Endoscopy in Liver Disease

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Preface

Endoscopy is an integral part of the diagnosis and therapy of several conditions related to liver disease. Over the past decade, there has been a dramatic improvement in the technology and the number of endoscopic techniques available to the hepatologist or gastroenterologist with an interest in liver disease. This book fulfills the need for a comprehensive cover of all aspects of endoscopic procedures in the patient with liver disease including post-liver transplantation. These range from well established procedures, such as endoscopic band ligation of varices, to novel approaches, such as EUS guided coil or glue injection of gastric varices and radiofrequency ablation of gastric antral vascular ectasia. The apparatus we use has improved continuously with the development of endoscopes for enhanced imaging, confocal probes, and dedicated stents for variceal tamponade, to mention but a few.

We, at the Mayo Clinic and at Royal Infirmary of Edinburgh, envisioned the utility of putting together a collection of articles about the role of endoscopy in liver disease, which would be of interest to those working or training in this area. We have been fortunate to enlist clinicians and scientists with international recognition in the field to contribute highly informative and practically useful chapters to the book. We acknowledge the support of Wiley for bringing this endeavor to fruition.

John N. Plevris
Peter C. Hayes
Patrick S. Kamath
Louis M. Wong Kee Song

About the Companion Website

This book is accompanied by a companion website:

www.wiley.com/go/plevris/endoscopyinliverdisease

The website includes 11 high quality videos illustrating optimum endoscopy practice, all clearly referenced in the text.

Video 4.1 Primary prophylaxis of esophageal varices with endoscopic band ligation.
Video 5.1 Endoscopic injection sclerotherapy as salvage modality for failed band ligation of bleeding esophageal varices.
Video 5.2 Endoscopic band ligation of esophageal varices with stigmata of recent bleeding.
Video 5.3 Endoscopic band ligation of an actively bleeding esophageal varix.
Video 5.4 Endoscopic band ligation of actively bleeding gastroesophageal varices type I (GOV1).
Video 5.5 Endoscopic cyanoacrylate injection of fundal varices with stigmata of recent bleeding.
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Equipment, Patient Safety, and Training

John N. Plevris[1] and Scott Inglis[2]

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Introduction

Liver disease and cirrhosis remain common causes of morbidity and mortality worldwide [1–3]. The significant advances in our understanding and treatment of liver disease, including liver transplantation over the last 25 years, have resulted in hepatology increasingly becoming a separate specialty. Although in many countries hepatologists have received background training in gastroenterology and endoscopy, subspecialization often means that they are no longer practicing endoscopists.

On the other hand, there are healthcare systems where hepatologists come from an internal medicine background with no prior training in endoscopy. It is therefore important for the modern hepatologist to have a full appreciation and up to date knowledge of the potential of endoscopy in liver disease and to ensure that there is a close collaboration between hepatology and endoscopic departments. In parallel to this, endoscopy has undergone a period of rapid expansion with numerous novel and specialized endoscopic modalities that are of increasing value in the investigation and management of the patient with liver disease.

The role of endoscopy in liver disease is both diagnostic and interventional. Endoscopy is commonly offered to patients with relevant symptoms (unsuspected liver disease may be diagnosed in this manner) and has a role in the management of inpatients with pre-existing liver disease, mainly for variceal screening and therapy. Furthermore, such patients can be challenging to sedate and the complexity and number of endoscopies in liver disease continue to increase with rising numbers of end-stage liver disease patients, patients who are considered for liver transplantation, and in post-liver transplant patients.

It is therefore not surprising that advanced endoscopic modalities, such as endoscopic ultrasound (EUS), endoscopic retrograde cholangiopancreatography (ERCP), cholangioscopy (e.g., SpyGlass™), confocal endomicroscopy, and double balloon enteroscopy, have all become integral in the detailed investigation and treatment of liver-related gastrointestinal and biliary pathology (Figure 1.1).

It is now clear that the role of endoscopy in liver disease is well beyond that of just treating varices. As endoscopic technology advances, so do the indications and role of the endoscopist in the management of liver disease.

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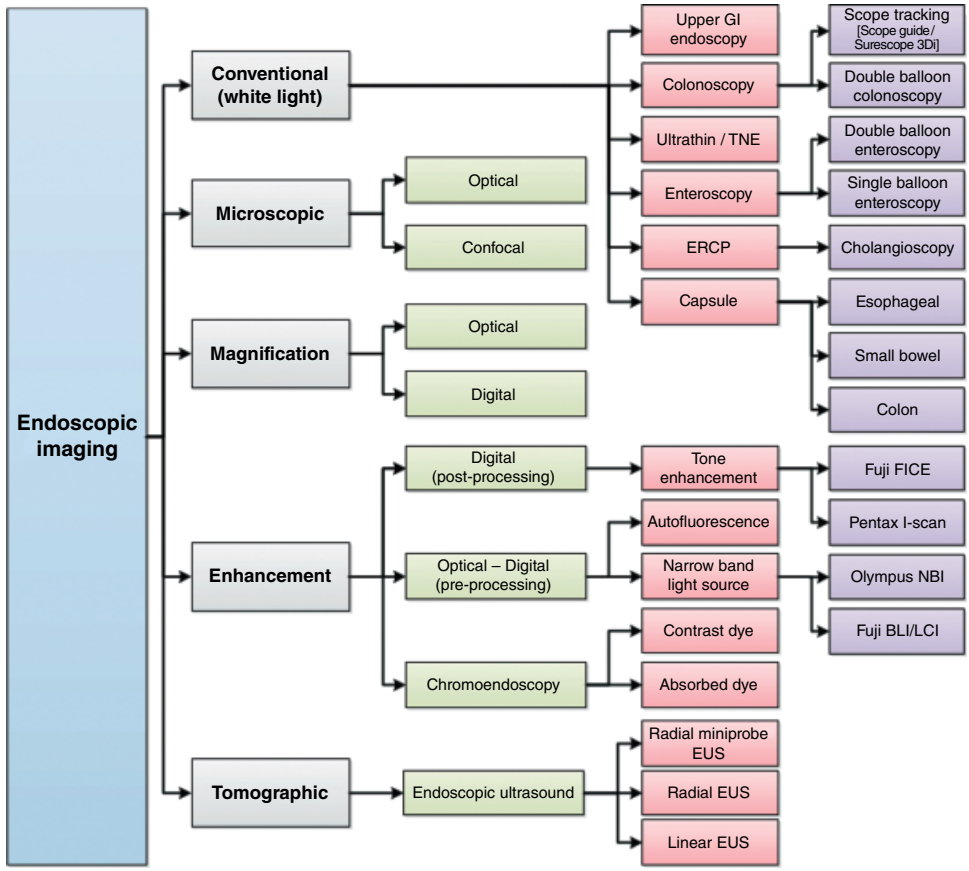

Figure 1.1 Endoscopic modalities used in the investigation and treatment of hepatobiliary disease and related disorders. BLI/LCI, blue color imaging/linked color imaging; ERCP, endoscopic retrograde cholangiopancreatography; EUS, endoscopic ultrasound; FICE, flexible spectral imaging color enhancement; GI, gastrointestinal; NBI, narrow band imaging; TNE, transnasal endoscopy.

Equipment

Endoscopy Room Setup

Optimum design and layout of the endoscopy room are important to ensure maximum functionality and safety while accommodating all the state of the art technology likely to be needed in the context of investigating complex patients with liver disease. The endoscopy room needs to be spacious with similar design principles to an operating theatre. Gas installations and pipes should descend from the ceiling and the endoscopy stack unit and monitors should be easy to move around and adjust according to the desired procedure, or mounted on pendants to maximize floor space.

A multifunctional endoscopy room able to accommodate different endoscopic procedures, such as esophagogastroduodenoscopy (EGD), enteroscopy, ERCP, and EUS, is advantageous. As such, the room design should be able to contain the following equipment:

1) An endoscopic stack system containing a light source and video processor unit that has advanced features (e.g., high definition (HD), alternate imaging modalities, image processing), HD capable monitor, and HD video and image capture device.

2) A physiological stats monitor to monitor vital signs such as blood pressure, heart rate, blood oxygenation levels, and electrocardiographic (ECG) readings.
3) An ultrasound (US) scanner/processor compatible with EUS endoscopes. Such a scanner usually includes modalities such as tissue harmonics, Doppler, color and power flow, contrast, and elastography.
4) A reporting system that allows for the speedy capture of images and the generation of reports connected to the central patient record system. This should be compatible with the hospital Picture Archiving and Communication System (PACS) for high resolution image transfer or videos.
5) A C-arm installation connected to a central PACS system for image archiving can be used in a well-equipped endoscopy room shielded for radiation. Alternatively, in many hospitals, ERCP or other interventional procedures requiring fluoroscopic guidance are carried out in the radiology department in order to benefit from regular updates of high quality radiology equipment and the presence of a radiographer.
6) Basic equipment required for patient treatment and safety, such as suction, water jet units, argon plasma coagulation (APC), electrosurgery, and emergency trolleys for acute cardiorespiratory arrest, as well as equipment for elective and emergency intubation and for delivery of general anesthesia.
7) Onsite pathology facilities (e.g., for real-time assessment of samples from EUS guided fine needle aspiration) may be found in many endoscopy units.

Endoscopic Stack

Modern endoscopic stacks have many common components – the light source to provide illumination and the video processor, which takes the endoscopic image from the charge coupled device (CCD) chip within the tip of the endoscope, processes the image and then displays it on the monitor in real time.

At present there are two methods employed for the transmission of light and display of the received image (Figure 1.2). One method is to transmit separate red (R), green (G), and blue (B) color spectrum wavelength components generated by RGB rotating filter lenses via an optical fiber bundle into the gastrointestinal tract. The reflected light intensity changes obtained from each RGB light are detected via a monochrome CCD where the video processor combines these with the appropriate R, G, or B color to generate a "white light" or color image, where each element of the CCD is one pixel of each frame of the video. The second option is to transmit white light, without alteration, and then detect the image using a color or RGB CCD, where multiple elements of the CCD are used to create one pixel in the video frame. A newer method, not widely used currently, that removes the need for the fiber transmission bundles, is the introduction of light emitting diodes (LEDs) built into the tip or bending section of the endoscope. The anatomy is imaged using a RGB CCD. Each transmission method has advantages and disadvantages, but in general visible resolution and detail definition of the image, due to advances in CCD manufacture and technology, have greatly improved irrespective of the technique used.

Furthermore, as camera chip or CCD technology has increased in resolution and decreased in size, manufacturers have been able to take advantage of improvements in display technology to visualize the gastrointestinal tract in high resolution, thus giving the endoscopist a new dimension in detecting pathology.

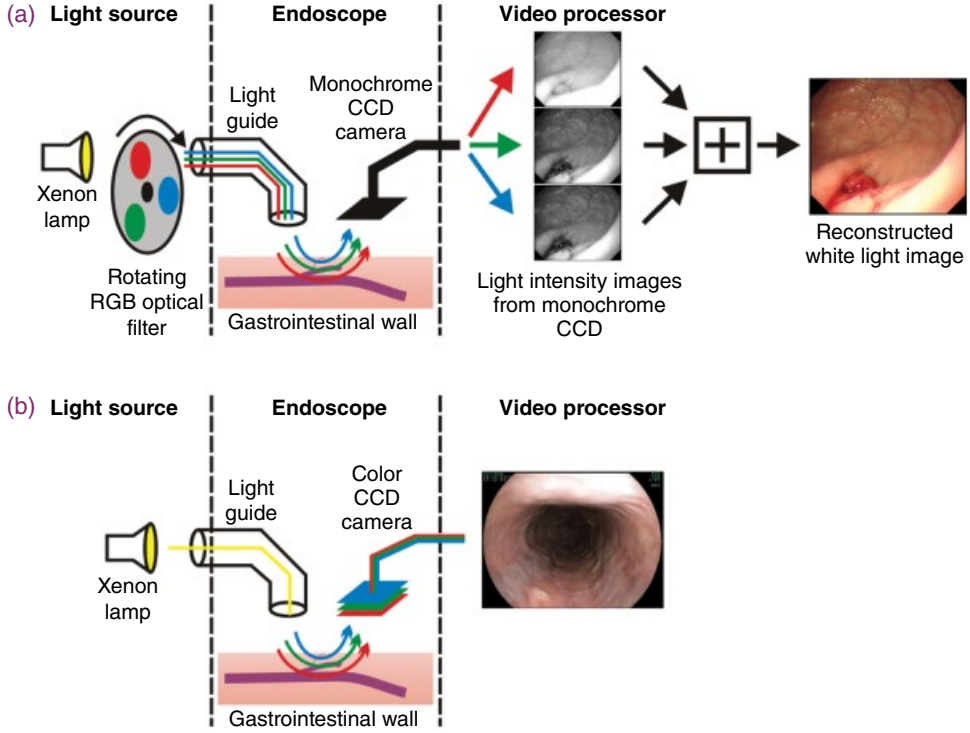

Figure 1.2 (a) Transmission of RGB (red, green, blue) light wavelengths that are detected using a monochrome charge coupled device (CCD). (b) Transmission of white light that is visualized using a color CCD.

Image Enhancing Modalities

Manufacturers have introduced various image enhancement techniques (Figure 1.3) to aid in the detection and delineation of pathology for more accurate diagnosis and targeted treatment [4]. Examples of these include narrow band imaging (NBI; Olympus Corp., Tokyo, Japan), flexible spectral imaging color enhancement (FICE; Fujinon Corp., Saitama, Japan), and i-Scan (Pentax Corp., Tokyo, Japan). NBI operates on a different principle to the other systems, as it limits the transmitted light to specific narrow band wavelengths centered in the green (540 nm) and blue (415 nm) spectra. This allows for detailed mucosal and microvascular visualization, thus facilitating early detection of dysplastic changes. Alternatively, FICE and i-Scan use post-image capture processing techniques that work on the principle of splitting the images into "spectral" components. Specific spectral components are then combined, with the "white light" image, in a number of permutations, thus creating different settings that aim to enhance the original endoscopic image and delineate the gastrointestinal mucosa or vascular structures.

New Advances in Image Enhancement

An alternate image enhancement technique to NBI, i-Scan, and FICE has been introduced by Fujifilm with the release of the ELUXEO™ endoscopy system, consisting of a new video processor and light source. Within the light source, Fujifilm have replaced the standard xenon lamp and have instead incorporated four LEDs with wavelengths in the red, green, blue,

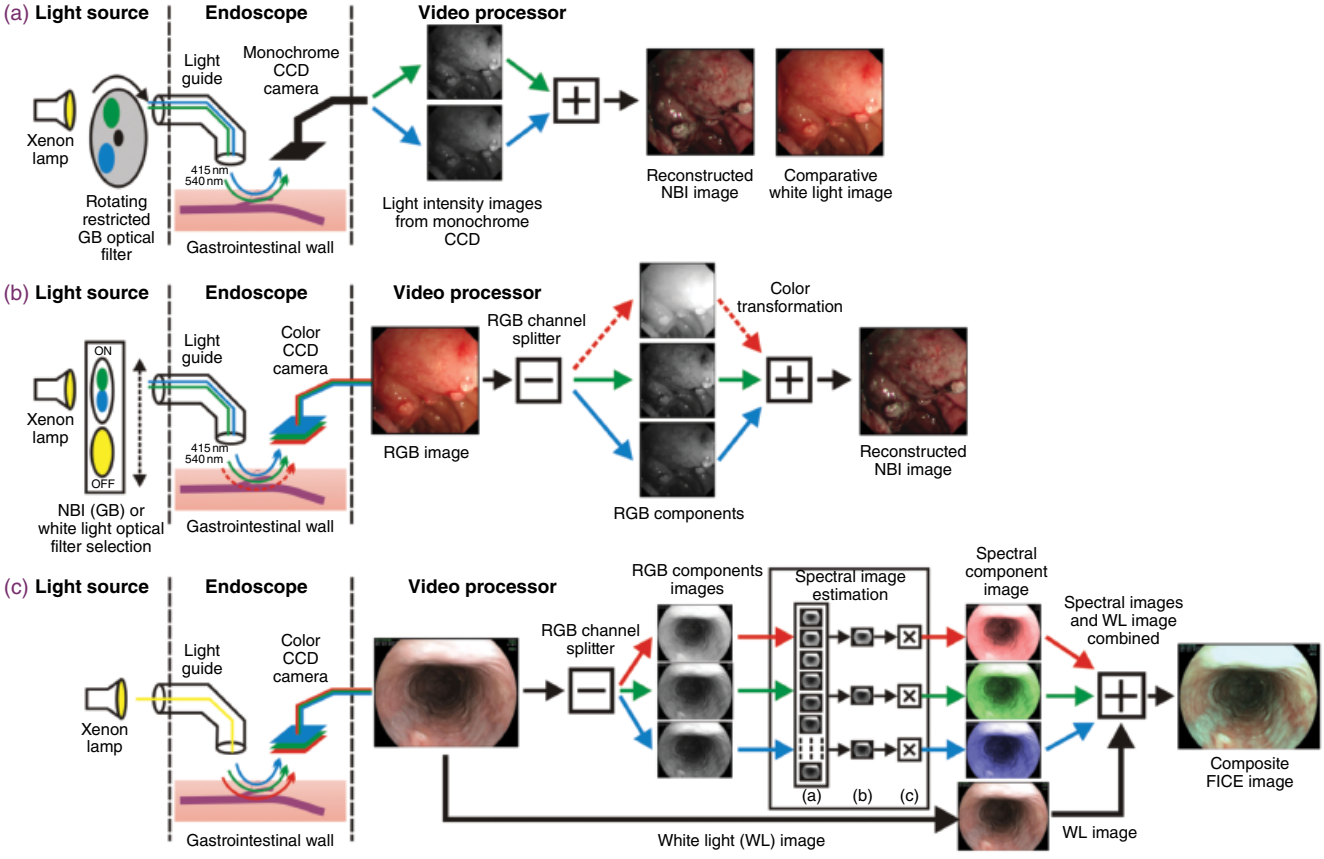

Figure 1.3 (a) Narrow band imaging (NBI) using a monochrome charge coupled device (CCD) camera (mainly used in UK and Japan). (b) Altered version of NBI for use with the color CCD camera (Europe and USA/rest of world). (c) Flexible spectral imaging color enhancement (FICE). B, blue; G, green; R, red; WL, white light.

and blue-violet spectra. They have replaced FICE with two dedicated image enhancement techniques: (i) blue light imaging (BLI); and (ii) linked color imaging (LCI). The incorporation of a dedicated blue-violet LED takes advantage of the short wavelength absorption of hemoglobin (410 nm), which can enhance the underlying superficial vascularity and mucosal patterns (Figure 1.4). LCI is an image processing technique that separates the four color channels to allow for the enhancement of the difference in the red color spectrum and improve the detection and delineation of mucosal inflammation (Figure 1.5).

