenic patient is constantly changing in conjunction with alterations in the management of the underlying disease.[6–8] Prophylactic use of antibacterials, mainly aimed at Gram-negative organisms, has certainly reduced the number of culture-proven infections by aerobic Gram-negative rods.[9] In addition, the hematopoietic colony-stimulating factors reduce the length of neutropenia, which allows the use of higher doses of cytotoxic drugs, and this promotes other complications such as severe mucositis. Extensive mucosal damage is often accompanied by impaired production of saliva, and mucin, if produced at all, may be extremely viscous and difficult to either swallow or cough up. Under these circumstances, viridans streptococci have become the predominant pathogens in patients who are treated for a hematologic malignancy.[10,11] Intravenous catheters are often essential for the successful management of immunocompromised patients. Subcutaneously implanted venous access devices are seldom used, because surgery is a dangerous procedure in patients with a bleeding tendency. Hence, a transcutaneously inserted catheter with or without a subcutaneous tunnel tract is the standard. Such catheters provide the single most effective means of breaching the skin barrier and creating ready access for microorganisms such as staphylococci, particularly *Staphylococcus epidermidis*, and, to a lesser extent, *Candida* and *Stenotrophomonas* spp.[12–14] In patients who undergo modern, very intensive treatment, even sepsis with *Clostridium perfringens* and *C. septicum* has been described. Under these circumstances, the 'non-pathogens' *Staphylococcus epidermidis*, JK bacteria, and *Corynebacterium parvum* or 'diphtheroids' cannot be dismissed as a possible cause of septicemia or organ infection.[15] Anaerobic organisms rarely feature as single pathogens; they play a role in mixed polymicrobial infections and represent 6–13% of all bacteremic episodes. Such multiple-organism infections often reflect an unremitting underlying disease, and carry a bad prognosis in spite of adequate antibiotic therapy.

Since the mid 1970s, antimicrobial agents have been given to patients in an attempt to reduce infectious complications arising during neutropenia.[9] Decontamination of the digestive tract was employed in an attempt to eliminate potentially pathogenic organisms from the alimentary tract, the major reservoir for Gram-negative bacilli, but later observations suggested that the systemic action of absorbable antibiotics may be more important than any local effect on the gut flora. Although total decontamination in combination with sterile food has generally been abandoned as a burden on patients' quality of life without improvement of survival rate, selective decontamination of the digestive tract still has supporters, mainly in Europe.[9] Considering only those prophylactic studies that are placebo-controlled, it is by no means clear what benefit prophylactically administered antibiotics offer. Bacteremia is reduced, but the rate of fever and the need to employ empiric therapy is not influ-

enced. It is therefore unfortunate that an adequate placebo-controlled study with sufficient power is lacking. Furthermore, probably because of the practice of giving prompt empiric therapy, the mortality ultimately attributable to Gram-negative rods, the principal target of prophylaxis, is identical to that in patients not receiving antibiotics prophylactically. Nevertheless, it is tempting to pursue this approach in neutropenic patients who are clearly colonized with virulent organisms such as *Enterobacter cloacae*, *Pseudomonas aeruginosa*, or yeasts. Regular monitoring of important body sites as well as the patient's environment would be mandatory to support this strategy.

It must be underscored that inadequate hygiene by visitors, nurses, doctors, and other personnel is invariably a prominent source of infection. Organisms such as *Legionella pneumophila*, *Ps. aeruginosa* and *Aeromonas hydrophila* can reach potentially dangerous concentrations in watery environments such as air-conditioning systems, sinks, bathrooms, and water for flowers and plants. Hence, many centers do not allow flowers or home-cooked food in patients' rooms. Whilst it is mandatory to eliminate notorious sources of infection within the hospital and at the patient's home, masks, gowns, gloves, and isolation of patients in a sterile environment are not required unless there is a specific indication, such as the carriage of virulent organisms. Laminar airflow or HEPA-filtered rooms can be recommended as an adjunct to care, if high concentrations of fungal spores in the air of a given ward dictate this. Besides, it is irrational that prescription of H_2-receptor antagonists and other antacids has gained such popularity, considering the possible colonization of the gut by Gram-negative bacilli and organisms such as *Listeria monocytogenes*.

EMPIRIC THERAPY: WHY, WHEN, WHAT?

As there is no reliable way to distinguish a fever of infectious origin from fever due to non-infectious causes, the possible presence of a life-threatening infection must be presumed whenever fever occurs in a neutropenic patient.[2] Of course, the possibility that a febrile episode is associated with drugs, such as allopurinol, antibiotics, bleomycin, or cytarabine, or with the underlying disease should always be contemplated, but such a connection is usually quite apparent. If left untreated, 40% of patients who are neutropenic and bacteremic will die within the first 48 hours after the onset of fever.[16] Hence, antimicrobial therapy should be commenced within an hour of the first signs or symptoms of infection. This strategy of prompt intravenous administration of broad-spectrum antibacterials in maximal therapeutic dosages has reduced the mortality associated with bacteremia caused by Gram-negative rods to approximately 10%, and has become a widely accepted principle of infection management during neutropenia for almost 30 years.[16,17] It is virtually impossible to cover for every conceivable pathogen, but, in view of their virulence, *S. aureus*, *Pseudomonas* spp., and other Gram-negative rods are among the primary targets of empiric antimicrobial therapy. However, partly because of the changing pattern of infection and the continuous marketing of new anti-infective agents, the question of what constitutes the optimal regimen for the febrile neutropenic patient has never been answered.[18,19] The discussion focuses on the number and kind of antibiotics to use for empiric purposes.[20,21] It simply illustrates that no uniformly superior combination has been found – and nor will one be in the future, because differences will always exist between individual patients, centers, and clinical circumstances.[3,20,22] It is essential to select a regimen on the basis of the most commonly encountered infectious pathogens, as well as the resistance pattern of causative microorganisms, because empiric use of a β-lactam antibiotic, either alone or in combination,

Table 6.1 Established empiric antibiotic regimens

Combination therapy
β-lactam (ceftazidime, cefepime, cefpirome, or piperacillin) with an aminoglycoside (amikacin or tobramycin) or a second β-lactam of a different class

Single-agent therapy
Ceftazidime, cefepime, cefpirome, imipenem–cilastatin, meropenem, and (probably) piperacillin–tazobactam

Addition of a glycopeptide to the combination or single agent
Vancomycin or (outside North America) teicoplanin

to which a significant rate of resistance has been found must be avoided.[7,17]

Basically, three different strategies have been universally accepted for empiric antibiotic therapy: (a) traditional combinations of either a β-lactam with an aminoglycoside or two β-lactams; (b) monotherapy with an extended-spectrum β-lactam; (c) both of these options supplemented by a glycopeptide from the onset of fever (see Table 6.1).[22–29] Depending on the criteria applied, the response rates vary from 30% to 70% and the overall survival rate is more than 90%. An aminoglycoside plus either a broad-spectrum penicillin or cephalosporin offers possible synergism and, theoretically, minimal emergence of resistant strains; disadvantages are limited activity against some Gram-positive bacteria and the risk of nephrotoxicity, hypokalemia, and ototoxicity, especially when other drugs with a similar toxicity profile are used concurrently. Such combinations have been tested at length in many trials employing numerous different antibacterials, and many physicians intuitively considered this the most suitable regimen for patients at high risk for Gram-negative infections.[19,22,23] Double β-lactam regimens appear to be an acceptable alternative if nephrotoxicity has to be avoided; however, because the targets are similar, it is conceivable that resistance may develop, although broad-spectrum penicillins have been combined with clavulanate or tazobactam to extend their spectrum to include the β-lactamase-producing organisms.[24–26] There are some indications that double β-lactam combinations can prolong the duration of neutropenia, whereas their high sodium content may be a burden for elderly patients. With regard to the individual drugs to be used in combination regimens, there is a choice of drugs rather than drugs of choice. The presently most frequently used aminoglycosides are amikacin and tobramycin, whereas from the broad-spectrum penicillins piperacillin–tazobactam and from the cephalosporins ceftazidime and cefepime are favored, although these compounds can be replaced by other antibiotics from the respective classes on the basis of local patterns of resistance. The availability of new broad-spectrum antibiotics has encouraged several investigators to assess the feasibility of single agents for empiric purposes. Another reason for changing the rationale in antibiotic management is the significant improvement in antineoplastic response rate, making the occurrence of antibiotic-related toxicity even less tolerable. It is also a fact that some of the traditional regimens involved up to 13 drug administrations per day, compounding costs and the potential for medication errors and sometimes causing delays in the administration of other parenteral medication. Initially, single agents were only acknowledged to constitute adequate empiric therapy for unexplained fevers and not for documented infections or episodes with prolonged neutropenia. However, randomized controlled trials of empiric monotherapy, employing the

third-generation cephalosporin ceftazidime, have shown no difference in efficacy in comparison with traditional combinations, not even in cases of Gram-negative bacteremia.[28] It is noteworthy that the addition of an aminoglycoside or vancomycin to ceftazidime was necessary in less than 15% of the episodes of fever and neutropenia.[28] Trials assessing the value of cefepime and cefpirome showed successes similar to those obtained with ceftazidime or the classic combinations. Imipenem–cilastatin and meropenem, with their extended spectrum, appear to be the most suitable candidates given the increasing challenge posed by Gram-positive infections.[7,18] These compounds, without being definitely superior, fulfilled most expectations as far as efficacy was concerned.[26,27,30,31] *Stenotrophomonas maltophilia* and other non-aeruginosa pseudomonads were responsible for treatment failures or breakthrough bacteremia, and therefore it seems prudent to avoid administration of these antibiotics in patients who are colonized with these organisms or in centers where these are prevalent pathogens. The occasionally occurring seizures and nausea associated with the maximum dose of imipenem–cilastatin are a cause of concern, particularly when the patient has a brain lesion or if drugs such as cyclosporin A and cisplatin are used concomitantly. In such cases, meropenem may serve as a safe alternative.[30,31] As empiric regimens for febrile neutropenic patients must always contain reliable anti-pseudomonal activity, other currently available broad-spectrum antibiotics should not be used, although, on theoretical grounds, piperacillin–tazobactam would be considered by some investigators. Finally, it should be emphasized that extensive use of single-drug therapy requires vigilance, since success depends upon continued susceptibility to the drug in question.

While the choice of a basic empiric regimen is relevant, the complex issue of whether and when to add a glycopeptide stays controversial. The glycopeptides seem to be the drugs of choice for these pathogens, but two opposing opinions prevail as to their inclusion in the initial regimen. One contends that drugs such as vancomycin can be added later when Gram-positive bacteria have been isolated or if no response is seen, with the powerful argument that glycopeptides do not contribute to the ultimate chances of cure in the vast majority of patients, because early mortality due to infections with most Gram-positive organisms is very low. The second opinion claims that addition from the start will provide earlier effective treatment and thus reduce overall morbidity, in spite of the fact that by following this approach, as many as seven out of ten cases will be overtreated. The results of several prospective studies do suggest that there is rarely need to utilize vancomycin as part of the front-line therapeutic regimen.[32–34] If, however, there is reason to suspect the possible presence of a methicillin-resistant *S. aureus* (MRSA) on the basis of local patterns of resistance, a glycopeptide must be included in the initial regimen to avoid unnecessary mortality. The choice between the available glycopeptides is trivial; teicoplanin, which is not available in North America, is easy to administer and has very few side-effects, whereas vancomycin has more reliable activity against certain subtypes of the coagulase-negative staphylococci.

Some of the problems associated with the traditional combinations may be circumvented by substitution of a β-lactam by a quinolone. The fluorinated quinolones show no cross-resistance with β-lactams, and they are highly active against the rapidly fatal Enterobacteriaceae. Their potential for use in an empiric setting is constrained by their commissioning for prophylactic purposes and their suboptimal activity against Gram-positive pathogens, notably viridans streptococci. In combination with a specific anti-Gram-positive agent, the efficacy of the quinolones appears comparable to that achieved with established regimens, and, after initial clinical improvement, a switch to an oral formulation seems feasible.[35] Experience with the monobactam aztreonam is limited, and the results achieved are too

conflicting to recommend employment of this antibiotic for first-line therapy, but it can play a role in the treatment of febrile neutropenic patients who are allergic or resistant to β-lactam antibiotics, provided that adequate Gram-positive cover is added.[36]

INDIVIDUAL ADAPTATIONS

Although the empirical regimen in a given hospital is usually identical for all febrile patients, it is evident that there is no regimen that will be appropriate for all febrile neutropenic patients. Approximately 20–30% of the febrile episodes in neutropenic patients are due to bacteremias, 20% to clinically documented infections, and 20% to non-bacteremic microbiologically documented infections, while the remaining 30–40% are possible or doubtful infections.[3] Amongst the clinically documented infections, the lower respiratory tract is the site of infection in about 55%, the upper respiratory tract and skin and soft tissue contribute approximately 20% each, whereas the other sites are restricted to 5%.[3,4] Patients with an obvious focus of infection clearly represent a population that is more difficult to treat than do those without any focus at all. Infectious death occurs in one-fifth of episodes with a focus of infection, in comparison with less than 5% for episodes without one.[22,27,37] Hence, it is reasonable to assume that a substantial number of febrile neutropenic patients might benefit from an individually tailored empiric approach.[20,22] Clinical and laboratory investigations can help to select the optimal empiric coverage (see Table 6.2). Studying the case notes can help to identify the cause of some fevers as being tissue damage by cytotoxic agents, the use of pyrogenic drugs, administration of blood products, or graft-versus-host disease. The history of a patient with regard to previous infections might reveal important information on possible drug allergy and on the actual infectious complication, since fever may represent a recrudescence of an infection acquired during a previous aplastic episode. For bacterial infections, this information has, unfortunately, only very limited predictive value. On the other hand, despite the common lack of physical signs and symptoms, a careful physical examination should be performed, paying special attention to vital signs such as blood pressure, pulse, and respiratory rate, and to oropharynx, lungs, venous access devices, perianal areas, and the course of the temperature during the preceding days. Imaging techniques should be used when appropriate. These diagnostic procedures are important, because different types of infection are preferentially associated with distinct causative organisms, and the results may help to consider an individual adaptation of the standard empiric scheme.[22,38]

Table 6.2 Important actions when fever occurs in a neutropenic patient

- History, including details of infections during previous neutropenic episodes and of concomitant drugs
- Physical examination, with special attention to catheter tunnel tract, lungs, perianal region, skin, and mouth
- Assess the state of the underlying disease
- Perform cultures from blood and clinically suspicious lesions (in the case of a central venous line, blood from the line – all lumens – as well as peripheral blood)
- Check the results of possible surveillance cultures
- Consider concurrent infections in other patients in the same ward
- Chest X-ray (and, in case of any suspicion of an abnormality, computed tomography (CT) scan)
- Assess kidney function, liver function, plasma minerals

Skin, soft tissue, abdominal, and catheter-related infections

The clinical spectrum of catheter-related infections ranges from asymptomatic bacteremia as a manifestation of intraluminal colonization or a process confined to the site of insertion, to marked inflammation of the tunnel tract and septicemia with metastatic emboli in the skin and other organs.[12,13] Malfunction of the catheter, as revealed by the impossibility of drawing blood from the line, is often the first sign of an infectious problem. Ecthyma gangrenosum with extensive necrosis represents a characteristic entity in patients with *Ps. aeruginosa* sepsis, but these cutaneous manifestations are reported in only 2% of cases.[6] Since pathogens such as *Candida* spp. and Mucorales order can cause similar lesions, a needle aspiration or biopsy should be performed to ascertain a definite and accurate diagnosis as early as possible in the course of the disease. Mucositis, gingivitis, and dental-related problems may occur in up to 85% of patients. Microbiologically documented infections are frequent, featuring *Candida albicans*, viridans streptococci, enterococci, or anaerobes. Herpes simplex virus (HSV) may also play a role. Mixed and polymicrobial infections are more or less the rule. Given the prevalence of Gram-positive organisms in these patients, selection of a regimen with improved anti-streptococcal activity or early addition of a glycopeptide appears legitimate. Life-threatening varicella zoster virus (VZV) infection or chickenpox, sometimes with visceral dissemination, is a feared entity among leukemic children.

Dysphagia or odynophagia in hematologic patients may be due to chemotherapy or gastric reflux, but esophagitis is of infectious origin in the majority of cases, HSV, either alone or together with *Candida* spp., being the most likely causative organism. Colitis or typhlitis in patients with acute leukemia is accompanied by a combination of profuse diarrhea and severe abdominal pain with virtually no bowel movements. It may create a very alarming situation, and since unnecessary surgical interventions may be detrimental, it is essential for physicians to be aware of the existence and symptomatology of this entity. This syndrome is typically chemotherapy-induced, but can be the result of other different etiologic factors.[39] Pseudomembranous colitis from *Clostridium difficile* can be severe and even fatal. Stools should be cultured and tested immediately for the presence of this microorganism and its toxin if the diagnosis is suspected. Relapses are frequent, and may follow cancer chemotherapy or courses with antibiotics such as clindamycin. Disproportional bacterial overgrowth in the gastrointestinal tract of patients with a damaged mucosa can serve as a source of bacteremia by normally exclusively enteric pathogens such as *C. septicum*. Considering the probable involvement of anaerobes, a carbapenem and the addition of metronidazole or vancomycin to a standard empiric regimen are obvious options when fever is accompanied by abdominal symptoms. Diagnostic problems are held accountable for underrating enteric viruses as causative agents in gastrointestinal infections. Perirectal cellulitis with painful lesions without abscess formation caused by Gram-negative rods, particularly *Escherichia coli*, with or without anaerobes and HSV, has become less common.

Pulmonary infections

Management of pulmonary infiltrates is complex, given that as many as 40% may be of non-infectious origin.[38,40,41] Bacterial infections account for most of the pulmonary infiltrates that appear as segmental shadows respecting the normal anatomic borders of the lung tissue.[38] Surveys have shown that response rates in pneumonia due to Gram-negative bacilli or *S. aureus* do not exceed 45%. An ominous finding in a patient with pneumonia is the concomitant presence of polymicrobial bacteremia. The majority of focal infiltrates are caused by fungi, in contrast to diffuse abnormalities, which are

usually not of direct bacterial or fungal origin. When a new infiltrate appears and progresses in patients who remain neutropenic, particularly in conjunction with fever and chest pain, *Aspergillus fumigatus* should be the leading diagnostic consideration, with the therapeutic consequence of early systemic antifungal therapy. Next to the adverse effects of cytotoxic therapy or irradiation, a number of causative microorganisms as well as pulmonary hemorrhage must be considered in the case of a diffuse infiltrate. *Pneumocystis carinii* used to be the leading pathogen, but now pneumonitis following bacteremia with viridans streptococci constitutes a more prominent problem.[11,42] Partly as a result of diagnostic limitations, infections with viruses such as respiratory syncytial virus (RSV), influenza, and adenoviruses seem to be rare. They are often complicated by either viral pneumonitis or secondary bacterial pneumonia. RSV presents with rhinorrhea, nasal congestion, sore throat, and cough. In most leukemic patients, a clinical course of viral infections comparable to that in immunocompetent adults is seen and this, in combination with the apparently low incidence, does not warrant a frontline place in the therapeutic considerations unless the actual symptoms are particularly prototypical.

Miscellaneous items

Urinary tract infections are rare in the absence of urinary catheters, and they are virtually all caused by Gram-negative rods.

Patients who receive potentially nephrotoxic drugs are the most obvious candidates for empiric therapy with a single agent. Conversely, many specialists recommend coverage with two appropriate antibacterial agents that do not exhibit cross-resistance for patients who are known to be colonized by resistant Gram-negative bacilli. Occurrence of a shock syndrome often reflects the presence of Gram-negative rods, streptococci or *S. aureus* in the bloodstream; under these circumstances, aminoglycosides are perceived to be necessary by some experts, in spite of the increased risk of nephrotoxicity.

Insidious onset of fever, accompanied by headache and confusion, is indicative of meningitis in patients with perturbed cellular immunity. The predominant pathogens include *L. monocytogenes*, *Cryptococcus neoformans* and *Toxoplasma gondii*. If a patient complains of seizures and headache, localization of leukemia or lymphoma, intracerebral cryptococcoma or cerebral abscesses caused by organisms such as staphylococci, *T. gondii*, *Nocardia*, or mycobacteria have to be considered.

There is increasing evidence showing that low-risk patients – for example those who are not very ill, and have unexplained fever and an increasing granulocyte count – can be treated as outpatients with home-administered intravenous antimicrobial therapy. Even an oral regimen based on a fluoroquinolone or cotrimoxazole (trimethoprim–sulfamethoxazole) can prove feasible, provided that there are no other adverse prognostic factors and that communication between attending physician and patient is optimal, with easy access to the hospital in case of emergency.[43–45] This may also apply to these patients who have received chemotherapy for acute leukemia with signs of incipient bone marrow recovery.

With such variation in prevalent organisms depending on the clinical presentation, and the availability of wide scale of broad-spectrum antibiotics with disparate properties, it is justified to consider a more individually tailored empiric approach (see Table 6.3). It is clear that an individual strategy related to clinical symptoms requires the clinician, who is daily attending the patient, to play a pivotal role.

ANTIBIOTIC MODIFICATIONS EARLY AFTER THE EMPIRIC PHASE

The basic aim with the use of empiric antibiotics in febrile neutropenic patients is to prevent mortality from septicemia due to

Table 6.3 Individually tailored empiric antibiotic therapy

Clinical situation	Empiric regimen
Concurrent diseases:	
Impaired kidney function	Monotherapy with ceftazidime or fourth-generation cephalosporin
Allergy to a given antibiotic	Avoid this class of drugs
Heart dysfunction	Avoid drugs with high sodium content
Concomitant potentially nephro- and ototoxic drugs	Monotherapy with ceftazidime, fourth-generation cephalosporin, or meropenem
Colonization by resistant organism	Specifically targeted prophylaxis; selection on the basis of susceptibility
No focus of infection present	Monotherapy with ceftazidime, fourth-generation cephalosporin, or carbapenem
Shock present	Consider addition of aminoglycoside
Patient in remission, not ill	Consider home antibiotic therapy
Focus of infection present:	
Upper respiratory tract	Carbapenem/piperacillin–tazobactam
Lower respiratory tract	Ceftazidime, fourth-generation cephalosporin or carbapenem; consider aminoglycoside; early addition of an antifungal agent
Skin and soft tissue (including central venous line)	Carbapenem/fourth-generation cephalosporin, piperacillin–tazobactam, but consider adding a glycopeptide
Urinary tract	Ceftazidime, fourth-generation cephalosporin
Abdominal symptoms	Carbapenem

Gram-negative rods and *S. aureus* during the first 2–3 days after the onset of fever when the results of the microbiological investigations are not yet available.[16,17] By the end of the truly empiric phase, the clinical condition will have deteriorated in 10% of patients, improved in 25%, and stabilized in 65%.[46] An initial response rate of about 35% may be expected among patients with shock, compared with 70% among patients without shock. Since, irrespective of the initial regimen, a substantial number of patients will not respond adequately, modifications are inevitable. For this purpose, a planned–progressive approach involving modification of the antimicrobial regimen every 2–3 days according to a predetermined schedule until the patient becomes afebrile is ill advised, since it ignores the individual differences between various febrile neutropenic patients.[8] It can also instill a false sense of security precisely

because the regimens chosen offer an increasing spectrum of activity, encouraging the lamentable belief that further attempts at diagnosis can be omitted. In contrast, it is imperative to have a standardized approach to the microbiological evaluation of the neutropenic patient with fever. Blood, sputum, and urine for bacterial and fungal cultures should be collected at the onset of fever and at regular intervals in the persistently febrile patient. If a central venous line is present, an extra blood specimen should be taken from each lumen of the catheter. While lysis centrifugation may be too expensive for use on all blood cultures, this technique produces superior results in detecting fungi in patients at risk. For patients with suspected wound or soft tissue infections, it is always preferable to obtain tissue samples. As this frequently proves unrealistic, swab samples of aspirates may be collected and transported immediately to the laboratory. Technical personnel should be instructed not to discard sputum samples on the basis of low numbers of leukocytes. The value of serodiagnosis for viral infections in the acutely ill patient is seriously restricted by the lag time between the infection and the immunologic response. Since information on this issue may become important later during the course of the disease, samples should be taken and stored.

A retrospective survey of 1951 cases showed that in patients with a lower respiratory tract infection, the modification rate was 69% whilst adjustments were deemed necessary in 51% of cases with a skin and soft tissue infection, in 44% of the febrile episodes accompanied by abdominal complaints, and in 37% of the upper respiratory tract infections.[47,48] The selection of additional antibiotics, if necessary, can be guided by clinical circumstances. Such an approach is validated by the fact that various categories of infection, as mentioned previously, are associated with different causative organisms.[22,37,38] This strategy, which puts a greater emphasis on diagnosis than empiric interventions, requires daily meticulous assessment of each case, but drugs that are potentially toxic can be added with more confidence once a positive diagnosis has been made.

Pulmonary infections, either as the primary focus or as a complication of septicemia, present a dismal prospect, and have been held responsible for 70% of all fatal infections after cytotoxic therapy.[38,40,41] Typically, chest radiographs performed early in the evolution of infection fail to show infiltrates; it may take more than 3 days for the infection to generate enough damage or for the few remaining granulocytes to concentrate around the infectious nidus to permit recognition on a radiograph. The critical decision faced by the clinician at the bedside of patients with pulmonary infiltrates is whether or not to perform invasive procedures such as bronchoscopy with or without bronchoalveolar lavage, transbronchial biopsy, transthoracic aspiration, or open lung biopsy. The value of these diagnostic approaches for the optimal management of patients remains controversial, because the yield depends on the collaboration and skill of various specialists. Besides, concurrent thrombocytopenia constrains invasive diagnostic interventions in most patients.

Coagulase-negative staphylococci and *Corynebacterium jeikeium* have to be isolated from at least two sets of blood cultures to be considered clinically significant, but single blood cultures that are positive for *S. aureus*, *Streptococcus pneumoniae*, or *Enterococcus faecalis* should be regarded significant. Although viridans streptococci are common blood contaminants in the general population, positive blood cultures in patients with oromucositis should not be disregarded, certainly not when *Streptococcus mitis* is isolated.[10,11] These streptococci can cause life-threatening infections in about 10% of cases, including septic shock and pneumonitis with an adult respiratory distress syndrome, with a mortality of around 60% despite aggressive antibiotic therapy – particularly if chemotherapy involved the use of high-dose cytarabine. These so-called 'alpha-strep syndromes' are almost certainly multifactorial in origin, and the streptococcal infection prob-

ably triggers off a sepsis syndrome when there is pre-existing tissue damage and alteration in the systemic or local immunity. Therefore, a combination of specific antibacterials with corticosteroids, rather than merely additional antibiotics, should be considered to manage patients affected by this complication.[42] Most catheter-related uncomplicated Gram-positive bacteremias can be easily eradicated by a glycopeptide-containing regimen but one should be prepared for relapses. In patients with insertion-site infections, tunnel infections, and septic emboli, removal of the line is virtually inevitable in the vast majority of cases. It is also advisable to remove the catheter in patients with atypical mycobacterial infections, fungemias, and bacteremias due to pathogens causing rapidly fatal infections. Infections with *Clostridium* spp. certainly require the addition of drugs such as penicillin G and vancomycin to amplify the antibiotic cover. If double- or triple-lumen catheters are being used, the antimicrobial therapy must be delivered in rotation to each of the lumen ports.

Persisting fever without any sign of clinical deterioration is a very questionable indicator of infection. It is generally contended that clinically or microbiologically defined infections cannot be expected to respond to therapy within 72 hours. Indeed, it has been demonstrated that more than half of the patients who are still febrile after 3 days of antibiotic therapy will defervesce without any alteration of the antibiotic regimen.[28,34] It is therefore remarkable that, particularly in cases where cultures fail to yield a pathogen, the temptation to escalate therapy by adding more drugs appears almost irresistible without there being any evidence of clinical deterioration, persistence of a pathogen, or development of a new site of infection.[47] Besides, if fever persists for 72 hours after adequate broad-spectrum antibacterial treatment in patients without any clinical or laboratory evidence of bacterial infection, the increased temperature is unlikely to be of bacterial origin. As far as possible, the number of changes to therapy should be kept to a minimum, because, rather than improving outcome, the liberal use of antibiotics actually enhances the risk of organ toxicity and the development of resistance, and generates excessive costs.[47,49] Modifications ought to be based on firm grounds, such as deterioration of vital signs, isolation of a relevant pathogen resistant to the antibiotics given, an antibiotic-related adverse event, or the occurrence of a new focus of infection or progression of an existing focus (Table 6.4).

When results from blood cultures taken before initiation of empiric therapy become available, changes should be considered according to the susceptibility pattern of the offending pathogen. Decisions should be guided by the

Table 6.4 Reasons for modifying an empiric regimen

- Deterioration of vital signs, such as blood pressure and ventilation
- Development of a new clinical focus without clinical improvement
- Progression of an existing clinical focus during persisting neutropenia
- Persistence of a causative pathogen in cultures taken during therapy
- In vitro resistant pathogen in the initial culture in the absence of clinical improvement
- Isolation of a new pathogen during therapy
- Occurrence of a new fever spike
- Unexplained fever for more than 5 days
- Adverse event attributable to an antibiotic of the empiric regimen
- Typical symptoms in conjunction with a known local epidemic with unusual microorganisms, such as *Legionella pneumophilia*

evolving clinical condition of the patient. It has to be underscored that as long as the patient remains febrile and neutropenic, antimicrobial cover should never be restricted to antibiotics that are active only against Gram-positive pathogens to avoid rapidly fatal breakthrough Gram-negative bacteremia.

Second infections emerge proportionally to the duration of granulocytopenia, and further febrile episodes may occur in one-fifth of patients with neutropenia lasting more than 28 days and in more than half of cases with neutropenia exceeding 4 weeks. Next to prosthetic-device-associated infections, these secondary febrile events mainly involve pulmonary infiltrates. Although bacteria account for more than 90% of culture-documented infections, invasive fungi have become prominent pathogens, particularly in patients who have protracted periods of neutropenia.[50] Consequently, empiric antifungal therapy is considered a mandatory modification whenever unexplained fever persists for more than 4 or 5 days or when a typical pulmonary infiltrate occurs.

There are no objective arguments against the current American and European guidelines for the use of hematopoietic growth factors as an adjunct to antimicrobial therapy in febrile neutropenic.[51,52] However, it is widely assumed that stimulation of granulopoiesis is beneficial in conditions where a long delay in marrow recovery is potentially disastrous. This pertains to pneumonias, severe cellulitis, and invasive fungal infections.

Discontinuation of antimicrobial therapy is recommended if granulocyte recovery ensues. Alternatively, if the persistently neutropenic patient has no complaints, and exhibits no clinical, radiological, or laboratory evidence of infection, stopping antibiotic therapy or a change to orally administered antibacterials should be considered after four days without symptoms. Any new fever or episode of clinical deterioration should prompt a recommencement of antimicrobial therapy, since infection may have only been suppressed, not eradicated.

REFERENCES

1. Bodey GP, Buckley M, Sathe YS, Freireich EJ, Quantitative relationships between circulating leukocytes and infection in patients with acute leukemia. *Ann Intern Med* 1966; **64:** 328–40.
2. Sickles AE, Greene WH, Wiernik PH, Clinical presentation of infection in granulocytopenic patients. *Arch Intern Med* 1975; **135:** 715–19.
3. Pizzo PA, Robichaud KJ, Wesley R, Commers JR, Fever in the pediatric and young adult patient with cancer. A prospective study of 1001 episodes. *Medicine* 1982; **61:** 153–65.
4. Dompeling EC, Donnelly JP, Raemaekers JMM et al, Evolution of the clinical manifestations of infection during the course of febrile neutropenia in patients with malignancy. *Infection* 1998; **26:** 349–54.
5. Fainstein V, Rodriguez V, Turck M et al, Patterns of oropharyngeal and fecal flora in patients with acute leukemia. *J Infect Dis* 1981; **144:** 82–6.
6. Bodey GP, The treatment of febrile neutropenia: from the dark ages to the present. *Support Care Cancer* 1997; **5:** 351–7.
7. Klastersky J, Zinner SH, Calandra T et al (European Organization for Research and Treatment of Cancer Antimicrobial Therapy Cooperative Group), Empiric antimicrobial therapy for febrile granulocytopenic cancer patients: lessons from four EORTC trials. *Eur J Cancer Clin Oncol* 1988; **24**(Suppl 1): S35–45.
8. Klastersky J, Empirical antibiotic therapy in neutropenic cancer patients. *Eur J Cancer* 1993; **29A**(Suppl 1): S6–10.
9. Donnelly JP, Selective decontamination of the digestive tract and its role in antimicrobial prophylaxis. *J Antimicrob Chemother* 1993; **31:** 813–29.
10. Cohen J, Donnelly JP, Worsley AM et al, Septicaemia caused by viridans streptococci in neutropenic patients with leukaemia. *Lancet* 1983; **321:** 1452–4.
11. Kern W, Kurrle E, Vonek H, High risk of streptococci septicemia after high dose of cytosine arabinoside treatment for acute myelogenous leukemia. *Klin Wochenschr* 1987; **67:** 773–80.
12. Press OW, Petersen SR, Larson EB et al, Hickman catheter infections in patients with malignancies. *Medicine* 1984; **63:** 189–200.
13. Raad II, Bodey GP, Infectious complications of indwelling vascular catheters. *Clin Infect Dis* 1992; **15:** 197–210.

14. Elting LS, Bodey GP, Septicemia due to *Xanthomonas* species and non-aeruginosa *Pseudomonas* species: increasing incidence of catheter-related infections. *Medicine* 1990; **69:** 296–306.
15. Whimbey E, Kiehn TE, Brannon P et al, Bacteremia and fungemia in patients with neoplastic disease. *Am J Med* 1987; **82:** 723–30.
16. Schimpff SC, Satterlee W, Young VM, Serpick A, Empiric therapy with carbenicillin and gentamicin for febrile patients with cancer and granulocytopenia. *N Engl J Med* 1971; **284:** 1061–5.
17. Bodey GP, Evolution of antibiotic therapy for infection in neutropenic patients: studies at MD Anderson Hospital. *Rev Infect Dis* 1989; **11**(Suppl 7): S1582–90.
18. The EORTC International Antimicrobial Therapy Cooperative Group, Gram-positive bacteraemia in granulocytopenic cancer patients. *Eur J Cancer* 1990; **26:** 569–74.
19. Hughes WT, Armstrong D, Bodey GP et al, 1997 Guidelines for the use of antimicrobial agents in neutropenic patients with unexplained fever. *Clin Infect Dis* 1997; **25:** 551–73.
20. De Pauw BE, Donnelly JP, Elves A et al, Towards individually tailored empiric antibiotic therapy in febrile granulocytopenic patients. *Neth J Med* 1990; **37:** 111–19.
21. Klastersky J, Treatment of neutropenic infection: trends towards monotherapy? *Support Care Cancer* 1997; **5:** 365–70.
22. Maschmeyer G, Hiddeman W, Link H et al, Management of infections during intensive treatment of hematologic malignancies. *Ann Hematol* 1997; **75:** 9–16.
23. The EORTC International Antimicrobial Therapy Cooperative Group, Ceftazidime combined with a short or long course of amikacin for empirical therapy of Gram-negative bacteremia in cancer patients with granulocytopenia. *N Engl J Med* 1987; **317:** 1692–8.
24. Anaissie EJ, Fainstein V, Bodey GP et al, Randomized trial of beta-lactam regimens in febrile neutropenic cancer patients. *Am J Med* 1988; **84:** 581–9.
25. Bodey GP, Fainstein V, Elting LS et al, β-lactam regimens for the febrile neutropenic patient. *Cancer* 1990; **65:** 9–16.
26. Winston DJ, Ho WG, Bruckner DA, Champlin RE, Beta-lactam antibiotic therapy in febrile granulocytopenic patients – a randomized trial comparing cefoperazone plus piperacillin, ceftazidime plus piperacillin, and imipenem alone. *Ann Intern Med* 1991; **115:** 849–59.
27. Rolston KVI, Berkey P, Bodey GP et al, A comparison of imipenem to ceftazidime with and without amikacin as empiric therapy in febrile neutropenic patients. *Arch Intern Med* 1992; **152:** 283–91.
28. De Pauw BE, Deresinski SC, Feld R et al, Ceftazidime compared with piperacillin and tobramycin for the empiric treatment of fever in neutropenic patients with cancer – a multicenter randomized trial. *Ann Intern Med* 1994; **120:** 834–44.
29. The EORTC International Antimicrobial Therapy Cooperative Group and National Cancer Institute of Canada, Vancomycin added to empirical combination antibiotic therapy for fever in granulocytopenic cancer patients. *J Infect Dis* 1991; **163:** 951–8.
30. De Pauw BE, for the Meropenem Study Group of Leuven–London–Nijmegen, Meropenem and ceftazidime are equally effective as single agents for empirical therapy of the febrile neutropenic patient. *J Antimicrob Chemother* 1995; **36:** 185–200.
31. Cometta A, Calandra T, Gaya H et al, Monotherapy with meropenem versus combination therapy with ceftazidime plus amikacin as empiric therapy for fever in granulocytopenic patients with cancer. *Antimicrob Agents Chemother* 1996; **40:** 1108–15.
32. The EORTC International Antimicrobial Therapy Cooperative Group and National Cancer Institute of Canada, Vancomycin added to empirical combination antibiotic therapy for fever in granulocytopenic cancer patients. *J Infect Dis* 1991; **163:** 951–8.
33. Nováková IRO, Donnelly JP, De Pauw BE, Ceftazidime as monotherapy or combined with teicoplanin for initial empiric treatment of presumed bacteremia in febrile granulocytopenic patients. *Antimicrob Agents Chemother* 1991; **35:** 672–8.
34. Ramphal R, Bolger M, Oblon DJ et al, Vancomycin is not an essential component of the initial empiric treatment regimen for febrile neutropenic patients receiving ceftazidime – a randomized prospective study. *Antimicrob Agents Chemother* 1992; **36:** 1062–7.
35. Kelsey SM, Weinhardt B, Collins PW, Newland AC, Teicoplanin plus ciprofloxacin versus

gentamicin plus piperacillin in the treatment of febrile neutropenic patients. *Eur J Clin Microbiol Infect Dis* 1992; **11:** 509–14.
36. Rolston KVI, Bodey GP, Elting L, Aztreonam in the prevention and treatment of infection in neutropenic cancer patients. *Am J Med* 1990; **88**(Suppl 3C): S24–9.
37. Donnelly JP, Nováková IRO, Raemaekers JMM, De Pauw BE, Empiric treatment of localized infections in the febrile neutropenic patients with monotherapy. *Leuk Lymphoma* 1993; **9:** 193–203.
38. Nováková IRO, Donnelly JP, De Pauw B, Potential sites of infection that develop in febrile neutropenic patients. *Leuk Lymphoma* 1993; **10:** 461–7.
39. Gomez L, Martino R, Rolston KV, Neutropenic enterocolitis: spectrum of the disease and comparison of definite and possible cases. *Clin Infect Dis* 1998; **27:** 695–9.
40. Commers JR, Robichaud KJ, Pizzo PA, New pulmonary infiltrates in granulocytopenic patients being treated with antibiotics. *Pediatr Infect Dis* 1984; **3:** 423–8.
41. Maschmeyer G, Link H, Hiddeman W et al, Pulmonary infiltrations in febrile patients with neutropenia. *Cancer* 1994; **73:** 2296–304.
42. Dompeling EC, Donnelly JP, Raemaekers JMM, De Pauw BE, Pre-emptive administration of corticosteroids prevents the development of ARDS associated with *Streptococcus mitis* bacteremia following chemotherapy with high-dose cytarabine. *Ann Hematol* 1994; **69:** 69–72.
43. Malik IA, Abbas Z, Karim M, Randomised comparison of oral ofloxacin alone with combination of parenteral antibiotics in neutropenic febrile patients. *Lancet* 1992; **339:** 1092–6.
44. Rubinstein EB, Rolston K, Benjamin RS et al, Outpatient treatment of febrile episodes in low-risk neutropenic patients with cancer. *Cancer* 1993; **71:** 3640–6.
45. Kern WV, Cometta A, de Bock R et al, Oral versus intravenous empirical antimicrobial therapy for fever in patients with granulocytopenia who are receiving cancer chemotherapy. *N Engl J Med* 1999; **341:** 312–18.
46. Dompeling EC, Donnelly JP, Raemaekers JMM et al, Evolution of the clinical manifestations of infection during the course of febrile neutropenia in patients with malignancy. *Infection* 1998; **26:** 349–54.
47. De Pauw BE, Dompeling EC, Antibiotic strategy after the empiric phase in patients treated for a hematological malignancy. *Ann Hematol* 1996; **72:** 273–9.
48. De Pauw BE, Raemaekers JMM, Schattenberg T, Donnelly JP, Empirical and subsequent use of antibacterials agents in the febrile neutropenic patient. *J Intern Med* 1997; **242:** 69–77.
49. O'Hanley P, Easaw J, Rugo H, Easaw S, Infectious disease management of adult leukemic patients undergoing chemotherapy: 1982 to 1986 experience at Stanford University Hospital. *Am J Med* 1989; **87:** 605–13.
50. Bodey GP, Bueltman B, Duguid W et al, Fungal infections in cancer patients: an international autopsy survey. *Eur J Clin Microbiol Infect Dis* 1992; **11:** 99–109.
51. Anaissie EJ, Vartivarian S, Bodey GP et al, Randomized comparison between antibiotics alone and antibiotics plus granulocyte–macrophage colony-stimulating factor (*Escherichia-coli*-derived) in cancer patients with fever and neutropenia. *Am J Med* 1996; **100:** 17–23.
52. Bennett CL, Weeks JA, Somerfield MR et al, for the Health Services Research Committee of the American Society for Clinical Oncology, Use of hematopoietic colony-stimulating factors: comparison of the 1994 and 1997 American Society of Clinical Oncology surveys regarding ASCO clinical practice guidelines. *J Clin Oncol* 1999; **17:** 3676–81.

7

Evaluation and management of fever in the neutropenic hematopoietic stem cell transplant patient

James C Wade

INTRODUCTION

Current estimates of the numbers of stem cell transplants performed each year range from 20 000 to 40 000, and continue to increase. Indications for transplantation now include malignant, non-malignant, and congenital diseases. The development of non-myeloablative approaches for allogeneic transplantation have expanded the ability to test transplantation as therapy for common solid tumors (e.g. renal, melanoma, prostate, breast, cervical, etc.), and to offer transplantation to individuals who because of age or major organ dysfunction were otherwise not candidates for a conventional transplant.[1,2] The sources of stem cells for transplantation include bone marrow, mobilized peripheral blood, cord blood, and fetal liver, which can be obtained from autologous or related and unrelated allogeneic sources. Marrow transplantation is now more appropriately referred to as hematopoietic stem cell transplantation (HSCT).

Increased susceptibility to infection remains a major obstacle and cause of mortality for patients undergoing HSCT.[3,4] The past decade has led to a better understanding of the pathogenesis of infection syndromes, the development of new diagnostic techniques, the introduction of new, more effective antimicrobials, and the adoption of empiric or preemptive therapy strategies have enhanced patient survival. However, the problem of infection for HSCT recipients remains a dynamic one, with shifts in the patterns of isolated pathogens, changes in the antimicrobial susceptibility of pathogens, introduction of new transplant conditioning regimens, and the increasing use of alternative donors. The incidence of infection-related death within the first 30 days after transplant ranges from 5% to 10%, but the susceptibility to infection for some patients may persist for months and years after HSCT.[4,5]

There is a characteristic pattern of immunodeficiency and immune reconstitution that accompanies an HSCT.[5] Four periods are now recognized:

1. *Pretransplant*, corresponding to the period of infection risk just prior to transplantation. This risk is secondary to the patient's previous therapy and underlying disease.
2. *Pre-engraftment*, corresponding to the weeks prior to marrow engraftment. This is the period of greatest risk for patients who receive an autologous graft, but is only the first risk period for allogeneic HSCT recipients.[5–7]
3. *Mid-recovery*, corresponding to the period

from engraftment to approximately day 100 post-engraftment.
4. *Late recovery*, corresponding to the time interval beyond 3 months after transplant.

Pretransplant

This is a critical period for all HSCT recipients. The increase in intensity of therapy given prior to transplantation makes the presence of subclinical vascular access device infection, occult hepatosplenic candidiasis, or subclinical invasive sinus or pulmonary fungal infections more common. Effective pretransplant treatment and post-transplant infection suppression is dependent on the identification of such infections before the conditioning therapy is started. This is also the time in which the presence of important latent herpes group viruses, or active hepatitis virus should be detected through serologic evaluations.

Pre-engraftment

This risk period begins with the onset of the conditioning regimen, and continues until approximately day 30 after transplantation. Neutropenia is the primary predisposing factor, but the absence of neutrophils and other phagocytes is usually accompanied by alimentary tract mucositis, the presence of central venous catheters, and microbial flora shifts.[6,7] HSCT recipients are compromised by the ability of their endogenous flora to invade through disrupted mucosal and cutaneous barriers and cause systemic bacterial and fungal infections.[8,9] These risks are further increased in patients with delayed engraftment after transplantation.

Mid-recovery

This period begins with engraftment, and continues until approximately day 100, when early B- and T-cell function begins to recover. This period is characterized by the reappearance of neutrophil function, and therefore infections associated with neutropenia are uncommon unless the marrow function remains fragile, due to graft rejection, disease relapse, marrow-suppressing factors such as medications (e.g. ganciclovir), or viral infection (e.g. cytomegalovirus (CMV) human herpesvirus-6 (HHV-6), or HHV-8).[10–12] Cellular immune dysfunction is the primary immune defect during this period. Late-onset aspergillosis occurs during this period, and affects 10–15% of allogeneic transplant recipients.[13]

Late-recovery

This post-transplant infection risk period begins with the 4th month after transplant, and continues until the patient has successfully been tapered off of all immunosuppression and is free of chronic graft-versus-host disease (GVHD). Persistent cellular and humoral immune dysfunction may lead to recurrent viral, bacterial, and fungal infections.[14–17]

The late-recovery period is also the time of greatest risk of relapse of the patient's primary disease. Relapse is often associated with the rapid onset of marrow failure and resultant neutropenia. Management of these patients is particularly complicated, because of the refractory nature of their primary disease, and the accompanying GVHD that may have been present prior to relapse or is induced as a mechanism to enhance primary disease control.[18,19]

EVALUATION, PREVENTION, AND MANAGEMENT OF INFECTION

This chapter will focus on the infections in HSCT recipients that occur primarily during periods of neutropenia. Many of the evaluation and management principles for patients with fever and neutropenia are applicable to HSCT recipients.[6,7] Consequently, this chapter will review evaluation and management approaches

in general, and discuss in greater depth those issues that are unique to HSCT recipients.

Neutropenia is primarily a consequence of the transplant-conditioning regimen or pre-transplant marrow failure state induced by the patient's primary disease. Fever and neutropenia are most common during the pretransplant and pre-engraftment period, although neutropenia may occur later as a consequence of infection (e.g. CMV, HHV-6, HHV-8, or parvovirus B19), medication toxicity (e.g. ganciclovir), graft rejection, or post-transplant relapse of the primary illness. The risk of neutropenia-associated infection for HSCT patients is enhanced by the presence of mucosal or integumentary barrier disruption induced by cytotoxic chemotherapy, irradiation, GVHD or the presence of long-term indwelling vascular access devices. Medication-induced central nervous system dysfunction, and the microbial floral shifts that accompany severe illness or the administration of antibiotics also enhance the infection risk.[4,5,8,9]

The primary sources of pathogens for neutropenic HSCT recipients are their endogenous bacterial and fungal flora, airborne molds and respiratory viruses, microorganisms on the hands of healthcare providers, and latent viruses. Sites of infection for HSCT patients are similar to those for other neutropenic hosts. Infections originate primarily from the alimentary tract (i.e. mouth, pharynx, esophagus, large and small bowel, and rectum), sinuses, lungs, and skin.[6,7] Most febrile episodes that occur during the pre-engraftment period are infectious in origin.[6,20,21] Bacterial infections account for more than 90% of the first infection during neutropenia. Herpes simplex virus (HSV) and the respiratory viruses (e.g. influenza A and B, parainfluenza, and respiratory syncytial virus (RSV)) are also identified as first-infection pathogens[22] (Table 7.1). Antibiotic-resistant bacteria, yeast, molds, and viruses are common causes of subsequent infections.[23] The initial bacterial pathogens for HSCT recipients are

Table 7.1 Infectious syndromes after HSCT pre-engraftment period

Syndrome	Relative frequency[a]	Relative life-threatening potential[a]
First fever:		
Staphylococci	3+	1+
Viridans streptococci	1+	2+
Gram-negative bacilli	1+	3+
Respiratory virus	1+	3+
Subsequent infection:		
Antibiotic-resistant bacteria	2+	
Gram-positive cocci		1+
Gram-negative bacilli		2–3+
Fungi	2–3+	3–4+
Respiratory virus	1+	3+

[a] Frequency and life-threatening potential increase from 1 to 4+.

usually Gram-positive cocci.[24] Of these, coagulase-negative staphylococci, streptococci, and enterococci predominate, but infections with *Staphylococcus aureus* and *Corynebacteria jeikeium* remain important.[25–29] Despite the perceived decreased virulence of many of these Gram-positive pathogens, there is attributable mortality ascribed to such infections. Wenzel and co-workers[30–32] reported that attributable mortality for coagulase-negative staphylococcal bloodstream infections was 13.6% (95% confidence interval (CI) 4.2–22.9%) and 37.1% (95% CI 10–64%) for bloodstream infections caused by vancomycin-resistant enterococci (VRE). A recent report from the Mayo clinic noted that colonization with VRE increased the risk of developing a VRE bloodstream infection, and was also associated with an increased risk of death post-transplant for allogeneic transplant recipients.[33] Several large series have reported rates of bloodstream infection with viridans streptococci of 15–25% among HSCT recipients.[26–28] Approximately 10% of viridans streptococcal infections are associated with a 'toxic-shock'-like syndrome that can be rapidly fatal even with the institution of appropriate antibiotics. Thus, while empiric therapy directed at such pathogens may not always be required, appropriate pathogen-directed therapy is mandatory when such organisms are isolated.

Gram-negative bacteria are the most virulent bacterial pathogens during the neutropenic period, and historically have been responsible for the highest rates of morbidity and mortality.[6,7] The common Gram-negative bacilli remain *Escherichia coli*, *Klebsiella* spp. and *Pseudomonas aeruginosa*. The increased use of broad-spectrum cephalosporins and the carbapenem antibiotics has increased the frequency of isolation of β-lactam resistant *Enterobacter* spp. and *Stenotrophomonas maltophilia*.[34–36]

Increasing resistance to multiple antibiotics among many of these pathogens poses a significant problem in planning empiric treatment for HSCT patients. It is critical to be aware of each institution's specific antibiotic susceptibility patterns and to remember that pathogens and antibiotic susceptibility patterns are a dynamic process and change over time. Antibiotic resistance remains most prominent among the Gram-positive pathogens, specifically the coagulase-negative staphylococci. Transplant recipients at the Fred Hutchinson Cancer Research Center (FHCRC) in the calendar year 1999 experienced 374 bloodstream infections, for a rate of 0.718 bloodstream infections/100 patient days (Table 7.2). Of these infections 359 were caused by a single pathogen, 63% occurred during the pre-engraftment period and more than half were caused by coagulase-negative staphylococci. The antibiotic resistance pattern for selected coagulase-negative staphylococci and viridans streptococci show a high level of resistance to standard β-lactam antibiotics. However, despite the almost exclusive referral nature of the FHCRC patient population, the incidence of bloodstream infections due to antibiotic-resistant *S. aureus* and VRE remains low.

The pathogens responsible for the subsequent or second infections include antibiotic-resistant bacteria, fungal pathogens, and viruses. Wingard et al[23] have reported that *Staphylococcus epidermidis* is responsible for 50% of the second or subsequent infections. Gram-negative bacilli are responsible for an additional 10%, with the majority of remaining pathogens being predominately fungal. These infections, with the exception of coagulase-negative staphylococci, are difficult to diagnose, more resistant to treatment, and associated with the highest rates of morbidity and mortality.[13,37–39]

EVALUATION AND MANAGEMENT OF NEUTROPENIA-ASSOCIATED INFECTIONS

There are several clinical guidelines for the prevention and empiric treatment of infection in the neutropenic host: the National Cancer Comprehensive Network (NCCN) Clinical Guidelines for Fever and Neutropenia; the

Table 7.2 Bacterial bloodstream isolates, FHCRC 1999

Single-organism bloodstream infections			
Total	359		
Coagulase-negative staphylococci		193	
Enterococci		41	
E. faecalis			22
E. faecium			11
VRE[a]			8
Streptococcus spp.		52	
Staphylococcus aureus		13	
MRSA[b]			2
Gram-negative bacilli		33	
Non-tuberculosis *Mycobacteria*		8	
Other		19	

[a] Vancomycin-resistant enterococci.
[b] Methicillin-resistant *S. aureus*.

Infectious Diseases Society of America (IDSA); and www.cancernetwork.com; www.cdc.gov.[20,21] There is also a diversity of infection management practices among the different transplant centers. However, effective care for HSCT recipients relies on a coordinated approach that utilizes center-wide infection control, infection prevention, and a combination of empiric and pre-emptive therapy. Transplant centers must customize their practices based on their own patient population, cytotoxic regimens used, and local infection and susceptibility patterns.

Infection control

The single most powerful preventive measure for the neutropenic HSCT patient is handwashing performed by the healthcare staff and other individuals who come into contact with these patients. Handwashing, while effective, continues to be difficult to implement and a challenge to maintain compliance. Hand soap that contains chlorhexidine adds residual antimicrobial effect to the mechanical cleansing that occurs with the physical washing. Gloves, if used, should be put on only after entering a patient's room and the handwashing has been completed. Gloves should be removed prior to leaving the patient's room, and should never be utilized for more than one patient contact. Antimicrobial hand rubs can be used if soap, water, and sinks are not easily accessible. The new alcohol-containing waterless products appear to be well tolerated and effective adjuncts to recurrent handwashing. Keeping staff and patient visitors who have respiratory symptoms (e.g. uncontrolled cough and respiratory secretions, conjunctivitis, or systemic symptoms) from having contact with patients may decrease the risk of patients acquiring a potentially serious respiratory viral infection. Annual vaccination of healthcare workers against viral influenza is also important.

HSCT patients are no longer routinely cared for during the pre-engraftment period in total

sterile environments (laminar-airflow (LAF) units). This change in practice does not suggest that measures to decrease the exposure of patients to potential pathogens are not beneficial, but rather that less intrusive infection control measures can be implemented and still accomplish the outcome goals. HSCT patients should only be hospitalized in single-bed rooms, and care should be delivered by a healthcare team that is familiar with transplant procedures and understands the importance of minimizing the nosocomial transmission of potential pathogens.[40] Inpatient and preferably outpatient clinics or day-hospital facilities should be ventilated with air that has been cleansed by high-efficiency air (HEPA) filters. Patient areas should also include a ventilation system that can deliver at least 15 air exchanges per hour. This level of clean-air ventilation is recommended with the intent of decreasing the incidence of mold and other airborne infections for HSCT patients. However, the protection with these measures is not complete. Increased proportions of the pre-engraftment period may occur outside of these 'clean' environments, and, even when hospitalized, HSCT recipients spend time away from the transplant unit while undergoing imaging or endoscopic procedures.

Barrier isolation has been relegated to those situations where one is attempting to minimize the spread by contact of potential pathogens. Isolation of patients known to be colonized or infected with a pathogen that is multiply antibiotic-resistant, or is known to have an increased propensity for nosocomial transmission (i.e. respiratory viruses), appears to be important.[22,41]

The presence of subclinical, or latent, infection must be determined prior to the initiation of the transplant-conditioning regimen. Some patients may be actively infected when they are referred for HSCT, and these infections may have a direct effect on the patient's outcome. The patient's history of infections during prior treatment may reveal important information regarding risks of infection that may occur during future periods of neutropenia. An infected HSCT candidate should not be excluded from transplantation unless the infection cannot be adequately controlled pretransplant and measures to maintain infection control during the post-transplantation period are unavailable. A prior history of either invasive mold (e.g. aspergillosis) or disseminated candidiasis (e.g. hepatosplenic candidiasis) often raises concerns about the patient's suitability for transplantation. A retrospective review conducted at the FHCRC reported 15 patients with documented hepatosplenic candidiasis pretransplant.[42] All patients had been treated with amphotericin B therapy before transplantation, and all had improvement in their infection documented by computed tomography (CT) scans before the transplant-conditioning therapy was initiated. These patients had no appreciable increased risk of recurrent yeast bloodstream infection after transplantation. Bjerke et al[42] concluded that a history of disseminated candidiasis was not an absolute contraindication to transplantation.

Transplantation for patients with a previously documented invasive mold infection has been more difficult. Offner et al[43] reported 48 patients who underwent HSCT with a pretransplant history of documented or presumed aspergillosis. Of these 48 patients, 11 received an autologous HSCT. One-third of these patients experienced a documented recurrence of aspergillosis post-transplant, with recurrent aspergillosis having an 88% mortality rate. The authors noted a trend toward a lower incidence of recurrent infection and improved survival for patients with a longer interval between the development of invasive aspergillosis and transplantation. Patients who received preemptive antifungal therapy or underwent an autologous transplant also had a lower frequency of recurrent infection. Surgical resection of disease pretransplantation provided no survival advantage for these patients.

The unpublished experience at the FHCRC for patients with a prior history of aspergillosis is equally discouraging. We have transplanted 34 such patients with conventional allogeneic

transplantation. All patients had been extensively treated with amphotericin B (>8 weeks), and prior to transplantation had shown clinical and radiological improvement or resolution of their infection. All received amphotericin B during the period of maximum immunosuppression. Of the 34 patients, 15 experienced a recurrent aspergillus infection post-transplant, and 12 others died from transplant-related mortality without a documented mold recurrence. Of the 6 patients who survived, 5 had an interval between diagnosis of aspergillosis and transplantation of at least 9 months (range 9 months–3.5 years). Recurrent aspergillosis was uniformly fatal. While some patients with a previous history of aspergillosis may be candidates for autologous transplantation, allogeneic transplantation is associated with a high incidence of recurrent infection and mortality despite pre-emptive antifungal therapy.

PREVENTION OF INFECTION

Bacterial

Antibacterial prophylaxis for patients with neutropenia remains controversial. Data supporting the effectiveness of chemoprophylaxis with antibiotic(s) are balanced by a similar number of reports that fail to show true efficacy. A meta-analysis of 19 randomized trials of fluoroquinolone prophylaxis in patients with neutropenia revealed a decrease in the number of documented Gram-negative bacillary infections, but no effect on the frequency of febrile episodes, febrile morbidity, or infection-associated mortality.[44] Many of these trials have shown an increase in Gram-positive infections among patients who received fluoroquinolones or trimethoprim/sulfamethoxazole prophylaxis. The use of prophylactic antibiotics has also been reported to increase the risk of subsequent or secondary fungal infections.[21] Few of these prophylactic trials have been performed exclusively in HSCT recipients, but this prophylactic approach has nonetheless been used liberally for HSCT recipients. Patients transplanted at the FHCRC are routinely given prophylactic, systemic antibacterial antibiotics when their neutrophil count decreases below 500/μl. This practice is based on a previously published study that compared the pre-emptive use of broad-spectrum antibiotics during the pre-engraftment period versus LAF unit isolation.[40] Infection morbidity and patient survival were similar for both groups. The pre-emptive antibiotic regimen used at the FHCRC has evolved over time, but presently consists of oral ciprofloxacin or intravenous ceftazidime. Whether pre-emptive antibiotic therapy truly increases patient survival if compared with withholding antibiotic treatment until the first sign of infection (fever) has not been tested.

Fungal

The incidence of fungal infections has increased among HSCT recipients during the last decade. Centers now report an incidence that varies between 10% and 20%.[4,5,13,37–39] Diagnosis and treatment remain suboptimal, and preventing exposure or blocking colonization with these pathogens is difficult. *Candida* colonization is present in as many as 80% of HSCT recipients pretransplantation, and persists throughout the first three months after transplantation unless patients receive azole suppression.[38] When the fungal pathogen originates from the environment, the protection provided by measures such as sterile environments and HEPA filtration are limited to the time period when patients are being cared for in these clean facilities. The true incidence of colonization with *Aspergillus* among HSCT recipients is unknown, but Wald et al[13] in their study of 2496 consecutive HSCT patients reported that 2% of such patients became colonized at some time post transplant. However, only 21% of patients who ultimately developed invasive aspergillosis had documented preinfection colonization. Yet, when *Aspergillus* colonization was detected, it was associated with a 60% positive predictive

value for the development of invasive aspergillosis. The positive predictive value increased to 94% if the HSCT patient was neutropenic.[13]

The use of masks by patients or healthcare workers has not consistently affected the incidence of fungal infections. This lack of efficacy may be in part due to poor patient tolerance, or the fact that the masks do not fit tightly enough to be an effective barrier against fungal spores. The use of aerosolized or intravenous amphotericin B has provided inconsistent prevention results.[45–50] The study by Perfect et al,[48] which tested low-dose intravenous amphotericin B prophylaxis, reported a similar incidence of invasive fungal infection for both the treatment and placebo groups (8.8% versus 14.3%, respectively). The potential efficacy of prophylaxis with lipid formulations of amphotericin B was also tested by Tollemar et al.[49] They reported that this therapy decreased fungal colonization but provided no mortality benefit. The need for intravenous administration and the potential toxicity and cost of the lipid formulations of amphotericin B makes them poorly suited for prophylaxis. Itraconazole is potentially useful for the prevention of a variety of fungal infections, including aspergillosis, but its efficacy as prophylaxis in HSCT patients has not been proven. Itraconazole has been difficult to administer to HSCT recipients because of erratic absorption, numerous drug–drug interactions (e.g. with cyclosporine and tacrolimus), and medication-associated gastrointestinal intolerance. Concomitant administration of cyclosporine and itraconazole causes altered cyclosporine metabolism, and results in the need to decrease the daily cyclosporine dosage by 20–50% (J Wingard, personal communication, 2000). The availability of a new oral cyclodextran–itraconazole formulation, plus an intravenous itraconazole preparation, may make this drug more efficacious.

Fluconazole has been shown to be highly effective for preventing *Candida albicans* infection among allogeneic HSCT recipients.[51,52] A dose of 400 mg daily, given from the time of conditioning therapy to day 75 after transplant, significantly reduced superficial infection and invasive disease and decreased the use of amphotericin B. In the trial reported by Slavin et al,[5] fluconazole not only decreased the incidence of *C. albicans* infections but also improved patient survival. Long-term follow-up of this study cohort has recently been reported by Marr et al.[52] After 8 years of follow-up, survival remains significantly better for fluconazole recipients (68/152 versus 41/148, respectively), and the incidence of invasive candidiasis and death due to candidiasis remain lower for fluconazole recipients. Patients treated with fluconazole also had a lower incidence of severe gut GVHD and death from GHVD complications.

The benefit of fluconazole for autologous HSCT patients remains controversial.[4] These patients appear to have a risk of developing candidiasis that is similar to that of patients with acute leukemia who undergo induction or reinduction therapy. Fluconazole has not been shown to provide a consistent benefit for such patients.[53] In general, fluconazole prophylaxis is probably not necessary for patients receiving an autologous transplant unless the conditioning regimen is expected to cause severe mucositis.

Viral

Viral infections that occur during the early post-transplant period include respiratory virus (e.g. RSV, parainfluenza, adenovirus, and influenza) and HSV. Early post-transplant CMV infection and disease do occur, but infrequently.[54] Infection control measures are critical for the prevention of respiratory virus infections. This may even require delaying patients' transplantation, if their underlying disease is stable and the incidence of such viral infections are epidemic in the surrounding community or excessive among the transplant center's healthcare team. When HSCT patients, primary caregivers, or family members are exposed to influenza,

prompt prophylaxis with zanamivir aerosol, 10 mg by inhalation daily, or oral oseltamivir, 75 mg orally twice daily, should be considered.

The use of acyclovir (5 mg/kg intravenously twice daily or 400–800 mg orally twice daily), famciclovir 500 mg twice daily, or valacyclovir 500 mg twice daily have all been shown to be highly effective in the prevention of HSV infections.[4,5,55] Suppression of HSV during the pre-engraftment period may decrease the mucosal disruption cause by this viral recurrence, and, as reported by Baglin et al,[56] the management of HSV infections can minimize the duration and frequency of febrile episodes.

ADJUNCTIVE MEASURES

Peripheral blood stem cells

The transition from bone marrow to growth-factor-mobilized peripheral blood stem cells (PBSC) as the hematopoietic stem cell product has been an important improvement. The use of PBSC has become standard practice for most autologous transplants. A randomized trial conducted by Weaver et al[57] reported that the infusion of at least 5×10^6 $CD34^+$ stem cells resulted in a median duration of post-transplant neutropenia (<500 polymorphonuclear leukocytes (PMN)/μl) of 11 days. This shortened period of neutropenia may potentially decrease a patient's risk of neutropenia-associated infection. However, the Seattle group has reported that when autologous PBSC products are preferentially selected for $CD34^+$ cells, immune reconstitution is delayed.[58,59] This delay has resulted in an increased incidence of CMV disease, varicella zoster virus (VZV) reactivation, and invasive bacterial, *Candida*, or severe respiratory viral infections.

The observation that PBSC speeds engraftment among autologous HSCT recipients led to the testing of such an approach for HSCT recipients who were to receive matched related donor transplants.[60–62] Bensinger et al[61] reported that the use of allogeneic PBSC decreases the duration of neutropenia (<500 PMN/μl) from a median of 21 days with bone marrow to 16 days with PBSC. This decrease in the duration of neutropenia was not associated with a statistically significant decrease in the incidence of fever or death from infection, but death from the idiopathic pneumonia syndrome was decreased. Most importantly, PBSC recipients had improved disease-free and overall survival. These results are consistent with other reports.[60,62] The retrospective International Bone Marrow Transplant Registry (IBMTR) review suggested that PBSC resulted in a decrease in duration of neutropenia and shorter hospital stays.[60] The appropriate dose for an allogeneic PBSC is unclear, but engraftment is enhanced with a dose of at least 5×10^6 $CD34^+$ cells/kg. The incidence of acute GHVD appears to be similar for both bone marrow and PBSC, but the incidence of chronic GHVD increases when the cell dose exceeds 8×10^6 $CD34^+$ cells/kg.[61] Chronic GVHD occurring among PBSC recipients may also be more severe and difficult to treat.[63] The finding of an increase in treatment-refractory chronic GVHD does not have a direct impact on the pre-engraftment period, but clinicians must be cautious when techniques such as PBSC minimize the immunosuppression (neutropenia) of one post-transplant period (pre-engraftment), but potentially increase the infection risk for a later period (late recovery).

Growth factors

The American Society of Clinical Oncology (ASCO) has recently updated their guidelines for the use of growth factors.[64] Granulocyte and granulocyte–macrophage colony-stimulating factors (G-CSF and GM-CSF) have consistently been shown to hasten hematopoietic cell recovery, but this increase in neutrophil recovery has not translated into a consistent decrease in neutropenia-associated infections or improvement in survival.[64,65] The ASCO guidelines now recommend limited 'primary neutropenia prophylaxis', and the standard practice at the

FHCRC is only to use them in cases of delayed engraftment (<500 PMN/μl) persisting beyond day 21 after transplantation.

Granulocyte transfusions

The primary immune defect during the pre-engraftment period is the absence of neutrophils. Early trials showed benefit for Gram-negative bacillary infections when donor granulocytes were transfused.[66,67] However, the routine use of transfused granulocytes has been compromised by the inability to collect adequate numbers, and these transfusions were often complicated by acute infusion reactions, an increased risk of alloimmunization, and the potential transmission of CMV infection from the donor to the transplant recipient.[68] There has recently been a resurgence of interest in granulocyte transfusions with the observation[69] that donor priming using growth factors and corticosteroids can increase the granulocyte yield to $(8–10) \times 10^{10}$. This dose of infused granulocytes can result in the transfusion recipient having a 1 hour post-transfusion white blood cell count of $(2.6 \pm 2.6) \times 10^3$ PMN/μl. Growth-factor-mobilized granulocyte transfusions to date have been tested primarily among HSCT patients with severe antibiotic-resistant fungal or bacterial infections.[70] While the efficacy of this approach has not yet been established, the Seattle group has shown that this type of transfusion can be effectively accomplished using a related or an unrelated community donor.[71] Adkins et al[72] have published results from the only prophylactic G-CSF-mobilized granulocyte trial in HSCT recipients. Patients received four transfusions on days 2, 4, 6 and 8 after autologous transplantation. Leukocyte compatibility of donor and recipient was determined by screening for lymphocytoxicity against a panel of HLA-identified cells. All recipients received G-CSF-mobilized granulocytes from a single donor. Leukocyte incompatibility adversely affected the recipients' neutrophil increments after transfusion, and resulted in a delay in neutrophil engraftment, and increased the number of days of fever, platelet transfusions, and intravenous antibiotics. While the number of granulocytes that can be collected has been increased with growth-factor mobilization, the clinical benefit of such a prophylactic or therapeutic approach has not yet been demonstrated.

EVALUATION AND TREATMENT OF INFECTION

Most episodes of fever during periods of neutropenia are infectious in origin. These infections have the potential to be rapidly fatal if not empirically treated.[9] First infections are most likely caused by bacterial pathogens, while subsequent infections are usually caused by fungal pathogens, antibiotic-resistant bacteria, or viral pathogens.[23] The initial evaluation and management of HSCT patients is not significantly different than that of patients undergoing remission-induction or intensive consolidation treatment for acute leukemia. Guidelines for the management of such patients have been developed by several groups.[20,21] The NCCN guidelines provide an excellent road map to manage HSCT patients during their pre-engraftment period.[20] In the latest version of these practice guidelines, a neutrophil count of <500 PMN/μl has been defined as neutropenia, and a single temperature of >38.0°C requires clinical intervention. The patient's evaluation should be focused on determining the causative organism and potential site of infection. HSCT recipients experience increased morbidity with respiratory viruses, so determining exposure to ill family members or caregivers is important. Laboratory assessment should focus on studies that help to define the functional status of the liver, kidneys, and lungs. Imaging procedures (e.g. chest radiographs, etc.) should be considered when patients have any site-specific symptoms. We routinely obtain a chest X-ray at the onset of fever, and consider a CT scan of the lungs for patients who remain febrile, have pulmonary symptoms, or have room-air oxygen

saturation levels below 90%. Sinuses are imaged most efficiently with a CT scan.

Specimens for culture should be collected during or immediately after completion of the patient's examination. Blood should be obtained prior to initiation of antibiotics, but antibiotic administration should not be delayed while radiographs or other site-specific cultures are obtained. There is general consensus that the volume of blood cultured is the most important variable in optimizing microbial recovery for adult patients.[73,74] It is recommended that at least two blood cultures, or 20–40 ml of blood, be collected. The IDSA clinical care guidelines recommend that two blood cultures be obtained – one from a peripheral site and a second from the central venous catheter.[21] The justification for this recommendation is the belief that disparity between the peripheral blood and the catheter blood culture may help identify catheter-related versus non-catheter-related infections. While drawing blood cultures from two different venipuncture sites may help to distinguish between clinically important and contaminant microorganisms, a meta-analysis of previously published studies has shown little utility for obtaining blood for culture from both the central indwelling venous catheter and a peripheral vein.[75] Thus, in many transplant centers, blood for culture is only drawn from the patient's vascular catheter. Quantitative blood cultures may be performed, but they are not routinely recommended because of cost and the limited impact they have on clinical care.[76,77]

Site-specific cultures are important for HSCT recipients. Cultures and biopsies from the sinus, lungs, and alimentary tract can be performed safely when they are coupled with appropriate platelet support and experienced subspecialty physicians (e.g. pulmonary critical/care, gastroenterologists, surgeons, and otolaryngologists). One must have a low threshold to biopsy cutaneous lesions that develop in the setting of fever and neutropenia. Histologic and microbiologic investigation of these cutaneous lesions may define the offending bacterial, fungal, or viral pathogen.

Diarrhea is common after transplantation. Diarrhea that occurs during the first 1–2 weeks after completion of the transplant-conditioning therapy usually results from treatment-induced mucosal injury. This type of diarrhea will usually resolve by day 10–14 after transplantation, but does signify additional mucosal injury that can be a portal for infection. Acute GVHD rarely occurs prior to day 14 post allogeneic transplant, but can be a major cause of diarrhea. Enteric infections that cause diarrhea are rare in the pre-engraftment period. Cox et al[78] prospectively studied 296 consecutive HSCT patients, and found that diarrhea occurred in 43%. However, diarrhea due to infection was uncommon, and accounted for only 13% of these episodes. In this study, organisms responsible for diarrhea included viruses (CMV, adenovirus, astrovirus, rotavirus) and bacteria (*Clostridium difficile* and *Aeromonas*). CMV enteritis is rare in the pre-engraftment period, and its overall incidence has decreased with the advent of CMV-specific prophylaxis or preemptive therapy.[4,5] Bacterial pathogens responsible for intestinal infection in the normal host (i.e. *Salmonella*, *Shigella*, *Campylobacter*, and *Yersinia*) almost never cause diarrhea in the hospitalized transplant recipient. Diarrhea secondary to intestinal parasites (e.g. *Cryptosporidium*, *Giardia lamblia*, and *Entamoeba histolytica*) is also unusual, but has been reported in center-specific outbreaks. The most common infectious cause of diarrhea during the pre-engraftment period is *C. difficile* colitis. The prevalence of this pathogen as part of a patient's endogenous alimentary flora varies. It is believed to be present in less than 3% of normal hosts but its incidence is higher among HSCT recipients.[79] A prospective study of all new patients arriving for transplantation at the FHCRC found that 21% of these patients had pre-existing colonization with *C. difficile*. These colonized individuals provide a center-specific reservoir of organisms that can be nosocomially transmitted to other susceptible patients, or for the colonized patient there can be future progression to

colitis once they are treated with antibiotic therapy. Optimal management of colonized patients is unclear, but infection control measures are imperative, and evaluation of diarrhea must always consider this pathogen.

INITIAL EMPIRIC THERAPY

HSCT recipients should be treated empirically with high-dose broad-spectrum antibiotics at the first sign (fever) of infection. At present, a large number of highly effective antibiotics are available. Despite many previous studies, it is not possible to recommend a single antibiotic or antibiotic combination as initial treatment for HSCT patients with fever and neutropenia.[20,21,80–83] The selection of antibiotics must take into consideration the following factors:

- The most common potential infecting pathogens.[4,5,36]
- The potential sites of infection.
- The antimicrobial susceptibility patterns of isolated pathogens. All infectious disease is local, and knowledge of local antimicrobial susceptibility patterns is critical in constructing the appropriate empiric regimen.
- Empiric regimens must provide broad-spectrum antibiotic coverage. Antibiotic regimens must provide a high-level of activity against Gram-negative bacilli, including *Ps. aeruginosa*, plus activity against Gram-positive organisms such as *S. aureus* and viridans streptococci.
- Pre-existing organ dysfunction. This is critical for HSCT patients, who often have been exposed to previous organ-damaging treatments (e.g. amphotericin B) or are receiving treatment that has inherent renal and liver toxicity (e.g. cyclosporine and tacrolimus). In general, aminoglycosides, with their inherent nephrotoxicity, should be used with caution in HSCT recipients.

There is considerable debate about the empiric use of vancomycin or antibiotics with increased broad-spectrum Gram-positive activity (e.g. Linezolid and Synercid) in patients with fever and neutropenia.[20,21] The primary justification for empiric therapy is the knowledge that a small number of Gram-positive pathogen infections can be rapidly fatal if not treated promptly with the appropriate antibiotics.[26,28,29] However, the only single large prospective randomized trial conducted in patients with fever and neutropenia failed to show a true clinical advantage for the use of empiric vancomycin.[84] This issue has not been directly studied in HSCT patients, but the European Organization for the Research and Treatment of Cancer (EORTC) trial reported that empiric use of vancomycin resulted in a decreased duration of fever, but did not improve survival and was associated with excess of renal and hepatic toxicity.

The primary barrier to the use of empiric vancomycin is the emergence of vancomycin-resistant pathogens. The development of colonization with vancomycin-resistant enterococci (VRE) has been associated with the increased use of vancomycin, although other antibiotics are also important.[30,85] Because of this risk of vancomycin-resistant pathogens, the initial empiric use of vancomycin or other new broad-spectrum Gram-positive antibiotics (Linezolid and Synercid) should be limited to HSCT patients who develop fever and have one or more of the following additional clinical factors.

1. Serious, clinically apparent catheter-related infections. Many of these infections are due to coagulase-negative staphylococci that have a very high (80%) level of β-lactam antibiotic resistance.
2. Substantial mucosal damage coupled with a high-risk of infection with penicillin-resistant viridans streptococci. Significant mucosal disruption is of constant concern for HSCT recipients, and, according to the SCOPE (Support of Commission Objectives and Project Environment) surveillance data, 18–29% of viridans streptococci isolated from blood cultures will be resistant to β-lactam antibiotics.[86,87]

3. Blood cultures positive for Gram-positive bacteria prior to final pathogen identification and susceptibility testing.
4. Known colonization with β-lactam-resistant pneumococci, methicillin-resistant *S. aureus* (MRSA), or VRE.
5. Previous prophylaxis with quinolone antibiotics or trimethoprim/sulfamethoxazole. Both of these agents have been associated with an increased risk of Gram-positive infections.[44,88,89] Recent molecular-epidemiology studies in HSCT recipients and patients with acute leukemia have confirmed the importance of alimentary tract colonization with coagulase-negative staphylococci as a risk factor for the development of blood stream infections with these pathogens.[90]
6. The development of hypotension or the sepsis syndrome without an identified pathogen.

Empiric vancomycin could be considered in any of these six clinical situations, but if vancomycin therapy is initiated, it should be discontinued after 3–4 days of treatment if an antibiotic-resistant organism is not identified. The empiric use of new agents such as Linezolid and Synercid is discouraged. Cost, lack of controlled trial experience, and potential marrow toxicity with Linezolid (personal communication Pharmacia/Upjohn) and significant musculoskeletal toxicity with Synercid provide reasons for caution when using these agents empirically in HSCT recipients.

PATIENTS WITH DOCUMENTED INFECTION SITES OR PATHOGENS

Identification of the causative pathogen allows the clinician the ability to optimize the antimicrobial regimen and use therapy with a lower incidence of adverse effects and costs. The duration of treatment for documented infections depends on the following factors:

- neutrophil recovery;
- rapidity of response to the antimicrobial therapy;
- the site of infection and isolated pathogen;
- status of the patient's engraftment;
- the patient's need for additional immunosuppression (e.g. corticosteroids).