Endoscopes

The quality of modern endoscopes has greatly improved; they are far more ergonomic in design and lighter, with superior picture resolution and definition. Endoscopes have also become slimmer and this has significantly impacted on patient safety and comfort. The incorporation of high resolution (up to 1 million pixels) and high definition (>1 million pixels) camera technologies into modern endoscopes and the introduction of new image enhancement techniques have significantly enhanced the endoscopist's arsenal in the detection and treatment of gastrointestinal pathologies. With such advanced optics, fine mucosal details can be visualized which may reveal subtle pathology, such as angioectactic lesions, watermelon stomach, portal hypertensive gastropathy, enteropathy, and ectopic varices at a far earlier stage than with older generation endoscopes.

Modern endoscopes are far more advanced than previous generation ones, resulting in more space being available in the insertion tube, and therefore larger working channels can be included, allowing for more powerful air suction and insufflation, as well as water irrigation to clean the lenses. Powerful air insufflation can often flatten even large varices. This has to be taken into account when grading varices using a commonly used classification system by Westaby et al. [5], which depends on the percentage of circumference of the esophageal lumen occupied by a varix and whether the varix can be flattened by air insufflation.

In general, the types of upper gastrointestinal endoscopes used in the context of liver disease are the standard endoscopes that possess a working channel of 2.8 mm, the therapeutic endoscopes with a working channel of 3.2 or 3.6 mm (often used in the context of upper gastrointestinal bleeding), and more recently the high resolution ultrathin endoscopes (5.9 mm). The latter have become more popular in the last few years, not only in diagnostics, but also in the assessment of varices, particularly for patients who have been finding frequent surveillance endoscopies to monitor variceal progression stressful. Such endoscopes can be used transnasally, which has been shown in some studies and select patient populations to be more comfortable than standard endoscopy [6]. Ultrathin endoscopes improve patient tolerance while maintaining an adequate or even near standard size working channel (2.4 mm) for endoscopic biopsies. Such endoscopes, however, are not suitable for endoscopic variceal banding (Figure 1.6).

Endoscopic Ultrasound

Side and front optical viewing endoscopes with appropriate technology have been used to perform EUS, and these are commonly used for diagnosis and therapy in the patient with liver disease. This technique can be of value in the diagnosis of varices, particular ectopic varices (Figure 1.7), in assessing eradication of varices, and in delivering EUS guided therapies, such as thrombin or cyanoacrylate injection for variceal obliteration [7]. EUS guided measurement of the hepatic venous pressure gradient (HVPG) is possible, as are biopsies of the hepatic parenchyma

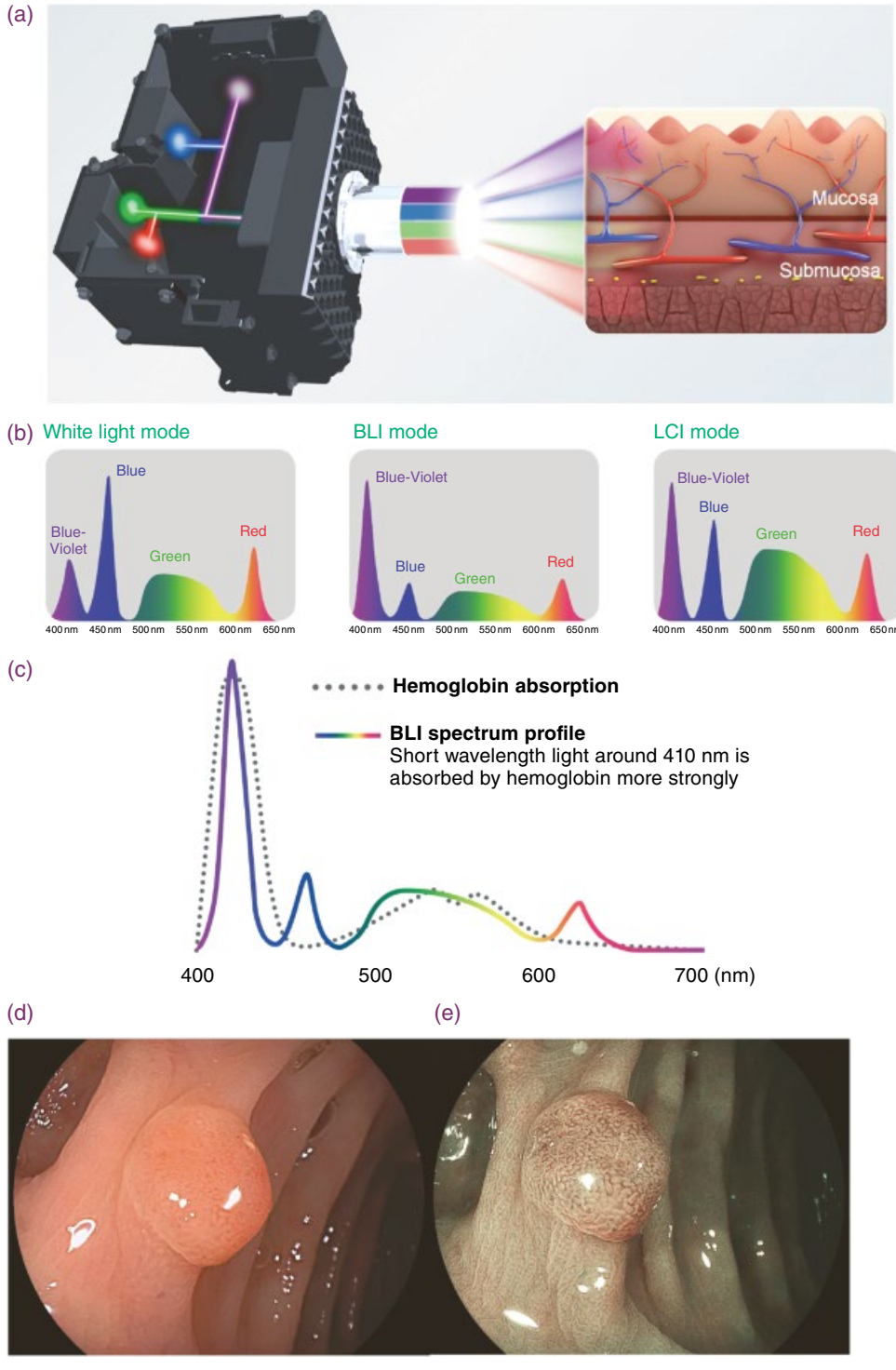

Figure 1.4 (a) The function of the four light emitting diodes (LEDs) in relation to the depth of penetration of the light spectra from the new ELUXEO™ light source. (b) The difference in the transmitted spectra when in white light, blue light imaging (BLI) and linked color imaging (LCI) modes. (c) The short wavelength absorption characteristics of hemoglobin in comparison to the transmitted light spectra of BLI. (d, e) Images of a polyp captured using (d) white light, and (e) BLI.
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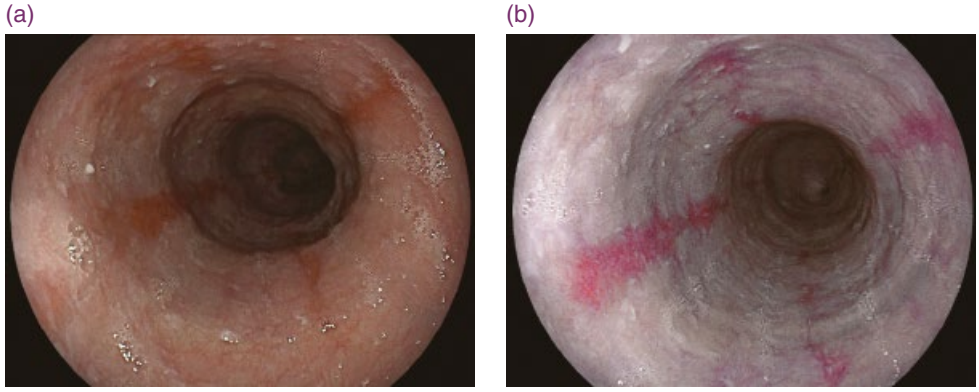

Figure 1.5 Views of the esophagus in (a) white light mode and (b) linked color imaging mode. Source: Reproduced with permission of Aquilant/Fujifilm.

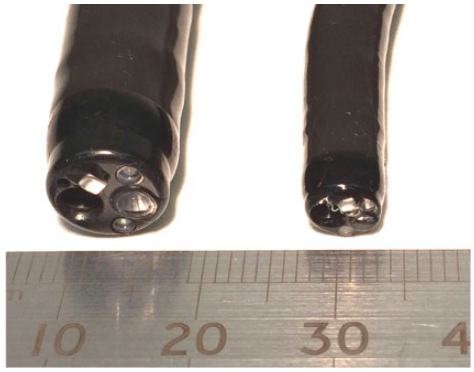

Figure 1.6 Tip of a standard endoscope (9.2 mm, left) versus the tip of an ultrathin endoscope (5.9 mm, right).

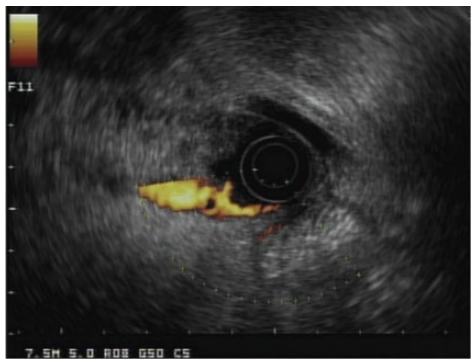

Figure 1.7 Appearance of an ectopic varix under endoscopic ultrasound in the second part of the duodenum.

and masses in the left lobe of the liver. Both linear and radial echoendoscopes (Figure 1.8) should be available with appropriate clinical expertise in a center dealing with complex patients with liver disease. Additional modalities, such as tissue harmonics, Doppler color and power flow, contrast, and elastography (for assessing tissue stiffness), are also of value in the context of liver disease. The use of high frequency (12 or 15 MHz) ultrasound miniprobes through the working channel of a standard or double channel therapeutic endoscope can also be used for a quick assessment of variceal obliteration (Figure 1.9).

Endoscopic Retrograde Cholangiopancreatography

The latest ERCP scopes, together with the SpyGlass™ technology [8], have enabled direct visualization of the biliary tree and this has significantly improved our ability to diagnose malignant biliary disease. In 2007, the first generation SpyGlass™ Direct Visualization System (Boston Scientific Corp., Natick, MA, USA) was introduced (Figure 1.10). This relied on a small fiberoptic bundle with an external CCD, introduced into a dedicated catheter, to visualize the biliary tree. The SpyGlass™ DS system introduced in 2015 has evolved

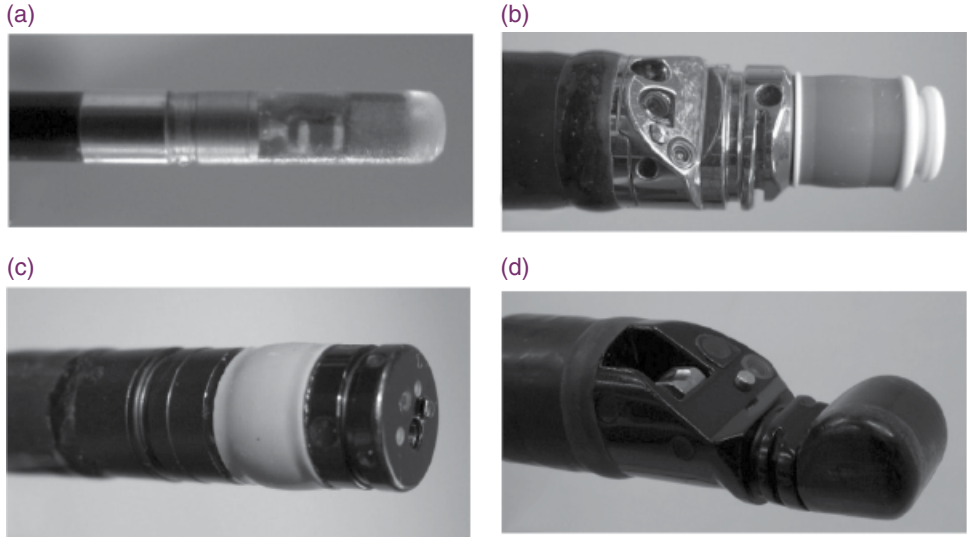

Figure 1.8 Endoscopic ultrasound (EUS) equipment with (a) a miniprobe 2.6 mm in diameter; (b) and (c) are 360° radial views, one with side viewing optics and the other with front viewing optics, respectively; and (d) the linear or fine needle aspiration EUS instrument.

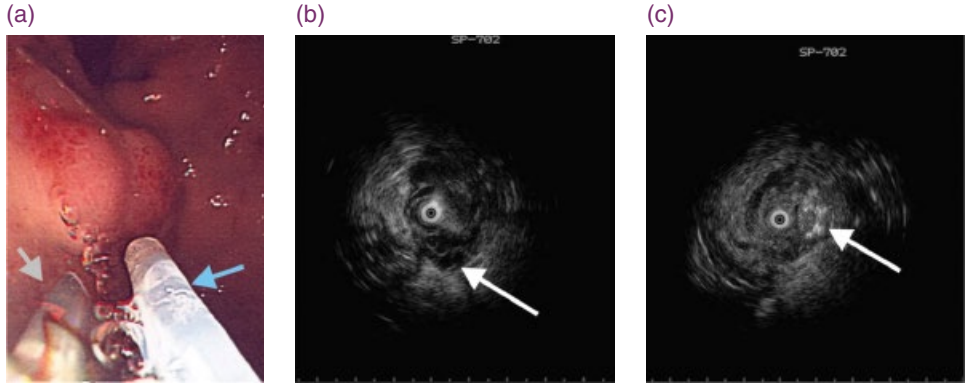

Figure 1.9 (a) Injection of thrombin for variceal obliteration using an endoscopic ultrasound miniprobe (grey arrow) and an injection needle (blue arrow). (b) Appearance of varices under a 12 MHz miniprobe (white arrow). (c) "Snow storm" appearance of an obliterated area of a varix (white arrow) following thrombin injection.

to be a small digital endoscope, with improved optical resolution (approximately × 4), a wider field of view (60%), and dedicated LED illumination.

Recently there have been safety concerns about the design of the ERCP endoscopes and their ability to be sterilized adequately as bacterial transmission of resistant bacteria from patient to patient has been reported [9–12]. As can be appreciated by the complex design of the tip of the ERCP endoscope (Figure 1.11), meticulous cleaning is required to ensure high level decontamination of such endoscopes. This has led to the revision of decontamination protocols [13] and calls for the revision of the design of the latest ERCP endoscopes [14].

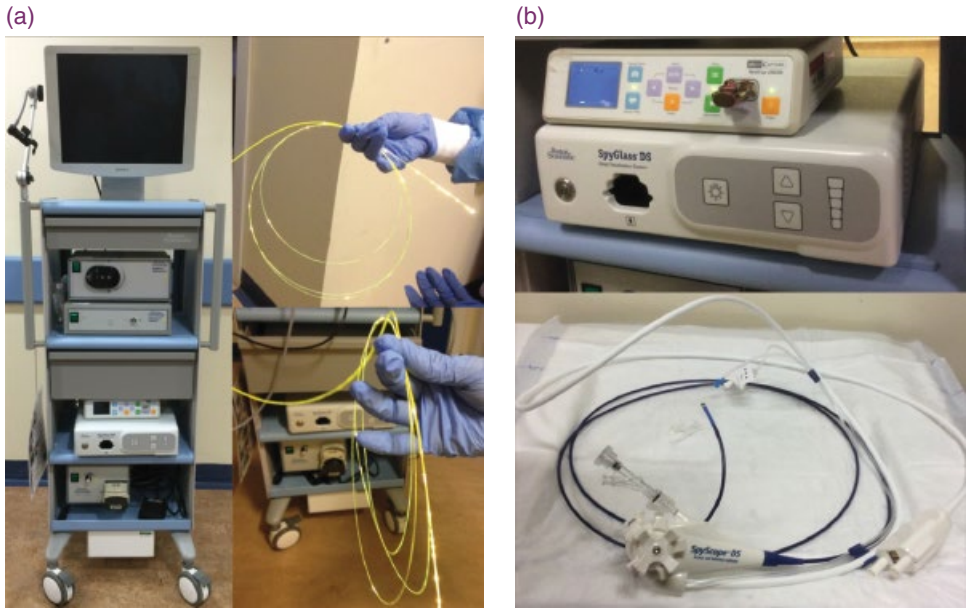

Figure 1.10 (a) SpyGlass™ system and first generation catheter for the direct visualization of the biliary tree. (b) Second generation SpyGlass™ DS processor and single use endoscope.

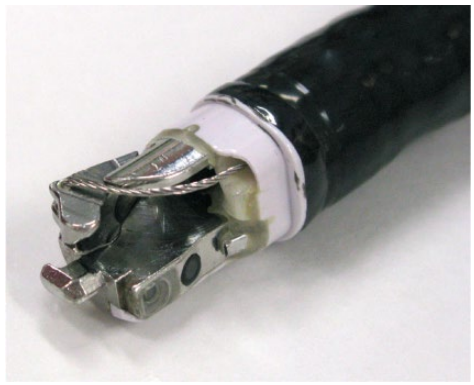

Figure 1.11 Tip of an ERCP endoscope. The complex design to ensure effective movement of the bridge is associated with increased risk of infection transmission despite appropriate decontamination.

There has been an increase in the use of deep enteroscopy (both single and double balloon) in the management of patients with chronic liver disease [15]. These endoscopes are used for deep intubation and access to the common bile duct (double balloon assisted– ERCP) in the context of altered anatomy (e.g., Roux-en-Y in cases of hepaticojejunostomy) or for the investigation and treatment of small bowel pathology in the patient with liver disease (e.g., treatment of ectopic varices or biopsies of the small bowel in the post-liver transplant patient to exclude sinister pathology such as lymphoma). Such procedures require special expertise, are time consuming, and preferably should be performed under general anesthesia.

Colonoscopy

Colonoscopy in the patient with liver disease is not dissimilar to other patients. HD colonoscopes should be used to ensure diagnosis and therapy are optimized. Appropriate enhanced imaging modalities, such as NBI and FICE, are available although their value in the colon has been debated compared with that in the upper gastrointestinal tract.

High quality colonoscopy is particularly important in the workup of patients prior to liver transplantation to ensure that colon cancer is not missed. This is particularly important in the context of primary

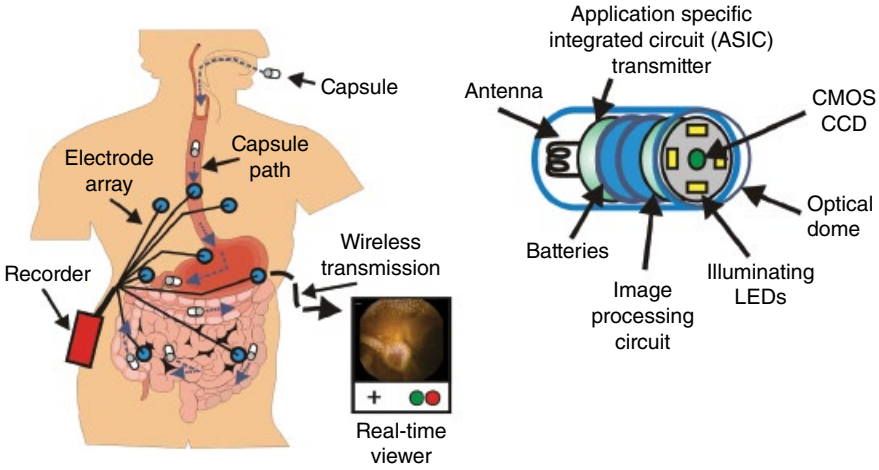

Figure 1.12 Wireless capsule measurement setup and basic capsule schematic. CCD, charge coupled device; CMOS, complementary metal oxide semiconductor; LED, light emitting diode.

sclerosing cholangitis. Colonoscopy may also be required in the evaluation of gastrointestinal bleeding and the treatment of colonic (mainly rectal) varices.

Wireless Endoscopy

Wireless capsule endoscopy is valuable in the assessment of esophageal varices in a selected group of patients with liver disease who for a number of reasons may not be keen to undertake routine endoscopic surveillance [16] and in patients with suspected small bowel sources of bleeding [17]. The basic schematic of the capsule and the procedure setup are detailed in Figure 1.12. They mainly consist of a power source (batteries), a CMOS (complementary metal oxide semiconductor) or CCD chip, lens and associated imaging board, illuminating LEDs, and a transmitter to wirelessly transmit or stream the video to an external recorder. Several companies now compete and produce high quality wireless systems with slightly different capsule characteristics (Figure 1.13).

Figure 1.13 Examples of the internal and external structure and components of the main capsule systems. Both (a) and (c) use radiofrequency (RF) transmission and dedicated RF receiver arrays for wireless video recording, whereas (b) uses the body to transmit the video to the recorder. Standard electrodes in an array are used to pick up the video signals.

Accessories and Consumables

A number of accessories are routinely used in the context of endoscopy in liver disease. These include variceal band ligators, endoloops, injection needles for delivering sclerosants (rarely used nowadays), thrombin or cyanoacrylate (superglue), and fine needle devices for the deployment of coils. All these techniques have been shown to be relatively minimally invasive but effective in controlling variceal bleeding [18–20]. Other modalities include APC for the

delivery of coagulation for bleeding from gastric vascular ectasia, as well as recently introduced radiofrequency ablation (RFA) probes for the therapy of obstructing cholangiocarcinoma. It is now widely accepted that single use accessories and consumables should be used to ensure maximum infection control.

In conclusion, a well-designed and well-equipped endoscopy unit is important for the delivery of state of the art endoscopic therapy for patients with liver disease, whose diseases for the most part are high risk and of high complexity.

Patient Safety and Training

Patient safety is best achieved by high standards of equipment disinfection and maintenance, appropriate patient selection, and endoscopy of high risk patients in a safe environment (e.g., critical care unit) with adequate support from anesthesiologists and an appropriately trained team of endoscopists and nurses.

Cleaning and Disinfection of Endoscopes

Endoscopes need to go through a complex disinfection/sterilization procedure to eliminate the transmission of bacteria, viruses, parasites, fungi, and spores, as well as prions that can transmit spongiform encephalopathy. As such, strict operating protocols should be in place and followed in a very rigorous manner based on published guidelines and standards relating to disinfection/sterilization processes. This improves the safety and minimizes the risk of infection in patients undergoing endoscopy. Publications such as the *Guidelines and Tools for the Sterile Processing Team* [21] and sterile processing accreditation surveys [22] published by the Association of periOperative Registered Nurses' (AORN) journal, and important communications and updates from regulatory bodies such as the Food and Drug Administration and Centers for Disease Control, raise awareness among healthcare professionals and ensure that a high level of safety is maintained [23,24].

Accreditation surveys performed by specialist agencies and professional organizations are peer reviewed and focus on safety and quality of patient care, thus encouraging the development and adherence to robust processes for endoscopy units in order to achieve accreditation.

In most endoscopy units, automated cleaning/washing machines are available for cleaning and reprocessing the endoscopes. Depending on the number of endoscopy rooms and the volume of endoscopic procedures per week, specific guidelines exist regarding the design of decontamination facilities to ensure effective risk control. The *Choice Framework for Local Policy and Procedures 01-06* by the UK Department of Health [25] details the best evidence based policies and gives comprehensive guidance on the management and decontamination of reusable medical devices.

It is particularly important to ensure that the workflow within the endoscopy unit is from dirty to clean. Such workflow avoids recontamination of reprocessed endoscopes from unprocessed, and thus contaminated, devices. An example of a high throughput reprocessing unit is illustrated in Figure 1.14.

Employment of appropriately trained staff accountable to a management structure is important to ensure adherence to decontamination protocols and best utilization of resources. The purchase of suitable automated endoscope reprocessors is important. Optimal reprocessing also depends on the local quality of water used, the decontamination agents used, and the endoscope manufacturer to ensure compatibility and minimization of the damaging effect of disinfection on endoscopes.

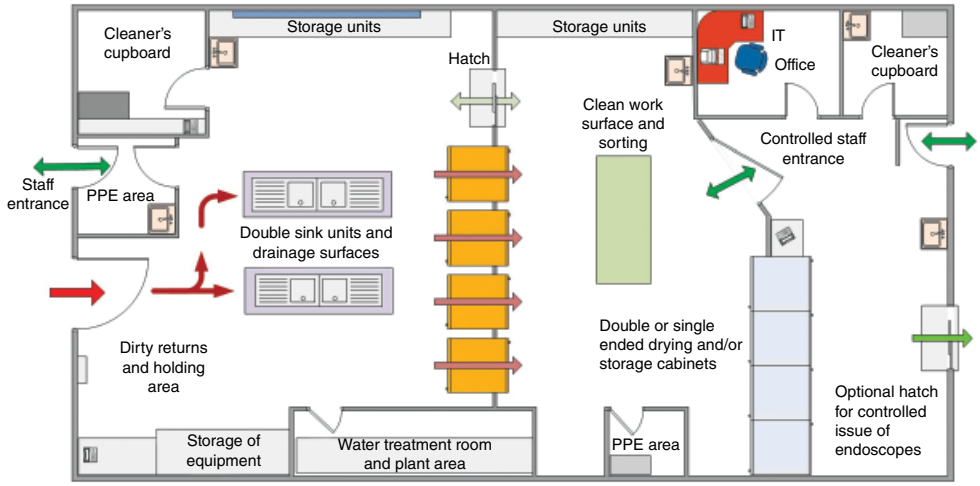

Figure 1.14 Optimum layout of a disinfection/decontamination unit as recommended by the UK Department of Health. PPE, personal protective equipment. Source: Adapted from © British Crown Copyright 2016, licensed under http://www.nationalarchives.gov.uk/doc/open-government-licence/version/3/.

The previously used aldehyde based detergent (glutaraldehyde) should be avoided as this may result in fixing prions inside the endoscopes, thus increasing the risk of transmission of prions, leading to spongiform encephalopathy. In general, neutral pH or neutral enzymatic agents are recommended because of their effective decontamination while having the least damaging effect on endoscopes.

Rigorous and regular microbiological tests reflecting the best evidence based practice are necessary to ensure that the decontamination process remains of high standard. The decontamination room staff should constantly be in communication with the infection prevention and control teams, which typically include medical and nursing personnel and a microbiologist trained in infection control.

Transmission of hepatitis viruses is very rare if all standard operating procedures are followed. It is, however, particularly important in the context of liver disease to ensure that there are robust systems in place for tracking all endoscopes used through a unique endoscope identifier, as well as being able to trace the journey of a particular endoscope through its decontamination and clinical usage. Such information is critical in the unfortunate event of a safety breach, which may expose several patients to risks of infection, so as to be able to recall all patients who underwent procedures with inadequately sterilized endoscopes and provide prophylactic therapy as appropriate.

Specifically in the context of prion transmission, it is of paramount importance that early action be taken in the event that the guidelines have not been followed during a procedure with a high risk for transmission of variant Creutzfeldt–Jakob disease (vCJD), thus potentially contaminating the endoscope. Such endoscopes need to be quarantined immediately, as once they have been contaminated there is no safe method of disinfection. These endoscopes should be reserved exclusively for an individual patient at high risk of vCJD if future endoscopic procedures are required. Specific guidelines regarding prion transmission are in place through the British and American Societies of Gastroenterology. A summary of these guidelines is presented in Figure 1.15 [26,27].

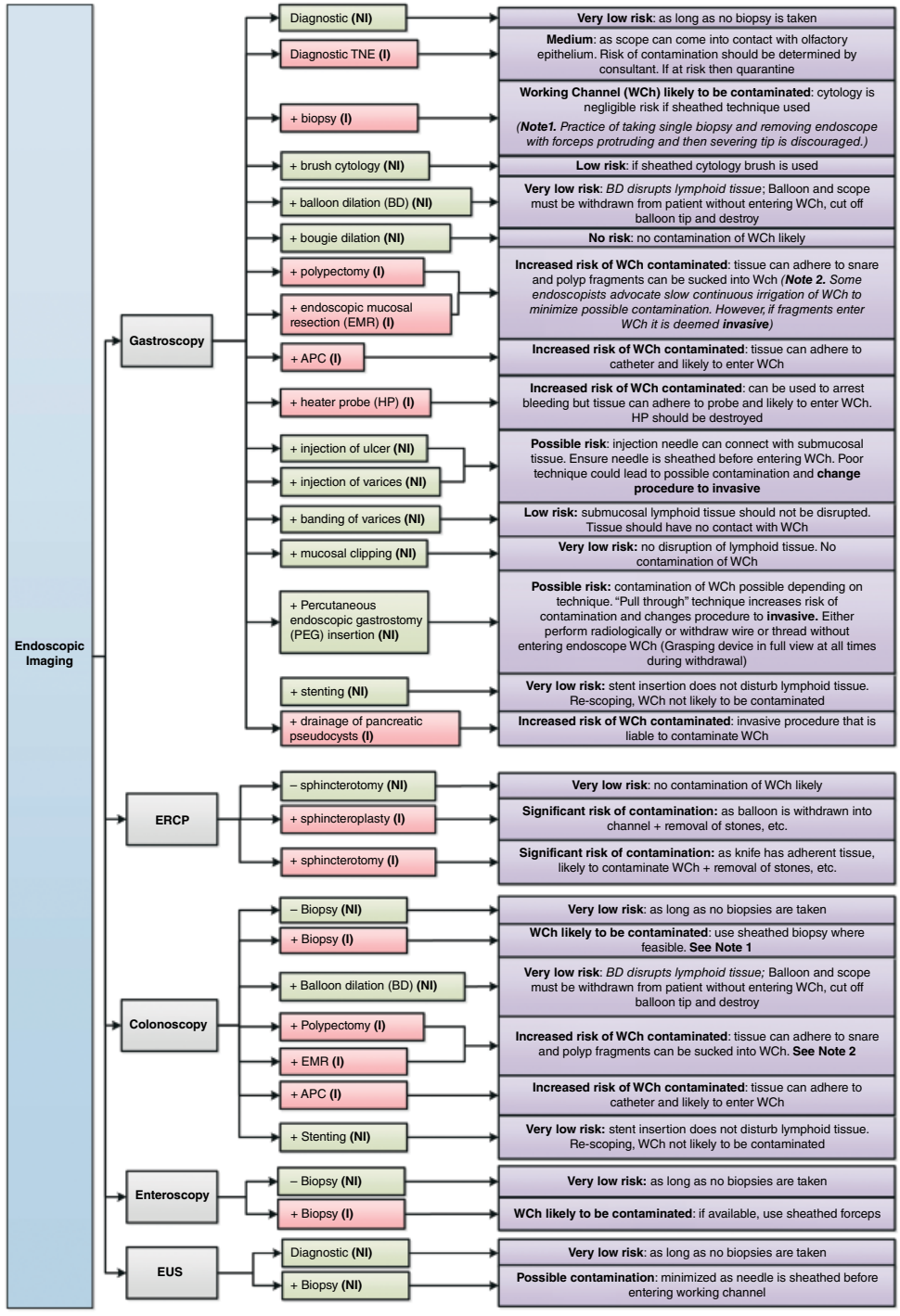

Figure 1.15 Endoscopic procedures considered high risk for prion transmission in pink and low risk in green. APC, argon plasma coagulation; ERCP, endoscopic retrograde cholangiopancreatography; EUS, endoscopic ultrasound; I, invasive; NI, non-invasive; TNE, transnasal endoscopy. Summarized from *Transmissible Spongiform Encephalopathy Agents: Safe Working and the Prevention of Infection: Annex F*: Endoscopy, 2015.

It is now recommended to routinely use single use endoscopic accessories, which minimize the risk of transmission of infection. Storage of disinfected endoscopes should be in designated clean and dry areas, preferably in dedicated storage cabinets with HEPA (high efficiency particulate air) filtered air, which allows the endoscopes to be stored and dry for 72 hours without the need for reprocessing. This is particularly useful in busy units with regular off hours endoscopy.

Patients

A detailed history of previous infection should be taken to ensure that high risk patients for viral hepatitis, as well as vCJD and other infectious diseases, are identified. In that respect, important information, such as travel to endemic areas for infections and previous blood transfusions or administration of blood products or surgery in the past, needs to be carefully recorded.

Patients with liver disease at risk of cardiorespiratory compromise should receive the endoscopy under anesthetic support. This is particularly important for patients with encephalopathy and those with alcohol withdrawal symptoms who are far more sensitive and run a high risk of permanent brain injury even after short periods of hypoxia following aspiration or cardiac arrest.

Endoscopy in patients at risk of multiorgan failure should be performed in a critical care environment. The decision and timing of endoscopy should always be balanced against the risks for the individual patient with liver disease. Optimization of the patient's clinical condition by correction of coagulopathy, prophylactic antibiotics, and judicious use of blood transfusion is the cornerstone of safe endoscopy in such patients.

Health Personnel and Training Issues

Since each patient or health staff member is a potential source of infection, precautions are necessary from the personnel point of view to avoid being infected or to pass infection to patients. Personnel should be vaccinated in case of hepatitis A or B or other infection, such as typhoid, depending on the prevalence of such infections in their environment. Meticulous hand washing before and after treating each patient should be practiced. It is also desirable that operators wear protective gowns during endoscopic procedures, as well as gloves, designated shoes, and, whenever appropriate, masks and protective eyewear. Training and operating protocols should be available in each endoscopy room, reviewed at regular intervals, and evaluated to ensure that they are followed. Any incident should be immediately notified to the hospital safety team to ensure that the incident is investigated. Such incidents should be reviewed at regular endoscopy quality improvement meetings to ensure that policies and procedures can be modified to avoid similar incidents in the future.

All practitioners performing endoscopy in patients with liver disease should have adequate training to recognize and treat esophagogastric varices in the elective and acute setting. Familiarization with appropriate equipment and accessories on models and simulators in "hands-on" workshop sessions can greatly enhance training prior to participating in real life cases.

Medical teams should be particularly aware that the patient with liver disease is often likely to have hepatic decompensation in the context of significant bleeding or a complication. Therefore, further management is often required in a critical care environment. This is particularly important for the cirrhotic patient with bleeding varices who has become encephalopathic and runs the risk of aspiration. Appropriate training to recognize such patients for transfer to a critical care unit and assisted ventilation is important. Close collaboration between the endoscopist and hepatologist is necessary, so that the endoscopist is fully aware of

hepatic complication risks and, likewise, the hepatologist is fully aware of the latest endoscopic developments available that can be used to maximize the quality of care of the patient with liver disease.

Acknowledgment

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2

Sedation and Analgesia in Endoscopy of the Patient with Liver Disease

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Introduction

Sedation for endoscopy in patients with liver disease can be a challenging issue. Endoscopists often face the dilemma over providing sufficient sedation to allow for maximum patient comfort whilst maintaining safety. Although performing endoscopy under sedation is not always necessary in the context of liver disease it ensures patient comfort, improved tolerance, and procedure success. This translates to compliance with future procedures, as repeat endoscopies are often necessary for screening or treatment of portal hypertension complications. Sedation is associated with increased patient satisfaction and greater willingness to have a repeat procedure [1].

Pharmacokinetics is altered in liver disease due to impaired metabolism and often coexisting renal impairment. An altered unbound drug fraction due to decreased albumin synthesis and portal–systemic shunting will affect drug distribution. This complex interplay alters first pass clearance and drug elimination. Furthermore, drug to drug interactions, coexisting alcohol consumption, cerebral sensitivity [2], and minimal hepatic encephalopathy (HE) also affect pharmacodynamics. The majority of patients with cirrhosis and portal hypertension may have covert or minimal HE [3,4]; these patients are more sensitive to benzodiazepines, which may then precipitate overt HE.

Deep sedation has substantial variability regarding its effect on portal pressure and hepatic blood flow [5]. Despite most drugs being metabolized in the liver, there are no widely agreed guidelines on sedation and analgesia for diagnostic or therapeutic endoscopic procedures in patients with liver disease.

Conscious sedation in gastrointestinal endoscopy is commonly practiced in the UK, North America, and most European centers. Endoscopists often choose to administer opioid analgesics in addition to a sedative medication, particularly for therapeutic endoscopy.

The need for sedation and/or analgesia is dictated by the complexity of the procedure,

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Table 2.1 Summary of sedatives and analgesics commonly used in gastrointestinal endoscopy.

Drug	Dose	Reversal agent	Advantages	Disadvantages
Topical agent (lidocaine pharyngeal anesthesia)	100–200 mg topical spray	None	45–90 seconds Rapid action	Anaphylaxis, aspiration
Midazolam	30–80 µg/kg	Flumazenil	3–5 minutes Quick action	Slower recovery* Higher risk of precipitating HE*
Propofol	2–2.5 mg/kg (<55 years) 1–1.5 mg/kg (>55 years)	None	30–45 seconds Rapid action	Narrow therapeutic window Expert administration needed Advanced monitoring needed
Fentanyl	50–100 µg	Naloxone	3–5 minutes Quick onset	May precipitate HE
Pethidine (meperidine)	25–50 mg	Naloxone	5–8 minutes Quick onset	Higher risk of precipitating HE†

* Relative to propofol.
† Relative to fentanyl.
HE, hepatic encephalopathy.

the presence of comorbidities, and the severity of the liver disease as determined by the Child–Pugh or Model for End-stage Liver Disease (MELD) score. In general, complex and prolonged therapeutic procedures require deeper sedation and the co-administration of analgesia. In such instances, it is important to receive input from an anesthesiologist to assess the need for general anesthesia or deeper sedation with a combination of propofol and opiates in a controlled and closely monitored environment.

In this chapter we discuss the commonly used medications for sedation and analgesia (Table 2.1) and the indications for deeper sedation, including a general anesthetic.