In general, most uncomplicated skin and alimentary tract mucosal infections are adequately treated with 5–7 days of treatment.[20] For most bacterial bloodstream infections, 1–2 weeks of therapy are usually adequate, but fungal bloodstream infections require more prolonged therapy.[20,21,91] Three to four weeks of therapy are needed to effectively control bacterial sinus and lung infections, but a more prolonged antimicrobial treatment is required if the causative pathogen is *Ps. aeruginosa* or a mold.[20]

Catheter-associated infections

Catheter-associated infections remain problematic. Long-term venous access devices were initially developed for use in HSCT recipients, and are the standard of care for almost all HSCT patients. The long-term indwelling venous access device allows the clinician to administer high-dose multi-agent therapy, provide consistent venous access for blood product support, administer parenteral nutrition and antimicrobial therapy, and function as a portal for withdrawal of blood for physiologic monitoring, microbiologic evaluation, or PBSC collection. Catheter-associated infections are categorized as entry-site infections, tunnel infections or bloodstream infections (Table 7.3). The delineation of an entry-site infection from a tunnel infection can be clinically challenging, but the occurrence of an apparent entry-site infection plus a bloodstream infection usually indicates that the catheter tunnel is also infected. It is now believed that the majority of entry-site infections can be managed effectively with antimicrobial therapy alone. Tunnel infections require catheter removal and culture, with modification of the empiric antibiotics based on

Table 7.3 Vascular-catheter-associated infections in HSCT recipients

Infection	Treatment/action
Entry-site infection	• Pathogen-specific therapy (consider empiric vancomycin)
Tunnel infection	• Catheter removal/culture • Pathogen-specific therapy (consider empiric vancomycin)
Bloodstream infection	
Fungi (yeast or mold) Non-tuberculosis mycobacteria Vancomycin-resistant enterococci	• Immediate catheter removal • Pathogen-specific therapy
Corynebacterium jeikeium *Bacillus* spp. *Staphylococcus aureus* *Pseudomonas aeruginosa* *Stenotrophomonas maltophilia*	• Consider early catheter removal • Pathogen-specific therapy
All other positive blood cultures	• Pathogen-specific therapy • Consider catheter removal for persistant[a] infection

[a] Positive blood culture >48 hours, no other site of infection.

culture and antibiotic susceptibility results. Determination of the true role of the venous catheter in a bloodstream infection is difficult unless there is evidence of tunnel or entry-site inflammation caused by the same organism that is recovered from blood cultures. The majority of bloodstream infections that occur in HSCT patients who have indwelling catheters can be managed effectively with antimicrobial therapy, and do not require catheter removal.[20,21] Immediate catheter removal is recommended for patients with bloodstream infections due to fungi, non-tuberculosis mycobacteria (*Mycobacterium fortuitum* complex and *M. chelonae/abscessus* group) and VRE.[30,39,92] Persistent bloodstream infections are more frequent if the catheter is not removed and the bloodstream pathogen is a *Bacillus* sp., *C. jeikeium*, *S. aureus*, *Ps. aeruginosa*, or *S. maltophilia*.[29,93–95] All other bloodstream infections can be initially treated with pathogen-specific antibiotics. Catheter removal in these latter cases should be considered if the bloodstream infection persists beyond 48 hours and no other site of infection is identified. It is also important to consider the possibility that the venous catheter is the pri-

mary site of bloodstream infections that recur after a full course of antimicrobial therapy.[20,96] There is not substantial data to support the recommendation that antibiotic administration be alternated through the different catheter lumens. One must believe that if the catheter is truly the source of infection, then antibiotics alone have a very low chance of sterilizing the venous access device.

LACK OF CLINICAL RESPONSE TO INITIAL EMPIRIC THERAPY

Management of HSCT patients with infection who do not clinically respond to antimicrobial therapy is challenging.[20] The lack of response may represent an infection with a pathogen resistant to the empiric antimicrobial regimen being administered, inadequate serum level or tissue levels of the antibiotics, infection at a vascular site (e.g. a catheter), closed-space infection, the emergence of a second infection, or an unusually slow clinical response. It is important to remember that the resolution of fever in patients who are neutropenic is frequently delayed. A recent review of 488 episodes of fever and neutropenia treated at the University of Texas MD Anderson Cancer Center revealed that the median time to fever resolution ranged from 5 to 7 days.[97] Less than 40% of patients became afebrile before day 5 of therapy. Patients with Gram-negative bloodstream infections were febrile for a mean of 6.6–8.2 days, while the time to fever defervescence was even longer for patients with Gram-positive bloodstream infections (range 6.6–12.4 days). These findings are consistent with the results published by Freifeld et al,[80] who reported that the mean time for patients to become afebrile was 4 days with ceftazidime therapy and 3 days for patients treated with imipenem. These studies provide evidence that the time to fever defervescence can be prolonged, but that the fever response may also vary depending upon the specific antibiotic regimen, site of infection, and infecting pathogen.

Patients in whom fever persists beyond 4–5 days of initial antimicrobial therapy should undergo reassessment. Broad-spectrum antibiotics should be maximized, but, if possible, antibiotic combinations that minimize organ toxicity should be used. Clinical evaluation must include a thorough daily evaluation, review of previous culture results, and further site-specific investigation as clinically indicated. Special attention should be given to the lungs and sinuses as occult sites of infection. The management of such patients may require serial antimicrobial changes, and infectious diseases consultation can be helpful.

The need for change in therapy should be based on the patient's clinical status and the likelihood of early marrow engraftment. Although fever resolution may be slow, persistent fever raises concern about an inadequately treated infection.[97] For HSCT patients who are persistently febrile and clinically unstable, additional Gram-negative bacillary coverage, empiric vancomycin, or empiric amphotericin B should be considered. The clinically stable but febrile patient can be followed carefully without alteration of antimicrobial therapy. However, most physicians will consider the use of empiric amphotericin B or Ambisome (liposomal amphotericin B) if fever persists beyond day 6 of antibiotics.[98] Walsh et al[99] have recently reported on a multicenter trial that compared voriconazole (a new second-generation triazole) with Ambisome as empiric treatment for patients with neutropenia and persistent fever. In this trial, voriconazole was comparable to Ambisome in therapeutic success, but superior in reducing breakthrough fungal infections, infusion-related toxicity and nephrotoxicity. These encouraging results warrant further study in HSCT patients.

EVALUATION AND MANAGEMENT OF FUNGAL INFECTIONS

Invasive fungal infections have become an increasingly important problem for HSCT

patients. Several studies have reported yearly increases in the incidence of candidiasis, aspergillosis, and some other mold infections.[3–5,13,37–39,100,101] With the progress that has been made in the management of CMV infection and pneumonia, aspergillosis is now the number one cause of infection death after allogeneic transplantation.[3,4,13,37] Fungal organisms are categorized into three general categories. The first group comprises the yeasts, which are distinguished by their inability to form true hyphae, and their propensity to colonize mucosal surfaces. *Candida* spp. are the most common, and were reported to occur in 10–20% of HSCT patients prior to the routine use of azole prophylaxis.[38,39,100] The second group comprises the molds, which are characterized by their ability to form true hyphae, and are primarily acquired by the inhalation of aerosolized spores. In the past, this was believed to be primarily contaminated air, but recent studies have also raised the importance of the inhalation of aerosolized contaminated water sources.[102] The most common molds are *Aspergillus* spp., but Mucorales order, *Fusarium*, *Bipolaris*, and *Pseudoallescheria* are being more commonly isolated. The incidence of *Aspergillus* infections has been reported to range from 6% to 20% based on the transplant center and the year of HSCT. The final group of fungi comprises the dimorphic fungi, which have both a yeast and a hyphal form. These are often referred to as the endemic fungi (e.g. *Histoplasma* and *Coccidiodomycetes*). Infections with these fungi are uncommon after HSCT, but should always be considered in patients with a significant history of previous exposure.

The diagnosis of candidiasis and mold infections continues to rely on recovery of the specific pathogen from blood culture, or identification by culture or histology from tissue samples. Rapid diagnosis of these infections using serum antigen detection as a surrogate marker for invasive disease remains a high priority. Galactomannan detection for the diagnosis of aspergillosis appears to be highly specific for invasive aspergillosis, but test sensitivity has varied from 43% to 83%, depending upon the test cut-off index.[103] The group from Belgium prospectively collected sera from HSCT recipients and then assessed the efficacy of galactomannan detection to predict invasive aspergillosis.[104] They reported that serial testing in HSCT recipients could identify invasive aspergillus a median of 6 days (range 0–14 days) before clinical parameters dictated empiric antifungal therapy, and a median of 17 days before the diagnosis of aspergillosis was confirmed. Clinical usefulness of this non-culture technique requires further prospective evaluation, but could potentially improve the ability to diagnose invasive aspergillosis and monitor the response to treatment.

Candidiasis

The frequency and occurrence of candidiasis has been well described.[38,39,100] Goodrich et al[39] reviewed the occurrence of candidiasis at the FHCRC before azole prophylaxis and the lipid-based amphotericin B products were being used. In this report, 1.4% of transplant recipients developed invasive candidiasis. The most common organisms were *C. albicans* (62%) and *C. tropicalis* (21%). The median time to the development of a *Candida* bloodstream infection was 15 days after transplantation, and these infections had an attributable mortality of 39%. Infection mortality was further increased to 88% if *Candida* tissue invasion was also documented. Autologous and allogeneic HSCT recipients had a similar risk of candidiasis during the pre-engraftment period, but the risk of developing candidiasis persisted for allogeneic transplant recipients despite the return of granulocyte function. Risk factors for this period included neutropenia, older age, HLA-mismatched donor, acute GVHD, and corticosteroid use (Table 7.4). The occurrence of bloodstream infections by *Candida* spp. was recently reassessed at the FHCRC after the introduction of fluconazole prophylaxis.[38] Forty-four percent of patients were colonized

Table 7.4 Risk factors (multivariate analysis) for candidiasis and aspergillosis after HSCT

	Candidiasis		Aspergillosis[13,52]	
	Pre-azole[39]	Azole treatment[52]	Early	Late
Increased age	Yes	Yes	No	Yes
Unrelated donor	Yes	No	No	Yes
GVHD	Yes	No	No	Yes
Corticosteroids	Yes	No	No	Yes
Neutropenia	Yes	No	Yes	No
Season (summer)	No	No	Yes	No
Concomitant infection	Yes	Yes	Yes	Yes
Laminar airflow units	No	No	Yes	No
Construction	No	No	No	Yes
CMV-positive	Yes	Yes	Yes	Yes

with *Candida* spp. at some time either prior to or during the first 75 days after transplant. *C. albicans* was more likely to be recovered before transplantation, with non-albicans species more likely to be recovered during the period of azole use. *C. albicans* resistance to fluconazole was modest (5.3% of isolates), with the most common bloodstream isolates being *C. glabrata*, *C. parapsilosis*, and *C. krusei*. *Candida* bloodstream infections occurred in 4.7% of patients, a median of 28 days after transplantation, and were associated with a 20% mortality rate. Of note in this study, the use of fluconazole prophylaxis negated the importance of neutropenia as a risk factor, but had no impact on infections with non-albicans species (Table 7.4).

Aspergillosis

Aspergillus infections primarily involve the respiratory tract. Invasive infection of the lung appears more common, but the true incidence of sinus involvement in HSCT recipients is known. There is a suggestion that different *Aspergillus* spp. may have different tissue tropisms, with *A. flavus* more likely to cause sinus infection than is *A. fumigatus*. It has become clear that *Aspergillus* infection after HSCT occurs in three distinct pathophysiologic conditions.[13] One group of patients will develop their infection during the pre-engraftment period with the primary risk factor being neutropenia (Table 7.4). The second group develops their infection later, between days 40 and 120 post transplantation, and are predisposed to infection because of a persistent cellular immune defect. The third group experience *Aspergillus* infections very late after transplantation, and these infections appear to be highly correlated with delayed immune reconstitution, CMV disease and chronic GVHD (K Marr, personal communication, 2000). Extrapulmonary spread of *Aspergillus* is more common with neutropenia-associated infections, while non-neutropenic *Aspergillus* pneumonia among HSCT recipients is more likely to present with progressive diffuse pulmonary infiltrates.[105] The

mortality rate for *Aspergillus* infection developing early or late after transplant remains very high, ranging from 60% to 88%.[13,38] Median survival after diagnosis is usually short (36 days) for patients with early and late aspergillosis, but can be longer when it occurs very late after transplantation. Diagnosis, prevention, and treatment of *Aspergillus* infections remain inadequate. Diagnosis is dependent on recovery of the infecting organism by histology or microbiology from tissue specimens or pulmonary or sinus lavage. Results of galactomann assays are encouraging.[103,104] While the use of surveillance cultures continues to be controversial in the care of HSCT recipients, the finding of *A. fumigatus* or *A. flavus* in respiratory specimens has been shown to be highly predictive of future invasive aspergillosis.[13] Mucosal eschars along the nasal septum are an important clinical clue to the diagnosis of *Aspergillus* sinusitis. Biopsy and culture of such lesions are always indicated. If nasal lesions are not observed, sinus aspirate and biopsy may establish the diagnosis and preclude the need for further diagnostic procedures.

Bronchoalveolar lavage (BAL) is the standard approach for evaluating an HSCT patient with pulmonary lesions. BAL is a less sensitive procedure if the pulmonary lesions are focal, small, and/or peripherally located. The sensitivity of BAL to diagnose *Aspergillus* is only 50–60%. Thus a negative procedure does not exclude the diagnosis of *Aspergillus*. Open lung biopsy is usually reserved for patients with a negative BAL, or for patients in whom the disease is progressive and a diagnosis must be immediately established. A thoracoscopic approach is now routinely utilized when possible because of lowered procedure morbidity. Biopsies of both peripheral and central areas of abnormal lung are recommended because of the focal nature of *Aspergillus* infections, and the wide distribution of organisms within the pneumonic process.

Treatment of established *Aspergillus* infections that occur in HSCT recipients remains inadequate, and is in a state of evolution. Early diagnosis and treatment remains critical. Prolonged (8–10 weeks) high-dose (1.0–1.5 mg/kg/day) amphotericin B or an equivalent dose of a lipid formulation of amphotericin B is the standard initial treatment.[20,21] Additional suppressive therapy with an oral agent such as itraconazole is often given if the patient remains immunosuppressed.[20] To date, the lipid formulations of amphotericin B have not been shown to increase survival, although the incidences of both acute infusion-related toxicity and nephrotoxicity are decreased.[98,106] Usage of lipid formulations of amphotericin B must be based on the risk of developing nephrotoxicity and the cost of treatment.[107,108] The use of antifungal combinations remains controversial, and some in vitro studies have suggested the possibility of clinically relevant antagonism if azoles such as itraconazole are combined with amphotericin B.

Voriconazole, a new triazole with enhanced activity against *Aspergillus*, is available in both an oral and an intravenous formulation, and appears encouraging as treatment of aspergillosis. Other new antifungal agents (e.g. posaconazole, ravuconazole, caspofungin, and liposomal nystatin) are being tested in phase II-III trials as treatment of invasive *Aspergillus* infections in HSCT recipients. These agents show promise, with response rates of 25–40% among patients who have failed to respond to amphotericin B. Efforts to enhance infected patients' immune status have been recommended, but the use of adjunct growth factors (G-CSF and GM-CSF), or G-CSF-mobilized granulocyte transfusion have not been shown to be beneficial.[64,109] The role of surgery as an adjunct to antimicrobial treatment for pulmonary *Aspergillus* infections remains controversial, but a preliminary analysis from the FHCRC (D Weiss, personal communication, 2000) shows little survival benefit if surgical resection is performed.

Respiratory viruses

RSV, parainfluenza, and infuenza type A or B are now recognized as important pathogens for

HSCT recipients during the pre-engraftment period.[22,110–113] These infections are usually seasonal (winter months), but outbreaks may persist within a transplant center beyond the time when healthy individuals in the community are no longer being infected. The true incidence of these infections is unknown, but some centers have reported an attack rate among HSCT recipients of 20%.[112] The progression of upper respiratory tract infection to lower tract disease varies among the specific viruses. Approximately 50% of patients who become infected with RSV will develop pneumonia.[22,112] The rate of progression is lower for parainfluenza (32%), and rare for influenza. The RSV pneumonia mortality rate has remained high (27–82%), but mortality may be even more severe when the infection and pneumonia develop pre-engraftment.[22] The mortality rate from parainfluenza pneumonia has varied between 32% and 57%, with the mortality rate among HSCT recipients who develop influenza pneumonia being in a similar range. There is no proven effective therapy for any of these respiratory virus infections after HSCT, although aerosolized ribavirin alone or in combination with either polyclonal or monoclonal RSV immunoglobulin has been used.[112] Supportive care and appreciation of the potential complications such as secondary bacterial and fungal pneumonia are the mainstay of treatment. Intravenous RSV immunoglobulin and preemptive therapy with aerosolized ribavirin are currently under investigation for the prevention and treatment of RSV pneumonia. Infection control efforts to minimize acquisition and transmission of these pathogens are critical.

SITE OF CARE FOR HSCT PATIENTS WITH FEVER AND NEUTROPENIA

There is increasing acceptance that certain patients with fever and neutropenia can be safely managed as outpatients, or with shortened hospital stays.[20,114–117] Several investigators have developed prospective models to help predict a population of patients who would be at low risk of developing infection-associated complications, and would therefore be candidates for outpatient therapy.[117,118] In general, most models have excluded HSCT recipients from the low-risk patient group because of the belief that their underlying immunosuppression and intensity of treatment inherently makes them a high-risk population.[117,118]

The FHCRC has not attempted to manage the first episode of fever and neutropenia during the pre-engraftment period on an outpatient basis. This has not been feasible because most patients experience significant comorbid illness during the pre-engraftment period (e.g. severe mucositis, or renal or hepatic dysfunction). However, approximately 5–10% of conventional allogeneic transplant recipients and occasional autologous HSCT recipients will develop a period of neutropenia (<500 PMN/μl) during periods following initial engraftment. Many of these neutropenic periods are complicated by the development of fever and infection. These neutropenic periods are caused by graft failure, disease relapse, and marrow suppression caused by infection (e.g. CMV, HHV-6, or HHV-8) or medications (e.g. ganciclovir). In general, we do not now admit all of these patients to the hospital for broad-spectrum antibiotics. Patients are evaluated at the first sign of infection (fever), with a thorough physical examination, blood cultures, chest X-ray, and pertinent physiologic assessments (e.g. hematological, kidney, liver, and lung). Patients who are clinically stable, and do not have hypotension, hypoxia ($Sa_{O_2} < 90\%$ on room air), a stool volume >500 cm^3/24 h, or renal insufficiency (serum creatinine > 2.0 mg/dl) are then treated with intravenous ceftazidime and ciprofloxacin in our day hospital/ambulatory facility and observed for 6–8 hours. Patients who remain stable are then allowed to continue their antibiotic therapy as outpatients. All patients return to the clinic the following morning for reassessment. Patients are assessed daily until clinically improved, antibiotics are adjusted based on culture results, and patients

who show signs of clinical deterioration are immediately hospitalized for more intense monitoring. The Center's infectious disease team evaluates all patients who remain febrile beyond day 3 of broad-spectrum antibiotic therapy. Experience with this pilot approach is limited, but critical issues for the success of this treatment strategy are willing, educated patients, full-time caregivers (part of the routine FHCRC transplant procedure), follow-up care available 24 hours/day, 7 days a week, and a low threshold for hospitalization if needed.

SUMMARY

The morbidity and mortality of infections for HSCT recipients during the pre-engraftment period have dramatically decreased, but during this same time period there has been the emergence of antibiotic-resistant bacteria, and a significant increase in the incidence of fungal infections. More potent and less toxic antibiotics have been developed. PBSC transplants have decreased the duration of pre-engraftment neutropenia, and progress has been made in the area of prophylaxis of *C. albicans* infections. However, patients now are at an increased risk of non-albicans *Candida* infections, and the mortality from mold infections (e.g. *Aspergillus*) remains high. The promise of new diagnostic techniques, additional antimicrobial agents, and strategies for treatment and prophylaxis hold the potential that HSCT may be safer in the future. It will be critical for the transplant team to remember that HSCT-associated infections are a dynamic process, with change a guarantee. Transplant physicians must not forget the value and importance of standard infection-control measures. It will be a challenge to implement such infection-control approaches as the care of HSCT patients becomes more focused in an ambulatory/day hospital facility.

REFERENCES

1. Maris MB, Sandmaier BM, Niederwieser D et al, Comparison of donor chimerism, graft rejection, and GVHD after hematopoeitic stem-cell transplants (HSCT) from HLA matched siblings and unrelated donors using conditioning with 2 GY TIB with and without fludarabine (FLU). *Blood* 2000; **96:** 520a.
2. Childs R, Chernoff A, Contentin N et al, Regression of metastatic renal-cell carcinoma after nonmyeloblative allogeneic peripheral-blood stem-cell transplantation. *N Engl J Med* 2000; **343:** 750–8.
3. Walter E, Bowden R, Infection in the bone marrow transplant recipient. *Infect Dis Clin North Am* 1995; **9:** 823–47.
4. VanBurik JH, Weisdorf DJ, Infections in recipients of blood and marrow transplantation. *Hematol Oncol Clin North Am* 1999; **13:** 1065–89.
5. Van Burk J-A, Weisdorf D, Infections in recipients of blood and marrow transplantation. In: *Principles and Practice of Infectious Diseases*, 5th edn (Mandell GL, Bennett JE, Dolin R, eds). Philadelphia: Churchill Livingstone, 2000: 3136–47.
6. Pizzo PA, Management of fever in patients with cancer and treatment-induced neutropenia. *N Engl J Med* 1993; **328:** 1323–32.
7. Wade JC, Management of infection in patients with acute leukemia. *Hematol Oncol Clin North Am* 1993; **7:** 293–315.
8. Bodey GP, Buckley M, Sathe YS et al, Quantitative relationships between circulating leukocytes and infection in patients with acute leukemia. *Ann Intern Med* 1966; **64:** 328–40.
9. Schimpff SC, Empiric antibiotic therapy for granulocytopenic cancer patients. *Am J Med* 1986; **80**(Suppl 5c): 13–20.
10. Imbert-Marcille BM, Tang XW, Lepelletier D et al, Human herpesvirus-6 infection after autologous or allogeneic stem cell transplantation: a single-center prospective longitudinal study of 92 patients. *Clin Infect Dis* 2000; **31:** 881–6.
11. Wang F-Z, Linde A, Hagglund H et al, Human herpesvirus 6 DNA in cerebrospinal fluid specimens form allogeneic bone marrow transplant patients: Does it have clinical significance? *Clin Infect Dis* 1999; **28:** 562–8.
12. Luppi M, Barozzi P, Schulz TF et al, Bone marrow failure associated with human herpesvirus

8 infection after transplantation. *N Engl J Med* 2000; **343:** 1378–85.
13. Wald A, Leisenring W, van Burik JA, Bowden RA, Epidemiology of *Aspergillus* infections in a large cohort of patients undergoing bone marrow transplantation. *J Infect Dis* 1997; **175:** 1459–66.
14. Sullivan KM, Nims J, Leisenring W et al, Determinants of late infection following marrow transplantation for aplastic anemia and myelodysplastic syndrome. *Blood* 1995; **86**(Suppl 1): 213a.
15. Sullivan KM, Mori M, Sanders J et al, Late complications of allogeneic and autologous marrow transplantation. *Bone Marrow Transplant* 1992; **10:** 127–34.
16. Hoyle C, Goldman JM, Life-threatening infections occurring more than 3 months after BMT. *Bone Marrow Transplant* 1994; **14:** 247–52.
17. Sullivan KM, Agura E, Anasetti C et al, Chronic graft-versus-host disease and other late complications of bone marrow transplantation. *Semin Hematol* 1991; **28:** 250–9.
18. Anderson KC, Weinstein HJ, Transfusion-associated graft-versus-host disease. *N Engl J Med* 1990; **323:** 315–21.
19. Flowers ME, Leisenring W, Beach K et al, G-CSF given to donors before apheresis does not prevent aplasia in patients treated with donor leukocyte infusions for recurrent CML after bone marrow transplantation. *Biol Blood Marrow Transplant* 2000; **6:** 321–6.
20. Wade JC, Rubenstein EB, and the NCCN Guidelines Committee, Clinical practice guidelines for fever and neutropenia. *Oncology* 1999; **13:** 197–257.
21. Hughes WT, Armstrong D, Bodey GP et al, 1997 guidelines for the use of antimicrobial agents in neutropenic patients with unexplained fever. *Clin Infect Dis* 1997; **25:** 551–73.
22. Harrington RD, Houton TM, Hackman RC et al, An outbreak of respiratory syncytial virus in a bone marrow transplant center. *J Infect Dis* 1992; **165:** 987–93.
23. Wingard JR, Santos GW, Saral R, Differences between first and subsequent fevers during prolonged neutropenia. *Cancer* 1987; **59:** 844–9.
24. Glauser M, Boogaerts M, Cordonnier C et al, Empiric therapy of bacterial infections in severe neutropenia. *Clin Microbiol Infect* 1997; **3**(Suppl 1): S77–86.
25. Engelhard D, Elishoov H, Strauss N et al, Nosocomial coagulase-negative staphylococcal infections in bone marrow transplantation recipients with central vein catheter – a 5-year prospective study. *Transplantation* 1996; **61:** 430–4.
26. Villablanca JG, Steiner M, Kersey J et al, The clinical spectrum of infections with viridans streptococci in bone marrow transplant recipients. *Bone Marrow Transplant* 1990; **6:** 387–93.
27. Classen DC, Burke JP, Ford CD et al, *Streptococcus mitis* sepsis in bone marrow transplant patients receiving oral antimicrobial prophylaxis. *Am J Med* 1990; **89:** 441–6.
28. Elting LS, Bodey GP, Keefe BH, Septicemia and shock syndrome due to viridans streptococci: a case–control study of predisposing factors. *Clin Infect Dis* 1992; **14:** 1201–7.
29. Stamm WE, Tompkins LS, Wagner KF et al, Infection due to *Corynebacterium* species in marrow transplant recipients. *Ann Intern Med* 1979; **91:** 167–73.
30. Edmond MB, Ober JF, Dawson JD et al, Vancomycin-resistant enterococcal bacteremia: natural history and attributable mortality. *Clin Infect Dis* 1996; **23:** 1234–9.
31. Martin MA, Pfaller MA, Wenzel RP, Coagulase-negative staphylococcal bacteremia: mortality and hospital stay. *Ann Intern Med* 1989; **110:** 9–16.
32. Wenzel RP, Perspective: Attributable mortality – the promise of better antimicrobial therapy. *J Infect Dis* 1998; **178:** 917–19.
33. Johnston PB, Litzow MR, Elliott MA et al, Colonization with vancomycin-resistant enterococcus correlates with poor outcome in patients undergoing allogeneic blood and marrow transplants. *Blood* 2000; **96:** 786a.
34. Brown AE, Kiehn TE, Armstrong DE, Bacterial resistance in patients with neoplastic disease. *Infect Dis Clin Pract* 1995; **4**(Suppl 3): S136–44.
35. Koll BS, Brown AE, The changing epidemiology of infections at a cancer hospital. *Clin Infect Dis* 1993; **17**(Suppl 2): S322–8.
36. Elting LS, Rubenstein EB, Rolston KV et al, Outcomes of bacteremia in patients with cancer and neutropenia. *Clin Infect Dis* 1997; **25:** 247–59.
37. Ribaud P, Chastang C, Latage JP et al, Survival and prognostic factors of invasive aspergillosis after allogeneic bone marrow transplantation. *Clin Infect Dis* 1999; **28:** 322–30.

38. Marr KA, Seidel K, White TC et al, Candidemia in allogeneic blood and marrow transplant recipients: evolution of risk factors after adoption of prophylactic fluconazole. *J Infect Dis* 2000; **181:** 309–16.
39. Goodrich JM, Reed EC, Mori M et al, Clinical features and analysis of risk factors for invasive candidal infection after marrow transplantation. *J Infect Dis* 1991; **164:** 731–40.
40. Petersen FB, Buckner CD, Clift RA et al, Infectious complications in patients undergoing marrow transplantation: a prospective randomized study of the additional effect of decontamination and laminar air flow isolation among patients receiving prophylactic systemic antibiotics. *Scand J Infect Dis* 1987; **19:** 559–67.
41. Hospital Infection Control Practices Advisory Committee (HIPAC), Recommendations for preventing the spread of vancomycin-resistance. *Infect Control Hosp Epidemiol* 1995; **16:** 105–13.
42. Bjerke J, Meyers JD, Bowden RA, Hepatosplenic candidiasis – a contraindication to marrow transplantation? *Blood* 1994; **84:** 2811–14.
43. Offner F, Cordonnier C, Ljungman P et al, Impact of previous aspergillosis on the outcome of bone marrow transplantation. *Clin Infect Dis* 1998; **26:** 1098–103.
44. Cruciani M, Rampazzo R, Malena M et al, Prophylaxis with fluoroquinolones for bacterial infections in neutropenic patients: a meta-analysis. *Clin Infect Dis* 1996; **23:** 795–805.
45. Conneally E, Cafferkey MT, Daly PA et al, Nebulized amphotericin B as prophylaxis against invasive aspergillosis in granulocytopenic patients. *Bone Marrow Transplant* 1990; **5:** 403–6.
46. O'Donnell MR, Schmidt GM, Tegtmeier BR et al, Prediction of systemic fungal infection in allogeneic marrow recipients: impact of amphotericin prophylaxis in high-risk patients. *J Clin Oncol* 1994; **12:** 827–34.
47. Rousey SR, Russler S, Gottlieb M, Ash RC, Low-dose amphotericin B prophylaxis against invasive aspergillus infections in allogeneic marrow transplantation. *Am J Med* 1991; **91:** 484–92.
48. Perfect JR, Klotman ME, Gilbert CC et al, Prophylactic intravenous amphotericin B in neutropenic autologous bone marrow transplant recipients. *J Infect Dis* 1992; **165:** 891–7.
49. Tollemar J, Ringden O, Andersson S et al, Prophylactic use of liposomal amphotericin B (Ambisome) against fungal infections: a randomized trial in bone marrow transplant recipients. *Transplant Proc* 1993; **25:** 1495–7.
50. Goodman JL, Winston DJ, Greenfield RA et al, A controlled trial of fluconazole to prevent fungal infections in patients undergoing bone marrow transplantation. *N Engl J Med* 1992; **326:** 845–51.
51. Slavin MA, Osborne B, Adams R et al, Efficacy and safety of fluconazole for fungal infections after marrow transplant – a prospective, randomized, double-blind study. *J Infect Dis* 1996; **171:** 1545–52.
52. Marr KA, Seidel K, Slavin MA et al, Prolonged fluconazole prophylaxis is associated with persistent protection against candidiasis-related death in allogeneic marrow transplant recipients: long-term follow-up of a randomized, placebo-controlled trial. *Blood* 2000; **96:** 2055–61.
53. Rotstein C, Bow EJ, Laverdiere M et al, Randomized placebo-controlled trial of fluconazole prophylaxis for neutropenic cancer patients: benefit based on purpose and intensity of cytotoxic therapy. *Clin Infect Dis* 1999; **28:** 331–40.
54. Broers AEC, van der Holt R, van Esser JWJ et al, Increased transplant-related morbidity and mortality in CMV-seropositive patients despite highly effective prevention of CMV disease after allogeneic T-cell-depleted stem cell transplantation. *Blood* 2000; **95:** 2240–5.
55. Wade JC, Newton B, Flournoy N et al, Oral acyclovir for the prevention of herpes simplex virus reactivation after marrow transplantation. *Ann Intern Med* 1984; **100:** 823–8.
56. Baglin TP, Gray JJ, Marcus RE, Wreghitt TG, Antibiotic resistant fever associated with herpes simplex virus infection in neutropenic cancer patients with haematological malignancy. *J Clin Pathol* 1989; **42:** 1255–8.
57. Weaver CH, Schulman KA, Wilson-Relyea B et al, Randomized trial of filgrastim, sargramostim, or sequential sargramostim and filgrastim after myelosuppressive chemotherapy for the harvesting of peripheral-blood stem cells. *J Clin Oncol* 2000; **18:** 43–53.
58. Holmberg LA, Boeckh M, Hooper H et al, Increased incidence of cytomegalovirus disease

after autologous CD34-selected peripheral blood stem cell transplantation. *Blood* 2000; **94:** 4029–35.
59. Crippa F, Holmberg L, Hooper H et al, Infections after autologous CD34 selected peripheral blood stem cell transplantation. *Blood* 2000; **96:** 586a.
60. Champlin RE, Schmitz N, Horowitz MM et al, Blood stem cells compared with bone marrow as a source of hematopoietic cells for allogeneic transplantation. *Blood* 2000; **95:** 3702–9.
61. Bensinger WI, Martin PJ, Storer B et al, Transplantation of bone marrow as compared with peripheral-blood cells from HLA-identical relatives in patients with hematologic cancers. *N Engl J Med* 2001; **344:** 175–81.
62. Powles R, Mehta J, Kulkarni S et al, Allogeneic blood and bone-marrow stem-cell transplantation in haematological malignant diseases: a randomised trial. *Lancet* 2000; **355:** 1231–7.
63. Flowers MED, Matos AVB, Storer B et al, Clinical manifestations of chronic graft-versus-host disease (cGVHD) after transplantation of peripheral blood stem cell (PBSC) compared to bone marrow. *Blood* 2000; **96:** 203a.
64. Ozer H, Armitage JO, Bennett CL et al, 2000 update of recommendations for the use of hematopoietic colony-stimulating factors: evidence-based, clinical practice guidelines. *J Clin Oncol* 2000; **18:** 3558–85.
65. Hartmann LC, Tchetter LK, Habermann TM et al, Granulocyte colony-stimulating factor in severe chemotherapy-induced afebrile neutropenia. *N Engl J Med* 1997; **336:** 1776–80.
66. Clift RA, Sanders JE, Thomas ED et al, Granulocyte transfusions for the prevention of infection in patients receiving bone marrow transfusions. *N Engl J Med* 1978; **298:** 1052–7.
67. Bhatia S, McCulough J, Perry EH et al, Granulocyte transfusions: efficacy in treating fungal infections in neutropenic patients following bone marrow transplantation. *Transfusion* 1994; **34:** 226–32.
68. Winston D, Ho WG, Young LS, Prophylactic granulocyte transfusions during human bone marrow transplantation. *Am J Med* 1980; **68:** 893–9.
69. Price TH, Bowden RA, Boeckh M et al, Phase I/II trial of neutrophil transfusions from donors stimulated with G-CSF and dexamethasone for treatment of patients with infections in hematopoietic stem cell transplantation. *Blood* 2000; **95:** 3302–9.
70. Pena E, Narvios A, Lichtiger B, Therapeutic granulocyte transfusions: retrospective study of 34 patients. *Blood* 2000; **96:** 63a.
71. Hubel K, Carter R, Liles WC et al, Community donors vs. related donors for granulocyte transfusion therapy in hematopoietic transplantations: a comparative analysis of feasibility and outcome. *Blood* 2000; **96:** 63a.
72. Adkins DR, Goodnough LT, Shenoy S et al, Effect of leukocyte compatibility on neutrophil increment after transfusion of granulocyte colony-stimulating factor-mobilized prophylactic granulocyte transfusions and on clinical outcomes after stem cell transplantation. *Blood* 2000; **95:** 3605–12.
73. Reimer LG, Wilson ML, Weinstein MP, Update on detection of bacteremia and fungemia. *Clin Microbiol Rev* 1997; **10:** 444–65.
74. Weinstein MP, Current blood culture methods and systems: clinical concepts, technology, and interpretation of results. *Clin Infect Dis* 1996; **23:** 4046.
75. Siegman-Igra Y, Anglim AM, Shapiro DE et al, Diagnosis of vascular catheter-related bloodstream infection: a meta-analysis. *J Clin Microbiol* 1997; **35:** 928–36
76. Whimbey E, Wong B, Kiehn TE et al, Clinical correlations of serial quantitative blood cultures determined by lysis-centrifugation in patients with persistent septicemia. *J Clin Microbiol* 1984; **19:** 766–71.
77. Benezra D, Kiehn TE, Gold JWM et al, Prospective study of infections in indwelling central venous catheters using quantitative blood cultures. *Am J Med* 1988; **85:** 495–8.
78. Cox GJ, Matsui SM, Lo RS et al, Etiology and outcome of diarrhea after marrow transplantation: a prospective study. *Gastroenterology* 1994; **107:** 1398–407.
79. McFarland LV, Mulligan ME, Kwok RYY et al, Nosocomial acquisition of *Clostridium difficile* infection. *N Engl J Med* 1989; **17:** 484–90.
80. Freifeld AG, Walsh T, Marshall D et al, Monotherapy for fever and neutropenia in cancer patients: a randomized comparison of ceftazidime vs. imipenem. *J Clin Oncol* 1995; **13:** 165–76.
81. Cometta A, Calandra T, Gaya H et al, Monotherapy with meropenem vs. combination

therapy with ceftazidime plus amikacin as empiric therapy for fever in granulocytopenic patients with cancer. *Antimicrob Agents Chemother* 1996; **40:** 1108–15.

82. Oblon D, Ramphal R, A randomized trial of cefepime vs. ceftazidime as initial therapy for patients with prolonged fever and neutropenia after intensive chemotherapy. *Proc Am Assoc Cancer Res* 1993; **34:** 1362a.
83. Cometta A, Zinner S, de Bock R et al, Piperacillin–tazobactam plus amikacin vs. ceftazidime plus amikacin as empiric therapy for fever in granulocytopenic patients with cancer: the International Antimicrobial Therapy Cooperative Group of the European Organization for Research and Treatment of Cancer. *Antimicrob Agents Chemother* 1995; **39:** 445–52.
84. Winston DJ, Lazarus HM, Beveridge RA et al, Randomized, double-blind, multicenter trial comparing clinafloxacin with imipenem as empirical monotherapy for febrile granulocytopenic patients. *Clin Infect Dis* 2001; **32:** 381–90.
85. Donskey CJ, Hanrahan JA, Hutton RA, Rice LB, Effect of parenteral antibiotic administration on persistence of vancomycin-resistant *Enterococcus faecium* in the mouse gastrointestinal tract. *J Infect Dis* 1999; **180:** 384–90.
86. Pfaller M, Jones R, Marshall S et al, Nosocomial streptococcal blood stream infections in the SCOPE Program: species occurrence and antimicrobial resistance: the SCOPE Hospital Study Group. *Diagn Microbial Infect Dis* 1997; **29:** 259–63.
87. Edmond MB, Wallace SE, McClish DK et al, Nosocomial bloodstream infections in United States hospitals: a three-year analysis. *Clin Infect Dis* 1999; **29:** 239–44.
88. Bow EJ, Loewen R, Vaughan D, Reduced requirement for antibiotic therapy targeting Gram-negative organisms in febrile, neutropenic patients with cancer who are receiving antibacterial chemoprophylaxis with oral quinolones. *Clin Infect Dis* 1995; **20:** 907–12.
89. Ward TT, Thomas RG, Fye CL et al, Trimethoprim–sulfamethoxazole prophylaxis in granulocytopenic patients with acute leukemia: evaluation of serum antibiotic levels in a randomized, double-blind, placebo-controlled Department of Veterans Affairs cooperative study. *Clin Infect Dis* 1993; **17:** 323–32.
90. Herwaldt LA, Hopis RJ, Boyken LD et al, Molecular epidemiology of coagulase-negative staphylococci isolated from immunocompromised patients. *Infect Control Hosp Epidemiol* 1992; **13:** 86–92.
91. Wendt C, Messer SA, Hollis RJ et al, Recurrent Gram-negative bacteremia: incidence and clinical patterns. *Clin Infect Dis* 1999; **28:** 611–17.
92. Roy V, Weisdorf D, Mycobacterial infections following bone marrow transplantation. A 20 year retrospective review. *Bone Marrow Transplant* 1997. **19:** 467–70.
93. Vassilomanolakis M, Plataniotis G, Koumakis G et al, Central venous catheter-related infections after bone marrow transplantation in patients with malignancies: a prospective study with short-course vancomycin prophylaxis. *Bone Marrow Transplant* 1995; 15:r 77–80.
94. Banerjee C, Bustamante CI, Wharton R et al, *Bacillus* infections in patients with cancer. *Arch Intern Med* 1988; **148:** 1769–74.
95. Press OW, Ramsey PG, Larsen EB et al, Hickman catheter infections in patients with malignancy. *Medicine* 1984; **63:** 189–200.
96. Engellard D, Elishoov H, Strauss N et al, Nosocomial coagulase-negative staphylococcal infections in bone marrow transplantation recipients with central vein catheter. A 5 year prospective study. *Transplantation* 1996; **61:** 430–4.
97. Elting LS, Rubenstein EB, Rolston K et al, Time to clinical response: an outcome of antibiotic therapy of febrile neutropenia with implications for quality and cost of care. *J Clin Oncol* 2000; **21:** 3699–706.
98. Walsh TJ, Finberg R, Arndt C et al, Liposomal amphotericin B is effective for empirical antifungal therapy in cancer patients with fever and neutropenia. *N Engl J Med* 1999; **340:** 764–71.
99. Walsh T, Pappas P, Winston D et al, Voriconazole versus liposomal amphotericin B for empirical antifungal therapy of persistently febrile neutropenic patients: a randomized, international, multicenter trial. In: Proceedings of *40th Interscience Conference on Antimicrobial Agents and Chemotherapy*, San Francisco, CA, 2000: 20 (Abst).
100. Viscoli C, Girmenia A, Marinus A et al, Candidemia in cancer patients: a prospective multicenter surveillance study by the Invasive

Fungal Infection Group (IFIG) to the European Organization for the Research and Treatment of Cancer (EORTC). *Clin Infect Dis* 1999; **28:** 1071–9.

101. Kontoyiannis DP, Sumoza D, Tarrand J et al, Significance of aspergillemia in patients with cancer: a ten-year study. *Clin Infect Dis* 2000; **31:** 188–9.
102. Anaissie E, Stratton S, Summerbell R et al, Opportunistic moulds in a hospital water system: a 3-year prospective study. *Blood* 2000; **96:** 787a.
103. Marr KA, Balajee A, Leisenring W et al, Utility of galactomannan detection for the diagnosis of invasive aspergillosis in HSCT recipients. *Blood* 2000; **96:** 786a.
104. Maertens JA, Verhaegen J, Van Eldere J, Boogaerts M, Detection of circulating galactomannan (GM) is an early and sensitive indicator of invasive aspergillosis (IA) in allogeneic stem cell transplant recipients (ASCTR). *Blood* 2000; **96:** 585a.
105. Marr KA, Carter K, Myerson D et al, Aspergillosis in HSCT recipients: evidence for two distinct pathophysiologic conditions associated with engraftment status. *Blood* 2000; **96:** 787a.
106. Walsh TJ, Hiemenez JW, Seibel NL et al, Amphotericin B lipid complex for invasive fungal infections: analysis of safety and efficacy of 556 cases. *Clin Infect Dis* 1998; **26:** 1383–96.
107. Wingard JR, Kubilis P, Lee L et al, Clinical significance of nephrotoxicity in patients treated with amphotericin B for suspected or proven aspergillosis. *Clin Infect Dis* 1999; **29:** 1402–7.
108. Cagnoni PJ, Walsh TJ, Prendergast MM et al, Pharmacoeconomic analysis of liposomal amphotericin B versus conventional amphotericin B in the empirical treatment of persistently febrile neutropenic patients. *J Clin Oncol* 2000; **18:** 2476–83.
109. Gaviria JM, van Burik JH, Dale DC et al, Comparison of interferon-γ, granulocyte colony-stimulating factor, and granulocyte-macrophage colony-stimulating factor for priming leukocyte-mediated hyphal damage of opportunistic fungal pathogens. *J Infect Dis* 1999; **179:** 1038–41.
110. Wendt CH, Weisdorf DJ, Jordan MC et al, Parainfluenza virus respiratory infection after bone marrow transplantation. *N Engl J Med* 1992; **326:** 921–6.
111. Aschan J, Ringden O, Ljungman P et al, Influenza B in transplant patients. *Scand J Infect Dis* 1989; **21:** 349–50.
112. Bowden RA, Respiratory virus infections after marrow transplant: the Fred Hutchinson Cancer Research Center experience. *Am J Med* 1997; **102:** 27–30.
113. Englund JA, Sullivan CJ, Jordan MC et al, Respiratory syncytial virus infection in immunocompromised adults. *Ann Intern Med* 1988; **109:** 203–8.
114. Talcott JA, Whalen A, Clark J et al, Home antibiotic therapy for low-risk cancer patients with fever and neutropenia: a pilot study of 30 patients, based on a validated prediction rule. *J Clin Oncol* 1994; **12:** 107–14.
115. Rubenstein EB, Rolston K, Benjamin RS et al, Outpatient treatment of febrile episodes in low-risk neutropenic patients with cancer. *Cancer* 1993; **7:** 3640–6.
116. Rolston KV, New trends in patient management: risk-based therapy for febrile patients with neutropenia. *Clin Infect Dis* 1999; **29:** 515–19.
117. Talcott J, Siegel R, Finberg R et al, Risk assessment in cancer patients with fever and neutropenia: a prospective, two-center validation of a prediction rule. *J Clin Oncol* 1992; **10:** 316–22.
118. Klastersky J, Paesmans M, Rubenstein EB et al, The Multinational Association for Supportive Care in Cancer Risk Index: a multinational scoring system for identifying low-risk febrile neutropenic cancer patients. *J Clin Oncol* 2000; **18:** 3038–51.

8

Initial clinical evaluation and risk assessment of the febrile neutropenic cancer patient

James A Talcott, Edward B Rubenstein

INTRODUCTION

Bodey et al,[1] by noting the relationship between absolute neutrophil counts (ANC) less than 1000/mm^3 and an increased risk of infection, especially serious infection, identified fever and neutropenia as a high-risk clinical state. Although assessing patient risk is an integral aspect of a physician's role, formal discussions of risk assessment are rare in medical textbooks. However, risk assessment has been central to the management of cancer patients with fever and neutropenia since its original description by Bodey and colleagues. Since that report, many papers have identified factors that either clinically or statistically are associated with outcomes in patients with fever and neutropenia. In this chapter, we will provide an overview of the initial clinical approach to the neutropenic cancer patient who presents with fever, provide a framework for risk assessment as it relates to the care of patients with fever and neutropenia, and detail some of the characteristics that define low- and high-risk subgroups that can be used to help the clinician make initial decisions regarding site of care (inpatient versus outpatient) and route for antibiotic therapy (oral versus intravenous).

Defining the clinical problem

The signs and symptoms of infection are often subtle in the neutropenic patient, but fever remains the cardinal sign of early infection. A single temperature of greater than 38.0°C (100.4°F) in the absence of an obvious environmental cause is generally considered a fever. Neutropenic patients who have just received blood products should not be considered to have simple pyrogenic febrile reactions from their transfusion if they remain febrile two or more hours after transfusion. These patients must be presumed to be infected and should be treated with broad-spectrum antibiotics. Similarly, initial febrile episodes in neutropenic patients should never be attributed to noninfectious causes such as tumor fever or drug fever. Numerous studies have shown that more than half of neutropenic patients who become febrile, if carefully evaluated, will end up having either a microbiologically documented infection (MDI) or a clinically documented infection (CDI).[2–7] Approximately 10–20% or more of febrile patients with neutrophil counts of less than 100/μl will have documented bacteremias.[8] The purpose of the initial evaluation is to try and elucidate the focus of the patient's infection so that the initial empiric antimicrobial regimen is appropriately selected based

upon the organism most likely to be responsible for the initial infection. Primary sites of infection include the alimentary tract from the oropharynx to the perirectum, including the periodontal area, mouth, pharynx, esophagus, large and small bowel and rectum, the sinuses, lungs, and skin. Common sites of infection include the skin and soft tissues surrounding central venous catheters or the catheters themselves (see Chapter 10). Patients with neutropenia and signs or symptoms of infection who present without fever should be evaluated and treated as if they were febrile, including those patients who are elderly or debilitated and those who have received corticosteroids, which may also initially blunt the febrile response. Neutropenic patients with infections due to *Clostridium septicum* may also present without fever.[9]

Essential elements of the history, examination, and evaluation

Since fever in the neutropenic cancer patient is traditionally considered an oncologic emergency, it is important for the clinician to rapidly perform a focused history and physical examination. Baseline history should include the timing of the onset of the fever, associated symptoms such as true rigors (which suggest bloodstream infection), chest pain, dyspnea or cough (which suggest respiratory tract infection), and other site-specific history and evaluations as outlined in Table 8.1. Although uncommon, the presence of headache and photophobia with or without neck stiffness should still suggest meningitis in a neutropenic febrile cancer patient.

Laboratory testing should include a complete blood count with differential and platelet count, serum electrolytes, blood urea nitrogen, serum creatinine, evaluation of liver transaminases (aminotransferases), bilirubin, alkaline phosphatase, and appropriate site-specific cultures. Initially, two blood cultures should be drawn, with a minimum of 20 cm^3 of blood per culture. If the patient has an indwelling vascular access device (VAD), the site should be examined for erythema, induration, or purulence. Routine VAD site cultures are not indicated. At least one blood culture should be taken through the lumen of the VAD, and, if the patient will allow a peripheral venous sample, then another blood culture from a vein should also be obtained.[10] For patients with urinary symptoms such as frequency or dysuria, Gram stain and culture is indicated. Routine urinalysis is rarely helpful, since neutropenic patients do not usually have pyuria. Routine chest radiographs in the absence of chest symptoms have a low yield, and a normal chest radiograph does not exclude the possibility of pneumonia, since the neutropenic patient cannot mount a vigorous inflammatory response.[11] The chest examination is important, however. Crackles or rales, if heard, are strongly suggestive of a pneumonic process, and should prompt further investigation even in the presence of a normal chest film. Chest computed tomography (CT) has been shown to be useful in the evaluation of potential fungal pneumonia in neutropenic transplant and leukemia patients.[12] The baseline clinical evaluation is important for planning non-infectious disease supportive care therapy such as blood product transfusions and hydration therapy, and for documenting the patient's clinical status at presentation. Patients who initially present without an obvious focus of infection may end up having subsequently documented infections if carefully evaluated and reassessed daily.[13]

SITE-SPECIFIC ASSESSMENT

Sinus and nasal passages

The sinuses are a common site of infection in neutropenic cancer patients. Predisposing factors may include prior chronic sinusitis and nasal polyps. Patients may complain of headache or unilateral facial pain involving the frontal, temporal, or occipital areas.

Table 8.1 History, examination and evaluation in the neutropenic cancer patient

Site of infection	Signs/symptoms	Diagnostic evaluation	Organisms to consider
Sinus/nasal passages	Unilateral pain/tearing Dysesthesias Periorbital cellulitis Rhinorrhea	Limited CT of sinuses ENT consult Consider sinus drainage, biopsy Appropriate stains/cultures	*Streptococcus pneumoniae* *Staphylococcus aureus* Gram-negative bacteria Anaerobic bacteria *Aspergillus* spp. and other molds/fungi
Skin/soft tissues/wounds	Pain Erythema Cellulitis Vesicular lesions Ecthyma gangrenosum Nodules/abscesses	Biopsy/aspiration Stains/cultures	Coagulase-negative staphylococci *S. aureus* Gram-negative bacteria: *Pseudomonas aeruginosa* Herpes simplex virus (HSV) Varicella zoster virus *Candida* spp. Rapidly growing mycobacterium (non-tuberculous)
Mouth/oropharynx	Pain, odynophagia Erythema, mucositis Plagues Gingivitis Necrotizing/vesicular lesions	Cultures/stains Consider dental oncology evaluation	HSV *Candida* spp. Streptococci Anaerobes Gram-negative bacteria
Esophagus	Persistent nausea Dysphagia Retrosternal burning	Endoscopy Biopsy and cultures	*Candida* spp. HSV Cytomegalovirus (CMV)
Liver/gallbladder/pancreas	Right upper quadrant pain nausea/vomiting ↑ alkaline phosphatase ↑ transaminases (aminotransferases) ↑ amylase/lipase ↑ bilirubin	CT scan Ultrasound Consider adverse effects of concomitant medications	Gram-negative bacteria Enterococcus Anaerobic bacteria *Candida* spp.
Colon/Intestines	Crampy abdominal pain Loose, watery, diarrhea Bloody diarrhea	CT scan Surgical consultation Enteric stool cultures *Clostridium difficile* toxin	*Salmonella* spp. *Shigella* spp. *Giardia lamblia* *Candida* spp. CMV

Contd

Table 8.1 History, examination and evaluation in the neutropenic cancer patient – *contd*

Site of infection	Signs/symptoms	Diagnostic evaluation	Organisms to consider
			Anaerobic bacteria *Clostridium septicum* *Strongyloides stercoralis* Enteric Gram-negatives *Ps. aeruginosa*
Perirectal/groin	Pain, induration	Surgical consultation GYN consultation Endoscopy	Gram-negative bacteria Anaerobic bacteria Enterococcus *Candida* spp.
Respiratory tract	Cough Sputum production Dyspnea Pleuritic chest pain	CXR, CT chest Sputum stains and cultures Bronchoscopy Bronchoalveolar lavage Lung biopsy	Gram-negative bacteria *S. aureus* *Haemophilus influenzae* *S. pneumoniae* Seasonal viruses (respiratory syncytial virus, influenza) *Aspergillus* spp. *Pneumocystis carinii* *Legionella* spp. *Candida* spp. Mycobacteria CMV
Vascular access device (VAD)	Entry site erythema, tenderness	Stains/cultures Quantitative cultures through VAD and peripheral blood	*Staphylococcus epidermidis* *S. aureus* *Corynebacterium* *Acinetobacter* *Ps. aeruginosa* *Stenotrophomonas maltophilia* *Bacillus* spp. *Candida* spp. Non-tuberculous mycobacteria

Occasionally, dysesthesias may also be noted. Unfortunately, many patients may have sinusitis without significant signs or symptoms, and – particularly in bone marrow transplant patients or patients with acute leukemia – the diagnosis may often be delayed. Owing to the unreliability of routine sinus radiographs, most experts now consider limited CT scans as the radiographic test of choice. Air fluid levels, mucosal thickening, or bone erosion may be noted as well. ENT consultation is frequently required in order to obtain material via aspiration or biopsy of the sinuses for appropriate stains and cultures to establish microbiologic diagnosis.

Etiologic agents include Gram-positive bacteria, especially *Streptococcus pneumoniae* and *Staphylococcus aureus*, and Gram-negative bacteria; mixed infections are also common, including anaerobic organisms. Although less common in solid tumor patients, *Aspergillus* spp., the *Zygomycetes*, and other molds may be the cause of sinus infections in patients who have undergone bone marrow transplantation or those who have acute leukemia.[14]

Mouth and oropharynx

The mouth and oropharynx are common sites of infection in neutropenic cancer patients. Mucositis due to chemotherapy disrupts the normal protective mechanism in the mouth and oropharynx, and creates a portal of entry into the bloodstream for potential pathogens. Unfortunately, pain and difficulty in swallowing are non-specific symptoms of mucositis, and are unreliable in determining which patients have oropharyngeal infections. Periodontal infections are common causes of fever in neutropenic cancer patients, and dental oncology consultation may be indicated for patients with poor dentition.[15] Oral lesions may become colonized with Gram-negative bacilli and cause bacteremia. Alpha-hemolytic streptococci may also enter the bloodstream via the disrupted mucosal membrane of patients with significant mucositis.[16] Mouth anaerobes and *Candida* spp., which are often of low pathogenic potential, may cause bloodstream infections and febrile episodes in neutropenic cancer patients with significant oral mucositis. Herpes simplex virus (HSV) may be reactivated in patients with mucositis, and may cause more extensive mucosal damage and prolong healing time.[17]

Esophagus

Mucositis may also include the mucosal surface of the esophagus, and the presence of retrosternal burning pain and dysphagia should prompt the clinician to consider an esophageal source for the patient's febrile episode. Endoscopic evaluation may be warranted, with appropriate platelet support, to obtain material for diagnosis if the patient is thrombocytopenic. HSV and cytomegalovirus (CMV) should be considered as potential pathogens in the appropriate patient setting.[18] Patients with oropharyngeal candidiasis may have esophageal candidiasis as well. Although the classic symptoms of retrosternal burning and odynophagia may suggest an esophageal cause for the patient's febrile episode, more commonly chronic nausea and/or vomiting may be the only symptoms of esophageal infection.

Liver, gallbladder, and pancreas

Infections of the hepatobiliary tract are usually suspected because patients present with abdominal pain or right upper quadrant pain, or are found to have elevations in their alkaline phosphatase, bilirubin, transaminases, or amylase/lipase. The classic triad of right upper quadrant pain, fever, and jaundice, suggesting colangitis, may be present in patients with hepatobiliary tract cancers who have either internal or external drainage devices. Initial evaluation for infections in these areas should include ultrasound, CT, or magnetic resonance imaging (MRI). Surgical consultation may be warranted, and, for patients who have internal or external biliary stents, these may need endoscopic evaluation to ensure that they are not obstructed. During the course of the patient's management, it may be necessary to exchange infected stents. In addition to Gram-negative enteric organisms, enterococci (including vancomycin-resistant enterococci), and *Candida* spp. are important pathogens to consider.[19] The clinician should also recognize that rising transaminases, bilirubin, and alkaline phosphatase in the setting of fever in the neutropenic cancer patient may not be due to an infection, but may be due to an adverse effect of one of the patient's concomitant medications.

Therefore, re-evaluation of the patient's medication profile is often warranted. Patients with acute leukemia or patients who have undergone bone marrow transplantation who had prolonged episodes of neutropenia may be predisposed to hepatosplenic candidiasis, which often initially presents as fever without an obvious focus of infection or as an elevated alkaline phosphatase.[20] CT scans may show multiple small lesions in the liver or spleen, which can be biopsied to obtain a definitive diagnosis.

Intestines and colon

The presence of crampy abdominal pain and diarrhea, with or without gastrointestinal bleeding, suggest the possibility of gastrointestinal mucositis as the cause of the patient's infection. Enteric pathogens that cause febrile episodes in non-neutropenic hosts should be considered, and stool cultured for *Giardia*, *Salmonella*, *Shigella*, and *Cryptosporidium*. Stool should also be tested for *Clostridium difficile* toxin, even in the absence of prior antibiotic therapy. Rarely, *Strongyloides* may be the cause of infection, and can lead to intestinal obstruction and peritonitis.[21] Typhilitis, or the so-called neutropenic enterocolitis, is suggested by fever, diarrhea, and abdominal pain. This syndrome usually occurs in patients with acute leukemia who are neutropenic and have had intensive cytotoxic chemotherapy, and is caused by enteric Gram-negatives, including *Pseudomonas aeruginosa*.[22] Other organisms in the differential diagnosis would include, as previously mentioned, *C. difficile* colitis, CMV, and graft-versus-host disease. Endoscopy may be occasionally warranted to obtain appropriate material for pathologic examination and culture. CT scans may be useful in making the diagnosis and can demonstrate cecal wall thickening, local intramural hemorrhage, and edema of the ileum or parts of the colon.[22] For patients with massive diarrhea, other supportive care measures such as hydration, electrolyte replacement, and total parenteral nutrition may be indicated.

Perirectum and groin

The patient may complain of painful defecation or may have a history of problems with rectal fissures or hemorrhoids. Examination of the perirectum and groin areas may reveal discrete erythema, induration, or fluctuance. Although routine internal rectal exams are usually not indicated because of concerns about inducing bacteremia, gentle perirectal examinations should be performed in all neutropenic febrile cancer patients. Perirectal infections may be associated with bacteremia, particularly with Gram-negative organisms, and up to 10% of these patients may present with shock.[23] For large perirectal infections, particularly those that are fluctuant, surgical consultation for drainage may be warranted. Cultures demonstrate that these infections are usually polymicrobial, and are due to a mixture of Gram-negative enteric organisms, anaerobes, and enterococci. *Candida* infections are also common. Perirectal infections are more common in patients with acute leukemia, particularly monocytic and myelomonocytic leukemia, compared with patients with solid tumors.[23]

In addition to appropriate antibiotics and surgical drainage, analgesics and stool softeners are indicated along with local therapy (e.g. sitz baths).

Skin, soft tissues, and wounds

In an immunocompetent host, skin infections are easily diagnosed owing to localized erythema pain, tenderness, and the typical signs and symptoms due to local inflammatory reactions. Unfortunately, in neutropenic cancer patients, many of these signs and symptoms are blunted. Skin infections in neutropenic cancer patients may be a sign of a localized process such as an infection around a VAD, or may be part of a hematogenous process due to bacteremia. Elting et al[24] reviewed the relationship between the size of soft tissue lesions and outcomes in 163 cases of non-bacteremic soft tissue

infections in neutropenic cancer patients. The response rate to initial antibiotic therapy was 43% in patients whose soft tissue lesions measured more than 5 cm, compared with 87% among those patients with smaller lesions ($p < 0.0001$). Soft tissue infections of any size with central necrosis and those more than 5 cm in size in the setting of bacteremia have also been found to be associated with a poor clinical outcome.

Organisms associated with soft tissue and wound infections include *S. aureus*, coagulase-negative staphylococci, Gram-negative bacteria (*Ps. aeruginosa* and *Stenotrophomonas maltophilia*), and mixed Gram-negative/anaerobic infections. Varicella zoster virus and HSV are also common causes of skin infections in neutropenic cancer patients. Initial evaluation of skin infections in neutropenic cancer patients should include aspiration and punch biopsies of infected sites, with appropriate stains and cultures for bacteria, fungi, and atypical mycobacteria.

Respiratory tract

Pulmonary infections are relatively frequent among neutropenic cancer patients. These patients may present with cough, dyspnea, and sputum production; however, one-third of neutropenic patients with pneumonia will have no signs of rales or other symptoms indicating a respiratory tract infection. Owing to the lack of an inflammatory response, a chest radiograph is often normal during initial evaluation of febrile neutropenic patients who present with pneumonia.[6] Patients with neutropenic pneumonia may present with mental status changes, hypoxemia, and significant dyspnea. Cancer patients with T-cell defects who are neutropenic may have a dry cough, and conversational dyspnea, which suggests *Pneumocystis carinii* pneumonia. Pneumonias that present at the onset of the febrile neutropenic episode are typically due to Gram-negative bacteria such as *Ps. aeruginosa*, *Klebsiella* spp., and other *Enterobacteriaceae*.[25] Seasonal respiratory viruses such as respiratory syncytial virus, influenza virus, and CMV, as well as *Legionella* spp., may also be important pathogens in neutropenic cancer patients.[26–29] The initial evaluation should include blood cultures and examination of the sputum for bacteria, fungi, and mycobacteria. CT scans of the chest should be considered when patients present with focal or nodular lesions, and bronchoalveolar lavage should be considered for those patients who initially present with interstitial infiltrates.[30] Additional laboratory tests such as fungal antigen assays may be warranted in certain situations.

Urinary tract

Patients with urinary tract infections (UTIs) typically present with complaints of dysuria, urinary frequency, nocturia, and occasionally hematuria. Unfortunately, because of the lack of inflammatory response in neutropenic cancer patients, many of these symptoms are absent. In the absence of instrumentation of the urinary tract, or a prior history of frequent UTIs, these infections are a relatively infrequent cause of fever in the neutropenic cancer patient. Nevertheless, routine Gram stain and urine cultures are warranted. Owing to the lack of pyuria, routine urinalysis is generally considered to be a low-yield test. Obviously, the most common causes of UTIs in neutropenic cancer patients would include *Escherichia coli* and other Gram-negative enterics; however, enterococci also need to be considered, since many of the initial empiric antibiotic regimens do not provide adequate enterococcal coverage.

RISK ASSESSMENT

Although the value of risk assessment in the care of patients with fever and neutropenia is well established, 'risk' has meaning only when the outcome of interest is specified. Risk assessment

implies arranging patients along a spectrum of risk – but a risk of *what*? In various fever and neutropenia contexts, risk has been defined as the likelihood of developing clinical infection,[1] serious bacterial or fungal infection,[31–33] a condition indicating medical instability, whether or not infection-related,[34,35] an incomplete clinical response to an initial antibiotic regimen,[36] or an effective but slower resolution of infection.[37] The varied definition of risk does not indicate muddled research, but rather the flexibility of the risk assessment methodology: the outcome can and should vary, depending on the clinical question. For example, when patients are being considered for outpatient treatment settings where medical surveillance is reduced and thus detection of new problems potentially delayed, any evidence of medical instability may be pertinent, while, when antibiotic drug regimens are being compared, prompt resolution of infection is the appropriate outcome of interest. The purpose of risk assessment at the time of the initial clinical evaluation is to substratify this heterogeneous population into rational groups based upon clinically meaningful outcomes.

The Talcott clinical prediction rule

Talcott and colleagues[34] were the first to develop a formal clinical prediction rule based upon statistical methods to stratify this heterogeneous patient population. They asked an important clinical question: are there easily identifiable factors that, when present on day one of the initial febrile episode, predict adverse outcomes during the remainder of the episode? Their goal was to identify a low-risk patient group defined by the absence of identifiable medical instability during the febrile neutropenic episode, using information available within 24 hours of presentation. To define 'medical instability', they identified events or conditions that they labeled 'major medical complications'. The investigators specified a number of these that required close medical attention or intervention, such as systemic hypotension, prolonged or heavy bleeding, a new cardiac dysrhythmia, altered mental status, or any other condition that required observation or intervention. These states were not confined to those resulting directly or indirectly from severe infections, although infection-related problems predominated. In order to assess risk more comprehensively, they included serious complications that were related to the patient's underlying malignancy or comorbid condition. A patient who is medically stable from the standpoint of infection but develops serious acute gastrointestinal bleeding during a febrile neutropenic episode would be a poor candidate for outpatient management.

In a retrospective study of 261 episodes of fever and neutropenia over 12 months, 22% resulted in one or more major medical complication. This one-in-five risk of a serious medical event empirically justified the standard policy of keeping all patients with fever and neutropenia in the hospital. However, most of these serious medical complications occurred in patients who were identified as having one of the following risk factors: those who were inpatients at the time at which fever and neutropenia developed (group I), evidence of another significant comorbid condition that independently justified hospitalization within 24 hours of presentation with fever and neutropenia (group II); or evidence of uncontrolled cancer (group III), defined as either acute leukemia not in documented complete remission or another cancer that had progressed either clinically or radiologically *during* the most recent evaluable chemotherapy regimen. These patients (groups I–III) had a complication rate of 36%, and 20% died (Table 8.2). The remaining patients without any one of these indicators of high risk (group IV) appeared to have a very low risk of serious medical complications (2%), and none of them died. The low-risk group was large: 70% of patients who developed fever and neutropenia as outpatients. When indicators of these high-risk groups were put into a multiple logistic regression model with the occurrence of any serious medical complication as the depen-

Table 8.2 Outcomes of patient groups: Talcott derivation study[34]

Patient group	Percentage of total	Number of patients	Serious complications	Death
Inpatients (group I)	39	101	34 (34%)	23 (23%)
Outpatients with concurrent comorbidity (group II)	8	22	12 (55%)	3 (14%)
Outpatients with uncontrolled cancer (group III)	10	26	8 (31%)	4 (15%)
Low-risk outpatients (group IV)	43	112	2 (2%)	0 (0%)
All patients	100	261	56 (21%)	30 (11%)

dent variable, they were so dominant (all factors significant $p < 0.0001$) that other factors conventionally associated with high risk, such as the diagnosis of acute leukemia ($p < 0.0001$), greater age ($p < 0.0001$), and more severe neutropenia ($p < 0.0001$), remained only marginally significant.[34]

To validate this prediction rule, these investigators prospectively evaluated the high-risk criteria in an additional population, including not only patients at the original site, the Dana-Farber Cancer Institute in Boston, but also cancer patients at the Miriam Hospital in Providence, Rhode Island. In this confirmatory study, clinical reviewers without access to information on the patients' clinical course after the initial 24-hour evaluation period assigned patients to one of the four risk groups. Other reviewers blinded to the initial 24-hour period determined whether or not a major medical complication subsequently occurred. These results confirmed the initial model, although the risk difference between the high-risk groups and the remaining low-risk patients decreased. Patients in groups I–III were more likely than those in group IV to have any medical complication, multiple medical complications, and death (25% versus 5%, 13% versus 0%, and 9% versus 0%, respectively).[35] Of the five group IV patients with complications, one appeared to be a documentation error, one had transient hypotension within minutes after the 24-hour observation period, and three developed unambiguous medical complications seven or more days after admission, an apparently adequate period for detection by an appropriate program of medical follow-up. The combined data for outcomes of the derivation set and validation set of this clinical prediction rule are shown in Table 8.3.

As a result of this work, clinicians had access to a clinical decision rule allowing them to identify a large group of low-risk patients within 24 hours of presentation with fever and neutropenia. This low-risk group (Talcott group IV) of patients appeared to have a low enough risk of medical instability to make them appropriate candidates for clinical trials of programs of outpatient medical management, where medical surveillance could only be episodic rather than the continued observation permitted by inpatient care. These criteria were used as entry criteria for a pilot study and a subsequent randomized trial of home intravenous antibiotic therapy by these investigators.[38] Some concerns were raised that the Talcott clinical

Table 8.3 Outcomes of patient groups: Talcott combined derivation and validation studies[34,35]

Patient group	Percentage of total	Number of patients	Serious complications	Death
Inpatients (group I)	52	369	128 (37)	48 (13)
Outpatients with concurrent comorbidity (group II)	9	65	26 (40)	8 (12)
Outpatients with uncontrolled cancer (group III)	8	55	14 (25)	8 (15)
Low-risk outpatients (group IV)	31	216	7 (3)	0 (0)
All patients	100	705	175 (25)	64 (9)

prediction rule was derived and validated with patients mostly from a single center.[39] In addition, sensitivity, specificity, and misclassification rates for the Talcott model were never reported.

The MASCC Risk Index

The Multinational Association for Supportive Care in Cancer (MASCC) Study Section on Infections developed an internationally validated scoring system to identify low-risk patients in a prospective cohort study.[40] Between December 1994 and November 1997, this group gathered information on 1351 patients at 20 institutions in 15 countries. After excluding patients with undocumented fever, neutropenia, or prior cytotoxic chemotherapy, 1139 patients were analyzed. The derivation and validation sets were developed by random allocation of participating institutions rather than patients, greatly enhancing the generalizability of the results compared with commonly used statistical approaches, such as bootstrapping.[41] Using a multiple logistic regression analysis, the authors identified eight statistically significant risk factors, including baseline demographic characteristics (age < 60 years, solid tumor), past medical history (no chronic obstructive pulmonary disease, no prior fungal infection, outpatient status at the time of presentation with fever and neutropenia), clinician assessment of overall patient status (no symptoms or mild symptoms or moderate symptoms indicating overall burden of illness) (Figure 8.1), and the absence of particular acute pathological states (no hypotension and no dehydration) (Table 8.4).

Based on the coefficient of each risk factor in the multiple regression derivation model, a scoring system was developed, allowing users of the index to vary the threshold for designating patients at low risk (Table 8.5). Increasing scores indicated lower levels of risk. Using the optimal cutoff of 21 points, the group were able to identify 80% of patients who subsequently proved not to have a complication (sensitivity 0.80), with an overall complication rate among low-risk patients of 6%. However, raising the threshold one point to 22 resulted in significantly fewer patients identified as at low risk, with the sensitivity falling from 80% to 57%, although associated with a lower complication rate of 3% among low-risk patients. In contrast, the Talcott clinical prediction rule, designed to

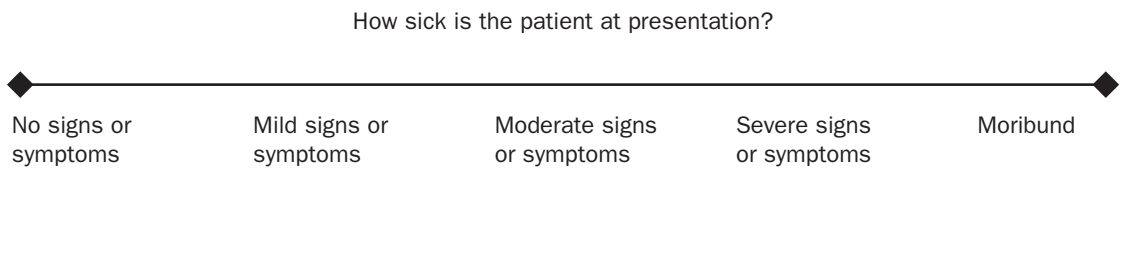


Figure 8.1 Visual analog score used in the MASCC Risk Index to measure burden of illness. No or mild symptoms corresponds to 5 points in the scoring system.

Table 8.4 Multiple logistic regression model based on 746 episodes of fever and neutropenia[40]

Characteristic	Coefficient	OR (95% CI)[a]	*p* value
Burden of illness:			
No or mild symptoms	2.1	8.2 (4.2–16.4)	<0.001
Moderate symptoms	1.3	3.7 (2.2–6.3)	<0.001
No hypotension	2.0	7.6 (2.9–19.9)	<0.001
No chronic obstructive pulmonary disease	1.7	5.3 (1.9–15.5)	0.002
Solid tumor or no previous fungal infection	1.6	5.1 (2.0–12.9)	<0.001
No dehydration	1.3	3.8 (1.9–7.7)	<0.001
Outpatient status	1.2	3.5 (2.0–6.0)	<0.001

[a] OR, odds ratio; 95% CI, 95% confidence interval.

Table 8.5 MASCC Risk Index scoring system[40]

Characteristic	Weight
Burden of illness: no or mild symptoms	5
No hypotension	5
No chronic obstructive pulmonary disease	4
Solid tumor or no previous fungal infection	4
No dehydration	3
Burden of illness: moderate symptoms	3
Outpatient status	3
Age < 60 years	2

Note: Points attributed to the variable 'burden of illness' are not cumulative. The maximum theoretical score is therefore 26.

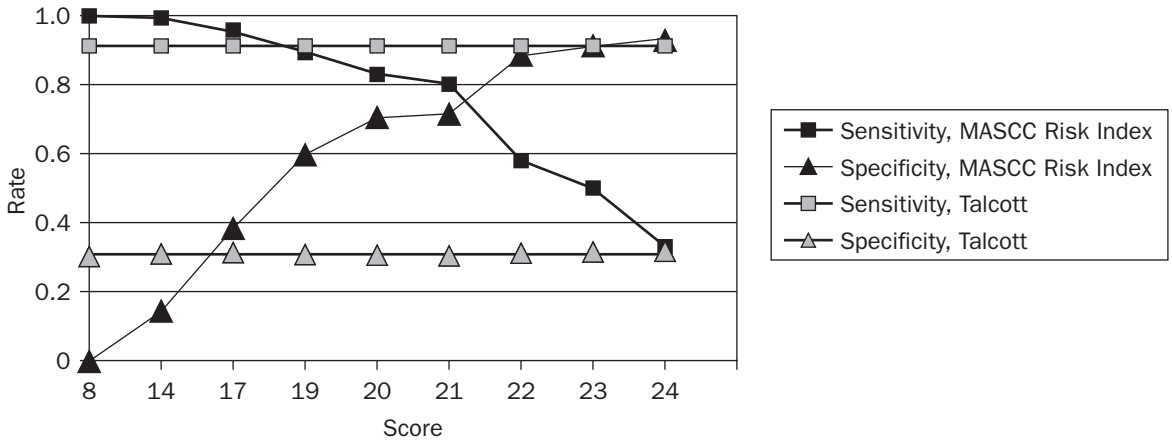


Figure 8.2 Sensitivity versus specificity for the MASCC Risk Index compared with the Talcott model (derivation set $N = 756$).

be conservative in designating patients at low risk, identified 32% of patients without subsequent complications and a 4% complication rate in patients designated as at low risk. The relationship between sensitivity and specificity in the derivation set of 756 patients for the MASCC Risk Index in comparison with the Talcott model can be demonstrated in graphic format (Figure 8.2).

In the validation set, a MASCC Risk Index score of 21 points identified 71% of patients without subsequent complications, with a 9% complication rate among designated low-risk patients. Using a threshold of 22 points, the sensitivity dropped to 47%, and the complication rate fell to 6%. The Talcott rule, which excluded all inpatients, identified only 30% of those patients with no complications as at low risk, with a 7% complication rate. Of interest, when the Talcott criterion of outpatient status was added to the MASCC scale using the authors' preferred threshold of 21, the sensitivity fell to 46% of all patients without complications, while the complication rate decreased to 6%. A comparison of the performance of the Talcott clinical prediction rule with the MASCC Risk Index for the validation set at a score of 21 is shown in Figure 8.3.

The development of the MASCC Risk Index represented an important advance in the generalizability of clinical prediction rules. Developed and tested in a broad range of clinical settings internationally, the study sharply reduced concerns regarding limited geographic applicability raised by the northeastern USA origins of the clinical prediction rule by Talcott and colleagues. The study also demonstrated the validity of the Talcott criteria in an international setting. The MASCC Risk Index increased the group of patients at low risk, expanding the potential patient population for less aggressive treatments, such as oral antibiotic regimens or outpatient management. The large difference in performance of the MASCC Risk Index associated with small changes in the numerical cutoff raises some concern about its robustness. However, the Index provides a flexible, valid clinical prediction rule developed and validated in a very broad range of clinical circumstances, and variation in individual beliefs about the proper threshold is made possible by the numerical form of its results. While its complexity may limit its use in routine clinical practice, it could easily be incorporated into prospective clinical trials. Currently, the Index is being used in two clinical trials based in Brussels.[42]

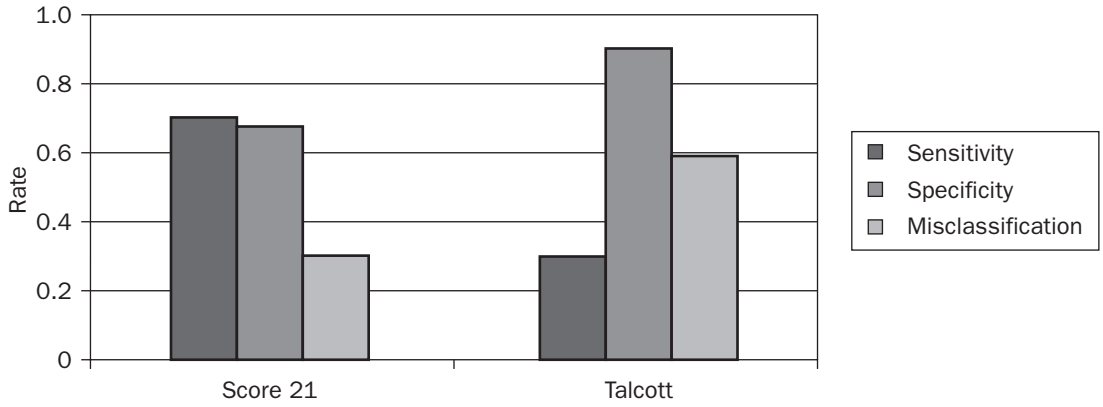


Figure 8.3 The sensitivity, specificity, and misclassification rates for the MASCC Risk Index at a proposed score of 21 points compared with the Talcott clinical prediction rule (validation set $N = 383$).

Risk assessment has been an integral part in the management of cancer patients with fever and neutropenia since its initial development. Through the years, there has been a steady increase in the methodological sophistication of risk-assessment studies, as well as in our formal understanding of how to integrate the process into clinical care. Risk assessment has provided powerful management tools for clinicians, and will likely continue to do so in the future.

REFERENCES

1. Bodey GP, Buckley M, Sathe YS, Freireich EJ, Quantitative relationships between circulating leukocytes and infection in patients with acute leukemia. *Ann Intern Med* 1966; **64:** 328–40.
2. Middleman EL, Watanabe A, Kaizer H, Bodey GP, Antibiotic combinations for infections in neutropenic patients. *Cancer* 1972; **30:** 573–9.
3. Bodey GP, Feld R, Burgess MA, β-lactam antibiotics alone or in combination with gentamicin for therapy of Gram-negative bacillary infections in neutropenic patients. *Am J Med Sci* 1976; **271:** 179–86.
4. Fainstein V, Bodey GP, Elting L et al, A randomized study of ceftazidime compared to ceftazidime and tobramycin for the treatment of infections in cancer patients. *J Antimicrob Chemother* 1983; **12:** 101–10.
5. Winston DJ, Ho WG, Bruckner DA et al, Controlled trials of double beta-lactam therapy with cefoperazone plus piperacillin in febrile granulocytopenic patients. *Am J Med* 1988; **85**(Suppl 1A): 21–30.
6. Flaherty JP, Waitley D, Edlin B et al, Multicenter, randomized trial of ciprofloxacin plus azlocillin versus ceftazidime plus amikacin for empiric treatment of febrile neutropenic patients. *Am J Med* 1989; **87**(Suppl 5a): 278S–82S.
7. Rolston KVI, Berkey P, Bodey GP et al, A comparison of imipenem to ceftazidime with or without amikacin as empiric therapy in febrile neutropenic patients. *Arch Intern Med* 1992; **152:** 283–91.
8. Schimpff SC, Empiric antibiotic therapy for granulocytopenic cancer patients. *Am J Med* 1986; **80**(Suppl 5c): 13–20.
9. Caya JG, Farmer SG, Ritch PS et al, Clostridial septicemia complicating the course of leukemia. *Cancer* 1986; **57:** 2045–8.
10. Weinstein MP, Current blood culture methods and systems: clinical concepts, technology, and interpretation of results. *Clin Infect Dis* 1996; **23:** 40–6.
11. Donowitz GR, Harman C, Pope T, Stewart M, The role of the chest roentgenogram in febrile neutropenic patients. *Arch Intern Med* 1991; **151:** 701–4.