Midazolam

General

Midazolam is a benzodiazepine that acts as a depressant of the central nervous system, with a sedation potency 1.5–3.5 times greater than that of diazepam [6]. Benzodiazepines have anxiolytic, amnesic, and sedative properties; and at higher doses act as anticonvulsants and muscle relaxants. Midazolam is preferred in most centers due to its pharmacokinetic profile as well as its potent amnesic properties [3]. It has a dose dependent action mediated through gamma aminobutyric acid (GABA) receptors and is reversed by the specific antagonist flumazenil.

Midazolam reaches its maximum effect after 3–4 minutes, although the duration of the effect is between 15 and 80 minutes, depending on cofactors including obesity, advanced age, and comorbidities such as liver or kidney disease [7].

Administration

Midazolam is usually given as an initial bolus of 30–50 µg/kg body weight for upper and lower gastrointestinal endoscopy [6]. This translates to an initial dose of 2–3 mg in a 70 kg male. Subsequent 0.5–1 mg bolus doses can be given until the desired sedation depth is reached.

Lower starting doses are recommended for patients who are frail, elderly, and with more advanced liver disease [6]. Midazolam administration by non-anesthesiologist is commonly practiced as there is an antagonist available (flumazenil) that can rapidly reverse sedation [1]. McQuaid and Laine [8], in their systematic review and meta-analysis, suggest that moderate sedation provides a high level of physician and patient satisfaction as well as a low risk of serious adverse events.

Midazolam is rapidly metabolized in the liver by the cytochrome P450 via hydroxylation and conjugation with glucuronic acid [9]; therefore, the elimination half-life and clearance of its metabolites can be significantly altered in liver disease [10]. MacGilchrist et al. [9] observed a twofold prolongation of the elimination half-life of midazolam (3.9 versus 1.6 hours) as a result of decreased clearance in patients with end-stage liver disease. In comparison with propofol, midazolam is more likely to precipitate overt HE in chronic liver disease [6,11,12], and even more so in advanced liver disease [13]. Therefore, caution is advised during administration, with adherence to dosages as recommended above. Midazolam in patients with decompensated cirrhosis can result in prolongation of the sedative effect for up to 6 hours following administration [2].

Chalasani et al. [14] showed that the bioavailability of midazolam in patients with cirrhosis and a transjugular intrahepatic portosystemic shunt was increased almost threefold compared with cirrhotic controls or healthy volunteers.

Propofol

General

Propofol is a sedative with minimal analgesic and amnesic effects. It is very lipophilic, which explains its rapid mode of action. It readily crosses the blood–brain barrier and acts on GABA receptors to induce its sedative effect. It has an onset of action of approximately 30–45 seconds, peaking at 2 minutes, with an overall duration of 4–8 minutes. The depth of propofol sedation depends on the dose; even a single dose can result in various levels of sedation, therefore administration of propofol requires significant clinical expertise in assessing the level of sedation so the dose can be adjusted appropriately [7].

A meta-analysis found evidence that propofol is superior to midazolam for rapid sedation and recovery, with minimal risk of sedation-related side effects [15]. Due to concerns of potential progression to general anesthesia from deep sedation, the American Society of Anesthesiologists (ASA) recommend propofol administration by trained healthcare professionals who are independent from the endoscopist carrying out the procedure. Their consensus statement prohibits non-anesthetists from using propofol [16]. The concept of non-physician assisted propofol sedation has been much debated; in established practices it has been deemed safe, although not completely free of risk even in healthy individuals [17].

Due to higher risk of apnea, prolongation of the QT interval, and hypotension, continuous cardiac and respiratory monitoring with capnography is recommended during propofol administration. Furthermore, propofol does not offer analgesia, and physiological response to pain can still be seen. Combining opiates may have additive benefit but the risk of deeper sedation and prolongation of recovery may be an undesirable effect. Propofol sedation during colonoscopy appears to have lower odds of cardiopulmonary complications compared with traditional agents, but for other procedures the risk of complications is similar [18].

Administration

The dose of propofol for anesthesia induction in those <55 years of age is 2–2.5 mg/kg administered as 40 mg IV boluses every 10 seconds until the onset of deep sedation. For patients >55 years age or debilitated or with stage ASA III/IV disease, the dose is 1–1.5 mg/kg administered as 20 mg IV boluses every 10 seconds until onset of deep sedation. As there is no reversal agent for propofol, personnel fully trained in performing cardiopulmonary resuscitation with the necessary equipment should be readily available throughout the procedure.

New drugs and drug delivery systems for endoscopic sedation, including fospropofol disodium, patient controlled sedation, target controlled infusion (TCI), and computer assisted personalized sedation, are currently being evaluated for effectiveness and safety [19]. TCI uses a mathematical model to calculate the initial dosage needed to achieve a desired concentration of drug and then makes appropriate adjustments in the rate of infusion to maintain that level. A computer assisted personalized sedation device (Sedasys, Ethicon Inc., Somerville, New Jersey, USA) has recently received US Food and Drug Administration (FDA) approval. This innovative device combines target controlled infusion of propofol, a unique feedback system based on patient response to audible and tactile stimuli, and a physiological monitoring unit. This system is programmed with a drug specific, population based pharmacokinetic model that calculates the infusion rate necessary to achieve the target or desired drug concentration in the blood, thus minimizing the risk of oversedation. However, this device has not gained clinical traction and has been pulled off the market.

Propofol provides more rapid sedation and recovery than midazolam and the risk of sedation related side effects does not differ significantly from that of midazolam [15]. Pharmacokinetics and protein binding of propofol are not significantly affected by moderate or compensated cirrhosis and, therefore, propofol is deemed safe in Child–Pugh A and B cirrhosis, although data in advanced liver disease are lacking. Nevertheless, experienced anesthetists usually administer lower doses in liver disease patients. Propofol is preferred for sedation in patients with liver disease due to its short half-life, reflected in rapid recovery and time to discharge [20]; additionally it has a lower risk of inducing HE compared with midazolam [1,6,11,15,21,22].

Opiate Analgesics

Opiates bind to receptors in the central nervous system and act by increasing the pain threshold and altering pain perception. The liver is the major site of biotransformation for most opiates. The oxidation of pethidine (meperidine) is reduced in patients with cirrhosis and its clearance is diminished, resulting in increased bioavailability. Thus, pethidine should be avoided in patients with liver disease. The onset of action for pethidine is 5 minutes, with the peak effect at 10 minutes, and duration of action lasting 2–4 hours.

Fentanyl, in contrast, is a lipophilic synthetic morphine analog that is chemically related to pethidine but is about 600 times more potent [7]. The maximum effect is expected after 6 minutes and the duration of effect is 20–30 minutes. The initial dose is usually 50–100 µg. Conversely, fentanyl has a shorter duration of effect due to redistribution into lipid storage sites. Fentanyl is transformed into an inactive metabolite that is excreted by the kidneys. However, in repeated or higher doses, it tends to accumulate.

Combination Therapy

Combination of Midazolam with Fentanyl or Pethidine (Meperidine)

Fentanyl and midazolam are a widely used combination that achieves adequate conscious sedation with analgesia and is very commonly used for most therapeutic endoscopies. The preferred combination is midazolam with fentanyl rather than pethidine (meperidine). The endoscopist usually administers both medications as the existing antagonists flumazenil and naloxone can rapidly reverse deeper sedation. Fentanyl is initially administered followed by a slow administration of midazolam, with boluses being given at the rate of 1 mg every minute until the effects of sedation are apparent. Radaelli et al. [23] demonstrated significant patient comfort and willingness to have repeat endoscopies when the combination of midazolam and pethidine were used. The combination of midazolam and fentanyl has a similar effect but with the additional benefit of rapid recovery [24].

Combination of Propofol with Midazolam

Owing to synergistic activity on GABA receptors, propofol and midazolam in combination mutually potentiate action. Midazolam has a longer half-life and duration of action than propofol. Therefore, a prolonged recovery time must be expected as compared with propofol monotherapy [7]. Such a combination should only be given by an experienced anesthetist as it has a higher risk of deeper sedation, and it is often used in procedures that are anticipated to be prolonged or associated with significant discomfort.

Combination of Propofol with Fentanyl or Pethidine (Meperidine)

VanNatta and Rex [25] showed a need for higher doses in propofol-only sedation and a more delayed recovery and discharge while achieving a similar level of sedation as compared with combination therapy of propofol and opiate or propofol and midazolam. The combination of propofol and opiate appears to be as safe as the combination of midazolam with opiate [26].

Administration

The usual analgesic dose for fentanyl is 50–100 μg through slow IV administration, 5–10 minutes prior to procedure. For pethidine it is 25–50 mg IV prior to procedure, although as previously stated pethidine is not favored in the context of liver disease.

The severity of liver cirrhosis is an independent variable in determining the duration of drug action. Mao et al. [27] showed that combined sedation with propofol plus fentanyl is safe for both screening and variceal banding in cirrhotic patients. Correia et al. [1] reported a similar safety profile for patients with cirrhosis who underwent endoscopy with propofol and fentanyl as compared with those who had midazolam and fentanyl.

Emergency Therapeutic Endoscopy

Emergency gastrointestinal endoscopy is often required in patients with liver disease to treat variceal bleeding. A complete assessment of the severity of the liver disease before endoscopy, including physical examination with grading of the severity of liver disease and documenting the presence of HE, is necessary. As a general rule, sedation significantly facilitates

endoscopy in patients undergoing ligation of varices [28], although it may worsen pre-existing HE. Patients with hematemesis are at serious risk of aspiration leading to respiratory arrest and hypoxia induced brain damage. Therefore, airway protection by endotracheal intubation and ventilation for airway support is mandatory in these patients. Patients at particular risk include those with alcohol withdrawal symptoms, overt HE, or a history of epilepsy. In these situations, complex endoscopy should take place in units with anesthesiologists present and, in addition, one to one nursing support for optimizing outcome.

Complex and lengthy procedures, such as endoscopic retrograde cholangiopancreatography (ERCP), double balloon enteroscopy (DBE) or interventional endoscopic ultrasound (EUS), require deeper sedation to ensure quality of endoscopic examinations and an adequate completion rate [29]. Therefore, when such procedures are contemplated in patients with liver disease, the use of general anesthesia or propofol based deep sedation with the use of carbon dioxide insufflation represents the safest practice.

Airway intubation not only protects the airway but also diminishes latent (post-procedural) side effects of sedation, such as prolonged recovery due to stimulation of central GABA receptors in patients with pre-existing encephalopathy.

Unsedated Endoscopy

Commonly, topical anesthesia with lidocaine is offered for unsedated oral gastroscopy to improve tolerability. Furthermore, the use of medical nitrous oxide and oxygen mixture (Entonox, BOC Healthcare, Manchester, UK) in lower gastrointestinal endoscopy is common. The advent of minimally invasive techniques has become a useful and expanding adjunct in gastrointestinal endoscopy. Capsule endoscopy remains a useful diagnostic modality that does not require any sedation. However, capsule endoscopy underperforms when compared with conventional per oral gastroscopy in the diagnosis and staging of esophageal varices [30].

The introduction of high definition, ultrathin endoscopes or single use (disposable) endoscopes via the transnasal approach have provided a convenient method to diagnose and stage esophageal varices. Trans-nasal gastroscopy with topical lidocaine and phenylephrine nasal application was found to be feasible, safe, and accurate for evaluating the presence of varices and red color signs in patients with cirrhosis; even in those with marked bleeding diathesis [31]. It was found to be significantly better tolerated by patients, without compromising endoscopists' confidence in diagnosis [31].

The main disadvantage of the above modalities is that they cannot offer therapeutic capabilities. Therefore, when treatment is required, conventional gastroscopy with sedation is still necessary.

Conclusion

When practicing sedation in endoscopy, geographic differences and preferences in practice across the world are inevitable. They depend on local facilities, equipment and personnel availability, expertise, and both patients' and endoscopists' preferences. For instance, due to limited anesthetic resources in many countries, the administration of propofol sedation by endoscopists has gained popularity [29]. The optimal sedation should be tailored to the individual patient's needs and should balance risks versus benefits in relation to the type of procedure performed [29].

The introduction of new "non-barbituric" intravenous anesthetics (propofol, ketamine, etomidate), with shorter half-lives and minimum accumulation of active metabolites, have greatly increased the

safety and efficacy of sedation, including in patients with liver disease.

Sedation and analgesia in liver disease are more challenging, and knowledge of the pharmacokinetics and pharmacodynamics of the administered agents, as well as potential drug-to-drug interactions are essential, including reversal agents. Careful drug administration, balancing patient comfort and safety, and knowledge of time to peak effect are all vital in avoiding oversedation. Furthermore, the choice of sedative either in isolation or in combination with opiates is at the endoscopist's discretion but should be based on national guidelines and locally approved protocols. In the UK, most endoscopic procedures are performed under conscious sedation achieved by a combination of an opioid (typically fentanyl) and a benzodiazepine (typically midazolam). In countries such as the USA and Australia, and certain European centers, propofol is more frequently used. Consumers (particularly in the USA) may expect largely painless medical procedures, and gastroenterologists may strive to enhance patient satisfaction as well as compliance with screening recommendations as a practice marketing strategy [19].

Finally, the purpose, type of procedure, ASA grade, and severity of the liver disease dictate the choice of sedation, with or without analgesia. Although maximum comfort is high desirable, patient safety is of paramount importance and the endoscopic consent process should reflect this.

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3

Endoscopy in the Setting of Coagulation Abnormalities in the Patient with Liver Disease

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Introduction

It is well recognized that patients with cirrhosis have altered hemostasis mechanisms, with impaired regulation of both bleeding and clotting [1,2]. The disturbance of hemostatic balance in liver disease poses a problem since existing diagnostic tests fail to adequately predict the clinical fate of the cirrhotic patient. Giannini et al. state that one in five cirrhotic patients who undergo various minimally invasive procedures have procedure related bleeding – a risk that garners any endoscopist's attention [3]. It is well known that patients with chronic liver disease are prone to hemorrhagic events due to multiple factors, including defects in primary hemostasis, coagulation pathway, and fibrinolysis [2]. In addition, hemodynamic alterations, both in the micro- and macrovasculature, contribute to the incidence of bleeding. There is, however, no accurate method of predicting post-procedural bleeding in patients with liver disease. More recently, it has been recognized that patients with cirrhosis also have thrombotic events and their presumed "hypocoagulopathy" does not have a protective effect against deep vein thrombosis [4,5]. In this chapter, we review coagulation abnormalities associated with liver disease and describe the risk stratification, monitoring, and treatment of these patients in the setting of endoscopic intervention.

Coagulation Mechanism

The "Normal" Patient

The mechanisms of coagulation and hemostasis in the normal state are shown in Figure 3.1. Based on the practical perspective of the cell based model of hemostasis, the three phases of clotting are: primary hemostasis, coagulation, and fibrinolysis [2,6]. The hemostatic cascade can further be viewed as involving initiation (or priming), propagation, and amplification. Hemostasis in the normal individual is initiated at the site of injury when tissue factor is released. This quickly forms a complex with factor VIIa, which in turn begins the cascade of activation of various factors until a priming amount of thrombin is formed. Thrombin cleaves fibrinogen to fibrin and participates in further activation of platelets, which serve as a phospholipid scaffold on which the reactions are amplified [2,4,7]. These activated platelets bind to a complex of multimeric endothelial derived von Willebrand

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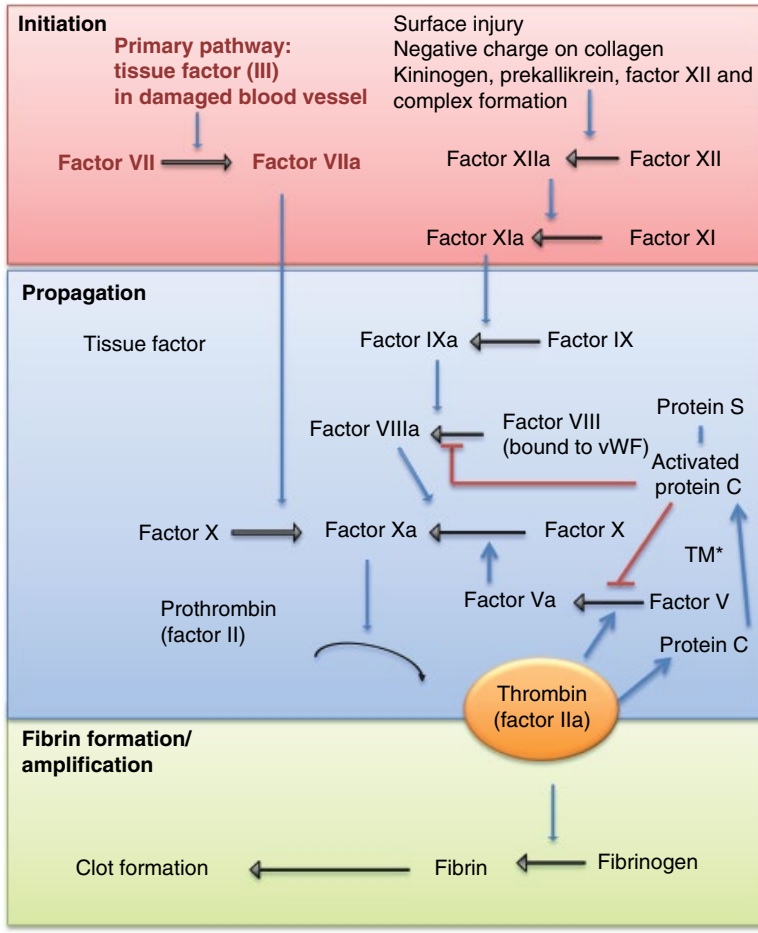

Figure 3.1 Normal coagulation cascade. TM, thrombomodulin; vWF, von Willebrand factor.

factor (vWF) and factor VIII to form a platelet plug, after which the coagulation cascade is amplified at the site of injury. This amplification process requires the platelet's second function as the site of assembly for activated factors for the generation of thrombin, ultimately stabilizing the thrombus matrix via complex interactions [2,6,7]. During the course of these hemostatic reactions, counter-regulatory elements (such as protein C) are also activated, as is fibrinolysis, which serve as a counterbalance to the coagulation cascade. The proenzyme plasminogen is converted to its active form, plasmin, which in turn lyses fibrin and ultimately degrades the clot [2]. This is a highly regulated process whereby the plasminogen to plasmin ratio is balanced by platelet derived *activators*, such as tissue plasminogen activator (t-PA), urokinase plasminogen activator, and activated factor XII, and *anti-activators*, such as plasminogen activator inhibitor (PAI), plasmin inhibitor, and thrombin activatable fibrinolysis inhibitor (TAFI) [2,4]. Any disturbance in this process may lead to excessive bleeding or clotting.

The "Liver" Patient

Historically, patients with cirrhosis were thought to have primarily a bleeding diathesis, with presumed decreased ability to clot based on the presence of an elevated

international normalized ratio (INR) and low platelet count. However, recent evidence reveals that multiple aspects of the coagulation cascade are affected in liver disease [2,4,7] and, more importantly, conventional assays do not accurately reflect the true hemostatic state of the cirrhotic patient, especially with regard to the poor performance of the INR.