12. Barloon TJ, Galvin JR, Mori M et al, High-resolution ultrafast chest CT in the clinical management of febrile bone marrow transplant patients with normal or nonspecific chest roentgenograms. *Chest* 1991; **99:** 928–33.
13. Rubenstein EB, Kim YJ, Legha R, Rolston KVI on behalf of the MASCC Infectious Disease Study Section, Documented infections in febrile neutropenic patients presenting with apparent fever of undetermined origin: a wolf in sheep's clothing. *Supp Care Cancer* 2000; **8:** 242 (Abst 5).
14. Goering P, Berlinger NT, Weisdorf DJ, Aggressive combined modality treatment of progressive sinonasal fungal infections in immunocompromised patients. *Am J Med* 1988; **85:** 619–23.
15. Peterson DE, Sonis ST, Oral complications of cancer chemotherapy: present status and future studies. *Cancer Treat Rep* 1982; **66:** 1251–6.
16. Elting LS, Bodey GP, Keefe BH, Septicemia and shock syndrome due to viridans streptococci: a case–control study of predisposing factors. *Clin Infect Dis* 1992; **14:** 1201–7.
17. Schubert MM, Peterson DE, Lloid ME, Oral complications. In: *Hematopoietic Cell Transplantation*, 2nd edn (Thomas ED, Blume KG, Forman SJ, eds). Oxford: Blackwell Science, 1999: 751–63.
18. Crumpacker CS, Cytomegalovirus. In: *Principles and Practice of Infectious Diseases*, 5th edn. (Mandell GL, Bennett J, Dolin R, eds). Philadelphia: Churchill Livingstone, 2000: 1586–9.
19. Rolston KVI, Dholakia N, Rodriguez S, Rubenstein EB, Nature and outcome of febrile episodes in patients with pancreatic and hepatobiliary cancer. *Supp Care Cancer* 1995; **3:** 414–17.
20. Thaler M, Pastakia B, Shawker TH et al, Hepatic candidiasis in cancer patients: The evolving picture of the syndrome. *Ann Intern Med* 1988; **108:** 88–100.
21. Powell RW, Moss JP, Nagar D et al, Strongyloidiasis in immunosuppressed hosts. Presentation as massive lower gastrointestinal bleeding. *Arch Intern Med* 1980; **140:** 1061–3.
22. Gomez L, Martino R, Rolston KVI, Neutropenic enterocolitis: spectrum of the disease and comparison of definite and possible cases. *Clin Infect Dis* 1998; **27:** 695–9.
23. Rolston KVI, Bodey GP, Diagnosis and management of perianal and perirectal infection in the granulocytopenic patient. In: *Current Clinical Topics in Infectious Diseases*, Vol 13 (Remington JS, Swartz MN, eds). Boston: Blackwell Scientific, 1993: 164–71.
24. Elting LS, Rubenstein EB, Rolston KVI, Bodey GP, Outcomes of bacteremia in patients with cancer and neutropenia: observations from two decades of epidemiological and clinical trials. *Clin Infect Dis* 1997; **25:** 247–59.
25. Keating MJ, Bodey GP, Valdivieso M, Rodriguez V, A randomized comparative trial of three aminoglycosides – comparison of continuous infusions of gentamicin, amikacin and sisomicin combined with carbenicillin in the treatment of infections in neutropenic patients with malignancies. *Medicine* 1979; **58:** 159–70.
26. Whimbey E, Bodey GP, Viral pneumonia in the immunocompromised adult with neoplastic disease: the role of common community respiratory viruses. *Semin Respir Infect* 1992; **7:** 122–31.
27. Wendt CH, Weisforf DJ, Jordan MC et al, Parainfluenza virus respiratory infection after bone marrow transplantation. *N Engl J Med* 1992; **326:** 921–6.
28. Emanuel D, Cunningham I, Jules-Elysee K et al, Cytomegalovirus pneumonia after bone marrow transplantation successfully treated with the combination of ganciclovir and high-dose intravenous immune globulin. *Ann Intern Med* 1988; **109:** 777–82.
29. Ampel NM, Wing EJ, Legionellosis in the compromised host. In: *Clinical Approach to Infection in the Compromised Host*, 2nd edn (Rubin R, Young LS, eds). New York: Plenum, 1988: 305–19.
30. National Comprehensive Cancer Network (Febrile Neutropenia Guidelines Panel Members), NCCN Practice Guidelines for Fever and Neutropenia. NCCN Proceedings. *Oncology* 1999; **13**(5A): 197–257.
31. Pizzo PA, Robichaud KJ, Gill FA, Witebsky FG, Empiric antibiotic and antifungal therapy for cancer patients with prolonged fever and granulocytopenia. *Am J Med* 1982; **72:** 101–11.
32. Pizzo PA, Robichaud KJ, Gill FA et al, Duration of empiric antibiotic therapy in granulocytopenic patients with cancer. *Am J Med* 1979; **67:** 194–200.
33. Pizzo PA, Infectious complications in the child with cancer. I. Pathophysiology of the compromised host and the initial evaluation and management of the febrile cancer patient. *J Pediatr* 1981; **98:** 341–54.
34. Talcott JA, Finberg R, Mayer RJ, Goldman L, The

medical course of cancer patients with fever and neutropenia. Clinical identification of a low-risk subgroup at presentation. *Arch Intern Med* 1988; **148:** 2561–8.

35. Talcott JA, Siegel RD, Finberg R, Goldman L, Risk assessment in cancer patients with fever and neutropenia: a prospective, two-center validation of a prediction rule. *J Clin Oncol* 1992; **10:** 316–22.
36. Pizzo PA, Hathorn JW, Hiemenz J et al, A randomized trial comparing ceftazidime alone with combination antibiotic therapy in cancer patients with fever and neutropenia. *N Engl J Med* 1986; **315:** 552–8.
37. Elting LS, Rubenstein EB, Rolston KVI et al, Time to clinical response: an outcome of antibiotic therapy of febrile neutropenia with implications for quality and cost of care. *J Clin Oncol* 2000; **18:** 3699–706.
38. Talcott JA, Whalen A, Clark J et al, Home antibiotic therapy for low-risk cancer patients with fever and neutropenia: a pilot study of 30 patients based on a validated prediction rule. *J Clin Oncol* 1994; **12:** 107–14.
39. Rubenstein EB, Rolston KVI, Outpatient treatment of febrile neutropenic patients with cancer. *Eur J Cancer* 1995; **31A:** 2–4.
40. Klastersky J, Paesmans M, Rubenstein EB et al for the Study Section on Infections of the Multinational Association for Supportive Care in Cancer, The Multinational Association for Supportive Care in Cancer Risk Index: a multinational scoring system for identifying low-risk febrile neutropenic cancer patients. *J Clin Oncol* 2000; **18:** 3038–51.
41. Justice AC, Covinsky KE, Berlin JA, Assessing the generalizability of prognostic information. *Ann Intern Med* 1999; **130:** 515–24.
42. Klastersky J, Chami J, Frankard J et al, Prospective validation study of the MASCC clinical prediction rule for identification of low-risk patients with febrile neutropenia and for therapeutic decision. *Proc Am Soc Clin Oncol* 2000; **19:** 440a (Abst 1726).

9

Risk-adjusted management of the febrile neutropenic cancer patient

Edward B Rubenstein, Kenneth VI Rolston

INTRODUCTION

Chapter 4 discussed the evolution of clinical prediction rules or statistically derived models for determining risk during the febrile neutropenic episode. Since the original paper by Bodey et al[1] describing the relationship between the circulating neutrophil count and the incidence of infections in patients with acute leukemia, clinicians have used clinical trials methodology to improve treatment for these patients, and have made observations about factors that influence the risk of good *or* bad outcomes during the febrile episode. A comparison of the characteristics of the two methods for determining risk stratification is shown in Table 9.1. In this chapter, we shall discuss several of these factors and provide an overview of the clinical-trials-based methods for risk-adjusted therapy in patients with fever and neutropenia.

OUTCOME AS A FUNCTION OF THE INITIAL AND CHANGING NEUTROPHIL COUNT

As early as 1966, the fatality rate due to severe infection in patients with acute leukemia was noted to be linked to the change in neutrophil count during the first week of infection.[1] Table 9.2 clearly demonstrates this relationship. The fatality rate was highest (80%) in patients who initially started with absolute neutrophil counts (ANC) $<100/mm^3$ that did not change during the first week of infection, compared with those patients who started out with ANC $<1000/mm^3$ that then rose to $>1000/mm^3$ (27%). Many clinical trials have reported that response rates to antibiotic regimens are strongly influenced by the trend in the neutrophil count during the febrile episode.[2–5] In a randomized trial of 520 evaluable febrile neutropenic episodes treated with carbenicillin plus gentamicin, amikacin or sisomicin, the overall response rate was higher (85%) when the neutrophil count rose, compared with when it remained stable or decreased (59%) ($p = 0.001$).[2] Thirteen years later, using more modern antibiotics, Rolston and colleagues[5] confirmed the influence of a rising neutrophil count on response rates in 750 febrile neutropenic episodes in 567 patients treated with imipenem or ceftazidime with or without amikacin. In this study, the overall response rate was 73% if the initial neutrophil count rose, compared with 43% if it decreased or remained

Table 9.1 Risk assessment in febrile neutropenia

	Clinical prediction rule(s)	Clinical trial(s)
Methods	• Statistical (logistic regression) • Training set (derivation) • Validation set	• Pilot study – feasibility • Phase II – reproducibility • Phase III – compare with standard of care
Endpoints	• Serious medical complication(s) • Death	• Response rate(s) • Adverse events
Advantages	• Large population – 'all comers' • Representative of true population	• Clinicians familiar with methods • Well-defined eligibility and methodology
Limitations	• Still needs testing in clinical trials	• Generalizibility of results • Prognostic factors derived from secondary analyses

unchanged ($p < 0.00001$). The response rate in patients who were initially profoundly neutropenic (ANC $< 100/mm^3$), but recovered from neutropenia was 67%, compared with only 32% in patients who remained profoundly neutropenic ($p < 0.0001$). Clearly, bone marrow recovery is a very important factor that influences outcome during the febrile neutropenic episode. Unfortunately it cannot be predicted at the time of initial evaluation and is of little use in helping to risk-stratify patients. Delayed bone marrow recovery might be anticipated in certain patient subsets (e.g. those who have received multiple cycles of myelosuppressive chemotherapy, those with known bone marrow metastases, or those who have received radiation therapy to the pelvis, spine, or long bones).

HOW DOES DURATION OF NEUTROPENIA INFLUENCE RISK?

In 1988, Rubin et al[6] published a study from the US National Cancer Institute (NCI) examining the influence of the duration of neutropenia on the response to empiric antimicrobial therapy and other important clinical outcomes in patients with fever of undetermined origin (FUO). Patients with less than 7 days of neutropenia had response rates to initial antimicrobial therapy of 95%, compared with only 32% in patients with more than 14 days of neutropenia ($p < 0.001$), whereas patients with intermediate durations of neutropenia of between 7 and 14 days had response rates of 79%. These outcomes are shown in Table 9.3. At greatest risk are patients with acute leukemia and recipients of high-dose chemotherapy with stem cell or bone marrow transplantation, because the duration of severe neutropenia often exceeds 15 days. In contrast, most patients with solid tumors have neutropenia lasting less than 7–10 days and are at much lower risk. Unfortunately, using duration of neutropenia as a decision rule at the onset of the febrile episode precludes its use in identification/management of the low-risk patient: determining the duration of neutropenia is not possible until the neutropenia

Table 9.2 Fatality rate of severe infections related to change in granulocyte level during the first week of infection[a]

Granulocyte level		Episodes	
Initial ANC/mm^3	Change	Total number	Percentage fatal
<100	None	15	80
<1000	None or fall	44	59
<1000	Rise, but still <1000	15	40
<1000	Rise to >1000	26	27
>1000	Rise	44	32

[a] Adapted from Bodey GP, Buckley M, Sathe YS, Freireich EJ, Quantitative relationships between circulating leukocytes and infection in patients with acute leukemia. *Ann Intern Med* 1966; **64:** 328–40.

has resolved. Pizzo and colleagues[7] refined the criterion from 'duration of neutropenia' to 'expected duration of neutropenia'. Presently, clinicians cannot accurately predict the expected duration of neutropenia at the onset of the febrile episode, although patients with solid tumors receiving conventional-dose chemotherapy are likely to have neutropenia lasting less than 7 days in the majority of cycles after chemotherapy. Observational studies are being conducted to add this important variable to current risk models.

PROGNOSTIC FACTORS IN PATIENTS WITH BACTEREMIA

Elting and colleagues[8] conducted an extensive analysis of 909 episodes of bacteremia in 799 febrile neutropenic cancer patients based upon 10 consecutive published randomized clinical trials of empiric antibiotic therapy[3,5,9–16] conducted at the University of Texas MD Anderson Cancer Center between 1980 and 1993. These trials in adults were prospectively conducted and had similar eligibility criteria. Five outcomes were reported for each episode: response to the initial antibiotic regimen, ultimate outcome of the infection, time to defervescence, duration of antibiotic therapy, and survival. In an initial analysis, bacteremic patients were subclassified according to the presence and amount of tissue involvement (simple versus complex) at the onset of the infectious episode. Table 9.4 shows the classification scheme used to distinguish simple from complex bacteremias. Twenty-one prognostic factors were studied, including demographic variables (age and gender), underlying malignancy/treatment (cancer diagnosis and bone marrow transplantation), clinical features at presentation/during therapy (shock, initial levels of serum creatinine, albumin, bilirubin, and serum transaminases, and neutrophil count/trend), infection-related variables (associated site of infection, size of soft-tissue lesions, necrosis, organism, and susceptibility to antibiotics), and treatment factors (initial antibiotic regimen, number of antibiotics, vancomycin use, and schedule of antibiotics).

Table 9.3 Clinical outcomes of patients with fever of unknown origin according to duration of neutropenia[a]

	Low-risk neutropenia: <7 days (331 patients)	Moderate-risk neutropenia: 7–14 days (166 patients)	High-risk neutropenia: >14 days (93 patients)
Time to defervescence (days):			
Median	2	4	5
Range	1–7	4–14	1–30
Recurrent fever	2 (0.6%)	2 (0.6%)	35 (38%)
Success without modification of initial empiric antibiotic regimen	315 (95%)	131 (79%)	30 (32%)
Success with modification of initial regimen	14 (4%)	32 (19%)	60 (65%)
Death	2 (1%)	3 (2%)	3 (3%)

[a] Adapted from Rubin M, Hathorn JW, Pizzo PA, Controversies in the management of febrile neutropenic cancer patients. *Cancer Invest* 1988; **6:** 167–84.

Results of the logistic regression for this analysis are shown in Figure 9.1 and Table 9.5 for the initial response (the point at which the initial antibiotic regimen was discontinued or modified) and the ultimate outcome for the episode. Certain factors, such as age, leukemia, prior bone marrow transplant, hematologic malignancy versus solid tumor, serum albumin, presence or absence of shock, and complex bacteremia, are either known or highly suspected early after the onset of the febrile episode, and can be used to stratify patients into high-risk subsets. The prognostic significance of complex infection associated with bacteremia on survival is demonstrated in Figure 9.2. At 21 days, 20% of patients with complex bacteremias were dead, compared with only 5% of patients with simple bacteremias ($p < 0.0001$). Other key findings from this study included the observation that the median time to defervescence for patients with simple bacteremias was half that observed for patients with complex bacteremias (2.5 days versus 5.3 days; $p < 0.0001$). As noted previously, response rates were strongly influenced by the trend in the neutrophil count during the febrile episode. Patients with complex bacteremias who were profoundly neutropenic ($ANC < 100/mm^3$) at the onset of their febrile

Table 9.4 A classification scheme for bacteremic febrile neutropenic cancer patients[a]

Concomitant site of infection	
Simple bacteremia	**Complex bacteremia**
• Bacteriuria • Otitis • Pharyngitis • Soft tissue infection <5 cm	• Major organ: Lungs Liver/spleen Kidneys Colon Bones/joints Veins/heart/meninges • Soft tissue infection, wound, or cellulitis >5 cm • Soft tissue infection any size with necrosis

[a] Adapted from Elting LS, Rubenstein EB, Rolston KVI, Bodey GP. Outcomes of bacteremia in patients with cancer and neutropenia: observations from two decades of epidemiological and clinical trials. *Clin Infect Dis* 1997; **25:** 247–59.

episode and did not experience neutrophil recovery had a 63% response rate compared to 86% for those patients whose neutrophils rose to ANC $>1000/mm^3$ ($p = 0.04$). Profoundly neutropenic patients with simple bacteremias had a much higher response rate to antibiotics (94% versus 70%, $p < 0.0001$) compared to patients with complex bacteremias.

Based upon these and other studies, clinical criteria can be used to stratify patients into high-, moderate-, and low-risk strata shortly after the onset of the febrile neutropenic episode. These clinical criteria are reviewed in Table 9.6. These criteria in one combination or other have been used to select patients for risk-adjusted clinical trials of antibiotic therapy as described in subsequent sections of this chapter.

TREATMENT OF HIGH-RISK PATIENTS

There is uniform agreement that high-risk neutropenic patients (see Table 9.6) need to be treated using standard, hospital-based, parenteral, broad-spectrum, empiric antibiotic therapy for the entire febrile episode.[17] The various benefits of this approach, and the many treatment options, including combination therapy and monotherapy, are discussed in detail in Chapters 1, 6, 7, and 14. There is also general agreement that many patients do not fall into the high-risk category, and that although improvements in the methods for identifying such patients accurately at the onset of a febrile episode still need to be made, alternative treatment strategies for moderate- and low-risk patients might be associated with substantial advantages and need to be explored.[18]

ORAL ANTIBIOTIC THERAPY – HISTORICAL PERSPECTIVES

The feasibility of oral therapy administered in the hospital was first demonstrated two decades ago with the use of trimethoprim/sulfamethoxazole in febrile neutropenic patients.[19] This experience was not limited to 'low-risk'

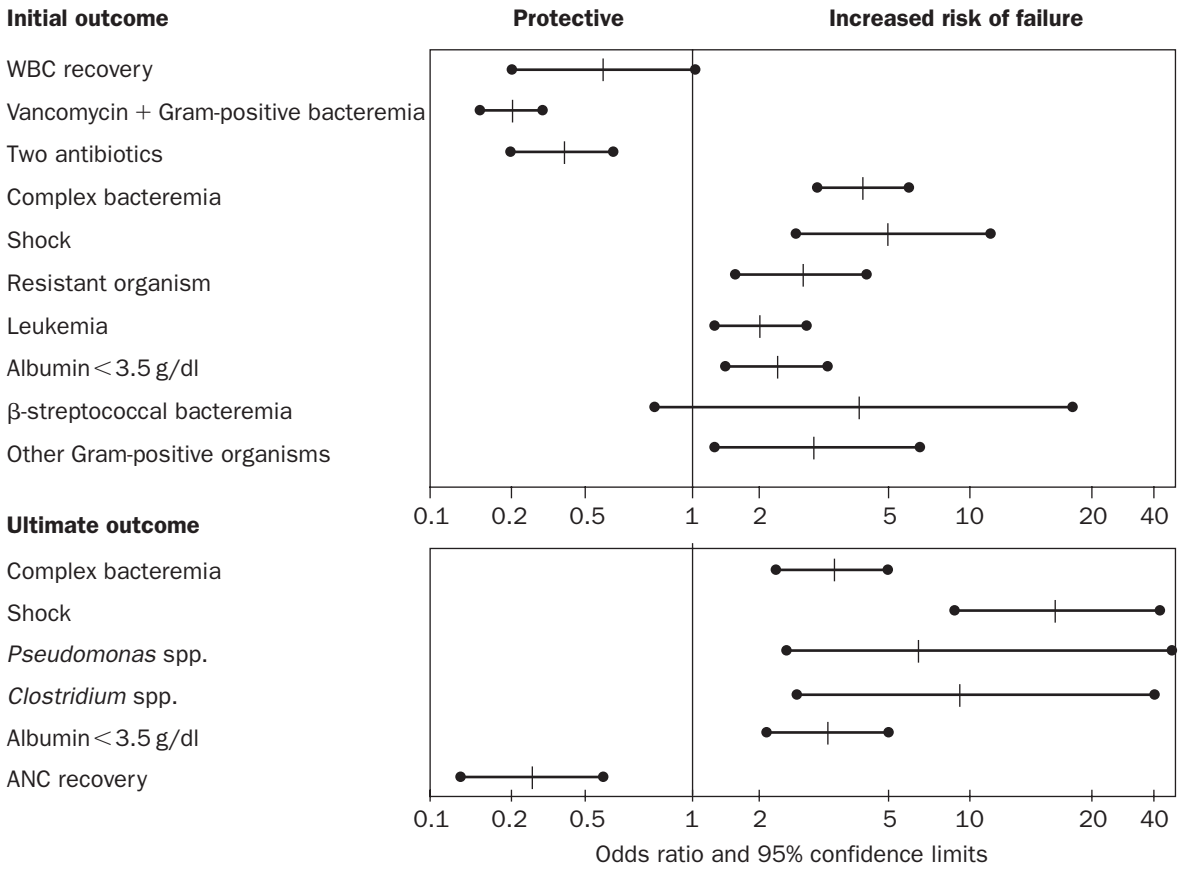


Figure 9.1 Results of logistic regression analysis of factors predicting the outcome of initial antibiotic therapy for and the ultimate outcome of infection in neutropenic patients with cancer and bacteremia who were enrolled in 10 clinical trials.[8] An odds ratio of greater than 1 indicates a greater risk of therapeutic failure; a value of less than 1 suggests a protective effect.

patients, and, although moderately successful, the most significant drawback of this approach was the lack of activity of trimethoprim/sulfamethoxazole against *Pseudomonas aeruginosa*, a frequent and aggressive pathogen in neutropenic patients. This was overcome with the development of the newer synthetic quinolones (ciprofloxacin and ofloxacin), and oral therapy became a potential option even for patients with severe neutropenia. Early experience with oral ciprofloxacin at the MD Anderson Cancer Center was associated with an overall response rate of 85%.[20] More recently Malik et al[21] compared several standard parenteral regimens in use at the Aga Khan University Hospital, Karachi, Pakistan (amikacin plus piperacillin, carbenicillin, or cloxacillin) with oral ofloxacin (400 mg bid) in a prospective randomized trial of hospitalized neutropenic patients with fever who were able to tolerate oral therapy. The response rates to the original regimen (53%) were identical for oral ofloxacin and parenteral therapy. The overall response rate (including response after modification of the original regi-

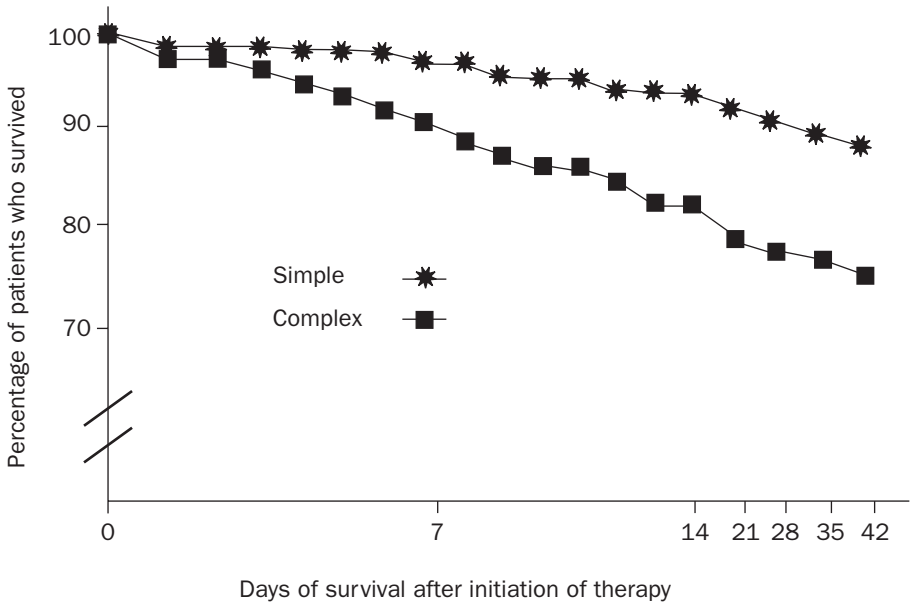


Figure 9.2 Duration of survival in neutropenic patients with cancer and simple bacteremias and in neutropenic patients with cancer and complex bacteremias who were enrolled in 10 clinical trials.[8] The observed difference is statistically significant at $p = 0.001$.

men) was 73% for patients treated with parenteral therapy and 77% (not statistically significant) for patients treated with oral ofloxacin. These data were encouraging, since these studies were not limited to low-risk patients, creating the expectation that better response rates might be seen in low-risk patients.

THE EMERGENCE OF OUTPATIENT THERAPY FOR LOW-RISK PATIENTS

The original impetus for exploring outpatient therapy was provided by the availability of computerized small-volume infusion pumps, which were being used to deliver outpatient chemotherapy. These had been tailored for outpatient parenteral antibiotic therapy of various infections in the general medical population (e.g. endocarditis, osteomyelitis, and diabetic soft-tissue infections). Furthermore, it was postulated that outpatient therapy for febrile neutropenic patients, if proven to be safe and effective, might improve the quality of life of cancer patients and their caregivers/family by limiting the amount of time patients spent in the confines of the hospital. Some investigators also theorized that the risk of nosocomial infections and potential iatrogenic complications might outweigh the benefits of inpatient therapy for low-risk patients. Another compelling reason to pursue this line of clinical investigation was the promise of reducing the cost of healthcare for this common complication of chemotherapy, with the principal premise being that oral outpatient therapy would be the least expensive method, if such therapy could be administered safely. In the late 1980s, the basic assumption made by the majority of clinicians caring for febrile neutropenic patients was that the hospital was the safest place to treat such patients, and that one must demonstrate that other settings are 'as safe as' the hospital before they are accepted as part of the standard of care.

Several pieces of information have recently come to light indicating that this assumption is probably erroneous. Data presented at the 4th Decennial International Conference on Nosocomial and Healthcare-Associated

Table 9.5 Prognostic factors for bacteremia in neutropenic patients with cancer who were enrolled in 10 clinical trials[a]

Factor	No. of episodes	Initial response rate (%)	*p* value	Ultimate response rate (%)	*p* value
Complex bacteremia[b]	138	38		73	
Simple bacteremia[b]	771	74	<0.0001	94	<0.0001
Shock	34	35		41	
No shock	875	70	<0.001	93	<0.001
Resistant organism	62	50		83	
Susceptible organism	748	70	0.001	92	0.02
Leukemia	516	63		89	
Other hematologic malignancies	152	74	0.0002	94	0.07
Solid tumor	241	77		93	
BMT[c]	189	59		88	
No BMT	720	71	0.002	92	0.11
Age ⩾50 years	423	73		92	
Age <50 years	486	64	0.006	90	0.33
Albumin level <3.5 g/dl	711	66		90	
Albumin level ⩾3.5 g/dl	198	77	0.005	96	0.01

[a] Adapted from Elting LS, Rubenstein EB, Rolston KVI, Bodey GP, Outcomes of bacteremia in patients with cancer and neutropenia: Observations from two decades of epidemiological and clinical trials. *Clin Infect Dis* 1997; **25:** 247–59.
[b] See Table 9.4.
[c] Bone marrow transplantation.

Infections (Atlanta, GA, March 2000) has demonstrated that each year, approximately two million patients in the USA acquire infections while hospitalized for other conditions. These infections account for 88 000 deaths and cost more than 4.6 billion dollars. Additionally, at least 70% of these healthcare-associated infections diagnosed in hospitals are caused by bacteria that are resistant to at least one antimicrobial agent generally used for the treatment of such infections, and an increasing proportion of hospital-acquired isolates are multidrug-resistant.[22] These data also demonstrate that although similar infections occur at other sites of healthcare delivery, such as nursing homes, dialysis centers, outpatient clinics, and patients' homes, they are much less frequent in a home-care setting than in a hospital or long-term care setting (1% versus 5%). Early discharge from the hospital to an outpatient clinic or homecare setting might, therefore, substantially reduce the frequency of resistant healthcare-associated infections, particularly in patients who are otherwise at very low risk of developing complications that require hospital-based monitoring.

Another disturbing document is the report entitled *To Err is Human*, produced by the

Table 9.6 Clinical risk stratification and guidelines for risk-adjusted therapy of febrile neutropenic patients

Risk group	Patient characteristics	Treatment options
High-risk	Hematologic malignancy Allogeneic bone marrow transplantation Severe and prolonged neutropenia (>14 days) Significant comorbidity or poor performance status Presentation with shock, hypoalbuminemia, or complex infection Slow response to initial therapy[a]	Traditional, empiric broad-spectrum, parenteral antibiotics for duration of febrile episode. Consider colony-stimulating factors
Moderate-risk	Solid tumor → intensive chemotherapy → autologous bone marrow or hematopoetic stem cell transplantation Moderate duration of neutropenia (7–14 days) Clinically/hemodynamically stable, with minimal comorbidity Early response to initial therapy[a]	Initial, parenteral, in-hospital therapy, followed by early discharge on parenteral or oral regimen
Low-risk	Solid tumor Conventional chemotherapy Short duration of neutropenia (<7 days) No comorbidity Fever of unknown origin or simple infection Clinically and hemodynamically stable	Outpatient therapy (parenteral, sequential, or oral)

[a] Although these responses are typical in high/moderate-risk patients, they cannot be used on day 1 to assign a particular patient to either risk group, since response to antibiotics is often not determined until 72–96 hours after the initiation of antibiotic therapy.

Institute of Medicine.[23] This report focuses on several studies conducted across the USA, and points out that the frequency of adverse events in US hospitals ranged between 2.9% and 3.7% of hospitalizations, and that between 8.8% and 13.6% of these events led to deaths.[24,25] Furthermore, over half of these adverse events resulted from medical errors that could have been prevented. When extrapolated to the more than 33.6 million admissions to US hospitals in 1997, these studies imply that between 44 000 and 98 000 Americans die each year as a result of medical errors. Although medical errors occur in all healthcare settings, the report also points out that four out of five such events occur in the hospital, with the rest occurring in physicians' offices, other non-hospital settings, or patients' homes. These data again suggest

that the hospital is not necessarily the safest place to deliver healthcare, and provide further impetus for the evaluation of non-hospital-based settings for healthcare delivery. Insistence upon clinical trials that compare hospital-based treatment with that delivered in non-hospital-based settings before accepting the latter as a standard of care seems counter-intuitive, since such trials would expose a substantial number of low-risk patients to the hazards of hospitalization. Fortunately, a significant amount of progress has been made in the development and evaluation of alternative strategies, including the route(s) of antibiotic administration and the setting(s) in which therapy is delivered. These are discussed below.

EARLY DISCHARGE AFTER INITIAL HOSPITALIZATION

Using their prediction model to select low-risk patients, Talcott et al[26] conducted a pilot study evaluating early discharge on parenteral antibiotics after an initial 48-hour hospitalization period. Patients with significant infections (pneumonia, bacteremia, urinary tract infection), and those aged 65 years or more were excluded, even if they were predicted to be low-risk. The initial hospital-based regimens included mezlocillin plus gentamicin, or monotherapy with ceftazidime. After 2 days of this therapy, stable patients were discharged to receive the same parenteral regimen at home, with daily home follow-up by a nurse. Patients were readmitted if fever persisted or if complications arose. Of the 30 patients treated in this manner, 16 (53%) responded to the original regimen. Five patients were readmitted for persistent fever, and four developed serious complications such as renal failure, hypotension, and bacterial and fungal superinfection. There was a documented improvement in the patients' quality of life and a 44% reduction in daily medical charges for patients receiving home antibiotics. Despite these favorable outcomes and the fact that there were no deaths during this trial, the high rate of readmission (30%) and alteration of the initial regimen raised some doubts about the practical application of Talcott's prediction model. Perhaps the inclusion of patients with acute leukemia and/or persistent neutropenia of more than 7 days (5 patients (17%) had neutropenia of 13–36 days duration) accounts for the disappointing results of this pilot study. A newer prediction model has been developed by the Multinational Association for Supportive Care in Cancer (MASCC), which is an improvement over Talcott's model and has a lower misclassification rate.[27] In this model, one of the factors predictive of low risk is the presence of a solid tumor. Models to better predict the duration of severe neutropenia are also being developed, and should further enhance our risk-assessment capabilities. Until these models have been developed and validated, it might be prudent to exclude patients with hematologic malignancies from those considered low-risk. Most patients who are stable enough to be discharged will probably have their parenteral regimen changed to an oral one, and parenteral home antibiotic therapy will probably be limited to stable patients who are unable to tolerate oral therapy because of factors such as mucositis.

HOSPITAL-BASED ORAL ANTIBIOTICS FOR LOW-RISK PATIENTS

Two recently published prospective randomized trials compared oral antibiotic therapy with standard parenteral regimens in hospitalized, low-risk, febrile neutropenic patients.[28,29] In the trial conducted by the International Antimicrobial Therapy Cooperative Group of the European Organization for Research and Treatment of Cancer, equivalence was demonstrated in the comparison of intravenous ceftriaxone plus amikacin (84% success rate) and oral ciprofloxacin plus amoxicillin/clavulanate (86% success rate). The frequency of

adverse events including death (related or unrelated to infection) was also similar for both regimens.[28]

In the trial from the NCI and allied institutions, the oral regimen of ciprofloxacin plus amoxicillin/clavulanate and the intravenous regimen of ceftazidime monotherapy were also associated with similar success rates (71% and 67% respectively). There was a higher rate of intolerance of the oral regimen (16%), in comparison with the intravenous regimen (1%). There were no deaths in either arm of this study. Patients with hematologic malignancies were eligible for both of these trials, and although the mean duration of neutropenia after the onset of infection was approximately 4 days, several patients had prolonged neutropenia (14–18 days), which may have contributed to the failure of the initial regimen and to intolerance of the oral regimen, and led to the modification of therapy in some patients.

The equivalence of oral and parenteral therapy demonstrated in these and other smaller trials may have significant implications for the management of neutropenic patients with fever, particularly in countries with limited resources. In the USA, and other countries with similar reimbursement and legal systems, hospital-based oral antibiotic therapy will probably not enjoy widespread use. In reality, most patients who are able to tolerate oral therapy and are clinically stable can probably be discharged from the hospital and treated as outpatients. A small number may require hospitalization for medical reasons not related to their febrile episode, or might live alone and be unable to adequately care for themselves. Such patients might benefit from hospital-based oral antibiotic therapy.

EARLY DISCHARGE ON ORAL THERAPY

The availability of expanded-spectrum oral quinolones has also enabled clinicians to switch from parenteral regimens in the hospital to oral regimens upon discharge, for moderate-risk patients after an initial period of stabilization in the hospital.[18] This strategy is known as sequential, early-switch, or stepdown therapy. Several clinical trials have successfully demonstrated the utility of this approach. In a multicenter randomized trial, comparing ceftazidime plus amikacin with ciprofloxacin plus azlocillin for empiric therapy of febrile neutropenia, early conversion to orally administered ciprofloxacin was compared with continuation of the parenteral regimen in patients showing initial response.[30] Conversion to orally administered ciprofloxacin was possible for 65% of eligible study patients after a mean of 6 days of parenteral therapy, resulting in cost savings and shortened hospital stays. In another trial conducted at the NCI, febrile neutropenic patients who defervesced within 72 hours of receiving a parenteral regimen (imipenem or ceftazidime) were randomized either to continue parenteral antibiotics or complete therapy with oral ciprofloxacin.[31] Twenty-four of 27 evaluable episodes (89%) in patients randomized to receive parenteral therapy, and 22 of 29 episodes (76%) in patients switched to oral therapy, were successfully managed without any further changes in antibiotic therapy or readmission to the hospital. A number of other studies, somewhat limited in size, suggest that there is a role for the strategy of switching from parenteral to oral antibiotics, enabling early discharge in selected febrile neutropenic patients.[32,33] Although many low-risk patients can be managed safely with initial outpatient treatment, sequential therapy with early discharge might offer a more comfortable management plan for some, particularly those with nausea or mucositis, which might limit oral intake at the onset.

OUTPATIENT ORAL ANTIBIOTIC THERAPY

Several trials conducted over the past decade have demonstrated the efficacy of outpatient antibiotic therapy for febrile neutropenic patients. In a study conducted in Pakistan,

Malik and colleagues[34] supplied oral ofloxacin (400 mg bid) for self-administration to low-risk neutropenic patients (patients with non-hematologic malignancies and an expected duration of neutropenia of less than 1 week) who were unable to afford hospitalization or lived too far away from the oncology center when they developed their febrile episode. Of the 111 febrile episodes treated in this manner, 92 (83%) responded without hospitalization, and the overall response rate to antibiotic therapy was 97%. In a subsequent study, these same investigators compared inpatient and outpatient therapy with oral ofloxacin in low-risk febrile neutropenic patients.[35] Overall, 78% of inpatients and 77% of outpatients responded to the initial regimens and required no modification of therapy. The mortality rate was 2% among inpatients and 4% among outpatients. Both of these studies demonstrated relatively high response rates, most probably because they were limited to low-risk patients. However, a mortality rate of 4% in the outpatient setting was of concern, and the question of whether hospitalization could have prevented any of these deaths was raised. Monotherapy with quinolones such as ofloxacin, as used in these two studies, is not endorsed in guidelines published by either the Infectious Disease Society of America or the National Comprehensive Cancer Network.[17,36]

Two studies among adult cancer patients and one in the pediatric population, comparing outpatient oral and parenteral antibiotic regimens in low-risk febrile neutropenic patients, have been conducted at the MD Anderson Cancer Center. In the first adult study, patients were randomized to either a parenteral regimen (aztreonam 2 g q8h, plus clindamycin 600 mg q8h) or an oral regimen (ciprofloxacin 750 mg q8h, plus clindamycin 600 mg q8h) upon becoming febrile.[37] In this trial, 83 episodes were evaluated: 40 in patients receiving the oral regimen and 43 in patients receiving the parenteral regimen. The parenteral regimen was associated with a response rate of 95%, compared with 88% for the oral regimen ($p = 0.19$), with a combined response rate of 92% for 'outpatient therapy'. There were no infection-related complications such as septic shock and no infection-related deaths in this trial. Renal toxicity, however, was documented in 10% of patients randomized to the oral arm. This was probably the result of multiple factors, including patients' age and state of hydration, the administration of other nephrotoxic drugs (cisplatin), and possibly the high dose of ciprofloxacin.[38] Consequently, in the second adult trial, the oral arm was modified (ciprofloxacin 500 mg q8h, plus amoxicillin/clavulanate 500 mg q8h), with the parenteral arm being the same as in the first study.[39] Of the 179 episodes that were evaluable, 91 received parenteral and 88 received oral therapy. The response rate for the parenteral regimen was 87% and that for the oral regimen 90%. Neither regimen was associated with any major toxicity, and no patients developed septic shock or died as a result of their infection.

In the pediatric study, low-risk patients (age range 2–16 years) were randomized to receive either oral ciprofloxacin (12.5 mg/kg q12h) or parenteral ceftazidime (50 mg/kg q8h) in the outpatient setting, after receiving one dose of parenteral ceftazidime during the initial evaluation/randomization period.[40] Out of the 73 episodes, 63 (86%) were successfully managed on an outpatient basis. The response rate for the parenteral arm (31 of 33 episodes) was slightly better than that for the oral arm (32 of 40 episodes), but this difference was not statistically significant. Of the 10 patients who were hospitalized, 4 had prolonged fever and 3 developed emesis. Protracted neutropenia was linked with the need for hospitalization. There were no deaths, intensive care unit admissions or transfers, or other serious complications during this trial.

These, and other smaller studies (Table 9.7), provide evidence that with careful patient selection, appropriate antimicrobial therapy, and adequate monitoring of patients, outpatient therapy (both parenteral and oral) for low-risk febrile neutropenic patients is safe and effective.

Table 9.7 Selected trials of outpatient therapy in low-risk, febrile neutropenic patients

Authors	Patient population and nature of study	Treatment regimen	Response rate to initial regimen (%)
Malik et al[34]	Non-randomized trial; 111 episodes; all adults	ofloxacin 400 mg p.o., bid	83
Malik et al[35]	Randomized trial of inpatient versus outpatient oral therapy; 169 episodes; all adults	Inpatient: ofloxacin 400 mg p.o., bid Outpatient: ofloxacin 400 mg p.o., bid	Inpatient: 78 outpatient: 77
Rubenstein et al[37]	Randomized trial of outpatient parenteral and oral regimens; 83 episodes; all adults	i.v. aztreonam 2 g q8h plus i.v. clindamycin 600 mg q8h versus p.o. ciprofloxacin 750 mg q8H plus p.o. clindamycin 600 mg q8H	i.v.: 95 p.o.: 88
Rolston and Rubenstein[39]	Randomized trial of outpatient parenteral and oral regimens; 179 episodes; all adults	i.v. aztreonam 2 g q8h plus i.v. clindamycin 600 mg q8h versus p.o. ciprofloxacin 500 mg q8h plus p.o. amoxicillin/clavulanate 500 mg q8h	i.v.: 87 p.o.: 90 i.v.: 94
Mullen et al[40]	Randomized trial of parenteral and oral regimens; 75 episodes; all pediatric	i.v. ceftazidime 50 mg/kg q8h versus p.o. ciprofloxacin 12.5 mg/kg q12h	p.o.: 80

RISK-ADJUSTED MANAGEMENT: GENERAL ISSUES

The above discussion has summarized much of the progress that has occurred regarding risk-adjusted management of febrile neutropenic patients. This progress is the result of (a) an increased understanding of 'febrile neutropenia', (b) technological advance in vascular access, infusion therapy, and outpatient monitoring, (c) the availability of newer, more potent, oral antimicrobial agents, and (d) the

current climate in the healthcare industry, which has provided much of the impetus for evaluating non-traditional methods and sites of delivery of care. It must be remembered that most of the trials and strategies discussed above have been conducted and developed in large tertiary-care hospitals or comprehensive cancer centers, with a particular interest and substantial experience in caring for cancer patients. The ability to create and maintain an infrastructure that can handle these management strategies and the logistics involved, sometimes in a large number of patients, is critical to the success of such programs. This infrastructure includes individuals from various disciplines – physicians, nurses, pharmacists, vascular access and infusion therapy teams, home healthcare personnel, and the patients and their caregivers, all acting in concert to ensure that the best possible care is delivered as efficiently and safely as possible. Some institutions caring for cancer patients may not have the ability to create or maintain such an infrastructure, nor a group of healthcare providers with sufficient interest or expertise to provide such care. In such institutions, standard hospital-based care should continue to be provided, until they acquire the ability to sustain a risk-adjusted therapeutic program.

Other issues that are vital to the success of risk-adjusted therapy (outpatient therapy in particular) are listed in Table 9.8. It is important to select appropriate empiric regimens, not merely convenient ones, taking into consideration local microbiology and susceptibility/resistance patterns. At the MD Anderson Cancer Center, infections caused by Gram-negative bacilli, including *Ps. aeruginosa*, are documented, even in low-risk patients.[37,39] Using once-a-day ceftriaxone (a regimen that has been used for empiric therapy in febrile neutropenic patients, and is convenient) in such a setting would not be appropriate as the initial empiric regimen.[41] Careful patient selection, taking into consideration not only clinical/statistical risk-assessment criteria, but also issues such as patient comfort and compliance, the availability of a caregiver at home, the availability of reliable transportation (automobile) and communication (telephone), and relative distance of the patients residence from the hospital (we chose a 30-mile radius, based on our local traffic patterns), are all important, and have an impact on the overall success of these new strategies. Frequent monitoring of patients for response, lack of response, the development of medical complications, toxicity, and to ensure compliance is also critical, and cannot be overstressed. All these issues need to be worked out in advance in order to ensure a successful outpatient treatment program.

Table 9.8 Requirements for a successful program of risk-adjusted therapy

- Institutional support for an adequate infrastructure
- Dedicated team of healthcare providers
- Local epidemiologic/susceptibility-resistance data
- Selection of appropriate (not merely convenient) antimicrobial regimens
- Motivated, compliant patients and family or other support personnel
- Adequate transportation and communication
- Adequate monitoring of non-hospitalized patients
- Access 24 hours a day to management team and ambulatory care facility (Emergency Department)

ADVANTAGES AND DISADVANTAGES OF RISK-ADJUSTED THERAPY

Standard, hospital-based therapy of the febrile neutropenic patient has been an extremely successful strategy. It has had a significant and positive impact on the overall survival of cancer patients, particularly on those who are prone to developing medical complications. This approach, however, is expensive, consumes valuable resources, and is not necessary or even beneficial for all febrile neutropenic patients. Risk-adjusted therapy is the new wave, and if implemented successfully, is associated with substantial benefits. These are outlined in Table 9.9. Several studies have demonstrated the positive economic benefits of early discharge and/or outpatient oral antibiotic therapy, compared to hospital based parenteral therapy.[26,37] There is also compelling data that hospitalization significantly increases the risk of acquiring infections with multidrug-resistant pathogens, and exposes patients to a number of other hazards of hospitalization, which can probably be avoided by early discharge and/or outpatient management.[22,23] Studies have also documented significant improvements in the quality of life of patients receiving risk-adjusted therapy, and increased convenience for their caregivers as well.[37,39] This aspect does not get much press in today's financially-focused health care environment where economics dictate many decisions. It is, however, an extremely important consideration in the care of cancer patients, and cannot be ignored any longer. We have had patients who have begged to be treated on our outpatient protocols/pathways, so that they may be able to eat home-cooked meals, sleep in their own beds, and smell the proverbial roses. Even high-risk, terminally ill, and dying patients have expressed the desire to spend their last few days at home. We as clinicians entrusted with the overall wellbeing of these patients (including those who are terminally ill) need to respond to their wishes and needs. Risk-adjusted management is a step in the right direction.

Table 9.9 Advantages and disadvantages of risk-based therapy

Advantages

- Avoidance of iatrogenic and other hazards of hospitalization
- Reduced rate of 'healthcare associated' infections
- Lower cost of care
- Enhanced quality of life (patients)
- Increased convenience (family)
- More efficient resource utilization

Disadvantages

- Potential for serious complications in an unsupervised setting
- Potential for non-compliance
- Need to maintain an (expensive?) infrastructure

There are some potential disadvantages of risk-adjusted therapy. Low-risk does not mean 'no risk', and the potential for developing complications such as septic shock or severe hemorrhage in a relatively unsupervised environment does exist. Careful patient selection and close monitoring of patients generally prevents the development of such events, or enables one to manage them promptly, should they occur. Some patients might be non-compliant, particularly those on oral therapy. Maintaining adequate venous access may occasionally become a problem that can be difficult to address in an ambulatory or home setting. Finally, patients might develop a false sense of security regarding their febrile episode, since it did not require hopsitalization or parenteral therapy, and might ignore early signs and symptoms of progressive infection or other complications because of a perceived trivialization of their illness. It is imperative that patients be given specific instructions regarding follow-up

monitoring, and be told to seek immediate medical attention at the earliest sign of complications. It has been our experience from more than a decade of administering risk-adjusted therapy that cancer patients are generally very compliant, follow instructions meticulously, and do 'whatever it takes' to stay out of hospital. Consequently, we have seldom encountered the problems listed above.

FUTURE CONSIDERATIONS

In recent years, much attention has been focused on devising risk-assessment and treatment strategies for low-risk patients.[18] Future considerations for this subset of patients include further refinements to increase the accuracy of risk-assessment models, and improvements in therapeutic regimens as newer antimicrobial agents become available. Currently, most moderate- and high-risk patients are managed with standard, hospital-based therapy. It is in this group of patients that newer evaluation and management strategies need to be developed in order to fully embrace the concept of risk-adjusted management of the febrile neutropenic patient.

EVALUATION AND MANAGEMENT OF MODERATE- AND HIGH-RISK PATIENTS

Our current systems for stratifying risk are not perfect, and misclassifications do occur.[27,42,43] High-risk patients, as we currently identify them, are a very heterogeneous population. In the MASCC Risk-Index derivation set, of the 205 patients identified initially as high-risk, 79 (39%) experienced a serious medical complication including 29 deaths (14%). This means that the majority – 126 patients (61%) – initially identified as being at high risk had resolution of their febrile episode without any problems. Errors of sensitivity lead to misclassification of low-risk patients as being high-risk, thereby exposing them to the hazards of hospitalization, including iatrogenic complications and nosocomial infections with resistant microorganisms.[22,23] Errors of specificity, on the other hand, result in a more dangerous misclassification, namely high-risk patients being labelled as low-risk. Such patients could initially receive their care in the outpatient setting and potentially develop serious complications without adequate monitoring and supervision. These errors in classification need to be minimized and more accurate risk assessment strategies need to be developed. Meanwhile, Elting and colleagues have suggested using a new outcome – the time to clinical response – to facilitate implementation of early-discharge strategies, thereby improving safety and quality of care for hospitalized patients initially classified as high-risk.

TIME TO CLINICAL RESPONSE

A traditional endpoint when comparing treatment regimens has been the overall response or success rate at the end of therapy. Elting and colleagues[44] developed a working definition of time to clinical response using pooled data from six prospective clinical trials of imipenem-based or ceftazidime based regimens conducted at the MD Anderson Cancer Center. The sensitivity, specificity, and predictive values of objective (temperature response) and subjective values (self-report of improvement) were compared, as were time to clinical response, days of hospitalization, and cost. An early-discharge strategy based upon the time to clinical response was generated and retrospectively applied to 488 episodes of fever in 466 patients. The characteristics of these comparisons are shown in Table 9.10. A combination of defervescence for 24 hours and patient-reported subjective improvement resulted in a sensitivity of 93% and a specificity of 76%, with no deaths occurring if an early-discharge strategy had been implemented using this model. The imipenem-based regimens had a quicker time to response (5 days versus 7 days) when compared with the ceftazidime-based regimens

Table 9.10 Development of a time to response definition: predictive values of subjective and objective clinical criteria[a]

Clinical Criterion to Predict response[b]	True-positive rate[c] (sensitivity) (%)	True-negative rate[d] (specificity) (%)	False-positive rate[e] (%)	False-negative rate[f] (%)	Selected for step-down care	Response to discharge regimen (positive predictive value)	Deaths
One temperature <37.8°C	99	8	28	21	474 (97%)	339 (72%)	29 (6%)
One temperature <37.8°C plus subjective response	96	68	13	12	375 (77%)	328 (87%)	9 (2%)
Three consecutive temperatures <37.8°C	97	34	23	17	429 (88%)	332 (77%)	29 (7%)
Three consecutive temperatures <37.8°C plus subjective response	94	72	11	15	364 (75%)	323 (89%)	9 (2%)
24 hours temperature <37.8°C	96	48	19	16	405 (83%)	329 (81%)	18 (4%)
24 hours temperature <37.8°C plus subjective response	93	76	10	16	356 (73%)	321 (90%)	0 (0%)
Subjective response only	96	65	13	12	380 (78%)	329 (87%)	9 (2%)

[a] Adapted from Elting LS, Rubenstein EB, Rolston KVI et al. Time to clinical response: an outcome of antibiotic therapy of febrile neutropenia with implications for quality and cost of care. *J Clin Oncol* 2000; **18:** 3699–706.
[b] Predictive value for response to the antibiotic regimen being received when the clinical criterion was met.
[c] Percentage of true antibiotic responses properly classified as responses.
[d] Percentage of true antibiotic failures properly classified as failures.
[e] Percentage of patients who would be selected for step-down care and would fail.
[f] Percentage of patients who would not be selected for step-down care but would nevertheless respond to therapy.

($p = 0.003$), providing another criterion for comparing regimens that might have been considered equivalent if only the endpoint of overall response rate had been used. If prospectively validated, this outcome measure could be used to identify appropriate regimens and implement early-discharge strategies, resulting in the advantages outlined in Table 9.9.

USE OF HEMATOPOIETIC GROWTH FACTORS

The hematopoietic growth factors G-CSF and GM-CSF (granulocyte and granulocyte–macrophage colony-stimulating factors) shorten the duration of neutropenia, and their role in the primary or secondary prevention of fever in neutropenic patients has been reasonably well clarified.[45] Their role as adjuncts to antimicrobial therapy in neutropenic patients with fever has been difficult to define (see Chapter 13). Studies evaluating the therapeutic role of G-CSF and GM-CSF have been hampered by the lack of risk stratification.[16,46–52] This has led to their use principally in patients with shock, pneumonia, and other complex infections, and their benefit has been difficult to demonstrate in this poor-prognosis group. A recent subset analysis from the MASCC Risk-Index study demonstrated higher response rates to the initial antibiotic regimen (86% versus 72%; $p = 0.016$), and fewer complications, including death (4.2% versus 13.4%; $p = 0.031$) in neutropenic solid tumor patients receiving prophylactic hematopoietic growth factors, in whom these factors were continued after the development of fever.[53] This benefit was most marked in patients with sarcoma, a subgroup that has a high proportion of low-risk neutropenic patients, and least apparent in patients with lung cancer, a subgroup with a low proportion of high-risk patients.[37,39] Factors that accounted for complications in the logistic regression model included: an interaction between ANC $< 100/mm^3$ at onset of fever and neutropenia and failure to respond to the initial regimen ($p < 0.001$), severe burden of illness or moribund appearance at time of presentation ($p < 0.001$), uncontrolled cancer ($p = 0.001$), age over 60 years, ($p = 0.004$), and presence of a complex infection ($p = 0.010$). In this regression model, prophylactic use of CSFs appeared to be protective ($p = 0.095$). In contrast, Garcia-Carbonero and colleagues[54] compared antibiotics with or without G-CSF in 'high-risk' solid tumor patients with fever and neutropenia, using days of hospitalization as their primary endpoint. The criteria used to determine 'high-risk', which failed to account for the impact of microbiologically documented infections on the time to defervescence, and the requirement that patients remain hospitalized until afebrile for 2 days were significant limitations of this study. Garcia-Carbonero et al concluded that patients receiving G-CSF had a shorter duration of subsequent neutropenia, antibiotic therapy, and hospital stay. Using the endpoint of time to clinical response (adjusted for microbiologically documented infections) might have produced different (more accurate) results. Determining the optimal role of the hematopoietic growth factors, particularly in high-risk patients, is a complex task and will require studies using prospective observational cohort designs, and risk-stratified clinical trials using validated risk-assessment criteria.

REFERENCES

1. Bodey GP, Buckley M, Sathe YS, Freireich EJ, Quantitative relationships between circulating leukocytes and infection in patients with acute leukemia. *Ann Intern Med* 1966; **64:** 328–40.
2. Keating MJ, Bodey GP, Valdivieso M, Rodriguez V, A randomized comparative trial of three aminoglycosides – comparison of continuous infusions of gentamicin, amikacin, and sisomicin combined with carbenicillin in the treatment of infections in neutropenic patients with malignancies. *Medicine* 1979; **58:** 159–70.
3. Fainstein V, Bodey GP, Elting L et al, A randomized study of ceftazidime compared to cef-

tazidime and tobramycin for the treatment of infections in cancer patients. *J Antimicrob Chemother* 1983; **12**(Suppl A): 101–10.
4. Winston DJ, Ho WG, Bruckner DA et al, Controlled trials of double beta-lactam therapy with cefoperazone plus piperacillin in febrile granulocytopenic patients. *Am J Med* 1988; **85**(Suppl 1A): 21–30.
5. Rolston KVI, Berkey P, Bodey GP et al, A comparison of imipenem to ceftazidime with or without amikacin as empiric therapy in febrile neutropenic patients. *Arch Intern Med* 1992; **152:** 283–91.
6. Rubin M, Hathorn JW, Pizzo PA, Controversies in the management of febrile neutropenic cancer patients. *Cancer Invest* 1988; **6:** 167–84.
7. Pizzo PA, Infectious complications in the child with cancer. I. Pathophysiology of the compromised host and the initial evaluation and management of the febrile cancer patient. *J Pediatr* 1981; **98:** 341–54.
8. Elting LS, Rubenstein EB, Rolston KVI, Bodey GP, Outcomes of bacteremia in patients with cancer and neutropenia: observations from two decades of epidemiological and clinical trials. *Clin Infect Dis* 1997; **25:** 247–59.
9. Fainstein V, Bodey GP, Bolivar R et al, Moxalactam plus ticarcillin or tobramycin for treatment of febrile episodes in neutropenic cancer patients. *Arch Intern Med* 1984; **144:** 1766–70.
10. Jones PG, Rolston KVI, Fainstein V et al, Aztreonam therapy in neutropenic patients with cancer. *Am J Med* 1986; **81:** 243–48.
11. Anaissie EJ, Fainstein V, Bodey GP et al, Randomized trial of beta-lactam regimens in febrile neutropenic cancer patients. *Am J Med* 1988; **84:** 581–9.
12. Bodey GP, Fainstein V, Elting LS et al, β-lactam regimens for the febrile neutropenic patient. *Cancer* 1990; **65:** 9–16.
13. Bodey G, Reuben A, Elting L et al, Comparison of two schedules of cefoperazone plus aztreonam in the treatment of neutropenic patients with fever. *Eur J Clin Microbiol Infect Dis* 1991; **10:** 551–8.
14. Bodey GP, Elting LS, Narro J et al, An open trial of cefoperazone plus sulbactam for the treatment of fever in cancer patients. *J Antimicrob Chemother* 1993; **32:** 141–52.
15. Raad II, Whimbey II, Rolston KVI et al, A comparison of aztreonam plus vancomycin and imipenem plus vancomycin as initial therapy for febrile neutropenic cancer patients. *Cancer* 1996; **77:** 1386–94.
16. Anaissie EJ, Vartivarian S, Bodey GP et al, Randomized comparison between antibiotics alone and antibiotics plus granulocyte–macrophage colony stimulating factor (*Escherichia coli*-derived) in cancer patients with fever and neutropenia. *Am J Med* 1996; **100:** 17–23.
17. Hughes WT, Armstrong D, Bodey GP et al, From the Infectious Diseases Society of America: 1997 guidelines for the use of antimicrobial agents in neutropenic patients with unexplained fever. *Clin Infect Dis* 1997; **25:** 551–73.
18. Rolston KVI, New trends in patient management: risk-based therapy for febrile patients with neutropenia. *Clin Infect Dis* 1999; **29:** 515–21.
19. Bodey GP, Grose WE, Keating MJ, Use of trimethoprim/sulfamethoxazole for treatment of infections in patients with cancer. *Rev Infect Dis* 1982; **4:** 579–85.
20. Haron E, Rolston KVI, Cunningham C et al, Oral ciprofloxacin therapy for infection in cancer patients. *J Antimicrob Chemother* 1989; **24:** 955–62.
21. Malik IA, Abbas Z, Karim M, Randomized comparison of oral ofloxacin alone with combination of parenteral antibiotics in neutropenic febrile patients. *Lancet* 1992; **339:** 1092–6.
22. Gerberding JL, *Preventing Antimicrobial-Resistant Healthcare Infections: Beyond 2000*. Clinical Updates in Infectious Diseases, National Foundation for Infectious Diseases, Vol V, Issue 2, August 2000.
23. Kohn L, Corrigan J, Donaldson M (eds), Committee on Quality of Health Care in America, *To Err is Human: Building a Safer Health System. Institute of Medicine Report.* Washington, DC: National Academy Press, 2000.
24. Brennan TA, Leape LL, Laird NM et al, Incidence of adverse events and negligence in hospitalized patients: results of the Harvard Medical Practice Study I. *N Engl J Med* 1991; **324:** 370–6.
25. *Hospital Statistics*. Chicago: American Hospital Association, 1999.
26. Talcott JA, Whalen A, Clark J et al, Home antibiotic therapy for low risk cancer patients with fever and neutropenia: a pilot study of 30 patients based on a validated prediction rule. *J Clin Oncol* 1994; **12:** 107–14.

27. Klastersky J, Paesmans M, Rubenstein EB et al for the Study Section on Infections of Multinational Association for Supportive Care in Cancer, The MASCC Risk-Index: a multinational scoring system to predict low-risk febrile neutropenic cancer patients. *J Clin Oncol* 2000; **18:** 3038–51.
28. Kern WV, Cometta A, DeBock R et al, Oral versus intravenous empirical antimicrobial therapy for fever in patients with granulocytopenia who are receiving cancer chemotherapy. International Antimicrobial Therapy Cooperative Group of the European Organization for Research and Treatment of Cancer. *N Engl J Med* 1999; **341:** 312–18.
29. Freifeld A, Marchigiani D, Walsh T et al, A double-blind comparison of empirical oral and intravenous antibiotic therapy for low-risk febrile patients with neutropenia during cancer chemotherapy. *N Engl J Med* 1999; **341:** 305–11.
30. Flaherty JP, Waitley D, Eldin B et al, Multicenter randomized trial of ciprofloxacin plus Azlocillin versus ceftazidime plus amikacin for empiric treatment of febrile neutropenic patients. *Am J Med* 1989; **87**(Suppl 5A): 278S–82S.
31. Rolston KVI, Rubenstein EB, Freifeld A, Early empiric antibiotic therapy for febrile neutropenic patients at low risk. *Infect Dis Clin North Am* 1996; **10:** 223–37.
32. Lav RC, King SM, Richardson SE, Early discharge of pediatric febrile neutropenic cancer patients by substitution of oral for intravenous antibiotics. *Pediatr Hematol Oncol* 1994; **11:** 417–21.
33. Bash RO, Katz JA, Cash JV et al, Safety and cost–effectiveness of early hospital discharge of lower risk children with cancer admitted for fever and neutropenia. *Cancer* 1994; **19:** 522–7.
34. Malik IA, Khan WA, Aziz A et al, Self-administered antibiotic therapy for chemotherapy-induced low-risk febrile neutropenia in patients with non-hematologic neoplasms. *Clin Infect Dis* 1994; **19:** 522–7.
35. Malik IA, Khan WA, Karim M et al, Feasibility of outpatient management of fever in cancer patients with low-risk neutropenia: results of a prospective randomized trial. *Am J Med* 1995; **98:** 224–31.
36. National Comprehensive Cancer Network (Febrile Neutropenia Guidelines Panel Members), NCCN Practice Guidelines for Fever and Neutropenia. NCCN Proceedings. *Oncology* 1999; **13(**5A): 197–257.
37. Rubenstein EB, Rolston K, Benjamin RS et al, Outpatient treatment of febrile episodes in low-risk neutropenic patients with cancer. *Cancer* 1993; **71:** 3640–6.
38. Rolston KVI, Rubenstein EB, Ciprofloxacin nephrotoxicity. *Arch Intern Med* 1993; **153:** 2705–6.
39. Rolston KVI, Rubenstein EB, Elting LS et al, Ambulatory management of febrile episodes in low risk neutropenic patients. In: *Program and abstracts of the 35th Interscience Conference on Antimicrobial Agents and Chemotherapy, San Francisco*. Washington, DC: American Society for Microbiology, 1995: Abst 2235.
40. Mullen CA, Petropoulos D, Robert WM et al, Outpatient treatment of fever and neutropenia for low risk pediatric cancer patients. *Cancer* 1999; **86:** 126–34.
41. Rolston KVI, Tarrand JJ, *Pseudomonas aeruginosa* – still a frequent pathogen in patients with cancer: 11 year experience from a comprehensive cancer center. *Clin Infect Dis* 1999; **29:** 463–4.
42. Talcott JA, Finberg R, Mayer RJ, Goldman L, The medical course of cancer patients with fever and neutropenia. Clinical identification of a low-risk subgroup at presentation. *Arch Intern Med* 1988; **148:** 2561–8.
43. Talcott JA, Siegel RD, Finberg R, Goldman L, Risk assessment in cancer patients with fever and neutropenia: a prospective, two-center validation of a prediction rule. *J Clin Oncol* 1992; **10:** 316–22.
44. Elting LS, Rubenstein EB, Rolston KVI et al, Time to clinical response: an outcome of antibiotic therapy of febrile neutropenia with implications for quality and cost of care. *J Clin Oncol* 2000; **18:** 3699–706.
45. Ozer H, Armitage JO, Bennett CL et al, 2000 update of recommendations for the use of hematopoietic colony-stimulating factors: evidence-based clinical practice guidelines. *J Clin Oncol* 2000; **18:** 3558–85.
46. Maher DW, Lieschke GJ, Green M et al, Filgrastim in patients with chemotherapy-induced febrile neutropenia: a double-blind, placebo-controlled trial. *Ann Intern Med* 1994; **121:** 492–501.
47. Mayordomo JI, Rivera F, Diaz-Puente MT et al, Improving treatment of chemotherapy-induced

neutropenic fever by administration of colony-stimulating factors. *J Natl Cancer Inst* 1995; **87:** 803–8.

48. Riikonen P, Saarinen UM, Makipernaa A et al, Recombinant human granulocyte–macrophage colony-stimulating factor in the treatment of febrile neutropenia: a double-blind placebo-controlled study in children. *Pediatr Infect Dis J* 1994; **13:** 197–202.
49. Biesma B, de Vries EG, Willemse PH et al, Efficacy and tolerability of recombinant human granulocyte–macrophage colony-stimulating factor in patients with chemotherapy–related leukopenia and fever. *Eur J Cancer* 1990; **26:** 932–6.
50. Vellenga E, Uyll-de Groot CA, de Wit R et al, Randomized placebo-controlled trial of granulocyte–macrophage colony-stimulating factor in patients with chemotherapy-related febrile neutropenia. *J Clin Oncol* 1996; **14:** 619–27.
51. Ravaud A, Chevreau C, Bonichon F et al, Granulocyte–macrophage colony-stimulating factor (GM-CSF) in patients with neutropenic fever is potent after low-risk but not after high-risk neutropenic chemotherapy regimens: results of a randomized phase III trial. *J Clin Oncol* 1998; **16:** 2930–6.
52. Mitchell PLR, Morland BJ, Dick G et al, Clinical benefits and cost savings of interventional G-CSF therapy in patients with febrile neutropenia following chemotherapy. *Blood* 1995; **86**(Suppl 1): 500a.
53. Kim YJ, Rubenstein EB, Rolston KVI et al, Colony stimulating factors may reduce complications and death in solid tumor patients with fever and neutropenia. *Proc Am Soc Clin Oncol* 2000; **19:** 612a (Abst 2411).
54. García-Carbonero R, Mayordomo JI, Tornamira MV et al, Granulocyte colony-stimulating factor in the treatment of high-risk febrile neutropenia: a multicenter randomized trial. *J Natl Cancer Inst* 2001; **93:** 31–8.

10

Evaluation and management of vascular access device infections in febrile neutropenic cancer patients

Claude Afif, Issam Raad

EPIDEMIOLOGY OF VASCULAR ACCESS DEVICE INFECTIONS

Vascular access devices (VADs) are indispensable tools in the management of cancer patients.[1] It is estimated that more than five million central venous catheters (CVCs) are used in the USA every year.[2] Of those, one million long-term CVCs (with duration of placement of greater than 30 days) are inserted in cancer patients. Four types of long-term CVCs are used in cancer patients: tunneled CVCs (Hickman/Broviac/Groshong), and implantable ports, non-tunneled subclavian CVC's, and peripherally inserted central catheters (PICCs).

In contrast to the many advantages that they offer (namely, easy vascular access, and increased ability to administer large volumes of fluids, medications, blood products, and parenteral nutrition), VADs are hampered by the occurrence of serious complications, including local site infection, thrombophlebitis (septic and non-septic), endocarditis, and catheter-related bloodstream infection (CRBSI). Short-term peripherally inserted devices such as peripheral venous catheters and peripheral arterial catheters, as well as midline catheters, are associated with lower risk of infections compared with CVCs. However, CVCs, including PICCs and short- and long-term vascular devices, are more often associated with CRBSI.

A review by Press et al[3] of 17 studies and another review by Decker and Edwards[4] of 21 studies involving cancer patients reported the incidence of long-term tunneled CVC infection to be approximately 1.4 per 1000 catheter-days. Howell et al[5] included 26 studies of 3948 tunneled catheters in 3478 adult cancer patients, and reported a CVC infection rate of 1.9 per 1000 catheter-days. The rate of non-tunneled CVC-related infection (including PICC lines) was 1.4 per 1000 catheter-days.[6] The direct implications of such infectious complications are an increased mortality and morbidity, with an extension of the hospital stay.[7]

PATHOGENESIS

Source of infection

Within 24 hours post-insertion, most VADs will be colonized with microorganisms (Figure 10.1). Electron microscopy studies have shown

that all VADs are colonized – even those with negative cultures.[8] Microorganisms causing VAD infection can originate from four potential sources: the skin insertion site, the hub, hematogenous seeding from a distant focus, and infusate contamination.

The external surface colonization of a short-term indwelling vascular device usually occurs within the first 10 days following its insertion, and results from the migration of skin flora along the intracutaneous segment to reach the distal intravascular segment, resulting in CRBSI.[8]

In contrast, luminal colonization occurs in long-term devices (after 30 days of insertion), and is the result of hub contamination following frequent manipulation, which leads to microbial migration along the internal surface of the catheter.[8,9]

Hematogenous seeding is an unusual source for VAD colonization. However, many infections by *Candida* spp. are thought to originate in the gastrointestinal tract, with secondary candidemia leading to VAD colonization.[10] Finally, parenteral nutrition solutions or lipid emulsions promote the growth of bacteria and fungi,[8] such as *Candida parapsilosis*[11] and *Malassezia furfur*,[10] resulting in CRBSI.

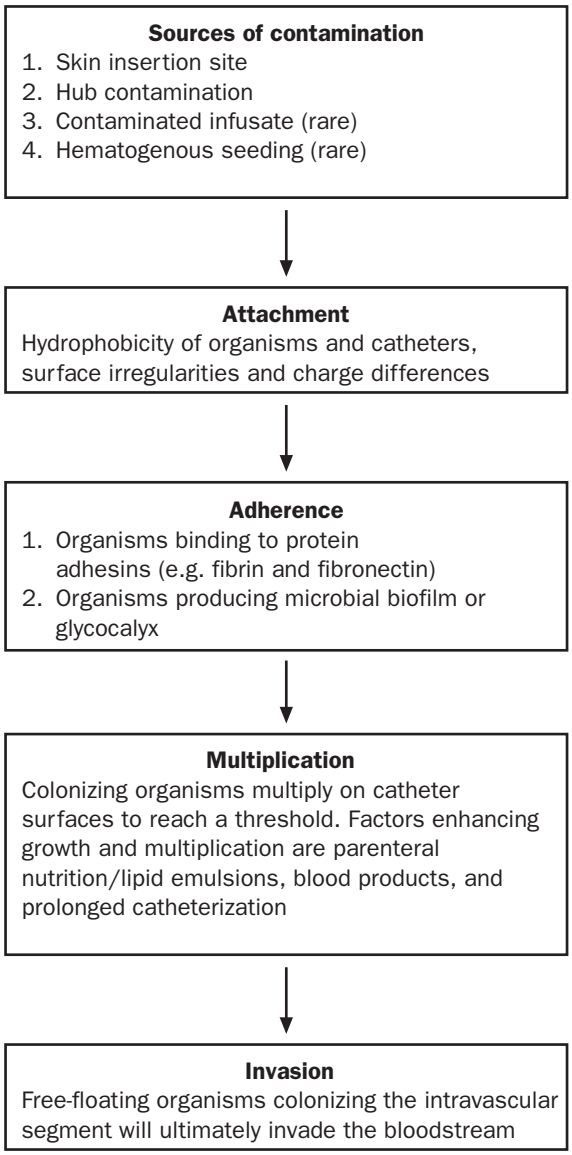


Figure 10.1 Flow diagram depicting the pathogenesis of catheter-related bloodstream infection.

Cofactors for adhesions of organisms

Microorganisms can be found on VAD surfaces in a sessile form embedded in a biofilm[12] or in a free-floating, disseminated form over the VAD surface. The adherence of microorganisms to a catheter surface depends on the interaction of the host, the microbial factors, and the catheter material in reaction to the foreign nature of the catheter.

The host reacts by enhancing the formation of a thrombin sheath by inducing the deposition of adhesin proteins such as fibrinogen, fibronectin, laminin, and thrombospondin, thus allowing the adherence of microorganisms such as *Staphylococcus aureus*, *S. epidermidis*, and *Candida albicans*.[13–15]

Additionally, bacteria can promote their own adherence mechanism. *S. aureus* and *C. albicans* are coagulase-producing organisms able to induce thrombogenesis. Other microorganisms,

such as *C. parapsilosis* and *S. epidermidis*, produce a biofilm, known as 'glycocalyx', which acts as a barrier against phagocytosis and opsonization.[16,17]

Finally, the attachment of microorganisms to the catheter surface depends on the intrinsic properties of the catheter polymers, including hydrophobicity, surface irregularities, and charge differences. Furthermore, microorganisms adhere to polyvinyl chloride and polyethylene surfaces better than to polyurethane or Teflon polymers.[18,19]

Microbiology

Although all VADs are colonized with microorganisms, only in a few cases will progression to CRBSI occur. In fact, infection depends on whether the organisms on the catheter surface, particularly those in the free-floating phase, exceed a certain quantitative threshold.

The microbiology of VAD-associated bloodstream infections is predominantly represented by skin flora such as *S. epidermidis*, *S. aureus*, and occasionally *Bacillus* spp.[20–23] The Gram-negatives are usually acquired from the hospital environment and from the hands of medical personnel, and include *Pseudomonas aeruginosa*, *Acinetobacter* spp., and *Stenotrophomonas maltophilia*. In addition to the *Candida* spp. that may occur in special settings, some reports have described the emergence of new fungi such as *Malassezia furfur* and *Rhodotorula* spp. Infection control surveillance at the MD Anderson Cancer Center detected 640 cases of CRBSI occurring between 1990 and 1996, with the following frequency: 25% caused by coagulase-negative staphylococci, 25% by *S. aureus*, 14% by Gram-negative bacilli, and 15% by other organisms such as enterococci, *Bacillus* spp., and *Corynebacterium*.

EVALUATION AND DIAGNOSIS

The diagnosis of catheter-related infection is difficult, and relies mostly on the isolation of the same organism from simultaneous blood cultures (from the CVC and a peripheral vein) or the isolation of the same organism from a catheter culture and from a peripheral blood culture with clinical signs and symptoms of infection (Table 10.1).[24]

Table 10.1 Diagnostic techniques for catheter infections

I. Semiquantitative or quantitative catheter culture techniques (with regular venipuncture blood cultures)
- Roll-plate catheter culture method (semiquantitative)
- Sonication catheter culture method (quantitative)
- Vortexing catheter culture method (quantitative)
- Centrifuging catheter culture method (quantitative)

II. Simultaneous blood cultures (from catheter and peripheral vein)
- Simultaneous quantitative blood cultures
- Differential time to positivity

III. Rapid techniques (experimental – require further validation)
- Staining of catheters
- Endoluminal brush techniques
- Acridine orange leukocyte cytospin test

Catheter culture technique

This method requires the removal of the catheter, and thus is retrospective. It has little impact on the clinical decision to remove or retain the VAD.

Semiquantitative culture of the catheter tip
This consists of culturing the catheter tip using the roll-plate technique.[22] A culture growth of 15 or more colony-forming units (CFU) of a given organism reflects catheter colonization. A growth of less than 15 CFU indicates catheter contamination. Despite a specificity of 76%, this technique is limited by the isolation of the organisms only from the external surface of the catheter, which is a major limitation for the long-term CVC.

Quantitative culture of catheter segments
This consists of culturing both the external and internal surfaces of a catheter segment (usually the catheter tip and/or the subcutaneous tunneled segment) by sonication and vortexing, thus releasing the microorganisms embedded in the biofilm from the internal and external surfaces of the CVC.[21] A cutoff value of 10^3 or greater is indicative of catheter colonization. This technique was found to be highly sensitive (93%) and specific (94%), and is of better diagnostic yield than the roll-plate technique for long-term CVCs.[25,26]

Simultaneous blood culture methods

In febrile neutropenic cancer patients, the CVC is often removed prior to making the diagnosis of CRBSI. This results in unnecessary removal of the CVC.[6] Catheter cultures require that the catheter be removed then cultured in order to make the diagnosis.[25,26] Paired blood cultures from the CVC and peripheral vein may help make the diagnosis prior to catheter removal, and hence many CVCs may be saved.

Paired quantitative blood cultures
Simultaneous quantitative blood cultures are drawn through the catheter and a peripheral vein. A ratio of 5–10 : 1 or greater of bacterial growth from the VAD relative to the peripheral vein is consistent with the VAD being the source of the bloodstream infection.[27]

Differential time to positivity
The time to detection of growth in a culture is closely related to the inoculum size of the microorganism. Simultaneous non-quantitative (regular) blood cultures are drawn from a CVC and peripheral vein. If the blood culture drawn from the CVC becomes positive at least two hours before the simultaneously drawn peripheral blood culture, then this is highly suggestive of CRBSI.[28,29]

PREVENTION

In order to develop useful strategies to prevent VAD-associated bloodstream infections, one should take into consideration the several factors (namely, host factors, catheter factors, and microbial factors) that interact to ultimately cause the release of the microorganisms that colonize the device surface into the blood, resulting in the infectious complication.

Neutropenia as a host factor might predispose to catheter infections. However, since it is associated with thrombocytopenia (which is a protective factor) in patients with hematologic malignancy, it has not been consistently shown to be a risk factor to CRBSI.

In a study conducted by Howell and colleagues[5] of patients with long-term indwelling tunneled CVCs who were followed for a total of 12 410 catheter-days, neutropenia of less than 500 neutrophils per mm^3 of blood was the only independent risk factor for catheter-related infection ($p = 0.018$). Catheter infections were significantly more likely to occur during the first week of neutropenia than during the remaining neutropenic days. However, in a study conducted at our center,[6] neutropenia,

bone marrow transplantation, use of high-dose steroids, or infusion of vesicant chemotherapy agents through the CVC did not predispose patients to catheter infection. The only statistically significant risk factor for catheter infection was hematologic malignancy (acute lymphoblastic leukemia or acute myeloid leukemia).

The same was observed by Groeger and colleagues[30] in a study of patients with leukemia, who had shorter infection-free periods compared with patients with lymphoma or myeloma ($p = 0.02$), but neutropenia was not evaluated as a risk factor except at the time of catheter insertion. In addition, patients with solid tumors who had catheters had longer infection-free periods than those who had hematologic diseases ($p = 0.005$).[30] Independent of neutropenia, patients with hematologic malignancies may be at higher risk of infection because of excessive manipulation of catheters resulting from the high frequency of blood transfusions and blood withdrawals done through the catheter.

Several preventive measures have been shown to decrease the rate of CRBSI (Table 10.2).

Maximum sterile barrier

In a large, prospective, randomized study done at the MD Anderson Cancer Center, the use of maximal sterile barrier precautions (hand washing, wearing sterile gloves, a mask, a gown, and a cap, and using a large drape) at the time of insertion of the VAD[31] was shown to decrease the risk of long-term catheter infection sixfold. Furthermore, the occurrence of the infectious complication may be delayed by an average of two months compared with a week when no sterile barriers were used. Given the significant decrease in CRBSI, the use of such precautions during insertion was found to be highly cost-effective.[31] Currently, the US Centers for Disease Control and Prevention highly recommend the use of maximal sterile barrier precautions during all CVC insertions.[24]

Infusion therapy team

The insertion and maintenance of a CVC by an experienced infusion therapy team not only helps decrease the rate of infections but also prolongs the duration of placement of non-tunneled catheters.[32,33] At the MD Anderson Cancer Center, the mean duration of placement of long-term non-tunneled, non-cuffed silicone catheters (PICC lines and non-tunneled silicone subclavians) was 109 days and the infection rate was 1.4/1000 catheter-days.[6] These figures are similar to those reported for tunneled Hickman catheters,[3–5] which is attributed in part to the presence of a skilled infusion therapy team at the MD Anderson Cancer Center.

Tunneling and ports

The surgically implantable devices and the completely implanted subcutaneous ports are designed to prevent the migration of skin flora

Table 10.2 Prevention of catheter infections

Aseptic insertion/maintenance	Novel/biotechnology
• Maximal sterile barrier • Infusion therapy team	• Antimicrobial/anticoagulant fluid solution • Antimicrobial impregnation of catheters • Silver iontophoresis

along the intercutaneous segment of the device, and hence to decrease the risk of CRBSI. Two prospective randomized studies evaluated the effect of catheter tunneling on catheter-related infections.[34,35] One study evaluated long-term CVCs (mostly silicone catheters) placed in immunocompromised patients.[34] The risks of catheter-related bacteremia associated with tunneled and non-tunneled CVCs were 2% and 5%, respectively. The difference was not significant, and was most likely due to the relatively small number of patients in each group (107 and 105 patients in each group). In another study involving short-term polyurethane catheters placed in the internal jugular veins of critically ill patients, tunneled CVCs were associated with a significantly lower rate of catheter-related bacteremia than non-tunneled CVCs. Therefore, tunneling of CVCs may decrease the risk of CRBSI. But is the additional cost of tunneling (the cost of insertion is $3000–4000 per device) justified by this risk reduction?

Ports seem to be associated with a lower CRBSI rate than tunneled CVCs. A study by Mirro and colleagues,[36] involving 120 Hickman catheters, 146 Broviac catheters, and 93 implantable ports in children with malignancy, showed that when all causes of catheter failure were considered (e.g. infection, obstruction, and dislodgment), indwelling ports had a significantly longer duration of use than did percutaneous Hickman or Broviac catheters ($p = 0.0009$). In a prospective, observational study conducted on 1630 long-term venous catheters (including 788 percutaneous catheters and 680 ports), Groeger and colleagues[30] found that the incidence of infection per device per day was 12 times greater with externalized catheters than with ports.

Selection of the VAD placement site

The risk of infection varies according to the site of insertion of any vascular device. In general, lower-extremity insertion sites are associated with a higher risk of infection, mainly because of exposure to enteric flora. Additionally, VADs inserted into the subclavian veins carry a lower risk for infections than those inserted in the jugular veins, because of the proximity of the latter to oropharyngeal secretions.[24]

Routine exchange of vascular catheters over a guidewire

The routine exchange of a CVC over a guidewire at fixed intervals of time is not recommended.[24] Use of a guidewire should be limited to replacing a malfunctioning non-tunneled catheter, converting an existing catheter, and determining the source of the bloodstream infection, allowing culture of the exchanged catheter.

Antimicrobial/anticoagulant flush solutions

The use of antimicrobial or anticoagulant flush solutions consists of flushing the lumen of the catheter with a combination of antimicrobial and antithrombotic agents. In several studies,[37–39] flushing of tunneled CVCs with a solution of heparin and vancomycin decreased the frequency of catheter-related bloodstream infection caused by Gram-positive organisms. However, this method is limited to the prevention of intraluminal colonization, and may select for the emergence of drug-resistant microorganisms such as vancomycin-resistant enterococci.

A new flush solution consisting of a mixture of EDTA and minocycline has recently been developed. This combination was found to have an in vitro activity against a broad spectrum of microorganisms, including Gram-positive and Gram-negative bacteria and some *Candida* spp., and was highly efficacious in preventing the recurrence of CRBSI in high-risk patients.[40] The efficacy of this combination in decreasing colonization and thrombotic occlusion associated with long-term CVCs used in hemodialysis patients has recently been

demonstrated in a prospective randomized study.[41]

Antiseptic and antimicrobial impregnation of catheters

Coating catheters with antiseptics and antimicrobials is one of the most promising methods for preventing CRBSI. However, this technique has only been applied to short-term polyurethane CVCs, and has been used mostly in critically ill patients.

Short-term catheters coated with chlorhexidine and silver sulfadiazine on the external surface were twofold less likely to become colonized and fourfold less likely to produce bacteremia when compared with uncoated catheters.[42] However, these short-term catheters are not effective if the catheter dwell time exceeds two weeks. In a recent prospective randomized study involving leukemia patients, in whom the average duration of catheter placement was three weeks, the use of antiseptic catheters impregnated with chlorhexidine and silver sulfadiazine failed to decrease the rate of CRBSI.[43]

In a prospective, randomized multicenter trial that included cancer patients, coating both the internal and external surfaces of a catheter with a combination of minocycline and rifampin was shown to be highly effective in preventing CRBSI.[44] Furthermore, when compared with antiseptic catheters coated with chlorhexidine and silver sulfadiazine, these catheters coated with minocycline and rifampin were 12-fold less likely to be associated with CRBSI.[45] Coating vascular devices with antimicrobials has proven to be highly cost-effective, and catheters impregnated with minocycline and rifampin were found to have more prolonged anti-infective effect for up to six weeks.[7] Currently, CVCs impregnated with minocycline and rifampin are being used in critically ill cancer patients and bone marrow transplant patients (pre-engraftment) at the MD Anderson Cancer Center. In critically ill cancer patients, these catheters were shown to decrease the risk of nosocomial bacteremia, and have resulted in cost savings of more than one million dollars.[46]

Novel methods of impregnating long-term silicone catheters with antimicrobials have been developed, and ongoing trials are being conducted to demonstrate their efficacy in PICC lines and non-tunneled silicone subclavian catheters. It is possible that non-tunneled silicone subclavian catheters could serve as a cost-effective alternative to surgically implantable catheters.

Silver iontophoretic catheters

Ionic silver has a broad spectrum of antimicrobial activity.[47] A silver-impregnated cuff that contains a biodegradable collagen with silver ions was attached to short-term CVCs, and was shown to reduce the incidence of CRBSI.[48] The half-life of a silver cuff is, however, short (five to seven days), and this is why it failed to offer protection in long-term catheters.[49] This can be palliated by continuously generating silver ions through an electric power source (a small battery connected to the catheter by silver wires). This novel method, which was developed by Bodey and colleagues, proved to have long antimicrobial durability in preventing catheter colonization in vitro, and also in an animal model.[50,51] However, the clinical efficacy and safety of this device needs to be demonstrated through clinical trials.

MANAGEMENT AND TREATMENT

The plan of management of a CRBSI is complex, and involves the decision whether or not to remove the catheter. However, this decision needs to take into consideration several factors, including the degree of complexity of the infection, the identification of the microbial etiology, availability of vascular access, and cost. A balanced approach to the management of the vascular catheter in febrile neutropenic patients

has been outlined in the National Comprehensive Cancer Network (NCCN) Practice Guidelines for Fever and Neutropenia.[52] This approach recommends the removal of the CVC in complicated cases with tunnel or pocket infection or with persistence of the septicemia (bloodstream infection) for more than 48 hours on broad-spectrum systemic antimicrobial agents. The removal of the CVC is to be strongly considered in patients with fungemias, rapidly growing mycobacteremias (*Mycobacterium chelonae* or *M. fortuitum*), and *S. aureus*, *Ps. aeruginosa*, *Stenotrophomonas maltophilia*, *Corynebacterium jeikeium*, and *Bacillus* spp. bacteremias where the CVC is considered as the likely source. A more detailed description of this approach is outlined below.

CRBSI complications

Complicated CRBSIs are those associated with the presence of a septic thrombosis or a deep-seated infection such as right-sided endocarditis, tunnel or port pocket infection, and/or the persistence of a bacteremia 48 hours after removal of the vascular device despite adequate therapy. Most CRBSIs are non-complicated, and require therapy for 10–14 days. However, in the presence of a complication, the catheter should be removed, and therapy should be prolonged for at least four weeks in the setting of septic thrombosis or endocarditis.[53]

Microbial etiology (Table 10.3)

Coagulase-negative staphylococci (CoNS)

CoNS are responsible for 25% of CBRSI, even though they are the most common cause of catheter colonization.[8] The optimal duration of therapy for CoNS is not yet defined; however, if the patient responds within 48–72 hours of therapy, a 7-day course of antimicrobials should be considered adequate.[54] Catheter removal may not be necessary; however, there is a 20% chance of recurrence of the bacteremia if the catheter is retained compared with 3% if it is removed.[55]

Staphylococcus aureus

S. aureus CRBSIs are associated with a high rate of complications, including septic thrombophlebitis and deep-seated infections such as endocarditis, septic emboli, abscesses, and osteomyelitis.[56] Retention of the catheter can lead to persistence of the bacteremia, to relapse, and to increased mortality.[57]

A short course of two weeks with parenteral antibiotics may be considered in uncomplicated cases responding within 72 hours of therapy. In the case of occurrence of complicated *S. aureus* CRBSI, treatment should be continued for at least four weeks.[56,57]

Candida *species*

All cases of catheter-related candidemia require systemic therapy because of the association with serious complications such as endophthalmitis, which may occur in up to 15% of cases.[58] Removal of the catheter is always preferred. Fluconazole 400 mg daily is usually adequate except when *C. glabrata* or *C. krusei* are suspected; then amphotericin B at doses of 0.7 mg/kg should be used.[59]

Gram-positive bacilli

Removal of the catheter is suggested for CRBSI caused by Gram-positive bacilli such as *Bacillus* spp. and coryneform bacteria.[60,61] Vancomycin for at least 7 days remains the therapy of choice. However, these suggestions are based on a small number of cases derived from anecdotal reports. In some situations, where the infection responds rapidly to antimicrobial therapy, catheter retention is a consideration.

Gram-negative rods

The common Gram-negative rods causing CRBSI are *Ps. aeruginosa*, *Acinetobacter* spp., and *S. maltophilia*. Failure to remove the catheter is associated with higher rates of treatment failure and recurrence of the bacteremia.[62,63] A treat-

Table 10.3 Treatment of catheter-infections according to microbial etiology

Organisms	Catheter removal required?	Antimicrobial	Duration (days)
Coagulase-negative staphylococci (CoNS)	No	Vancomycin Quinupristin/dalfoprisitin Linezolid	7
Staphylococcus aureus	Yes	MRSA[a]: like CoNS MSSA[a]: antistaphylococcal penicillins or cephalosporins	10–14
Gram-positive bacilli	Yes	Vancomycin	7–10
Gram-negative bacilli[b]	Yes	Third-generation cephalosporin Carbapenems Quinolones	7–10
Candida spp.	Yes	Fluconazole (for *C. albicans* and *C. parapsilosis*) Amphotericin B (for *C. kruseii* and *C. glabrata*)	14

[a] MRSA, methicillin-resistant *S. aureus*; MSSA, methicillin-sensitive *S. aureus*.
[b] For *Pseudomonas aeruginosa* bacteremia, a combination of a β-lactam and aminoglycoside is recommended.

ment course of 7–10 days should be considered satisfactory in non-complicated cases. Further studies are underway at our institution to further delineate the appropriate management of Gram-negative bacillary bloodstream infection.

CONCLUSIONS

The long-term VADs used in cancer patients are tunneled catheters, non-tunneled subclavian catheters, ports and PICC lines. The rate of infection for these catheters ranges from 1.4 to 1.9 per 1000 catheter-days. The major route of catheter colonization and subsequent bloodstream infection is luminal colonization originating from hub contamination. The leading organisms causing CRBSI are coagulase-negative staphylococci, *S. aureus*, Gram-negative bacilli, such as *Ps. aeruginosa* and *S. maltophilia*, *Candida* spp. (*C. albicans* and *C. parapsilosis*), and Gram-positive bacilli, such as *Bacillus* spp. and *Corynebacterium* spp. The diagnosis of CRBSI without removing the catheter requires simultaneous blood cultures drawn from the CVC and peripheral vein. If quantitative blood cultures are used, then a ratio of five-fold or greater of bacterial growth from the VAD relative to the peripheral vein is consistent with CRBSI. CRBSI is also highly suggested

if the blood culture drawn from the CVC becomes positive at least two hours before the simultaneously drawn peripheral blood culture. Measures to prevent long-term catheter-related infections consist of maximal sterile barrier precautions during insertion, insertion by a skilled infusion therapy team, the use of ports, and the use of an antimicrobial/anticoagulant flush solution. Antimicrobial impregnation of short-term catheters has been shown to decrease the frequency of CRBSI. This novel biotechnology could be quite useful for long-term CVCs used in cancer patients, and could represent a cost-effective alternative to surgically implantable uncoated catheters. The management of the vascular catheter in febrile neutropenic cancer patients includes removal of the CVC in situations with tunnel or pocket infection or with persistence of the bloodstream infection for more than 48 hours on broad-spectrum antimicrobial agents. In addition, CRBSI caused by *Candida* spp., rapidly growing mycobacteria, *S. aureus*, *Ps. aeruginosa*, and *S. maltophilia* often require removal of the catheter.

REFERENCES

1. Raad II, Bodey GP, Infection complications of indwelling vascular catheters. *Clin Infect Dis* 1992; **15:** 197–208.
2. Maki DG, *Infection Caused by Intravascular Devices: Pathogenesis Strategies for Prevention.* London: Royal Society of Medicine, 1991.
3. Press OW, Ramsey PG, Larson EB et al, Hickman catheter infections in patients with malignancies. *Medicine* 1984; **63:** 189–200.
4. Decker MD, Edwards KM, Central venous catheter infections. *Pediatr Clin North Am* 1988; **35:** 579–612.
5. Howell PB, Walters PE, Donowitz GR, Farr BM, Risk factors for infection of adult patients with cancer who have tunneled central venous catheters. *Cancer* 1995; **75:** 1367–74.
6. Raad I, Davis S, Becker M et al, Low infection rate and long durability of nontunneled silastic catheters: a safe and cost-effective alternative for long-term venous access. *Arch Intern Med* 1993; **153:** 1791–6.
7. Saint S, Veenstra DL, Lipsky BA, The clinical and economic consequences of nosocomial central venous catheter related infection. Are antimicrobial catheters useful? *Infect Control Hosp Epidemiol* 2000; **21:** 375–80.
8. Raad II, Costerton W, Sabharwal U et al, Ultrastructural analysis of indwelling vascular catheters: a quantitative relationship between luminal colonization and duration of placement. *J Infect Dis* 1993; **168:** 400–7.
9. Linares J, Sitges-Serra A, Garau J et al, Pathogenesis of catheter sepsis: a prospective study with quantitative and semiquantitative cultures of catheter hub and segments. *J Clin Microbiol* 1985; **21:** 357–60.
10. Maki DG, Pathogenesis, prevention and management of infections due to intravascular devices used for infusion therapy. In: *Infections Associated with Indwelling Medical Devices* (Bisno AL, Waldvogel FA, eds). Washington, DC: American Society for Microbiology, 1989: 161–77.
11. Clarke DE, Raffin TA, Infectious complications of indwelling long term central venous catheters. *Chest* 1990: **97:** 966–72.
12. Calwell DE, Korber DR, Lawrence JR, Imaging of bacterial cells by fluorescence exclusion using scanning confocal laser microscopy. *J Microbiol Meth* 1992; **15:** 249–61.
13. Hermann M, Vaudaux PE, Pittet D et al, Fibronectin, fibrinogen and laminin act as mediators of adherence of clinical staphylococcal isolates to foreign material. *J Infect Dis* 1988; **158:** 696–701.
14. Vaudaux P, Pittet D, Haeberli A et al, Host factors selectively increase staphylococcal adherence on inserted catheters: a role for fibronectin and fibrinogen or fibrin. *J Infect Dis* 1989; **160:** 865–75.
15. Bouali A, Robert R, Tronchin G, Senet JM, Characterization of binding of human fibrinogen to the surface of germ tubes and mycelium of *Candida albicans*. *J Gen Microbiol* 1987; **133:** 545–51.
16. Christensen GD, Simpson WA, Younger JJ et al, Adherence of coagulase negative staphylococci to plastic tissue culture plates: a quantitative model for the adherence of staphylococci to medical devices. *J Clin Microbiol* 1985; **22:** 996–1006.

17. Costerton JW, Irvin RT, Cheng KJ, The bacterial glycocalyx in nature and disease. *Annu Rev Microbiol* 1981; **35:** 299–324.
18. Sheth NK, Franson TR, Rose HD et al, Colonization of bacteria on polyvinyl chloride and Teflon intravascular catheters in hospitalized patients. *J Clin Microbiol* 1983; **18:** 1061–3.
19. Sherertz RJ, Carruth WA, Marosok RD et al, Contribution of vascular catheter material to the pathogenesis of infection: the enhanced risk of silicone in vivo. *J Biomed Mater Res* 1995; **29:** 635–45.
20. Raad II, Darouiche RO, Catheter related septicemia: risk reduction. *Infect Med* 1996; **13:** 807–12; 815–16; 823.
21. Sherertz RJ, Raad II, Balani A et al, Three year experience with sonicated vascular catheter cultures in a clinical microbiology laboratory. *J Clin Microbiol* 1990; **28:** 76–82.
22. Maki DG, Weise CE, Sarofin HW, A semiquantitative culture method for identifying intravenous catheter infection. *N Engl J Med* 1997; **296:** 1305–9.
23. Kiehn TE, Armstrong D, Changes in the spectrum of organisms causing bacteremia and fungemia in immunocompromised patients due to venous access devices. *Dur J Clin Microbiol Infect Dis* 1990; **9:** 869–72.
24. Pearson ML, Guidelines for prevention on intravascular device related infections. Part I: Intravascular device related infections: an overview. Part II: Recommendations for the prevention of nosocomial intravascular device related infections. Hospital Infection Control Practices Advisory Committee. *Am J Infect Control* 1996; **24:** 262–93.
25. Raad II, Sabbagh MF, Rand KH, Sherertz RJ, Quantitative tip culture methods and the diagnosis of central venous catheter related infections. *Diagn Microbiol Infect Dis* 1992; **15:** 13–20.
26. Sherertz RJ, Heard SO, Raad II, Diagnosis of triple-lumen catheter infection: a comparison of roll plate, sonication, and flushing methodologies. *J Clin Microbiol* 1997; **35:** 641–6.
27. Capdevila JA, Planes AM, Palomar M et al, Value of differential quantitative blood cultures in the diagnosis of catheter related sepsis. *Eur J Clin Microbiol Infect Dis* 1992; **11:** 403–7.
28. Blot F, Schmidt E, Nitenberg G et al, Earlier positivity of central venous versus peripheral blood cultures is highly predictive of catheter related sepsis. *J Clin Microbiol* 1998; **36:** 105–9.
29. Blot F, Nitenberg G, Chachaty E et al, Diagnosis of catheter related bacteremia: a prospective comparison of the time to positivity of hub-blood versus peripheral-blood cultures. *Lancet* 1999; **354:** 1071–7.
30. Greoger JS, Lucas AB, Thaler HT et al, Infectious morbidity associated with long-term use of venous access devices in patients with cancer. *Ann Intern Med* 1993; **119:** 1168–74.
31. Raad II, Hohn DC, Gilbreath BJ et al, Prevention of catheter related infections by using maximal sterile barrier precautions during insertion. *Infect Control Hosp Epidemiol* 1994; **15:** 231–8.
32. Abi Said D, Raad I, Umphrey J et al, Infusion therapy team and dressing changes of central venous catheters. *Infect Control Hosp Epidemiol* 1999; **20:** 101–5.
33. Tomford JW, Hershey CO, McLaren CE et al, Intravenous therapy team and peripheral venous catheter associated complications: a prospective control study. *Arch Intern Med* 1984; **133:** 1191–4.
34. Andrivet P, Bacquer A, Vu Ngoc C et al, Lack of clinical benefit from subcutaneous tunnel insertion of central venous catheters in immunocompromised patients. *Clin Infect Dis* 1994; **18:** 199–206.
35. Timset JF, Sebille V, Farkas JC et al, Effect of subcutaneous tunneling on internal jugular catheter related sepsis in critically ill patients: a prospective randomized study. *JAMA* 1996; **276:** 1416–20.
36. Mirro J, Rao BN, Kumar M et al, A comparison of placement techniques and complications of externalized catheters and implantable port use in children with cancer. *J Pediatr Surg* 1990; **25:** 122–4.
37. Schwartz C, Henrickson KJ, Roghmann K, Powell K, Prevention of bacteremia attributed to luminal colonization of tunneled central venous catheters with vancomycin susceptible organisms. *J Clin Oncol* 1990; **8:** 591–7.
38. Carratala J, Niubo J, Fernandez-Sevilla A et al, Randomized, double-blind trial of an antibiotic-lock technique for prevention of Gram-positive central venous catheter-related infection in neutropenic patients with cancer. *Antimicrob Agents Chemother* 1999; **43:** 2200–4.
39. Henrickson KJ, Axtell RA, Hoover SM et al, Prevention of central venous catheter-related infections and thrombotic events in immunocompromised children by the use of vancomycin/

ciprofloxacin/heparin flush solution: a randomized, multicenter, double-blind trial. *J Clin Oncol* 2000; **18:** 1269–78.
40. Raad I, Buzaid A, Rhyne J et al, Minocycline and EDTA for the prevention of recurrent vascular catheter infections. *Clin Infect Dis* 1997; **25:** 149–51.
41. Bleyer A, Mason L, Raad I, Sherertz R, A randomized, double-blind trial comparing minocycline EDTA vs heparin as flush solutions for hemodialysis catheters. In: *Program and Abstracts of the 4th Decennial Conference Program Committee, March 5–9, 2000, Atlanta, GA*: 91 (Abstr P-S1-32).
42. Maki DG, Stolz SM, Wheeler S, Mermel LA, Prevention of central venous catheter related bloodstream infection by use of an antiseptic impregnated catheter: a randomized, controlled trial. *Ann Intern Med* 1997; **127:** 257–66.
43. Logghe C, Van Ossel C, D'Hoore W et al, Evaluation of chlorhexidine and silver–sulfadiazine impregnated central venous catheters for the prevention of bloodstream infection in leukemia patients: a randomized controlled trial. *J Hosp Infect* 1997; **37:** 145–56.
44. Raad I, Darouiche R, Dupuis J et al, Central venous catheters coated with minocycline and rifampin for the prevention of catheter related colonization and bloodstream infections. *Ann Intern Med* 1997; **127:** 267–74.
45. Darouiche RO, Raad II, Heard SO et al, A comparison of two antimicrobial impregnated central venous catheters. *N Engl J Med* 1999; **340:** 1–8.
46. Raad I, Hackett B, Hanna H et al, Use of antibiotic impregnated catheters associated with significant decrease in nosocomial bloodstream infections in critically ill cancer patients. In: *Proceedings of the 10th Annual Meeting of the Society for Healthcare Epidemiology, March 5–9, 2000, Atlanta, GA.*
47. Spadaro JA, Berger TJ, Barranco SD et al, Antibacterial effects of silver electrodes with weak direct current. *Antimicrob Agents Chemother* 1974; **6:** 637–42.
48. Maki DG, Cobb L, Garman JK et al, An attachable silver impregnated cuff for prevention of infection with central venous catheters: a prospective randomized multicenter trial. *Am J Med* 1988; **85:** 307–14.
49. Groeger JS, Lucas AB, Coit D et al, A prospective randomized evaluation of silver-impregnated subcutaneous cuffs for preventing tunneled chronic venous access catheter infections in cancer patients. *Ann Surg* 1993; **218:** 206–10.
50. Raad I, Hachem R, Zermeno A et al, In vitro antimicrobial efficacy of silver iontophoretic catheter. *Biomaterials* 1996; **17:** 1055–9.
51. Raad I, Hachem R, Zermeno A et al, Silver iontophoretic catheter: prototype of long-term anti-infective vascular access device. *J Infect Dis* 1996; **173:** 495–8.
52. National Comprehensive Cancer Network, NCCN practice guidelines for fever and neutropenia. *Oncology* 1999; **13:** 197–257.
53. Strinden WD, Helgerson RB, Maki DG, *Candida* septic thrombosis of the great central veins associated with central catheters. *Ann Surg* 1985; **202:** 653–8.
54. Hiemenz J, Skelton J, Pizzo PA, Perspective on the management of catheter related infections in cancer patients. *Pediatr Infect Dis J* 1986; **5:** 6–11.
55. Raad I, Davis S, Khan A et al, Catheter removal affects recurrence of catheter related coagulase negative staphylococci bacteremia. *Infect Control Hosp Epidemiol* 1992; **13:** 215–21.
56. Raad I, Narro J, Khan A et al, Serious complications of vascular catheter related *Staphylococcus aureus* bacteremia in cancer patients. *Eur J Clin Microbiol Infect Dis* 1992; **11:** 675–82.
57. Raad II, Sabbagh MF, Optimal duration of therapy for catheter related *Staphylococcus aureus* bacteremia: a study of 55 cases and review. *Rev Infect Dis* 1992; **14:** 75–82.
58. Rose HD, Venous catheter associated candidemia. *Am J Med Sci* 1978; **275:** 265–9.
59. Rex JH, Walsh TJ, Sobel JD et al, Practice guidelines for the treatment of candidiasis. *Clin Infec Dis* 2000; **30:** 662–78.
60. Saleh RH, Schorin MA, *Bacillus* spp. sepsis associated with Hickman catheters in patients with neoplastic diseases. *Pediatr Infect Dis J* 1987; **6:** 851–6.
61. Young VM, Meyers WF, Moddy MR, Schimpff SC, The emergence of coryneform bacteria as a cause of nosocomial infections in compromised hosts. *Am J Med* 1981; **70:** 646–50.
62. Elting LS, Bodey GP, Septicemia due to *Xanthomonas* species and non *aeruginosa Pseudomonas* species: increasing incidence of catheter related infections. *Medicine* 1990; **60:** 196–206.
63. Benezra D, Kiehn TE, Gold JWM et al, Prospective study of infections in indwelling central venous catheters using quantitative blood cultures. *Am J Med* 1988; **85:** 495–8.

11

Special considerations in children with fever and neutropenia

Sarah W Alexander, Philip A Pizzo

INTRODUCTION

Fever and neutropenia is a common complication of cancer therapy in both pediatric and adult patients. The general principles regarding the care of these patients are the same irrespective of age. However, there are some important factors that make the management of children with fever and neutropenia unique. The purpose of this chapter is to review both the similarities and the important differences between children and adults with fever and neutropenia.

CANCER IN CHILDREN

Although cancer in children is a rare disease, it continues to be the cause of approximately 10% of deaths during childhood, and is the leading cause of disease-related death in 3- to 14-year-olds.[1] There are an estimated 12 000 new cases of cancer diagnosed each year in children between birth and 19 years in the USA, compared with approximately 1 000 000 new cases in the adult population.[2,3]

The types of cancer are different in children compared with adults (Table 11.1). Overall, brain tumors and leukemia account for approximately 50% of all pediatric oncology diagnoses.[1] Within the pediatric group, there are distinct patterns of diagnoses based on specific age group. In the first two years of life, the most common tumors include neuroblastoma, Wilms' tumor, retinoblastoma, primitive neuroectodermal tumors, and hepatoblastoma. Acute lymphoblastic leukemia (ALL) has a sharp incidence peak in the age range 2–4 years. Later in childhood, osteosarcoma, Ewing's sarcoma, Hodgkin's disease, and non-Hodgkin's lymphomas are all more common.[4]

In addition to the types of disease, the responsiveness to therapy is, in general, more favorable in children. Over the last three decades, significant progress has been made in the success rates in some types of pediatric cancer, most notably ALL, lymphomas, and some soft tissue sarcomas. Overall, it is estimated that more than 65% of children with cancer are cured of their disease. There remain, however, some diagnoses in pediatric oncology where little therapeutic progress has been made and the prognosis remains dismal – for example brainstem gliomas and rhabdoid tumors.

TREATMENT OF CANCER IN CHILDREN

The treatment of children with cancer involves the same three primary modalities as used in adult oncology care: chemotherapy, radiation,

Table 11.1 Predominant pediatric cancers by age[a]

Type of disease	Percentage of disease type by age			
	<5 years	5–9 years	10–14 years	15–19 years
Leukemia	36.1	33.4	21.8	12.4
Lymphoma	3.9	12.9	20.6	25.1
Central nervous system tumors	16.6	27.7	19.6	9.5
Neuroblastoma	14.3	2.7	1.2	0.5
Retinoblastoma	6.3	0.5	0.1	0
Wilms' tumor	9.7	5.4	0.7	0.2
Hepatoblastoma	2.2	0.4	0.6	0.6
Malignant bone tumors	0.6	4.6	11.3	7.7
Soft tissue sarcomas	5.6	7.5	9.1	8.0
Germ cell tumors	3.3	2.0	5.3	13.9
Carcinomas	0.9	2.5	8.9	20.9
Other	0.5	0.4	0.8	1.2

[a] Adapted from Ries LAG, Smith MA, Gurney JG et al, *Cancer Incidence and Survival Among Children and Adolescents: United States SEER Program 1975–1995*. NIH Publication 99-4649, 1999.

and surgery. Chemotherapy is most often administered in multiagent regimens. For some pediatric tumors, dose intensity, defined as the amount of drug administered over a given period of time, is thought to be important. In general, children tolerate intensive therapy better than their adult counterparts, and often the doses used are higher than they would be for adults.[5]

The ability of children to tolerate very aggressive chemotherapeutic regimens compared with older individuals is at least in part due to the fact that children have fewer comorbid conditions. Sixty percent of all cancers in adults occur in patients more than 65 years old, many of whom are likely to have pre-existing conditions at the time of their cancer diagnosis that pose additional clinical challenges.[6,7] For some clinical events that are analogous in the pediatric and adult populations, such as febrile neutropenia in oncology patients, children consistently have lower reported incidence of serious morbidity and mortality.

COMMON INFECTIONS IN CHILDREN

Febrile illnesses are very common during normal childhood. In the pre-school-age child, it is estimated that the average number of febrile illnesses per year ranges from 2 to 8.[8] Children have on average twice as many upper respiratory tract infections per year as their adult counterparts.[9] This is largely due to the fact that the most common site for spread of viral illnesses is the school and group daycare setting, with secondary infections of siblings and adults at home.[10] Otitis media, a relatively rare infection in adults, accounts for approximately one-third of all pediatrician office visits and is diagnosed in 60–70% of all children by the age of one year.[11] Children are at risk for primary

infection with varicella zoster, with approximately two-thirds of the cases occurring in children between the ages of five and nine years (prior to universal vaccination strategies).

Children with cancer are at risk for these 'regular' childhood infections, in addition to being susceptible to other infectious pathogens secondary to their immunocompromised state. In addition, 'regular' childhood infections can cause significant morbidity in compromised children. For example, respiratory syncytial virus (RSV) can cause severe pneumonia in patients receiving chemotherapy, especially in those undergoing bone marrow transplantation.[12,13] Otitis media can be recurrent or chronic, can be due to bacteria not usually associated with the disease, and can, in rare cases, progress to mastoiditis in the compromised host.[14] Varicella zoster virus (VZV) and cytomegalovirus (CMV) are more likely to cause disease by primary infection in children, in contrast to reactivation disease in older individuals. Primary varicella in immunocompromised hosts can cause severe encephalopathy, hepatitis, and pneumonia. In the 1970s, prior to the use of acyclovir, this infection carried a 10% mortality rate in children with cancer.[15]

FEVER

In a prospective review of 1001 episodes of fever in pediatric and young adult patients with cancer being treated at the US National Cancer Institute in the late 1970s and early 1980s, approximately one-half of all patients became febrile during their course of therapy.[16] Of these episodes, 80% occurred when the patients were neutropenic, while 20% occurred in patients who were not neutropenic. Fevers in the non-neutropenic population were most often ascribed to use of chemotherapy (especially methotrexate, cytarabine arabinoside, cyclophosphamide, and actinomycin D), to the underlying malignancy, and to viral infections.

Fever in the setting of chemotherapy-induced neutropenia in the pediatric patient with cancer remains a common problem. At Children's Hospital, Boston over a one-year period, 21% of 1107 admissions to the oncology inpatient service were for children with fever and neutropenia.[17] Of all patients receiving systemic chemotherapy during the period of observation, 47% had at least one episode of fever and neutropenia.

ASSESSMENT OF THE CHILD PRESENTING WITH FEVER AND NEUTROPENIA

The initial assessment of the child with fever and neutropenia is guided by the same general principles as those used in adult oncology patients. A careful history and meticulous physical examination are imperative. Special attention should be paid to areas at increased risk for infection in patients receiving cytotoxic therapy, including the oropharynx, perianal region, central-line site if present, and any foci of recent invasive procedures.

Very young children usually cannot report their own symptoms. The history often relies on observations by caregivers. In addition, in infants and toddlers, fewer 'typical' symptoms may be recognizable. For example, the child with mucositis may present with fussiness, difficulty sleeping, or reduced oral intake.

Blood cultures should be obtained both peripherally and from indwelling central venous catheters, if present. Other microbiological tests should be based on clinical suspicions, for example nasopharyngeal aspirate for respiratory viruses, stool assays for *Clostridium difficile*, or skin scrapings for herpesviruses. Radiologic studies should be ordered based on specific symptoms or physical findings. Screening chest radiographs should be considered in all children with an anticipated prolonged duration of febrile neutropenia (>7 days) to provide a baseline study for future comparison. Serum chemistries, including an assessment of renal function, are usually obtained to ensure appropriate organ function and antimicrobial dosing.

It is sometimes necessary to modify diagnostic techniques on the basis of age. The volume of blood that can be obtained for blood culture often is less in a neonate or small child. Young children are often not able to provide urine samples. Children often require sedation for radiologic tests that require being still for a period of time, for example computed tomography (CT) or magnetic resonance imaging (MRI) scans.[18,19] More invasive diagnostic techniques also often require consideration of the child's size. In general, very small infants can undergo bronchoscopy; however, transbronchial biopsies are often difficult in the very young owing to limitations in the size of the equipment.[20,21] Similarly, thorascopic lung biopsies are challenging in young children because of the small size of the thorax, although continued miniaturization of the equipment may make this less of a limitation in the future.[22]

THERAPY IN CHILDREN WITH FEBRILE NEUTROPENIA

Initial antimicrobial coverage strategies have been studied extensively both in adult and in pediatric populations. Empiric therapy is based on early antibiotic coverage for the most likely infecting organisms as well as those organisms that have the potential of being rapidly lethal if not appropriately treated. There is no single best regimen for all patients with fever and neutropenia, with the choice being influenced by local patterns of infecting organisms and their resistance spectra, as well as consideration of toxicities, ease of administration, and cost.

The antibiotic regimens used in children do not, in general, differ from those used in adults. Either monotherapy or combination therapy, usually with a β-lactam and an aminoglycoside, is employed. Common antibiotics used in children with fever and neutropenia, together with doses, are listed in Table 11.2.

Ceftazidime was the first agent to undergo significant evaluation as monotherapy for empiric coverage of patients with fever and neutropenia. Use of this agent has been shown to be as safe as that of combination regimens.[23,25] Other agents that have been shown to be efficacious and safe as monotherapy are cefepime and the carbapenems imipenem and meropenem.[26–30] The majority of the large studies of empirical antibiotic therapy for fever and neutropenia with monotherapy have included both adult and pediatric patients.[23,26,31]

Vancomycin is not generally required for the initial empiric therapy of children with febrile neutropenia.[32–34] There are, however, certain circumstances where its use should be considered. The 1997 recommendations from the Infectious Diseases Society of North America in their guidelines for use of antimicrobial agents in neutropenic patients with unexplained fever is that vancomycin should 'probably' be used as part of initial therapy in institutions with high rates of Gram-positive organisms leading to fulminant infections (e.g. *Streptococcus viridans*), as well as in those individuals with obvious central-line infections, those with significant mucositis or who are hypotensive at presentation, and those with known colonization with Gram-positive organisms resistant to the standard empiric regimen.[35]

PROLONGED FEVER AND NEUTROPENIA

Children and adults with prolonged neutropenia are at high risk for serious infections, and require vigilant care.[36] Persistent fever in the absence of other findings in the neutropenic host is not in itself an indication for changing antibiotic therapy, except for the addition of empiric antifungal therapy.[37,38] Changes in clinical status or new microbiological data should be used to guide antibiotic modifications.

Prolonged neutropenia puts the patient at significant risk for invasive fungal infection. The diagnosis of fungal infections in the neutropenic patient remains challenging, with fever often being the only presenting clinical sign. Even in proven disseminated candidal disease, blood cultures often remain negative. Imaging

Table 11.2 Common antibiotics and doses used in children with fever and neutropenia[a]

Antibiotic	Dose	Comments
Antibacterial agents		
Ceftazidime	30–50 mg/kg/dose i.v. q8h	Broad-spectrum coverage, including *Pseudomonas aeruginosa*
Cefipime	50 mg/kg/dose i.v. q8h	Broader Gram-positive spectrum than ceftazidime
Imipenem/cilastin	15 mg/kg/dose i.v. q6h	Cross-reactivity with 50% of patients with anaphylaxis to penicillin
Meropenem	20 mg/kg/dose i.v. q8h	Less likely than imipenem to cause seizures
Piperacillin	75 mg/kg/dose i.v. q6h	Should be combined with an aminoglycoside for coverage of *Ps. aeruginosa*
Pipericilin–tazobactam	75 mg/kg/dose i.v. q6h	Insufficient data to date to use this agent as monotherapy
Gentamicin	2.5 mg/kg/dose i.v. q8h	Levels should be monitored to prevent ototoxicity and nephrotoxicity
Amikacin	10 mg/kg/dose i.v. q8h	Levels should be monitored
Vancomycin	15 mg/kg/dose i.v. q8h	Is not needed for empiric therapy in most patients
Aztreonam	30 mg/kg/dose i.v. q6h	Gram-negative coverage only
Antifungals		
Amphotericin	0.5 mg/kg/dose i.v. q4h	Higher doses may be needed for *Aspergillus*. Significant nephrotoxicity
Lipid formulations (ABLC, AmBiosome)	3–5 mg/kg/dose i.v. q24h	Significantly less nephrotoxicity with equal efficacy
Fluconazole	6–12 mg/kg/dose i.v. or p.o.	Good coverage for *Candida albicans*; less good for other candidal species
Antivirals		
Acyclovir	750–1500 mg/m^2/day divided q8h	Dose for VZV is twice that for HSV, hydration should be ensured when giving high doses
Ganciclovir	5 mg/kg bid (for induction for CMV) 5 mg/kg/day (for maintenance)	Granulocytopenia is the major dose limiting toxicity
Foscarnet	60–120 mg/kg/day divided q8h	Nephrotoxicity is the major dose-limiting toxicity; renal function and electrolytes require close monitoring

[a] Doses in children less than 28 days old may need to be modified.

with CT and MRI has become a routine part of the care of the persistently febrile neutropenic patient to assess for evidence of hepatosplenic candidiasis at the time of resolution from neutropenia, although this infection has become much less common in patients receiving antifungal prophylaxis. Subtle pulmonary findings can be the first signs of invasive *Aspergillus* infection, definitively diagnosed often only by open lung biopsy.

The rational for empiric antifungal therapy is the same as that for antibacterials – mainly to decrease infection related mortality by early initiation of therapy. Two prospective randomized trials reported a benefit of empiric therapy with amphotericin B when started at either day 4 or day 7 of fever and neutropenia.[36,39] Both of these studies included both adult and pediatric patients.

Empiric therapy with amphotericin B has been limited by significant renal toxicity. Several large prospective trials comparing liposomal preparations of amphotericin B with standard amphotericin B for empiric therapy in febrile neutropenic patients have shown equal efficacy but less renal toxicity in those patients receiving the liposomal formulations.[40–43] These studies enrolled both adult and pediatric patients. Empiric therapy with fluconazole has also been shown to be efficacious and less toxic. It should not, however, be used in those patients with clinical signs suggestive of aspergillosis or in those who have received fluconazole prophylaxis and are therefore at higher risk for infection with fluconazole-resistant candidal species.[44,45]

RISK STRATIFICATION IN CHILDREN WITH FEVER AND NEUTROPENIA

It has become increasingly clear that not all patients with fever and neutropenia are at equal risk for serious infection.[46–48] The identification of a subgroup at low risk for serious infection may allow for modifications of empiric therapy, with a goal of less therapy-related toxicity, an improved 'quality of life', and decreased cost. These modifications may include the use of oral antibiotics as opposed to intravenous antibiotics, and care of the low-risk febrile neutropenic patient in the outpatient setting.

Factors available at the time of presentation that consistently appear to confer low risk are a short duration of neutropenia (<7–10 days), being clinically well without significant comorbid medical conditions or significant focal infections, and having cancer that is not progressive.[49,50] These predictive factors have been evaluated in pediatric populations, with similar findings.[17,51,52] In general, given the decreased frequency of comorbid factors and the overall better outcome,[53] modification of therapy for low-risk patients may have the most relevance for children with fever and neutropenia.

Based on risk stratification, there is now evidence both in adults and in children that the use of oral antibiotics in a subset of patients with low-risk fever and neutropenia is safe and effective.[54–56] The oral regimen that was employed in the two large randomized studies[55,56] was ciprofloxacin and amoxicillin/sulbactam. Outpatient therapy with intravenous and oral antibiotics in pediatric patients with low-risk febrile neutropenia has also been shown to be feasible,[57–59] as has early discontinuation of antibiotic coverage in clinically well children with negative blood cultures and evidence of early bone marrow recovery.[60–62]

OUTCOMES IN CHILDREN WITH FEVER AND NEUTROPENIA

Many of the large clinical trials evaluating different therapies for fever and neutropenia have been conducted in combined pediatric and adult populations. In general, patient age has not been used as one of the criteria when evaluating subgroup outcomes. The largest body of data addressing the question of whether there is a difference between pediatric and adult

patients with fever and neutropenia has come from a retrospective analysis of several large European trials.[53] This study of 3080 patients with fever and neutropenia compared the pediatric group, which comprised 25% of the study population, with the adult group in terms of infection types and outcomes.

The rate of clinically documented infections in the pediatric group was lower, and consequently children had a higher incidence of fever of unknown origin. Of the sites of infection documented clinically, children were more likely to have upper respiratory tract infections, compared with lower respiratory tract infections in their adult counterparts.

The rate of bacteremia in the two groups was similar (22% versus 24%). The organisms causing bacteremia were similar in children and adults. Gram-negative pathogens accounted for 28% of the episodes in children, compared with 30% of adults. Gram-positive infections caused 64% of the bacteremias in children, compared with 57% in adults. Children were noted to have a significantly higher rate of streptococcal infections (29% versus 18%). Adults had a higher incidence of polymicrobial infections than children (12% versus 7%).

Overall mortality was lower in children (3% versus 10%), as was the incidence of death related to infection (1% versus 4%, $p = 0.001$). In a separate study comparing pediatric and adult cancer patients with documented bacteremia or fungemia, children had a lower overall mortality as well as mortality related to infection (7% versus 25%, $p = 0.02$; 4% versus 8%, $p = 0.03$, respectively).[63]

SPECIAL CONSIDERATIONS IN ANTIBIOTIC CHOICE IN CHILDREN

The US Food and Drug Administration (FDA) now permits the approval of drugs for use in children based on efficacy data gathered in adults, if the disease in children and adults is similar, provided that pharmaceutical companies submit pharmacokinetic and toxicity data from trials performed in an adequate number of children. If the drug is likely to be used in children, it is now mandatory for pharmaceutical companies to provide such data in a timely fashion.[64,65]

There are, however, a substantial number of antimicrobials used commonly in children with febrile neutropenia (as is the case with many drugs in use in pediatrics) that have not been formally studied in children and are not FDA-approved. For example, ceftazidime has been studied and is approved for children of all ages; meropenem and imipenem are approved for those over the age of 3 months; and pipericillin, pipericillin–tazobactam, and cefepime are only approved for use in those over 12 years of age. For many of these agents, however, there is significant clinical experience with use of these drugs in young children.

There are only a limited number of antimicrobials that have been shown to have the potential for significant and unique toxicity in children. Tetracyclines are avoided in children less than 8 years old owing to associated permanent dental discoloration. The routine use of fluoroquinolones in pediatrics has been limited by the concern of a unique toxicity in young individuals leading to arthropathy. In experimental juvenile animals, exposure to fluoroquinolones has been associated with a risk of arthropathy expressed clinically as lameness and associated with characteristic histologic findings of blisters and erosions of articular cartilage. This finding has been consistent for all fluoroquinolones tested.[66] There is, however, a growing body of evidence supporting the safety of quinolone antibiotics in the pediatric population. Nalidixic acid, a non-fluorinated quinolone, has been used in children for decades. In animal studies, it causes the classic cartilage changes, but it has not been found to cause any arthropathy in children, including those treated for prolonged periods of time.[67,68] In 1997, Hampel et al[69] reviewed the worldwide experience with ciprofloxacin in pediatric patients based on its compassionate use, and concluded that short courses of ciprofloxacin

appear to be safe. No cases of the experimentally induced cartilage damage have been confirmed in humans.

SPECIAL CONSIDERATIONS IN ANTIBIOTIC DOSING AND ADMINISTRATION IN CHILDREN

Antibiotic dosing is based on the child's weight or, less commonly, body surface area. In addition, the differences in pharmacokinetics and pharmacodynamics between children and adults need to be taken into consideration, particularly in the very young. The hepatic glucuronidation process, for example, is relatively immature during the first 2–3 months of life, thus decreasing the metabolic clearance of many drugs. Renal excretion reaches adult levels between 6 and 12 months of life, owing to slow maturation of glomerular filtration and tubular function, as well as an increase in renal blood flow.[70] Conversely, children may have more rapid clearance of some agents. For example, the pharmacokinetics of atovaquone would suggest dosing of 30 mg/kg/day for those less than 3 months and greater than 24 months, but 45 mg/kg/day in those from 3 to 24 months of age.[71]

Administration of oral antibiotics to children often poses unique challenges. Children less than 5 years of age have difficulty swallowing tablets or capsules. Compliance with a regimen may be limited if the agent is not palatable. Often there is no appropriate pediatric formulation available, and therefore provision of the agent requires an innovative pharmacist.

PROPHYLAXIS

The best infection prophylaxis in the care of immunocompromised patients (and others) is diligent handwashing before and after contact with patients. Teachers or daycare workers should be made aware of the child's immunocompromised state and asked to notify the parents in case of an outbreak of a contagious disease, such as varicella. Limiting social contacts for infection prevention is usually recommended for a period of time after allogeneic bone marrow transplantation.

Prophylactic antimicrobial regimens are used extensively in patients receiving cytotoxic chemotherapy. Early on, it was noted that the patient's own enteric flora was often the culprit in documented infections during periods of fever and neutropenia. Initially, it was shown that non-absorbable antibiotics decreased the rate of infectious complications; however, these agents are in general unpalatable, and were limited by difficulty with patient compliance, particularly in children.

The two agents that have received the most attention as prophylactic therapy for bacterial infections in neutropenic cancer patients have been trimethoprim–sulfamethoxazole (TMP–SMX) and the oral quinolones, primarily ciprofloxacin.[72–74] Both agents have been shown to decrease documented infections, primarily bacteremia, in neutropenic patients; however, an impact on overall mortality has not been shown. The use of TMP–SMX is complicated by a significant rate of allergic reactions and a risk of bone marrow suppression, with the potential for prolongation of neutropenia. Fluoroquinolones are in general well tolerated, but have been associated with a higher than expected rate of streptococcal bacteremia, leading some to suggest the addition of penicillin or clindamycin to the prophylactic regimen. Newer quinolones with an expanded spectrum and greater potency against Gram-positive organisms might be more effective. The utility of any of these regimens is limited by the potential for the emergence of resistant pathogens.[75,76] In children, the fluoroquinoles as prophylaxis have been avoided because of concerns of cartilage toxicity with prolonged exposure (see above).

USE OF GROWTH FACTORS

Growth factors, primarily granulocyte colony-stimulating factor (G-CSF, filgrastim) and gran-

ulocyte–macrophage colony-stimulating factor (GM-CSF, sargramostin), are used extensively in the care of pediatric cancer patients.[77–79] These agents increase the number and phagocytic function of polymorphonuclear cells in the peripheral blood.[80–84] Given the association of the degree and duration of neutropenia with the risk of serious infection, there was initially great excitement about the potential impact that growth factors might have in patients receiving myelosuppressive chemotherapy. Guidelines for the use of these cytokines in patients have been developed by the American Society of Clinical Oncology (ASCO).[85,86]

Two strategies for growth factor use have received the greatest attention. The first is initiating therapy at the time of diagnosis with fever and neutropenia. Studies in both pediatric and adult patients have had variable results, with some investigators reporting a moderate decrease in the number of days with fever, neutropenia, and antibiotic administration, as well as a decrease in the length of hospitalization.[87–91] No study has shown a reduction in the rate of serious infection or infection-related mortality. Overall, there is no strong evidence supporting the initiation of growth factors at the time of fever and neutropenia.

The second strategy for growth factor use has been one of primary prophylaxis, initiating therapy after completion of each cycle of chemotherapy. Despite encouraging early clinical trials, multiple subsequent studies have shown a decreased duration of neutropenia and a variable effect on the incidence of fever and neutropenia and of documented infection, but no discernible effect on infection-related mortality.[79,92–95]

The ASCO guidelines recommend primary prophylaxis with growth factors when the expected rate of fever and neutropenia is greater than 40%. This guideline is difficult to apply, particularly in pediatrics, where the data regarding incidence of febrile neutropenia for standard treatment regimens has not been systematically evaluated. The patterns of growth factor use have been explored both in adults and in children.[85,86] Pediatric oncologists are much more likely than their adult counterparts to use growth factors as primary prophylaxis, often because of protocol requirements, but also owing to the fact that most chemotherapeutic regimens used for pediatric malignancies will predictably result in periods with marked neutropenia.

FUTURE DIRECTIONS IN THE CARE OF CHILDREN WITH CANCER AND FEBRILE NEUTROPENIA

Significant progress has been made in the treatment of children with cancer. This has been accomplished by progress both in the use of the primary therapeutic modalities of chemotherapy, surgery, and radiation therapy, and in supportive care measures.

The rapid and thorough assessment and appropriate management of children with chemotherapy-induced fever and neutropenia will remain a common and important part of the care of children with cancer. Progress in the care of these individuals will rely in part on the use of risk-based stratification to allow for modification of therapy based on individual risk factors. Ongoing evaluation of the safety and efficacy, as well as cost and ease of administration, of new antimicrobial agents will act to broaden the therapeutic armamentarium, and will hopefully increase the success rate and decrease the burden of illness for children treated for cancer.

REFERENCES

1. Robison LL, General principles of the epidemiology of childhood cancer. In: *Principles and Practice of Pediatric Oncology*, 3rd edn (Pizzo PA, Poplack DG, ed). Philadelphia: Lippincott-Raven, 1997: 1–10.
2. Grovas A, Fremgen A, Rauck A et al, The National Cancer Data Base report on patterns of childhood cancers in the United States. *Cancer* 1997; **80:** 2321–32.

3. Ries LAG, Smith MA, Gurney JG et al, *Cancer Incidence and Survival among Children and Adolescents: United States SEER Program 1975–1995.* NIH Publication 99-4649, 1999.
4. Gurney JG, Severson RK, Davis S, Robison LL, Incidence of cancer in children in the United States. Sex-, race-, and 1-year age-specific rates by histologic type. *Cancer* 1995; **75:** 2186–95.
5. Balis FM, Holcenberg JS, Poplack DG, General principles of chemotherapy. In: *Principles and Practice of Pediatric Oncology*, 3rd edn (Pizzo PA, Poplack DG, eds). Philadelphia: Lippincott-Raven, 1997: 215–72.
6. Yancik R, Epidemiology of cancer in the elderly. Current status and projections for the future. *Rays* 1997; **22**(1 Suppl): 3–9.
7. Yancik R, Wesley MN, Ries LA et al, Comorbidity and age as predictors of risk for early mortality of male and female colon carcinoma patients: a population-based study. *Cancer* 1998; **82:** 2123–34.
8. Cherry J, The common cold. In: *Textbook of Pediatric Infectious Disease*, 4th edn (Feigin RCJ, Cherry T, ed). Philadelphia: Saunders, 1998: 128–33.
9. Badger GF, Dingle JH, Feller AE, A study of illness in a group of Cleveland families: Incidence of the common respiratory diseases. *Am J Hyg* 1953; **58:** 31–40.
10. Hurwitz ES, Gunn WJ, Pinsky PF, Schonberger LB, Risk of respiratory illness associated with day-care attendance: a nationwide study. *Pediatrics* 1991; **87:** 62–9.
11. Teele DW, Klein JO, Rosner B, Epidemiology of otitis media during the first seven years of life in children in greater Boston: a prospective, cohort study. *J Infect Dis* 1989; **160:** 83–94.
12. Hall CB, Powell KR, MacDonald NE et al, Respiratory syncytial viral infection in children with compromised immune function. *N Engl J Med* 1986; **315:** 77–81.
13. Whimbey E, Couch RB, Englund JA et al, Respiratory syncytial virus pneumonia in hospitalized adult patients with leukemia. *Clin Infect Dis* 1995; **21:** 376–9.
14. Berkow RL, Weisman SJ, Provisor AJ et al, Invasive aspergillosis of paranasal tissues in children with malignancies. *J Pediatr* 1983; **103:** 49–53.
15. Feldman S, Hughes WT, Daniel CB, Varicella in children with cancer: seventy-seven cases. *Pediatrics* 1975; **56:** 388–97.
16. Pizzo PA, Robichaud KJ, Wesley R, Commers JR, Fever in the pediatric and young adult patient with cancer. A prospective study of 1001 episodes. *Medicine (Baltimore)* 1982; **61:** 153–65.
17. Alexander SW, Wade KC, Hibberd PL, Parsons SK, Evaluation of risk prediction criteria for episodes of febrile neutropenia in pediatric cancer patients. *J Pediatr Hematol Oncol*, Submitted for publication.
18. Hubbard AM, Markowitz RI, Kimmel B et al, Sedation for pediatric patients undergoing CT and MRI. *J Comput Assist Tomogr* 1992; **16:** 3–6.
19. Krauss B, Green SM, Sedation and analgesia for procedures in children. *N Engl J Med* 2000; **342:** 938–45.
20. Perez CR, Wood RE, Update on pediatric flexible bronchoscopy. *Pediatr Clin North Am* 1994; **41:** 385–400.
21. Wood R, Pediatric Bronchoscopy. *Chest Surg Clin N Am* 1996; **6:** 237–51.
22. Rothenberg SS, Thoracoscopy in infants and children. *Semin Pediatr Surg* 1998; **7:** 194–201.
23. Pizzo PA, Hathorn JW, Hiemenz J et al, A randomized trial comparing ceftazidime alone with combination antibiotic therapy in cancer patients with fever and neutropenia. *N Engl J Med* 1986; **315:** 552–8.
24. Sanders JW, Powe NR, Moore RD, Ceftazidime monotherapy for empiric treatment of febrile neutropenic patients: a meta-analysis. *J Infect Dis* 1991; **164:** 907–16.
25. De Pauw BE, Deresinski SC, Feld R et al, The Intercontinental Antimicrobial Study Group, Ceftazidime compared with piperacillin and tobramycin for the empiric treatment of fever in neutropenic patients with cancer. A multicenter randomized trial. *Ann Intern Med* 1994; **120:** 834–44.
26. Freifeld AG, Walsh T, Marshall D et al, Monotherapy for fever and neutropenia in cancer patients: a randomized comparison of ceftazidime versus imipenem. *J Clin Oncol* 1995; **13:** 165–76.
27. Lindblad R, Rodjer S, Adriansson M et al, Empiric monotherapy for febrile neutropenia – a randomized study comparing meropenem with ceftazidime. *Scand J Infect Dis* 1998; **30:** 237–43.
28. The Meropenem Study Group of Leuven, London and Nijmegen, Equivalent efficacies of meropenem and ceftazidime as empirical monotherapy of febrile neutropenic patients. *J Antimicrob Chemother* 1995; **36:** 185–200.

29. Biron P, Fuhrmann C, Cure H et al, Cefepime versus imipenem-cilastatin as empirical monotherapy in 400 febrile patients with short duration neutropenia. CEMIC (Study Group of Infectious Diseases in Cancer). *J Antimicrob Chemother* 1998; **42:** 511–18.
30. Wang FD, Liu CY, Hsu HC et al, A comparative study of cefepime versus ceftazidime as empiric therapy of febrile episodes in neutropenic patients. *Chemotherapy* 1999; **45:** 370–9.
31. Cometta A, Calandra T, Gaya H et al, Monotherapy with meropenem versus combination therapy with ceftazidime plus amikacin as empiric therapy for fever in granulocytopenic patients with cancer. The International Antimicrobial Therapy Cooperative Group of the European Organization for Research and Treatment of Cancer and the Gruppo Italiano Malattie Ematologiche Maligne dell'Adulto Infection Program. *Antimicrob Agents Chemother* 1996; **40:** 1108–15.
32. European Organization for Research and Treatment of Cancer (EORTC) International Antimicrobial Therapy Cooperative Group, National Cancer Institute of Canada – Clinical Trials Group, Vancomycin added to empirical combination antibiotic therapy for fever in granulocytopenic cancer patients. *J Infect Dis* 1991; **163:** 951–8.
33. Rubin M, Hathorn JW, Marshall D et al, Gram-positive infections and the use of vancomycin in 550 episodes of fever and neutropenia. *Ann Intern Med* 1988; **108:** 30–5.
34. Ramphal R, Bolger M, Oblon DJ et al, Vancomycin is not an essential component of the initial empiric treatment regimen for febrile neutropenic patients receiving ceftazidime: a randomized prospective study. *Antimicrob Agents Chemother* 1992; **36:** 1062–7.
35. Hughes WT, Armstrong D, Bodey GP et al, 1997 guidelines for the use of antimicrobial agents in neutropenic patients with unexplained fever. Infectious Diseases Society of America. *Clin Infect Dis* 1997; **25:** 551–73.
36. Pizzo PA, Robichaud KJ, Gill FA, Witebsky FG, Empiric antibiotic and antifungal therapy for cancer patients with prolonged fever and granulocytopenia. *Am J Med* 1982; **72:** 101–11.
37. Lee JW, Pizzo PA, Management of the cancer patient with fever and prolonged neutropenia. *Hematol Oncol Clin North Am* 1993; **7:** 937–60.
38. De Pauw BE, Raemaekers JM, Schattenberg T, Donnelly JP, Empirical and subsequent use of antibacterial agents in the febrile neutropenic patient. *J Intern Med Suppl* 1997; **740:** 69–77.
39. EORTC International Antimicrobial Therapy Cooperative Group, Empiric antifungal therapy in febrile granulocytopenic patients. *Am J Med* 1989; **86**(6 Pt 1): 668–72.
40. White MH, Bowden RA, Sandler ES et al, Randomized, double-blind clinical trial of amphotericin B colloidal dispersion vs. amphotericin B in the empirical treatment of fever and neutropenia. *Clin Infect Dis* 1998; **27:** 296–302.
41. Prentice HG, Hann IM, Herbrecht R et al, A randomized comparison of liposomal versus conventional amphotericin B for the treatment of pyrexia of unknown origin in neutropenic patients. *Br J Haematol* 1997; **98:** 711–18.
42. Walsh T, Bodensteiner D, Hiemenz J et al, A randomized, double blind trial of AmBisome (liposomal amphotericin B) in the empirical treatment of persistently febrile neutropenic patients. In: *Program and Abstracts of the 37th Interscience Conference on Antimicrobial Agents and Chemotherapy, Toronto*. Washington, DC: American Society for Microbiology, 1997: Abstr LM-90.
43. Walsh TJ, Finberg RW, Arndt C et al, Liposomal amphotericin B for empirical therapy in patients with persistent fever and neutropenia. National Institute of Allergy and Infectious Diseases Mycoses Study Group. *N Engl J Med* 1999; **340:** 764–71.
44. Viscoli C, Castagnola E, Van Lint MT et al, Fluconazole versus amphotericin B as empirical antifungal therapy of unexplained fever in granulocytopenic cancer patients: a pragmatic, multicentre, prospective and randomised clinical trial. *Eur J Cancer* 1996; **32A:** 814–20.
45. Viscoli C, Castagnola E, Machetti M, Antifungal treatment in patients with cancer. *J Intern Med Suppl* 1997; **740:** 89–94.
46. Freifeld AG, Pizzo PA, The outpatient management of febrile neutropenia in cancer patients. *Oncology (Huntingt)* 1996; **10:** 599–606; 611–12; discussion 615–16.
47. Buchanan GR, Approach to treatment of the febrile cancer patient with low-risk neutropenia. *Hematol Oncol Clin North Am* 1993; **7:** 919–35.
48. Elting LS, Rubenstein EB, Rolston KV, Bodey GP, Outcomes of bacteremia in patients with cancer and neutropenia: observations from two

decades of epidemiological and clinical trials. *Clin Infect Dis* 1997; **25:** 247–59.
49. Talcott JA, Finberg R, Mayer RJ, Goldman L, The medical course of cancer patients with fever and neutropenia. Clinical identification of a low-risk subgroup at presentation. *Arch Intern Med* 1988; **148:** 2561–8.
50. Talcott JA, Siegel RD, Finberg R, Goldman L, Risk assessment in cancer patients with fever and neutropenia: a prospective, two-center validation of a prediction rule. *J Clin Oncol* 1992; **10:** 316–22.
51. Lucas KG, Brown AE, Armstrong D et al, The identification of febrile, neutropenic children with neoplastic disease at low risk for bacteremia and complications of sepsis. *Cancer* 1996; **77:** 791–8.
52. Klaassen RJ, Goodman TR, Pham B, Doyle JJ, 'Low-risk' prediction rule for pediatric oncology patients presenting with fever and neutropenia. *J Clin Oncol* 2000; **18:** 1012–19.
53. Hann I, Viscoli C, Paesmans M et al, A comparison of outcome from febrile neutropenic episodes in children compared with adults: results from four EORTC studies. International Antimicrobial Therapy Cooperative Group (IATCG) of the European Organization for Research and Treatment of Cancer (EORTC). *Br J Haematol* 1997; **99:** 580–8.
54. Malik IA, Abbas Z, Karim M, Randomised comparison of oral ofloxacin alone with combination of parenteral antibiotics in neutropenic febrile patients. *Lancet* 1992; **339:** 1092–6.
55. Freifeld A, Marchigiani D, Walsh T et al, A double-blind comparison of empirical oral and intravenous antibiotic therapy for low-risk febrile patients with neutropenia during cancer chemotherapy. *N Engl J Med* 1999; **341:** 305–11.
56. Kern WV, Cometta A, De Bock R et al, Oral versus intravenous empirical antimicrobial therapy for fever in patients with granulocytopenia who are receiving cancer chemotherapy. International Antimicrobial Therapy Cooperative Group of the European Organization for Research and Treatment of Cancer. *N Engl J Med* 1999; **341:** 312–18.
57. Mustafa MM, Aquino VM, Pappo A et al, A pilot study of outpatient management of febrile neutropenic children with cancer at low risk of bacteremia. *J Pediatr* 1996; **128:** 847–9.
58. Shemesh E, Yaniv I, Drucker M et al, Home intravenous antibiotic treatment for febrile episodes in immune-compromised pediatric patients. *Med Pediatr Oncol* 1998; **30:** 95–100.
59. Mullen CA, Petropoulos D, Roberts WM et al, Outpatient treatment of fever and neutropenia for low risk pediatric cancer patients. *Cancer* 1999; **86:** 126–34.
60. Bash RO, Katz JA, Cash JV, Buchanan GR, Safety and cost effectiveness of early hospital discharge of lower risk children with cancer admitted for fever and neutropenia. *Cancer* 1994; **74:** 189–96.
61. Aquino VM, Tkaczewski I, Buchanan GR, Early discharge of low-risk febrile neutropenic children and adolescents with cancer. *Clin Infect Dis* 1997; **25:** 74–8.
62. Wacker P, Halperin DS, Wyss M, Humbert J, Early hospital discharge of children with fever and neutropenia: a prospective study. *J Pediatr Hematol Oncol* 1997; **19:** 208–11.
63. Krupova I, Kaiserova E, Foltinova A et al, Bacteremia and fungemia in pediatric versus adult cancer patients after chemotherapy: comparison of etiology, risk factors and outcome. *J Chemother* 1998; **10:** 236–42.
64. Regulations requiring manufacturers to assess the safety and effectiveness of new drugs and biological products in pediatric patients-FDA Final Rule. *Fed Regist* 1998; **63:** 66631–72.
65. Miller JL, FDA to require pediatric studies for drugs commonly used in children. *Am J Health Syst Pharm* 1999; **56:** 203.
66. Lietman PS, Fluoroquinolone toxicities. An update. *Drugs* 1995; **49**(Suppl 2): 159–63.
67. Schaad UB, Wedgwood-Krucko J, Nalidixic acid in children: retrospective matched controlled study for cartilage toxicity. *Infection* 1987; **15:** 165–8.
68. Nuutinen M, Turtinen J, Uhari M, Growth and joint symptoms in children treated with nalidixic acid. *Pediatr Infect Dis J* 1994; **13:** 798–800.
69. Hampel B, Hullmann R, Schmidt H, Ciprofloxacin in pediatrics: worldwide clinical experience based on compassionate use – safety report. *Pediatr Infect Dis J* 1997; **16:** 127–9; discussion 160–2.
70. Reed MD, Besunder JB, Developmental pharmacology: ontogenic basis of drug disposition. *Pediatr Clin North Am* 1989; **36:** 1053–74.
71. Hughes W, Dorenbaum A, Yogev R et al, Phase I safety and pharmacokinetics study of micronized atovaquone in human immunodefi-

ciency virus-infected infants and children. Pediatric AIDS Clinical Trials Group. *Antimicrob Agents Chemother* 1998; **42:** 1315–18.
72. Gualtieri RJ, Donowitz GR, Kaiser DL et al, Double-blind randomized study of prophylactic trimethoprim/sulfamethoxazole in granulocytopenic patients with hematologic malignancies. *Am J Med* 1983; **74:** 934–40.
73. Kauffman CA, Liepman MK, Bergman AG, Mioduszewski J, Trimethoprim/sulfamethoxazole prophylaxis in neutropenic patients. Reduction of infections and effect on bacterial and fungal flora. *Am J Med* 1983; **74:** 599–607.
74. Cruciani M, Rampazzo R, Malena M et al, Prophylaxis with fluoroquinolones for bacterial infections in neutropenic patients: a meta-analysis. *Clin Infect Dis* 1996; **23:** 795–805.
75. Carratala J, Fernandez-Sevilla A, Tubau F et al, Emergence of quinolone-resistant *Escherichia coli* bacteremia in neutropenic patients with cancer who have received prophylactic norfloxacin. *Clin Infect Dis* 1995; **20:** 557–60; discussion 561–3.
76. Donnelly JP, Is there a rationale for the use of antimicrobial prophylaxis in neutropenic patients? *J Intern Med Suppl* 1997; **740:** 79–88.
77. Nemunaitis J, Rosenfeld CS, Ash R et al, Phase III randomized, double-blind placebo-controlled trial of rhGM-CSF following allogeneic bone marrow transplantation. *Bone Marrow Transplant* 1995; **15:** 949–54.
78. Piguet D, Chapuis B, Recombinant human granulocyte–macrophage colony-stimulating factor in acquired or chemotherapy-induced neutropenia. An open clinical trial. *Acta Oncol* 1994; **33:** 639–43.
79. Pui C-H, Boyett JM, Hughes WT et al, Human granulocyte colony-stimulating factor after induction chemotherapy in children with acute lymphoblastic leukemia. *N Engl J Med* 1997; **336:** 1781–7.
80. Wang JM, Chen ZG, Colella S et al, Chemotactic activity of recombinant human granulocyte colony-stimulating factor. *Blood* 1988; **72:** 1456–60.
81. Welte K, Zeidler C, Reiter A et al, Differential effects of granulocyte–macrophage colony-stimulating factor and granulocyte colony-stimulating factor in children with severe congenital neutropenia. *Blood* 1990; **75:** 1056–63.
82. Weisbart RH, Golde DW, Clark SC et al, Human granulocyte–macrophage colony-stimulating factor is a neutrophil activator. *Nature* 1985; **314:** 361–3.
83. Sieff CA, Emerson SG, Donahue RE et al, Human recombinant granulocyte–macrophage colony-stimulating factor: a multilineage hematopoietin. *Science* 1985; **230:** 1171–3.
84. Roilides E, Walsh TJ, Pizzo PA, Rubin M, Granulocyte colony-stimulating factor enhances the phagocytic and bactericidal activity of normal and defective human neutrophils. *J Infect Dis* 1991; **163:** 5790–83.
85. American Society of Clinical Oncology, American Society of Clinical Oncology recommendations for the use of hematopoietic colony-stimulating factors: evidence-based, clinical practice guidelines. *J Clin Oncol* 1994; **12:** 2471–508.
86. American Society of Clinical Oncology, 1997 update of recommendations for the use of hematopoietic colony-stimulating factors: evidence-based, clinical practice guidelines. *J Clin Oncol* 1997; **15:** 3288.
87. Maher DW, Lieschke GJ, Green M et al, Filgrastim in patients with chemotherapy-induced febrile neutropenia. A double-blind, placebo-controlled trial. *Ann Intern Med* 1994; **121:** 492–501.
88. Mitchell PL, Morland B, Stevens MC et al, Granulocyte colony-stimulating factor in established febrile neutropenia: a randomized study of pediatric patients. *J Clin Oncol* 1997; **15:** 1163–70.
89. Anaissie EJ, Vartivarian S, Bodey GP et al, Randomized comparison between antibiotics alone and antibiotics plus granulocyte–macrophage colony-stimulating factor (*Escherichia coli*-derived) in cancer patients with fever and neutropenia. *Am J Med* 1996; **100:** 17–23.
90. Riikonen P, Saarinen UM, Mäkipernaa A et al, Recombinant human granulocyte–macrophage colony-stimulating factor in the treatment of febrile neutropenia: a double blind placebo-controlled study in children. *Pediatr Infect Dis J* 1994; **13:** 197–202.
91. Vellenga E, Uyl-de Groot CA, de Wit R et al, Randomized placebo-controlled trial of granulocyte–macrophage colony-stimulating factor in patients with chemotherapy-related febrile neutropenia. *J Clin Oncol* 1996; **14:** 619–27.
92. Pettengell R, Gurney H, Radford JA et al,

Granulocyte colony-stimulating factor to prevent dose-limiting neutropenia in non-Hodgkin's lymphoma: a randomized controlled trial. *Blood* 1992; **80:** 1430–6.

93. Gerhartz HH, Engelhard M, Meusers P et al, Randomized, double-blind, placebo-controlled, phase III study of recombinant human granulocyte–macrophage colony-stimulating factor as adjunct to induction treatment of high-grade malignant non-Hodgkin's lymphomas. *Blood* 1993; **82:** 2329–39.
94. Heil G, Chadid L, Hoelzer D et al, GM-CSF in a double-blind randomized, placebo controlled trial in therapy of adult patients with de novo acute myeloid leukemia (AML). *Leukemia* 1995; **9:** 3–9.
95. Ohno R, Tomonaga M, Ohshima T et al, A randomized controlled study of granulocyte colony stimulating factor after intensive induction and consolidation therapy in patients with acute lymphoblastic leukemia. *Int J Hematol* 1993; **58:** 73–81.

12

Prophylaxis of infections

J Peter Donnelly

INTRODUCTION

The treatment of cancer, particularly hematologic malignancies, entails using toxic drug cocktails that inflict considerable damage on two primary host defenses: the phagocytic line of defense, primarily the neutrophils, and the integument, i.e. the skin and the mucosa of the oral cavity and digestive tract. The importance of neutropenia has been recognized for over 30 years since the seminal publication of Bodey and colleagues.[1] More recently, it has become increasingly clear that injury to the mucosal barrier of the oral cavity and alimentary tract that results from the same intensive chemotherapy is not simply an inevitable side-effect but is also responsible for much of the morbidity that accompanies myelotoxicity.[2–4] In fact, patients exposed to intensive radiotherapy and cytotoxic chemotherapy are placed in double jeopardy, because concurrent mucositis and neutropenia leave them bereft of defenses against infection.

Prevention or cure

That prevention is better than cure is a long-held axiom of medicine, particularly where vulnerable individuals are concerned and the disease is preventable. Infections in neutropenic patients can be devastating, often culminating in the death of a patient who might otherwise have achieved remission or even cure. When a cause is identified, it is more often than not a common rather than exotic microbial species that is involved – frequently one that belongs to the normally harmless commensal flora that reside on body surfaces. This fact has motivated many in the past to resort to prophylactic regimens that seemed reasonable at the time but had not been shown properly to work. Looked at with hindsight, almost all the early trials of prophylaxis fall short of modern standards, and advocates of prophylaxis adopted regimens based upon meager evidence. In fact, it is only very recently that the spotlight of evidence-based medicine has been turned upon the febrile neutropenic patient, and, not surprisingly, the claims made for antibacterial prophylaxis and, in particular, antifungal prophylaxis, have been found wanting and based, at best, on low-level evidence. Equally unsurprisingly, the criticism leveled at prophylaxis by investigators who are considered deskbound by those facing the challenge presented by febrile neutropenia every day has only served to fuel debate that has often shed more heat than light. Meanwhile there is probably no hematopoietic stem cell transplant center in the Western world that

does not give prophylaxis of one sort or another, and very few centers dealing with leukemia who opt to do entirely without such regimens. The purpose of this chapter is to try to critically appraise prophylaxis and to examine alternatives, if such exist. This cannot take place without first placing the issue in the context of neutropenia induced by chemotherapy used to treat malignant diseases and for the ablative conditioning therapy for a hematopoietic stem cell transplant.

IMPAIRMENT OF HOST DEFENSES BY CANCER THERAPIES

Physical barriers

The physical barrier presented by the skin and the mucosa of the respiratory, urinary, genital, and alimentary tracts forms first line of defense against resident and transient microorganisms. Anatomically, the skin and these other organs form part of the external surface of the body, and comprise a continuum. Inevitably, these surfaces come into daily contact with microorganisms, of which some are harmless, some beneficial, and others detrimental. Evolution has ensured a formidable array of obstacles that a potential pathogen must overcome before gaining entry into the host.

The outer body surface – the skin

The skin is a particularly effective barrier as long as it remains intact, since it forms a barren, dry, hostile environment suited to a few Gram-positive bacteria, including *Staphylococcus epidermidis*, coryneforms, and certain yeasts.[5] The salt in sweat, fatty acids released from the sebaceous secretions, a low pH, the presence of bacteriocins, and secretory IgA all help the healthy skin to resist colonization by foreign microorganisms, particularly the Gram-negative bacilli.

The inner body surfaces – the oral cavity

From a microbial perspective, the oral cavity presents an extremely complex environment with varied topography, offering an enormous diversity of ecological niches. Each surface possesses its own unique consortium of commensal bacteria, from anaerobic bacteria such as *Fusobacterium* spp. to the aerobes such as *Neisseria* spp. For instance, the oral viridans streptococci are not uniformly distributed in the oral cavity. Rather, different species occupy different niches, with *Streptococcus sanguis* and *Streptococcus mitis* biovar 1 predominating on the buccal mucosa, *Streptococcus mitis* biovar 2 residing on the dorsum of the tongue, and *Streptococcus oralis* being found almost exclusively in initial dental plaque.[6] Besides being populated by commensal flora, the oral cavity is also the first port of call to most exogenous bacteria. Fortunately, in health, professional and opportunistic pathogens do not normally colonize the oropharynx, since they are unable to overcome the formidable array of different defense mechanisms of antibacterial substances and immunoglobulins secreted by the host and the direct competition posed by the indigenous microflora.[7] However, poor dental hygiene, peridontitis, diseased teeth, ill-health, and the loss of integrity of the oral cavity through drug-induced mucositis or by local infections such as herpes or candidiasis all increase the opportunities for certain potential pathogens to settle and establish an infective nidus. The Gram-negative bacilli, notably *Pseudomonas aeruginosa*, are adept at exploiting weaknesses, and are able to establish colonization of damaged tissue, where local infection can occur and even lead to disseminated infection.

The inner body surfaces – the stomach

The extreme low pH of the normal stomach provides an effective barrier to the transfer of oral bacteria to the intestinal tract. However, many patients treated with chemotherapy with or without irradiation experience nausea and vomiting and later gastric reflux, for which antacids, H_2 receptor antagonists, and proton-pump inhibitors are prescribed. Consequently, such patients are effectively achlorhydric and hence bereft of a barrier to microbial access.

This mechanism has been proposed to explain the onset of severe infections due to *S. mitis*,[8] and may also explain why these patients are more at risk of developing *Candida* infections, including gastrointestinal candidiasis.[9]

The inner body surfaces – the intestinal tract

In health, the small intestine is virtually sterile, whereas the large intestine is colonized by a variety of different bacterial species, which together account for almost half of the solids found in formed feces. Viable counts are estimated to be of the order of 10^{14} microorganisms per gram. It is a testament to evolution that very few species are capable of establishing infection – usually certain Gram-negative bacilli (e.g. *Escherichia coli*) and the *Candida* yeasts – even in the most profoundly immunosuppressed individual. The gut microflora are dominated by anaerobes, including *Bacteroides* spp. and *Clostridium* spp., but it appears that less-familiar Gram-positive non-sporing, lactic-acid-producing bacilli such as bifidobacteria are essential in maintaining a healthy commensal flora by providing the so-called 'colonization resistance'.[10,11] A loss of this facility is marked by yeast overgrowth and the recovery of enterococci in almost pure culture from stool samples. The loss of the normal bowel flora effectively creates an ecological vacuum in which transient exogenous bacteria are now able to gain a foothold and establish colonization (Figure 12.1).

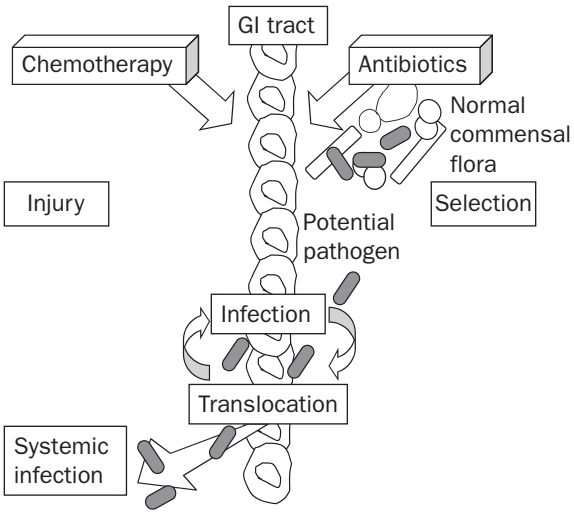


Figure 12.1 The origins of endogenous infection.

Impact of chemotherapy and radiation therapy on body surfaces

Injury to the skin

Chemotherapy and irradiation can radically change the microenvironment, since they cause hair loss, dryness, and loss of sweat production. Infections can develop around the hair follicles, providing a potential nidus for systemic infection. Abraded skin can also lead to local infection, which can be a reservoir that promotes further spread to entry sites of intravenous catheters. Needle punctures and vascular catheters produce trauma, and provide a ready means for microorganisms to gain direct access to the bloodstream. See Chapter 10.

Effect of chemotherapy and irradiation on the oral cavity

Neutropenic patients will experience varying degrees of mucosal damage, depending upon the nature of their chemotherapy.[12,13] Oral mucositis is not just a simple matter of failure of damaged cells to be replaced. Rather, it appears to be complex biological response to chemotherapy and irradiation involving initial damage to the endothelial and connective tissues, which triggers an initial inflammatory response.[14] Briefly, mucositis proceeds in four phases – namely, inflammatory, epithelial, ulcerative and healing phases. The cytokines tumor necrosis factor α (TNF-α) and interleukin (IL)-1β appear to initiate and amplify the process and their production can be moderated by recombinant IL-11.[15] Mucositis becomes clinically manifest during the epithelial phase and infection during the ulcerative/bacteriological phase. Florid mucositis is initially characterized by dryness, then by edema, erythema, and pain. Ulcers then

occur singly or severally, and there may be significant amounts of viscid mucus. Mucositis progresses to a peak that is often accompanied by fever, and then the signs and symptoms gradually subside as healing takes place.