In 2011, Tripodi and Mannucci reviewed the key elements of the "procoagulant imbalance" in liver disease [2]. Patients with cirrhosis have reset to a new equilibrium of hemostasis whereby the newly established antihemostatic elements in the cirrhotic state are compensated by prohemostatic elements (Table 3.1) [2]. Much of this hinges on diminished levels of liver derived protein C, which is a key counter-regulatory element. Its role has been revealed by thrombin generation assays performed with and without a key protein C co-activator: endothelial derived thrombomodulin.

In liver disease, each of the three phases of clotting described in the "normal" patient (primary hemostasis, coagulation, and fibrinolysis) is altered [2,6]. Patients have low procoagulant factors, low and possibly dysfunctional platelets, decreased thrombopoietin production, and increased endothelial derived nitric oxide and prostacyclin production (Table 3.1) [2,8]. These elements are in turn balanced by low anticoagulant factors (protein C, protein S, and antithrombin) and high endothelial derived factors (factor VIII and vWF). When each defect is seen in isolation in the context of normal physiology, one would expect either active bleeding or clotting. However, in the patient with liver disease, it is basically "organized dysfunction," which has essentially reset a new and sometimes precariously balanced state of hemostasis.

Thus, the question naturally arises as to what leads to the tendency of these patients to bleed? Portal hypertension, leading to significant hemodynamic alterations, plays a significant role, as well as renal failure and endothelial dysfunction (possibly due to bacterial infections) that tip the hemostatic scale (Table 3.2) [2]. We now recognize that patients with cirrhosis are also at risk for venous thrombotic events [5]. One explanation may be the relative protein C resistant state that favors clotting, in addition to relative hemodynamic changes (i.e., stasis in hospitalized patients) [4,9].

Measuring the Bleeding Risk in Liver Disease: Knowns and Unknowns

Some studies demonstrate the bleeding risk to be as high as 20% amongst patients with advanced liver disease undergoing minimally invasive procedures or non-major surgeries [3]. With a relatively high rate for bleeding, one understands the

Table 3.1 Drivers of hemostasis in cirrhosis. Source: Adapted from Tripodi et al. 2006 [7].

Prohemostatic drivers	Phases of hemostasis	Antihemostatic drivers
↑ von Willebrand factor ↓ ADAMTS13	Primary hemostasis	↓ Platelet count
↓ Anticoagulant factors (protein C, antithrombin)	Blood coagulation	↓ Procoagulants (fibrinogen, factors II, V, IX, X, and XI)
↓ Plasminogen	Fibrinolysis	↑ Tissue plasminogen activator ↓ Plasmin inhibitor

Table 3.2 Likely triggers for bleeding in patients with decompensated liver disease. Source: Adapted from Tripodi et al. 2006 [7].

Trigger	Proposed pathophysiology
Hemodynamic changes due to portal hypertension	↑ Intrahepatic resistance ↑ Splanchnic blood flow, thus engorged collateral vessels ↑ Afterload, thus profound vasodilation
Endothelial dysfunction	↑ vWF and FVIII Change in nitric oxide
Renal failure (i.e., HRS, ATN)	Renal vasoconstriction ↑ RAAS
Bacterial infections	May lead formation of bacterial heparin-like products

ATN, acute tubular necrosis; HRS, hepatorenal syndrome; RAAS, renin–angiotensin–aldosterone; vWF, von Willebrand factor.

reservation and concern that endoscopists have for cirrhotic patients. Thus, in an attempt to reduce this bleeding risk, it is important to tease out and identify the primary drivers (Table 3.2) so that measures can be taken to specifically mitigate or optimize them, or make appropriate plans to manage complications should they occur. Traditional tests, such as the INR and even platelet count, poorly reflect the hemostatic state of bleeding or clotting in cirrhotic patients, making risk assessment difficult. Although platelet levels over 50×10^9/L are an important indicator of thrombin (and hence fibrin) generation, both in vivo and in vitro studies suggest that the best predictor of bleeding in patients with cirrhosis is the degree of portal hypertension and changes in their hemodynamics [4,9,10].

Portal hypertension can thus be monitored clinically by assessing for the presence of varices, portal hypertensive gastropathy, ascites, renal dysfunction, and encephalopathy. Although the use of INR in the model for end-stage liver disease (MELD) score may not accurately reflect bleeding risk, Reverter et al. have shown that the MELD score may be a good predictor of mortality in the setting of acute variceal bleeding [11]. The Child–Pugh classification may be another relatively objective method of clinical assessment, whereby patients with Child–Pugh class C tend to have increased risk of bleeding [11] – this could well reflect increasing portal pressure and associated endothelial dysfunction.

Patients with renal dysfunction in the setting of cirrhosis may have a higher risk of bleeding, not only due to hemodynamic changes, but also due to endothelial dysfunction and volume expansion. Blood urea nitrogen (BUN) and creatinine can be used in these patients, although the exact levels at which uremic bleeding diatheses occur are difficult to ascertain. Infection can exert complex effects, including increased clot lysis through the activity of endogenous heparin-like substances from the endothelium [12,13].

Prothrombin time (PT) is a measure of the activity of fibrinogen (factor I), thrombin (factor II), and factors V, VII, and X. In the cirrhotic patient, the prolonged PT/INR ratio is an unreliable, if not misleading, value. The INR was devised to standardize the PT in various patients who were receiving vitamin K antagonists, such as warfarin. In light of the hemostatic state of the patient with liver disease (low fibrinogen, thrombin, and factor VII), it is difficult to establish a normal value for these patients. Thus, comparing a "normal" PT/INR to that of a cirrhotic patient's PT/INR is essentially comparing "apples

and oranges" and fails to account for the diminished liver derived protein C, which results in a relatively procoagulant state. Without a clear normal value for the patient with chronic liver disease who has a reset hemostatic equilibrium, the PT/INR ratio is not an accurate predictor of bleeding or clotting, thus making it a poor target for therapeutic intervention.

Platelet count has been extensively studied, both in vivo and in vitro, in patients with cirrhosis [6,7,14]. In extrapolating in vitro data, a platelet count of $\geq 50 \times 10^9$/L in cirrhotic patients appears sufficient to achieve adequate thrombin formation [7], and fibrin production would also be expected to be suitable provided adequate stores of fibrinogen are available. Thus, it should be standard practice to monitor platelet count for bleeding risk, although further clinical studies are warranted to confirm this.

Fibrinogen levels can be easily monitored in patients and possibly even restored with cryoprecipitate, a less voluminous alternative to using plasma. It is comprised of factors VIII and XIII, vWF, and fibrinogen, and should be given to reach a target value of 100–150 mg/dL or greater [15] in the setting of bleeding or anticipated bleeding. As with platelet levels, suggested values can only be surmised from laboratory studies until the completion of prospective clinical studies.

Multiple other tests have been used, including thromboelastograms (TEGs) and bleeding time. Although bleeding time has fallen out of favor, TEGs may eventually be shown to be useful. However, variation in methodology and lack of standardization and clinical translational trials have hampered the use of TEGs. Recent studies have shown that the application of TEGs as a clinical tool diminishes the use of blood products, such as plasma, without compromising the bleeding risk [16]. Given the uncertainty surrounding the measurement of bleeding risk, it remains to be seen whether prophylactic intervention in the form of minimizing volume and focusing on a targeted rescue approach is ultimately a better strategy [4,9].

In the future, we anticipate studies on the development of diagnostic tests that will accurately demonstrate the bleeding risk in patients with cirrhosis. One such test may be sonorheometry, which is a very sensitive form of TEG that is undergoing investigation as a clinical tool [17].

Prophylactic Interventions: Advantages and Disadvantages

Once bleeding risk is assessed in patients with liver disease, carefully targeted prophylactic measures may be undertaken to prevent bleeding. The current day practice is shifting with the understanding that patients with cirrhosis have reset to a new "normal" hemostatic equilibrium. An attempt to correct the myriad of abnormal serological values in the cirrhotic patient may be more dangerous than beneficial. For instance, Shah et al. found that hospitalized patients with cirrhosis received up to 40% of the plasma dispensed in their institution, mostly given as prophylactic intervention, which is likely similar to standard practice in many institutions [17]. As discussed below, the effects of this intervention may be more detrimental than beneficial. Of course, given the possibility of malnutrition in the cirrhotic patient, it is always prudent to replete vitamin K, especially if there is a suspicion of deficiency.

Plasma

Since the hemodynamic state of the cirrhotic patient may be a predictor of bleeding, it is imperative to limit interventions that may alter this variable in the hemostatic equilibrium. Attempts to correct the INR with plasma (factors II, V, VII, IX, X, and XI)

have been shown to add significant volume to the cirrhotic patient. One needs to be aware of the expected increase in portal pressure for a given volume of plasma transfused with the aim of correcting the INR. For instance, to correct an INR of 2.0 to a procedural "standard target" of 1.5, approximately 1.5 L of fresh frozen plasma (FFP) would have to be infused. An old study suggested that an increase of 1.4 mmHg in portal pressure would result from every 100 mL of plasma infused [18]. Therefore, correcting the INR from 2.0 to 1.5 would result in a >15 mmHg increase in portal pressure in the patient [3,18,19]. The literature supports this observation; Massicotte et al. also noted that changes in the central volume directly correlated with changes in portal pressure gradient [20]. This significant increase in portal pressure may lead to a paradoxical bleeding event, thus highlighting the need to cautiously interpret the INR in the cirrhotic patient (Table 3.3). Moreover, Argo et al. estimated that with the infusion of 1 L of FFP one may only replete about 10% of the clotting factors in the setting of cirrhosis [15,19]. Another possible pitfall of plasma administration includes the risk of transfusion related acute lung injury (TRALI), which can occur within 6 hours of transfusion. Although more common with FFP due to the amount of volume infused, TRALI may also be seen with platelet transfusions due to high concentrations of antileukocyte alloantibodies [15,21].

Table 3.3 Calculated increase in portal pressure needed to reach a target INR of 1.5. Source: Adapted from Giannini et al. 2010 [3].

Initial INR	Volume transfused (L)	Expected increase in portal pressure (mmHg)
2.0	1.5	15.5
3.0	2.0	20.6
4.0	2.5	25.8

Platelets

In contrast to the INR, the platelet count is possibly the closest currently available predictor of bleeding in liver disease and is a good target for prophylactic intervention prior to invasive procedures [3]. Additionally, platelet infusion is not associated with significant volume expansion: 1 unit of platelets is only about 50 mL and contains platelets pooled from five to six donors. This unit dose would give an expected platelet rise of $20–25 \times 10^9$/L, although the response may be blunted in cirrhosis. The risk of intervention should dictate the target platelet count to aim for. For high risk procedures, it is reasonable to transfuse platelets to $>50 \times 10^9$/L [7]. One could possibly aim for a platelet count of 100×10^9/L, but this is usually a difficult goal to achieve in liver disease. These suggested platelet thresholds are based on extrapolated data from the literature [2,4,6,7] and, unfortunately, there are no prospective studies that set targets to aim for in liver disease. Similar to other blood product infusions, platelet transfusions carry a small (2%) risk of infections and fever.

Thrombopoietin Receptor Agonists

Eltrombopag and romiplostim are thrombopoietin receptor agonists that increase platelet count significantly by stimulating bone marrow production. Data are limited regarding the use of these agents in the cirrhotic patient, and the risk of thrombosis in the setting of elevated vWF is high enough to warrant caution [4,22].

Cryoprecipitate

Cryoprecipitate is an alternative to plasma which can be used in liver disease to replete, in particular, one of the procoagulant factors, fibrinogen. The hypofibrinogenemia seen in liver disease plays

a role in perpetuating bleeding by virtue of depleted levels of substrate for clot formation. Although directed fibrinogen repletion makes conceptual sense, prospective studies are needed to confirm the utility of such an intervention. Cryoprecipitate is especially attractive for both prophylactic and rescue therapy due to the small volume required to adequately replenish systemic fibrinogen levels, as well as the repletion of other possibly useful procoagulants, such as factors VIII and XIII.

Clotting Factors

Factor repletion has been done in the form of recombinant factor VIIa and "balanced" prothrombin complex concentrates (PCCs), which contain factors II, VII, IX, and X, and proteins C and S. The administration of these agents is somewhat limited by cost and lack of strong evidence demonstrating significant efficacy in preventing bleeding. Recombinant factor VIIa (rFVIIa) at 40 g/kg IV has been used prophylactically during intracranial pressure monitor placement in the setting of acute liver failure with presumed coagulopathy and significant INR elevation [23,24]. However, this practice is questionable since Stravitz et al. recently reported that patients with acute liver failure had normal or balanced TEG parameters despite a high INR, indicating that these patients have the ability to form a stable clot and may even be hypercoagulable [16,24]. rFVIIa has also not shown benefit in controlled studies of acute variceal rebleeding. However, it is the authors' opinion that rFVIIa has not been systematically studied as a rescue agent, for example, when ongoing hemorrhage impedes endoscopic treatment. Costs and thrombotic risks temper its use in this setting [23]. Balanced PCCs are relatively new to the field and further studies are needed to investigate their role as prophylactic or rescue agents.

Desmopressin

Desmopressin (1-deamino-8-D-arginine vasopressin, abbreviated DDAVP) has been studied as a procoagulant agent in cirrhosis for many years. It is one of the few procoagulant agents to have undergone prospective study in the setting of procedures and prophylaxis against bleeding in cirrhotic patients. Stanca et al. randomized cirrhotic patients undergoing dental extractions to either plasma (10 mL/kg) and/or platelets, depending on pre-procedure laboratory values, or DDAVP (300 µg administered intranasally) prior to the extraction [25]. No bleeding occurred in the DDAVP group as compared with one episode of bleeding and one episode of hypersensitivity in the plasma/platelet groups. Intervention with DDAVP was also significantly less expensive. While caution is warranted regarding hyponatremia, these results offer promise for a more rational approach to prophylaxis in this population. Notably, this study lacked a placebo group, which may now be justifiably considered based on a refined understanding of the coagulopathy of liver disease.

Antifibrinolytic Agents

The occurrence of a hyperfibrinolytic state in cirrhotic patients has remained controversial, probably as a result of the challenges in measuring this process in the clinical laboratory, patient heterogeneity, and variable dominance of opposing clotting mechanisms, as mentioned previously [10,26,27]. Biochemical hyperfibrinolysis is estimated to be present in about one third of hospitalized cirrhotic patients and to be clinically apparent in about 6% of cases [28]. As a result, prophylactic measures using antifibrinolytic agents are limited and they are probably better utilized in the setting of recurrent or ongoing bleeding and as "rescue agents" in post-procedural bleeding.

Relative Risk of Endoscopic Procedures

Colonoscopy with Polypectomy

Diagnostic colonoscopy is a low risk procedure even in patients with chronic liver disease. Approximately 12–38% of cirrhotic patients undergoing pre-transplant screening colonoscopy are found to have polyps [29,30]. Given the increased bleeding risk associated with chronic liver disease, there is reasonable concern for polypectomy related bleeding, especially with the evidence of diffusely increased mucosal vascularity in this patient population [31,32]. In fact, the increased vascularity is proportional to the degree of portal hypertension [29]. Despite these data, there is little evidence to support an actual overall increased bleeding risk with polypectomy in the cirrhotic population. Thus, prophylactic measures are not usually recommended. However, it is prudent to evaluate the specific clinical situation and size of polyp to be removed, and to discuss with the patient and referring team when a particularly high risk polyp (i.e., large and hypervascular) is encountered. In addition, one should have a lower threshold when using mechanical prophylactic intervention, such as endoscopic clip placement, after the removal of high risk polyps in this patient population.

Variceal Band Ligation and Post-Banding Ulcer Bleeding

Post-banding ulcer bleeding occurs in about 4–7% of patients with cirrhosis [33]. Those at high risk appear to be patients with Child–Pugh class C cirrhosis and possibly those with a high aspartate aminotransferase (AST) to platelet ratio [33]. Otherwise, there appears to be no direct relationship between post-banding ulcer bleeding and PT/INR, platelet count, and levels of factor V, fibrinogen, D-dimer, protein C or S, as well as vWF, TEG pattern, or the use of beta-blockers [34]. Although the evidence does not support the routine administration of prophylactic blood products or procoagulants, it is reasonable to approach patients with Child–Pugh class C cirrhosis cautiously, especially those with a clinically apparent bleeding diathesis, with the aim of optimizing the platelet count in order to increase thrombin (and thus fibrin) production.

Endoscopic Retrograde Cholangiopancreatogaphy and Sphincterotomy

Studies of patients with chronic liver disease who require pancreaticobiliary intervention with endoscopic retrograde cholangiopancreatography (ERCP) have reported rates of post-sphincterotomy hemorrhage in the 4–30% range and a related mortality of about 15% [35,36]. These adverse events are especially increased in Child–Pugh class C patients, without a clear relationship to platelet count or PT/INR [35,36]. We surmise the role of portal hypertension related vascular congestion to be directly correlated to sphincterotomy related bleeding and mortality. Optimal ERCP techniques in these patients have been debated, with some supporting the use of balloon dilation instead of sphincterotomy, without significant differences in rates of post-ERCP pancreatitis [36]. There are also data that describe no difference in the rates of bleeding between sphincterotomy and balloon dilation [35]. Given the lack of clear evidence regarding the best ERCP approach, the latter is left to the discretion of the endoscopist, with close monitoring for bleeding being essential. In addition, since other prophylactic measures are not well described in particularly high risk patients, we recommend minimizing adverse events by the administration of octreotide at the time of the procedure, with the aim of reducing portal pressure and mucosal congestion.

Rescue Approach

Given the risks of procedure related bleeding and the limitations of risk stratification, a rescue plan is essential when procedures are needed in the patient with cirrhosis who subsequently has a bleeding complication. The key to choosing the appropriate therapy is identifying and targeting the defect that may be driving the bleeding diathesis.

Pharmacological Management of Portal Hypertension

Since portal hypertension is one of the main contributors to the bleeding diathesis in cirrhotic patients, it becomes an important prophylactic or even rescue target. It is associated with increased portal inflow and outflow resistance, and a hepatic venous pressure gradient of >12 mmHg has been shown to be closely associated with esophageal variceal bleeding [37]. Although the systemic sequelae of portal hypertension are extensive, the most notable is the hyperdynamic circulation, characterized by splanchnic as well as systemic vasodilation, resulting in low systemic resistance [38]. This in turn leads to sodium retention, with resultant plasma volume expansion and ultimately an increased cardiac index. As a result, portosystemic collateral circulation develops as a physiological response to mitigate the increasing portal pressure. Although several therapeutic options aimed at managing portal hypertension and variceal bleeding are available, the best studied agents currently utilized in the clinical setting are terlipressin and octreotide.

Octreotide is a somatostatin analog whose use is well established for esophageal variceal bleeding. It acts by primarily reducing portal pressure via portosystemic collateral vasoconstriction and possibly even intrahepatic resistance, thus restoring some degree of vascular tone [39]. One of the rationales for the use of octreotide is that it inhibits the secretion of glucagon, a humoral vasodilator associated with portal hypertension [40]. Terlipressin is a vasopressin analog and a potent vasoconstrictor used in the setting of acute variceal bleeding for its effects of immediate, significant systemic and splanchnic vasoconstriction and, thus, a reduction in portal pressure [41–43]. Although its side effects are less frequent than vasopressin, terlipressin does have its pitfalls, including a risk of bradycardia and myocardial infarction [44]. When a vasoactive agent is used in conjunction with targeted blood product repletion and antibiotics, we believe that this multimodal rescue approach can lead to successful hemostasis and may even be considered for prophylaxis in high risk patients.

Platelets and Procoagulants

In addition to prophylactic transfusions, as discussed earlier, blood components may be used for rescue purposes. Standard resuscitation measures are appropriate if significant hemodynamic instability due to hypovolemia is encountered, although one should avoid over-transfusion and volume over-expansion. Once stabilized, targeted rescue therapy is essential. Platelet administration may be one of the most important interventions in the bleeding cirrhotic patient, with a target platelet count of $\geq 50 \times 10^9$/L. The above-mentioned procoagulants, such as rFVIIa and PCCs, may be considered, but these agents are costly with as yet no proven role and with the potential for thrombosis.

Antifibrinolytics

If hyperfibrinolysis is established or strongly suspected based on clinical findings, one may consider the early use of antifibrinolytics to avoid unnecessary blood product administration and volume. Aminocaproic acid and tranexamic acid are two of the most commonly used agents, which work

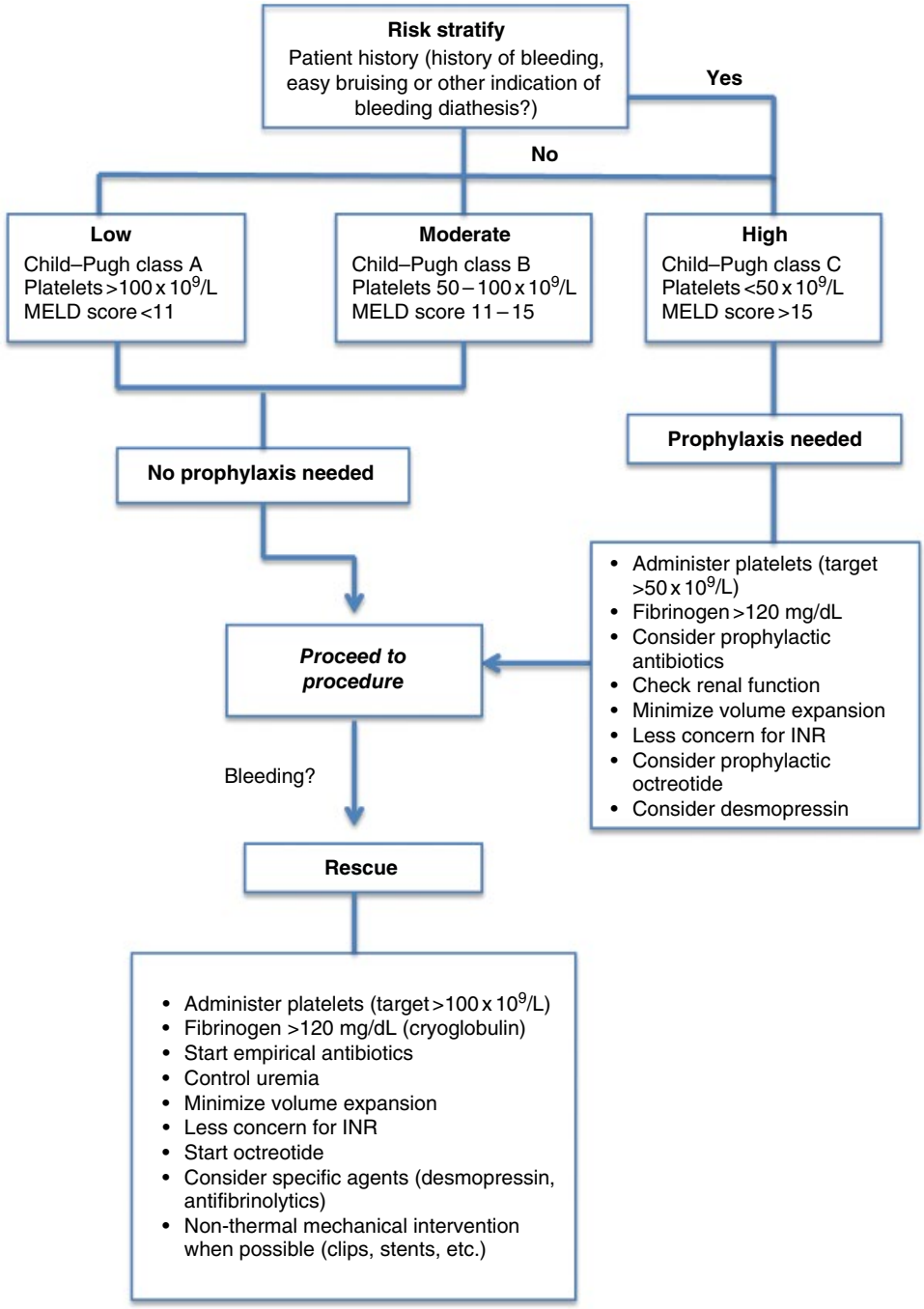

Figure 3.2 Proposed algorithm for endoscopy in the setting of coagulation abnormalities due to chronic liver disease. INR, international normalized ratio; MELD, model for end-stage liver disease.

by inhibiting plasmin [45]. They are generally more effective for bleeding in body cavities (e.g., after dental extraction or soft tissue bleeding). These agents can be administered topically, orally, or intravenously, thus making them versatile and potentially effective for difficult to control bleeding with minimal administered volume. A significant concern about these agents is the clotting risk, although this seems infrequent, especially when weighed against the alternative of significant hemorrhage [45].

Conclusion

A basic understanding of the reset equilibrium of hemostasis in the patient with chronic liver disease is needed – a complex process with many moving and relatively unstable parts. However, our growing understanding of the hemostatic mechanisms in cirrhosis will likely require inclusion of placebo controlled studies to fully define optimal interventions.

Based on existing literature, we suggest a systematic approach to performing endoscopy in patients with coagulation abnormalities of chronic liver disease, starting with pre-procedure risk stratification to guide prophylactic measures (Figure 3.2). Because it is difficult to accurately measure the associated bleeding risk in these patients, it is also critical that the endoscopist be prepared for a possible rescue intervention should there be significant bleeding. As the field of study regarding coagulopathy in liver disease continues to grow, we anticipate that the suggested algorithms and guidelines will need updating in the near future. Measures aimed at controlling sepsis, improving renal function, and lowering portal pressure are equally critical to reducing procedure related bleeding risks.

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4

Varices: Screening, Staging, and Primary Prophylaxis

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Introduction

Portal hypertension is defined by a pathological increase in portal venous pressure in which the hepatic venous pressure gradient (HVPG) is increased above normal values (>5 mmHg) [1]. In cirrhosis, portal hypertension results from the combination of: (i) increased intrahepatic vascular resistance secondary to fibrosis or regenerative nodules and the contraction of sinusoidal and pre-sinusoidal contractile cells; and (ii) increased blood flow through the portal venous system due to splanchnic vasodilation [2]. Low levels of intrahepatic nitric oxide contribute to an increased resistance to portal flow [2]. When the HVPG rises above 10 mmHg, complications of portal hypertension, such as the development of esophageal varices, can arise. Therefore, this value represents the threshold for defining portal hypertension as being clinically significant and plays a crucial role in the transition from the preclinical to the clinical phase of the disease. The threshold for varices to bleed is an HVPG of ≥12 mmHg [3].

The management of the patient with cirrhosis and variceal bleeding depends on the phase of portal hypertension – from the patient who has not yet developed varices to the patient with acute variceal hemorrhage for whom the objective is to control the active episode and prevent rebleeding. At the time of initial diagnosis, about half of patients with cirrhosis have esophageal varices [3]. During progression of the disease, up to 80–90% of patients develop esophageal varices in the latter stages of the disease (Child–Pugh class C cirrhosis). The risk of bleeding in these patients relates to several factors, such as the size and characteristics of varices and the stage of cirrhosis. Preventing the first episode of bleeding from varices is termed primary prophylaxis.

Natural History of Varices

Increased resistance to portal blood flow is the initial and most important factor leading to the development of portosystemic collaterals. As collaterals develop, the portal venous inflow increases because of splanchnic vasodilation, which maintains and worsens portal pressure elevation. The maintenance of an increased intravascular pressure, together with a high collateral blood flow, causes dilatation of the varices and, as the varices dilate, their walls become thinner. At this point, any further

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increase in variceal pressure or size, or any defect in the variceal wall, will cause rupture and hemorrhage.

The development of varices in cirrhotic patients is associated with a risk of death of 1–3% per year, and bleeding varices will increase this risk even more with a 1-year mortality rate as high as 55–60% [4]. In patients without varices at initial endoscopy, the rate of appearance of varices is 6–7% per year (>10% in those with an HVPG >10 mmHg). In the absence of primary prophylaxis, bleeding occurs within 2 years in 10–30% of patients with varices, depending on variceal size, presence of red color signs, degree of liver failure, and elevation of HVPG [5]. Patients without varices have a bleeding risk of <2% per year, whereas this risk increases to 5% in those with small varices and up to 15% in those with large varices. Current medical treatment decreases the risk of first and/or recurrent variceal bleeding by approximately 50–60% [6].

Variceal Screening and Staging

The majority of patients with cirrhosis need to be screened for varices in order to determine the need for primary prophylaxis.

Esophagogastroduodenoscopy

Esophagogastroduodenoscopy (EGD) is considered the gold standard for diagnosis of gastroesophageal varices as it permits direct visualization of the varices, as well as the ability to determine their size and the presence of overlying red signs.

One of the most important risk factors for variceal hemorrhage is variceal size. According to the Baveno Consensus Statement and the American Association for the Study of Liver Diseases (AASLD) guidelines, varices can be classified as small or large, based on a cut-off diameter of 5 mm (Figure 4.1) [7,8]. Other classifications systems, such as the Beppu classification that grades varices as small, medium, and large, are also commonly used. Since medium/large varices are treated in the same fashion, the simpler classification scheme of small versus large varices is preferred due to ease of use.

The mucosal red signs, such as red wale markings and hematocystic spots, refer to small areas of a varix with a thin and weak wall due to maximum distension of the vessel (Figure 4.2). These red signs also indicate a risk of rupture [9].

When performing EGD for screening purposes, a complete examination is mandatory in order to also evaluate for portal hypertensive gastropathy and/or gastric varices. Grading of esophageal varices is performed during withdrawal of the endoscope. The esophagus must be maximally inflated with air after the stomach has been decompressed. This flattens out any esophageal folds that may masquerade as varices. Varices are usually present in the middle to distal third of the esophagus and special attention must be paid when examining the gastroesophageal junction and cardia since gastroesophageal varices may be present in these locations. Uphill varices in the upper third of the esophagus are not related to portal hypertension and are mostly due to conditions that occlude the superior vena cava.

The frequency of surveillance endoscopy in patients with no or small varices depends on the degree of hepatic dysfunction. In patients with compensated cirrhosis who have no varices on screening EGD, the procedure should be repeated in 2–3 years [8,10]. In those with small varices, EGD should be repeated in 1–2 years. Any patient with decompensated cirrhosis should undergo screening EGD on a yearly basis [8,10].

Capsule Endoscopy

De Franchis et al. published the first prospective multicenter study comparing capsule endoscopy (CE) with EGD [11].

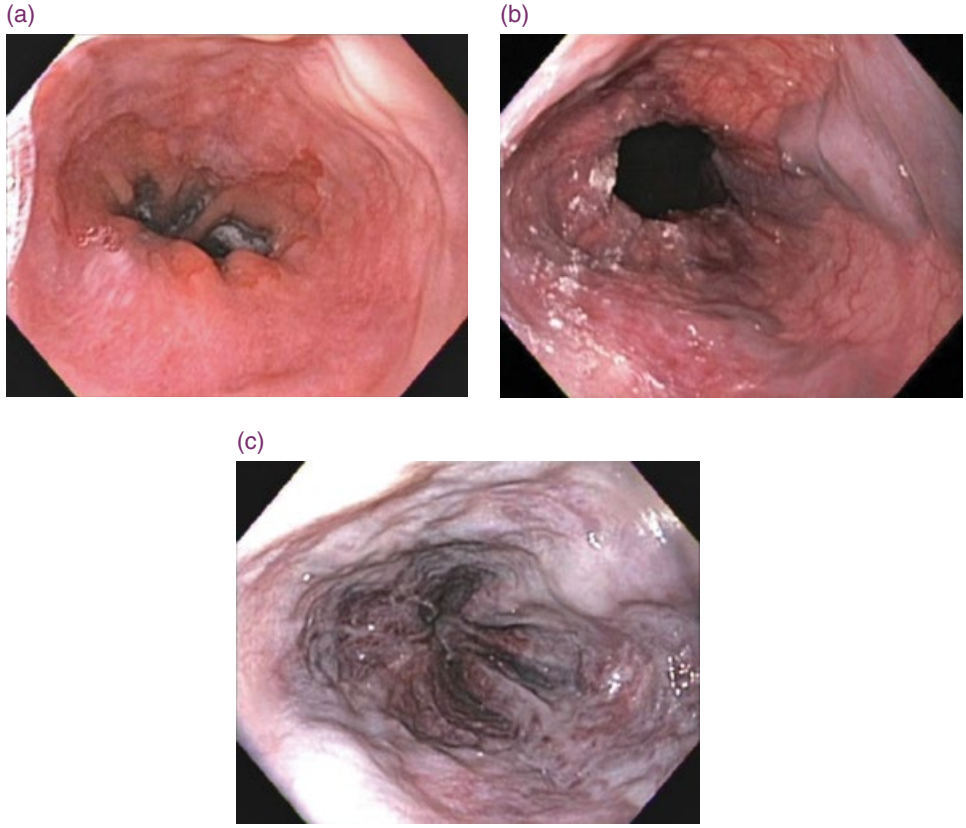

Figure 4.1 Upper endoscopy showing three possible scenarios when a patient is screened for varices: (a) no varices; (b) small varices; and (c) large varices. For staging purposes, varices are classified as small or large.

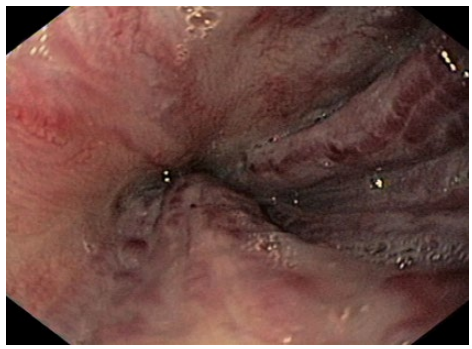

Figure 4.2 Large varices with red wales; both of these features place the patient at risk for variceal bleeding.

The study included 228 patients of whom 195 underwent screening and 93 underwent surveillance of known varices. All patients had both procedures. During the EGD, varices were graded according to the proportion of the radius of the esophagus occupied by the largest varix at full insufflation. By CE, varices were graded as small or large if the largest varix occupied less or more than 25% of the circumference of the capsule picture frame, respectively. The sensitivity, specificity, positive predictive value, and negative predictive value of CE to detect varices were 84%, 88%, 92%, and 77%, respectively [11]. Additional studies and a Cochrane systematic review revealed lower sensitivities for capsule detection of large varices, so CE appears to be less effective than EGD for the detection of esophageal varices. However, it may be an option for patients who are unable to tolerate or unwilling to undergo EGD [12–14].

Ultrasonography

Ultrasound with Doppler examination of the liver is routinely performed to evaluate the architecture of the liver and to examine for complications of portal hypertension, including ascites and the development of collaterals. Ultrasound can detect signs of portal hypertension, including splenomegaly and reversal of flow in the portal vein. A portal vein diameter of >13 mm on ultrasound correlates with the presence of esophageal varices (odds ratio of 2.92). Ultrasound also can detect portal vein thrombosis [15]. Although ultrasound is not considered a screening tool for the detection and staging of varices, the above-mentioned features of ultrasound in patients with suspected cirrhosis should prompt an endoscopic examination.

Transient Elastography

Bureau et al. evaluated the correlation between liver stiffness, as measured by transient elastography (TE; FibroScan®), and an increase in portal pressure [16]. The optimal cut-off value was found to be 21 kPa (which correlates with an HVPG of >10 mmHg), with an accurate prediction of significant portal hypertension in 92% of the 144 patients in whom TE was successful [16]. TE also has been used for the prediction of esophageal varices. Kazemi et al. [17] evaluated 175 consecutive patients with cirrhosis who underwent endoscopy for variceal screening. The primary objective of the study was the prediction by liver stiffness measurement of the "presence of esophageal varices" compared to the "absence of varices." The area under the receiver operating curve was 0.84 (95% confidence interval 0.78–0.90). The cut-off value defined by a higher total of sensitivity and specificity was 19.0 kPa. The overall sensitivity and specificity for a cut-off of 13.9 kPa were 95% and 92%, respectively.

Spleen stiffness measurement has also been studied as a promising non-invasive alternative to EGD for the diagnosis of varices in patients with cirrhosis, although data are limited. Based on a meta-analysis, the current techniques for measuring spleen stiffness are suboptimal and, thus, preclude its widespread use in clinical practice at this time [18].

TE has been extensively studied and validated in patients with cirrhosis due to hepatitis C and current guidelines suggest that patients with HCV and elastography values of stiffness <20 kPa and a platelet count over 150,000 could avoid screening endoscopy because the risk of having varices is extremely low [10]. Although TE seems to be an acceptable tool that predicts clinically significant portal hypertension, it cannot confidently predict the presence of esophageal varices and, thus, should not be used as a tool to screen all cirrhotic patients [19].

Primary Prophylaxis of Esophageal Varices

Preprimary Prophylaxis

Forty to sixty percent of patients with compensated and decompensated cirrhosis develop varices. In cirrhotic patients without esophageal varices, the incidence of new varices is <5% per year. In cirrhotic patients without varices but with an HVPG >10 mmHg, there is double the risk of developing esophageal varices compared with those with an HVPG <10 mmHg (50% versus 25% at 5 years) [20]. Varices increase in size with time, and the progression rate ranges from 5% to 30% per year.

In a trial of 213 cirrhotic patients without varices who received timolol or placebo, no difference was noted in the incidence of new varices between the two groups [21]. A significantly larger proportion of patients with moderate and severe adverse events was observed in the timolol group (48%) compared with the placebo group (32%). Serious symptomatic adverse events occurred in 20 patients

(18%) in the timolol group and in six patients (6%) in the placebo group. Current evidence, therefore, suggests that beta-blockers cannot be recommended for the prevention of the development of varices. In patients without esophageal varices, screening EGD should be performed every 2–3 years [9,21].