The degree of mucositis and its onset and course vary, depending upon the constitution of the myeloablative regimen(s) used to prepare for a hematopoietic stem cell (HSC) transplant.[2] Similarly, the use of cytarabine (cytosine arabinoside) in high doses and idarubicin have been associated with bacteremia due to oral viridans streptococci.[16,17] Oral mucositis not only provides a portal of entry for these streptococci but also for *Stomatococcus mucilaginosus*,[18,19] *Capnocytophaga* spp.,[20–22] the anaerobes *Fusobacterium necrophorum* and *Eubacterium* spp., *Leptotrichia buccalis*,[21–23] as well as *Candida albicans*, Gram-negative bacilli, and possibly also *S. epidermidis*.[25] Active herpes simplex infection can exacerbate existing mucositis,[26] as well as increasing the incidence of oral thrush.[27]

Effect of chemotherapy and irradiation on the gastric acid barrier

Dyspepsia is sufficiently commonplace for antacids such as H_2 receptor antagonists, and even the proton-pump inhibitors such as omeprazole, to be regularly prescribed. The resulting lower gastric acidity inadvertently destroys the natural barrier, allowing bowel colonization by oral commensals to ensue. When these bacteria are also only marginally susceptible to antibiotics used for prophylaxis, their chances of establishing colonization are increased. This might explain why only a minority of patients who develop viridans streptococcal bacteremia progress towards sepsis, the so-called 'alpha-strep syndrome', which is associated with gut toxicity[28] and the use of H_2 receptor antagonists.[8,17] The sudden appearance in the bloodstream of overwhelming numbers of streptococci from multiple sites of mucosal damage may provide the mechanism for inducing shock,[29] since the cell wall material of Gram-positive bacteria is capable of inducing TNF-α and other cytokines.[30]

Effect of chemotherapy and irradiation on the intestinal tract

The epithelia and connective tissue of the gut are damaged by chemotherapy and irradiation,[15] and the mucosal barrier (at least that of the ileum) is compromised by the loss of the so-called 'mucous blanket', which can facilitate epithelial colonization.[31] Even standard chemotherapy for acute myeloid leukemia induces malabsorption and markedly increases the risk of candidiasis.[32] Besides the damage to the mucosa, chemotherapy and irradiation impair gut function and lead to rapid alterations in permeability and increased absorption of sugars.[32–36] Perturbed gut function has been shown to be one of the factors that, together with antibiotic usage and colonization with *Candida* spp., predisposes patients with leukemia to invasive candidiasis, and also appears to be a risk factor for neutropenic enterocolitis.[4,32] Impaired gut function and integrity may also facilitate translocation, particularly of Gram-negative bacilli such as *Ps. aeruginosa*, into the bloodstream of patients colonized with the organism.[37]

Mucosal barrier injury is determined not only by the nature of the chemotherapy and irradiation, but also by the accumulation of pro-inflammatory and other cytokines, the translocation of the resident microflora and their products across the mucosal barrier, exposure to antimicrobial agents that modulate the microflora, and the origin of the HSC graft.[4] Gut toxicity has also been shown to be responsible for reduced absorption of fluoroquinolones,[38,39] and has been implicated in the erratic bioavailabililty of the antifungal agent itraconazole.[40,41] Finally, a dysfunctional gut will have a marked effect upon the nutritional status of the patient. Some cytotoxic drugs may even exert direct influence on oral and gut flora, since some of these agents have been shown to possess antibacterial activity, and even to enhance the effects of antimicrobial agents.[42–47] The protracted diarrhea that often results from total-body irradiation (TBI) leads to a lower microbial biomass, which may be more vulner-

able to antimicrobial agents. Aztreonam and imipenem are normally inactivated by feces, but in its absence may retain more of their activity.[48,49] The ecology of the bowel flora will also be altered markedly by diarrhea induced by cytotoxic agents (e.g. cytarabine[50]), by graft-versus-host disease,[51] and by TBI.[52] In addition, prior exposure to antimicrobial agents that inhibit the Gram-positive anaerobic flora of the bowel, such as the penicillins, rifamycin, clindamycin, erythromycin, and vancomycin, will further alter the ecology considerably, since this is associated with a measurable loss of 'colonization resistance'.[53]

THE HOST AND THE MICROBIAL WORLD

Environment

Normal daily activity exposes us many times to exogenous microorganisms. Fortunately, the vast majority that are encountered are harmless. Unless the individual is a carrier, professional pathogens are acquired exclusively from the environment – either by direct contact with an infected individual or indirectly by inhaling infected air, ingesting infected food and drink, or by coming into contact with infected objects. Bottled non-carbonated mineral water has been identified as a source of *Pseudomonas* spp. and *Stenotrophomonas maltophilia*.[54] Flowers (both cut and potted) are notorious sources of water- and soil-borne Gram-negative bacilli, including *Ps. aeruginosa*. The global nature of floristry, with plants being imported from all over the world, may also increase the risk of infection by exotic species and by multiply resistant strains. Fresh fruit and vegetables also arrive in supermarkets from all corners of the globe, and present a similar risk. Widespread travel may also open new avenues for acquiring infection, as can leisure and sports activities involving water. Even visiting a humble flower show where whirlpools are used can increase the risk of legionellosis.[55]

Increasing concern for the environment has afforded molds such as *Aspergillus fumigatus* a wider domain. This outstanding saprophyte is already found almost everywhere, including fireproofing material,[56] silage,[57] building dust,[58–61] household dust,[62] decaying matter such as dead leaves and old rotting furniture,[63] compost heaps,[64] biocontainers,[65] potted plants, and foodstuffs such as ground pepper.[66] *Aspergillus* and *Penicillium* prevail in the autumn and winter months.[67] Other fungi, such as the phycomycetes *Mucor* and *Rhizopus*, are also ubiquitous saprophytes. Molds, including *Aspergillus* spp., *Penicillium* spp., *Fusarium* spp., *Absidia* spp., and *Cladosporium* spp., are dispersed in the air during the handling of grain.[68] Hence, exposure to microorganisms is a constant factor of daily life in both normal hosts and patients receiving antineoplastic therapy.

Microbial diseases of the neutropenic patient

There are in excess of 900 bacterial species known to inhabit the body surfaces, but only a very few have been reported as causing infection, even in the most immunosuppressed patients. Infections in neutropenic patients derive from two principal sources: the endogenous flora and the exogenous or environmental flora. The resident commensal flora found on the skin and mucosal surfaces contains potential pathogens, but occasionally organisms can also be acquired exogenously by ingestion of contaminated fluids and food or through direct contact. Such organisms may be transient, being unable to establish a foothold and establish colonization. Their opportunity to infect is therefore limited unless there is repeated exposure, prolonged transit, and a ready-made portal of entry available, such as an ulcer, abrasion, or direct access via a catheter. Reverse barrier isolation, HEPA-filtered air, and a diet of low microbial content all help reduce the chance of acquiring potential pathogens exogenously. As a consequence, most pathogens in neutropenic patients arise from the resident flora inhabiting the skin, the airways and the alimentary tract.

An extensive review of the epidemiology of infections in neutropenic patients is provided in Chapter 4. Infections by much less common bacteria have been attributed to catheter infection by, for example, *Tsukamurella paurometabolum (Gordona aurantiaca)*,[69] to oral mucositis due to, for example, *Capnocytophaga* spp.,[22] or to both routes (e.g. *Stomatococcus mucilaginosus*).[19] The lesson again seems to be that the presence of a portal of entry and a potential pathogen both conspire to cause infection.

CHEMOPROPHYLAXIS

The debate about the utility or otherwise of chemoprophylaxis continues to ebb and flow, although the emphasis has shifted from bacteria to fungi – probably because of prompt empiric antibiotic therapy successfully reducing mortality through the years. The trend towards relying more on evidence than eminence may have lowered the scientific appeal of prophylaxis, but not its intuitive attraction, since it has become very much the norm. The estimation of risk and benefit is also in a continuous state of flux, and the concept of cost–effectiveness has taken hold. In essence, choosing whether or not to give chemoprophylaxis depends upon answering four basic questions (Table 12.1): Is there an effective treatment for the infection? Is the infection serious? Is prophylaxis effective in preventing the infection? Does prophylaxis have few adverse effects?

Is there an effective treatment for the infection?

When chemoprophylaxis was first attempted it was aimed at reducing the morbidity and mortality that arose from infections caused by *Staphylococcus aureus* and the Gram-negative bacilli *E. coli*, *Klebsiella pneumoniae*, and *Ps. aeruginosa*, for which therapy was limited. However, nowadays, effective therapy is available for these infections if given to the patient promptly after the onset of fever.[70,71]

Infections involving viridans streptococci also have a high rate of cure using standard empiric regimens, even when there is evidence of bacteremia. However, acute respiratory distress syndrome associated with bacteremia due to viridans streptococci, usually *S. mitis*, fares less well, but whether or not adding another antimicrobial agent such as penicillin is beneficial is uncertain. Instead, the syndrome may be better managed by complementing the empiric regimen with a short course of high-dose corticosteroids.[29]

Similarly, effective therapy is available for treating candidiasis, whether localized or disseminated.[72–75] By contrast, although effective treatment is available for the most common mold infection, invasive aspergillosis, inability to recognize the disease soon enough leads to a delay in starting treatment.[76–82]

Treatment of herpes simplex infection with acyclovir is highly effective, although resistant strains have been encountered, resulting in therapeutic failure.[83–85] Infections due to cytomegalovirus (CMV) pose a similar problem as does aspergillosis insofar as treating established disease such as CMV pneumonitis is ineffective although, unlike aspergillosis, the disease is invariably restricted to seropositive recipients of an allogeneic HSC transplant.[86] Whilst graft-versus-host disease (GVHD) plays the greatest role in the development of CMV disease, CMV viremia is the best predictor of its development.[87]

Is the infection serious?

All infections that occur during neutropenia are regarded as serious, although those caused by coagulase-negative staphylococci are generally seen as indolent. Even when the attributable mortality is only marginal, few are prepared to run the risk of doing nothing and adopting a wait-and-see approach. Instead, empiric treatment is given on suspicion of infection and

Table 12.1 Prophylaxis or not?

	Infection due to				
	Gram-negative bacillus	**Herpes simplex**	***P. carinii***	***Candida* spp.**	***Aspergillus* spp.**
Is there an effective treatment for the infection?	Yes	Yes	Yes	Yes	Yes
Is it a serious infection?	Yes	No	Yes	Yes	Yes
Is the prophylaxis effective in preventing the infection?	Yes	Yes	Yes	Yes	No
Does the prophylaxis have few adverse effects?	Yes[a]	Yes	Yes[b]	Yes	No[c]
Regimen	Ciprofloxacin	Acyclovir	Co-trimoxazole	Fluconazole	None

[a] Provided antibiotic resistance is uncommon.
[b] If skin rash is considered unimportant.
[c] Interferes with cyclosporin.

even complemented with other empiric agents such as a glycopeptide or amphotericin B. Hence it is a moot point whether or not infection is serious in terms of increased morbidity and mortality, since clinicians act as though it is and this has become a standard of care.

Is prophylaxis effective in preventing bacterial infection?

Antimicrobial agents were first given to cancer patients and those with hematologic malignancy in the early 1970s to try to reduce the infectious complications arising during neutropenia.[88–91] Non-absorbable regimens, particularly gentamicin plus vancomycin plus nystatin (GVN), were employed to sterilize the gut,[92,93] but this proved futile – the compliance was erratic and the risk of selecting resistant bacteria was actually higher. This was explained by the antibiotics destroying the anaerobic flora of the alimentary tract to such an extent that much fewer exogenous Gram-negative bacilli were required to establish colonization than was the case under normal conditions.[94] It therefore seemed more appropriate to aim for partial or selective decontamination rather than attempt complete sterilization of the body sites. This approach was known by several acronyms, including SDD (selective decontamination of the digestive tract), PAD (partial antimicrobial decontamination), and even by SAM (selective antimicrobial modulation).[53] All the regimens employed were targeted against the undesirable Gram-negative bacilli found within the resident flora while preserving the microflora responsible for colonization resistance. However, it was only when Hughes and colleagues[95] reported that children given co-trimoxazole to prevent infection due to *Pneumocystis carinii* also suffered fewer episodes of bacterial infections that the demise of total gut decontamination was assured and the adopted standard approach became one of selective oral antimicrobial prophylaxis.

Co-trimoxazole

Co-trimoxazole seems the ideal agent because it prevents infection with *P. carinii*, is effective against a wide range of respiratory pathogens, including *Streptococcus pneumoniae* and *Haemophilus influenzae*, and offers protection against both *S. aureus* and the enteric Gram-negative bacilli.[95] Small placebo-controlled trials indicated that co-trimoxazole was beneficial as selective prophylaxis,[96–102] as did comparative studies.[90,103–109] However, the risk of resistance emerging and causing bacteremia was apparent,[96,110] as was co-trimoxazole's lack of activity against *Ps. aeruginosa*, necessitating the addition of colistin.[108]

The fluoroquinolones

The introduction of the newer fluoroquinolones – norfloxacin,[111] ciprofloxacin,[112] ofloxacin,[113] and pefloxacin[114,115] – further expanded the range of agents available for prophylaxis. Moreover, compliance is better, side-effects are lower with these drugs than with co-trimoxazole, and they do not seem to have any deleterious effect on hematopoeisis.[116] Their spectrum of activity includes the most common causes of infection due to Gram-negative bacilli, *S. aureus*, and many of the coagulase-negative staphylococci.[117,118] The viridans streptococci and enterococci are only marginally susceptible, if at all. Although only one of the many prophylactic trials with the fluoroquinolones has been placebo-controlled,[111] it is clear that they all provide better protection against infection due to Gram-negative bacilli than does co-trimoxazole.[113,114,119–127] However, among the drugs studied so far, only ciprofloxacin offers the most complete protection against Gram-negative bacilli, including *Ps. aeruginosa*.[114,123,124,126]

Norfloxacin was the first to be made available, and was quickly followed by ciprofloxacin, then pefloxacin and ofloxacin. By the time some of the newer fluoroquinolones became available, practice patterns had developed, and clinicians fell into two opposing camps: those who employed a fluoroquinolone,

even though the evidence was far from conclusive that they were effective, and those who abhorred the idea, fearing the emergence of resistance. It is indeed surprising that there has been no satisfactory placebo-controlled, double-blind trial of sufficient size to prove significant benefit with enough power. The arguments for and against these drugs rest on a series of small, mostly single-center, studies. Moreover, a variety of endpoints were employed, including the prevention of infection due to Gram-negative bacilli, infection per se, and even fever. A meta-analysis of 12 comparative and controlled studies is the best evidence available, and shows that whilst prophylaxis with a fluoroquinolone is more effective than either placebo or alternative regimens in preventing infection due to Gram-negative bacilli,[128] there was no measurable benefit in terms of bacteremia as a whole. There were more episodes of bacteremia due to Gram-positive cocci and no evidence of less mortality. Also, more episodes of fever of undetermined origin occurred with more than 80% of patients still receiving empiric therapy with broad-spectrum antibiotics.

Special cases – viridans streptococci

Recognition that the oral viridans streptococci were in the ascendancy prompted studies in which a fluoroquinolone was complemented by a penicillin,[129–131] amoxycillin,[132,133] vancomycin,[134] or roxithromycin.[135] Whilst there was less bacteremia due to these streptococci, resistance developed against penicillin,[128] and there was no measurable impact on the incidence of fever and other infective complications such as pneumonia and septic shock.[135]

Special cases – catheter-related infections

It might seem logical to attempt to prevent these infections by providing antibiotic coverage during insertion or by instilling antibiotics through the lumen to apply an antibiotic block. A single bolus intravenous injection of 400 mg teicoplanin resulted in a lower incidence of exit site and tunnel infections and catheter-related Gram-positive bacteremia, particularly among patients who were already neutropenic when the Hickman catheter was inserted.[136] A short course of three injections of 500 mg vancomycin perioperatively resulted in fewer of the central venous catheters in the vancomycin prophylaxis group becoming infected with Gram-positive microorganisms than in the control group.[137] Giving vancomycin twice daily at a dose of 15 mg/kg from two days before HSC transplant until resolution of neutropenia or until the first episode of fever prevented bacteremia and focal infection, resulting in fewer days with fever, and hence fewer days of empiric antibiotic therapy.[138] However, because the clinical course of coagulase-negative staphylococcal infections is relatively benign, treatment with a glycopeptide is only warranted if there is a tunnel infection or coexistent thrombophlebitis.[139,140] The enthusiasm for giving vancomycin prophylactically has since given way to a realization that there are significant hazards associated with the practice due to the emergence of vancomycin resistance among the enterococci species (particularly *Enterococcus faecium*) and the real fear that the tranposon responsible could cross over to more dangerous pathogens, such as *S. aureus*.[141] The concern is such that most authorities advise specifically against using vancomycin for prophylaxis even in neutropenic patients who might benefit.[142]

Others have introduced antibiotic blocks to prevent contamination of the catheter lumen via the hub.[143] Vancomycin at the low concentration of 25 μg/ml in heparin has been used – apparently effectively.[144] The justification for this approach is that catheters can easily become infected with a nosocomial strain of *S. epidermidis*, since several clones survive on the same hematology ward for quite some time by colonizing patients' skin.[145] However, whether the putative benefit of using such blocks is generally found remains to be confirmed by studies done on a much larger scale. The same can be said of the claims made for impregnated catheters. If the patient's skin is the principal

source of the staphylococcus and infections originate from the exit site, then coating the external surface of the catheter might provide some benefit.[146,147] However, there are as yet too few data to support this practice. In the absence of good evidence, it seems more prudent to manage catheters carefully, use them only as absolutely necessary, remove them as soon as they are no longer needed, and treat catheter-related infections with antibiotics when there is an obvious tunnel infection, evidence of infected thrombosis, or Gram-positive bacteremia that persists for longer than 3–4 days; this should always be accompanied by swift removal of the device.

Does antibacterial prophylaxis have few side-effects?

Although bacteremia due to Gram-negative bacilli is reduced by prophylaxis, this results in more unexplained fevers and more bacteremias due to Gram-positive cocci, which are either naturally resistant to the fluoroquinolones, such as in the case of viridans streptococci, or have apparently acquired resistance, as do many coagulase-negative staphylococci, and this has been observed during treatment with ciprofloxacin.[148] This observation is explicable, since ciprofloxacin is both excreted in the sweat and induces resistance amongst skin staphylococci within a few days of exposure.[149,150] These staphylococci are commonly resistant to tobramycin, co-trimoxazole, and methicillin, and may also be resistant to ciprofloxacin.[151]

Resistance among *E. coli* to the fluoroquinolones norfloxacin,[152] ofloxacin,[153] and pefloxacin[154] has also been observed. A recent study done in Taiwan may have inadvertently revealed why, since 3 of 12 allogeneic HSC transplant recipients given ciprofloxacin for prophylaxis developed bacteremia due to resistant *E. coli* during neutropenia, resulting in two deaths from septic shock.[155] Instead of using the more usual dose of 1000 or 1500 mg/day, the authors opted for 500 mg/day, believing it to be sufficient for prophylaxis. However, the dose may well have been too low to achieve adequate systemic levels for two reasons. Firstly, absorption of this drug is impaired following chemotherapy, when mean peak concentrations are reduced by half to 2.0 mg/l just around the time neutropenia has reached its nadir and mucositis its peak and shortly before bacteremia occurs.[39] Secondly, the fluoroquinolones bind to feces,[156] making even less drug available to inhibit the *E. coli*. The lower dose of 500 mg/day would achieve even lower peak concentrations, reducing local and systemic efficacy. The impairment of drug absorption might be explained by the fact that this takes place in the upper part of the intestinal tract, i.e. duodenum and jejunum,[157] which is also where most damage occurs to the mucosal barrier.[33] Hence, apart from anything else, gut mucositis appears to result in altered drug disposition. Lower absorption has also been noted for ofloxacin.[38]

Bacteremia due to Gram-positive cocci such as viridans streptococci might occur simply as a result of plasma levels of the drug being lower than the minimum inhibitory concentration.[117] Under these conditions, other multiply resistant Gram-positive cocci, including staphylococci and enterococci, would also have a selective advantage.[123,148,151,158–161] Combine this selective pressure with colonization of the mucosal surfaces by resistant bacteria and severe mucositis, and all the necessary ingredients for infection are present.

Generally, co-trimoxazole is well tolerated, but it induces a skin rash in 15% of patients receiving remission induction therapy, particularly when cytarabine is included.[162] Moreover, the onset of skin rash frequently coincides with allergy to allopurinol and cytarabine, as well as oral mucositis, nausea, and diarrhea (e.g. after remission induction of acute myeloid leukemia). This leads to less compliance and interruption, if not to total discontinuation of prophylaxis. Co-trimoxazole has also been associated with delayed hematopoiesis in bone marrow transplant recipients.[163] Fluoroquinolones

induce fewer side-effects, and although rashes do occur, they do so much less frequently than with co-trimoxazole and seldom lead to premature discontinuation. Side-effects are therefore seldom the reason for stopping prophylaxis. Patients who discontinue taking medication for reasons other than the onset of fever or side-effects mostly do so simply because they are unable to swallow because of severe oral mucositis. Logically, the drug could have been continued parenterally when the oral route was not feasible, but this has never been done because such a move was perceived as therapy rather than prophylaxis. The fact that the doses of both co-trimoxazole and the fluoroquinolones were therapeutic was simply overlooked. Clearly, the psychological barrier imposed by the understanding of 'prophylaxis' and 'therapy' was too great to overcome. Even the elegant study by Bow and colleagues[164] that showed ciprofloxacin to be safe as an effective strategy to reduce the amount and duration of empiric therapy directed against Gram-negative organisms in febrile neutropenic patients did not attempt to switch to parenteral administration to deliver the bioequivalent amount of drug. So, despite over a decade of use, not only is the correct dosage of fluoroquinolones not yet known, but neither is the proper route of administration. Since there has been no trial of fluoroquinolone that allowed continuation of the drug parenterally when drug concentrations fell, we shall never know whether or not failure to maintain adequate levels was the reason for breakthrough infection. A more rational approach to prophylaxis would, in fact, be to administer ciprofloxacin orally at a dose equivalent to the optimum therapeutic dose (e.g. 1500 mg/day), and to continue prophylaxis parenterally should the patient be unable to swallow the tablet or when blood levels fall below a certain threshold (Figure 12.2). Oral treatment can then resume once mucositis subsides.

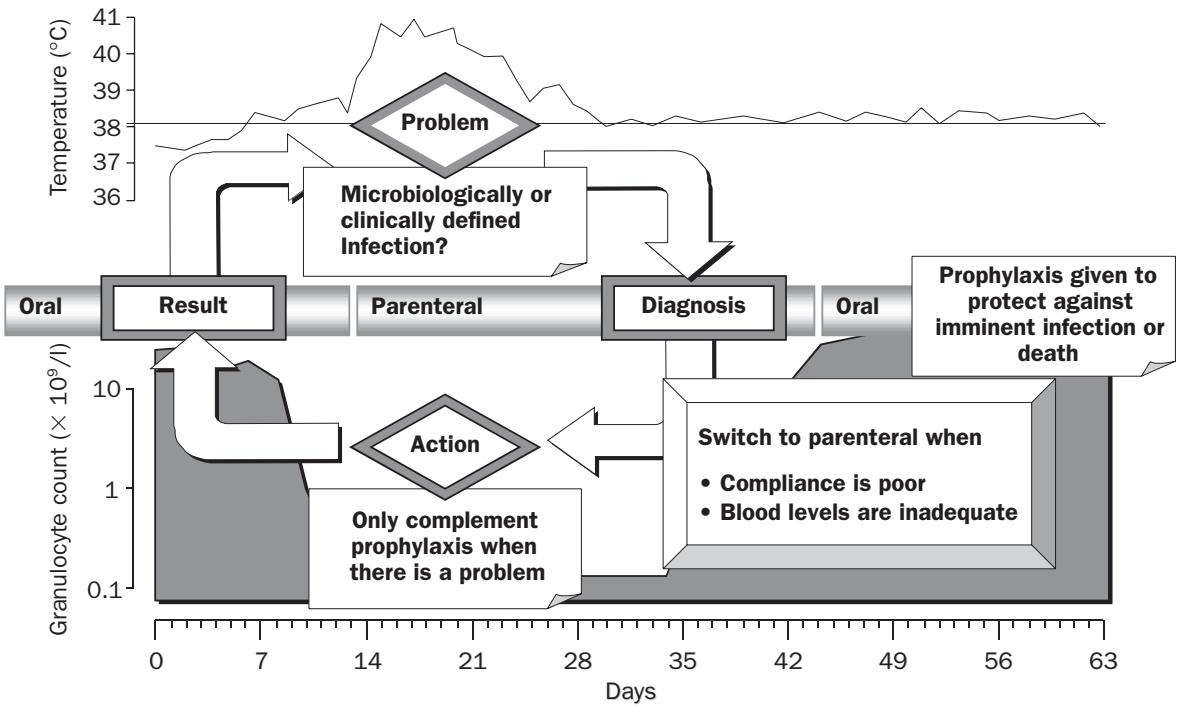


Figure 12.2 Prophylaxis as the backbone for managing infections.

Should antibacterial prophylaxis be used?

Besides the problems of resistance, further doubts have been cast upon the practice of antibacterial prophylaxis in a recent review,[165] which suggested that antibacterial prophylaxis has outstayed its welcome since timely administration of empiric broad-spectrum antibiotics has been very successful in reducing mortality attributed to Gram-negative infections. In addition, there have been no controlled clinical trials fulfilling the criteria required for firm evidence (high-power, prospective, randomized, blinded, multicenter studies), although there are still reports being published that appear to show that specific populations such as HSC transplant recipients do benefit.[166] If put to a jury of other than hematologists, a verdict of 'not proven' for prophylaxis would probably be returned. But, despite the lack of evidence, prophylaxis with fluoroquinolones will still continue to be given – certainly to recipients of HSC transplants, and to other patients receiving the sort of intensive chemotherapy that induces protracted neutropenia and injures the mucosal barrier, if only because the fear of bacteremia due to Gram-negative bacilli is being assuaged. That being the case, it would still be desirable to conduct a formal trial to help establish the correct dose and means of administration and identify those patients who would gain the most benefit, although it is doubtful whether or not a placebo would now be considered ethical. However, this reservation is more than compensated for by having the safeguard of modern empiric regimens.

Is prophylaxis effective in preventing fungal infection?

Prophylaxis of invasive fungal infectious diseases (IFIDs) has had a checkered history. Initially, studies were small, uncontrolled, done in single centers, and invariably inconclusive. Moreover, efficacy measures were indirect and soft, relying on such entities as number of febrile days, use of empirical amphotericin B and so on. Lately, there have been a few studies that did meet the rigorous requirements of a randomized, controlled trial, although the results were not universally applicable. For instance, there are data that show fluconazole effective in preventing disseminated candidiasis in recipients of allogeneic HSC transplant,[167,168] and possibly in those being treated for acute myeloid leukemia,[169,170] but there is no agreement about the optimum dose. In North America, 400 mg/day of fluconazole is used, whereas other investigators elsewhere have achieved similar results with only 100–200 mg/day,[171–176] calling into question the need for the higher dose of fluconazole. Moreover, the drug offers no protection against mold infections, including aspergillosis.

A recent meta-analysis showed so little benefit from prophylaxis that the authors concluded there was insufficient evidence for its use.[177] This certainly seemed to be the case in terms of long-term survival, but doubts still remain about the prevention of IFID per se. The studies included in the meta-analysis also employed different criteria for IFID. Thus, the fact remains that a study necessary to prove a clear benefit of prophylaxis over placebo at reasonable cost has yet to be done, although this now seems highly unlikely, since few will feel comfortable offering allogeneic HSC transplant recipients a placebo.

The goal of prophylaxis must also be clear and explicit. Preventing death due to IFID is not the same as preventing IFID itself. This is not simply an academic issue. Death is regarded as a 'hard' fact, and, as such, is the preferred endpoint for meta-analysis, health economics, and by decision-makers. In contrast, clinicians are much more interested in preventing morbidity, and thus, by implication, reducing mortality. Although all studies of prophylaxis will take account of deaths, the primary endpoint is the occurrence of IFID – hence the importance of standard definitions, which, fortunately, we now have at our disposal.

Apart from selecting natively resistant non-

albicans *Candida*, including *C. glabrata* and *C. krusei*, prophylaxis with fluconazole might also lead to the development of superinfection by *Aspergillus fumigatus*.[178]

A further problem will be in obtaining agreement about how long such prophylaxis should be maintained, since there are good reasons for continuing it for as long as the patient is at any risk of IFID, i.e. 1–2 years post HSC transplant, or even for life.[179] Other problems will arise in choosing the agent for study. The azole antifungal agents are the first choice, but the benefit of fluconazole is limited to preventing IFID due to *Candida* spp.; confidence in itraconazole is still lacking, and other potential alternatives are still to complete phase III trials. A lipid form of amphotericin B would be worth studying, but for the inordinate acquisition costs and the reluctance to use the same drug for prophylaxis that one would choose for treatment.

IFID – What's in a name?

Intuitively, prevention of fungal infection seems the simplest approach, especially since the consequences of missing a case can be disastrous – but it is not. Firstly, candidiasis and aspergillosis account for most IFIDs in allogeneic HSC transplant recipients and in neutropenic patients in general,[77,180,181] but these are radically different entities. Candidiasis almost invariably develops in patients already colonized with the offending yeast,[9,182,183] but there are no internationally accepted criteria for defining colonization and no standard methods for determining it, although there is some agreement that the same yeast should be recovered from the same site on two separate occasions or from at least two different sites on the same occasion.[9,182,183] The *Candida* spp., particularly *C. albicans*, form part of the normal resident flora of the gastrointestinal tract, and are easily detected in the oral cavity by culturing the mucosal surfaces of the mouth or an oral gargle. The gut is less straightforward to sample, since stools are not always available and there is a general reluctance to take a rectal swab because of the risk of bleeding. There is also evidence that catheter-related infection due to *Candida* is preceded by colonization by the same species around the exit site, particularly where *Candida parapsilosis* is concerned,[184,185] but routine surveillance swabs are not done. Differences in sampling alone account for much of the different sensitivities for detecting colonization. Cultures may be done to obtain a present/absent result (qualitative), or they can be performed in such a manner as to provide an estimate of numbers. Various different media are used, with some simply relying solely on standard bacteriological media, whilst others include one specially designed to recover fungi. A medium supplemented with an antibiotic to suppress growth of bacteria to enhance detection of yeast without allowing any discrimination between the different species of yeast is also inferior to the newer differential media such as CHROMagar, which facilitate differentiation of yeasts reliably.[186] Not surprisingly, no two methods yield the same results and many will not even bear comparison. It is therefore no surprise that many centers simply do not make any attempt to detect colonization, deeming it a waste of time and resources. Yet there are data to show a clear association between carriage of yeast and subsequent infection, and, just as importantly, the lack of colonization is highly predictive of IFID due to *Candida* spp. being unlikely.[182,183,187–189]

There have been many attempts at suppressing colonization by yeasts, including administering the polyenes by mouth as well as giving each of the azole drugs available, but success varies and is unpredictable.[176,190,191] Both nystatin and amphotericin B have been given orally to prevent fungal infection, although there has never been a randomized controlled trial. The practice seemed to have evolved from several considerations. Nystatin was included in the early decontamination regimens[92,93,192] to suppress the overgrowth by *C. albicans* that occurred as a result of altering the ecology of the gut microflora. The introduction of so-called selective decontamination in Europe and the availability of amphotericin B lozenges, tablets,

and suspension led to its inclusion for the same purpose.[53,100,120] Doses vary widely, and up to 4×10^6 U/day nystatin is given, with variable success and compliance. The suspension has been most widely used, but tablets may be more palatable and effective.[193] Amphotericin B may be effective against candidiasis when at least 200 mg/day is given orally, although at least 8 times this amount appears necessary to suppress gut colonization,[194] and, once again, compliance is inconsistent.

Miconazole and clotrimazole suppress oral colonization, and may both be more effective than placebo, but the data are sparse.[183,199] Ketoconazole, fluconazole, and itraconazole are all effective in suppressing colonization, but this is not translated into reducing infection.[177,194] By contrast, fluconazole not only reduces colonization and superficial infection but also lowers the risk of developing disseminate candidiasis significantly.[167,168,177,194,195] Similarly, itraconazole appears effective in suppressing yeast colonization[196–198] IFID due to *Candida* spp., but not for that due to *Aspergillus* spp.[77,171,199] Also, no study has shown an appreciable reduction in overall mortality, and there has been little impact on fungal deaths.[177,197] Moreover, because compliance will be variable during mucositis and while the patient is suffering the side-effects of ablative treatment, both drugs may be given parenterally if treatment is to be continued, which, up until recently, limited the choice to fluconazole because of the lack of a parenteral form of itraconazole.

In stark contrast to candidiasis, aspergillosis only develops once the fungus has established itself in the airways, and *Aspergillus* spp. are never normal residents of the upper respiratory tract. Thus, screening individuals at risk by taking specimens for culture is doomed from the start. Certain specific molds such as *A. niger* can be detected beforehand from nasal secretions,[200] and, as such, can identify those patients at risk, but this seems to be of very limited value and only to have been true in the context of an outbreak. In theory, at least, it should be possible to prevent the acquisition of molds such as *Aspergillus* spp. simply by supplying HEPA-filtered air. Many centers also ask patients to inhale amphotericin B administered in spray or nebulized form to destroy any spores that might have been inhaled or be lingering in the airways. Whilst single centers that espouse the practice are convinced that it is effective,[201–205] a large multicentre study failed to confirm this.[206] Besides, even if this strategy were to work, it would only help to suppress nosocomial IFID, and would have little, if any, influence on the course of disease established before admission. Ultimately, the best prevention against aspergillosis in neutropenic patients is still the control of the underlying disease, with subsequent return of normal marrow function and resolution of neutropenia[207] and control of GVHD in allogeneic HSC transplant recipients.[76]

Special case – Pneumocystis carinii

This erstwhile protozoon has now been reclassified as a fungus. Infections seldom develop, and when they do occur, it is usually in patients who are not protected by co-trimoxazole prophylaxis,[208,209] such as following allogeneic HSC transplant in a setting of chronic steroid use or GVHD. Co-trimoxazole 960 mg given once daily or three times a week or 960 mg bid twice weekly is still the first choice for prophylaxis, with nebulized pentamidine providing a safer, though less effective alternative when there is intolerance.[209,210] Dapsone is not considered sufficiently effective, since significantly higher rates of *P. carinii* pneumonitis have been reported.[211] When disease is apparent, co-trimoxazole given parenterally at the higher dose of 120 mg/kg/day in divided doses for 21 days remains first choice for therapy, irrespective of the severity.[209]

Does antifungal prophylaxis have few side-effects?

Unlike polyenes, all the azoles have the potential drawback of selecting the resistant species

such as *C. krusei* and *C. glabrata*, and even, in the long term, of inducing resistance in *C. albicans*.[212] However, reality does not quite bear this out, since in one study, recovery of *C. glabrata* steadily increased equally to around 30% in patients whether or not fluconazole was given, whilst *C. krusei* were isolated exclusively from patients given the drug.[213] In another study of a similar patient population, the reverse was true, with more *C. glabrata* being isolated from patients given fluconazole, and *C. krusei* being recovered equally.[214]

The azole drugs are all relatively safe, and treatment seldom needs to be stopped prematurely because of actual side-effects. However the nausea and vomiting experienced by patients following cytotoxic chemotherapy is sufficiently troublesome that one in every four or five patients stop taking itraconazole altogether.[199,215] This makes the argument all the more compelling for switching to parenteral treatment – at least until all gastrointestinal toxicities are resolved and normal intake is resumed. By contrast, patients seem to tolerate fluconazole much better, and physicians are already used to switching from oral to parenteral therapy and back again.

Fluconazole has the least potential to interact with other drugs, although interactions with cyclosporin have been reported when fluconozole doses higher than 200 mg/day are given.[216,217] This can be remedied by close monitoring of cyclosporin concentrations and renal function.[217] The increases in cyclosporin and tacrolimus concentrations seen are modest when these drugs are given orally, and may be a result of fluconazole inhibition of gut metabolism, resulting in greater absorption.[218]

By contrast ketoconazole, and to a lesser extent itraconazole are more potent inhibitors of cytochrome P450 3A4 which metabolize drugs such as cyclosporin and tacrolimus. Consequently a reduction in the dosage of the immune suppressants is required and is even seen by some as a beneficial interaction because it results in lower drug consumption and, hence, cost.[219]

Should antifungal prophylaxis be used?

Although most would wish for a broad-spectrum agent that can be given both orally and parenterally, an ideal candidate has yet to become available. The presence of colonization should be used to select those patients at higher risk of IFID due to *Candida* spp., especially since there has been no attempt to look at the potential benefit of antifungal prophylaxis only in patients who actually carry the yeast on their mucosal surfaces. Similarly, the type of cytotoxic chemotherapy used should be factored into a decision about whether or not to give prophylaxis.

Given the low incidence of aspergillosis in the recent studies of prophylaxis, an alternative approach seems to be warranted. The example of ganciclovir is instructive here, since the drug was considered too toxic to be given to every allogeneic HSC transplant recipient at risk of CMV infection. Investigators decided to turn to the laboratory, which had a test at its disposal for detecting the pp65 antigen of CMV. This led to the creative solution of screening for the antigen in patients at risk and only treating with ganciclovir when there was a significant rise in antigen titers, which was assumed to indicate imminent infection. This pre-emptive approach might prove worthwhile for patients at high risk of developing pulmonary aspergillosis, since there is an enzyme-linked immunosorbent assay (ELISA) test for detecting galactomannan antigen; patients' plasma can be monitored two to three times weekly, and, if antigen is detected, treatment could be started on the assumption that disease is imminent.[82,220] A further refinement would be to take a high-resolution computed tomography scan of the lung, and only start treatment if this showed abnormalities consistent with an infective process. One strategy for managing aspergillosis would be to define the risk as shown in Figure 12.3 and then choose the type of treatment. When the risk is remote, prophylaxis would only be indicated for special groups, such as allogeneic HSC transplant recipients.

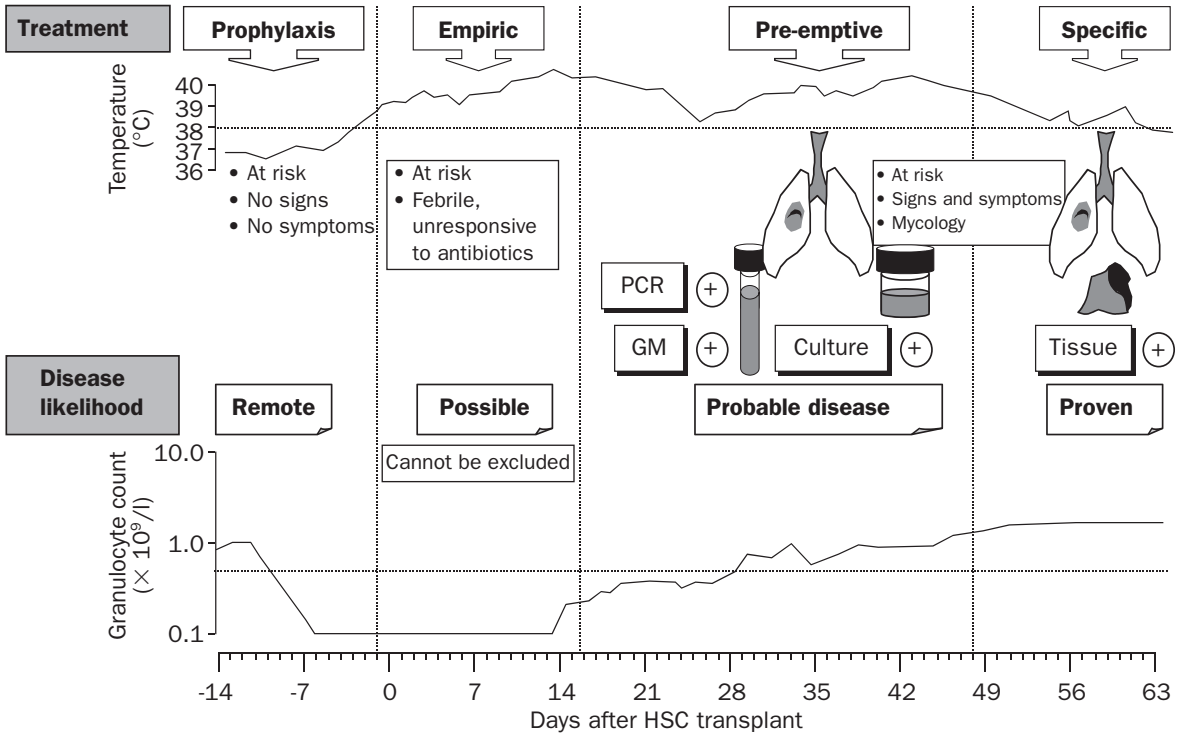


Figure 12.3 Management of a patient at risk for aspergillosis.

During neutropenia, any patient at risk who has developed fever that persists for 3–5 days but remains unexplained and is refractory to empiric antibacterial therapy would be considered a candidate for empiric antifungal therapy. At the other extreme, the few cases for which the diagnosis is proven by detecting fungus in the tissue obtained from the site of infection would clearly be candidates for vigorous specific therapy. Those patients who are at risk, and have some clinical manifestation of disease such as a pulmonary infiltrate, would be considered probable cases, provided that the laboratory has detected the presence of the fungus in blood or other body fluids and secretions directly by culture or microscopy or indirectly by detecting antigen or by polymerase chain reaction (PCR).

Is prophylaxis effective in preventing viral infection?

Herpes simplex

Acyclovir has been used routinely for HSC transplant recipients for the two decades since it was shown to be very effective in preventing lesions after reactivation of viral infection but less so in halting viral shedding.[221] Reactivation tends to occur when pretransplantation herpes simplex IgG titers exceed 10 000 units using the ELISA test. This method has been used by some to decide whether or not to initiate prophylaxis in patients being treated with conventional-dose chemotherapy for malignant diseases. In contrast, prophylaxis forms an integral part of the prophylaxis schedule of HSC transplant recipients.[222] The discussion has focused more on for how long treatment should be continued and whether or not there is any measurable effect on

the development of CMV disease.[222] Opinions are still divided, with some concluding categorically that acyclovir has no impact whatsoever on the frequency of CMV infections,[223] or on the incidence of CMV disease and CMV-related mortality – at least when ganciclovir is given either at engraftment or for CMV pp65 antigenemia.[224] Others claim the contrary, with a 20% survival advantage one year from transplant, provided that acyclovir is given intravenously in high doses (500 mg/m^2 three times a day) 5 days before transplant to 30 days after transplant, followed by 800 mg given orally four times a day for 6 more months.[225] There is also some dissent about general prophylaxis for HSC transplant recipients, since restricting the drug to treating active infection would prove more cost-effective,[226] and many centers administer it to every patient no matter what their serological status. Restricting prophylaxis to only those who are seropositive would clearly be justified, as might the application of a more stringent policy, such as using a titer higher than 10 000 as a threshold to institute therapy. Few clinicians would be happy nowadays to await infection before acting, since this would be seen as leading to unnecessary suffering, especially since acyclovir has so few side-effects.

It has also been suggested that herpes simplex infection might account for over 90% of episodes of otherwise unexplained persistent fever.[227] The role that herpes plays in causing fever seems to be clear, since the number of non-fungal oral infections was reduced and the onset of fever was delayed by the use of acyclovir prophylaxis, although the duration of fever, use of antibacterial treatment, occurrence of bacteremia, and need for systemic antifungal therapy were not affected.[228] An earlier study showed that oral prophylaxis was associated with a reduction of all microbiologically defined infections, although the drug was only given during remission-induction therapy.[229]

Cytomegalovirus

Acyclovir given intravenously in high doses has been advocated as prophylaxis, but the issue is still controversial. A survey conducted by the European Group for Blood and Marrow Transplantation of 70 centers in 20 countries showed that prophylaxis was used in 59 centers (84%), with high doses of acyclovir being employed in 42 centers and ganciclovir in only 7.[230] Fifty four (77%) of the 70 centers who responded to the survey used prophylaxis. However, therapy was started early by 53 centers (76%), mostly on the basis of detection of viremia or CMV antigen in the blood, with CMV pneumonia being treated by using a combination of ganciclovir and intravenous immunoglobulin in 64 (91%) centers. Prophylactic therapy with ganciclovir is generally given from the time of engraftment up to 3–4 months post-transplantation to all patients at risk of CMV disease, whilst the pre-emptive approach is reserved for those with evident CMV infection. Each strategy has advantages and disadvantages, and there is no evidence for the superiority of one over the other, since the overall survival is the same and the incidence of death from CMV disease is similar.[231]

Fortunately, laboratories are now equipped with the means of detecting active CMV infection before disease becomes apparent, thereby allowing ganciclovir to be given pre-emptively, which has significantly decreased the incidence of disease and mortality following allogeneic HSC transplantation.[232] There are several assays available for quantifying human CMV in the blood of immunocompromised patients, providing the only reliable indication of the degree of dissemination of CMV infection. These tests all detect CMV in peripheral blood leukocytes by culture, pp65 antigenemia, or quantitative PCR. The threshold values above which CMV-related clinical symptoms are likely to appear have been estimated to be 10 or more for viremia, 100 for antigenemia and 1000 genome equivalents respectively.[233] However, as with all diagnostic tests, each test differs in its ability to predict a positive or negative risk of developing CMV disease.[234] Moreover, the underlying prevalence of CMV disease will differ from one study to the next, depending upon

the risk factors present and the degree of bias in selecting the population. For instance, T-cell-depleted stem cell grafts result in less GVHD, which, in turn, lowers the risk of CMV disease. Each strategy has its strengths and weaknesses, and there is no evidence that the overall survival differs or that the incidence of death from CMV disease is different.[235]

Does antiviral prophylaxis have any side-effects?

Acyclovir has proven remarkably safe with resistance occurring rarely. In contrast, routine use of ganciclovir is considered too toxic to be justified for prophylaxis, except in very high-risk patients, since the risk of harm is considered to outweigh the perceived benefit, mainly because of persistent neutropenia.[87]

Should antiviral prophylaxis be used?

There is more evidence in favor of giving acyclovir as prophylaxis against herpes simplex infection than there is for waiting until infection develops to institute therapy. With CMV, quite the opposite is true. Patients at risk should be monitored for reactivation, which, when it occurs, should provide the trigger for starting treatment pre-emptively with ganciclovir.

CONCLUSIONS

Since not all neutropenic patients are the same, and some risk factors are already known, perhaps it is now time to apply this knowledge prospectively. For instance, we know that patients given selective oral antimicrobial prophylaxis who develop mucositis and bacteremia due to Gram-positive cocci and who are colonized with *Candida* are at higher risk of candidiasis than are other patients. We also know that cytotoxic regimens prone to induce damage to the gut mucosa also place the patient at greater risk for developing the same disease. Hence, treatment with cytarabine, colonization with *C. albicans*, and prophylaxis with a fluoroquinolone could be used to select candidates for fluconazole or itraconazole prophylaxis. On the other hand, there seems no point in attempting prophylaxis against Gram-negative infection when neutropenia is likely to be shorter than 7 days or neutrophils are unlikely to drop below 0.5×10^9/l and mucositis is likely to be mild or absent, since co-trimoxazole and the fluoroquinolones both require at least a week before the bacilli are effectively suppressed.[235–237] Similarly, seronegativity for herpes simplex should be used to preclude acyclovir prophylaxis, whilst allogeneic HSC transplant recipients are at greater risk of aspergillosis if they have been given methotrexate for prophylaxis against GVHD and have experienced other nosocomial infections before the diagnosis of pneumonia.[238] Prolonged neutropenia is also a major risk factor for aspergillosis.[239]

From being as much a matter of faith as science, chemoprophylaxis is slowly evolving to a more rationale basis for its use as our understanding of the prognostic factors for infection during neutropenia becomes more comprehensive and we start to apply the tools at our disposal to identify those most at risk. The principles of evidence-based medicine are now being adopted more readily to help us move from conviction to fact. Equally important, the Hippocratic principle of at least doing no harm if one cannot do any good has acquired new life as we embrace the two sides of chemoprophylaxis – namely a drug may still be effective, but not good enough to outweigh the toxicities. Also, we now accept the need to have a better estimate of the prevalence of an infectious disease in our own particular patient group and to decide on the size of risk reduction that we consider important before deciding on whether to act on the evidence. The costs of implementing prophylaxis or not also have to be considered in the broadest sense, since effective drugs tend also to be expensive and should not be squandered, whilst losing a patient because of parsimony is usually a false economy, winning only

opprobrium. Equally, these decisions cannot be taken alone or in isolation, since they need to involve laboratories, pharmacists, and nurses, as well as clinical managers, more directly in decision making and in melding the evidence with experience to achieve optimum results.

REFERENCES

1. Bodey GP, Buckley M, Sathe YS, Freirich EJ, Quantitative relationships between circulating leucocytes and infection in patients with acute leukaemia. *Ann Intern Med* 1966; **64:** 328–40.
2. Wardley AM, Jayson GC, Swindell R et al, Prospective evaluation of oral mucositis in patients receiving myeloablative conditioning regimens and haemopoietic progenitor rescue. *Br J Haematol* 2000; **110:** 292–9.
3. Epstein JB, Schubert MM, Oral mucositis in myelosuppressive cancer therapy. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 1999; **88:** 273–6.
4. Blijlevens NM, Donnelly JP, De Pauw BE, Mucosal barrier injury: biology, pathology, clinical counterparts and consequences of intensive treatment for haematological malignancy: an overview. *Bone Marrow Transplant* 2000; **25:** 1269–78.
5. Roth RR, James WD, Microbial ecology of the skin. *Ann Rev Microbiol* 1988; **42:** 441–64.
6. Frandsen EVG, Pedrazzoli V, Kilian M, Ecology of viridans streptococci in the oral cavity and pharynx. *Oral Microbiol Immunol* 1991; **6:** 129–33.
7. Heimdahl A, Nord CE, Colonization of the oropharynx with pathogenic microorganisms – a potential risk factor for infection in compromised patients. *Chemioterapia* 1985; **4:** 186–91.
8. Elting LS, Bodey GP, Keefe BH, Septicemia and shock syndrome due to viridans streptococci: a case-control study of predisposing factors. *Clin Infect Dis* 1992; **14:** 1201–7.
9. Guiot HF, Fibbe WE, van 't Wout JW, Risk factors for fungal infection in patients with malignant hematologic disorders: implications for empirical therapy and prophylaxis. *Clin Infect Dis* 1994; **18:** 525–32.
10. Van der Waaij D, The ecology of the human intestine and its consequences for overgrowth by pathogens such as *Clostridium difficile*. *Ann Rev Microbiol* 1989; **43:** 69–87.
11. Vollaard EJ, Clasener HAL, Colonization resistance. *Antimicrobial Agents Chemother* 1994; **38:** 409–14.
12. McGuire DB, Altomonte V, Peterson DE et al, Patterns of mucositis and pain in patients receiving preparative chemotherapy and bone marrow transplantation. *Oncol Nurs Forum* 1993; **20:** 1493–502.
13. Sable CA, Donowitz GR, Infections in bone marrow transplant recipients. *Clin Infect Dis* 1994; **18:** 273–81.
14. Sonis ST, Mucositis as a biological process: a new hypothesis for the development of chemotherapy-induced stomatotoxicity. *Oral Oncol* 1998; **34:** 39–43.
15. Sonis ST, Peterson RL, Edwards LJ et al, Defining mechanisms of action of interleukin-11 on the progression of radiation-induced oral mucositis in hamsters. *Oral Oncol* 2000; **36:** 373–81.
16. Donnelly JP, Dompeling EC, Meis JF, de Pauw BE, Bacteremia due to oral viridans streptococci in neutropenic patients with cancer: cytostatics are a more important risk factor than antibacterial prophylaxis. *Clin Infect Dis* 1995; **20:** 469–70.
17. Bochud PY, Calandra T, Francioli P, Bacteremia due to viridans streptococci in neutropenic patients: a review. *Am J Med* 1994; **97:** 256–64.
18. Weers-Pothoff G, Nováková IRO, Donnelly JP, Muytjens HL, Bacteraemia caused by *Stomatococcus mucilaginosus* in a granulocytopenic patient with acute lymphocytic leukaemia. *Neth J Med* 1989; **35:** 143–6.
19. McWhinney PHM, Kibbler CC, Gillespie SH et al, *Stomatococcus mucilaginosus*: an emerging pathogen in neutropenic patients. *Clin Infect Dis* 1992; **14:** 641–6.
20. Bilgrami S, Bergstrom SK, Peterson DE et al, *Capnocytophaga* bacteremia in a patient with Hodgkin's disease following bone marrow transplantation: case report and review. *Clin Infect Dis* 1992; **14:** 1045–9.
21. Baquero F, Fernandez J, Dronda F et al, Capnophilic and anaerobic bacteremia in neutropenic patients: an oral source. *Rev Infect Dis* 1990; **12**(Suppl 2): S157–60.
22. Shenep JL, Combination and single-agent empirical antibacterial therapy for febrile cancer patients with neutropenia and mucositis. *NCI Monographs* 1990; **990:** 117–22.

23. Reig M, Baquero F, Garcia-Campello M, Loza E, *Leptotrichia buccalis* bacteremia in neutropenic children. *J Clin Microbiol* 1985; **22:** 320–1.
24. Vidal AM, Sarria JC, Kimbrough RC 3rd, Keung YK, Anaerobic bacteremia in a neutropenic patient with oral mucositis. *Am J Med Sci* 2000; **319:** 189–90.
25. Wade JC Schimpff SC, Newman KA, Wiernik PH, *Staphylococcus epidermidis*: an increasing cause of infection in patients with granulocytopenia. *Ann Intern Med* 1982; **97:** 503–8.
26. Seto BG, Kim M, Wolinsky L et al, Oral mucositis in patients undergoing bone marrow transplantation. *Oral Surg Oral Med Oral Pathol* 1985; **60:** 493–7.
27. Beattie G, Whelan J, Cassidy J et al, Herpes simplex virus, *Candida albicans* and mouth ulcers in neutropenic patients with non-haematological malignancy. *Cancer Chemother Pharmacol* 1989; **25:** 75–6.
28. van der Lelie H, van Ketel RJ, von dem Borne AE et al, Incidence and clinical epidemiology of streptococcal septicemia during treatment of acute myeloid leukemia. *Scand J Infect Dis* 1991; **23:** 163–8.
29. Dompeling EC, Donnelly JP, Raemaekers JM, De Pauw BE, Pre-emptive administration of corticosteroids prevents the development of ARDS associated with *Streptococcus mitis* bacteremia following chemotherapy with high-dose cytarabine. *Ann Hematol* 1994; **69:** 69–71.
30. Bone RC, Gram-positive organisms and sepsis. *Arch Intern Med* 1994; **154:** 26–34.
31. Walker RI, Brook I, Costerton JW et al, Possible association of mucous blanket integrity with postirradiation colonization resistance. *Radiat Res* 1985; **104:** 346–57.
32. Bow EJ, Loewen R, Cheang MS, Schacter B, Invasive fungal disease in adults undergoing remission-induction therapy for acute myeloid leukemia: the pathogenetic role of the antileukemic regimen. *Clin Infect Dis* 1995; **21:** 361–9.
33. Bow EJ, Loewen R, Cheang MS et al, Cytotoxic therapy-induced D-xylose malabsorption and invasive infection during remission-induction therapy for acute myeloid leukemia in adults. *J Clin Oncol* 1997; **15:** 2254–61.
34. Fegan C, Poynton CH, Whittaker JA, The gut mucosal barrier in bone marrow transplantation. *Bone Marrow Transplant* 1990; **5:** 373–7.
35. Johansson JE, Ekman T, Gastro-intestinal toxicity related to bone marrow transplantation: disruption of the intestinal barrier precedes clinical findings. *Bone Marrow Transplant* 1997; **19:** 921–5.
36. Keefe DM, Cummins AG, Dale BM et al, Effect of high-dose chemotherapy on intestinal permeability in humans. *Clin Sci* 1997; **92:** 385–9.
37. Tancrede CH, Andremont AO, Bacterial translocation and Gram-negative bacteremia in patients with hematological malignancies. *J Infect Dis* 1985; **152:** 99–103.
38. Brown NM, White LO, Blundell EL et al, Absorption of oral ofloxacin after cytotoxic chemotherapy for haematological malignancy. *J Antimicrob Chemother* 1993; **32:** 117–22.
39. Johnson EJ, MacGowan AP, Potter MN et al, Reduced absorption of oral ciprofloxacin after chemotherapy for haematological malignancy. *J Antimicrob Chemother* 1990; **25:** 837–42.
40. Prentice AG, Warnock DW, Johnson SAN et al, Multiple dose pharmacokinetics of an oral solution of itraconazole in patients receiving chemotherapy for acute myeloid leukaemia. *J Antimicrob Chemother* 1995; **36:** 657–63.
41. Prentice AG, Warnock DW, Johnson SAN et al, Multiple dose pharmacokinetics of an oral solution of itraconazole in autologous bone marrow transplant recipients. *J Antimicrob Chemother* 1994; **34:** 247–52.
42. Bodet III CA, Jorgensen JH, Drutz DJ, Antibacterial activities of antineoplastic agents. *Antimicrob Agents Chemother* 1985; **28:** 437–9.
43. Neuman M, The antimicrobial activity of non-antibiotics – interactions with antibiotics. *Acta Pathologica, Microbiologica et Immunologica Scandinavia* 1992; **100**(Suppl 30): 15–23.
44. Jacobs JY, Michel J, Sacks T, Bactericidal effect of combinations of antimicrobial drugs and antineoplastic antibiotics against *Staphylococcus aureus*. *Antimicrob Agents Chemother* 1979; **15:** 580–6.
45. Michel J, Jacobs JY, Sacks T, Bactericidal effect of combinations of antimicrobial drugs and antineoplastic antibiotics against Gram-negative bacilli. *Antimicrob Agents Chemother* 1979; **16:** 761–6.
46. Moody MR, Morris MJ, Young VM et al, Effect of two cancer chemotherapeutic agents on the antibacterial activity of three antimicrobial agents. *Antimicrob Agents Chemother* 1978; **14:** 737–42.

47. Bergström P, Grankvist K, Henriksson R, Interaction between antibiotics and antineoplastic drugs on antibacterial activity in vitro: estramustine phosphate sensitizes pneumococci to amikacin. *Int J Oncol* 1994; **4:** 43–9.
48. Welling GW, Groen G, Inactivation of aztreonam by faecal supernatants of healthy volunteers as determined by HPLC. *J Antimicrob Chemother* 1989; **24:** 805–10.
49. Welling GW, Slootmaker-vandermeulen C, Jansen GJ, Inactivation of imipenem by faecal fractions from human volunteers and the effect of clavulanate and cilastatin. *J Antimicrob Chemother* 1993; **31:** 617–19.
50. Peters WG, Willemze R, Colly LP, Guiot HFL, Side effects of intermediate- and high-dose cytosine arabinoside in the treatment of refractory or relapsed acute leukaemia and non-Hodgkin's lymphoma. *Neth J Med* 1987; **30:** 64–74.
51. Guiot HF, Biemond J, Klasen E et al, Protein loss during acute graft-versus-host disease: diagnostic and clinical significance. *Eur J Haematol* 1987; **38:** 187–96.
52. Callum JL, Brandwein JM, Sutcliffe SB et al, Influence of total body irradiation on infections after autologous bone marrow transplantation. *Bone Marrow Transplant* 1991; **8:** 245–51.
53. Donnelly JP, Selective decontamination of the digestive tract and its role in antimicrobial prophylaxis. *J Antimicrob Chemother* 1993; **31:** 813–29.
54. Wilkinson FH, Kerr KG, Bottled water as a source of multi-resistant *Stenotrophomonas* and *Pseudomonas* species for neutropenic patients. *Eur J Cancer Care (Engl)* 1998; **7:** 12–14.
55. Hoepelman IM, *Legionella* epidemic in the Netherlands. *Ned Tijdschr Geneeskd* 1999; **143:** 1192–6 (in Dutch).
56. Aisner J, Schimpff SC, Bennett JE et al, *Aspergillus* infections in cancer patients. Association with fireproofing materials in a new hospital. *JAMA* 1976; **235:** 411–12.
57. Bui AM, Germaud P, Normand De La Tranchade M, Touranchet A, Silage and allergic bronchopulmonary aspergillosis. *Arch Mal Prof Med Trav* 1994; **55:** 335–7.
58. Ansorg R, van den Boom R, von Heinegg EH, Rath PM, Association between incidence of *Aspergillus* antigenemia and exposure to construction works at a hospital site. *Zentralbl Bakteriol* 1996; **284:** 146–52.
59. Dewhurst AG, Cooper MJ, Khan SM et al, Invasive aspergillosis in immunosuppressed patients: potential hazard of hospital building work. *BMJ* 1990; **301:** 802–4.
60. Streifel AJ, Lauer JL, Vesley D et al, *Aspergillus fumigatus* and other thermotolerant fungi generated by hospital building demolition. *Appl Environ Microbiol* 1983; **46:** 375–8.
61. Hopkins CC, Weber DJ, Rubin RH, Invasive *Aspergillus* infection: possible non-ward common source within the hospital environment. *J Hosp Infect* 1989; **13:** 19–25.
62. Korpi A, Pasanen AL, Pasanen P, Kalliokoski P, Microbial growth and metabolism in house dust. *Int Biodeterioration and Biodegradation* 1997; **40:** 19–27.
63. Streifel AJ, Stevens PP, Rhame FS, In-hospital source of airborne *Penicillium* species spores. *J Clin Microbiol* 1987; **25:** 1–4.
64. Marsh PB, Millner PD, Kla JM, A guide to the recent literature on aspergillosis as caused by *Aspergillus fumigatus*, a fungus frequently found in self-heating organic matter. *Mycopathologia* 1979; **69:** 67–81.
65. Reiss J, Molds in containers with biological wastes. *Microbiol Res* 1995; **150:** 93–8.
66. Nolard N, Links between risks of aspergillosis and environmental contamination. Review of the literature. *Pathol Biol Paris* 1994; **42**(7): 706–10 (in French).
67. Beaumont F, Kauffman HF, van der Mark TH et al, Volumetric aerobiological survey of conidial fungi in the North-East Netherlands. I. Seasonal patterns and the influence of metereological variables. *Allergy* 1985; **40:** 173–80.
68. Lappalainen S, Nikulin M, Berg S et al, *Fusarium* toxins and fungi associated with handling of grain on eight Finnish farms. *Atmos Environ* 1996; **30:** 3059–65.
69. Lai KK, A cancer patient with central venous catheter-related sepsis caused by *Tsukamurella-paurometabolum* (*Gordona-aurantiaca*). *Clin Infect Dis* 1993; **17:** 285–7.
70. Hughes WT, Armstrong D, Bodey GP et al, 1997 guidelines for the use of antimicrobial agents in neutropenic patients with unexplained fever. Infectious Diseases Society of America. *Clin Infect Dis* 1997; **25:** 551–73.
71. Pizzo PA, Current concepts: fever in immunocompromised patients. *N Engl J Med* 1999; **341:** 893–900.

72. Goa KL, Barradell LB, Fluconazole: an update of its pharmacodynamic and pharmacokinetic properties and therapeutic use in major superficial and systemic mycoses in immunocompromised patients. *Drugs* 1995; **50:** 658–90.
73. Voss A, de Pauw BE, High-dose fluconazole therapy in patients with severe fungal infections. *Eur J Clin Microbiol Infect Dis* 1999; **18:** 165–74.
74. Anaissie E, Bodey GP, Kantarjian H et al, Fluconazole therapy for chronic disseminated candidiasis in patients with leukemia and prior amphotericin B therapy. *Am J Med* 1991; **91:** 142–50.
75. Akova M, Akalin HE, Uzun O et al, Efficacy of fluconazole in the treatment of upper gastrointestinal candidiasis in neutropenic patients with cancer – factors influencing the outcome. *Clin Infect Dis* 1994; **18:** 298–304.
76. Paterson DL, Singh N, Invasive aspergillosis in transplant recipients. *Medicine (Baltimore)* 1999; **78:** 123–38.
77. Warnock DW, Fungal infections in neutropenia: current problems and chemotherapeutic control. *J Antimicrob Chemother* 1998; **41**(Suppl D): 95–105.
78. Severens JL, Donnelly JP, Meis J et al, Two strategies for managing invasive aspergillosis: a decision analysis. *Clin Infect Dis* 1997; **25:** 1148–54.
79. De Pauw BE, Practical modalities for prevention of fungal infections in cancer patients. *Eur J Clin Microbiol Infect Dis* 1997; **16:** 32–41.
80. Warnock DW, Fungal complications of transplantation: diagnosis, treatment and prevention. *J Antimicrob Chemother* 1995; **36:** 73–90.
81. Winston DJ, Prophylaxis and treatment of infection in the bone marrow transplant recipient. *Curr Clin Top Infect Dis* 1993; **13:** 293–321.
82. Verweij PE, Donnelly JP, De Pauw BE, Meis JFGM, Prospects for the early diagnosis of invasive aspergillosis in the immunocompromised host. *Rev Med Microbiol* 1996; **7:** 105–13.
83. Darville JM, Ley BE, Roome AP, Foot AB, Acyclovir-resistant herpes simplex virus infections in a bone marrow transplant population. *Bone Marrow Transplant* 1998; **22:** 587–9.
84. Engel JP, Englund JA, Fletcher CV, Hill EL, Treatment of resistant herpes simplex virus with continuous-infusion acyclovir. *JAMA* 1990; **263:** 1662–4.
85. Snoeck R, Andrei G, Gerard M et al, Successful treatment of progressive mucocutaneous infection due to acyclovir- and foscarnet-resistant herpes simplex virus with (*S*)-1-(3-hydroxy-2-phosphonylmethoxypropyl)cytosine (HPMPC). *Clin Infect Dis* 1994; **18:** 570–8.
86. Tsinontides AC, Bechtel TP, Cytomegalovirus prophylaxis and treatment following bone marrow transplantation. *Ann Pharmacother* 1996; **30:** 1277–90.
87. Wood MJ, Viral infections in neutropenia – current problems and chemotherapeutic control. *J Antimicrob Chemother* 1998; **41**(Suppl D): 81–93.
88. Schimpff SC, Infection prevention during profound granulocytopenia: new approaches to alimentary canal microbial suppression. *Ann Intern Med* 1980; **93:** 358–61.
89. Van Der Waaij D, The colonization resistance of the digestive tract of man and animals. *Zentralblatt für Bakteriologie* 1979; Suppl 7: 155–61.
90. Enno A, Catovsky D, Darrell J et al, Co-trimoxazole for prevention of infection in acute leukaemia. *Lancet* 1978; **ii:** 395–7.
91. Guiot HF, Furth R, Partial antibiotic decontamination. *BMJ* 1977; **i:** 798–800.
92. Bender JF, Schimpff SC, Young VM et al, Role of vancomycin as a component of oral nonabsorbable antibiotics for microbial suppression in leukemic patient. *Antimicrob Agents Chemother* 1979; **15:** 455–60.
93. Levi JA, Vincent PC, Jennis F et al, Prophylactic oral antibiotics in the management of acute leukaemia. *Med J Austr* 1973; **1:** 1025–9.
94. Van Der Waaij D, Berghuis-De Vries JM, Lekkerkerk-Van Der Wees JEC, Colonization resistance of the digestive tract of individual mice. *J Hygiene* 1971; **69:** 404–11.
95. Hughes WT, Kuhn S, Chaudhary S et al, Successful chemoprophylaxis for *Pneumocystis carinii* pneumonitis. *N Engl J Med* 1977; **297:** 1419–26.
96. The EORTC International Antimicrobial Therapy Project Group, Trimethoprim–sulfamethoxazole in the prevention of infection in neutropenic patients. *J Infect Dis* 1984; **150:** 372–9.
97. Gurwith MJ, Brunton JL, Lank BA et al, A prospective controlled investigation of prophylactic trimethoprim–sulfamethoxazole in hospitalized granulocytopenic patients. *Am J Med*

1979; **66:** 248–56.

98. Kauffman CA, Liepman MK, Bergman AG, Mioduszewski J, Trimethoprim–sulphamethoxazole prophylaxis in neutropenic patients: reduction of infections and effect on bacterial and fungal flora. *Am J Med* 1983; **74:** 599–607.
99. Henry SA, Armstrong D, Kempin S et al, Oral trimethoprim/sulfamethoxazole in attempt to prevent infection after induction chemotherapy for acute leukaemia. *Am J Med* 1984; **77:** 663–6.
100. Dekker A, Rozenberg-Arska M, Sixma JJ, Verhoef J, Prevention of infection by trimethoprim–sulfamethoxazole plus amphotericin B in patients with acute nonlymphocytic leukaemia. *Ann Intern Med* 1981; **95:** 555–9.
101. Weiser B, Lange M, Fialk MA et al, Prophylactic trimethoprim–sulfamethoxazole during consolidation chemotherapy for acute leukemia: a controlled trial. *Ann Intern Med* 1981; **95:** 436–8.
102. Gualtieri RJ, Donowitz GR, Kaiser DL et al, Double-blind randomized study of prophylactic trimethoprim/sulfamethoxazole in granulocytopenic patients with hematologic malignancies. *Am J Med* 1983; **74:** 934–40.
103. Starke ID, Donnelly JP, Catovsky D et al, Cotrimoxazole alone for the prevention of bacterial infection in patients with acute leukaemia. *Lancet* 1982; **i:** 5–6.
104. Wade JC, Schimpff SC, Hargadon MT et al, A comparison of trimethoprim–sulfamethoxazole plus nystatin with gentamicin plus nystatin in the prevention of infections in acute leukemia. *N Engl J Med* 1981; **304:** 1057–62.
105. Bow EJ, Louie TJ, Riben PD et al, Randomized controlled trial comparing trimethoprim/sulfamethoxazole and trimethoprim for infection prophylaxis in hospitalized granulocytopenic patients. *Am J Med* 1984; **76:** 223–33.
106. Kurrle E, Dekker AW, Gaus W et al, Prevention of infection in acute leukaemia: a prospective randomized study of the efficacy of two different drug regimens for antimicrobial prophylaxis. *Infection* 1986; **14:** 226–32.
107. Malarme M, Meunier-Carpentier F, Klastersky J, Vancomycin plus gentamicin and cotrimoxazole for prevention of infections in neutropenic cancer patients (a comparative, placebo-controlled pilot study). *Eur J Cancer Clin Oncol* 1981; **17:** 1315–22.
108. Rozenberg-Arska M, Dekker A, Verhoef J, Colistin and trimethoprim–sulfamethoxazole for the prevention of infection in patients with acute nonlymphocytic leukaemia: decrease in the emergence of resistant bacteria. *Infection* 1983; **11:** 167–9.
109. Watson JG, Jameson B, Powles RL et al, Co-trimoxazole versus non-absorbable antibiotics in acute leukaemia. *Lancet* 1982; **i:** 6–7.
110. Wilson JM, Guiney DG, Failure of oral trimethoprim–sulfamethoxazole prophylaxis in acute leukemia: isolation of resistant plasmids from strains of enterobacteriaciae causing bacteremia. *N Eng J Med* 1982; **306:** 16–20.
111. Karp JE, Merz WG, Hendriksen C et al, Oral norfloxacin for prevention of Gram-negative bacterial infections in patients with acute leukemia and granulocytopenia: a randomized, double-blind, placebo-controlled trial. *Ann Intern Med* 1987; **106:** 1–7.
112. Rozenberg-Arska M, Dekker AW, Prevention of bacterial and fungal infections in granulocytopenic patients. In: *Antimicrobial Agents Annual* (Verhoef P, ed). Amsterdam: Elsevier, 1987: 471–81.
113. Arning M, Wolf HH, Aul C et al, Infection prophylaxis in neutropenic patients with acute leukaemia – a randomized, comparative study with ofloxacin, ciprofloxacin and cotrimoxazole/colistin. *J Antimicrob Chemother* 1990; **26**(Suppl D): 137–42.
114. D'Antonio D, Iacone A, Fioritoni G et al, Comparison of norfloxacin and pefloxacin in the prophylaxis of bacterial infection in neutropenic cancer patients. *Drugs Exp Clin Res* 1992; **18:** 141–6.
115. Meunier F, Prevention of infections in neutropenic patients with pefloxacin. *J Antimicrob Chemother* 1990; **26**(Suppl B): 69–73.
116. De Pauw BE, De Witte T, Raemaekers JMM et al, Impact of ciprofloxacin and co-trimoxazole on bone marrow growth as measured by CFU-GM and BFU-E assays. In: *Ciprofloxacin. Microbiology–Pharmacokinetics, Clinical Experience – Proceedings of 6th Mediterranean Congress of Chemotherapy, Taormina, Italy*, 1988: 94–7.
117. King A, Phillips I, The comparative in-vitro activity of pefloxacin. *J Antimicrob Chemother* 1986; **17**(Suppl B): 1–10.
118. Reeves DS, The effect of quinolone antibacterials on the gastrointestinal flora compared with that of other antibacterials. *J Antimicrob Chemother* 1986 **18**(Suppl D): 89–102.

119. Dekker AW, Rozenberg-Arska M, Verhoef J, Infection prophylaxis in acute leukemia: a comparison of ciprofloxacin with trimethoprim–sulfamethoxazole and colistin. *Ann Intern Med* 1987; **106:** 7–12.
120. Donnelly JP, Maschmeyer G, Daenen S, Selective oral antimicrobial prophylaxis for the prevention of infection in acute leukaemia – ciprofloxacin versus co-trimoxazole plus colistin. The EORTC–Gnotobiotic Project Group. *Eur J Cancer* 1992; **28:** 873–8.
121. Warren RE, Wimperis JZ, Baglin TP et al, Prevention of infection by ciprofloxacin in neutropenia. *J Antimicrob Chemother* 1990; **26**(Suppl F): 109–23.
122. Bow EJ, Louie TJ, Emerging role of quinolones in the prevention of Gram-negative bacteremia in neutropenia cancer patients and in the treatment of enteric infections. *Clin Invest Med* 1989; **12:** 61–8.
123. Del Favero A, Menichetti F, The new fluorinated quinolones for antimicrobial prophylaxis in neutropenic cancer patients. *Eur J Cancer* 1993; **29A:** 52–6.
124. The GIMEMA Infection Program, Gruppo Italiano Malattie Ematologiche Maligne dell'Adulto, Prevention of bacterial infection in neutropenic patients with hematologic malignancies. A randomized, multicenter trial comparing norfloxacin with ciprofloxacin. *Ann Intern Med* 1991; **115:** 7–12.
125. Brodsky AL, Minissale CJ, Melero MJ, Avalos JCS, Prophylactic use of fluoroquinolones in neutropenic patients. *Medicina – Buenos Aires* 1993; **53:** 401–7.
126. D'Antonio D, Piccolomini R, Iacone A et al, Comparison of ciprofloxacin, ofloxacin and pefloxacin for the prevention of the bacterial infection in neutropenic patients with haematological malignancies. *J Antimicrob Chemother* 1994; **33:** 837–44.
127. Jansen J, Cromer M, Akard L et al, Infection prevention in severely myelosuppressed patients – a comparison between ciprofloxacin and a regimen of selective antibiotic modulation of the intestinal flora. *Am J Med* 1994; **96:** 335–41.
128. Cruciani M, Rampazzo R, Malena M et al, Prophylaxis with fluoroquinolones for bacterial infections in neutropenic patients: a meta-analysis. *Clin Infect Dis* 1996; **23:** 795–805.
129. Guiot HF, van der Meer JW, van den Broek PJ et al, Prevention of viridans-group streptococcal septicemia in oncohematologic patients: a controlled comparative study on the effect of penicillin G and cotrimoxazole. *Ann Hematol* 1992; **64:** 260–5.
130. Zinner SH, Calandra T, Meunier F et al, Reduction of fever and streptococcal bacteremia in granulocytopenic patients with cancer – a trial of oral penicillin V or placebo combined with pefloxacin. *JAMA* 1994; **272:** 1183–9.
131. Broun ER, Wheat JL, Kneebone PH et al, Randomized trial of the addition of Gram-positive prophylaxis to standard antimicrobial prophylaxis for patients undergoing autologous bone marrow transplantation. *Antimicrob Agents Chemother* 1994; **38:** 576–9.
132. Gluckman E, Roudet C, Hirsch I et al, Prophylaxis of bacterial infections after bone marrow transplantation. A randomized prospective study comparing oral broad-spectrum nonabsorbable antibiotics (vancomycin–tobramycin–colistin) to absorbable antibiotics (ofloxacin–amoxicillin). *Chemotherapy* 1991; **1:** 33–8.
133. Fanci R, Leoni F, Bosi A et al, Chemoprophylaxis of bacterial infections in granulocytopenic patients with ciprofloxacin vs. ciprofloxacin plus amoxicillin. *J Chemother* 1993; **5:** 119–23.
134. Archimbaud E, Guyotat D, Maupas J et al, Pefloxacin and vancomycin vs. gentamicin, colistin sulphate and vancomycin for prevention of infections in granulocytopenic patients: a randomised double-blind study. *Eur J Cancer* 1991; **27:** 174–8.
135. Kern WV, Hay B, Kern P et al, A randomized trial of roxithromycin in patients with acute leukemia and bone marrow transplant recipients receiving fluoroquinolone prophylaxis. *Antimicrob Agents Chemother* 1994; **38:** 465–72.
136. Lim SH, Smith MP, Machin SJ, Goldstone AH, A prospective randomized study of prophylactic teicoplanin to prevent early Hickman catheter-related sepsis in patients receiving intensive chemotherapy for haematological malignancies. *Eur J Haematol Suppl* 1993; **54:** 10–13.
137. Vassilomanolakis M, Plataniotis G, Koumakis G et al, Central venous catheter-related infections after bone marrow transplantation in patients

with malignancies: a prospective study with short-course vancomycin prophylaxis. *Bone Marrow Transplant* 1995; **15:** 77–80.
138. Attal M, Schlaifer D, Rubie H et al, Prevention of Gram-positive infections after bone marrow transplantation by systemic vancomycin: a prospective, randomized trial. *J Clin Oncol* 1991; **9:** 865–70.
139. Engelhard D, Elishoov H, Strauss N et al, Nosocomial coagulase negative staphylococcal infections in bone marrow transplantation recipients with central vein catheter: a 5 year prospective study. *Transplantation* 1996; **61:** 430–4.
140. Dompeling EC, Donnelly JP, Deresinski SC et al, Early identification of neutropenic patients at risk of Gram-positive bacteraemia and the impact of empirical administration of vancomycin. *Eur J Cancer* 1996; **32A:** 1332–9.
141. Edmond MB, Wenzel RP, Pasculle AW, Vancomycin-resistant *Staphylococcus aureus*: perspectives on measures needed for control. *Ann Intern Med* 1996; **124:** 329–34.
142. Recommendations of the Hospital Infection Control Practices Advisory Committee (HICPAC), Recommendations for preventing the spread of vancomycin resistance. *Morb Mortal Wkly Rep* 1995; **44**(Rr-12): 1–13.
143. Kentos A, Struelens MJ, Thys JP, Antibiotic-lock technique for the treatment of central venous catheter infections. *Clin Infect Dis* 1996; **23:** 418–19.
144. Carratala J, Niubo J, Fernandez-Sevilla A et al, Randomized, double-blind trial of an antibiotic-lock technique for prevention of Gram-positive central venous catheter-related infection in neutropenic patients with cancer. *Antimicrob Agents Chemother* 1999; **43:** 2200–4.
145. Nouwen JL, van Belkum A, de Marie S et al, Clonal expansion of *Staphylococcus epidermidis* strains causing Hickman catheter-related infections in a hemato-oncologic department. *J Clin Microbiol* 1998; **36:** 2696–702.
146. Maki DG, Stolz SM, Wheeler S, Mermel LA, Prevention of central venous catheter-related bloodstream infection by use of an antiseptic-impregnated catheter. A randomized, controlled trial. *Ann Intern Med* 1997; **127:** 257–66.
147. Raad I, Darouiche R, Dupuis J et al, Central venous catheters coated with minocycline and rifampin for the prevention of catheter-related colonization and bloodstream infections. A randomized, double-blind trial. The Texas Medical Center Catheter Study Group. *Ann Intern Med* 1997; **127:** 267–74.
148. Kotilainen P, Nikoskelainen J, Huovinen P, Emergence of ciprofloxacin-resistant coagulase-negative staphylococcal skin flora in immunocompromised patients receiving ciprofloxacin. *J Infect Dis* 1990; **161:** 41–4.
149. Høiby N, Johansen HK, Ciprofloxacin in sweat and antibiotic resistance. *Lancet* 1995; **346:** 1235.
150. Høiby N, Jarløv JO, Kemp M et al, Excretion of ciprofloxacin in sweat and multiresistant *Staphylococcus epidermidis*. *Lancet* 1997; **349:** 167–9.
151. Hedin G, Hambraeus A, Multiply antibiotic-resistant *Staphylococcus epidermidis* in patients, staff and environment – a one-week survey in a bone marrow transplant unit. *J Hosp Infect* 1991; **17:** 95–106.
152. Carratala J, Fernandez Sevilla A, Tubau F et al, Emergence of quinolone-resistant *Escherichia coli* bacteremia in neutropenic patients with cancer who have received prophylactic norfloxacin. *Clin Infect Dis* 1995; **20:** 557–60.
153. Kern WV, Andriof E, Oethinger M et al, Emergence of fluoroquinolone-resistant *Escherichia coli* at a cancer center. *Antimicrob Agents Chemother* 1994; **38:** 681–7.
154. Cometta A, Calandra T, Bille J, Glauser MP, *Escherichia coli* resistant to fluoroquinolones in patients with cancer and neutropenia. *N Engl J Med* 1994; **330:** 1240–1.
155. Yeh SP, Hsueh EJ, Yu MS et al, Oral ciprofloxacin as antibacterial prophylaxis after allogeneic bone marrow transplantation: a reappraisal. *Bone Marrow Transplant* 1999; **24:** 1207–11.
156. Nord CE, Effect of quinolones on the human intestinal microflora. *Drugs* 1995; **49**(Suppl 2): 81–5.
157. Staib AH, Beermann D, Harder S et al, Absorption differences of ciprofloxacin along the human gastrointestinal tract determined using a remote-control drug delivery device (HF-capsule). *Am J Med* 1989; **87:** 66S–69S.
158. Giuliano M, Pantosti A, Gentile G et al, Effects on oral and intestinal microfloras of norfloxacin and pefloxacin for selective decontamination in bone marrow transplant patients. *Antimicrob Agents Chemother* 1989; **33:** 1709–13.

159. Schaberg DR, Dillon WI, Terpenning MS et al, Increasing resistance of enterococci to ciprofloxacin. *Antimicrob Agents Chemother* 1992; **36:** 2533–5.
160. Hillery SJ, Reisslevy EA, Increasing ciprofloxacin resistance in MRSA. *Med J Austr* 1993; **158:** 861.
161. Oppenheim BA, Hartley JW, Lee W, Burnie JP, Outbreak of coagulase-negative staphylococcus resistant to ciprofloxacin in a leukemia unit. *BMJ* 1989; **299:** 294–7.
162. Verhagen C, Stalpers LJ, De Pauw BE, Haanen C, Drug-induced skin reactions in patients with acute non-lymphocytic leukemia. *Eur J Haematol* 1987; **38:** 225–30.
163. Schey SA, Kay HEM, Myelosuppression complicating co-trimoxazole prophylaxis after bone marrow transplantation. *Br J Haematol* 1984; **56:** 179–80.
164. Bow EJ, Loewen R, Vaughan D, Reduced requirement for antibiotic therapy targeting Gram-negative organisms in febrile, neutropenic patients with cancer who are receiving antibacterial chemoprophylaxis with oral quinolones. *Clin Infect Dis* 1995; **20:** 907–12.
165. Kerr KG, The prophylaxis of bacterial infections in neutropenic patients. *J Antimicrob Chemother* 1999; **44:** 587–91.
166. Engels EA, Ellis CA, Supran SE et al, Early infection in bone marrow transplantation: quantitative study of clinical factors that affect risk. *Clin Infect Dis* 1999; **28:** 256–66.
167. Goodman JL, Winston DJ, Greenfield RA et al, A controlled trial of fluconazole to prevent fungal infections in patients undergoing bone marrow transplantation. *N Engl J Med* 1992; **326:** 845–51.
168. Slavin MA, Osborne B, Adams R et al, Efficacy and safety of fluconazole prophylaxis for fungal infections after marrow transplantation – a prospective, randomized, double-blind study. *J Infect Dis* 1995; **171:** 1545–52.
169. Winston DJ, Chandrasekar PH, Lazarus HM et al, Fluconazole prophylaxis of fungal infections in patients with acute leukemia. Results of a randomized placebo-controlled, double-blind, multicenter trial. *Ann Intern Med* 1993; **118:** 495–503.
170. Rotstein C, Bow EJ, Laverdiere M et al, Randomized placebo-controlled trial of fluconazole prophylaxis for neutropenic cancer patients: benefit based on purpose and intensity of cytotoxic therapy. The Canadian Fluconazole Prophylaxis Study Group. *Clin Infect Dis* 1999; **28:** 331–40.
171. Morgenstern GR, Prentice AG, Prentice HG et al, A randomized controlled trial of itraconazole versus fluconazole for the prevention of fungal infections in patients with haematological malignancies. UK Multicentre Antifungal Prophylaxis Study Group. *Br J Haematol* 1999; **105:** 901–11.
172. Ehninger G, Schuler HK, Sarnow E, Fluconazole in the prophylaxis of fungal infection after bone marrow transplantation. *Mycoses* 1996; **39:** 259–63.
173. Alangaden G, Chandrasekar PH, Bailey E et al, Antifungal prophylaxis with low-dose fluconazole during bone marrow transplantation. *Bone Marrow Transplant* 1994; **14:** 919–24.
174. Ellis ME, Clink H, Ernst P et al, Controlled study of fluconazole in the prevention of fungal infections in neutropenic patients with haematological malignancies and bone marrow transplant recipients. *Eur J Clin Microbiol Infect Dis* 1994; **13:** 3–11.
175. Akiyama H, Mori S, Tanikawa S et al, Fluconazole versus oral amphotericin-B in preventing fungal infection in chemotherapy-induced neutropenic patients with haematological malignancies. *Mycoses* 1993; **36:** 373–8.
176. Menichetti F, Delfavero A, Martino P et al, Preventing fungal infection in neutropenic patients with acute leukemia: fluconazole compared with oral amphotericin B. *Ann Intern Med* 1994; **120:** 913–18.
177. Gotzsche PC, Johansen HK, Meta analysis of prophylactic or empirical antifungal treatment versus placebo or no treatment in patients with cancer complicated by neutropenia. *BMJ* 1997; **314:** 1238–44.
178. Meis JF, Donnelly JP, Hoogkamp-Korstanje JA, De-Pauw BE, *Aspergillus fumigatus* pneumonia in neutropenic patients during therapy with fluconazole for infection due to *Candida* species. *Clin Infect Dis* 1993; **16:** 734–5.
179. Wald A, Leisenring W, van Burik JA, Bowden RA, Epidemiology of *Aspergillus* infections in a large cohort of patients undergoing bone marrow transplantation. *J Infect Dis* 1997; **175:** 1459–66.
180. Bodey G, Bueltmann B, Duguid W et al, Fungal

infections in cancer patients – an international autopsy survey. *Eur J Clin Microbiol Infect Dis* 1992; **11:** 99–109.
181. Denning DW, Marinus A, Cohen J et al, An EORTC multicentre prospective survey of invasive aspergillosis in haematological patients: diagnosis and therapeutic outcome. EORTC Invasive Fungal Infections Cooperative Group. *J Infect* 1998; **37:** 173–80.
182. Martino P, Girmenia C, Micozzi A et al, Prospective study of *Candida* colonization, use of empiric amphotericin B and development of invasive mycosis in neutropenic patients. *Eur J Clin Microbiol Infect Dis* 1994; **13:** 797–804.
183. Martino P, Girmenua C, Venditti M et al, *Candida* colonization and systemic infection in neutropenic patients. *Cancer* 1989; **64:** 2030–4.
184. De Pauw BE, Raemaekers JMM, Schattenberg T, Donnelly JP, Empirical and subsequent use of antibacterial agents in the febrile neutropenic patient. *J Intern Med* 1997; **242:** 69–77.
185. Weems JJ Jr, *Candida parapsilosis*: epidemiology, pathogenicity, clinical manifestations, and antimicrobial susceptibility. *Clin Infect Dis* 1992; **14:** 756–66.
186. Odds FC, Bernaerts R, CHROMagar candida, a new differential isolation medium for presumptive identification of clinically important candida species. *J Clin Microbiol* 1994; **32:** 1923–9.
187. Wenzel RP, Nosocomial candidemia: risk factors and attributable mortality. *Clin Infect Dis* 1995; **20:** 1531–4.
188. Bow EJ, Invasive fungal infections in patients receiving intensive cytotoxic therapy for cancer. *Br J Haematol* 1998; **101**(Suppl 1): 1–4.
189. Richet HM, Andremont A, Tancrede C et al, Risk factors for candidemia in patients with acute lymphocytic leukemia. *Rev Infect Dis* 1991; **13:** 211–15.
190. Johansen HK, Gotzsche PC, Problems in the design and reporting of trials of antifungal agents encountered during meta-analysis. *JAMA* 1999; **282:** 1752–9.
191. De Gregorio M, Lee W, Ries C, *Candida* infections in patients with acute leukemia: ineffectiveness of nystatin prophylaxis and relationship between oropharyngeal and systemic candidiasis. *Cancer* 1982; **50:** 2780–4.
192. Dietrich M, Rasche H, Rommel K, Hochapfel G, Antimicrobial therapy as a part of the decontamination procedures for patients with acute leukemia. *Eur J Cancer* 1973; **9:** 443–7.
193. Schaferkorting M, Blechschmidt J, Korting HC, Clinical use of oral nystatin in the prevention of systemic candidosis in patients at particular risk. *Mycoses* 1996; **39:** 329–39.
194. Denning DW, Donnelly JP, Hellreigel KP et al, Antifungal prophylaxis during neutropenia or allogeneic bone marrow transplantation: what is the state of the art? Ad Hoc Working Group. *Chemotherapy* 1992; **1:** 43–9.
195. Schuler US, Haag C, Prophylaxis of fungal functions. *Mycoses* 1997; **40**(Suppl 2): 41–4.
196. Glasmacher A, Hahn C, Molitor E et al, Fungal surveillance cultures during antifungal prophylaxis with itraconazole in neutropenic patients with acute leukemia. *Mycoses* 1999; **42:** 395–402.
197. Gubbins PO, Bowman JL, Penzak SR, Antifungal prophylaxis to prevent invasive mycoses among bone marrow transplantation recipients. *Pharmacotherapy* 1998; **18:** 549–64.
198. Ninane J, Sluysmans T, Vermylen C et al, Itraconazole versus ketoconazole for the prophylaxis of fungal infection in neutropenic children: results of two consecutive nonrandomized studies. *Pediatr Hematol Oncol* 1989; **6:** 349–53.
199. Harousseau JL, Dekker AW, Stamatoullas-Bastard A et al, Itraconazole oral solution for primary prophylaxis of fungal infections in patients with hematological malignancy and profound neutropenia: a randomized, double-blind, double-placebo, multicenter trial comparing itraconazole and amphotericin B. *Antimicrob Agents Chemother* 2000; **44:** 1887–93.
200. Martino P, Raccah R, Gentile G et al, *Aspergillus* colonization of the nose and pulmonary aspergillosis in neutropenic patients: a retrospective study. *Haematologica* 1989; **74:** 263–5.
201. Egger T, Gratwohl A, Tichelli A et al, Comparison of fluconazole with oral polyenes in the prevention of fungal infections in neutropenic patients. A prospective, randomized, single-center study. *Support Care Cancer* 1995; **3:** 139–46.
202. De Laurenzi A, Matteocci A, Lanti A et al, Amphotericin B prophylaxis against invasive fungal infections in neutropenic patients: a single center experience from 1980 to 1995. *Infection* 1996; **24:** 361–6.
203. Erjavec Z, Woolthuis GM, de Vries-Hospers HG et al, Tolerance and efficacy of amphotericin B

inhalations for prevention of invasive pulmonary aspergillosis in haematological patients. *Eur J Clin Microbiol Infect Dis* 1997; **16:** 364–8.

204. Conneally E, Caffeky MT, Daly PA, Nebulized amphotericin B as prophylaxis against invasive aspergillosis in granulocytopenic patients. *Bone Marrow Transplant* 1990; **5:** 403–6.
205. Hertenstein B, Stefanic M, Novotny J et al, Low incidence of invasive fungal infections after bone marrow transplantation in patients receiving amphotericin B inhalations during neutropenia. *Ann Hematol* 1994; **68:** 21–6.
206. Schwartz S, Behre G, Heinemann V et al, Aerosolized amphotericin B inhalations as prophylaxis of invasive *Aspergillus* infections during prolonged neutropenia: results of a prospective randomized multicenter trial. *Blood* 1999; **93:** 3654–61.
207. Jeffery GM, Beard ME, Ikram RB et al, Intranasal amphotericin B reduces the frequency of invasive aspergillosis in neutropenic patients. *Am J Med* 1991; **90:** 685–92.
208. Hoyle C, Goldman JM, Life-threatening infections occurring more than 3 months after BMT. 18 UK Bone Marrow Transplant Teams. *Bone Marrow Transplant* 1994; **14:** 247–52.
209. Miller RF, Le Noury J, Corbett EL et al, *Pneumocystis carinii* infection: current treatment and prevention. *J Antimicrob Chemother* 1996; **37**(Suppl B): 33–53.
210. Vasconcelles MJ, Bernardo MV, King C et al, Aerosolized pentamidine as *Pneumocystis* prophylaxis after bone marrow transplantation is inferior to other regimens and is associated with decreased survival and an increased risk of other infections. *Biol Blood Marrow Transplant* 2000; **6:** 35–43.
211. Souza JP, Boeckh M, Gooley TA et al, High rates of *Pneumocystis carinii* pneumonia in allogeneic blood and marrow transplant recipients receiving dapsone prophylaxis. *Clin Infect Dis* 1999; **29:** 1467–71.
212. Edwards JE Jr, Bodey GP, Bowden RA et al, International Conference for the Development of a Consensus on the Management and Prevention of Severe Candidal Infections. *Clin Infect Dis* 1997; **25:** 43–59.
213. Chandrasekar PH, Gatny CM, and the Bone Marrow Transplantation Team, The effect of fluconazole prophylaxis on fungal colonization in neutropenic cancer patients. *J Antimicrob Chemother* 1994; **33:** 309–18.
214. Laverdiere M, Rotstein C, Bow EJ et al, Impact of fluconazole prophylaxis on fungal colonization and infection rates in neutropenic patients. *J Antimicrob Chemother* 2000; **46:** 1001–8.
215. Menichetti F, Del Favero A, Martino P et al, Itraconazole oral solution as prophylaxis for fungal infections in neutropenic patients with hematologic malignancies: a randomized, placebo-controlled, double-blind, multicenter trial. GIMEMA Infection Program. Gruppo Italiano Malattie Ematologiche dell' Adulto. *Clin Infect Dis* 1999; **28:** 250–5.
216. Venkatakrishnan K, von Moltke LL, Greenblatt DJ, Effects of the antifungal agents on oxidative drug metabolism: clinical relevance. *Clin Pharmacokinet* 2000; **38:** 111–80.
217. Lopez-Gil JA, Fluconazole–cyclosporine interaction: a dose-dependent effect? *Ann Pharmacother* 1993; **27:** 427–30.
218. Osowski CL, Dix SP, Lin LS et al, Evaluation of the drug interaction between intravenous high-dose fluconazole and cyclosporine or tacrolimus in bone marrow transplant patients. *Transplantation* 1996; **61:** 1268–72.
219. Dresser GK, Spence JD, Bailey DG, Pharmacokinetic-pharmacodynamic consequences and clinical relevance of cytochrome P450 3A4 inhibition. *Clin Pharmacokinet* 2000; **38:** 41–57.
220. Maertens J, Verhaegen J, Demuynck H et al, Autopsy-controlled prospective evaluation of serial screening for circulating galactomannan by a sandwich enzyme-linked immunosorbent assay for hematological patients at risk for invasive aspergillosis. *J Clin Microbiol* 1999; **37:** 3223–8.
221. Saral R, Burns WH, Laskin OL et al, Acyclovir prophylaxis of herpes-simplex-virus infections. *N Engl J Med* 1981; **305:** 63–7.
222. Gluckman E, Lotsberg J, Devergie A et al, Prophylaxis of herpes infections after bone-marrow transplantation by oral acyclovir. *Lancet* 1983; **ii:** 706–8.
223. Ljungman P, Wilczek H, Gahrton G et al, Long-term acyclovir prophylaxis in bone marrow transplant recipients and lymphocyte proliferation responses to herpes virus antigens in vitro. *Bone Marrow Transplant* 1986; **1:** 185–92.
224. Boeckh M, Gooley TA, Bowden RA, Effect of high-dose acyclovir on survival in allogeneic marrow transplant recipients who received

ganciclovir at engraftment or for cytomegalovirus pp65 antigenemia. *J Infect Dis* 1998; **178:** 1153–7.

225. Prentice HG, Gluckman E, Powles RL et al, Long term survival in allogeneic bone marrow transplant recipients following acyclovir prophylaxis for CMV infection. *Bone Marrow Transplant* 1997; **19:** 129–33.
226. Sinnige LG, van der Meer JW, Gratama JW et al, Is acyclovir prophylaxis necessary after bone marrow transplantation? *Infection* 1986; **14:** 122–4.
227. Baglin TP, Gray JJ, Marcus RE, Wreghitt TG, Antibiotic resistant fever associated with herpes simplex virus infection in neutropenic patients with haematological malignancy. *J Clin Pathol* 1989; **42:** 1255–8.
228. Bergmann OJ, Mogensen SC, Ellermann-Eriksen S, Ellegaard J, Acyclovir prophylaxis and fever during remission-induction therapy of patients with acute myeloid leukemia: a randomized, double-blind, placebo-controlled trial. *J Clin Oncol* 1997; **15:** 2269–74.
229. Lonnqvist B, Palmblad J, Ljungman P et al, Oral acyclovir as prophylaxis for bacterial infections during induction therapy for acute leukemia in adults. The Leukemia Group of Middle Sweden. *Support Care Cancer* 1993; **1:** 139–44.
230. Ljungman P, De Bock R, Cordonnier C et al, Practices for cytomegalovirus diagnosis, prophylaxis and treatment in allogeneic bone marrow transplant recipients: a report from the Working Party for Infectious Diseases of the EBMT. *Bone Marrow Transplant* 1993; **12:** 399–403.
231. Stocchi R, Ward KN, Fanin R et al, Management of human cytomegalovirus infection and disease after allogeneic bone marrow transplantation. *Haematologica* 1999; **84:** 71–9.
232. Dix SP, Wingard JR, Management of viral infections in bone marrow transplant recipients. *Clin Immunother* 1996; **6:** 352–82.
233. Gerna G, Furione M, Baldanti F et al, Quantitation of human cytomegalovirus DNA in bone marrow transplant recipients. *Br J Haematol* 1995; **91:** 674–83.
234. Hebart H, Kanz L, Jahn G, Einsele H, Management of cytomegalovirus infection after solid-organ or stem-cell transplantation. Current guidelines and future prospects. *Drugs* 1998; **55:** 59–72.
235. De Vries-Hospers HG, Sleijfer DT, Mulder NH et al, Bacteriological aspects of selective decontamination of the digestive tract as a method of infection prevention in granulocytopenic patients. *Antimicrob Agents Chemother* 1981; **19:** 813–20.
236. Bow EJ, Raynor E, Scott BA, Louie TJ, Selective gut decontamination with nalidixic acid or trimethoprim–sulfamethoxazole for infection prophylaxis in neutropenic cancer patients: relationship of efficacy to antimicrobial spectrum and timing of administration. *Antimicrob Agents Chemother* 1987; **31:** 551–7.
237. Rozenberg-Arska M, Dekker AW, Verhoef J, Ciprofloxacin for selective decontamination of the alimentary tract in patients with acute leukemia during remission induction treatment: the effect on fecal flora. *J Infect Dis* 1985; **152:** 104–7.
238. Pannuti C, Gingrich R, Pfaller MA et al, Nosocomial pneumonia in patients having bone marrow transplant – attributable mortality and risk factors. *Cancer* 1992; **69:** 2653–62.
239. Gerson SL, Talbot GH, Hurwitz S et al, Prolonged granulocytopenia: the major risk factor for invasive pulmonary aspergillosis in patients with acute leukemia. *Ann Intern Med* 1984; **100:** 345–51.

13

Cytokines and WBC transfusions

Katarzyna J Finiewicz, John R Wingard

INTRODUCTION

Neutropenia in cancer patients most often results from cytotoxic chemotherapy or irradiation. Occasionally, a low granulocyte count may also be caused by marrow replacement with the tumor. Bone marrow failure states not related to a malignancy or its treatment account for only a minority of the cases of neutropenia seen in clinical practice.

The association of neutropenia with infection was first recognized and reported in 1966 by Bodey et al.[1] The depth as well as the duration of neutropenia both contribute to the risk of infectious complications. The frequency of infection increases progressively as the neutrophil count decreases below 1000/μl, reaching the highest level when the count falls below 100/μl. The likelihood of neutropenic infection also correlates with the duration of neutropenia; patients in whom the process of recovery lasts longer than 10–14 days are at particularly high risk for serious infectious complications. While most neutropenic infections are bacterial, after the first 10–14 days, the spectrum of infectious pathogens expands to encompass invasive fungi as well as other opportunistic organisms.[2,3] Long-lasting neutropenia is associated with poor response rates to antibiotics and prolonged hospital stay.[4]

Neutropenic fever after chemotherapy has customarily been treated with intravenous antibiotics. In severe infections not responding to antibiotics, granulocyte transfusions have occasionally been employed. Despite remarkable progress attained in the treatment of neutropenic fever, achieved with the use of empiric broad-spectrum antibiotics, morbidity from neutropenic infections remains considerable. As effective as antibiotics are, they are ultimately limited by the potential for emergence of drug resistance. Thus, other measures that can reduce the use of antibiotics have been sought. Attempts to attenuate neutropenia led to the development of recombinant myeloid growth factors. Two myeloid growth factors currently available for therapeutic use in the USA are recombinant human granulocyte colony-stimulating factor and recombinant human granulocyte–macrophage colony-stimulating factor. Both of these growth factors stimulate proliferation and maturation of myeloid progenitor cells. Both molecules predictably decrease the depth and duration of neutropenia after myelotoxic cancer therapy.

In this chapter, we shall summarize the data from available clinical trials conducted to evaluate the efficacy of hematopoietic growth factors in the treatment of a neutropenic patient after myelotoxic cancer therapy. We shall

present and discuss the indications for hematopoietic growth factors in light of the changes in treatment of neutropenic fever that have evolved over the last few years. The role of granulocyte infusions as an alternative method of abating the effects of prolonged neutropenia will also be reviewed.

MYELOID GROWTH FACTORS

Hematopoiesis and hematopoietic growth factors

Hematopoiesis is an orderly, continuous process by which primitive, multipotent progenitor cells give rise to mature hematopoietic cells.[5,6] The net composition of the hematopoietic cell compartment is a result of continuous interplay between pluripotent stem cells, maturing progenitors, bone marrow stroma, and hematopoietic growth factors. The interactions between the specific components of the hematopoietic cell compartment maintain a state of dynamic equilibrium, a state precisely regulated to maintain the concentration of mature blood cells in the circulation within a narrow homeostatic range. In response to a specific stimulus, the hematopoietic system is capable of rapid expansion of production of mature cells, up to 10-fold within several days. This occurs mainly owing to an increased maturation of committed progenitors.

The compartment of the hematopoietic system predominantly engaged in the response to infection is myelopoiesis. The baseline production of the neutrophils in the bone marrow is about 1.0×10^{11}/day in a healthy individual, which increases several-fold with infection.[6,7] After myeloid precursors mature, they are released into peripheral blood, where they survive approximately 6–10 hours. Half of the neutrophils in peripheral blood freely circulate, while the other half remain in the microcirculation, adherent to vascular walls in the marginal pool. Neutrophils from the microcirculation can be mobilized to circulate by stress or by medications such as epinephrine (adrenaline) or corticosteroids. However, neutrophilia induced by growth factors occurs mainly through the stimulation of the myeloid progenitors in the bone marrow to increase production.

In the complex process of hematopoiesis, the role of hematopoietic growth factors is both permissive and instructive.[8–12] Hematopoietic growth factors maintain the survival of the early hematopoietic progenitor cells by preventing apoptosis. They also promote their proliferation, facilitate and direct their differentiation, and activate effector functions in mature cells. Although the commitment of multipotent hematopoietic progenitor cells to a specific lineage is most likely random, further development depends on the instructional influence of the microenvironment, in which hematopoietic growth factors serve a crucial role.

Hematopoietic growth factors are produced by a variety of stromal and hematopoietic cells. Most act locally, where they are produced, but some have hormone-like activity. One cell may be capable of producing several growth factors. The production of each growth factor is subject to precise regulation by multiple autocrine and paracrine loops. Like hematopoietic cells, hematopoietic growth factors exist in hierarchy; some are multipotent and affect both early and late progenitor cells, while others are lineage-specific. The pleotropic potential of many of the hematopoietic growth factors significantly limits their application as therapeutic agents, since the clinically desired effect may be accompanied by a spectrum of potentially deleterious effects. Hematopoietic growth factors interact with progenitor cells through specific receptors. Each growth factor receptor is characterized by affinity for several different growth factors, which can act in synergy.

Clonal culture techniques to grow different marrow progenitor colonies in vitro have allowed the identification of hematopoietic growth factors with colony-stimulating activities: granulocyte–macrophage colony-stimulating factor (GM-CSF), granulocyte

colony-stimulating factor (G-CSF), macrophage colony-stimulating factor (M-CSF), and multicolony stimulating factor (multi-CSF) or interleukin-3 (IL-3).[11] All four have been purified and defined genetically. The first two, GM-CSF and G-CSF, have been manufactured through recombinant engineering technology and made available for clinical use. The latter two, M-CSF and IL-3, were tested in clinical trials, but were withdrawn from further development because of undesirable toxicities. As the names indicate, GM-CSF and G-CSF preferentially stimulate growth and maturation of cells with myeloid differentiation, and for this reason will be referred to further as myeloid growth factors (MGFs).

The wide use of hematopoietic growth factors in clinical practice raised theoretical concerns about potential deleterious influences on hematopoiesis, leading to stem cell exhaustion or 'stem cell steal'. Stem cell steal can theoretically result from preferential commitment of stem cells to one specific lineage directed by the specific growth factor, limiting differentiation to other lineages. Stem cell exhaustion refers to the hypothetical possibility of stem cell depletion from repeated stimulation of marrow by growth factors. Neither of the two myeloid growth factors currently available in clinical practice appears to be able to recruit the stem cell directly, since they act on more committed myeloid precursors. Based on observations of patients treated with MGFs for months and even years, the concern that any of these two phenomena truly occur in humans does not seem substantiated, and MGFs seem quite safe in this regard.

Biology of recombinant myeloid growth factors

Human G-CSF is a glycoprotein of approximately 20 kDa.[13,14] G-CSF is encoded by a single gene located on human chromosome 17q21–22. G-CSF is produced by activated macrophages, endothelial cells, and fibroblasts, as well as by bone marrow stromal cells. The G-CSF receptor is a type I membrane protein belonging to the hematopoietic growth factor receptor family, but, unlike other receptors in this family (including the GM-CSF receptor), which function as heterodimers or heterotrimers to bind to their ligands, the receptor for G-CSF seems to function as a homodimer. Expression of the G-CSF receptor is specifically restricted to neutrophilic progenitors, mature neutrophils, and various myeloid leukemia cells (Figure 13.1). After stimulation, the G-CSF receptor transduces the signals for both proliferation and differentiation.

G-CSF functions as the physiologic regulatory factor for circulating granulocytes. Increased serum levels of G-CSF can be detected in patients with neutropenia, falling with neutrophil recovery. Recombinant G-CSF elevates the level of circulating neutrophils in a dose-dependent fashion.[15,16] Neutrophilia results from the shortening of the postmitotic marrow transit time from approximately 6 days to as short as 3 days with higher doses, without affecting circulating neutrophil lifespan or the distribution between the marginal and circulating pools. Within 3–4 days after the start of G-CSF, immature and committed progenitor cells appear in the circulation (Figure 13.1). In addition to its hematopoietic effect, G-CSF appears to modulate the function and microbicidal capacity of mature neutrophils (Table 13.1).[16–20]

Human GM-CSF is a glycoprotein with a molecular mass of approximately 22 kDa and a three-dimensional structure composed of two pairs of antiparallel α helices.[21,22] The human GM-CSF gene is located on the long arm of chromosome 5, near other cytokine genes. GM-CSF can be produced by a number of different cells: T lymphocytes, macrophages, endothelial cells, fibroblasts, and stromal cells, as well as various malignant cells. GM-CSF receptors are found on hematopoietic cells as well as on various non-hematopoietic cells such as trophoblasts, endothelial cells, oligodendrocytes, and some malignant cells.[23] GM-CSF

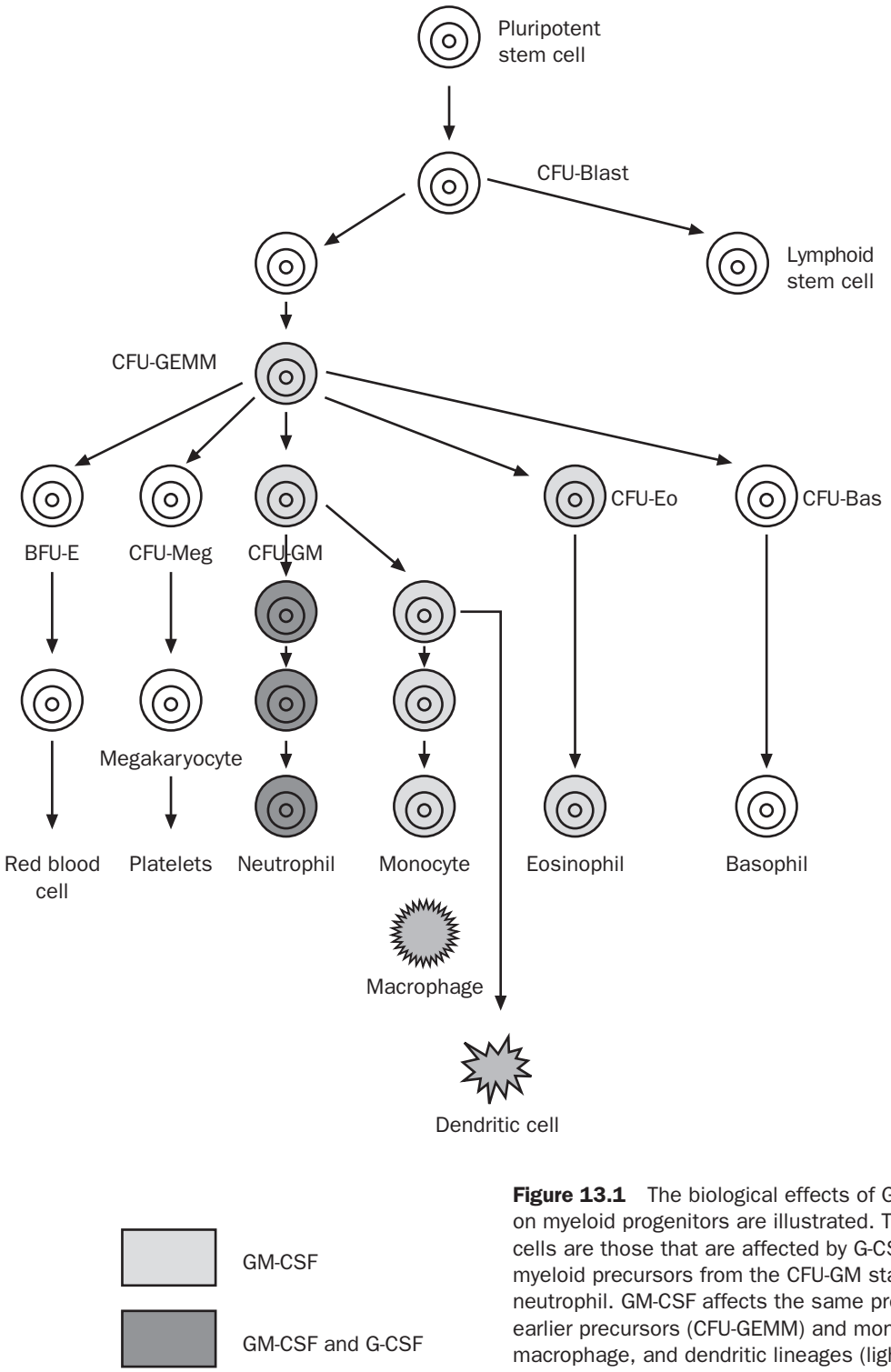


Figure 13.1 The biological effects of G-CSF and GM-CSF on myeloid progenitors are illustrated. The darkly shaded cells are those that are affected by G-CSF: differentiated myeloid precursors from the CFU-GM stage to the mature neutrophil. GM-CSF affects the same progenitors, but also earlier precursors (CFU-GEMM) and monocytoid, macrophage, and dendritic lineages (lightly shaded cells).

Table 13.1 Comparison of biologic functions of G-CSF and GM-CSF

Target hematopoietic cell	Biologic function	G-CSF	GM-CSF	Therapeutic applications
Myeloid progenitor cells	• Increased proliferation	+	+	Mobilization of myeloid progenitor cells to peripheral blood in preparation for SCT[a]
	• Increased differentiation	+	+	
Neutrophils	• Maintenance of steady-state neutrophil numbers	+	−	Control of infection
	• Increased antimicrobial activity	+	+	
	• Increased phagocytosis	+	+	
	• Increased chemotaxis	+	+	
	• Increased cytokine release	+	+	
	• Enhanced oxidative activity	+	+	
Macrophages and monocytes	• Increased intracellular killing	−	+	Control of infection
	• Increased phagocytosis	−	+	Enhancement of immune system response to infection and/or tumor
	• Increased APC[b] function; ADCC[c]	−	+	
	• Increased cytokine release	−	+	
	• Enhanced oxidative activity	−	+	
Dendritic cells	• Increased production	−	+	Enhancement of immune system response to infection and/or tumor
	• Increased differentiation	−	+	
	• Increased APC[b] function	−	+	
Structural cells (endothelial cells, fibroblasts, keratinocytes)	• Induction of migration and proliferation	+	+	Promotion of wound healing
	• Increased adhesion molecule expression	−	+	

[a] SCT, stem cell transplantation. [b] APC, antigen-presenting cell. [c] ADCC, antibody-dependent cellular cytotoxicity.

receptors have not been found on lymphocytes. The GM-CSF receptor is composed of two subunits: a ligand-specific α chain that forms a low-affinity complex with GM-CSF and a β chain that has no detectable binding to GM-CSF, but, together with the α chain, forms a high-affinity receptor. The β chain is essential for high-affinity binding and signaling of IL-3 and IL-5.

The recombinant GM-CSF molecule stimulates proliferation and maturation of a bipotential neutrophil and macrophage progenitor, which leads to the release into peripheral blood of monocytes and macrophages in addition to neutrophils (Figure 13.1).[24–26] Treatment with GM-CSF also enhances the function of mature neutrophils, monocytes, and macrophages by increasing antimicrobial activity, chemotaxis, and proinflammatory cytokine release. GM-CSF has a significant effect on the antigen-presenting function of antigen-presenting cells (APC). Specifically, in vitro studies have demonstrated that GM-CSF acts as the major stimulatory cytokine for the production, differentiation, and viability of dendritic cells (Table 13.1). Thus, GM-CSF appears to act not only as a stimulant of peripheral blood neutrophil recovery but also as an enhancer of several other components of the immune system's response to infection and malignancy.[27,28]

Both GM-CSF and G-CSF have been tested to shorten neutropenia in chemotherapy-induced aplasia and in bone marrow failure states from other causes. MGFs have also been utilized in the collection of stem cells in preparation for stem cell transplantation. The impact of MGFs, especially GM-CSF, on the function of mature myeloid cells holds great potential for future use, but at the present time remains investigational.

Parameters used to evaluate the benefits of MGFs

The parameters that should be considered in the assessment of the benefit from MGFs in a particular clinical situation can be grouped into three categories: (1) laboratory values, (2) clinical events, and (3) resource utilization (Table 13.2).[29] The accelerated recovery from neutropenia consistently seen with MGFs does not always translate into less infectious morbidity and mortality. Therefore, the duration of neutropenia is not necessarily a useful surrogate

Table 13.2 Parameters considered in the assessment of the benefit from recombinant myeloid growth factors

Laboratory values	• Leukocyte count, neutrophil count • Functional assays of neutrophils and monocytes
Clinical events	• Rates and severity of documented infection, fever, sepsis syndrome, infectious morbidity, and infectious mortality • Disease control • Survival • Quality of life • Mucositis and other toxicities
Resource utilization	• Antibiotics, antifungal agents and granulocyte transfusions • Length of hospitalization • Diagnostic procedures • Cost

marker for clinically relevant outcomes. The most important measure of the value of MGFs is their effect on clinical events, such as rate and severity of infections, survival, and quality of life (QoL).

Savings in resource utilization (e.g. antibiotic utilization, diagnostic tests performed, and duration of hospitalization) are becoming more relevant in an increasingly cost-conscious environment, and are now commonly used to justify treatment with costly MGFs, even in situations where clinical gains are not apparent. However, pharmacoeconomic calculations may be misleading. The lack of consistency in parameters used in clinical decision making by various investigators limits the extrapolation of the information obtained from clinical trials and prevents valid comparative analyses. The threshold for initiating supportive treatment such as antibiotics or blood product transfusions or the criteria used for discharge vary significantly from center to center. Practices using more stringent criteria may not appreciate the same magnitude of savings as observed in clinical trials where much more conservative approaches were applied. Additionally, savings in the field of supportive care are subject to change over time. This is best illustrated by the shifting care of cancer patients from an inpatient to outpatient setting, which obviously undermines the significance of shortened hospital stay demonstrated by many studies.

Role of MGFs in the management of patients undergoing chemotherapy

In 1991, recombinant G-CSF (filgrastim, Neupogen) became approved by the US Food and Drug Administration (FDA) for clinical use, initially for protection from chemotherapy-induced neutropenia and then for shortening of neutropenia and reduction of fever following bone marrow transplantation (BMT). This was soon followed by approval of GM-CSF (sargramostim, Leukine) for acceleration of neutrophil recovery after autologous BMT in patients with lymphoid malignancies (see Table 13.3 for a summary of the available formulations of G-CSF and GM-CSF and their approved indications). Since then, both G-CSF and GM-CSF have gained wide acceptance in oncology clinical practice as an adjunct to chemotherapy in three clinical settings:

(1) primary prophylaxis, during the first chemotherapy cycle to prevent anticipated neutropenic infectious complications;
(2) secondary prophylaxis, during subsequent chemotherapy cycles, after documented occurrence of neutropenic fever during the prior cycle;
(3) therapeutic setting, for adjunctive treatment of established neutropenia with or without fever.

The potential for broad application of these costly agents called for the need to define the clinical settings for their most appropriate use. A group of oncologists was convened by the American Society of Clinical Oncology (ASCO) to review information obtained from clinical trials and comment on the appropriateness of use of MGFs in the treatment of neutropenia and neutropenia-related complications. As a result, in 1994, a set of guidelines for the use of MGFs in particular clinical situations was published (the ASCO guidelines).[30] In short, the ASCO guidelines judged the use of MGF to be suitable: (1) in primary prophylaxis for patients with an expected likelihood of neutropenic fever of over 40%; (2) in secondary prophylaxis, after a documented neutropenic fever during the prior chemotherapy cycle to reduce infectious complications and maintain chemotherapy dose intensity in subsequent cycles; and (3) after stem cell transplantation (SCT) to enhance hematopoietic recovery and to treat engraftment failure. The use of MGFs was judged to offer only a marginal benefit in other clinical settings, and was not supported by published evidence under usual circumstances. Since guidelines are meant to be updated periodically, on the basis of new evidence, the ASCO guidelines panel reviewed the interim literature

Table 13.3 Commercially available formulations of recombinant G-CSF and GM-CSF, and their approved uses[a]

	Generic name	Trade name	Countries	Indications[b]
G-CSF	Filgrastim	Neupogen	Europe, USA, Canada, Australia	CIN, BMT, PBPC, SCN, AL
		Gran	Japan, Taiwan, Korea, China	CIN, BMT, AL, AA, SCN, MDS, HIV
	Lenograstim	Neutrogin	Japan, China	CIN, BMT, SCN, MDS, AA
		Granocyte	Europe, Australia	CIN, BMT
	Nartograstim	Neu-UP	Japan	CIN, BMT, SCN, AA
GM-CSF	Molgramostim	Leukomax	Europe	CIN, BMT, AIDS
			Canada	CIN, BMT
	Sargramostim	Leukine	USA	PBPC, BMT, AL

[a] Reprinted with permission from Armitage.[27]
[b] AA, aplastic anemia; AIDS, acquired immune deficiency syndrome; AL, acute leukemia; BMT, bone marrow transplantation; CIN, chemotherapy-induced neutropenia; HIV, human immunodeficiency virus; MDS, myelodysplastic syndrome; PBPC, peripheral blood progenitor cell transplantation; SCN, severe chronic neutropenia.

and in 1996 published an update that added a recommendation to use MGFs in patients over 54 years of age with acute myeloid leukemia (AML) after completion of induction chemotherapy.[31] An extensive revision to the original 1994 ASCO guidelines was recently published, based upon a review of all the new literature since 1994.[32] A current summary of the 2000 ASCO Clinical Practice Guidelines for MGFs is given in the Appendix.

Owing to a paucity of data on MGF influence on such clinical events as infectious morbidity and mortality, the ASCO panel used a number of indirect measurements of clinical benefit in assessing trial results: effects on neutrophil count, rates of neutropenic fever, antibiotic therapy requirements, and need for hospitalization. These secondary endpoints were considered valid surrogate measures if they were thought to be reflective of more meaningful clinical outcomes, such as decreased infectious morbidity and mortality or an improvement in QoL. The same measures were also used to estimate the magnitude of economic gain from MGFs. It should be noted that both improvement in QoL and economic gains can be measured directly, by applying QoL scales and by performing cost–benefit analyses. However, the direct methods, although more accurate and reliable, were used in only a few randomized trials performed prior to 1994. They are being increasingly incorporated in the design of more

recent trials, which will hopefully provide more precise assessments.

Use of MGFs as primary prophylaxis in patients with solid tumors and lymphomas

The majority of trials examining primary prophylaxis were aimed at demonstrating a decrease in the incidence and duration of neutropenia, leading to a reduction in the rate of serious infections and improved survival. Four studies utilizing G-CSF and five studies utilizing GM-CSF in primary prophylaxis had been reported by 1994, and were considered in the ASCO guidelines analysis (Tables 13.4 and 13.5).[30] Patient population in these trials was heterogenous, and included solid tumors as well as non-Hodgkin's lymphomas (NHL).

All four of the studies evaluating G-CSF demonstrated a reduction in the severity and duration of neutropenia (Table 13.4).[33–36] In addition, a decrease in the incidence of neutropenic fever by approximately 50% was seen. None of the studies showed a reduction in serious morbidity or mortality from infectious complications. A decreased length of hospital stay and length of treatment with intravenous antibiotics was appreciated in only two studies.[33,34] One more recent study of G-CSF in primary prophylaxis involved adults with lymphoma.[37] Similar to the results of the earlier investigations, there was a shortening of neutropenia and a decrease in neutropenic fever, but no other advantage.

Three of five trials of GM-CSF for primary prophylaxis demonstrated a shortening of neutropenia (Table 13.5).[38–42] The effect on neutropenic fever was inconsistent. A possible explanation for an apparent diminished efficacy of GM-CSF in comparison with G-CSF was inclusion of patients with a lower risk of neutropenia in the GM-CSF trials, which made detection of a positive effect more difficult. Alternatively, differences in biologic effects between the two growth factors could also account for the observed different results. Interestingly, the only randomized trial directly comparing the two agents in primary prophylaxis of chemotherapy-related neutropenic fever found them to be equivalent in efficacy.[43]

The impact of MGFs on healthcare resource utilization was examined using a risk-assessment model developed by Lyman et al to allow extrapolation of the data from the above cited trials to a broad population of patients treated with various chemotherapy regimens.[44,45] In general, the use of prophylactic MGFs was found to be cost-effective only in patients whose risk of neutropenic fever exceeded 40% over the course of chemotherapy. The model assumed that all patients with neutropenic fever would be hospitalized and treated with intravenous antibiotics until resolution of neutropenia and all signs of infection.

However, one can justly question whether such an analysis is applicable today. In response to the necessity to control health care costs, many oncologic therapies, including supportive care, have been moved from an inpatient to outpatient setting, as noted earlier.[46–49] The introduction of long-acting and oral broad-spectrum antibiotics, as well as the widespread availability of home care services, now allow many low-risk patients with neutropenic fever to be treated on an outpatient basis. Such changes in practice necessitate re-examination of the assumptions that formed the recommendations for the use of MGFs based on cost analyses performed years ago.

The decision analysis model employed by the ASCO expert panel has another important limitation: the estimate of the risk of neutropenic fever has been based exclusively on the myelotoxic potential of the chemotherapy regimen. Inclusion of additional factors that could help to predict prolonged, severe neutropenia in an individual patient was encouraged, but left entirely to the judgement of the treating physician. These risk factors were: bone marrow compromise from marrow involvement by the tumor, cumulative toxicity from prior chemotherapy and/or irradiation, and a history of severe neutropenia with prior

Table 13.4 Summary of randomized trials of G-CSF in primary prophylaxis[a]

Reference	Disease group[a]	No. of patients	Treatment arms	Shortened neutropenia[c]		Clinically relevant events[a]			Resource utilization[c]	
						Incidence of neutropenic fever		Infectious mortality rate (%)	Lower rate of antibiotic usage	Lower rate of hospitalization
				First cycle (%)	All cycles (%)	First cycle (%)	All cycles (%)			
Crawford et al[33]	SCLC	199	G-CSF Placebo	S	S	28[d] 57	40[d] 77	3 3	S[e]	S[e]
Trillet-Lenoir et al[34]	SCLC	129	G-CSF Placebo	S	S	20[d] 41	26[d] 53	2 5	S	S
Pettengell et al[35]	NHL	80	G-CSF Placebo	NS	S	—	23[d] 44	5 5	NS	NS
Gebbia et al[36]	Various	86	G-CSF Placebo	—	S	—	12[d] 32	—	—	—
Zinzani et al[37]	NHL	149	G-CSF Control	—	S	—	5[d] 21	—	—	—

[a] Modified and updated with permission from ASCO recommendations.[30]

[b] SCLC, small cell lung carcinoma; NHL, non-Hodgkin's lymphoma.

[c] S, significant difference; NS, no significant difference; —, not assessed.

[d] Significantly different.

[e] First cycle only.

Table 13.5 Summary of randomized trials of GM-CSF in primary prophylaxis[a]

Reference	Disease group[b]	No. of patients	Treatment arms	Shortened neutropenia[c]	Clinically relevant events[c]		Resource utilization[c]	
					Incidence of neutropenic fever	Infectious mortality rate (%)	Lower rate of antibiotic usage	Lower rate of hospitalization
Kaplan et al[38]	HIV-related NHL	21	GM-CSF (*E. coli*) Control	S	S	10 18	—	S
Gerhartz et al[39]	NHL	125[d]	GM-CSF (*E. coli*) Control	S[d]	S[d]	2 3	S[d]	S[d]
Hamm et al[40]	SCLC	148	GM-CSF (*E. coli*) Control	S[e]	NS	—	NS	—
Nichols et al[41]	Germ cell	61	GM-CSF (*E. coli*) Control	NS	NS	—	NS	—
Hamm et al[42]	SCLC	213	GM-CSF (yeast) Control	NS	I	—	NS	NS

[a] Modified and updated with permission from ASCO recommendations.[30]
[b] NHL, non-Hodgkin's lymphoma; SCLC, small cell lung carcinoma.
[c] S, significant difference; NS, no significant difference; I, inferior; —, not assessed.
[d] Selected patients (intention-to-treat data not available).
[e] First cycle only.

chemotherapy regimens. More recent clinical observations demonstrated that the risk of infectious complications following chemotherapy is also clearly influenced by a number of other host-related and disease-related factors, such as age, the presence of comorbidity, the type and degree of control of the primary cancer, and whether or not the fever occurred in an inpatient or outpatient setting.[50–57] A better understanding of all risk factors could allow development of a better risk-stratified approach.

Quality of life is often considered another way to appraise the value of MGF. An improvement in QoL is certainly an important goal in the management of cancer patients; however, it is one that is not easy to measure. It has never been convincingly demonstrated that shortening the duration of a hospital stay represents an appreciable improvement in QoL. An answer to this question should be directly evaluated in future clinical studies.

Interestingly, an ASCO survey investigating the compliance of oncologists with the ASCO guidelines concluded that many physicians tend to use growth factors freely, regardless of the myelosuppressive potential of the chemotherapy regimen employed.[58] The tendency to overuse growth factors in primary prophylaxis may be in part explained by a lack of appreciation of the fact that only a few of the chemotherapy regimens routinely used for treatment of solid tumors or lymphoma produce severe myelosuppression with associated risk of febrile neutropenia exceeding 40% (see Table 3 in the ASCO recommendations[30]). It should be noted that none of the chemotherapy regimens used in any of the positive trials of primary prophylaxis could be described as the standard of care for the neoplasms treated. Instead, the regimens that are considered the standard of care today are much less myelosuppressive.

Use of MGFs in dose-intensive regimens

The effectiveness of dose intensification by combining multiple agents in non-cross-resistant combinations, as outlined in the Goldie–Coleman hypothesis,[59] has been established for such tumors as leukemia, lymphoma, early-stage breast cancer, and small cell lung cancer. Introduction of growth factors allowed the development of new dose-intensive and/or schedule-intensive chemotherapy regimens, with the hope that they would lead to increased tumor response rates and improved survival. Many such intensified regimens are currently being tested in clinical trials. The studies evaluating the role of MGFs in delivery of intensive chemotherapy can be grouped into two categories: (1) randomized studies between two identical intensive regimens with or without MGF support,[60–64] and (2) randomized studies between a new intensive chemotherapy regimen that could not be administered without MGF support tested against the less intensive standard of care that usually does not require MGF support.[65]

Whether such a strategy will demonstrate a beneficial impact on disease control or long-term survival outcomes remains to be proven. The early results of clinical trials have been quite variable.[60–64] Most studies failed to show an improved survival. Interestingly, one recent trial of dose-intensive chemotherapy regimen with G-CSF support in patients with small cell lung cancer demonstrated improved survival without impairment in QoL.[66] However, in light of the disappointing experience with treating small cell lung cancer by high dose chemotherapy with stem cell support, this finding is surprising and needs confirmatory trials. Although MGF usage was successful in alleviating neutropenia, the non-hematologic toxicities became limiting with dose escalation. For example, a higher incidence of dose-limiting thrombocytopenia offset the benefit of shorter duration of neutropenia in one trial. Additionally, the preliminary analysis of a trial of dose-escalated chemotherapy regimen for Hodgkin's disease, BEACOPP, revealed an increased rate of secondary malignancies in patients on the dose-intensified treatment arm – a finding that raises valid concerns.[65]

Several trials testing the role of dose-intensified treatment regimens are underway.

Their results will be of utmost interest, particularly in two diseases with well-documented dose–response effect: lymphoma and breast cancer.

Use of MGFs in secondary prophylaxis

There has been no large prospective randomized trial to validate the use of MGFs for secondary prophylaxis. A small study of GM-CSF patients with lymphoma was inconclusive.[67] The 1994 ASCO recommendation for the use of MGF in this setting had been based on the data provided by the study of G-CSF in primary prophylaxis for patients receiving chemotherapy for small cell lung cancer.[33] In that study, patients on the placebo arm who developed neutropenic fever during the first chemotherapy cycle were crossed over to the G-CSF arm for the second cycle. Treatment with G-CSF significantly shortened the duration of neutropenia (2.5 days versus 6 days) and prevented the recurrence of fever following the second, full-dose cycle of chemotherapy in 77% of patients. The impact on serious morbidity and mortality was not assessed. Interestingly, only 5% of patients on both arms who did not have fever during the first cycle of chemotherapy developed neutropenic fever during the second cycle. Based on this observation, the ASCO expert panel found the use of MGF in the setting of secondary prophylaxis justifiable, with the caveat, however, that an alternative maneuver, namely chemotherapy dose reduction, should be given first consideration in the palliative setting.

The appropriateness of choosing MGF support over chemotherapy dose reduction remains a matter of controversy. An ASCO poll of MGF usage conducted in 1997[58] found that in diseases with particularly high cure rates (such as testicular cancer), oncologists tend to use MGF for secondary prophylaxis after the first-cycle neutropenia, even in the absence of fever.[58,68,69] This pattern of clinical care can be accounted for by the practitioner's belief that chemotherapy dose reduction might negatively affect the final outcome. The benefit from MGFs in maintaining dose intensity of standard chemotherapy regimens has not been proven (in part owing to their low myelosuppressive potential), although subset analyses within large trials do suggest that treatment with G-CSF may allow delivery of more optimal doses in patients who otherwise could not tolerate it.[70–72]

Use of MGFs for treatment of afebrile and febrile neutropenia

The ASCO MGF survey revealed that most oncologists prescribe MGFs for patients with established severe neutropenia with or without fever, despite the fact that the efficacy of MGFs in this context has never been established.[58] Several randomized trials demonstrated that G-CSF, GM-CSF, or both administered as adjuncts to antibiotics for febrile neutropenia shorten the duration of severe neutropenia, but have no effect on mortality due to infections or resource utilization such as duration of hospital stay or number of days of antibiotic therapy (Table 13.6).[73–83] In a subset of these patients characterized by the presence of documented serious infection, support with MGFs may intuitively seem more beneficial and justifiable, but awaits validation by clinical trials.[45,73]

What about initiating treatment with MGFs during severe neutropenia but before the development of fever? This approach, if found successful, would be of particular interest as primary prophylaxis as it could limit the use of MGFs only to patients at high risk for serious infection.[84] Disappointingly, a randomized trial of G-CSF performed on outpatients with severe chemotherapy-induced afebrile neutropenia found that the time to neutrophil recovery was significantly shorter on the G-CSF arm, but there was no effect on the rate of hospitalizations, number of days in hospital, duration of treatment with intravenous antibiotics, or number of culture-positive infections.[85] One explanation for the lack of effectiveness in this study

Table 13.6 Summary of randomized trials of MGFs in the treatment of febrile neutropenia

Reference	Disease group[a]	No. of patients	MGF	Neutropenia (medial duration, days)[b]	Clinically relevant events[b]		Resource utilization[b]	
					Fever (median duration, days)	Infectious mortality rate (%)	Antibiotic usage (median duration, days)	Hospitalization (median duration, days)
Maher et al[73]	Solid tumors ALL Lymphoma	216	G-CSF Placebo	3[c] 4	NS	NS	NS	8 8
Mayordomo et al[74]	Solid tumors Lymphoma	60	G-CSF Placebo	2[c] 3	NS	NS	5[c] 7	5[c] 7
Mayordomo et al[74]	Solid tumors Lymphoma	61	GM-CSF (*E. coli*) Placebo	2[c] 3	NS	NS	5[c] 7	5[c] 9
Riikonen et al[75]	Pediatric ALL Solid tumors	58[d]	GM-CSF (*E. coli*) Placebo	4.5[c] 6	2[c] 4	0 2	S	S
Anaissie et al[76]	Solid tumors Lymphoma Leukemia	107	GM-CSF (*E. coli*) Control	NS	4 4	NS	NS	9 10
Biesma et al[77]	Solid tumors ALL Lymphoma	30	GM-CSF Placebo	S[e]	NS	—	NS	—
Vellenga et al[78]	Solid tumors Lymphoma	134	GM-CSF (*E. coli*) Placebo	3 4	3 3	1(?) 0	—	6 7
Ravaud et al[79]	Solid tumors Lymphoma	68	GM-CSF (*E. coli*) Placebo	3[c] 4	2 2	0 1	5[c] 6	6[c] 7
Mitchell et al[80,81]	Solid tumors Pediatric ALL Lymphoma	186[d]	G-CSF Placebo	3[c] 5	2 3	—	5[c] 6	5[c] 7

[a] ALL, acute lymphoblastic leukemia. [b] S, significant difference; NS, no significant difference; —, not analyzed.
[c] Statistically significant. [d] Episodes of neutropenia. [e] In non-BMT patients.

may be the late start of G-CSF. It is thought that in order to exert their beneficial effect, MGFs have to be initiated soon after completion of chemotherapy, before the development of neutropenia, and continued through the period of neutropenia.[86]

Role of MGFs in acute leukemia

Despite appreciable progress in supportive care, infectious morbidity and mortality remain a major impediment in the treatment of acute leukemia, particularly in older patients. Preexisting immune deficiency caused by the disease, as well as the profound and prolonged neutropenia associated with chemotherapy for acute leukemia, both contribute to the high risk of infectious complications in leukemia therapy.

MGFs have been assessed as an adjunct to induction and to consolidation chemotherapy in acute leukemia. Several randomized studies utilizing G-CSF or GM-CSF during induction chemotherapy for AML have generated quite consistent results: a modest decrease in the duration of neutropenia was observed, with a variable effect on the incidence of serious infections and resource utilization (Tables 13.7 and 13.8).[87–97] There has been no reproducible improvement in the clinically significant measures of outcome: complete response (CR) rate, CR duration, or overall survival (OS). Only one study[88] demonstrated a benefit in a subgroup of patients with persistent leukemia who received a second course of chemotherapy during neutropenia.[98] One other study using G-CSF showed an effect on CR rate,[96,97] which did not translate, however, into a decrease in induction-related mortality or improved OS. These results have been summarized in several reviews.[99–103] The majority of patients enrolled on these protocols were over 60–65 years old.

Elderly patients' tolerance of chemotherapy is especially poor. Patients older than 60 years have a risk of dying during the course of induction chemotherapy for acute leukemia approaching 50%.[104] The high mortality rate is primarily due to uncontrolled infections developing during neutropenia. Thus not surprisingly, most of the trials of MGFs administered in conjunction with induction for AML targeted this particular patient population (Tables 13.7 and 13.8).

Two large randomized trials[94,105] and one sequential cohort study[106] evaluated the role of G-CSF during consolidation therapy for AML. Although there was no effect on overall survival, the reduction in the duration of neutropenia appeared more substantial: 5–6.5 days with consolidation versus 2–5 days with induction. As opposed to induction therapy, most patients after consolidation can be followed on an outpatient basis. Thus, a decrease in the rate of even uncomplicated febrile neutropenia could result in less hospitalization. None of the three studies, however, was designed to assess the impact of MGFs on clinical endpoints.

The role of MGFs as an adjunct to intensive chemotherapy for adult acute lymphoblastic leukemia (ALL) has been studied less extensively.[107–110] One large trial[107] demonstrated a trend towards a higher CR rate and fewer deaths during remission induction, particularly in older patients: the ultimate outcome, though, was not altered, and the leukemia-free survival and OS were the same in the two arms. Interestingly, the time to completion of intensive chemotherapy was not shortened in patients on the G-CSF arm, despite an accelerated recovery of the blood counts. This may be due to the fact that infectious complications were not different between the two groups. There was also no apparent advantage to MGFs administered in consolidation cycles. The investigators felt that, based on the results of this trial, G-CSF may be recommended in conjunction with induction chemotherapy, but should not be used routinely in the postremission treatment. The two other randomized trials confirmed the finding of decreased neutropenia with MGFs administered during induction chemotherapy; one trial showed a significant reduction in the incidence of infections, while the other only a trend to fewer infections.[108,109]

Table 13.7 Summary of randomized trials of GM-CSF with initial induction therapy for patients with AML[a]

Trial (cooperative group)	No. of patients	Age[b] (years)	Start of MGF in relation to chemotherapy (days)	Arms	Neutropenia (median duration, days)	Clinically relevant events		Resource utilization[d]	
						Induction deaths (%)	CR[c] (%)	Antibiotic usage	Hospitalization
Stone et al[87] (CALBG)	388	≥60 (69)	8	GM-CSF (*E. coli*)	15[e]	27	51		28
				Placebo	17	23	54	—	30
Rowe et al[88] (ECOG)	124	55–70 (64)	11 (if marrow aplastic)	GM-CSF (yeast)	11[e]	6	60	—	—
				Placebo	14	15	44		
Witz et al[89] (GOELAM)[f]	244	55–75 (67)	1	GM-CSF (*E. coli*)	24[e]	18	63	23[e]	30
				Placebo	29	15	60	25	33
Zittoun et al[90] (EORTC/GIMEMA)[f]	102	17–59 (43)	−1 or 8	GM-CSF (*E. coli*)	21	6	43[e]	—	—
				Placebo	24.5	8	77		
Buchner et al[91]	63	16–75 (51)	−1	GM-CSF (*E. coli*)	Reduced	5	74	—	—
				Control		5	82		
Lowenberg et al[92] (HOVON/SAKK)[f]	253	<60 (42)	−1 or 8–9	GM-CSF (*E. coli*)	24[e]	7 (all)	77	—	30
				Control	27		77		31
Lowenberg et al[93] (EORTC/HOVON)[f]	326	>60 (68)	−1 to neutrophil recovery	GM-CSF (*E. coli*)	23[e]	14	56	20	32.5
				Control	25	13	55	16	32

[a] Modified and reprinted with permission from Schiffer CA, *Blood* 1995; **88**: 3675–85.[99]
[b] Median in parentheses.
[c] Complete response rate. [d] —, not assessed. [e] $p < 0.05$.
[f] Studies that also evaluated priming.

Table 13.8 Summary of randomized trials of G-CSF with initial induction therapy for patients with AML[a]

Trial (cooperative group)	No. of patients	Age[b] (years)	Start of MGF in relation to chemotherapy (days)	Arms	Neutropenia (median duration, days)	Clinically relevant events		Resource utilization[d]	
						Induction deaths (%)	CR[c] (%)	Antibiotic usage	Hospitalization
Heil et al[94] (Amgen Multi-Institutional)	521	16–89 (54)	8	G-CSF Placebo	20[e] 25	NA	69 68	15[e] 18.5	23[e] 29
Godwin et al[95] (SWOG)	211	>55 (68)	11 (if marrow hypocellular)	G-CSF Placebo	Reduced by 3–4 days[e]	20 19	41 50	22 26	29 29
Dombert et al[96] (AML Cooperative Study Group: France/Belgium)	173	>65 (71)	8	G-CSF Placebo	21[e] 27	23 27	70[e] 47	—	—

[a] Modified and reprinted with permission from Schiffer CA, *Blood* 1995; **88**: 3675–85.[99]
[b] Median in parentheses.
[c] Complete response rate. [d] —, not assessed. [e] $p < 0.05$.

No benefit from MGFs on resource utilization was seen. The impact on long-term survival was not reported in either of the two studies.

A few randomized studies looked at adjuvant G-CSF after induction chemotherapy in childhood ALL.[111–114] As with the results of the trials in adult ALL, no beneficial effect on clinical events was demonstrated in this setting either.

In summary, the use of MGFs in the treatment of acute leukemia appears to be safe, but a beneficial effect on clinically important events, such as lower rates of serious neutropenic infections, improved CR rate, or improved OS, has not been convincingly proven. Using GM-CSF and G-CSF with induction chemotherapy in elderly patients does deserve consideration, although supportive data in this regard do not appear very convincing.

Role of MGFs in high-dose chemotherapy with stem cell transplantation

The severity of neutropenia – depth as well as duration – is dependent on the dose intensity of the treatment regimen, and is particularly profound in the SCT population because of the intensive conditioning regimens employed. Recovery of hematopoiesis after SCT follows a predictable pattern of pancytopenia lasting 2–4 weeks. A variable degree of other non-hematopoietic conditioning-regimen-induced toxicities affecting vital body organs usually occurs during this period of time, which greatly contributes to the risk of infections. Owing to the relatively high morbidity and mortality associated with the early post-transplant period, necessitating intensive use of health care resources to treat these patients, the setting of SCT appears as a potentially attractive application for MGFs.

Twenty-two randomized controlled trials have evaluated the effectiveness of MGFs in facilitating engraftment; 16 trials were conducted in autologous SCT, two in both autologous and allogeneic SCT, and four exclusively in allogeneic SCT patients (Table 13.9).[115–136] Disappointingly, the results, in general, were similar to the conclusions of studies investigating the role of MGFs in non-transplant settings. All but three studies demonstrated statistically significant shortening of time to granulocyte recovery by 3–13 days in the autologous transplant setting and by 2–6 days in the allogeneic transplant setting. However, the impact on other outcome parameters (especially infection) seems much less impressive. Only a few studies showed a reduction in infectious episodes or number of days with fever. No study showed any effect on the rate or severity of fungal infections. Most importantly, no study demonstrated a reduced infectious mortality or improved OS. A reduction in resource utilization and cost was demonstrated in 12 out of the 22 studies, mainly in terms of shortening of the hospital stay. In only a few of the studies did the use of MGFs also affect the use of intravenous antibiotics or utilization of amphotericin B.

The magnitude of clinical benefit appears much smaller in the allogeneic SCT setting. Among four studies of MGFs performed exclusively in allogeneic SCT recipients, two were negative and two were positive. The two negative studies showed no evidence of improvement in any of the parameters: laboratory, clinical, or resource utilization. In general, available data do not offer support for the routine use of MGFs in the allogeneic transplant setting.

It is not clear why a shortening of neutropenia after SCT has not translated into a greater clinically measurable benefit. Certainly, the rate of serious infectious morbidity or mortality after autologous SCT, although much higher than in a conventional chemotherapy setting, is still so small that many of the clinical trials discussed here were underpowered to document the difference, if it exists. In the setting of allogeneic SCT, neutropenia is only one of the numerous risk factors for infectious complications, modification of which may not be sufficient to change the overall risk.

The remarkable efficacy of MGFs in mobilizing stem cells from bone marrow into the circu-

Table 13.9 Effect of G-CSF and GM-CSF on engraftment after SCT as evaluated in randomized controlled trials

Reference	No. of patients	MGF	Transplant type[a]	Stem cell source[b]	Neutropenia[c,d]		Clinically relevant events[d]			Resource utilization[d]		
					ANC <100/μl	ANC <500/μl	Fever	Any infection	Bacteremia	Hospital stay	Antibiotic therapy	Use of amphotericin B
Khwaja et al[115]	61	GM-CSF	Auto	BM	NS	S	NS	NS	NS	NS	NS	NS
Gorin et al[116]	91	GM-CSF	Auto	BM	—	S	NS	NS	NS	S	NS	—
Gulati et al[117]	24	GM-CSF	Auto	BM	—	—	—	NS	NS	S	—	—
Link et al[118]	81	GM-CSF	Auto	BM	—	S	NS	S	NS	NS	NS	—
Nemunaitis et al[119]	128	GM-CSF	Auto	BM	NS	S	NS	NS	NS	S	S	NS
Schmitz et al[120]	54	G-CSF	Auto	BM	—	S	NS	NS	NS	NS	NS	—
Stahel et al[121]	43	G-CSF	Auto	BM	—	S	S	NS	NS	NS	NS	—
Advani et al[122]	69	GM-CSF	Auto	PB, BM	—	S	—	S	NS	NS	—	—
Legros et al[123]	50	GM-CSF	Auto	PB	—	NS	S	NS	—	NS	NS	—
Spitzer et al[124]	37	G&GM	Auto	PB	NS	S	—	NS	NS	S	NS	—
Klumpp et al[125]	41	G-CSF	Auto	BM	—	S	NS	—	—	S	S	—
Linch et al[126]	63	G-CSF	Auto	BM	—	S	—	—	—	S	—	—
Bishop et al[127]	54	G-CSF	Allo	PB	—	S	—	—	—	NA	—	—
Lee et al[128]	24	G-CSF	Auto	PB	—	S	NS	—	—	S	NS	NS
McQuaker et al[129]	38	G-CSF	Auto	PB	NS	S	NS	—	—	S	NS	S
Kawano et al[130]	63	G-CSF	Auto	PB	—	S	NS	—	—	NA	—	—
Ojeda et al[131]	50	G-CSF	Auto	PB	—	S	—	NS	—	NS	—	—
Gisselbrecht et al[132]	315	G-CSF	Allo, Auto	PB, BM	—	S	S	—	S	S	NS	—
DeWitte et al[133]	57	GM-CSF	Allo	BM	S	NS	NS	NS	NS	NS	NS	—
Nemunaitis et al[134]	109	GM-CSF	Allo	BM	S	S	NS	S	S	S	NS	NS
Powles et al[135]	40	GM-CSF	Allo	BM	—	NS	I	NS	NS	NS	I	—
Linch et al[136]	121	G-CSF	Allo, Auto	BM	—	S	NS	NS	NS	S	NS	S

[a] Auto, autologous; Allo, allogeneic. [b] BM, bone marrow; PB, peripheral blood. [c] ANC, absolute neutrophil count.
[d] S, $p < 0.05$; NS, not significantly different; —, not assessed; I, MGF group inferior to control.

lation made peripheral blood stem cell transplants (PBSCT) possible, and, within a short period of time, peripheral blood replaced bone marrow as the major source of the stem cells for autologous SCT and is currently being evaluated in allogeneic SCT. The main advantage of PBSCT over BMT is the ability to collect more stem cells, which facilitates faster engraftment. Many of the studies that demonstrated a benefit from MGFs after autologous SCT were performed before PBSCT became available. Whether the conclusions from these trials apply to PBSCT is debatable. An accelerated recovery of peripheral blood counts and a reduction in the antibiotic requirements with MGFs after PBSCT have been confirmed in a few small studies.[123,124,137–139] However, the same studies plus a few small single-arm ones strongly suggest that the benefit of MGFs may be very small, and may even be negligible if the number of the stem cells is optimal.[128–131,138,140] The only published randomized trial of G-CSF after allogeneic PBSCT showed faster recovery of granulocytes in this setting.[141]

Choosing a more cost-effective dosing schedule may be a method to decrease the cost of transplant if one opts to use MGFs. Different schedules of treatment with MGFs following SCT have been evaluated. The dose of 5 μg/kg/day appears equivalent to 10 μg/kg/day.[142] Furthermore, the results of several studies,[143–152] including five randomized,[143–147] strongly imply that the delayed initiation of treatment with MGF until day 5–7 does not negatively affect engraftment. Another way to possibly reconcile the potential clinical benefit with pharmacoeconomic demands would be to adopt a modified risk-stratified approach, which would call for MGF support only in patients who receive a suboptimal quality graft.

Dose and schedule of administration of recombinant MGFs

The MGF dose recommendations issued in the ASCO guidelines were 5 μg/kg/day for G-CSF and 250 μg/m^2/day for GM-CSF.[30] The initial approval of MGF by the FDA for use in particular clinical settings was accompanied by specific dose and schedule directions.[153,154] The doses of G-CSF initially approved by the FDA were G-CSF 5 μg/kg/day in conventional chemotherapy and 10 μg/kg/day in the transplant setting. In the clinical trials that followed, the issue of optimal dose was rarely raised.[155,156] One exception was the setting of autologous SCT, where a randomized study demonstrated equal efficacy of G-CSF at 5 μg/kg/day and 10 μg/kg/day.[142] Although the issue of increased efficacy of the higher dose levels has not been addressed by randomized trials in the non-transplant setting, circumstantial evidence suggests this to be of no benefit. Interestingly, there is some information suggesting that lower doses of G-CSF, but not GM-CSF, may be equally efficacious.[155–157] In lieu of this information, rounding the dose to the nearest vial size has been considered acceptable. Both subcutaneous and intravenous routes of administration are comparable, with the subcutaneous route preferred by both physicians and patients owing to cost and convenience.[158–160]

Initiation and stopping rules for MGFs relative to chemotherapy have been a matter of controversy. Based on available data, it appears that starting MGFs 24–72 hours after completion of chemotherapy may be optimal. Initiation of MGFs prior to chemotherapy can lead to more profound neutropenia, and therefore should be avoided.[161] Delayed start of therapy with MGFs has been employed by various centers to decrease utilization of these costly drugs. One small phase II randomized study suggested that a delay in initiation of G-CSF from day 4 of chemotherapy to day 6 was associated with a similar pattern of hematologic recovery, but a further delay to day 8 resulted in a less favorable response.[86] This contrasts with the autologous SCT trials, where no advantage to an early start (vs delayed until day 5–7) was seen.

The optimal duration of therapy with MGFs is even more controversial. The FDA-approved package circulars specify for G-CSF to be con-

tinued until the absolute neutrophil count (ANC) is $> 10\,000/\mu l$ in the conventional chemotherapy setting and until the ANC is $> 1000/\mu l$ for three consecutive days in the transplant setting.[153] The discontinuation instruction for GM-CSF specifies recovery of the absolute neutrophil count to an ANC $> 20\,000/\mu l$.[154] These recommendations are certainly safe and effective, but such prolonged courses of treatment appear not to be necessary for optimal effect. Indeed, many centers have introduced early-stopping rules for MGFs with no deleterious effect on the outcome.

Toxicities with recombinant MGFs

In general, both G-CSF and GM-CSF are very well tolerated at therapeutic doses. The side-effects seen in association with MGFs are summarized in Table 13.10. The main toxicity of MGFs is mild-to-moderate bone pain, usually easily controllable by acetaminophen (paracetamol). Bone pain is practically the only significant side-effect from G-CSF. The common adverse reactions seen in patients treated with GM-CSF are those characteristic of proinflammatory cytokine stimulation, such as fever, myalgia, and malaise.

The first dose of *Escherichia coli*-derived GM-CSF can cause rash, pruritus, arthralgias, and even cardiovascular events such as tachycardia and hypotension. The administration of subsequent doses, though, is usually uneventful. A capillary leak syndrome has been reported to occur in a dose-dependent fashion, but with dosages much higher than those routinely used in clinical practice. These untoward side-effects, including the 'first-dose effect', have been described mainly with the *E. coli* product, and not with yeast GM-CSF.

The majority of clinical trials looking at the clinical activity of GM-CSF used the *E. coli*-derived formulation, which has a much less favorable toxicity profile in comparison with the yeast-derived formulation. The toxicities of the only GM-CSF formulation commercially available at present in the USA, i.e. a yeast-derived formulation, appear to be comparable with those of G-CSF.[43,162,163]

GRANULOCYTE TRANSFUSIONS

The role of granulocyte transfusions (GTX) in restoration of the host defense system in severely neutropenic patients has been studied for more than 30 years (reviewed in references 164–168). The initial trials performed in the early 1970s yielded encouraging results. The intuitive appeal of this approach gained many proponents who argued that controlled trials of the seemingly obvious efficacy of GTX might not be necessary. However, reports of frequent, often severe, complications associated with GTX slowly dampened the initial enthusiasm. Additionally, the process of collection and storage of granulocytes proved very cumbersome. The required technology was not widely available. As a consequence, GTX slowly fell out of favor as a therapeutic tool. This coincided in time with significant advances in the treatment of neutropenic infections due to availability of new classes of antibiotics and MGFs.

However, in recent years, the emergence of new and more resistant pathogens, especially invasive fungi and antibiotic-resistant bacteria, has led to renewed interest in this treatment modality. Additionally, advances in collection methods now allow the collection of much larger numbers of granulocytes, making the whole procedure more feasible.

Methods of collection of white blood cells for GTX

The inability to collect a sufficient amount of granulocytes has been a major obstacle to the use of GTX until the advent of MGFs in 1991. G-CSF administered to normal donors can increase the number of circulating granulocytes 10-fold and the number of circulating granulocyte progenitors 40-fold.[15] This permits the

Table 13.10 Side-effects associated with MGFs[a]

	GM-CSF	G-CSF
Non-dose-related		
Fever	Common	Rare
Bone pain	Common (10%)	Common (10%)
Myalgia	Common	Rare
Catheter thrombosis	Rare	Not reported
Splenomegaly	Rare	Rare
Dose related (>32 μg/kg/day)		
Effusion		
Pericardial	+	−
Pleural	+	−
Ascites	+	−
Pulmonary emboli	+	−
Edema	+	−
Weight gain	+	−
Laboratory[b]		
Increased LDH	+	+
Increased LAP	+	+
Increased uric acid	+	+
Increased ALP	+	+
Increased eosinophils	+	−

[a] Reprinted with permission from Negrin RS, Clinical applications of hematopoietic growth factors. In: *The Cytokine Handbook*, 3rd edn (Thomson A, ed). London: Academic Press, 1998.
[b] LDH, lactate dehydrogenase; LAP, leukocyte alkaline phosphatase; ALP, alkaline phosphatase.

collection of a large number of neutrophils by routine centrifugation leukapheresis. The average yield of G-CSF-stimulated granulocytes represents a three- to fivefold increase (range $3–7 \times 10^{10}$) over that reported historically following stimulation of donors with corticosteroids alone.[169,170] The progressive and sustained increases in precollection leukocyte count achieved with G-CSF result in greater numbers of leukocytes collected during consecutive leukapheresis days.[171,172] GM-CSF appears to be less effective in this regard, since it causes only a twofold rise in precollection leukocyte count, without a continuing rise during successive days of collection.[171] In the majority of studies, G-CSF was administered at a dose of 5 μg/kg/day subcutaneously, 8–12 hours before the first scheduled leukapheresis, and then continued daily. After multiple doses of G-CSF, neutrophilia was maintained. Therefore, the timing of subsequent leukaphereses in respect to the G-CSF injections is not as critical.

A daily dose schedule of 10 μg/kg/day and an alternative-day schedule appear to be comparable.[173] More recently, the combined use of G-CSF and corticosteroids to increase yield and to maintain the function of collected neutrophils was reported in this setting.[174,175] It remains to be seen which mobilization regimens will prove superior.

Filtration leukapheresis through nylon/wool fibers has been used in the past for collection of granulocytes for GTX. This procedure was later discovered to cause significant changes in neutrophil function,[176–178] which were believed to be responsible for many serious reactions observed in both the donor and the recipient.[179] Currently, granulocytes are collected exclusively by centrifugal separation.[180]

The quality of GTX product

At present, GTX is not an FDA-approved treatment modality, and optimal granulocyte concentrate specifications have not been defined or officially formulated. It is generally accepted that a minimum of 1×10^{10} cells should be present in each unit of a concentrate.[180] In vitro assays to test granulocyte function in a concentrate would be desirable for quality assurance, but are not routinely performed.

Both G-CSF and corticosteroids included in the mobilization regimen are known to alter neutrophil function. The clinical importance of the reported enhanced phagocytic and bactericidal activity of granulocytes exposed to G-CSF has not been studied extensively, but appears relatively minor.[177,181] The decreased recovery and prolonged circulatory half-life of G-CSF-stimulated granulocytes have raised the concern of impairment in cellular mobility.[174,175] However, the ability of these neutrophils to migrate into skin window chambers and into sites of inflammation and infection has been documented, reaffirming the lack of detrimental effects of G-CSF/corticosteroids in this regard.[17,175–181] Information about the properties of stimulated granulocytes is still scant, and hopefully will be studied further.

Irradiation is generally performed as a method to prevent transfusion-associated graft-versus-host-disease; whether this is necessary remains unresolved. While this almost invariably fatal complication has been reported after granulocyte transfusion, it is rare.

Dose and side-effects of GTX

The optimal dose of granulocytes for the treatment of neutropenic infections is not known. Early trials using donors with CML suggested that a dose of $1 \times 10^{10}/m^2$ or more would be desirable.[182] Thus, a daily transfusion of a minimum of 1×10^{10} cells, which corresponds roughly to the product of one leukapheresis procedure contained in one unit of the concentrate, seems a logical target.[183] The prolonged circulation of G-CSF-stimulated transfused granulocytes suggests that an every-other-day schedule may provide sufficient support.[173,184] It is thought that GTX should be continued until resolution of infection or recovery of blood counts.

Acute toxicities such as fever, chills, and urticaria can occur during GTX. It appears that a slow rate of GTX infusion is crucial to avoid these symptoms. Should they occur, further slowing down the infusion rate could alleviate them. Routine premedication with antihistamines and/or antipyretics might be helpful. In the event of a severe reaction, the infusion should be stopped and the patient should be tested for the presence of antileukocyte antibodies.

Respiratory distress and appearance of pulmonary infiltrates have also been seen in association with GTX. Severe pulmonary reactions reported in the early 1980s were attributed to the concomitant administration of GTX with amphotericin B.[185,186] However, later reports failed to confirm the interaction between GTX and amphotericin B in causing lung injury.[187,188] Indeed, in more recent studies, adverse reactions to G-CSF-mobilized granulocyte transfusions

have been rare in general. Interestingly, there was no correlation between the risk of untoward side-effects from GTX and the degree of leukocyte antigen incompatibility between the donor and the recipient,[173–175] although, traditionally, GTX-related toxicities have been thought to be more severe and more common in alloimmunized recipients.[189,190]

Differences in the method of collection of granulocytes could explain the disconcordant results between the older and newer studies. Many of the side-effects observed in the early trials might have been due to damage to granulocytes procured through filtration leukapheresis. In vitro experiments demonstrated that amphotericin B can trigger aggregation of neutrophils injured by filtration leukapheresis. Whether the same interaction occurs with intact neutrophils collected through centrifugal separation is uncertain, but seems unlikely. None of the leukocyte antibodies detected in patients treated on the newer protocols showed neutrophil agglutination, a postulated prerequisite for causing transfusion related acute lung injury.[175,189] Based on the reports of serious toxicities in early studies, it has become common practice to separate temporally the infusions of amphotericin B and GTX by at least 8 hours.