Patients with Small Varices

Variceal hemorrhage occurs at an annual rate of about 15%, and although current mortality from an episode of variceal hemorrhage is lower than that in the past two decades, it still remains significant at 7–15% [22,23]. The size of varices, presence of red wale markings on varices, and severity of liver disease (Child–Pugh class C) identify patients at the highest risk of variceal hemorrhage.

Compensated cirrhotic patients with small varices and an absence of high risk features at endoscopy should have repeat EGD in 1–2 years [8–10]. These patients have an annual bleeding risk of 7% over 2 years. A large, multicenter, placebo controlled study showed that nadolol (n = 83) reduced the rate of growth from small to large esophageal varices compared with placebo (n = 78) [24]. During the study period, nine patients randomized to nadolol and 29 randomized to placebo had growth of esophageal varices. Variceal growth was more likely in patients with advanced liver disease. Therefore, it is recommended that patients with small esophageal varices who are of Child–Pugh class B or C should be placed on non-selective beta-blockers (NSBBs) [7–10].

Patients with Large Varices and High Risk Features

Non-Selective Beta-Blockers

Esophageal varices may rupture and bleed when the HVPG exceeds a critical threshold of 12 mmHg. A reduction in the risk of bleeding has been observed when a reduction of HVPG to <12 mmHg or by more than 20% its baseline level is achieved. NSBBs decrease portal pressure and, consequently, HVPG through blockade of both beta-1 and beta-2 adrenergic receptors. Beta-1 blockade decreases cardiac output and beta-2 blockade increases splanchnic vascular resistance. The combination of beta-1 and beta-2 blockade decreases portal pressure. When compared with placebo, NSBBs (e.g., propranolol or nadolol) reduce the risk of a first variceal bleeding event and of mortality in patients with large varices. A systematic review of 11 trials that included 1189 patients confirmed the benefit of NSBBs in patients with small/large varices in preventing a first bleeding episode [25]. The risk of a first episode of bleeding was reduced significantly from 24% on placebo to 15% on an NSBB [25].

Propranolol and nadolol are administered in a stepwise fashion until maximum tolerance or the resting heart rate decreases to between 50 and 60 beats/min. Propranolol is typically started at 20 mg twice daily and nadolol at 40 mg once daily. The dose of propanolol can be titrated up, depending on how the patient responds, to a maximum tolerated dose of 160 mg twice daily. Nadolol can be titrated up to 240 mg once daily.

The advantages of NSBBs include: (i) low cost; (ii) expertise is not required for their use; and (iii) prevention of other complications, such as bleeding from portal hypertensive gastropathy, ascites, and hepatorenal syndrome, by virtue of a reduction in portal pressure. The disadvantages of NSBBs include relatively common side effects (e.g., lightheadedness, fatigue, impotence, and shortness of breath) that preclude treatment or require discontinuation in 15–20% of patients. Contraindications to their use occur in nearly 15% of patients (e.g., in asthma, severe chronic obstructive pulmonary disease, poorly controlled diabetes, peripheral vascular disease, and cardiac conduction abnormalities).

Carvedilol, an anti-alpha-adrenergic agent, may be more effective than propranolol in primary prophylaxis, and results in reduced rates of bleeding compared with band ligation. Carvedilol at low doses (6.25–12.5 mg/day) was compared with endoscopic variceal ligation in a recent randomized controlled trial [26]. Carvedilol was associated with lower rates of first variceal hemorrhage (10% versus 23%) and had an acceptable side effect profile, unlike band ligation, for which compliance was low and the rate of first hemorrhage was at the upper end of published rates in previous studies [26]. A meta-analysis of five studies has shown that carvedilol reduced portal hypertension significantly more than propranolol [27].

Endoscopic Band Ligation

Endoscopic band ligation (EBL) is an alternative to NSBBs for primary prophylaxis in patients who have contraindications to or cannot tolerate NSBBs due to side effects (Figure 4.3 and Video 4.1). Meta-analyses have shown that EBL reduces the risks of variceal bleeding and mortality compared with untreated controls [28–31]. Several studies have compared EBL with propranolol for primary prophylaxis of variceal bleeding. Meta-analyses of these trials show that EBL is superior to NSBBs in reducing bleeding but that there are no differences in survival [28–31]. The most recent meta-analysis, which included a study that compared EBL with carvedilol, suggested that EBL is superior to NSBBs in reducing the occurrence of first variceal hemorrhage, with no differences in mortality. Although EBL appears to be superior to NSBBs, the data are limited by the quality of the trials included in the analysis (Figure 4.4) [31]. Since EBL requires several sessions and can result in significant adverse events (e.g., post-ligation bleeding ulcers in up to 7% of patients), and varices may recur post-ligation needing re-eradication, a reasonable approach is to initiate therapy with NSBBs if there are no contraindications [9]. Patients who develop side effects or have contraindications to NSBBs should be offered EBL.

There is no consensus as regards EBL schedules for variceal eradication and the interval between sessions varies from 2 to 4 weeks among trials. Shortening the interval between endoscopic sessions increases the risk of having to omit a session due to the presence of ulcers or retained bands from the previous session. In a trial comprised mostly of patients

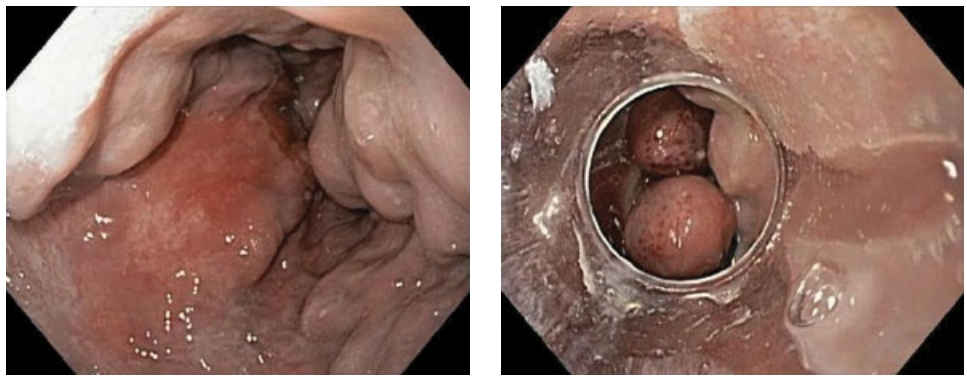

Figure 4.3 (a) Large esophageal varices. (b) Endoscopic band ligation performed for primary prophylaxis of variceal bleeding.

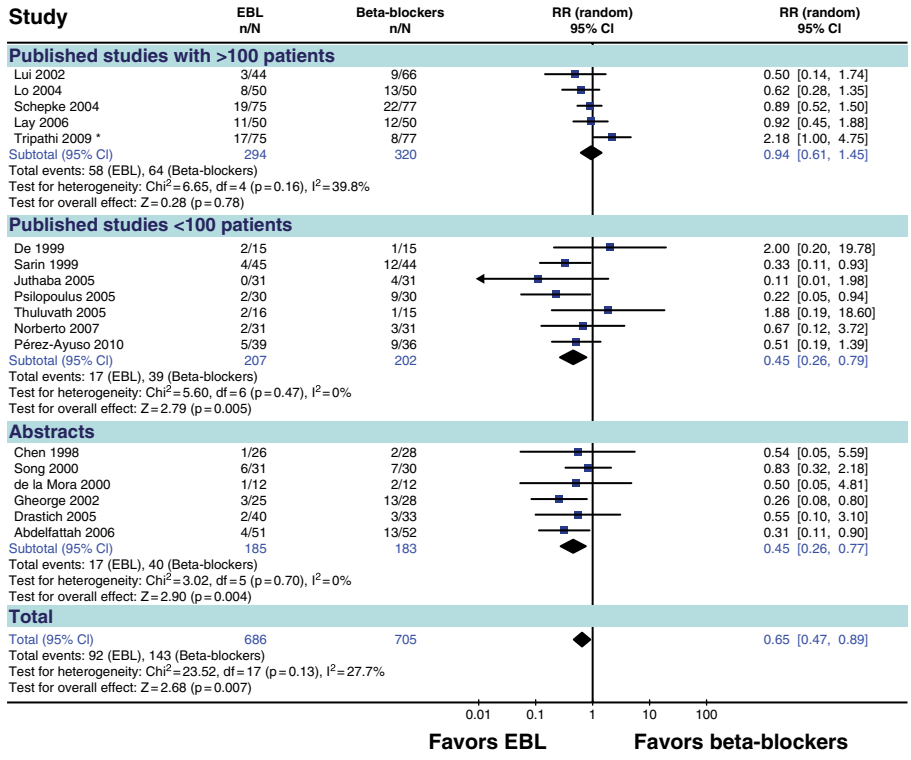

Figure 4.4 Meta-analysis of randomized controlled trials comparing endoscopic band ligation (EBL) with beta-blockers in the prevention of first variceal bleeding stratified according to trial size and publication status. No differences in the risk of bleeding could be demonstrated in fully published trials with large sample size (over 100 patients). *Carvedilol was used as beta-blocker. Source: Abraldes et al. 2014 [31]. Reproduced with permission of Clinical Liver Disease.

without previous variceal bleeding, a comparison of biweekly versus bimonthly EBL sessions showed a higher rate of variceal eradication and lower rate of recurrence in favor of the bimonthly schedule [32].

Measurement of Hepatic Venous Pressure Gradient

In patients receiving NSBBs for primary prophylaxis, one therapeutic target is to decrease the resting heart rate by 25%. There is, however, no evident correlation between the reduction in heart rate and that of portal pressure. An HVPG reduction to <12 mmHg eliminates the risk of bleeding and need for surveillance with endoscopy [20]. Although measurement of HVPG in all patients may be impractical, the determination of HVPG can identify patients with a beneficial treatment effect using the criterion of a ≥10% reduction in HVPG during an acute infusion of a beta-blocker. This allows a more rapid increase in dosage regime in order to achieve the desired reduction in pressure [20]. The hemodynamic response to beta-blockers can predict the risk of the first variceal bleeding. A study of 105 patients showed that a hemodynamic response to an intravenous beta-blocker in terms of a reduction in HVPG of >10 mmHg from baseline was a predictor of the long term efficacy of primary prevention [33]. A second retrospective study of 166 patients showed that a

reduction in portal pressure of 12% after use of an intravenous beta-blocker was the optimal cut-off point to identify patients who significantly benefited from treatment in terms of rebleeding and death [34].

Gastric Varices

The prevalence of gastric varices is estimated to be 17–20%, but these numbers are based only on one study; therefore, the actual magnitude of the problem is not well known. Screening for gastric varices is always performed in the setting of EGD when patients are screened for esophageal varices. At endoscopy, gastric varices are categorized according to Sarin classification based on the presence or absence of anatomical continuation with esophageal varices, as well as their location in the stomach [35,36]. Gastric varices are classified as follows:

1) *Type 1 gastroesophageal varices (GOV1).* These extend below the gastroesophageal junction along the lesser curve of the stomach. They are considered an extension of esophageal varices and the recommended management is the same as that of esophageal varices.
2) *Type 2 gastroesophageal varices (GOV2).* These extend along the fundus and tend to be longer and more tortuous than GOV-1.
3) *Isolated gastric varices (IGV1).* These are located in the fundus in the absence of esophageal varices and tend to be tortuous and complex (Figure 4.5).
4) *Isolated gastric varices (IGV2).* These are located in the body, antrum, or around the pylorus.

According to Sarin et al. [36], GOV1, GOV2, IGV1, and IGV2 constitute about 75%, 21%, <2%, and 4% of all gastric varices, respectively.

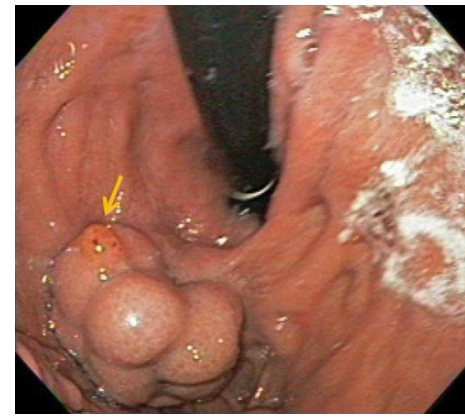

Figure 4.5 A large isolated gastric varix (IGV1) as seen in retroflexion on upper endoscopy. Note the red spot (arrow), which indicates that the patient recently had a bleeding episode.

Primary Prophylaxis

According to a large study, the incidence of bleeding from gastric varices is 16%, 36%, and 44% at 1, 3, and 5 years, respectively [37]. Similar to esophageal varices, the bleeding risk depends on the size of varices, the presence of red signs, and the degree of liver dysfunction. The risk of bleeding ranges from an annual incidence of 4% in patients with Child–Pugh A cirrhosis with small varices and without red signs to 65% in patients with Child–Pugh C cirrhosis with red signs. The 1-year bleeding risk of a small, untreated subgroup of patients (n = 30) involved in a recent randomized trial comparing cyanoacrylate injection (n = 30) with NSBBs (n = 29) was about 10% [38]. Injection of cyanoacrylate was favored for the prevention of bleeding and survival when compared with the no treatment group, and only for the prevention of bleeding when compared with propranolol. Given the risk of serious adverse events with cyanoacrylate injection (2–3% embolic risk) and limited data, we do not currently recommend primary prophylaxis with cyanoacrylate injection in patients with isolated gastric varices.

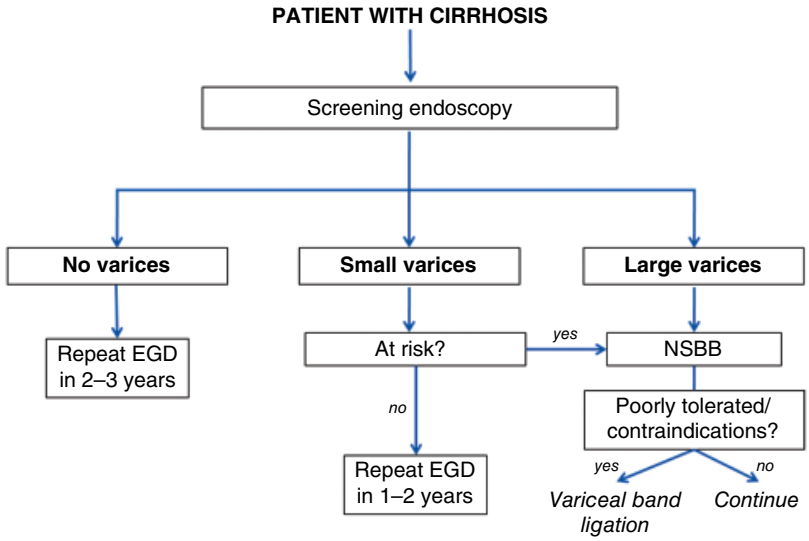

Figure 4.6 Management algorithm for primary prophylaxis of esophageal varices. At-risk patients include those with Child–Pugh class B and C cirrhosis or the presence of red wale markings on varices. EGD, esophagogastroduodenoscopy; NSBB, non-selective beta-blockers.

Conclusion

Patients with cirrhosis should be screened for varices. The currently recommended tool is EGD since it allows assessment of variceal size and high-risk features, such as red color signs. In addition, EGD determines the presence and classification of gastric varices. If no esophageal varices are found, repeat EGD is recommended in 2–3 years, depending on the Child–Pugh class. If small varices are present in high-risk patients or large varices are seen, both NSBBs and EBL are effective modalities at reducing the risk of a first episode of bleeding from varices. We do not favor primary prophylaxis of gastric varices using cyanoacrylate injection until additional evidence supports such a practice. A recommended management algorithm for primary prophylaxis of esophageal varices is depicted in Figure 4.6.

Videos relating to this chapter are:

Video 4.1 Primary prophylaxis of esophageal varices with endoscopic band ligation.

All videos cited in this book can be found on the companion website at
www.wiley.com/go/plevris/endoscopyinliverdisease

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5

Endoscopic Management of Acute Variceal Bleeding

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Introduction

Acute variceal bleeding (AVB) is a common and life threatening complication occurring in patients with portal hypertension and represents a leading cause of death in patients with cirrhosis [1]. Hemorrhage from varices is still associated with substantial mortality; traditionally the mortality rate associated with each episode of AVB was quoted as 30–50% [1–3]. With advances in care, mortality in more recent studies has significantly improved but remains at 11–20% [4–7]. The improvement in outcomes following an episode of AVB is undoubtedly multifactorial and relates to recognition of the importance of adequate resuscitation, early endoscopy, and accurate diagnosis. The therapeutic armamentarium, which now includes endoscopic, adjunctive pharmacological, and radiological therapies, has also significantly expanded, and several practice guidelines that outline optimal care for patients presenting with AVB have been developed [8–10]. In addition, secondary prevention, consisting of either endoscopic eradication of varices or use of non-selective beta-blockers, has been shown to improve patient outcomes.

Several factors have been validated for the prediction of complications, such as early rebleeding and mortality, following an episode of variceal bleeding. Overwhelmingly, mortality is dictated by the severity of the underlying liver disease, and scores – such as the model for end-stage liver disease (MELD) score [11,12] and the Child–Pugh score – along with the presence of hepatic encephalopathy are predictive of outcome [13]. Other risk factors that confer a poorer prognosis include shock, renal failure, bacterial infection at admission or shortly after, hepatocellular carcinoma, certain characteristics and severity of the bleed (active bleeding at the time of endoscopy, high risk stigmata on varices, red cell transfusion requirements), presence of portal vein thrombosis, and measures of portal hypertension (hepatic venous pressure gradient (HVPG) >20 mmHg) [14–18].

This chapter presents the evidence for the treatment of acute variceal hemorrhage with a focus on endoscopic treatment strategies.

Pathophysiology of Variceal Bleeding

The pathophysiology of portal hypertension and variceal formation is important in conceptualizing variceal hemorrhage and the rationale behind treatment strategies.

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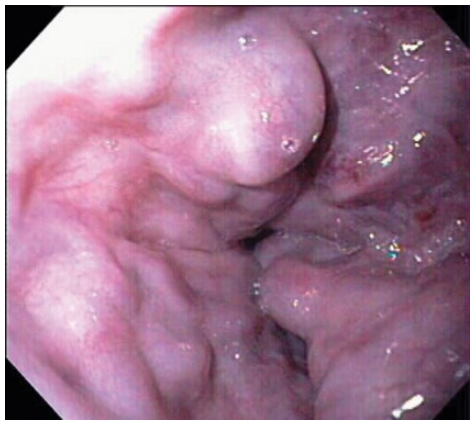

Figure 5.1 Large esophageal varices.

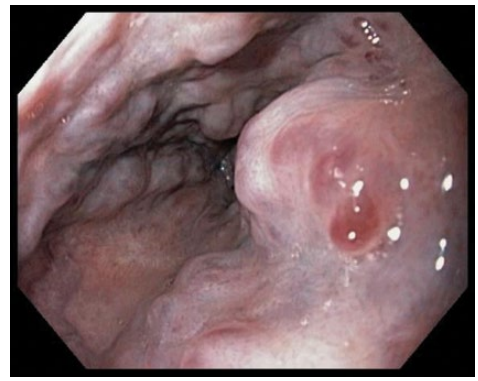

Figure 5.2 Larges esophageal varices with red signs.