Factors affecting the dynamics of transfused granulocytes

Transfusions of G-CSF-mobilized granulocytes into neutropenic recipients produce increments in circulating granulocyte levels, measurable for hours after transfusion – even up to 24 hours.[191] This was not observed when corticosteroids alone were used for stimulation.[171] A sustained increase in the granulocyte count after G-CSF-mobilized GTX may be due possibly to the large cell dose or possibly to infusion of early progenitors, with a longer half-life. Interestingly, though, a consistent relationship between the cell dose delivered over a number of days and the increments over a baseline neutrophil count has not been found in a study designed to address this question.[173,191]

The impact of alloimmunization of the recipient on the effectiveness of treatment with GTX is a matter of controversy.[192,193] In non-alloimmunized patients, granulocytes can be transfused safely. Granulocyte concentrates usually contain large numbers of erythrocytes, and for this reason transfusions should be ABO-compatible. However, there is no evidence that ABO incompatibility affects the transfused granulocytes. Patients can develop two types of antibodies directed against two different classes of antigens on the surface of neutrophils: HLA antibodies detectable by lymphocytotoxicity assays and granulocyte-specific antibodies detectable by leukoagglutination or by indirect immunofluorescence. Alloimmunization is a known complication of GTX in immunocompetent patients.[192] However, some of the newer studies suggest that alloantibodies may be less of a problem in SCT recipients. A few conflicting reports as to the significance of the alloantibodies in GTX recipients have appeared in the recent literature. The presence of detectable antibodies prior to the start of treatment or acquired antibodies during treatment with granulocyte infusions adversely affected neutrophil increments after transfusion of granulocytes and delayed engraftment in one recent study.[172]

Evidence of efficacy of treatment with GTX: summary of clinical trials

Early clinical trials investigating granulocyte transfusions strongly suggested a considerable benefit of this treatment modality. However, the findings were not consistent, and the clinical effects in individual patients were not always obvious (see Table 13.11 for a summary of the trials[194–200]). Most of the patients studied had Gram-negative bacterial septicemia. Significant benefits from GTX were seen only when bone marrow recovery was delayed for more than 1 week (but did occur within 2–3 weeks) and when leukocyte transfusions were

Table 13.11 Controlled studies of therapeutic granulocyte transfusion (GTX) in neutropenic patients[a]

Reference	Randomized	Treatment arms	No. of patients	Survival rate (%)	Dose[b] ($\times 10^{10}$ cells)	HLA–WBC[c]	Success of GTX
Higby et al[194]	Yes	GTX	17	76	2.2 (FL)	No–Yes	Yes
		Control	19	26			
Vogler et al[195]	Yes	GTX	17	59	2.7 (CL)	Yes–Yes	Yes
		Control	13	15			
Herzig et al[196]	Yes	GTX	13	75	1.7 (FL)	No–Yes	Yes
		Control	14	36	0.4 (CL)		
Alavi et al[197]	Yes	GTX	12	82	5.9 (FL)	No–No	Partial
		Control	19	62			
Winston et al[198]	Yes	GTX	48	63	0.5 (CL)	No–No	No
		Control	47	73			
Graw et al[199]	No	GTX	39	46	2.0 (FL)	No–Yes	Partial
		Control	37	40	0.6 (CL)		
Fortuny et al[200]	No	GTX	17	78	0.4 (CL)	No–Yes	No
		Control	22	80			

[a] Modified and reprinted with permission from Strauss RG, *J Pediatr Hematol Oncol* 1999; **21:** 475–8.[165]
[b] CL, centrifugation leukapheresis; FL, filtration leukapheresis.
[c] HLA, human leukocyte antigen; WBC, white blood cell.

given for at least 4–7 days. There appears to be a dose-threshold effect, since the negative trials used low doses ($<1 \times 10^{10}$). The positive trials used higher doses ($>1 \times 10^{10}$). Two other factors might explain the negative results of some studies: (1) good response to antibiotics in both arms, making the detection of the benefit, if any, difficult in two studies; (2) not testing for leukocyte incompatibility.

Several encouraging case reports and pilot studies utilizing G-CSF (±corticosteroid)-stimulated granulocyte infusions have been reported in the past few years.[173,174,201–204] The trials suggest a benefit of G-CSF-stimulated GTX in the treatment of bacteriemias and candidemias. However, activity in the treatment of invasive mold infections such as aspergillus has not been consistently demonstrated.[175] Unfortunately, most patients in these studies were quite sick before starting treatment with GTX. Worsening of overall clinical status and progression to multiorgan failure has been observed in many cases, despite evidence of clearing the infection. Thus, very few patients in these trials emerged as long-term survivors. This suggests that the GTX might have been

started too late. Improvements in early diagnostic methods for fungal infections are needed to allow timely initiation of treatment with GTX.

In the face of a lack of randomized, controlled clinical trials, it is premature to draw a definitive conclusion as to the effectiveness of GTX collected from G-CSF-stimulated donors in the prevention or treatment of severe neutropenic infections. The collection, storage, and reinfusion of granulocytes are both complex and costly. A randomized trial designed to assess the efficacy of G-CSF-stimulatd GTX in the treatment of serious infections would be of great interest.

CONCLUSIONS

It is apparent that recombinant growth factors have a role in the management of febrile neutropenia. A hastened recovery from neutropenia has been consistently found. However, by and large, they have failed to fulfill all of their early promise. The observed decrease in depth and duration of neutropenia was expected to reduce the rate of infectious complications. While most clinicians believe that it does, the trials have not convincingly demonstrated this. Adjuvant treatment with MGFs was also anticipated to allow delivery of full and even escalated doses of chemotherapy without delays caused by prolonged neutropenia, and thus to improve its effectiveness. Disappointingly, only some decrease in the number of febrile episodes has been appreciated, but no reduction in the frequency of severe infections and no improved survival from treatment with growth factors have been convincingly demonstrated. In light of the lack of convincing efficacy of MGFs in reducing serious morbidity or mortality, treatment with MGFs is often justified by economical or QoL considerations. Yet, even with these considerations, more information is needed. Clinical trials designed with these endpoints as primary objectives could allow more precise and reliable measurement of the magnitude of this benefit.

It is perplexing why shortening of neutropenia has not translated into clinically measurable benefits. Certainly, rates of serious infectious morbidity or mortality in populations studied were often relatively small, and many of the clinical trials were underpowered to document differences, if they exist. Another explanation is that MGFs may not be able to prevent or affect the duration of severe neutropenia of less than 100/μl, the circumstance in which most neutropenic infections occur. Indeed, MGFs seem most efficient in hastening the recovery of granulocytes between 100/μl and 1000/μl, as seen in the SCT trials. It is also possible that alterations in neutrophil migratory function reported by some investigators affect the capability of mature granulocytes to reach infected tissues, although this certainly remains disputable.

Much has been learned from the early clinical trials evaluating the efficacy of MGFs in particular clinical settings. Identification of populations of patients who could uniformly benefit from adjuvant treatment with MGFs remains a challenge and would be of the utmost importance. The insights gained from studies identifying patients at high and low risk for severe neutropenic infection should be used in the design of future growth factor trials.

Treatment of neutropenic infections with GTX has become more feasible thanks to the availability of MGFs. More importantly, the risks associated with these G-CSF-stimulated GTX appear to be acceptable. The concerns regarding serious pulmonary reactions that limited widespread application of this treatment modality in 1970s have been dissipated by the more recent studies of G-CSF-stimulated GTX. Indeed, GTX now seem well tolerated by recipients. However, large trials to establish the efficacy of this treatment modality in particular clinical settings are needed.

REFERENCES

1. Bodey GP, Buckley M, Sathe YS et al, Quantitative relationship between circulating leukocytes and infection in patients with acute leukemia. *Ann Intern Med* 1966; **64:** 328–40.
2. Wingard JR, Santos, Saral R, Differences between first and subsequent fevers during prolonged neutropenia. *Cancer* 1987; **59:** 844–9.
3. Hughes WT, Armstrong D, Bodey GP et al, Guidelines for the use of antimicrobial agents in neutropenic patients with unexplained fever. *Clin Infect Dis* 1997; **25:** 551–73.
4. Rubin M, Hathorn JW, Pizzo PA, Controversies in the management of febrile neutropenic cancer patients. *Cancer Invest* 1988; **6:** 167–84.
5. Babior BM, Golde DW, Production, distribution and fate of neutrophils. In: *Williams' Hematology* (Beutler E, Lichtman MA, Coller BS, Kipps TJ, eds). New York: McGraw-Hill, 1995: 773–9.
6. Sieff CA, Williams DA, Hematopoiesis. In: *Blood: Principles and Practice of Hematology* (Handin RI, Stossel TP, Lux SE, eds). Philadelphia: JB Lippincott, 1995: 171–224.
7. Marsh JC, Boggs DR, Cartwright GE, Wintrobe MM, Neutrophil kinetics in acute infection. *J Clin Invest* 1967; **46:** 1943–53.
8. Dancey JT, Deubelbeiss KA, Harket LA, Finch CA, Neutrophil kinetics in man. *J Clin Invest* 1976; **58:** 705–15.
9. Leary AG, Strauss LC, Civin KC, Ogawa M, Disparate differentiation in hemopoietic colonies derived from human paired progenitors. *Blood* 1985; **66:** 327–32.
10. Lemishka IR, Raulet DH, Mulligan RC, Developmental potential and dynamic behavior of hematopoietic stem cells. *Cell* 1986; **45:** 917–24.
11. Metcalf D, *Clonal Culture of Hemopoietic Cells*. Amsterdam: Elsevier/North American Biomedical Press, 1984.
12. Shivdasani RA, Orkin SH, The transcriptional control of hematopoiesis. *Blood* 1996; **87:** 4025–39.
13. Demetri GD, Griffin JD, Granulocyte colony-stimulating factor and its receptor. *Blood* 1991; **78:** 2791–808.
14. Lieschke GJ, Burgess AW, Granulocyte colony-stimulating factor and granulocyte–macrophage stimulating factor. *N Engl J Med* 1992; **327:** 28–35; 99–106.
15. Price TH, Chatta GS, Dale DC, The effect of recombinant granulocyte colony-stimulating factor of neutrophil kinetics in normal young and elderly humans. *Blood* 1996; **88:** 335–40.
16. Welte K, Gabrilove J, Bronchud MH et al, Filgrastim (r-metHuG-CSF): the first 10 years. *Blood* 1996; **88:** 1907–29.
17. Dale DC, Liles WC, Summer W, Nelson S, Granulocyte colony-stimulating factor: role and relationship in infectious diseases. *J Infect Dis* 1995; **172:** 1061–75.
18. Liles WC, Huang JE, van Burik JH et al, Granulocyte colony-stimulating factor administered in vivo augments neutrophil-mediated activity against opportunistic fungal pathogens. *J Clin Infect Dis* 1997; **175:** 1012–15.
19. Allen RC, Stevens P, Price TH et al, In vivo effects of recombinant human granulocyte colony-stimulating factor on neutrophil oxidative functions in normal human volunteers. *J Infect Dis* 1997; **175:** 1184–92.
20. Chatta GS, Price TH, Allen RC, Dale DC, The effects of in vivo recombinant human granulocyte colony-stimulating factor (rhG-CSF) on neutrophil response and peripheral blood colony forming cells in healthy young and elderly volunteers. *Blood* 1994; **84:** 2923–9.
21. Aglietta M, Piacibello W, Sanavio F et al, Kinetics of human hematopoietic cells after in vivo administration of granulocyte–macrophage colony-stimulating factor. *J Clin Invest* 1989; **83:** 551.
22. Neumunitis J, Granulocyte–macrophage colony-stimulating factor: a review from clinical development to clinical application. *Transfusion* 1993; **33:** 70–83.
23. Foulke RS, Marshall MH, Trotta PP, Von Hoff DD, In vitro assessment of the effects of granulocyte–macrophage colony-stimulating factor on primary human tumors and derived lines. *Cancer Res* 1990; **50:** 6264–7.
24. Gasson JC, Molecular physiology of granulocyte–macrophage colony-stimulating factor. *Blood* 1991; **77:** 1131–45.
25. Cannistra SA, Griffin JD, Regulation of the production and function of granulocytes and monocytes. *Semin Hematol* 1988; **25:** 173–88.
26. Hill ADK, Naama HA, Calvano SE, Daly JM, The effect of granulocyte–macrophage colony-stimulating factor on myeloid cells and its clinical applications. *J Leucocyte Biol* 1995; **58:** 634.

27. Armitage JO, Emerging applications of recombinant human granulocyte–macrophage colony-stimulating factor. *Blood* 1998; **92:** 4491–508.
28. Root RK, Dale DC, Granulocyte colony-stimulating factor and granulocyte–macrophage colony-stimulating factor: comparisons and potential for use in the treatment of infections in nonneutropenic patients. *J Infect Dis* 1999; **179**(Suppl 2): S342–52.
29. Wingard JR, Growth factors and other immunomodulators. In: *Transplant Infections* (Bowden R, Ljungman P, Paya C, eds). Philadelphia: Lippincott-Raven, 1998: 367–78.
30. American Society of Clinical Oncology Recommendations for the Use of Hematopoietic Colony-Stimulating Factors: evidence-based, clinical practice guidelines. *J Clin Oncol* 1994; **12:** 2471–508.
31. American Society of Clinical Oncology Recommendations for the Use of Hematopoietic Colony-Stimulating Factors: evidence-based clinical practice guidelines. *J Clin Oncol* 1996; **14:** 1957–60.
32. Ozer H, Armitage JO, Bennett CL et al, 2000 update of Recommendations for the Use of Hematopoietic Colony-Stimulating Factors: evidence-based clinical practice guidelines. *J Clin Oncol* 2000; **18:** 3558–85.
33. Crawford J, Ozer H, Stoller R et al, Reduction by granulocyte colony-stimulating factor of fever and neutropenia induced by chemotherapy in patients with small-cell lung cancer (r-metHuG-CSF). *N Engl J Med* 1991; **325:** 164–70.
34. Trillet-Lenoir V, Green J, Manegold C et al, Recombinant granulocyte colony-stimulating factor reduces the infectious complications of cytotoxic chemotherapy. *Eur J Cancer* 1993; **33A:** 319–24.
35. Pettengell R, Gurney H, Radford JA et al, Granulocyte colony-stimulating factor to prevent dose-limiting neutropenia in non-Hodgkin's lymphoma: a randomized controlled trial. *Blood* 1992; **80:** 1430–6.
36. Gebbia V, Testa A, Valenza R et al, A prospective evaluation of the activity of human granulocyte-colony stimulating factor on the prevention of chemotherapy-related neutropenia in patients with advanced carcinoma. *J Chemother* 1993; **5:** 186–90.
37. Zinzani PL, Pavone E, Storti S et al, Randomized trial with or without colony-stimulating factor as adjunct to induction VNCOP-B treatment in elderly high grade non-Hodgkin's lymphoma. *Blood* 1997; **89:** 3975–9.
38. Kaplan LD, Kahn JO, Crowe F et al, Clinical and virologic effects of recombinant human granulocyte–macrophage colony-stimulating factor in patients receiving chemotherapy for human immunodeficiency virus-associated non-Hodgkin's lymphoma: results of a randomized trial. *J Clin Oncol* 1991; **9:** 929–40.
39. Gerhartz HH, Engelhard M, Meusers P et al, Randomized double-blind, placebo-controlled phase III study of recombinant human granulocyte–macrophage colony-stimulating factor as adjunct to induction treatment of high-grade malignant non-Hodgkin's lymphomas. *Blood* 1993; **82:** 2329–39.
40. Hamm JT, Schiller JH, Oken MM et al, Granulocyte–macrophage colony-stimulating factor (GM-CSF) in small cell carcinoma of the lung (SCCL): preliminary analysis of a randomized controlled trial. *Proc Am Soc Clin Oncol* 1991; **10:** 255.
41. Nichols C, Bajorin D, Schmoll HJ et al, VIP chemotherapy with/without GM-CSF for poor risk, relapsed, or refractory germ cell tumors (GCT): preliminary analysis of a randomized controlled trial. *Proc Am Soc Clin Oncol* 1991; **10:** 167.
42. Hamm JT, Schiller J, Oken MM et al, Dose ranging study of recombinant human granulocyte-macrophage colony stimulating factor in small cell lung cancer. *Proc Am Soc Clin Oncol* 1993; **12:** 335.
43. Beveridge RA, Miller JA, Kales AN et al, A comparison of efficacy of sargramostim (yeast-derived RhuGM-CSF) and filgrastim (bacteria-derived RhuG-CSF) in the therapeutic setting of chemotherapy-induced myelosuppression. *Cancer Invest* 1998; **16:** 366–73.
44. Lyman GH, Lyman CG, Sanderson RA et al, Decision analysis of hematopoietic growth factor use in patients receiving cancer chemotherapy. *J Natl Cancer Inst* 1993; **85:** 488–93.
45. Mayordomo JI, Rivera F, Diaz-Puente MT et al, Decision analysis of hematopoietic growth factor use in patients receiving cancer chemotherapy. *J Natl Cancer Inst* 1993; **85:** 1251–2.
46. Bash RO, Katz JA, Cash JV et al, Safety and cost effectiveness of early discharge of relatively low

risk children with cancer hospitalized for fever and neutropenia (F/N). *Proc Am Soc Clin Oncol* 1992; **11:** 381.

47. Rolston KVI, Rubenstein EB, Elting L et al, Ambulatory management of febrile episodes in low-risk neutropenic patients. In: *Program and Abstracts of the 35th Interscience Conference of Antimicrobial Agents and Chemotherapy, San Francisco, CA*, 1995: 333 (Abst 2235).
48. Kern WV, Cometta A, de Bock R et al, Oral versus intravenous empirical antimicrobial therapy for fever in patients with granulocytopenia who are receiving cancer chemotherapy. *N Engl J Med* 1999; **341:** 312–18.
49. Finberg RW, Talcott JA, Fever and neutropenia – how to use a new treatment strategy. *N Engl J Med* 1999; **341:** 362–3.
50. Talcott JA, Finberg R, Mayer RJ, Goldman L, The medical course of cancer patients with fever and neutropenia. *Arch Intern Med* 1988; **148:** 2561–8.
51. Talcott JA, Siegel RD, Finberg R, Goldman L, Risk assessment in cancer patients with fever and neutropenia: a prospective, two-center validation of a prediction rule. *J Clin Oncol* 1992; **10:** 316–22.
52. Talcott JA, Whalen A, Clark J et al, Home antibiotic therapy for low-risk cancer patients with fever and neutropenia: a pilot study of 30 patients based on a validated prediction rule. *J Clin Oncol* 1994; **12:** 107–14.
53. Rubenstein EB, Rilston K, Benjamin RS et al, Outpatient treatment of febrile episodes in low-risk neutropenic patients with cancer. *Cancer* 1993; **71:** 3640–6.
54. Lau RC, King SM, Richardson SE, Early discharge of pediatric febrile neutropenic cancer patients by substitution of oral for intravenous antibiotics. *Pediatr Hematol Oncol* 1994; **11:** 417–21.
55. Rolston KVI, Rubenstein EB, Freifeld A, Early empiric antibiotic therapy for febrile neutropenic patients at low risk. *Infect Dis Clin North Am* 1996; **10:** 223–7.
56. Freifeld A, Marchigiani D, Walsh T et al, A double-blind comparison of empirical oral and intravenous antibiotic therapy for low-risk febrile patients with neutropenia during cancer chemotherapy. *N Engl J Med* 1999; **341:** 305–11.
57. Klastersky J, Paesmans M, Rubenstein EB et al, The Multinational Association for Supportive Care in Cancer Risk Index: a multinational scoring system for identifying low-risk febrile neutropenic cancer patients. *J Clin Oncol* 2000; **18:** 3038–51.
58. Bennett CL, Weeks JA, Somerfield MR et al, Use of hematopoietic colony-stimulating factors: comparison of the 1994 and 1997 American Society of Oncology Surveys regarding ASCO Clinical Practice Guidelines. *J Clin Oncol* 1999; **17:** 3676–81.
59. Goldie JH, Coldman AJ, A mathematical model for relating the drug sensitivity of tumors to their spontaneous mutation rate. *Cancer Res* 1982; **42:** 965–73.
60. Logothesis CJ, Finn LD, Smith T et al, Escalated MVAC with and without recombinant granulocyte–macrophage colony-stimulating factor for the clinical treatment of advanced malignant urothelial tumors: results of a randomized trial. *J Clin Oncol* 1995; **13:** 2272.
61. Yau J, Neidhart J, Triozzi P et al, Randomized placebo-controlled trial of granulocyte–macrophage colony-stimulating factor support for dose intensive cyclophosphamide, etoposide, and cisplatin. *Am J Hematol* 1996; **51:** 289.
62. Steward W, von Pawel J, Gatzenmeier U et al, Effects of granulocyte–macrophage colony-stimulating factor and dose intensification of V-ICE chemotherapy in small cell lung cancer: a prospective randomized study of 300 patients. *J Clin Oncol* 1998; **16:** 642.
63. Bajetta E, DiBartolomeo M, Carnaghi C et al, FEP regimen in advanced gastric cancer, with and without low-dose GM-CSF: an Italian Trial in Medical Oncology study. *Br J Cancer* 1998; **77:** 1149.
64. Gisselbrecht C, Haioun C, Lepage E et al, Placebo controlled phase III study of lenograstim (glycosylated recombinant human granulocyte-stimulating factor) in aggressive non-Hodgkin's lymphoma. *Leuk Lymphoma* 1997; **25:** 289–300.
65. Sieber M, Engert A, Diehl V, Treatment of Hodgkin's disease: results and current concepts of the German Hodgkin's Lymphoma Study Group. *Ann Oncol* 2000; **11**(Suppl 1): S81–5.
66. Thatcher N, Girling DJ, Hopwood P et al, Improving survival without reducing the quality of life in small cell lung cancer patients by increasing the dose intensity of chemotherapy with granulocyte colony-stimulating factor sup-

port: results of British Medical Research Council Multicenter Randomized Trial. *J Clin Oncol* 2000; **18:** 395–404.
67. Kaku K, Takhashi M, Moriyama Y et al, Recombinant human granulocyte–macrophage colony-stimulating factor after chemotherapy in patients with non-Hodgkin's lymphoma. A placebo controlled double-blind phase III trial. *Leuk Lymphoma* 1993; **11:** 229–38.
68. Bennett CL, Smith TJ, Weeks JC et al, Use of hematopoietic colony-stimulating factors: the American Society of Clinical Oncology Survey. The Health Services Research Committee of the American Society of Clinical Oncology. *J Clin Oncol* 1996; **14:** 2511–20.
69. Swanson G, Bergstrom K, Stump E et al, Growth factor usage patterns and outcomes in the community setting: collection through a practice-based computerized clinical information system. *J Clin Oncol* 2000; **18:** 1764–770.
70. De Graaf H, Willemse PH, Bong SB et al, Dose intensity of standard adjuvant CMF with granulocyte colony-stimulating factor for premenopausal patients with node-positive breast cancer. *Oncology* 1996; **53:** 289–94.
71. Ribas A, Albanell J, Bellmund J et al, Frequent dose delays and growth factor requirements with the sequential doxorubicin–CMF schedule. *Acta Oncol* 1997; **36:** 701.
72. Silvestri F, Velisig M, Fanim R et al, Granulocyte colony-stimulating factor (G-CSF) allows the delivery of effective doses of CHOP and CVP regimens in non-Hodgkin's lymphoma. *Leuk Lymphoma* 1995; **16:** 465.
73. Maher DW, Lieschke GJ, Green M et al, Filgrastim in patients with chemotherapy-induced febrile neutropenia: a double-blind, placebo-controlled trial. *Ann Intern Med* 1994; **121:** 492–501.
74. Mayordomo JI, Rivera F, Diaz-Puente MT et al, Improving treatment of chemotherapy-induced neutropenic fever by administration of colony-stimulating factors. *J Natl Cancer Inst* 1995; **87:** 803–8.
75. Riikonen P, Saarinen UM, Makipernaa A et al, Recombinant human granulocyte–macrophage colony-stimulating factor in the treatment of febrile neutropenia: a double-blind placebo-controlled study in children. *Pediatr Infect Dis J* 1994; **13:** 197–202.
76. Anaissie E, Vartivarian S, Bodey GP et al, Randomized comparison between antibiotics alone and antibiotics plus granulocyte–macrophage colony-stimulating factor (*Escherichia coli*-derived) in cancer patients with fever and neutropenia. *Am J Med* 1996; **100:** 17–23.
77. Biesma B, de Vries EG, Willemse PH et al, Efficacy and tolerability of recombinant human granulocyte–macrophage colony-stimulating factor in patients with chemotherapy-related leukopenia and fever. *Eur J Cancer* 1990; **26:** 932–6.
78. Vellenga E, Uyll-de Groot CA, de Wit R et al, Randomized placebo-controlled trial of granulocyte–macrophage colony-stimulating factor in patients with chemotherapy-related febrile neutropenia. *J Clin Oncol* 1996; **14:** 619–27.
79. Ravaud A, Chevreau C, Bonichon F et al, Granulocyte–macrophage colony-stimulating factor (GM-CSF) in patients with neutropenic fever is potent after low-risk but not after high-risk neutropenic chemotherapy regimens: results of a randomized phase III trial. *J Clin Oncol* 1998; **16:** 2930–6.
80. Mitchell PLR, Morland BJ, Dick G et al, Clinical benefits and cost savings of interventional G-CSF therapy in patients with febrile neutropenia following chemotherapy. *Blood* 1995; **86**(Suppl 1): 500a.
81. Mitchell PL, Morland B, Stevens MC et al, Granulocyte colony-stimulating factor in established febrile neutropenia: a randomized study of pediatric patients. *J Clin Oncol* 1997; **15:** 1163–70.
82. Yoshida M, Karasawa M, Naruse T et al, Effect of granulocyte-colony stimulating factor on empiric therapy with flomoxef sodium and tobramycin in febrile neutropenic patients with hematological malignancies. Kan-etsu Hematological Disease and Infection Study Group. *Int J Hematol* 1999; **69:** 81–8.
83. Aviles A, Guzman R, Garcia E et al, Results of a randomized trial of colony-stimulating factor in patients with infection and severe granulocytopenia. *Anticancer Drugs* 1996; **7:** 392–7.
84. Blay JY, Chauvin F, Le Cesne et al, Early lymphopenia after cytotoxic chemotherapy as a risk factor for febrile neutropenia. *J Clin Oncol* 1996; **14:** 636–43.
85. Hartmann LC, Tschetter LK, Habermann TM et al, Granulocyte colony-stimulating factor in

severe chemotherapy induced afebrile neutropenia. *N Engl J Med* 1997; **336:** 1776–80.
86. Crawford J, Kreisman H, Garewal H et al, The impact of filgrastim schedule variation on hematopoietic recovery postchemotherapy. *Ann Oncol* 1997; **8:** 1117–24.
87. Stone RM, Berg DT, Stephen LG et al, Granulocyte–macrophage colony-stimulating factor after initial chemotherapy for elderly patients with primary acute myelogenous leukemia. *N Engl J Med* 1995; **25:** 1671–7.
88. Rowe JM, Andersen J, Mazza JJ et al, Phase III randomized placebo-controlled study on granulocyte–macrophage colony stimulating factor (GM-CSF) in adult patients (55–70 years) with acute myelogenous leukemia (AML). A study of the Eastern Cooperative Oncology Group (ECOG). *Blood* 1995; **86:** 257.
89. Witz F, Sadoun A, Perrin M-C et al, A placebo-controlled study of recombinant human macrophage colony-stimulating factor administered during and after induction treatment for de novo acute myelogenous leukemia in elderly patients. *Blood* 1998; **91:** 2722–30.
90. Zittoun R, Suciu S, Mandelli F et al, Granulocyte–macrophage colony-stimulating factor associated with induction treatment of acute myelogenous leukemia: a randomized trial by the European Organization for the Research and Treatment of Cancer Leukemia Cooperative Group. *J Clin Oncol* 1996; **14:** 2150–9.
91. Buchner T, Hiddemann W, Wormann B et al, GM-CSF multiple course priming and long-term administration in newly diagnosed AML. Hematologic and therapeutic effect. *Blood* 1994; **84**(Suppl 1): 27a.
92. Lowenberg B, Boogaerts MA, Daenen SMGJ et al, Value of different modalities of granulocyte–macrophage colony-stimulating factor applied during or after induction therapy of acute myeloid leukemia. *J Clin Oncol* 1997; **15:** 3496–506.
93. Lowenberg B, Suciu S, Archimbaud E et al, Use of recombinant granulocyte–macrophage colony-stimulating factor during and after remission induction chemotherapy in patients aged 61 years and older with acute myeloid leukemia (AML): final report of AML-11, a phase III randomized study of the Leukemia Cooperative Group of European Organization for the Research and Treatment of Cancer (EORTC–LCG) and the Dutch Belgian Hemato-Oncology Cooperative Group (HOVON). *Blood* 1997; **90:** 2952–61.
94. Heil G, Hoelzer D, Sanz MA et al, for the International Leukemia Study Group, A randomized, double-blind, placebo-controlled, phase III study of filgrastim in remission induction and consolidation therapy for adults with de novo acute myeloid leukemia. *Blood* 1997; **90:** 4710–18.
95. Godwin JE, Kopecky KJ, Head DR et al, A double-blind placebo-controlled trial of granulocyte-colony stimulating factor in elderly patients with previously untreated acute myeloid leukemia: a Southwest Oncology Group Study (9031). *Blood* 1998; **91:** 3607–15.
96. Dombret H, Yver A, Chastang C et al, the Cooperative Study Group, Increased frequency of complete remission by lenograstim recombinant human granulocyte colony-stimulating factor (rhG-CSF) administration after intensive induction chemotherapy in elderly patients with de novo acute myeloid leukemia (AML): final results of a randomized multicenter double-blind controlled study. *N Engl J Med* 1995; **332:** 1678.
97. Dombert H, Chastang C, Fenaux P et al, A controlled study of recombinant human granulocyte colony-stimulating factor in elderly patients after treatment for acute myelogenous leukemia. *N Engl J Med* 1995; **332:** 1678–83.
98. Bennett CL, Stinson TJ, Tallman MS et al, Economic analysis of a randomized placebo-controlled phase III study of granulocyte macrophage colony stimulating factor in adult patients (>55 to 70 years of age) with acute myelogenous leukemia. Eastern Cooperative Oncology Group (E1490). *Ann Oncol* 1999; **10:** 177–82.
99. Schiffer CA, Hematopoietic growth factors as adjunct to the treatment of acute myeloid leukemia. *Blood* 1995; **88:** 3675–85.
100. Geller RB, Use of cytokines in the treatment of acute myelocytic leukemia: a critical review. *J Clin Oncol* 1996; **14:** 1371–82.
101. Rowe JM, Liesveld JL, Hematopoietic growth factors in acute leukemia. *Leukemia* 1997; **11:** 328–41.
102. Nemunaitis J, Use of cytokines in the treatment of acute lymphoblastic leukemia. *Leukemia* 1997; **11**(Suppl 4): S36–7.

103. Estey E, Hematopoietic growth factors in the treatment of acute leukemia. *Curr Opin Oncol* 1998; **10:** 23–30.
104. Hiddemann W, Kern W, Schoch C et al, Management of acute myeloid leukemia in elderly patients. *J Clin Oncol* 1999; **17:** 3569–76.
105. Harousseau JL, Witz F, Lioure B et al, Granulocyte colony-stimulating factor after intensive consolidation chemotherapy in acute myeloid leukemia: results of a randomized trial of the Groupe Ouest–Est Leucémies Aiguës Myéloblastiques (GOELAM). *J Clin Oncol* 2000; **18:** 780–7.
106. Moore JO, Dodge RK, Amrein PC et al, Granulocyte-colony stimulating factor (filgrastim) accelerates granulocyte recovery following intensive postremission chemotherapy for acute myeloid leukemia with aziridinyl benzoquinone (AZO) and mitoxantrone: Cancer and Leukemia Group B Study 9022. *Blood* 1997; **89:** 780–8.
107. Larson RA, Dodge RK, Linker CA et al, A randomized controlled trial of filgrastim during remission induction and consolidation chemotherapy for adults with acute lymphoblastic leukemia: CALGB Study 9111. *Blood* 1998; **92:** 1556–64.
108. Ottman OG, Hoelzer D, Gracien E et al, Simultaneous administration of granulocyte colony-stimulating factor (filgrastim) and induction chemotherapy in acute lymphoblastic leukemia. A randomized phase III trial. *Blood* 1995; **86:** 444.
109. Gessler K, Koller E, Hubmann E et al, Granulocyte colony-stimulating factor as an adjunct to induction chemotherapy for adult acute lymphoblastic leukemia – a randomized phase III study. *Blood* 1997; **90:** 590–6.
110. Ohno R, Tomonaga M, Ohshima T et al, A randomized controlled study of granulocyte colony stimulating factor after intensive induction and consolidation therapy in patients with acute lymphoblastic leukemia. Japan Adult Leukemia Study Group. *Int J Hematol* 1993; **58:** 73–81.
111. Pui CH, Boyett JM, Hughes WT et al, Human granulocyte colony-stimulating factor after induction chemotherapy in children with lymphoblastic leukemia. *N Engl J Med* 1997; **336:** 1781–7.
112. Laver J, Amylon M, Desai S et al, Randomized trial of r-metHu granulocyte colony-stimulating factor in an intensive treatment for T-cell leukemia and advanced-stage lymphoblastic lymphoma of childhood: a Pediatric Oncology Group pilot study. *J Clin Oncol* 1998; **16:** 522–6.
113. Welte K, Reiter A, Mempel K et al, A randomized phase III trial of the efficacy of granulocyte colony-stimulating factor in children with high-risk acute lymphoblastic leukemia. *Blood* 1997; **87:** 3143.
114. Michel G, Landman-Parker J, Auclerc M et al, Use of recombinant human granulocyte colony-stimulating factor to increase chemotherapy dose-intensity; a randomized trial in very high-risk childhood acute lymphoblastic leukemia. *J Clin Oncol* 2000; **18:** 1517–24.
115. Khwaja A, Linch DC, Goldstone AH et al, rhG-CSF after bone marrow transplantation for malignant lymphoma: a BNLI double-blind placebo-controlled trial. *Br J Haematol* 1992; **82:** 317.
116. Gorin NC, Coiffier B, Hayat M et al, rhGM-CSF after high dose chemotherapy and ABMT with unpurged and purged marrow in non-Hodgkin's lymphoma: a double-blind placebo-controlled trial. *Blood* 1992; **80:** 1149.
117. Gulati SC, Bennett CL, GM-CSF as adjunct therapy in relapsed Hodgkin disease. *Ann Intern Med* 1992; **116:** 177.
118. Link H, Boogaerts MA, Carella AM et al, A controlled trial of rhGM-CSF after TBI, high-dose chemotherapy, and ABMT for ALL or malignant lymphoma. *Blood* 1992; **80:** 2188.
119. Nemunaitis J, Rabinowe SN, Singer JW et al, rhGM-CSF after ABMT for lymphoid cancer. *N Engl J Med* 1991; **324:** 1773.
120. Schmitz N, Dreger P, Zander AR et al, Results of a randomized controlled multicenter study of rhG-CSF in patients with Hodgkin's disease and non-Hodgkin's lymphoma undergoing ABMT. *Bone Marrow Transplant* 1995; **15:** 261–6.
121. Stahel RA, Jost LM, Cerny T et al, Randomized study of rhG-CSF after high-dose chemotherapy and ABMT for high-risk lymphoid malignancies. *J Clin Oncol* 1994; **12:** 1931.
122. Advani R, Chao NJ, Horning SJ et al, GM-CSF as an adjunct to autologous hemopoietic stem cell transplantation for lymphoma. *Ann Intern Med* 1992; **116:** 183.
123. Legros M, Fleury J, Bay JO et al, rhGM-CSF vs placebo following rh-GM-CSF-mobilized PBSC transplantation. A phase III double-blind ran-

domized trial. *Bone Marrow Transplant* 1997; **19:** 209.
124. Spitzer G, Adkins DR, Spencer V et al, Randomized study of growth factors post PBPC transplant: neutrophil recovery is improved with modest clinical benefit. *J Clin Oncol* 1994; **12:** 661.
125. Klumpp TR, Mangan KF, Goldberg SL et al, G-CSF accelerates neutrophil engraftment following PBSC transplantation: a prospective, randomized trial. *J Clin Oncol* 1995; **13:** 1323.
126. Linch DC, Milliagan DW, Winfield DA et al, G-CSF significantly accelerates neutrophil recovery after PBSC transplantation in lymphoma patients and shortens the time in hospital: preliminary results of a randomized BNLI trial. *Blood* 1995; **86:** 102a.
127. Bishop MR, Tarantolo SR, Geller RB et al, A randomized, double-blind trial of filgrastim (granulocyte colony-stimulating factor) versus placebo following allogeneic blood stem cell transplantation. *Blood* 2000; **96:** 80–5.
128. Lee SM, Radford JA, Dobson L et al, Recombinant human granulocyte colony-stimulating factor (filgrastim) following high dose chemotherapy and peripheral blood progenitor cell rescue in high grade non-Hodgkin's lymphoma: clinical benefits at no extra cost. *Br J Cancer* 1998; **77:** 1294.
129. McQuaker IG, Hunter AE, Pacey S et al, Low-dose filgrastim significantly enhances neutrophil recovery following autologous peripheral-blood stem-cell transplantation in patients with lymphoproliferative disorders: evidence for clinical and economic benefit. *J Clin Oncol* 1997; **15:** 451.
130. Kawano Y, Takaue Y, Mimaya J et al, Marginal benefit/disadvantage of granulocyte colony-stimulating factor therapy after autologous blood stem cell transplantation in children: results of a prospective randomized trial. *Blood* 1998; **92:** 4040–6.
131. Ojeda E, Garcia-Bustos J, Aguado MJ et al, A randomized study of filgrastim (G-CSF) after autologous peripheral blood transplantation. *Blood* 1998; **92**(Suppl 1): 325b.
132. Gisselbrecht C, Prentice HG, Bacigalupo A et al, Placebo-controlled phase III trial of lenograstim in bone marrow transplantation. *Lancet* 1994; **343:** 696.
133. DeWitte T, Gratwohl A, Van Der Lely N et al, rhGM-CSF accelerates neutrophil and monocyte recovery after allogeneic T-cell-depleted bone marrow transplantation. *Blood* 1992; **79:** 1359.
134. Nemunaitis J, Rosenfeld CS, Ash R et al, Phase III randomized, double-blind placebo-controlled trial of rhGM-CSF following allogeneic bone marrow transplantation. *Bone Marrow Transplant* 1995; **15:** 949.
135. Powles R, Smith C, Milan S et al, rhGM-CSF in allogeneic bone-marrow transplantation for leukaemia: double-blind, placebo-controlled trial. *Lancet* 1990; **336:** 1417.
136. Linch DC, Scarffe H, Proctor S et al, Randomized vehicle-controlled dose-finding study of glycosylated rhG-CSF after bone marrow transplantation. *Bone Marrow Transplant* 1993; **11:** 307.
137. Cortelazzo S, Viero P, Bellavita P et al, G-CSF following PBPC transplant in non-Hodgkin's lymphoma. *J Clin Oncol* 1995; **13:** 935.
138. Szilvassy SF, Hoffman R, Hematopoietic growth factors do not accelerate neutrophil recovery after transplantation of optimally mobilized peripheral blood stem cells. *Biol Blood Marrow Transplant* 1996; **2:** 2.
139. Brandwein JM, Callum J, Sutcliffe SB et al, Analysis of factors affecting hematopoietic recovery after ABMT. *Bone Marrow Transplant* 1990; **6:** 291.
140. Bensinger WI, Longin K, Appelbaum F et al, Peripheral blood stem cells (PBSC) collected after recombinant granulocyte colony-stimulating factor (rhG-CSF): an analysis of factors correlating with the tempo of engraftment after transplantation. *Br J Haematol* 1994; **87:** 825–31.
141. Bensinger W, Martin P, Clift R et al, A prospective, randomized trial of peripheral blood stem cells (PBSC) or marrow (BM) for patients undergoing allogeneic transplantation for hematologic malignancies. *Blood* 1999; **94:** 369a (Abst 1637).
142. Stahel RA, Jost LM, Honegger H et al, Randomized trial showing efficacy of filgrastim 5 μg/kg/day and 10 μg/kg/day following high dose chemotherapy and autologous bone marrow transplantation in high risk lymphomas. *J Clin Oncol* 1997; **15:** 1730–5.
143. Faucher C, Le Corroller AG, Chabannon C et al, Administration of G-CSF can be delayed after transplantation of autologous G-CSF-primed

blood stem cells: a randomized study. *Bone Marrow Transplant* 1996; **17:** 533–6.
144. Bence-Bruckler I, Bredeson C, Atkins H et al, A randomized trial of granulocyte colony-stimulating factor (Neupogen) starting day 1 vs day 7 post-autologous stem cell transplantation. *Bone Marrow Transplant* 1998; **22:** 965–9.
145. Ciernik IF, Schanz U, Gmur J, Delaying treatment with granulocyte colony-stimulating factor after allogeneic bone marrow transplantation for hematological malignancies: a prospective randomized trial. *Bone Marrow Transplant* 1999; **24:** 147–51.
146. Hagglud H, Ringden O, Oman S et al, A prospective randomized trial of filgrastim (r-metHuG-CSF) given at different times after unrelated bone marrow transplantation. *Bone Marrow Transplant* 1999; **24:** 831–6.
147. Torres Gomez A, Jimenez MA, Alvarez MA et al, Optimal timing of granulocyte colony-stimulating factor (G-CSF) administration after bone marrow transplantation. A prospective randomized study. *Ann Hematol* 1995; **71:** 65–70.
148. Sobrevilla-Calvo P, Cortes P, Solano P et al, Starting G-CSF on day +7 or on day 0 is equally effective in accelerating neutrophil recovery after autologous peripheral blood stem cell transplantation. *J Clin Oncol* 1996; **15:** 272 (Abst 724).
149. Vey N, Molnar S, Faucher C et al, Delayed administration of granulocyte colony-stimulating factor after autologous bone marrow transplantation: effect of granulocyte recovery. *Bone Marrow Transplant* 1994; **14:** 779.
150. Khwaja A, Mills W, Leveridge K et al, Efficacy of a delayed granulocyte colony-stimulating factor after autologous bone marrow transplantation. *Bone Marrow Transplant* 1993; **11:** 479–82.
151. Viret F, Molina L, Plantaz D, Impact of delayed start (day +5) G-CSF after allogeneic bone marrow transplantation: a pilot study. *Blood* 1994; **84**(Suppl 1): 63 (Abst 369).
152. Masaoka T, Takaku F, Kato S et al, rhG-CSF in allogeneic bone marrow transplantation. *Exp Hematol* 1989; **17:** 1047.
153. NEUPOGEN (filgrastim) prescribing information. Package Circular (P40047H 50M Rev 4-98).
154. LEUKINE (sargramostim) Package Circular (Rev 0230-01).
155. Ikeda K, Tasaka T, Sasaki K et al, Low-dose continuous subcutaneous infusion of granulocyte colony-stimulating factor for chemotherapy-induced neutropenia in acute myelogenous leukemia and its pharmacokinetics. *Leukemia* 1994; **8:** 1838–41.
156. Toner GC, Shapiro JD, Laidlaw CR et al, Low-dose versus standard-dose lenograstim prophylaxis after chemotherapy: a randomized, crossover comparison. *J Clin Oncol* 1998; **16:** 3874–9.
157. Kubota M, Akiyama Y, Mikawa H et al, Comparative effect of 100 versus 250 $\mu g/m^2$/day of G-CSF in pediatric patients with neutropenia induced by chemotherapy. *Pediatr Hematol Oncol* 1995; **12:** 393–7.
158. Kessinger A, Bishop MR, Anderson JR et al, Comparison of subcutaneous and intravenous administration of recombinant human granulocyte–macrophage colony-stimulating factor for peripheral blood stem cell mobilization. *J Hematother* 1995; **4:** 81–4.
159. Sturgill MG, Huhn RD, Drachtman RA et al, Pharmacokinetics of intravenous recombinant human colony-stimulating factor (rhG-CSF) in children receiving myelosuppressive cancer chemotherapy: clearance increases in relation to absolute neutrophil count. *Am J Hematol* 1997; **54:** 124–30.
160. Sugiura M, Yamamoto K, Sawada Y, Iga T, Pharmacokinetic/pharmacoeconomic analysis of neutrophil proliferation induced by recombinant granulocyte colony-stimulating factor (rhG-CSF): comparison between intravenous and subcutaneous administration. *Biol Pharm Bull* 1997; **20:** 684–9.
161. Broxmeyer HE, Benninger L, Patel S et al, Kinetic response of human marrow progenitor cells to in vivo treatment of patients with granulocyte colony-stimulating factor is different from the response with granulocyte–macrophage colony-stimulating factor. *Exp Hematol* 1994; **22:** 100–2.
162. Bennett C, Stinson T, Bhoopalam N et al, A double-blind, randomized trial of toxicity, resource use and costs for filgrastim and sargramostim. *Proc Am Soc Clin Oncol* 2000; **19:** 436a (Abst 1712).
163. Beveridge R, Miller J, Kales A et al, Randomized trial comparing the tolerability of sargramostim (yeast-derived RhuGM-CSF) and filgrastim (bacteria-derived RhuG-CSF) in cancer patients receiving myelosuppressive

chemotherapy. *Support Care Cancer* 1995; **5:** 289–98.
164. Strauss RG, Therapeutic granulocyte transfusions in 1993. *Blood* 1993; **81:** 1675–8.
165. Strauss RG, Rebirth of granulocyte transfusions: Should it involve pediatric oncology and transplant patients? *J Pediatr Hematol Oncol* 1999; **21:** 475–8.
166. Ditcher JP, The potential benefit of granulocyte transfusion therapy. *Cancer Invest* 1989; **7:** 457–62.
167. Klein HG, Strauss RG, Schiffer CA, Granulocyte transfusion therapy. *Semin Hematol* 1996; **33:** 359–68.
168. Dale DC, Liles WC, Return of granulocyte infusions. *Curr Opin Pediatr* 2000; **12:** 18–22.
169. Casper C, Seger R, Burger J, Gmur J, Effective stimulation of donors for granulocyte transfusions with recombinant methionyl granulocyte colony-stimulating factor. *Blood* 1993; **81:** 2866–71.
170. Bensinger WI, Price TH, Dale DC et al, The effects of daily recombinant human granulocyte colony-stimulating factor administration on normal granulocyte donors undergoing leukapheresis. *Blood* 1993; **81:** 1883.
171. Jendiroba DB, Lichtinger B, Freireich EJ, The use of hematopoietic growth factors for recruitment of leukocytes after transfusions. In: *Clinical Applications of Cytokines and Growth Factors* (Wingard JR, Demetri GD, eds). Dordrecht: Kluwer, 1999.
172. Adkins DR, Goodnough LT, Shenoy S et al, Effect of leukocyte compatibility on neutrophil increment after transfusion of granulocyte colony-stimulating factor-mobilized prophylactic granulocyte transfusions and on clinical outcomes after stem cell transplantation. *Blood* 2000; **95:** 3605–12.
173. Jendiroba D, Lichtiger B, Anaissie E et al, Evaluation and comparison of three mobilization methods for the collection of granulocytes. *Transfusion* 1998; **38:** 722–8.
174. Price TH, Bowden RA, Boeckh M et al, Phase I/II trial of neutrophil transfusions from donors stimulated with G-CSF and dexamethasone for treatment of patients with infections in hematopoietic stem cell transplantation. *Blood* 2000; **95:** 3302–9.
175. Dale DC, Liles WC, Llewellyn A et al, Neutrophil transfusions: kinetics and function of neutrophils mobilized with granulocyte colony-stimulating factor (G-CSF) and dexamethasone. *Transfusion* 1998; **38:** 713–21.
176. Djerassi I, Filtration leukapheresis for the separation and concentration of transfusable amounts of normal human granulocytes. *J Med (Basel)* 1970; **1:** 358–64.
177. Ts'ao C, Ruder EA, Ultrastructural damage of leukocytes procured by Leukopak: vulnerability of leukocytes to mechanical injury. *Transfusion* 1976; **16:** 336–44.
178. Schiffer CA, Buchholz DH, Aisner J et al, Clinical experience with transfusion of granulocytes obtained by continuous flow filtration leukapheresis. *Am J Med* 1975; **58:** 373–81.
179. Hammerschmidt DE, Carddock PR, McCullough F et al, Complement activation and pulmonary leukostasis during nylon fiber filtration leukapheresis. *Blood* 1978; **51:** 721–30.
180. Loftus TJ, White RF, Huestis DW, Leukapheresis: increasing the granulocyte yield with the Fenwal CS-3000. *J Clin Apheresis* 1983; **1:** 109–14.
181. Adkins D, Goodgold H, Hendershott L et al, Indium-labeled white blood cells apheresed from donors receiving G-CSF localize to sites of inflammation when infused into allogeneic bone marrow transplant recipients. *Bone Marrow Transplant* 1997; **19:** 809–14.
182. Freii E III, Levin RH, Bodey GP et al, The nature and control of infections in patients with acute leukemia. *Cancer Res* 1965; **25:** 1511–15.
183. Boggs DR, Transfusion of neutrophils as prevention or treatment of infection in patients with neutropenia. *N Engl J Med* 1974; **290:** 1055.
184. Colotta F, Re F, Polentarutti N et al, Modulation of granulocyte survival and programmed cell death by cytokines and bacterial products. *Blood* 1992; **80:** 2012–20.
185. Wright DG, Robichaud KJ, Pizzo PA et al, Lethal pulmonary reactions associated with the combined use of amphotericin B and leukocyte transfusions. *N Engl J Med* 1981; **304:** 1185–9.
186. Schroeder ML, Louie TJ, Pulmonary complications in patients receiving granulocyte transfusions and amphotericin B. *Can Med Assoc J* 1984; **130:** 593–7.
187. Dana BW, Durie DG, White RF et al, Concomitant administration of granulocyte transfusions and amphotericin B in neutropenic patients: absence of significant pulmonary toxicity. *Blood* 1981; **57:** 90–4.

188. Dutcher JP, Kendall J, Norris D et al, Granulocyte transfusion therapy and amphotericin B: adverse reactions? *Am J Hematol* 1989; **31:** 102–8.
189. Schiffer CA, Aisner J, Daly PA et al, Alloimmunization following prophylactic granulocyte transfusion. *Blood* 1979; **54:** 766–74.
190. Bux J, Becker F, Seeger W et al, Transfusion-related acute lung injury due to HLA-A2-specific antibodies in recipient and NB1-specific antibodies in donor blood. *Br J Haematol* 1996; **93:** 707.
191. Adkins D, Spitzer G, Johnston M et al, Transfusions of granulocyte-colony-stimulating factor-mobilized granulocyte components to allogeneic transplant recipients: analysis of kinetics and factors determining posttransfusion neutrophil and platelet counts. *Transfusion* 1997; **37:** 737–48.
192. Stroncek DF, Leonard K, Eiber G et al, Alloimmunization after granulocyte transfusions. *Transfusion* 1996; **36:** 1009–15.
193. Stroncek DF, Neutrophil antibodies. *Curr Opin Hematol* 1997; **4:** 455–8.
194. Higby DJ, Yates JW, Henderson ES, Holland JF, Filtration leukapheresis for granulocyte transfusion therapy. *N Engl J Med* 1975; **292:** 761–6.
195. Vogler WR, Winton EF, A controlled study of the efficacy of granulocyte transfusions in patients with neutropenia. *Am J Med* 1977; **63:** 548–55.
196. Herzig RH, Herzig GP, Graw RG Jr et al, Successful granulocyte transfusion therapy for Gram-negative septicemia. *N Engl J Med* 1977; **296:** 701–5.
197. Alavi JB, Root RK, Djerassi I et al, A randomized clinical trial of granulocyte transfusions for infection in acute leukemia. *N Engl J Med* 1977; **296:** 706–11.
198. Winston DJ, Ho WB, Gale RP, Therapeutic granulocyte transfusions for documented infections. A controlled trial in ninety-five infectious granulocytopenic episodes. *Ann Intern Med* 1982; **97:** 509–15.
199. Graw RG Jr, Herzig G, Perry S, Henderson ES, Normal granulocyte transfusion therapy. *N Engl J Med* 1972; **287:** 367–76.
200. Fortuny IE, Bloomfield CD, Hadlock DC et al, Granulocyte transfusions: a controlled study in patients with acute nonlymphocytic leukemia. *Transfusion* 1986; **15:** 548–58.
201. Dignani M, Anaissie E, Hester J et al, Treatment of neutropenia-related fungal infections with granulocyte colony-stimulating factor-elicited white blood cell transfusions: a pilot study. *Leukemia* 1997; **11:** 1621–30.
202. Di Mario A, Sica S, Salutari P et al, Granulocyte colony-stimulating factor-primed leukocyte transfusions in *Candida tropicalis* fungemia in neutropenic patients. *Haematologica* 1997; **82:** 362–3.
203. Catalano L, Fontana R, Scarpato N et al, Combined treatment with amphotericin B and granulocyte transfusion from G-CSF-stimulated donors in an aplastic patient with invasive aspergillosis undergoing bone marrow transplantation. *Haematologica* 1997; **82:** 71–2.
204. Ozsahin H, von Planta M, Muller I et al, Successful treatment of invasive aspergillosis in chronic granulomatous disease by bone marrow transplantation, granulocyte colony-stimulating factor-mobilized granulocytes, and liposomal amphotericin B. *Blood* 1998; **15:** 2719–24.
205. Beyer J, Schwella N, Aingsem J et al, Hematopoietic rescue after high-dose chemotherapy using autologous peripheral-blood progenitor cells or bone marrow: a randomized comparison. *J Clin Oncol* 1995; **13:** 1328–35.
206. Schmitz N, Linch DC, Dreger P et al, Randomized trial of filgrastim-mobilized peripheral blood progenitor cell transplantation versus autologous bone marrow transplantation in lymphoma patients. *Lancet* 1996; **347:** 353–7.
207. Nademanee A, Sniecinski I, Schmidt GM et al, High-dose chemotherapy followed by autologous peripheral-blood stem-cell transplantation for patients with Hodgkin's disease and non-Hodgkin's lymphoma using unprimed and granulocyte colony-stimulating factor mobilized peripheral blood stem cells. *J Clin Oncol* 1994; **12:** 2176–86.
208. Korbling M, Przepiorka D, Huh YO et al, Allogeneic blood stem cell transplantation for refractory leukemia and lymphoma: potential advantage of blood over marrow allografts. *Blood* 1995; **85:** 1659–65.
209. Dreger P, Haferlach T, Eckstein V et al, G-CSF-mobilized peripheral blood progenitor cells for allogeneic transplantation: safety,

kinetics of mobilization, and composition of the graft. *Br J Haematol* 1994; **87:** 609–13.

210. Schmitz N, Dreger P, Suttorp M et al, Primary transplantation of allogeneic peripheral blood progenitor cells mobilized by filgrastim (granulocyte colony-stimulating factor). *Blood* 1995; **85:** 1666–72.
211. Bensinger WI, Weaver CH, Appelbaum FR et al, Transplantation of allogeneic peripheral blood stem cells mobilized by recombinant human granulocyte colony-stimulating factor. *Blood* 1995; **85:** 1655–8.
212. Snowden JA, Biggs JC, Milliken ST et al, A randomized, blinded, placebo-controlled, dose escalation study of the tolerability and efficacy of filgrastim for hematopoietic stem cell mobilization in patients with severe rheumatoid arthritis. *Bone Marrow Transplant* 1998; **22:** 1035–41.
213. Ho AD, Young D, Maruyama M et al, Pluripotent and lineage-committed CD34+ subsets in leukapheresis products mobilized by G-CSF, GM-CSF vs. a combination of both. *Exp Hematol* 1996; **24:** 1460–8.
214. Meisenberg B, Brehm T, Schmeckel A et al, A combination of low-dose cyclophosphamide and colony-stimulating factors is more cost-effective than granulocyte-colony-factors alone in immobilizing peripheral blood stem and progenitor cells. *Transfusion* 1998; **38:** 209–15.
215. Cesana C, Carlo-Stella C, Regazzi E et al, CD34+ cells mobilized by cyclophosphamide and granulocyte colony stimulating factor (G-CSF) are functionally different from CD34+ cells mobilized by G-CSF. *Bone Marrow Transplant* 1998; **21:** 561–8.
216. Krishnan A, Bhatia S, Slovak ML et al, Predictors of therapy-related leukemia and myelodysplasia following autologous transplantation for lymphoma: an assessment of risk factors. *Blood* 2000; **95:** 1588–93.
217. Weisdorf D, Miller J, Verfaillie C et al, Cytokine-primed bone marrow stem cells vs. peripheral blood stem cells for autologous transplantation: a randomized comparison of GM-CSF vs G-CSF. *Biol Blood Marrow Transplant* 1997; **3:** 217–23.

APPENDIX: SUMMARY OF GUIDELINES UPDATES*

1. Guidelines for primary prophylactic MGF administration

1996 Recommendation: Primary administration of MGFs was shown to reduce the incidence of febrile neutropenia (FN) by approximately 50% in the three major randomized trials in adults in which the incidence of FN was greater than 40% in the control group. The value of primary MGF administration has not been clearly established in less myelosuppressive regimens, and the cost–benefit of primary versus secondary administration for the majority of initial chemotherapy regimens is unproven. It is recommended that primary administration of MGFs be reserved for patients expected to experience levels of FN that are at least comparable to or greater than those seen in control patients in these randomized trials, i.e. an expected incidence of 40% or more. Thus, for previously untreated patients receiving most chemotherapy regimens, primary administration of MGFs cannot be recommended.

2000 Recommendation: No change.

Special circumstances

1996 Recommendation: Clinicians may occasionally be faced with patients who might benefit from relatively non-myelosuppressive chemotherapy but who have potential risk factors for FN or infection because of bone marrow compromise or comorbidity. It is possible that primary MGF administration may be exceptionally warranted in patients at higher risk for chemotherapy-induced infectious complications, even though the data supporting such use are not conclusive. Such risk factors might include the following: pre-existing neutropenia due to disease, extensive prior chemotherapy, or previous irradiation to the pelvis or other areas containing large amounts of bone marrow; a history of recurrent FN while receiving earlier chemotherapy of similar or lesser dose intensity; or conditions potentially enhancing the risk of serious infection, e.g. poor performance status and more advanced cancer, decreased immune function, open wounds, or already-active tissue infections. This is not meant to be an all-inclusive list; it is anticipated that, depending on the unique features of the clinical situation, there will be instances when the administration of an MGF will be appropriate outside of uses recommended in other guidelines.

2000 Recommendation: No change.

* References are cited as superior numbers, and are given in the reference list to the main text of this chapter.

2. Guidelines for secondary prophylactic MGF administration

1996 Recommendation: There is evidence that MGF administration can decrease the probability of FN in subsequent cycles of chemotherapy after a documented occurrence in an earlier cycle. Even if FN has not occurred, the use of MGFs may be considered if prolonged neutropenia is causing excessive dose reduction or a delay in chemotherapy. However, in the absence of clinical data supporting maintenance of chemotherapy dose intensity, physicians should consider chemotherapy dose reduction as an alternative to the use of MGFs.

2000 Recommendation: In the setting of many tumors, exclusive of curable tumors (e.g. germ cell tumors), dose reduction after an episode of severe neutropenia should be considered as a primary therapeutic option. No published regimens have demonstrated disease-free or overall survival benefits when the dose of chemotherapy was maintained and secondary prophylaxis was instituted. In the absence of clinical data or other compelling reasons to maintain chemotherapy dose intensity, physicians should consider chemotherapy dose reduction after neutropenic fever or severe or prolonged neutropenia after the previous cycle of treatment.

3. Guidelines for MGF therapy

A. Afebrile patients

1996 Recommendation: Data are inadequate with regard to whether patients with neutropenia but no fever will benefit clinically from the initiation of an MGF at the time neutropenia is diagnosed; intervention with an MGF in afebrile neutropenic patients is not recommended.

2000 Recommendation: Current evidence supports the recommendation that MGFs should not be routinely used for patients with neutropenia who are afebrile. The strength of this recommendation has increased with the trial reported in 1997.[85]

B. Febrile patients

1996 Recommendation: For the majority of patients with FN, the available data do not clearly support the routine initiation of MGFs as adjuncts to antibiotic therapy. However, certain FN patients may have prognostic factors that are predictive of clinical deterioration, such as pneumonia, hypotension, multiorgan dysfunction (sepsis syndrome), or fungal infection. The use of MGFs together with antibiotics may be reasonable in such high-risk patients, even though the benefits of administration under these circumstances have not been definitively proven.

2000 Recommendation: The collective results of the eight trials[73–79,81] provide strong and consistent support for the recommendation that MGFs should not be routinely

used as adjunct therapy for the treatment of uncomplicated fever and neutropenia. Uncomplicated fever and neutropenia are defined as follows: fever of 10 days or less in duration; no evidence of pneumonia, cellulitis, abscess, sinusitis, hypotension, multiorgan dysfunction, or invasive fungal infection; and no uncontrolled malignancies. The eight trials have consistently shown a decrease in the duration of neutropenia of less than 500/μl, but clinical benefit has not consistently accompanied the decreased duration of neutropenia.

Certain patients with fever and neutropenia are at higher risk for infection-associated complications and have prognostic factors that are predictive of poor clinical outcome. The use of an MGF for such high-risk patients may be considered, but the benefits of an MGF in these circumstances have not been proven. These factors include profound (absolute neutrophil count (ANC) < 100/μl) neutropenia, uncontrolled primary disease, pneumonia, hypotension, multiorgan dysfunction (sepsis syndrome), and invasive fungal infection. Age greater than 65 years and post-treatment lymphopenia may also be high-risk factors, but have not been consistently confirmed by multicenter trials.

4. Guidelines for use of MGFs to increase chemotherapy dose intensity

1996 Recommendation: Outside of clinical research trials, there is little justification for the use of MGFs to increase chemotherapy dose intensity. In settings in which clinical research demonstrates that dose-intensive therapy not requiring progenitor cell support produces improvement in disease control, MGFs should be used when these therapies are expected to produce significant rates of FN (e.g. in 40% or more of patients).

2000 Recommendation: In the absence of more trials demonstrating a favorable effect on overall survival, disease-free survival, quality of life, or toxicity, there is no justification for the use of MGFs to increase chemotherapy dose intensity or schedule or both outside of a clinical trial. This application of MGF use remains the domain of appropriately designed clinical investigation.

5. Guidelines for use of MGFs as adjuncts to progenitor cell transplantation

1996 Recommendation: MGFs can successfully shorten the period of neutropenia and reduce infectious complications in patients undergoing high-dose cytotoxic therapy with autologous bone marrow transplantation (BMT). MGFs are effective in mobilizing autologous peripheral blood progenitor cells (PBPC) for transplantation, and autologous PBPC transplantation (PBPCT) has been shown to lead to earlier hematopoietic recovery than autologous BMT.[205,206] Trials have demonstrated the value of MGF administration after high-dose chemotherapy and PBPCT.[120,125,207] Available data suggest clinical benefits after allogeneic BMT, and routine primary MGF administration in this setting seems warranted.[134] MGFs can also be used to mobilize donor PBPC for allogeneic transplantation.[208–211] There may also be a role for MGFs in assisting in the recovery

of patients who experience delayed or inadequate neutrophil engraftment after PBPCT. MGFs can be routinely recommended as adjuncts to allogeneic and autologous PBPCT, both for mobilization of PBPC and as a means to speed hematopoietic reconstitution after BMT or PBPCT. Administration of a MGF in cases of engraftment failure is warranted.

2000 Recommendation: MGFs are recommended to help mobilize PBPC and after PBPC infusion. Mobilized PBPC have largely replaced bone-marrow-derived cells for use in autologous transplantation. Side-effects associated with mobilization and subsequent apheresis are usually limited, and include constitutional symptoms and a decrease in platelets and other hematopoietic elements, especially after mobilization with combinations of chemotherapeutic agents and an MGF. The optimal dose of MGFs and chemotherapaeutic agents is the subject of ongoing investigations, but a higher (10 μg/kg/day) dose of G-CSF in the setting of mobilization may yield a greater content of $CD34^+$ progenitor cells in the PBPC product, as documented in patients with hematologic malignancies and in patients with rheumatoid arthritis.[207,212] Although the optimal method of mobilization needs further investigation, especially in heavily pretreated patients, administration of G-CSF, either alone or in combination with GM-CSF, or after the use of chemotherapeutic agents, generates PBPC, leading to rapid hematopoietic recovery, shorter hospitalization, and possibly reduced costs.[206,213–215] Further investigations are necessary to assess the potential risks, especially that of secondary hematologic malignancies associated with the use of combining chemotherapeutic agents and MGFs.[216] The role of MGF-mobilized donor bone marrow in the autologous transplant setting is also under assessment.[217]

6. Guidelines for use of MGFs in patients with acute leukemia and myelodysplastic syndromes

A. Acute myeloid leukemia (AML)

1996 Recommendation: Primary administration of an MGF can be used after completion of induction chemotherapy in patients 55 years of age or older. Although there are fewer data, it is likely that the results showing shortening of the duration of neutropenia may apply to younger patients as well. MGFs given before and/or concurrently with chemotherapy for priming effects still cannot be recommended outside of a clinical trial.

2000 Recommendation: MGF use can be considered in this setting if benefits in terms of possible shortening of hospitalization outweigh the costs of MGF use. Several studies have shown that MGF administration can produce modest decreases in the duration of neutropenia when begun shortly after completion of the initial days of chemotherapy of the initial or repeat induction. Beneficial effects on endpoints such as duration of hospitalization and incidence of severe infections have been variable and modest,

although patients 55 years of age or older are most likely to benefit from MGF use. No study has yet demonstrated significant improvement in complete response rates or long-term outcome. Thus, while there seems to be minimal risk associated with the use of MGFs in this situation, the choice of whether or not to use the MGF is likely to be determined by cost considerations. In a nutshell, the cost of the cytokine must be balanced against any possible shortening of hospitalization associated with the slightly more rapid marrow recovery, as, for example, in patients 55 years of age or older. It is not known from the published data whether the MGFs significantly accelerate recovery to an ANC of 100–200/μl. In most patients, regenerating counts of this level are sufficient to protect against infection so as to permit safe discharge of patients from hospital.

There is no evidence that MGFs given either before or concurrently with chemotherapy for priming effects are of benefit, and their use in this fashion cannot be recommended outside the setting of a clinical trial.

There seems to be more profound shortening of the duration of neutropenia after consolidation chemotherapy for patients with AML in remission. Although the randomized studies did not address this issue, it is likely that this will be associated with decreased rates of hospitalization and possibly shorter durations of hospitalization in such patients. No benefit has been demonstrated in terms of prolongation of complete response duration or overall survival; however, the available evidence indicate that MGFs can be recommended after the completion of consolidation chemotherapy.

B. Myelodysplastic syndromes (MDS)

1996 Recommendation: MGFs can increase the ANC in neutropenic patients with MDS. Data supporting the routine, long-term, continuous use of MGFs in these patients are lacking. Intermittent administration of MGFs may be considered in a subset of patients with severe neutropenia and recurrent infection.

2000 Recommendation: No change.

C. Acute lymphoblastic leukemia (ALL)*

2000 Recommendation: The data are sufficient to recommend G-CSF administration begun after completion of the first few days of chemotherapy of the initial induction or first post-remission course, thus shortening the duration of neutropenia of less than 1000/μl by approximately 1 week. Effects on the incidence and duration of hospitalization and the acquisition of serious infections are less consistent. Although there was a trend for improved complete response rates in one large study,[107] particularly in older adults, there was no prolongation of disease-free or overall survival in any of the trials. G-CSF can be given together with continued corticosteroid/antimetabolite therapy, which is a feature of many ALL regi-

* This topic is new to the guidelines in 2000.

mens, without evidence that such concurrent therapy prolongs the myelosuppressive effects of the chemotherapy. As in AML, it is not known from the published data whether the MGFs significantly accelerate ANC recovery to 100–200/μl. In most patients, regenerating counts of this level are sufficient to protect against infection so as to permit safe discharge of patients from hospital. The use of G-CSF for children with ALL was associated with small benefits in days of antibiotic use or in-hospital days, although a small amount of additional costs was incurred, after the costs of the MGFs were taken into consideration. Cost estimates of MGFs for adults with ALL have not been reported.

D. Leukemia in relapse*

2000 Recommendation: The available data are not sufficient to recommend either for or against the use of MGFs in patients with refractory or relapsed ALL. Few controlled studies have evaluated MGFs in patients with relapsed or refractory acute leukemia. The available data suggest a shortening of the duration of neutropenia, but are inadequate to allow comment on any effects on infectious complications and, in particular, on whether there may be an adverse effect on response rates in some patients with myeloid malignancies because of a stimulatory effect on leukemia growth in a situation in which there is less of a guarantee that chemotherapy will produce sufficient cytoreduction. Therefore, there is no evidence that MGFs are of important benefit in patients with refractory or relapsed myeloid leukemia, and they should be used judiciously or not at all in such patients.

7. Guidelines for use of MGFs in patients receiving concurrent chemotherapy and irradiation

1996 Recommendation: MGFs should be avoided in patients receiving concomitant chemotherapy and radiation therapy.

2000 Recommendation: MGFs should be avoided in patients receiving concomitant chemotherapy and radiation therapy, particularly involving the mediastinum. In the absence of chemotherapy, in patients receiving radiation therapy involving large fields, therapeutic use of MGFs may be considered if prolonged delays secondary to neutropenia are expected.

8. Guidelines for use of MGFs in the pediatric population

1996 Recommendation: In the absence of conclusive pediatric data, the guidelines recommended for adults are generally applicable to the pediatric age group. However, optimal MGF doses have yet to be determined. Further clinical research into the use of these factors in support of chemotherapy and PBPCT in the pediatric age group should be given high priority.

2000 Recommendation: No change.

* This topic is new to the guidelines in 2000.

9. Guidelines for MGF dosing and route of administration

1996 Recommendation: In adults, the recommended MGF doses are 5 μg/kg/day for G-CSF (filgrastim) and 250 μg/m^2/day for GM-CSF (sargramostim). These agents can be administered subcutaneously or intravenously as clinically indicated. MGF dose escalation is not advised. The available data suggest that rounding the dose to the nearest vial size may enhance patient convenience and reduce costs without clinical detriment.

2000 Recommendation: In adults, the recommended MGF doses are 5 μg/kg/day for G-CSF (filgrastim) and 250 μg/m^2/day for GM-CSF (sargramostim) for all clinical settings other than PBPC mobilization. In the setting of PBPC mobilization, if G-CSF is used, a dose of 10 μg/kg/day seems preferable. Outside of this indication, MGF dose escalation is not advised. Rounding the dose to the nearest vial size is an appropriate strategy to maximize cost benefit. The preferred route of MGF administration is subcutaneous.

10. Guidelines for initiation and duration of MGF administration

1996 Recommendation: Existing clinical data suggest that starting G-CSF or GM-CSF between 24 and 72 hours subsequent to chemotherapy may provide optimal neutrophil recovery. Continuing the MGF until the occurrence of an ANC of 10 000/μl after the neutrophil nadir, as specified in the G-CSF package insert, is known to be safe and effective. However, a shorter duration of administration that is sufficient to achieve clinically adequate neutrophil recovery is a reasonable alternative, considering issues of patient convenience and cost.

2000 Recommendation: The optimal timing and duration of MGF administration are still under investigation. Starting MGFs up to 5 days after PBPC reinfusion is reasonable based on available clinical data.

11. Special commentary on comparative clinical activity of G-CSF and GM-CSF

1996 Recommendation: Guidelines about equivalency of the available recombinant preparations of G-CSF and GM-CSF cannot be proposed, because there have been no large-scale, prospective, comparative trials evaluating relative MGF efficacy. The strength of evidence to support the use of G-CSF or GM-CSF varies based on the specific indication for MGF administration, e.g. support after BMT or use with non-transplantation chemotherapy regimens. The panel strongly encourages additional clinical investigation that will guide clinical application of these biologically distinct molecules by addressing issues of comparative clinical activity, toxicity, and cost–effectiveness.

2000 Recommendation: No change.

14

Clinical practical guidelines in patients with fever and neutropenia

Natasha Leighl*, Ronald Feld

INTRODUCTION

Fever in the neutropenic cancer patient is among the most serious complications related to chemotherapy, and is also among the most common. Management of this complication can vary widely, relating to differing geographic patterns of commonly infecting organisms and of antimicrobial resistance, as well as issues of treatment availability and cost containment. To help promote evidence-based quality improvements in the care of cancer patients with neutropenic fever, a number of societies have developed clinical practice guidelines.

Practice guidelines are statements that are systematically developed to assist practitioner and patient decisions about appropriate healthcare for specific circumstances.[1] Many factors influence the use of guidelines, including ease of accessibility, endorsement by a recognized and respected body, perceived quality of evidence contained within the guideline, and the method of synthesis into recommendations. Also, perceptions of relevance of the guidelines to local practice, and their usefulness and applicability, as well as practitioner attitudes towards guideline use in general and the method of guidelines promotion (e.g. peer review publication and criteria for reimbursement), all factor into whether guidelines are adopted in clinical practice.

Similar to critical appraisal of original research, one should not adopt a practice guideline at face value, but rather appraise the methodology of guidelines, their development, and their recommendations before incorporating them into day-to-day clinical practice. In addition to a review of content, the methodology of guidelines for therapy of febrile neutropenic patients will be briefly reviewed. Guides for the clinician include a critical appraisal instrument for clinical guidelines published by Cluzeau et al at St George's Hospital Medical School, London, UK (http://www.sghms.ac.uk/phs/hceu/form.htm),[2] and the popular 'Users' guide to the medical literature' series.[3,4]

ANTIMICROBIAL THERAPY IN NEUTROPENIC PATIENTS WITH FEVER

Using an English-literature search through Medline (up to June 2000), and the Agency for Healthcare and Policy Research Guideline

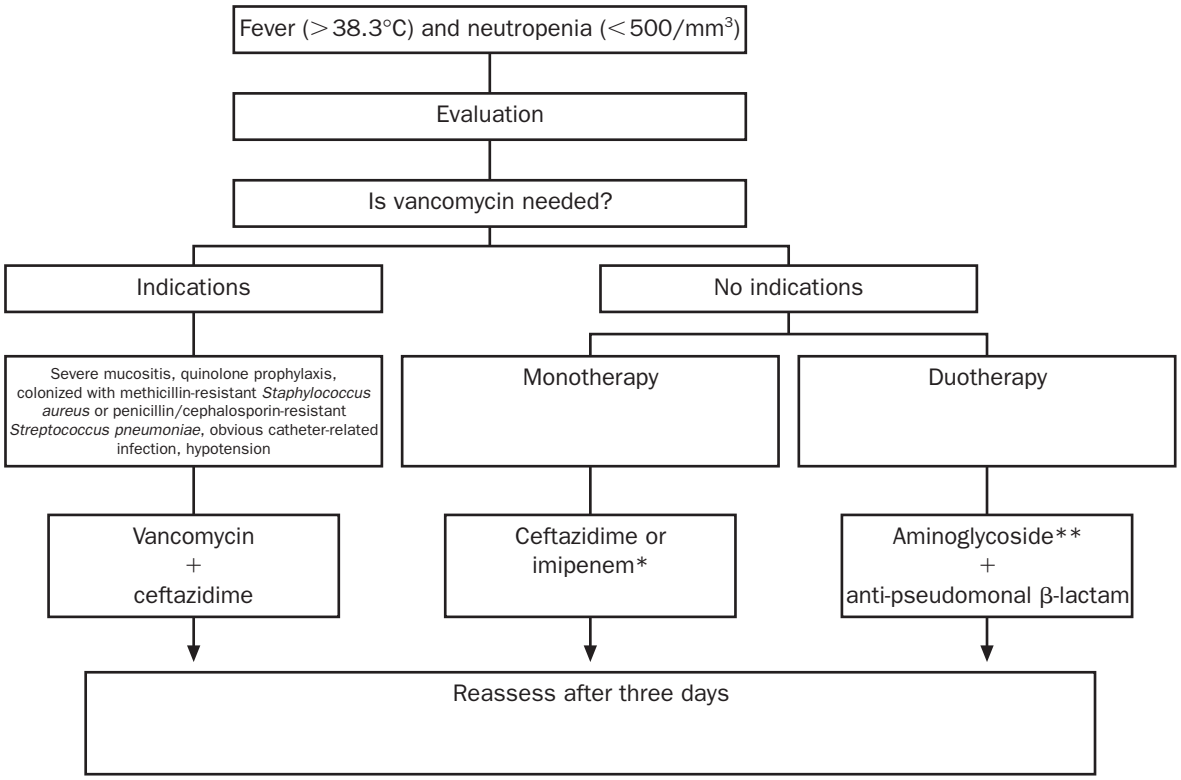
* NL was supported in part by the Department of Medical Oncology, Princess Margaret Hospital, Toronto through the Aventis Fellowship Award in Lung Cancer.

Clearinghouse,[5] several guidelines for empiric therapy in febrile neutropenia have been identified. These include the guidelines commissioned by the Infectious Diseases Society of America, initially developed in 1990 and subsequently revised in 1997.[6,7] The National Comprehensive Cancer Network,[8] the Federation of French Cancer Centers,[9] and the Japanese Infectious Disease Society[10] have also published guidelines in this area. The Italian Association for Pediatric Hematology and Oncology recently published clinical guidelines for empiric antimicrobial therapy of febrile neutropenia in the pediatric population.[11] We have been unable to identify published evaluations of these guidelines, but anticipate that these may be available in the future.

Guidelines from the Infectious Diseases Society of America

The Infectious Diseases Society of America (IDSA) sponsored the development of these guidelines, involving infectious disease and oncology experts in both the adult and pediatric populations, adequately representing the key disciplines in the area, and including one of the authors of this chapter (RF). The initial guidelines were published in 1990,[6] with a revision in 1997 to address several new issues that had emerged in the management of febrile neutropenia, namely the emergence of antibiotic-resistant bacteria, the use of colony-stimulating factors, and the issue of cost containment.[7] While the methodology for identifying studies was not explicit, the sources used as well as the individual studies are clearly listed. In the earlier publication, the rating of strength of the recommendation from the guidelines committee was intertwined with the strength of the supporting evidence, making the rating system occasionally confusing. In the revised document, these are clearly separated, with both a rating system for the strength of the recommendation made and a rating of the quality of evidence for that recommendation. Formulation of the 1997 recommendations was based upon the level of evidence presented, and where adequate data were lacking, consensus of expert opinion was offered. The methodology for resolution of disagreements among the experts was not reviewed in the document. The guidelines were externally reviewed through the peer review process as well as by the Practice Guidelines Committee, and were further subject to approval by the IDSA Council.

In the 1997 IDSA guidelines, a consensus definition of febrile neutropenia is offered, namely a temperature of 38.3°C, or 38.0°C for an hour's duration, in combination with an absolute neutrophil count less than 500/μl, or less than 1000/μl with an anticipated drop to below 500/μl. The consensus for standard evaluation in neutropenic patients was described, with some discussion of controversy surrounding surveillance cultures for colonization, and the role of routine central catheter versus peripheral blood cultures. Prompt initial therapy was recommended in all patients, with three empiric options (see Figure 14.1). One approach includes combination therapy with vancomycin and ceftazidime, particularly where empiric vancomycin is felt to be clinically appropriate. On the whole, less empiric use of vancomycin is recommended in the revised guidelines compared with the previous ones, in an effort to help reduce the frequency of development of vancomycin-resistant organisms. Indications for empiric vancomycin use include obvious catheter-related infections, in the setting of intensive chemotherapy with mucosal damage, quinolone prophylaxis, colonization with β-lactam-resistant *Streptococcus pneumoniae* or with methicillin-resistant *Staphylococcus aureus*, Gram-positive bacteria identified in a blood culture prior to final identification and susceptibility testing, and evidence of hemodynamic instability. The other two options for empiric therapy include monotherapy (with ceftazidime, imipenem, meropenem, or cefepime) and duotherapy (with an aminoglycoside and an anti-pseudomonal β-lactam). Duotherapy with two β-lactam agents is discussed but not



*Recent studies suggest that cefepime or meropenem may be as effective as ceftazidime or imipenem as monotherapy.
**Avoid if patient is also receiving nephrotoxic, otoxic, or neuromuscular blocking agents; has renal or severe electroyte dysfunction; or is suspected of having meningitis.

Figure 14.1 Guide to the initial management of the febrile neutropenic patients. (Reproduced with permission from Hughes WT et al, *J Infect Dis* 1990; **161**: 381–96.[7])

clearly endorsed – a shift from the 1990 recommendations, where it was presented as a clear alternative in initial empiric therapy.

In cases where there is patient defervescence within three days of treatment, it is recommended that clinically stable patients be considered for a change to oral antibiotics, while higher-risk patients continue on initial therapy, or that treatment be tailored to microbiologic evidence of infection where appropriate. In those patients with ongoing fever, reevaluation is recommended on the fourth or fifth day of therapy. If patients are clinically unchanged, options include continuing the same management, or discontinuing vancomycin therapy. If a patient has deteriorated, a change in antibiotics is warranted, incorporating coverage that was not started empirically. This includes amphotericin B institution if patients remain febrile on the fifth to seventh day of therapy, with or without a change in the other antibiotics administered (see Figure 14.2).

With respect to the duration of therapy, patients who are afebrile by the third day of treatment, with granulocyte recovery, can be considered for a seven-day course of therapy. Additional recommendations for treatment duration are outlined in Figure 14.3, and

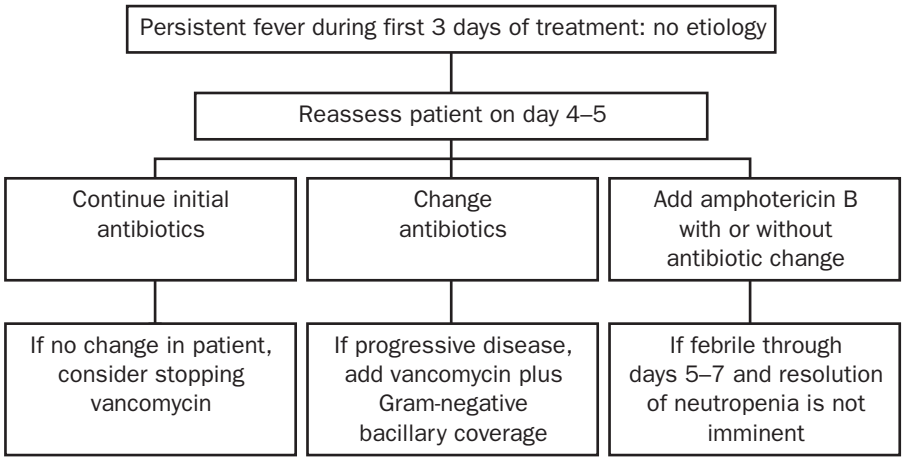


Figure 14.2 Treatment of patients who have persistent fever after three days of treatment and for whom the etiology of the fever is not found. (Reproduced with permission from Hughes WT et al, *J Infect Dis* 1990; **161**: 381–96.[7])

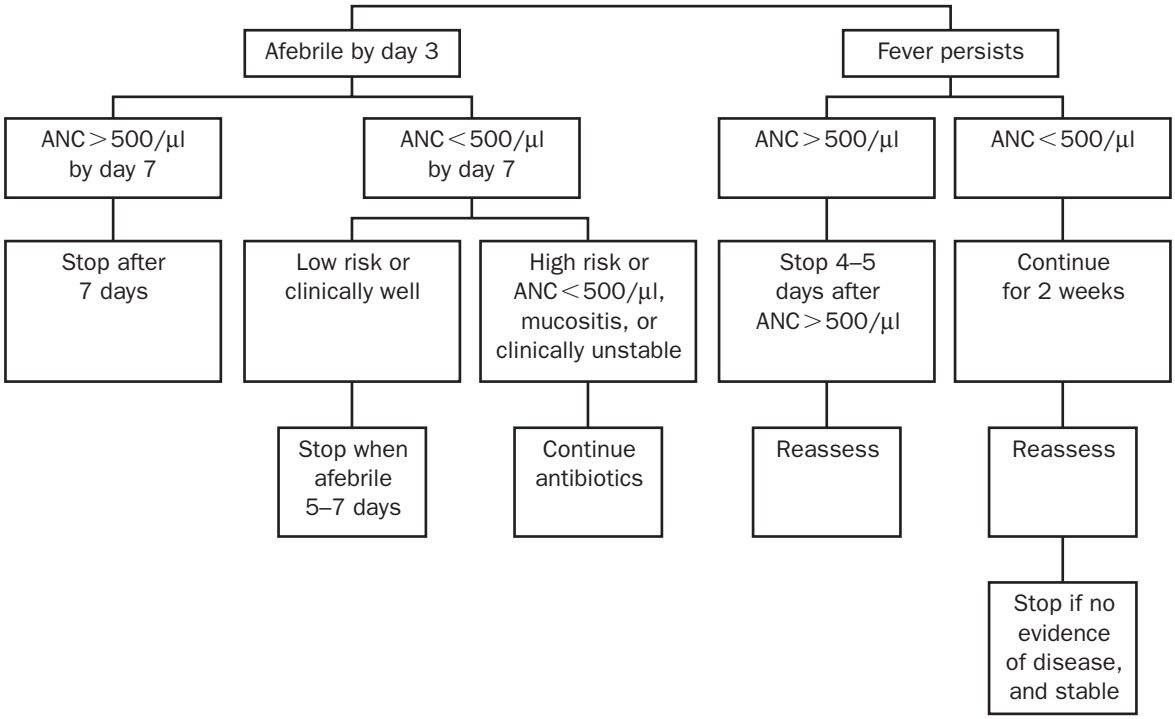


Figure 14.3 Duration of antibiotic therapy (ANC, absolute neutrophil count). (Reproduced with permission from Hughes WT et al, *J Infect Dis* 1990; **161**: 381–96.[7])

include discontinuation of therapy at four to five days after neutrophil recovery. In persistently febrile patients without neutrophil recovery, it is suggested that all antimicrobials may be discontinued after two weeks of therapy including amphotericin B, provided there is no evidence of clinical infection (including computed-tomographic lung and abdominal scans to rule out systemic fungal infection). These patients must then be followed with close observation.

Antivirals are not routinely recommended by the IDSA as part of initial empiric therapy unless clinically indicated, and for the use of hematopoietic colony-stimulating factors (CSFs), clinicians are referred to the American Society of Clinical Oncology guidelines for CSF use.[12–14] However, it was suggested that empiric CSF use might be indicated in patients with hypotension or sepsis-related multiorgan dysfunction, as well as in those with pneumonia, systemic fungal infections, severe cellulitis or sinusitis, and an anticipated delay in marrow recovery. Granulocyte transfusions were not recommended. Except for prophylaxis of *Pneumocystis carinii* infection, these guidelines did not recommend routine antibiotic prophylaxis. The panel reviewed the effectiveness of trimethoprim–sulfamethoxazole (TMP–SMZ) or quinolone prophylaxis, which demonstrated a reduction in infection rates but not in mortality with TMP–SMZ, and a reduction in Gram-negative bacillary infections but not in the rate of infections overall with quinolones. Despite this evidence, the panel declined to recommend routine antibiotic prophylaxis in neutropenic patients because of the concern regarding the emergence of drug-resistant bacteria due to extensive antibiotic use. This represents a shift from the 1990 guidelines, which had endorsed prophylaxis with TMP–SMZ in certain patients. Finally, the updated guidelines review several cost-containment suggestions, including the use of lower-dose antibiotic therapy, stepping down to outpatient oral therapy where possible, and avoiding expensive agents (e.g. liposomal amphotericin B and CSFs) where they are unnecessary. While initial empiric outpatient therapy is not endorsed, it is highlighted as an area of promise, and potential cost containment.

With respect to the appraisal of guideline content, the reasons for and objectives of guideline development are clear, with a satisfactory description of the disease definition and patients to whom the guidelines apply. It is clearly stated that the guidelines are to be used in the context of appropriateness for the individual patient and setting, and should not be used blindly or against the better judgment or experience of the clinician. A multiplicity of treatment options is clearly stated, and the recommendations are clearly presented for clinicians, with an adequate description of treatment benefits, as well as treatment toxicities. As mentioned, there is a section reviewing economic considerations, and most recommendations do appear supported by the benefits, toxicity, and costs of the interventions. Where this is not the case, the panel did highlight reasons for the discrepancy. The IDSA is presently revising the guidelines again, and publication of the revision is anticipated in 2001.

Guidelines from the National Comprehensive Cancer Network

The National Comprehensive Cancer Network (NCCN) has also drafted guidelines for febrile neutropenia management, using consensus of expert opinion and published in 1999.[8] The panel of experts was drawn from member institutions of the NCCN, with the co-chair having also been on the IDSA guidelines development panel. The document states that the recommendations made are based on scientific publications, peer-reviewed information formally presented at meetings, and, where data are lacking, expert opinion. The rating system of recommendations is based on the degree of consensus achieved, ranging from uncontested recommendations to those that caused clear disagreement among the panel experts. The

definition and evaluation of febrile neutropenia outlined in the document parallel those of the IDSA. There is also a review of the utility of two-site culturing for serum cultures, which is not routinely recommended. Initial treatment recommendations again parallel those of the IDSA, with recommendations for monotherapy (using imipenem, meropenem, ceftazidime, cefepime), duotherapy with aminoglycosides and anti-pseudomonal penicillins, and also mention of the use of two β-lactam agents, although this was not universally supported, similar to the IDSA guidelines. Initial use of vancomycin as part of combination therapy was introduced as an option, with similar clinical indications to those of the IDSA. One clear difference from the IDSA guidelines is the option of duotherapy with ciprofloxacin and a ureidopenicillin.

The guidelines are unique in the development of easy-to-use algorithms on site-directed therapy. Various scenarios of clinical infection in the neutropenic cancer patient are reviewed, including clinical signs, appropriate testing strategies, evaluation of treatment response, and duration. There is also a focus on potential etiologic agents and site-specific therapy, including recommendations for empiric antiviral and antifungal therapy tailored to specific clinical scenarios. While these algorithms are very attractive to the clinician for their ease of practical application, the quality of the evidence underpinning the specific therapies in the algorithms is not always explicit in the document, making critical appraisal of that evidence difficult.

The NCCN guidelines include a section on outpatient therapy, with clear recommendations to consider outpatient therapy in experienced centers, based upon the Talcott model of risk assessment and small, randomized trials.[15–18] For the use of CSFs, conformation to the ASCO guidelines is recommended.[12–14] With respect to prophylaxis, there are several recommendations for specific use, in contrast to the IDSA guidelines. These recommendations include the use of quinolone or TMP–SMZ prophylaxis for severe neutropenia (<100 neutrophils/μl for ⩾7 days, but not for routine short-term neutropenia. Antifungal and antiviral prophylaxis are also recommended in specific settings, with a review of the existing evidence (namely fluconazole in marrow transplant patients, herpes simplex virus prophylaxis in marrow transplant and acute leukemia patients with re-induction). With respect to *P. carinii* prophylaxis, several groups are identified as appropriate candidates. These include recipients of allogeneic marrow transplantation and patients receiving therapy for acute lymphoblastic leukemia, and mention is made of consideration of prophylaxis for patients on fludarabine, those with high steroid use (i.e. >20 mg/day of prednisone), and those receiving autologous peripheral blood stem cells. Expert opinion likely underpins consideration of prophylaxis of the latter group, although this is not explicit. Additional suggestions include the use of antibiotic-impregnated vascular catheters, and antifungal treatment strategies including multiple antifungal agents, and adjunctive therapy such as CSFs or even granulocyte transfusions. Again, the overall specificity of the recommendations lends itself well to practical application in the clinical setting, but a clear rating of the supporting evidence for these was not clearly stated in the document text.

Guidelines from the Federation of French Cancer Centers

Recommendations for the management of brief neutropenia from the Federation of French Cancer Centers were published in 1998, in abstract form in English.[9] The practice guideline was developed by a multidisciplinary group of experts, with feedback from oncologists. Data using literature search (Medline and Current Contents) and personal reference lists were used, with clearly defined outcomes for study endpoints. Reviewers from 20 French cancer centers reviewed the evidence and formulated

recommendations. These recommendations are not dissimilar to those of the IDSA. They include informing patients of the risks of chemotherapy, observing afebrile neutropenic episodes without antibiotic prophylaxis, and empiric antibiotic therapy for all febrile neutropenic episodes, which may include β-lactam and aminoglycoside combination therapy or monotherapy with a broad-spectrum β-lactam except in the case of septic shock or respiratory disease. Glycopeptides such as vancomycin can be added if catheter-related or cutaneous infection is obvious, as well as in the case of microbiologically documented infection caused by oxacillin-resistant Gram-positive bacteria, or in the clinically deteriorating patient with persistent fever. The evidence supporting outpatient treatment was felt to be insufficient to recommend it at that time, and participation in studies to identify factors predicting low risk and assessing feasibility and safety of early discharge and outpatient therapy was recommended.

Guidelines from the Japanese Infectious Disease Society

Available in abstract form in English, guidelines developed by the Japanese Infectious Disease Society were published in 2000, using formal consensus methodology where individual panel members vote on each recommendation.[10] The definition and evaluation are similar to those in the guidelines previously discussed, as is empiric therapy, with a recommendation for either monotherapy with a carbapenem or third-generation β-lactam or combination of either with an aminoglycoside. Initial glycopeptide treatment is not mentioned in the abstract, but may well be discussed in the full text. If additional therapy is required, the use of glycopeptide or antifungal agents is recommended. The abstract states that the guidelines require study for confirmation, implying future outcome assessment, including evaluation of response rates of different recommended treatment regimens, and the potential for use in evaluation of newer agents for febrile neutropenia.

Guidelines from the Italian Association of Pediatric Hematology and Oncology

The aim of these guidelines was to address the tremendous variability in management of febrile neutropenia in children in Italian centers, and the impact on costs and development of antibiotic resistance.[11] A chairperson was nominated to prepare a first draft based upon evidence, which was subsequently reviewed by experts in the society. Through publication, the document also underwent external peer review. The rating system is similar to that used by the IDSA in 1990, linking recommendation acceptance by experts with quality of evidence, and without a separate rating of the quality of supporting evidence. A similar definition of febrile neutropenia to that in the adult population is reached. As with other guidelines in this area, clinicians are cautioned to apply the guidelines with awareness of their local patterns of infecting organisms and antimicrobial resistance. Standard evaluation without surveillance cultures is recommended, with a review of evidence for additional tests. A recommendation formulated from expert opinion for ongoing cultures daily or even twice daily was presented – a contrast to the IDSA guidelines for adults. It is recommended that all patients receive inpatient therapy, with recognition that oral or outpatient therapy is a feasible approach currently under investigation. The three recommended options for empiric therapy of febrile neutropenia in children are similar to those in adults, namely combinations of β-lactams and aminoglycosides, double β-lactam coverage, and monotherapy with a carbapenem or third-generation cephalosporin. Intravenous or oral monotherapy with a quinolone is also mentioned, but the supporting evidence is not clearly reviewed in the document. The pros and cons of all options, including cost, are

presented. The favored option, particularly in higher-risk patients (i.e. those with prolonged duration of neutropenia), is combination therapy with a β-lactam and aminoglycoside. Overall, empiric use of vancomycin or teicoplanin is discouraged for fear of development of resistant organisms, and their use is not endorsed unless staphylococcal infection risk is clinically likely, in centers with high rates of methicillin resistance. A similar caution is made regarding the development of resistant organisms through the use of single-agent carbapenem therapy, and the authors conclude that this should not be used routinely as part of initial empiric treatment. Single daily dosage of aminoglycosides, specifically amikacin given the burden of evidence evaluating this drug, is supported.

With respect to the duration of treatment, continuing antibiotics for four to seven days after defervescence is suggested, with consideration of early discharge if patients are afebrile and at low risk. Patients at low risk include those with evidence of marrow recovery and controlled disease, and who have access to proper monitoring at home. The use of antifungal therapy was reviewed, and empiric antifungal therapy was discouraged, except in selected groups of patients. Planned outcome evaluation of the guideline development and plans for revision were not specified in the text, but may be published in the future.

GUIDELINES FOR METHODOLOGY IN CLINICAL TRIALS IN FEVER AND NEUTROPENIA

While guidelines for practice are becoming increasingly sophisticated in the evaluation of treatments and comparison of different agents, a major problem remains in the lack of uniformity in available evidence, particularly in clinical trial endpoints. It is intuitively clear that as the definition of failure of response to therapy changes, so will a study's results and its conclusions about treatment efficacy. This was elegantly demonstrated in a study conducted by Elliott and Pater,[19] in which three different measures of outcome were used to define response in testing new antibiotic regimens for febrile neutropenic episodes. Using two of the definitions, a significant difference between responses to treatment regimens were demonstrated, but using the third definition, only treatment equivalence was shown. This latter definition used death from infection as the only definition of treatment failure, and since patients could be rescued with treatment modifications as part of the study, the infection-related death rates are, not surprisingly, equivalent. Thus, changing the height of the benchmark of the trial endpoint can change the success rate in these trials.

Several definitions of treatment response in trials of febrile neutropenia exist, including guidelines proposed by the Immunocompromised Host Society (ICHS),[20] the International Antimicrobial Therapy Cooperative Group of the European Organization for Research and Treatment of Cancer (EORTC),[21] Pizzo and co-workers,[22,23] and others (see Table 14.1).

An earlier attempt to develop a consensus guideline in this area resulted in adoption of the ICHS guidelines for response,[24] and has been extensively reviewed elsewhere.[25,26] Despite the US Food and Drug Administration requirement that trials carried out to obtain approval for antimicrobials in patients with febrile neutropenia comply with these guidelines, this has not resulted in the widespread report of these endpoints in the actual publications of trial results. As the published results are what clinicians use to guide therapy, and comprise the evidence on which practice guidelines are commonly based, this is a key area of concern. It seems clear that in our paradigm shift in the clinical practice of medicine to a more evidence-based approach, the use of a uniform guideline on how to conduct investigation and establishment of that evidence must be promoted. To that end, the ICHS guidelines for methodology of the design and conduct of clini-

Table 14.1 Criteria for response in studies of empiric therapy for neutropenic sepsis[a]

Pizzo criteria for response

1. **Evaluation:** at 72 hours and end of treatment
2. **Success:** survival of febrile episode until neutrophil recovery with no modification of original regimen
3. **Success with modification:** survival of febrile episode but requiring addition of another agent or complete change of regimen
4. **Failure:** death from infection

EORTC criteria for response

1. **Evaluation:** at 72–96 hours and end of treatment
2. **Success:** all signs of infection resolved and infecting organisms eradicated without any modification of primary regimen; must be maintained for 7 days after stopping initial antibiotics
3. **Failure:** death from infection; bacteremia for more than 24 hours; breakthrough bacteremia; no response to initial therapy; documented resistance of pathogen to initial therapy; modification of regimen with shock, acute respiratory failure, disseminated intravascular coagulation
4. **Non-evaluable for response:** mixed or non-bacterial infection; non-infectious febrile episode; treatment stopped because of toxicity
5. **Protocol violation:** change of therapy from β-lactam, with susceptible Gram-positive infection in setting of persistent fever

ICHS criteria for response

Microbiologically defined infection

1. **Success:** eradication of signs and microbiologic evidence of infection on primary therapy; no recurrence for 7 days after stopping initial antibiotics
2. **Initial response but regimen modified:** success as above, but secondary infection arises requiring addition of another agent
3. **Failure:** death from infection; any change to the initial antibiotic regimen to eradicate infection

Clinically defined infection (i.e. no microbiologic isolate)

1. **Success:** same as above without evidence of bacteriologic cure
2. **Initial response but regimen modified:** same as above
3. **Failure:** same as above

Unexplained fever

1. **Success:** patient defervesces on initial regimen and recovers from neutropenia; no recurrence of fever within 7 days of completing initial antibiotic regimen
2. **Initial response but regimen modified:** patient develops new fever after initial defervescence, requiring additional agent outside spectrum of initial therapy
3. **Non-response or failure:** death from infection; any change to initial regimen for persistent fever

[a]Adapted with permission from Feld R, *Support Cancer Care* 1998; **6**: 444–8.[26]

cal trials in febrile neutropenia are being updated, with the assistance of the Multinational Association for Supportive Care in Cancer (MASCC). In addition to the emphasis on patients considered high-risk, they will also include guidelines for trials of outpatient therapy, in patients at lower risk, using the Talcott[15] and/or MASCC criteria for this definition.[27] These guidelines are currently being produced by both international societies, and ideally would be endorsed by other societies such as ASCO and IDSA prior to publication, which is expected in 2001.

Predicting the future of guidelines is not an exact science. But it can be seen from this review that many local documents are based on one or two major guideline publications, and we anticipate this will be the way of the future. While local guidelines assist practitioners in applying minor regional differences to general management approaches – for example tailoring therapy guidelines to pathogens and antimicrobial resistance patterns in a specific geographic area – we expect that only a few major guidelines in each subject area will continue to be updated. Through the maintenance of these guidelines as current and relevant to clinical practice, we can continue to promote quality improvements in our practice patterns and in the supportive care of tomorrow's cancer patient.

REFERENCES

1. Grimsahw J, Eccles M, Clinical practice guidelines. In *Evidence Based Practice in Primary Care* (Silagy C, Haines A, eds). Plymouth, UK: Latimer Trend, 1998: 110–22.
2. Cluzeau F, Littlejohns P, Grimshaw J, Feder G, *Appraisal Instrument for Clinical Guidelines*. London: St George's Hospital Medical School, 1997.
3. Hayward RSA, Wilson MC, Tunis SR et al, Users' guides to the medical literature VIII. How to use clinical practice guidelines A. Are the recommendations valid? *JAMA* 1995; **274:** 570–4.
4. Wilson MC, Hayward RSA, Tunis SR et al, Users' guides to the medical literature VIII. How to use clinical practice guidelines B. What are the recommendations and will they help you in caring for your patients? *JAMA* 1995; **274:** 1630–2.
5. ECRI (International Nonprofit Health Services Research Agency), Collaborating Center of the World Health Organization (WHO), and EPC (Evidence-based Practice Center) of the US Agency for Healthcare Research and Quality (AHRQ). National Guidelines Clearinghouse, 1997 (http://www.guidelines.gov)
6. Hughes WT, Armstrong D, Bodey GP et al, Guidelines for the use of antimicrobial agents in neutropenic patients with unexplained fever. *J Infect Dis* 1990; **161:** 381–96.
7. Hughes WT, Armstrong D, Bodey GP et al, 1997 Guidelines for the use of antimicrobial agents in neutropenic patients with unexplained fever. *Clin Infect Dis* 1997; **25:** 551–73.
8. National Comprehensive Cancer Network, NCCN practice guidelines for fever and neutropenia. *Oncology* 1999; **13:** 197–257.
9. Biron P, Guhrmann C, Escande MC et al, Standards, options, and recommendations for the management of brief neutropenias. Federation Nationale des Centres de Lutte Contre le Cancer. *Bull Cancer* 1998; **85:** 695–711.
10. Masaoka T, Febrile neutropenia – guideline in Japan. *Gan To Kagaku Ryoho* 2000; **27:** 161–5.
11. Viscoli C, Castagnola E, Caniggia M et al, Italian guidelines for the management of infectious complications in pediatric oncology: empirical antimicrobial therapy of febrile neutropenia. *Oncology* 1998; **55:** 489–500.
12. American Society of Clinical Oncology Ad Hoc Colony-stimulating Factor Guidelines Expert Panel, American Society of Clinical Oncology, Recommendations for the use of hematopoietic colony-stimulating factors: evidence-based, clinical practice guidelines. *J Clin Oncol* 1994; **12:** 2471–508.
13. Ozer H, Miller LL, Schiffer CA et al, American Society of Clinical Oncology update of recommendations for the use of hematopoietic colony-stimulating factors: evidence-based clinical practice guidelines. *J Clin Oncol* 1996; **14:** 1957–60.
14. Ozer H, Armitage JO, Bennett CL et al, 2000 update of recommendations for the use of hematopoietic colony-stimulating factors: Evidence-based clinical practice guidelines. *J Clin Oncol* 2000; **18:** 3558–85.

15. Talcott JA, Siegel RD, Finberg R, Goldman L, Risk assessment in cancer patients with fever and neutropenia: a prospective, two-center validation of a prediction rule. *J Clin Oncol* 1992; **10:** 316–22.
16. Talcott JA, Whalen A, Clark J et al, Home antibiotic therapy for low-risk cancer patients with fever and neutropenia: a pilot study of 30 patients based on a validated prediction rule. *J Clin Oncol* 1994; **12:** 107–14.
17. Rubenstein EB, Rolston K, Benjamin RS et al, Outpatient treatment of febrile neutropenia in low-risk neutropenic patients with cancer. *Cancer* 1993; **71:** 3640–6.
18. Rolston KVI, Rubenstein EB, Eltin LS et al, Ambulatory management of febrile episodes in low risk neutropenic patients. In: *Programs and Abstracts of the 35th Interscience Conference on Antimicrobial Agents and Chemotherapy, San Francisco.* Washington, DC: American Society of Microbiology, 1995: Abst 2235.
19. Elliott C, Pater JL, The effect of different measures of outcome on the results of studies of empiric antibiotic therapy in febrile neutropenic patients. *Clin Invest Med* 1988; **11:** 327–30.
20. Immunocompromised Host Society, Consensus panel of the design analysis and reporting of clinical trials on the empirical antibiotic management of the neutropenic patient. *J Infect Dis* 1990; **161:** 397–401.
21. Cometta A, Zinner S, de Bock R et al, The International Antimicrobial Therapy Cooperative Group of the European Organization of Research and Treatment of Cancer, Piperacillin-tazobactam plus amikacin versus ceftazidime plus amikacin as empiric therapy for fever in granulocytopenic patients with cancer. *Antimicrob Agent Chemother* 1995; **39:** 445–52.
22. Pizzo PA, Hathorn JW, Hiemen ZJ et al, A randomized trial comparing ceftazidime alone with combination antibiotic therapy in cancer patients with fever and neutropenia. *N Engl J Med* 1986; **315:** 552–8.
23. Freifeld AG, Walsh T, Marshall D et al, Monotherapy for fever and neutropenia in cancer patients: a randomized comparison of ceftazidime versus imipenem. *J Clin Oncol* 1995; **13:** 165–76.
24. Hughes W, Pizzo PA, Wade JC et al, Evaluation of new anti-infective drugs for the treatment of febrile episodes in neutropenic patients. *Clin Infect Dis* 1992; **15**(Suppl 1): S206–15.
25. Feld R, Methodology for clinical trials in cancer patients with febrile neutropenia: Do we have a consensus? *Support Care Cancer* 1998; **6:** 423–4.
26. Feld R, Criteria for response in patients in clinical trials of empiric antibiotic regimens for febrile neutropenia: Is there agreement? *Support Care Cancer* 1998; **6:** 444–8.
27. Klastersky J, Paesmans M, Rubenstein EB et al for the Study Section on Infections of the Multinational Association for Supportive Care in Cancer, The Multinational Association for Supportive Care in Cancer Risk Index: a multinational scoring system to predict low-risk febrile neutropenic cancer patients. *J Clin Oncol* 2000; **18:** 3038–51.

15

Healthcare economic concepts in fever and neutropenia

Thomas D Szucs

I am finally summing up with an urgent appeal to adopt this or some uniform system of publishing the statistical records of hospitals. If they were obtained, they would show subscribers how their money was being spent, what amount was really being done with it, or whether the money was doing more mischief than good.

Florence Nightingale, 1863

WHY MEDICAL ECONOMICS?

In the past few years, the discipline of health economics has experienced an extraordinary boom within the healthcare sector. Researchers from a wide range of disciplines have developed new techniques to evaluate the impact of clinical care and medical technology. Clinicians, pharmacists, economists, epidemiologists, and operations researchers have contributed to the new field of medical economics to study how different approaches to patient care influence the resources consumed in clinical medicine. Faced with the basic economic notion that resources are limited and desires as well as needs are infinite, health economists try to find solutions to the problem of how these resources can be allocated appropriately to maximize the production of health. The common denominator is the search for increased efficiency and effectiveness of healthcare services and products. Among these efforts, several researchers from a wide range of disciplines have begun to study the economic impact of medicines on healthcare provision on micro- and macroeconomic levels. The new field of pharmacoeconomics has grown at a tremendous rate, supplying ample evidence of the economic benefits of modern therapeutics.

Not all medical interventions and procedures, however, have to be subject of an economic evaluation. A simple decision tool is displayed in Figure 15.1. This box takes the two main outcomes of a potential evaluation into consideration: costs and clinical results or quality of a medical intervention. In circumstances

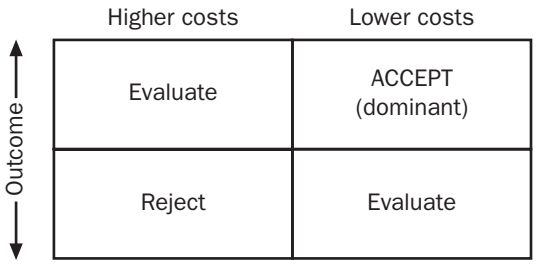


Figure 15.1 The four possible outcomes of an economic evaluation.

where a drug is costly and leads to better results, an economic evaluation is advisable. Where a drug is cheaper and yields better outcomes, the drug should be accepted. In the opposite case, where a more costly drug or procedure produces less favorable outcomes, one should reject it. Economic evaluations may, however, assist in identifying those drugs that have poorer outcomes but are also cheaper.

THE MAJOR COMPONENTS OF AN ECONOMIC EVALUATION

All economic studies investigate the balance between inputs (the consumption of resources) and outcomes (improvements in the state of health of individuals and/or society).

Inputs (costs)

Although the unit price of a drug or procedure is often a prime factor in decision making, economic outcomes research provides a more comprehensive interpretation of cost. This is accomplished by determining the overall cost of a given diagnostic and therapeutic process from the initiation of diagnosis until a final outcome is achieved. The various types of costs can be grouped under the following categories: direct medical costs, direct non-medical costs, and indirect costs.

Direct medical costs

Interpretations of what belongs in each of these categories vary in the economic literature. Direct medical costs are defined as those resources used by the provider in the delivery of medical care. As an example, direct medical costs for a hospital include:

- drugs;
- laboratory tests;
- medical supplies;
- use of diagnostic equipment (e.g. magnetic resonance imaging, CAT scans, X rays);
- medical staff time for personnel such as physicians, nurses, pharmacists, physical therapists, laboratory technicians, etc.;
- room and board: the cost of supplies, equipment, and personnel required for routine patient-related services such as food, laundry, and housekeeping.

These are examples of costs that can be directly related to the care of patients. Other costs of operating a hospital include plant maintenance and repairs, utilities, telephone, accounting, legal fees, insurance, taxes, real estate costs, and interest expenses. In general, most economic studies do not factor general operating costs into the dollar value assigned to the cost of resources expended for a given medicine.

Looking down the list of direct medical expenses, it is easy to see why length of stay is an important cost factor to hospitals, especially when payment is determined by diagnosis-related groups (DRGs). Costs such as room and board are directly tied to the length of stay, regardless of the reason. The cost of laboratory tests, supplies, and medical staff time vary with the medical condition being treated, but are multiplied by the length of stay.

Since the introduction of DRGs, a common selling strategy has been to emphasize how a given technology such as a new antimicrobial drug can help shorten hospital stays. More recently, economic studies began to collect and analyze data linking specific diagnostic strategies to length of stay.

Length of stay in hospital settings translates to the number of patient visits in managed care settings. Although the specific items included under the category of direct medical costs will be slightly different in managed care organizations, the same principles of cost analysis apply. Drugs that achieve results quickly and predictably not only benefit the patient, but also benefit the provider by reducing the number of patient visits. Every patient visit incurs provider resource costs that may not be reimbursed by a third-party payer. Interventions that minimize patient visits are clearly cost savings for the healthcare organization.

Direct non-medical costs

Economic literature generally defines direct non-medical costs as out-of-pocket expenses paid by the patient for items outside the healthcare sector. This category includes such costs as:

- travel to and from the hospital, clinic, or doctor's office;
- travel and lodging for family members who live elsewhere;
- domestic help or home nursing services;
- insurance co-payments and premiums;
- treatment not covered by third-party payers.

Although these costs are generally classified as 'non-medical', to the patient they are real and often substantial costs of medical care. What makes them 'non-medical' is that they are not costs incurred by the healthcare provider, and are somewhat difficult to measure. For example:

- A patient's inability to afford competent follow-up care at home may result in poor compliance with drug therapies and eventual treatment failure. This may lead to additional hospital stays or office visits, which affect the provider's bottom line.
- A patient's inability to bear the unreimbursed cost of medications may also lead to poor compliance and costly complications.
- High transportation costs may lead to missed appointments for necessary follow-up visits, which can result in deterioration of a patient's medical condition and increased treatment costs for the provider.

Even though the provider may not directly incur these costs, they can be used in specific situations by making the provider aware of their potential economic impact. It may also be possible to use these costs to encourage payers (e.g. employers and insurance companies) to discuss the use of a more cost-effective test with the healthcare provider.

Indirect costs

One definition of indirect costs (also called 'intangible costs' by some economic analysts) is the overall economic impact of illness on the patient's life. These include:

- loss of earnings due to temporary, partial, or permanent disability;
- unpaid assistance by family members in providing home healthcare;
- loss of income to family members who forfeit paid employment in order to remain at home and care for the patient.

Like direct non-medical costs, indirect costs are real to the patient, but abstract to the provider – but may impact the provider's direct medical costs. For example, patients who cannot earn income may not be able to pay their bills – including medical bills. Economic hardship may result in poor compliance with drug therapies as patients reduce doses or fail to refill prescriptions in order to save money. The medical provider may have to bear the additional costs of managing complications. Economic hardship may also result in missed follow-up appointments, leading to the same types of problems for providers as described previously with direct non-medical costs.

Consequences and outcomes

Final states or outcomes can be negative (sometimes referred to as the 'five D's'):

- death;
- disability (the patient is permanently disabled and unable to return to work or school, perform household chores, etc.);
- discomfort (the patient is in a constant state of moderate to severe pain);
- dissatisfaction (the patient is not satisfied with the course of treatment or services provided);
- disease (the patient's condition is not being controlled, resulting in frequent relapses, rehospitalization, and expenditure of additional resources).

There are also positive outcomes:

- the patient is cured;

- the patient is able to resume normal functions;
- there is an improved or satisfactory quality of life;
- the patient's medical condition is successfully managed or stabilized by continued drug therapy.

The use of outcomes research (see below) represents an important advance in medical economic analysis because of the relationship between the final state, or result, of diagnosis and therapy and overall cost–effectiveness. If it can be demonstrated that a product or intervention will achieve cost-effective, positive outcomes, this will increase the chances of the technology being diffused within healthcare.

IMPORTANT ECONOMIC CONCEPTS

Average, marginal, and joint costs

Most decisions in healthcare are not concerned with whether or not a service should be provided, or whether or not a particular procedure should be undertaken, but rather with how much of the service should be provided. That is, should existing levels of provision be expanded or contracted? For example, should the existing provision of daycare for people with mental illness be expanded, and, if so, by how much? What family planning services should be made available? How many patients presenting with head injuries should have computed tomograms? All these decisions require that attention should be focused on marginal costs – that is, the change in total costs resulting from a marginal change in activity.

In the short run, there is often an important difference between the marginal cost of an activity and its average cost, where the average cost is defined as the total cost divided by the total number of units of output (Table 15.1). An example is provided by a study of the cost–effectiveness of antihyperlipemic treatment in the prevention of coronary heart disease.[1] In this study, the marginal cost was calculated per life-year saved of continuing drug treatment for successive periods of 5 additional years for patients between 35 and 70 years of age. These indicated large differences between average and marginal cost–effectiveness, since marginal costs increased quite steeply after 55 years of age.

Another context in which the distinction between average and marginal costs is important is in relation to the duration of hospital stay of inpatients. Many new procedures have reduced the amount of time necessary for a patient to remain in hospital, and thereby yield cost savings. When valuing these savings, however, it is important to keep in mind that using average costs/day will generally overstate the savings, since the later days of a stay usually cost less than the earlier ones. It is the marginal cost/day that is the relevant measure.

Another problem of cost measurement arises in connection with joint costs. Often a single production process can result in multiple outputs. For example, a single chemical analysis of a blood sample can diagnose the presence of many diseases. How should the cost be allocated to each diagnosis? Similarly, within a

Table 15.1 Total, average, and marginal costs: an illustration

No. of patients treated	Total cost ($)	Average cost ($)	Marginal cost ($)
10	4000	400	0
20	5000	250	100
30	6000	200	100
40	6800	170	80
50	7400	148	60

hospital setting, there are many common services (such as medical records, radiology, operating theatres, laundry, catering, and cleaning) that contribute to a number of specialities. Economic evaluation requires some method for allocating the joint costs of these services to individual programs or procedures. There are several methods that may be used to do this. Most of them use some physical unit of utilization, such as the number of laboratory tests, hours of operating theatre use, or square meters of ward space, to apportion total laboratory, operating theatre, and ward cleaning costs.

Costs of capital

Investments in buildings and equipment that yield a flow of services over a number of years give rise to capital costs. Generally, investment expenditure will be undertaken at the beginning of a project, but the use of items of capital equipment will generate annual capital costs over the lifetime of the asset.

These costs have two components: interest and depreciation. Interest costs should be included even if the asset was not acquired with borrowed money, because tying-up money in an item of capital equipment involves an opportunity cost, namely, interest foregone. Depreciation costs arise because of the wear and tear that an asset receives through use and the consequent reduction in the length of its useful life. Land, however, is a capital asset, which is not assumed to incur depreciation costs.

Sometimes an item of capital expenditure is unique to a particular use, and has little or no alternative use value (opportunity cost). In such cases, it is referred to as a sunk cost. A hospital building or an item of medical equipment may, for example, have considerable value in its existing use but little resale value. This can provide a powerful case for continuing to use existing assets instead of undertaking new investments, because, in an economic evaluation, sunk costs should not be included among annual capital costs. In practice, this consideration is likely to be more important in the case of major capital developments than of individual procedures.

Adjusting for differences in timing: discounting

The current (operating) costs associated with most procedures can be expected to extend over a number of years into the future, but their time profiles may differ. In the case of many preventive procedures, such as treatment for hypertension, costs will be incurred regularly over a number of years. The alternative of no preventive treatment may well incur zero expenditure in the early years, but incur the costs of surgery earlier than would otherwise have been the case. Discounting offers a means of standardizing different cost–time profiles so that total costs can be compared.

Discounting is based on the assumption that costs incurred in the immediate future are of greater importance than costs incurred in the distant future. This is because earlier access to finance would permit investment at a positive rate of interest, thereby yielding a larger sum in the future (there is an opportunity cost) or because people and society attach more importance to current opportunities than to future ones (positive time preference).

For these reasons, economic evaluation weights costs by a discount rate, according to the year in which they accrue, before adding them up and expressing total costs in present-value terms (values in the current year).

In essence, discounting is the reverse application of the more familiar compound interest formula – instead of sums being calculated forwards, they are discounted backwards. Fortunately, the application of discounting does not require close familiarity with the formula, since many finance and accounting textbooks include discount tables. These indicate the present values of the dollar at different discount rates.

Table 15.2 Present value of 1$

	Discount rate					
Year	3%	4%	5%	6%	7%	8%
1	0.9709	0.9615	0.9524	0.9434	0.9346	0.9259
5	0.8626	0.8219	0.7835	0.7473	0.7130	0.6806
10	0.7441	0.6756	0.6139	0.5584	0.5083	0.4632
15	0.6419	0.5553	0.4810	0.4173	0.3624	0.3152
20	0.5537	0.4564	0.3769	0.3118	0.2584	0.2145
25	0.4776	0.3751	0.2953	0.2330	0.1842	0.1460

Table 15.2 shows how present discounted values will vary for selected combinations of the discount rate and the years in which the costs accrue. Looking across the second row of the table, for example, shows that in the fifth year, $1.00 will be worth 86 cents at a discount rate of 3%, but only 68 cents at a discount rate of 8%. The choice of the appropriate discount rate depends in part on national recommendations. Given the sensitivity of valuations to the choice of discount rate, however, and the fact that the ranking of different projects with different time profiles could depend on the rate chosen, it is good practice to compute costs in terms of a range of discount rates.

Inflation

Most programs that extend over several years will be affected by inflation. It is important, however, to distinguish between changes in the general price level and changes in relative prices. In the case of general inflation, there will be no change in the relative cost of inputs (their opportunity costs remain constant). As such, all future inputs can be valued at current prices and discounted by a real (excluding inflationary effect) rate of interest.

If, however, some input prices are expected to increase more than others, there will be relative changes in their opportunity costs, and these need to be taken into account. One way of doing this is to use the general rate of inflation as a benchmark and to adjust the future prices of individual inputs – upwards or downwards – by an amount that reflects the difference between their rate of inflation and the general rate. Thereafter, all costs should once again be discounted by the same real rate of interest.

METHODS OF HEALTH ECONOMIC EVALUATION

The most common methods employed by health economists are based on classical research designs such as cost-minimization, cost–benefit, cost–effectiveness, and cost–utility analyses.[2–4] (Table 15.3).

Cost-minimization analyses (CMA)

Cost-minimization analysis is concerned with comparing the costs of different treatment modes that produce the same result. For example, this form of analysis could be used to com-

Table 15.3 Overview of the main types of pharmacoeconomic evaluations

Type of study	Intervention costs	Consequences	Measurement of consequences	Compares alternatives	Assumes equivalent effectiveness
Cost–benefit analysis (CBA)	Monetary value of resources consumed	Monetary value of outcomes	Economic	Not necessarily, although comparisons are implicit	No
Cost–effectiveness analysis (CEA)	Monetary value of resources consumed	Effects on health	• Lives saved • Cases treated • Years of life saved	Yes	No
Cost–utility analysis (CUA)	Monetary value of resources consumed	1. Utility of health effects 2. Indirect costs 3. Subsequent use of resources	1. Quality-adjusted life-years (QALYs) 2. Economic 3. Economic	Yes	No

pare the cost of two programs that involve minor surgery for adults. Both have the same outcome in terms of the surgical procedure, but the first program might require the patient to stay overnight at the hospital, while the second might be done through day surgery without requiring hospitalization. Given these two alternatives, the search would be for the least costly treatment. While we might be interested in the extent to which daycare surgery shifts costs from the institution to the patient, the main efficiency comparison would be on a cost per surgical procedure basis.

As far as pharmaceuticals are concerned, this type of study is used most frequently when a new drug is introduced into a therapeutic class that includes close competitors and no measurable therapeutic effect between them has been documented.

When the costs of two interventions are being compared, cost-minimization analysis often assumes that they lead to identical health outcomes. Studies of this nature should report evidence to support the contention that outcome differences are non-existent or trivial in nature. In most cases, however, the issues are more than that of cost alone. It is rarely the case that two therapies having the same indication produce identical health outcomes in every respect.

Cost–benefit analyses (CBA)

As applied to healthcare, cost–benefit analysis measures all costs and benefits of competing therapies in terms of monetary units. Generally, a ratio of the discounted value of benefits to

costs (the present value of both) is calculated for each competing therapy. The ratios for each of the competing therapies and for competing programs (e.g. intensive care unit versus new diagnostic equipment) can be readily compared.

Cost–benefit analysis has the shortcoming of requiring the assignment of a dollar value to life and to health improvements, including quality-of-life variables. This presents equal benefit issues as well as substantial measurement problems. For these reasons cost–benefit analysis has not been widely used in recent years for evaluating drug therapies.

Cost–effectiveness analyses (CEA)

Cost–effectiveness studies measure changes in the costs of all relevant treatment alternatives, but measure the differences in outcomes in some natural unit such as actual lives saved, years of lives saved, or children immunized. Cost–effectiveness analysis can also be applied equally to cases where the outcome is in terms of quality of life. Cost–effectiveness analysis is useful in comparing alternative therapies that have the same outcome units (e.g. years of life expectancy or lives saved) but where the treatments do not have the same effectiveness (i.e. one drug may lead to greater life expectancy). The measure compared is the cost of therapy divided by the units of effectiveness, and hence a lower number signifies a more cost-effective outcome.

The most challenging endpoint of a cost–effectiveness analysis is the *cost per life-year gained*. This requires the researcher to calculate the survival benefit of comparative strategies. This is sometimes not an easy task, specifically when the medical economist does not have access to the raw data. When Kaplan–Meier survival curves are available, the life-years gained are represented by the area between the two curves. Without such survival curves, life expectancy has to be estimated by using life tables,[5] epidemiological formulas (declining exponential approximation of life expectation, DEALE),[6,7] or modeling techniques.[8]

This type of study has the advantage that it does not require the conversion of health outcomes to monetary units, and thereby avoids equal benefit and other difficult issues of the valuation of benefits. It has the disadvantage of not permitting comparison across programs, which have different endpoints. In other words, a drug whose function is aimed at reducing infant mortality rates cannot be compared with a drug designed to improve functional status of senior citizens. Moreover, it cannot compare outcomes measured in clinical units with quality-of-life measures.

Cost–utility analyses (CUA)

Cost–utility analysis compares the added costs of therapy with the number of *quality-adjusted life-years (QALY)* gained. The quality adjustment weight is a utility value, which can be measured as part of clinical trials or independently. The advantage of cost–utility analysis is that therapies that produce different or multiple results can be compared.

The QALY, which has been the standard measure of benefit thus far, is arrived at in each case by adjusting the length of time affected through the health outcome by the utility value (on a scale of 0 to 1) of the resulting health status. Many analysts are more comfortable with this measure of the consequence of medical care than with the use of money as the measure of benefits.

With respect to drug therapy, cost–utility analysis is an improvement over cost–effectiveness analysis because it can measure the effects of multiple outcomes (such as the impact of laboratory tests on both morbidity and mortality or the impact on both pain and physical functional status).

In contrast to classical quality-of-life measures, utility assessments focus on health state preference valuation. Some programs may have the ability to save lives; the years of life gained

across the entire population that could be helped are often used as a measure of success of the program. However, this measure has been refined to recognize that even though the benefits may be in years of life saved, the physical state of affairs of the affected group may be less than optimum during this extended time. As noted previously, weights are attached to the extended time, with a value of 1 given to normal function and a value less than 1 given to a state of less than normal activity or discomfort. A value of 0 would represent death (at times where life is said to be worse than death, a value less than zero is the minimum). These weights are termed utilities, and they are used as the adjusting factor to multiply the years of life extended to obtain the quality-adjusted life-year. Cost per QALY can be computed and compared across alternative treatment scenarios[9] (Table 15.4).

Utilities can be assessed either through direct measurement approaches (e.g. standard gamble or time-tradeoff techniques) or through multi-attribute instruments (e.g. the Quality of Wellbeing Index,[10] the Rosser Index,[11] or the Health Utility Index[12]). The direct methods originate from research in the field of game theory, as early as the 1950s.[13] (Table 15.5 lists utility values exemplified by the case of metastatic breast cancer.)

In addition, the field of quality-of-life studies has been increasingly integrated into economic studies. Preferably, these analyses require a prospective study design and should be incorporated into the early clinical development process. In cases where this is not feasible, sound retrospective studies may be performed, employing analytical tools such as meta-analysis, modeling, and decision analysis. The concept of costs plays an important role in the conduct of such studies, and exerts a great impact on the corresponding results. The approach used by health economists is to consider costs as opportunity costs; i.e. they define a cost to be the consumption of a resource that could otherwise be used for another purpose. Once the resource has been used, the opportunity to use it for another purpose is lost. The value of that resource is that of the next best use. In pharmacoeconomic studies, costs as well as benefits are classified in three classes: direct, indirect, and intangible costs. It is important to determine all costs and consequences within the relevant timeframe and to avoid omitting costs that may not be readily available. Before conducting an economic analysis, the perspective or point of view of the study must be defined. The view may be on the level of society, the patient, payer, or provider.

OUTCOMES RESEARCH

Against this background, what is now called outcomes research or medical effectiveness research has a tremendously important role to play.[14,15] Several different activities fall under the general rubric of outcomes research. The first is clarification of the clinical, functional, and economic impacts of individual technologies and practice alternatives. Outcomes research also involves evaluating patients' preferences and combining these in conjunction with the results of technology assessments to define what might be considered optimal practice. Once optimal practice has been defined, an additional type of outcomes research seeks to compare actual practice with the standards of practice developed from the preceding evaluations. When actual and preferred practices differ, outcomes researchers need to evaluate why they differ, and then develop interventions that will shift actual practice into closer compliance with what is thought to be optimal practice. Outcomes research will ultimately provide the information that is needed to make product pricing decisions, coverage decisions, payment decisions, acquisition decisions, and usage decisions in a cost-conscious and value-driven environment. It will be critical to providers' and manufacturers' survival in an increasingly competitive environment. Given this perspective, researchers have clearly been performing outcomes and effectiveness research for a long time.

Table 15.4 League table for various medical interventions in oncology

Intervention	Costs/life-year	Ref
Routine carcinoembryonic antigen monitoring of colon cancer	31 000–6 600 000	32
Allogenous bone marrow transplantation for relapse of Hodgkin's disease	421 000	33
Bone marrow transplantation and high (versus standard) chemotherapy for breast cancer	129 179	34
Allogeneic bone marrow transplantation in metastatic breast cancer	115 800	34
Chemotherapy of acute non-lymphocytic leukemia	80 300	35
Adjuvant CMF (cyclophosphamide, methotrexate, 5-fluorouracil) in 75-year-old women with breast cancer	44 000	36
Postsurgical chemotherapy for 60-year-old women with breast cancer	22 105	36
Postsurgical chemotherapy for premenopausal women with breast cancer	18 107	36
Interferon-α2b in hairy cell leukemia	13 800	37
Paclitaxel as first-line chemotherapy of ovarian cancer (six European countries)	6 400–11 400	38
Adjuvant CMF in 45-year-old women with breast cancer	4 900	36
Tamoxifen in advanced breast cancer	810	39

Table 15.5 Utility values exemplified by the case of metastatic breast cancer[38]

Health state	Utility
Partial response	0.81
Stable disease	0.62
Before commencement of 2nd-line therapy	0.59
Partial response plus severe neuropathy	0.53
Progressive disease	0.41
Sepsis	0.20
Terminal disease	0.16

What is it then that is new about outcomes and effectiveness research? First, researchers are now focusing on a broader spectrum of outcome measures than has historically been the case. Newer measures include functional status, health-related quality of life, and costs. Second, they are now interested in measuring outcomes in everyday practice, not just in the settings in which randomized trials are typically conducted. Third, they are using new types of data sets, such as insurance claims and hospital discharge abstracts, to perform outcomes research. The use of such datasheets, as well as the use of non-randomized trial methodologies in outcomes research, is controversial. Researchers, however, simply are not going to be able to do a randomized trial on everything, and in many circumstances it would not be cost-effective to do so. Finally, increased attention is being paid to the patients' viewpoints in the outcomes research that is currently being performed.

HEALTH ECONOMIC ASPECTS OF FEBRILE NEUTROPENIA

During the past decade, several excellent economic evaluations have been performed in the field of febrile neutropenia, with great emphasis on antimicrobial therapy and colony growth factors. These studies have clarified the costs and consequences of drug interventions and, in several instances, have significantly impacted formulary decisions. The conduct of economic analyses in febrile neutropenia is quite easy, because the benefits of therapy can usually be seen within a relatively short time frame. Thus, future costs and consequences do not have to be discounted to their present value.

What are the costs of treating patients with febrile neutropenia?

There have been only few studies to date assessing the costs of febrile neutropenia. Faulds et al[16] noted that the costs of treatment varied widely among institutions. Chaplin[17] summarized the financial implications of febrile neutropenia management, and concluded that detailed cost studies were urgently required.

In a retrospective study, Leese et al[18] collected data over a 1-year period from the medical records of patients admitted to a district general hospital – either with febrile neutropenia or who developed this complication whilst receiving inpatient chemotherapy. Costs were calculated for inpatient stay, drug treatment, and diagnostic tests. The median total costs for 46 episodes of febrile neutropenia were £2068.35 and the median total cost per day was £139.41. Inpatient bed-days accounted for 57.8% of total costs, followed by drug treatment at 25.8% and diagnostic tests at 16.4%. The costs of blood products were excluded, since they are frequently administered irrespective of the neutropenia.

Which treatment setting is more cost-effective and preferred by patients and families?

Mullen et al[19] measured resource allocation in outpatient management of fever and neutropenia in low-risk pediatric patients with cancer

and its impact on their families in a prospective clinical trial. Eligible patients received a single dose of intravenous antibiotics, and were observed for several hours in clinic. Patients were randomly assigned to continue either intravenous or oral antibiotics, and were seen daily as outpatients. Charges were calculated based on the number of resources used and Medicare/Medicaid reimbursement schedules. A questionnaire was used to measure the impact of outpatient treatment on the family. A total of 73 episodes of fever and neutropenia were studied. The median duration of treatment was 4 days. Of the episodes, 86% were managed without hospitalization. The median calculated charge was $1840. The median calculated charge for patients receiving oral antibiotics was $1544, and was significantly less than the $2039 median charge for outpatients treated with intravenous antibiotics. The estimated charge for comparable inpatient treatment was $4503. Nearly all families preferred outpatient care, and few reported a loss of work hours or increased childcare expenses. The investigators concluded that outpatient treatment of low-risk episodes of fever and neutropenia is substantially less costly than inpatient care, and is preferred by most families.

What has been learned by the expanded use of costly colony-stimulating factors from an economic point of view?

The colony-stimulating factors have been used effectively in a variety of clinical settings to prevent febrile neutropenia and to assist patients receiving dose-intensive chemotherapy with or without stem cell support. Several studies have confirmed the clinical efficacy of the colony-stimulating factors used prophylactically in both solid tumors and hematologic malignancies. The cost of these agents, along with their large-scale clinical use, has prompted a number of economic investigations. Economic analyses based on measures of resource utilization derived from randomized clinical trials have provided febrile neutropenia risk threshold estimates for the cost-saving use of prophylactic colony-stimulating factors. A number of important studies concerning the clinical and economic impact of these agents have been reported recently. These include a revised cost-minimization study based on improved febrile neutropenia cost information and a cost–effectiveness analysis in the adjuvant breast cancer setting based on a clinical prediction model to select patients at high risk for neutropenic complications. Continuing clinical and economic evaluation along with updating of clinical practice guidelines is needed owing to the rapid technological and clinical advances in this area.

Which type of antibacterial regimen is more cost-effective in the empiric management of febrile neutropenia?

There is evidence to suggest that single-agent broad-spectrum antibacterials may be cost-effective alternatives to combination antibiotics for the empiric management of febrile neutropenia in cancer patients. Dranitsaris et al[20] compared the clinical effectiveness of ceftazidime monotherapy with that of two combination antibiotic regimens in cancer patients with febrile neutropenia. The two comparator regimens consisted of tobramycin plus piperacillin, either with (CAP regimen) or without (AP regimen) cefazolin. They also performed a cost–effectiveness analysis of the three regimens. Meta-analysis of randomized comparative trials between the three therapy groups was performed to determine the average overall response rate after 3–5 days of treatment. Seven clinical studies were selected for analysis. The overall incidence of adverse drug reactions (ADRs) was determined using the results of comparative and non-comparative studies. A comparative cost-analytic model was applied from a hospital perspective. The costs of primary therapy, hospitalization, laboratory tests, routine patient care, and treating ADRs were calculated, as were future costs.

Monotherapy with ceftazidime was associated with an overall response rate of 63.5% and mean per-patient costs of C$12 000 to C$14 000. In comparison, the AP regimen was associated with an overall response rate of 58.8% and mean costs of C$13 000 to C$16 000 per patient. The overall response rate in patients receiving the CAP regimen was 75.3%, and the mean cost per patient was C$11 000 to C$12 000. Thus, the CAP regimen was the most cost-effective therapy from a hospital perspective.

What is the economic benefit of a step-down regimen in high-risk neutropenic patients?

In a recent study, Marra and co-workers[21] determined treatment outcomes and the economic impact of a ciprofloxacin step-down program for high-risk febrile neutropenic adults from the hospital's perspective. In an unblinded, two-phase, single-center study, adult leukemia and stem cell transplant (high-risk) adults with febrile neutropenia were studied. Two approaches were analyzed: a multidisciplinary ciprofloxacin step-down program involving a reduction in parenteral ciprofloxacin dose from 400 to 200 mg and conversion to oral ciprofloxacin when criteria were met; and an approach without the parenteral step-down program. In total, 46 sequential treatment courses were compared with a 42-treatment course from 6-month periods in pre-intervention (P1) and post-intervention (P2) phases. Assessed parameters were clinical and microbiologic outcomes, ADRs, and direct medical resource use and costs (1998 Canadian dollars) for the episode of febrile neutropenia. A decision-analytic model was used to map probabilities and costs and to conduct sensitivity analyses. To supplement standard statistical testing, 1000 bootstrap samples were created, and the mean cost difference was calculated between phases for each sample. Patient demographics, percentage intravenous-to-oral step-down, and duration of therapy were similar between phases. Clinical success (83% P1, 81% P2), microbiologic eradication (15% P1, 24% P2), and possible ADRs (6% P1, 9% P2) did not differ. Intravenous-to-intravenous dose step-down occurred in 33% of P2 and no P1 treatment courses ($p = 0.001$). Resource use and costs were similar between phases, although a reduction was seen in the drug's mean total cost/day (C$58 P1, C$52 P2, $p = 0.04$). There was also a trend toward a decrease in mean total treatment costs (C$4843 P1, C$3493 P2, $p = 0.08$). Of 1000 bootstrap samples, 99.8% showed a cost advantage for P2. The model was robust to sensitivity analyses. Finally, the authors concluded that this intervention influenced the administration of ciprofloxacin without an apparent compromise of patient outcomes and resulted in a reduction in total costs of treating febrile neutropenia.

USING ECONOMIC ANALYSES IN DECISION MAKING

Just conducting pharmacoeconomic research is often not enough. What has to be done is to increase the impact of such evaluations. A lot of economic data has already been compiled, but is not being used properly. So the future lies also in using results and increasing the impact of those evaluations.[22] One means, for example, is to involve decision makers in the planning of such studies. In the past, manufacturers have produced data and tried to convince decision makers, instead of working together with decision makers beforehand. It should always be noted that economic analysis and economic data represent only part of the information required for the decision process. The next step is to make decision makers aware of the usefulness of an economic evaluation. Whoever the decision maker is, there will be no use, if they don't feel that they can make a better decision based on this economic evidence. It is extremely important to have the data present *before* the decision is being taken.

The next point is to make the study known in the community by all means of publication and

Table 15.6 Rank order of methodologies in terms of credibility, financial cost and time to completion

- Economic analysis integrated into a randomized controlled clinical trial
- Economic analysis integrated into case–control or cohort observational study
- Model based on published randomized clinical trial
- Model based on published observational study
- Model based on expert opinion
- Model with unclear or incomplete source of data

communication, preferably through the channels that reach decision makers. This means that methodologies have to be reviewed in terms of their credibility, financial costs, and time completion. Classifications such as those used in the Cochrane Collaboration may also be suitable for analyzing and rating the sources for economic evaluations.[23] Table 15.6 lists a rank order of methodologies for assessing credibility. In those cases where economic studies cannot be combined with randomized controlled studies, modeling techniques have to be employed.[24] However, also here good modeling practice should be envisaged.[25] Checklists have been developed in order to facilitate the appraisal of the quality of economic analyses and assist in minimizing possible bias.[26,27] These criteria are also being increasingly used in the peer-review process by many biomedical journals[28] and discussed accordingly.[29]

In many countries, such as Canada and Australia, economic appraisal is a prerequisite for acceptance of a new pharmaceutical product to be considered reimbursable.[30,31]

FUTURE OUTLOOK

Medical economics will become one of the most significant strategic success factors for healthcare providers in an era of cost containment. The challenge will be not only to meet the requirements of government agencies and payers who are increasingly asking for economic assessments of commercial products, but also to address the value of medical economics to clinicians. In the future, it will certainly be necessary for clinicians to apply the tools of economic analyses both in research and in practice. Instead of waiting for policy analysts, third-party payers, or governmental agencies to hand down decisions about which services are deemed worth the cost, physicians could eventually become practicing clinical economists. Another approach is to explore ways in which clinical decisions are influenced by as well as influencing the cost of care. Clinicians need to integrate economic thinking into their decision making if medical care is to be rational but not rationed. Pharmaceutical and device-manufacturing companies can contribute significantly to this process by expanding economic research on their products, by providing training and know-how to medical professionals, and by encouraging customers to acknowledge the validity of such research.

REFERENCES

1. Oster G, Epstein AM, Cost–effectiveness of antihyperlipemic therapy in the prevention of coronary heart disease. *JAMA* 1987; **258:** 2381–7.
2. Luce BR, Elixhauser A, *Standards for the Socioeconomic Evaluation of Health Care Services.* Berlin: Springer-Verlag, 1990.
3. Drummond MF, O'Brien B, Stoddart GL, Torrance GW, *Methods for the Evaluation of Health Care Programmes*, 2nd edn. Oxford: Oxford University Press, 1997.
4. Siegel JE, Weinstein MC, Russell LB, Gold MR, for the Panel on Cost–Effectiveness in Health and Medicine, Recommendations on reporting

cost–effectiveness analyses. *JAMA* 1996; **276:** 1339–41.
5. Metropolitan Life Insurance Company, *Blood Pressure: Insurance Experience and its Implications.* New York: Metropolitan Life Insurance Company, 1961.
6. Beck, JR, Kassirer JP, Pauker SG, A convenient approximation of life expectancy – the DEALE. I. Validation of the method. *Am J Med* 1982; **73:** 883–8
7. Beck JR, Kassirer JP, Pauker SG, A convenience approximation of life expectancy – the DEALE. II. Use in medical decision-making. *Am J Med* 1982; **73:** 889–97.
8. Sonnenberg FA, Beck JR, Markov models in medical decision making: a practical guide. *Med Decis Making* 1993; **13:** 322–38.
9. Drummond M, Cost–effectiveness league tables: more harm than good. *Soc Sci Med* 1993; **37:** 33–40.
10. Kaplan R, Bush J, Health-related quality of life measurement for evaluation research and policy analysis. *Health Psychol* 1982; **1:** 61–80.
11. Rosser R, Kind P, A scale of valuations of states of illness: Is there a social consensus? *Int J Epidemiol* 1978; **7:** 347–58.
12. Feeny D, Furlong W, Boyle M, Torrance GW, Multi-attribute health classification systems: Health Utilities Index. *PharmacoEconomics* 1995; **7:** 490–502.
13. von Neumann J, Morgenstern O, *Theory of Games and Economic Behavior*, 3rd edn. New York: Wiley, 1953.
14. Epstein AM, The outcomes movement: Will it get us where we want to go? *N Engl J Med* 1990; **323:** 266–70.
15. Wennberg JE, Outcomes research, cost containment, and the fear of health cure rationing. *N Engl J Med* 1990; **323:** 1202–4.
16. Faulds D, Lewis N, Milne RJ, Recombinant granulocyte colony-stimulating factor: pharmacoeconomic considerations in chemotherapy-induced neutropenia. *PharmacoEconomics* 1992; **1:** 231–49.
17. Chaplin S, Cancer therapy complication costly to treat. *Hosp Doctor* 1991; May 9: 308.
18. Leese B, Collin R, Clark DJ, The cost of treating febrile neutropenia in patients with malignant blood disorders. *PharmacoEconomics* 1994; **6:** 233–9.
19. Mullen CA, Petropoulos D, Roberts WM et al, Economic and resource utilization analysis of outpatient management of fever and neutropenia in low-risk pediatric patients with cancer. *J Pediatr Hematol Oncol* 1999; **21:** 212–18.
20. Dranitsaris G, Tran TM, McGeer A, Narine L, Pharmacoeconomic analysis of empirical therapy with ceftazidime alone or combination antibiotics for febrile neutropenia in cancer patients. *PharmacoEconomics* 1995; **7:** 49–62.
21. Marra CA, Frighetto L, Quaia CB et al, A new ciprofloxocin stepdown program in the treatment of high-risk febrile neutropenia: a clinical and economic analysis. *Pharmacotherapy* 2000; **20:** 731–40.
22. Coyle D, Increasing the impact of economic evaluations on health-care decision making. Discussion Paper 108, York University, York, 1993.
23. Chalmers I, Haynes B, Reporting, updating, and correcting systematic reviews of the effects of health care. *BMJ* 1994; **309:** 862–5.
24. Hillner BE, role of decision analysis in relation to clinical trials and a US perspective of the Battelle model. *PharmacoEconomics* 1996; **9**(Suppl 2): 30–6.
25. Buxton MJ, Drummond MF, Hout BA et al, Modelling in economic evaluation. A first and last resort? *Health Econ* 1997; **6:** 217–27.
26. Drummond MF, Stoddard GL, Torrance GW, *Methods for the Economic Evaluation of Health Care Programmes.* Oxford: Oxford University Press, 1987.
27. Task Force on Principles for Economic Analysis of Health Care Principles, Economic analysis of health care technology. A report on principles. *Ann Intern Med* 1995; **123:** 61–70.
28. Drummond MF, Jefferson TO, Guidelines for authors and peer reviewers of economic submissions to the *BMJ*. *BMJ* 1996; **313:** 275–83.
29. Kassirer JP, Angell M, The journal's policy on cost effectiveness analysis. *N Engl J Med* 1994; **331:** 669–70.
30. Commonwealth Department of Health, Housing and Community Services, *Guidelines for the Pharmaceutical Industry on the Preparation of Submissions to the Pharmaceutical Benefits Advisory Committee.* Canberra: Australian Government Publishing Service, 1992.
31. Canadian Coordinating Office of Health Technology Assessment (CCOHTA), *Guidelines for the Economic Evaluation of Pharmaceuticals*. Ottawa: CCOHTA, 1994 (www.ccohta.com).
32. Kievit J, van de Velde CJH, Utility and cost of

carcinoembryonic antigen monitoring in colon cancer follow-up evaluation. A Markov analysis. *Cancer* 1990; **65:** 2580–7.
33. Desch CE, Lasala MR, Smith TJ et al, The optimal timing of autologous bone marrow transplantation in Hodgkin's disease patients following a chemotherapy relapse. *J Clin Oncol* 1992; **10:** 200–9.
34. Hillner BE, Smith TJ, Desche CE, Efficacy and cost–effectiveness of autologous bone marrow transplantation in metastatic breast cancer. *JAMA* 1992; **267:** 2055–61.
35. Welch HG, Larson EB, Cost–effectiveness of bone marrow transplantation in acute nonlymphocytic leukemia. *N Engl J Med* 1989; **321:** 807–12.
36. Hillner BE, Smith TJ, Efficacy and cost–effectiveness adjuvant chemotherapy in women with node-negative breast cancer. *N Engl J Med* 1991; **324:** 160–8.
37. Ozer H, Golomb HM, Zimmerman H et al, Cost–benefit analysis of interferon alpha 2b in treatment of hairy cell leukemia. *J Natl Cancer Inst* 1989; **81:** 594–602.
38. Berger K, Szucs T, Cost–effectiveness analysis of paclitaxel and cisplatin versus cyclophosphamide and cisplatin as first-line therapy in advanced ovarian cancer. A European perspective. *Eur J Cancer* 1998; **34:** 1894–901.
39. Rees GJG, Cost–effectiveness in oncology. *Lancet* 1985; **ii:** 1405–8.

16

Fever in the neutropenic patient: Past lessons and future prospects

Philip A Pizzo

The association of fever, neutropenia, and risk of infection began with the seminal observations of the individuals to whom this book is dedicated. It was Gerry Bodey who reported in the mid-1960s that a drop in the neutrophil count in cancer patients, especially when profound and protracted, is associated with a heightened risk for infection. When these infections go unrecognized or are not treated promptly, morbidity and mortality are significant. The first and perhaps most enduring impact on the infection-related mortality associated with fever and neutropenia emanated from the studies of Jean Klastersky in Europe and Stephen Schimpff in the USA, who demonstrated the role of early empiric antibiotic therapy in the management of fever and neutropenia.

It is now more than three decades that have unfolded since these initial discoveries, and much has changed in the diagnosis, management, prevention and outcome of the infectious complications that occur in conjunction with fever and neutropenia. In this book, a number of distinguished experts have reviewed and codified the many advances and progress that have been accomplished, and the challenges that remain.

PAST LESSONS AND THE PROGRESS OBSERVED DURING THE PAST THREE DECADES

Although the approach to the diagnosis and management of fever in the neutropenic patient employed today is thematically consonant with principles generated more than a quarter of a century ago, there have been considerable changes as well. These include the patients at risk for infection, the types of anticancer therapy they receive, the nature of the infecting organism and the patterns of infections observed, the antimicrobial armamentarium, the increasing availability of biological therapies, and evolving concepts regarding preventive strategies. Many of these changes have been discussed in detail in this book. In this chapter, I shall summarize some of these developments and offer some perspective on how they inform current management and future research.

Changes in the patients at risk

When the principles surrounding empiric antimicrobial therapy for neutropenic patients who became febrile were initially elucidated, they largely applied to individuals receiving

chemotherapy for acute leukemias, especially adults with acute myeloid leukemia. These patients generally suffered the greatest periods of neutropenia and were among the most intensively treated with chemotherapy.

Since the late 1960s and early 1970s, more intensive chemotherapy regimens have been administered to adults and children with various solid tumors as well as those with leukemias and lymphomas. Although the duration of bone marrow suppression, and hence the risk of infection, is greatest in individuals with underlying bone marrow disease or those who have received marrow-ablative regimens, such a risk is now clearly extended to other patient populations. These include both adults and children with solid tumors who are receiving chemotherapy (especially dose-intensive regimens with or without stem cell reconstitution), patients with primary or secondary bone marrow failure states, and individuals who may be treated with cytotoxic therapies for non-malignant processes.

Accordingly, with the exception of patients who have transient neutropenias associated with antecedent viral infections, it can be generally assumed that broad-spectrum antibiotic therapy should be promptly and empirically administered to every individual who has developed a fever while neutropenic. This is especially true for individuals who have received prior cytotoxic chemotherapy.

It should also be noted that, even in the absence of fever, neutropenic patients with localizing symptoms that are compatible with a possible site of infection (e.g. abdominal pain) should be treated similarly to neutropenic patients with fever. Indeed, certain organisms (e.g. *Clostridium septicum*) can cause devastating infections in neutropenic patients in the absence of fever.

Changes in cancer treatment and their impact on outcome

Combination chemotherapy began in the mid 1960s and early 1970s with the treatment of acute leukemias and lymphomas (especially Hodgkin's disease). Multimodal therapy is now part of most therapeutic regimens, and, in many cases, dose-intensive therapies are a component of the therapeutic regimen. At the same time, based on the underlying disease and the chemotherapy regimen, it is possible to categorize patients as 'low-risk' or 'high-risk'. As detailed in Chapters 8 and 9, this risk stratification has important implications for patient management, including the type and route of initial empiric antimicrobial drug delivery, the need for subsequent modifications of therapy, and even whether patients are treated in or out of hospital.

It has also become clear that while the depth and duration of neutropenia are perhaps the most important determinants for the risk of infection, both the underlying disease and chemotherapy regimen that is administered can impact other host defenses. Notably, the impact on cellular immunity, measured by sustained age-related depressions in $CD4^+$ cell number, underscores the multidimensional impact of cancer therapy on innate and acquired host defenses.

Change in the organisms causing infection and the patterns of disease

As discussed in Chapters 1, 6 and 7, the need for prompt empiric broad-spectrum antibiotic therapy in the 1960s–1980s was underscored by the dominance of Gram-negative organisms causing severe infections in cancer patients. Most notable were infections due to *Pseudomonas aeruginosa*, *Escherichia coli*, and *Klebsiella* spp. Although these organisms can still be responsible for serious infections, there has been a notable decline in Gram-negative infections in most centers treating cancer patients in the 1990s through the present. The reasons for this decline are not fully understood, but it is also clear that Gram-negative bacteria remain a significant problem at selected institutions and, in particular, in developing nations.

At the same time that Gram-negative organisms declined, Gram-positive isolates increased, especially with coagulase-negative staphylococci. Although this is largely attributed to the remarkably increased use of indwelling sialastic catheters in cancer patients, it is important to note that some of the trends with Gram-positive organisms occurred prior to frequent catheter use. In addition to the coagulase-negative staphylococci, *S. aureus*, streptococci (perhaps most notably some of the viridans streptococci), and enterococci have also emerged as significant pathogens.

As also detailed in Chapters 1, 5, 6 and 7, the choice of empiric antibiotic therapy and outcome of the patient can be linked to the infecting organism. However, because empiric antibiotic therapy is initiated with the onset of fever and includes broad-spectrum regimens, it is also notable that the ability to diagnose either a site of infection or microbiological etiology is now the exception rather than the rule. Indeed, unlike the patterns observed in the 1960s and 1970s, when a clinical or microbiological site of infection was diagnosed in two-thirds of patients presenting with fever and neutropenia, this now occurs in less than a third of patients. Of course this does not mean that these patients are uninfected, but rather that early therapy has suppressed or muted the ability to define a clinical or microbiological site or cause of the fever. Clearly, this also makes management decisions more challenging, since the initial therapeutic regimen, and its modification and duration, are now guided by persistent or recurrent fever rather than clinical or microbiological endpoints.

Although bacteria account for the majority of the initial fevers in neutropenic cancer patients, it has also become clear during the last three decades that other classes of organisms are responsible for primary or secondary fevers or infections. Among these are the herpesviruses as well as the respiratory viruses, fungi (which can be influenced by geography), and various parasites, either due to reactivation or new acquisition.

Given the wide range of potential offending organisms, it has also become increasingly clear that neutropenic cancer patients can have multiple infectious complications during a period of neutropenia, especially when the length of neutropenia exceeds 10 days. These 'high-risk' patients deserve scrupulous attention and careful management, as has been reviewed in Chapters 1, 6 and 7.

Changes in the therapeutic armamentarium and impact on supportive care

In addition to changes in the patients at risk and the organisms responsible for infection, one of the most remarkable changes during the last three decades has been in the antimicrobial agents available for supportive management. Although the limited spectrum of antibiotic coverage mandated that combination therapy be administered during the 1960s and 1970s, this began changing in the 1980s with the availability of third-generation cephalosporins, and then subsequently, the carbapenems and fluoroquinolones. As discussed in Chapters 5 and 9, these newer agents have permitted new approaches to empiric antibiotic management, including monotherapy and, in 'low-risk' patients, the prospect of oral regimens and outpatient management.

Of course, advances in antibiotic therapy have been coupled with the emergence of resistant microorganisms, making antibiotic utilization an area that requires considerable scrutiny and regulation. Inappropriate or unnecessary antibiotic use, especially with drugs such as vancomycin, aminoglycosides, and fluoroquinolones, has been associated with the emergence of drug resistance in a number of centers around the world. This has further underscored that empiric therapy is not an excuse for unregulated or indiscriminate drug regimens. Moreover, the routine use of antibiotics that are important parts of the therapeutic armamentarium (e.g. fluoroquinolones) should not be employed as prophylaxis.

In addition to advances in antibiotics, progress has also been made in newer antiviral and antifungal agents, driven in part because of the role that some of these organisms play in patients with AIDS. Although there has been progress, there is still much work to be done in this area, since there remain serious limitations in the antiviral and antifungal therapeutic armamentarium.

Over the past two decades, attention has also turned to the use of biologicals as either therapeutic adjuncts or as a means to bolster or restore the altered host defenses in cancer patients. The initial forays into this area of research addressed the role of leukocyte transfusions, passive and active immunization, and the use of interferons. Although some of these approaches were grounded in logic, technical limitations most often precluded their success.

Beginning in the late 1980s and extending to the present, considerable attention has been given to the hematopoietic cytokines (granulocyte and granulocyte–macrophage colony-stimulating factors: G-CSF and GM-CSF) to shorten the duration of neutropenia in cancer patients. As discussed in Chapter 13, a truly evidence-based evaluation of these cytokines limits their utilization to relatively specific clinical indications, focusing particularly on higher risk patients.

In summary, it is increasingly clear that the supportive management of fever in neutropenic patient is closely linked to their risk status. Low-risk patients with short durations of neutropenia (i.e. <10 days) can be treated with simpler antimicrobial therapies, either parenterally or orally, and with relatively little need for additional antimicrobial additions or modifications of the initial regimen. There is little need for hematopoietic cytokines in these low-risk patients. Moreover, therapy for many of these patients can be done in an ambulatory setting, potentially at home.

In contrast, high-risk patients, categorized by prolonged durations of neutropenia (>10 days), require inpatient management, are at risk for multiple secondary infections that require additions or modifications of their initial regimen, and may benefit biological response modifiers that improve immune or hematologic recovery.

Changes in clinical trial design and related expectations

Improving the management of fever and infection in neutropenic cancer patients is closely dependent on evidence-based data emerging from appropriately conducted clinical studies. Because of the progress that has been made in reducing infection-related mortality, and since a clinical or microbiological cause of the initial fever is frequently lacking, the conduct of clinical trials is methodologically challenging. To optimize the design and analysis of clinical trials in febrile neutropenic cancer patients, a number of international societies including the International Immunocompromised Host Society (ICHS), the Infectious Disease Society of America (IDSA), and the Multinational Association for Supportive Care in Cancer (MASCC) have attempted to establish guidelines that optimize clinical trial design and the ability to compare the results of studies done in different settings and patient populations. The issues and governing concerns have also been covered in Chapters 2 and 14.

CURRENT PROBLEMS AND CHALLENGES FOR THE FUTURE

The past three decades have witnessed major progress in the supportive management of cancer patients who develop fever and neutropenia. Morbidity and mortality have been dramatically reduced, and therapies are simpler and less toxic and more appropriately delineated according the patient's risk status, disease, age, and clinical setting. Despite this progress, however, numerous challenges and opportunities remain to be addressed and problems solved.

Almost certainly as a result of the early initi-

ation of empiric therapy when neutropenic patients become febrile, the ability to diagnose whether a patient is truly infected, and, if so, at what site and with what organism(s), remains a major challenge. Improved rapid non-culture-dependent diagnostic tests from accessible body sites or fluids are needed. These assays need to address bacteria, viruses, fungi, and selected parasites. Clearly, these measures need to be available to children as well as adults. In addition, improved imaging studies that could help to localize occult sites of infection would be a significant advance.

Improved risk stratification of patients is also important. This can be based on improved clinical measures of risk, but should also address the biological factors within the host that contribute to the risk of infection or their specific expressions. For example, genetic predisposition to colonization or infection could address both the host and the pathogen.

Refined assessment of host defense factors are also important in determining which patients are at risk for specific infections. This could include rapid determination of innate or acquired host immune factors that modulate the risk for infection during neutropenia. Pharmacogenetic assessment may also help determine which patients are more susceptible to toxic effects from anticancer therapies.

Development of new antimicrobial agents that overcome resistance or that provide more effective therapy, especially for viruses and fungi, is also critically needed. With improved antibacterial agents, opportunistic fungi and a number of herpesviruses and respiratory viruses have emerged as major pathogens. Clearly, an expanded and enhanced therapeutic armamentarium is important. Improving host defenses with cellular or humoral biological therapies is another goal.

Although treating or preventing infections with antimicrobial agents and/or biologicals is important when patients receive cytotoxic immunosuppressive therapies, the greatest impact will come with more selective and specific anticancer therapies that do not damage the host defense matrix. While this was a dream just years ago, the rapid progress in elucidating the molecular pathogenesis of cancer is leading to the development of new agents that impact cancer cells without resulting in side-effects such as neutropenia. When such therapies become available, the problems and challenges associated with fever and neutropenia may well be overcome.

Index

Key: autoPBSCT, autologous peripheral blood stem cell reinfusion; BSCT, blood stem cell transplantation; BMT, bone marrow transplantation; HSCT, hematopoietic stem cell transplantation; PBSC, peripheral blood stem cells; PBSCT, peripheral blood stem cell transplants.