Portal hypertension is a well known and common complication of chronic liver disease, in which a combination of increased splanchnic blood flow and intrahepatic resistance to portal blood flow can lead to the development of portosystemic collaterals, of which the most clinically significant are those from gastroesophageal varices. Therapeutic strategies tend to be directed towards reducing portal inflow, reducing portal pressure, or compressing or obliterating the varices [19].

The presence of varices is common in patients with cirrhosis, although bleeding will occur in only approximately one third of patients [19]. Many factors have been implicated in precipitating hemorrhage, the most significant of which are large varices [20], the presence of high risk variceal stigmata collectively known as "red signs," and a HVPG >12 mmHg [21,22].

The presence of large varices has been demonstrated to be a major risk factor for the development of variceal hemorrhage; in patients with nearly identical portal hypertension, the likelihood of AVB is markedly increased in patients with large varices (Figure 5.1) [20]. In addition, certain endoscopic findings have been associated with a significantly increased risk of AVB. These include red signs (red wale markings, cherry red spots, nipple sign, hematocystic spots) (Figure 5.2), blue varices, giant coiled varices and pan-esophageal varices [22–24]. Patients with severe liver disease (Child–Pugh score C) are also more likely to experience AVB.

The HVPG is a useful clinical marker of portal pressure that has been shown to correlate well with portal pressure in both alcoholic cirrhosis and hepatitis C. It is defined as the gradient between the wedged hepatic venous pressure and the free hepatic venous pressure (normal HVPG <5 mmHg) [19,25,26]. Many investigators have demonstrated that a portal pressure gradient of 12 mmHg is the baseline elevated pressure above which variceal bleeding may occur. Reducing the HVPG by at least 20% or below 12 mmHg is associated with significant protection against bleeding [27]. In practice, however, HVPG is rarely measured due to the invasiveness of the test.

Definitions

Gastroesophageal variceal hemorrhage is defined as (i) active bleeding from an esophageal or gastric varix (Figure 5.3); (ii) the presence of varices with an overlying clot or fibrin plug (Figure 5.4); or (iii) the presence of large esophageal and/or gastric varices with blood in the stomach

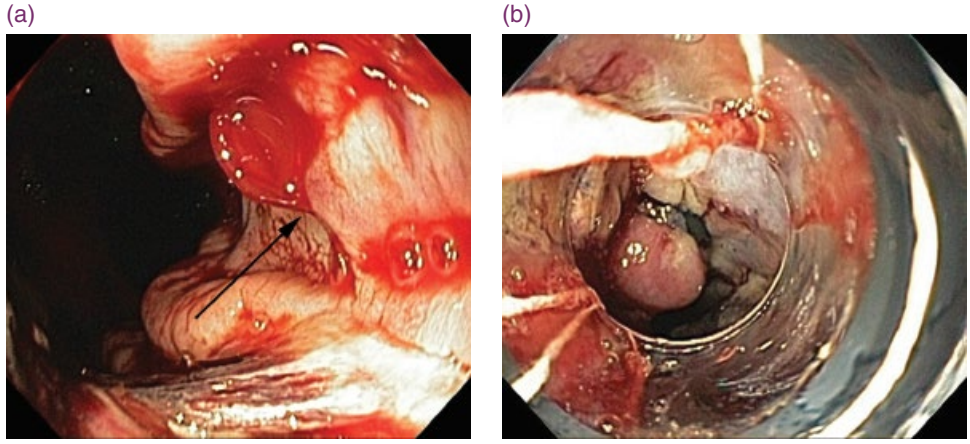

Figure 5.3 (a) Actively bleeding varix (arrow) at the gastroesophageal junction. (b) Successful band ligation of the bleeding varix.

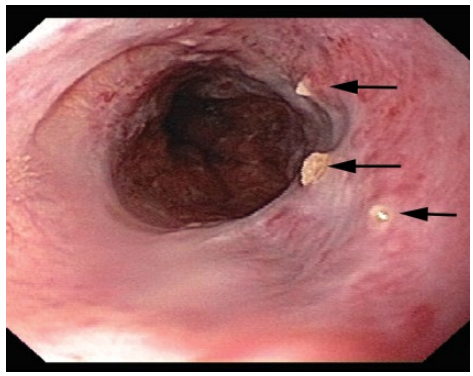

Figure 5.4 Esophageal varices with multiple fibrin plugs (arrows).

and no other recognizable cause of bleeding at the time of endoscopy [8].

Rebleeding is defined as the occurrence of new hematemesis or melena more than 24 hours after the patient has had stable vital signs and hemoglobin/hematocrit levels following an index bleed.

General Treatment Measures

The management of patients with AVB includes not only treatment and control of active bleeding, but also the prevention of complications, such as rebleeding, infections, and renal failure [28,29]. Primary management goals upon presentation of a patient with AVB include hemodynamic resuscitation, prevention and treatment of complications, and early endoscopic intervention aimed at controlling bleeding.

Resuscitation

Acute variceal bleeding is often a dramatic event and patients may be hemodynamically unstable or in hemorrhagic shock on presentation. Initial resuscitation should be aimed at restoring appropriate delivery of oxygen to the tissues [30]. All patients with suspected AVB should receive immediate large bore intravenous access and consideration of central line insertion. Blood volume replacement should be initiated as soon as possible with plasma expanders, aiming to maintain a systolic blood pressure around 90–100 mmHg. Avoiding prolonged periods of hypotension is particularly important in preventing complications, such as infection and renal failure, which are both associated with increased risks of rebleeding and death [30,31].

Transfusion of blood should be done cautiously using a restrictive strategy aimed at maintaining the hemoglobin level between 7 and 8 g/dL. Aside from risks inherent with

blood transfusion, a restrictive strategy has been associated with significantly improved outcomes in patients with acute upper gastrointestinal bleeding [32]. Patients with rapid ongoing bleeding and those with underlying ischemic heart disease may benefit from a more liberal transfusion policy. Correction of coagulopathy and thrombocytopenia is widely practiced with the use of fresh frozen plasma (FFP) and platelets. However, there is no evidence to support this practice and endoscopy should not be delayed. Two randomized controlled trials (RCTs) have examined the use of recombinant activated factor VII [33,34]; these studies failed to show any beneficial effect compared with standard therapy and, thus, this expensive therapy cannot be currently recommended.

Protection of the airway is paramount in order to prevent pulmonary aspiration. Endotracheal intubation is mandatory if there is any concern about the safety of the airway, and should be considered at an early stage in encephalopathic patients, in those with an altered conscious state or a Glasgow coma scale score <9, and in those with active hematemesis or severe uncontrolled bleeding.

Ascites and Renal Function

Patients with AVB and tense ascites should be treated with paracentesis along with albumin replacement as this intervention has been shown to decrease both portal and variceal pressures [35–37]. Acute kidney injury occurs in approximately 11% of cirrhotic patients following an AVB and confers an extremely poor prognosis with a mortality rate of 55% [31,38]. The presence of hypovolemic shock, number of packed red blood cells transfused, Child–Pugh class on admission, and baseline platelet count are independent predictors of renal failure [31]. Renal function should be closely monitored and supported by adequate fluid resuscitation. Nephrotoxic drugs, such as aminoglycosides and non-steroidal anti-inflammatory agents, should be avoided.

Nutrition

Malnutrition is highly prevalent among patients with chronic liver disease and is associated with increased morbidity and mortality [39–41]. Malnutrition may also be an independent risk factor for variceal bleeding [42]. The vast majority of patients presenting with AVB are fasted to facilitate treatment. Feeding should be resumed as soon as possible after hemostasis is achieved; practically this tends to be at least 24 hours following the control of bleeding. Enteral nutrition is always preferable due to lower cost and complications when compared with parenteral nutrition. If a nasogastric tube is ever required, current guidelines recommend delaying insertion until at least 72 hours after hemostasis and the use of a fine bore tube [43].

The possibility of alcohol withdrawal should be considered in all patients. Judicious use of benzodiazepines may be necessary to treat an acute withdrawal syndrome. Administration of thiamine should also be given to alcoholic or malnourished patients to prevent Wernicke syndrome.

Pharmacological Management

Prophylaxis and Treatment of Infection

Infection is a poor prognostic indicator in AVB and is associated with both early rebleeding and greater mortality [15,44–47]. Bacterial infections are frequently associated with upper gastrointestinal bleeding in cirrhotic patients, with Gram negative bacilli as the most frequent pathogens [48,49]. Multiple studies have shown that use of empirical prophylactic antibiotics significantly reduces the incidence of infection, resulting in a decreased

risk of rebleeding [50], all-cause mortality [51], and hospital length of stay [47]. Thus, it is considered standard of care that all cirrhotic patients presenting with gastrointestinal bleeding should receive prophylactic antibiotic therapy on admission [52–54].

A Cochrane review noted that survival benefits are observed independently of the type of antibiotic used [47]; therefore the choice of agent should be made considering local conditions, such as bacterial resistance profile and treatment cost. Oral quinolones, such as norfloxacin (400 mg bid for 7 days) or ciprofloxacin (500 mg bid for 7 days), have frequently been used due to low cost and ease of administration [55,56]. If oral administration is not possible, quinolones can also be given intravenously. In the setting of concerns about increasing fluoroquinolone resistance, third generation cephalosporins such as ceftriaxone (1 g IV daily) have been studied and may in fact be more efficacious in patients with advanced cirrhosis presenting with AVB [57]. Third generation cephalosporins or other agents with broad Gram negative coverage, such as piperacillin-tazobactam, are used in many centers.

Pre-Endoscopic Vasoactive Therapy

Vasoactive medications aim to decrease splanchnic blood flow and portal pressure, and are commonly used in the treatment of AVB. Medications include vasopressin and its analog, terlipressin, and somatostatin and its analog, octreotide. In a meta-analysis of 30 randomized trials involving 3111 patients presenting with AVB, the use of vasoactive medications (compared with placebo) was associated with improved hemostasis, decreased 7-day mortality, decreased transfusion requirements, and/or shorter hospital length of stay [58]. However, terlipressin is the only agent individually shown to reduce mortality [59].

Vasoactive therapy should be considered at the time of presentation in patients presenting with hematemesis who have known varices or are at risk for varices; it should not be delayed until diagnosis is confirmed. In situations where endoscopy is unavailable, vasoactive therapy should be considered to be first line therapy. Treatment is generally continued for up to 5 days.

Vasopressin

Due to its short half-life, vasopressin necessitates delivery by continuous intravenous infusion. Significant systemic side effects are common, including increased risk of myocardial infarction and mesenteric ischemia [60]. Multiple trials have shown improved hemostasis but this did not result in any significant improvement in mortality [2,60–63]. In these trials serious adverse effects were encountered: 25% of patients were withdrawn from the trials and 3% died due to side effects; vasopressin is no longer recommended as monotherapy in AVB. The addition of nitrates (potent vasodilators) to vasopressin reduces its side effects and the combined therapy may lower portal pressure more effectively [64–67].

Terlipressin

Terlipressin is a synthetic vasopressin analog with a longer half-life (enabling bolus administration) and less adverse effects [29,68]. It is given as a 1–2 mg IV bolus every 4–6 hours. Terlipressin is the preferred vasoactive agent in many countries outside the USA. Multiple studies have shown increased hemostasis and improved mortality. Terlipressin achieves control of bleeding in 75–80% and 67% of patients at 48 hours and 5 days, respectively [29,59,69]. A Cochrane review of 20 RCTs (of which seven compared terlipressin with placebo) found terlipressin to be associated with a 34% relative risk reduction in mortality [59]. This study concluded that

terlipressin is effective in the treatment of AVB and since no other vasoactive agent has been shown to reduce mortality in single studies or meta-analyses, it represents the vasoactive agent of choice in AVB, where available [59]. Importantly, adverse events were uncommon and not statistically higher than in the control group.

Somatostatin

Somatostatin is administered as an initial bolus of 250 µg IV followed by a 250–500 µg continuous infusion until a bleed-free period of 24 hours is achieved [28]. Somatostatin has shown superior hemostasis compared with vasopressin in multiple studies, and also has a superior safety profile with fewer side effects [70–74]. Studies have shown somatostatin to be as effective as either terlipressin [75,76] or sclerotherapy [77].

Octreotide

Octreotide is a synthetic analog of somatostatin with a longer half-life and is the most common agent used in the USA. It is given as a 50 µg IV bolus, followed by a continuous infusion at a rate of 25–50 µg/h. Octreotide has been compared with terlipressin [78,79], sclerotherapy [80,81], and endoscopic variceal banding [82]; studies have shown octreotide to be more effective than vasopressin but equivalent to other treatments. Terlipressin and octreotide appear to be equivalent as adjuvant therapy for the control of AVB in conjunction with endoscopic variceal band ligation. No difference in in-hospital mortality was observed, although hospital length of stay was shorter in the terlipressin group [83]. The addition of octreotide to terlipressin does not appear to have any additive effect over terlipressin monotherapy [84].

Both somatostatin and octreotide have a good safety profile. Possible side effects include hyperglycemia and abdominal cramping.

Summary of Vasoactive Therapy

Vasoactive therapy should be considered in all patients presenting with possible AVB. Vasoactive drugs are safe and effective, especially in scenarios where endoscopic therapy is not promptly available. Vasoactive therapy should be commenced early, with endoscopy performed after initial resuscitation [30,53,85]. Meta-analyses and guidelines advocate that combined vasoactive drug and endoscopic therapy is superior to either intervention alone. Recent systematic reviews also indicate that, in conjunction with endoscopic treatment, all vasoactive agents are comparable in terms of reduction in rebleeding [86,87], although only terlipressin has been shown to reduce mortality [59].

A Cochrane analysis in 2010 compared vasoactive drugs to emergency endoscopic sclerotherapy, a largely superseded treatment for AVB, in the management of bleeding esophageal varices in cirrhotic patients. No convincing evidence was found to favor emergency sclerotherapy as the first, single treatment when compared with vasoactive drugs, which were associated with less adverse events than sclerotherapy [79,88].

Esophageal Varices

Endoscopic Management of Acute Esophageal Variceal Bleeding

The gold standard for the diagnosis and treatment of variceal hemorrhage is endoscopy. Current guidelines recommend performing emergency endoscopy as soon as safely possible after admission in order to confirm a variceal origin of the hemorrhage – which represents the leading cause of upper gastrointestinal bleeding in cirrhotic patients – and to perform definitive hemostatic therapy [52,53,85,89,90]. About 80–90% of AVB

episodes are successfully controlled with endoscopic therapy [29]. Delayed endoscopy (variably defined as endoscopy more than 12–15 hours after admission) is associated with both increased rebleeding and mortality [91,92].

The two principal methods for management of esophageal varices are endoscopic injection sclerotherapy (EIS) and endoscopic variceal band ligation (EVL). Both have been shown to be effective in the control of AVB.

Endoscopic Injection Sclerotherapy

Endoscopic injection sclerotherapy was first described by Crafood and Frenckner in 1939 [93] and has been used to treat AVB for over 50 years. EIS is a technique whereby a flexible catheter with a needle tip is passed through the accessory channel of the endoscope and used to inject a sclerosing agent either into the variceal lumen (intravariceal) or adjacent to the varix (paravariceal). Sclerosing agents are oily or aqueous chemicals, which induce thrombosis of the vessel and inflammation of the surrounding tissues [94–96]. The technique was widely adopted in the 1970s using rigid endoscopes, and was then replaced by flexible endoscopic sclerotherapy in the 1980s [24]. During an episode of AVB, EIS can achieve hemostasis by variceal thrombosis and/or external compression of the varix by tissue edema [94]. Widespread introduction of EIS corresponded to a significant improvement in survival of patients presenting with AVB [94]. EIS is successful in controlling active bleeding in at least 90% of patients [97] and can reduce the frequency and severity of recurrent variceal bleeding [10,98].

EIS varies widely in its application, with considerable differences in:

- *Technique* – type of endoscope, use of overtubes, sclerotherapy needles, intra- versus paravariceal injections, sclerosant volumes, number of injections, and operator expertise.
- *Sclerosant* – sodium morrhuate, sodium tetradecyl sulfate, ethanolamine oleate, polidocanol, and absolute ethanol.
- *Follow-up practice* – treatment intervals [24].

This variability makes both individual and comparative EIS trials difficult to interpret. Multiple sclerosing agents have been effective in controlled trials [99]; the most commonly used agents are ethanolamine oleate or polidocanol in Europe, and sodium morrhuate or sodium tetradecyl sulfate in the USA [94,100,101]. The concentration and volume of sclerosant used, and the number of injections used, differ widely among endoscopists. Although trials have been attempted to compare different sclerosants, results have been conflicting and no definitive conclusions have been drawn [102–107]. More frequent EIS treatments achieve more rapid variceal obliteration but are associated with greater mucosal ulceration [108–110].

EIS has a number of advantages. It is a low cost and easy to use technique, the injection catheter can fit through the working channel of a diagnostic endoscope, it can be quickly assembled, and treatment of bleeding varices does not require a second oral intubation as is the case with band ligation. Additionally, the sclerosants induce rapid thrombosis [94].

A major disadvantage of EIS is the local and systemic adverse events (AEs) associated with the procedure. Minor AEs are common following EIS, including low grade fever, retrosternal chest discomfort or pain, dysphagia, asymptomatic pleural effusions, and non-specific transient chest radiographic changes [95]. These AEs do not generally require treatment and resolve spontaneously. More significant AEs can be classified as local, cardiorespiratory or systemic (Table 5.1).

Bacteremia [111], post-EIS esophageal ulcer bleeding, and esophageal strictures

Table 5.1 Adverse events of endoscopic injection sclerotherapy (EIS).

Category	Adverse event
Minor post-procedure	Low grade fever
	Retrosternal chest pain
	Transient dysphagia
	Non-specific chest X-ray changes
Local	Injection-induced bleeding
	Esophageal ulcers/mucosal ulcerations
	Post-EIS delayed ulcer bleeding
	Esophageal strictures
	Perforation
Cardiorespiratory	Pleural effusions
	Adult respiratory distress syndrome (ARDS)
	Pericarditis
	Mediastinitis
	Bronchoesophageal fistula
Systemic/ infectious	Fever
	Bacteremia
	Spontaneous bacterial peritonitis
	Distant embolism
	Distant abscess

[112] are the most frequent and significant AEs encountered [113–116]. These hazardous complications can be a consequence of incorrect injection technique, with either a large volume or a high concentration of sclerosant being injected, resulting in extensive wall necrosis [117]. Ulceration of the esophageal mucosa is the most common local AE, occurring in up to 90% of patients within 24 hours of injection, although it heals rapidly in most cases [94]. Sclerosant induced esophageal ulcers are also common and may cause bleeding in up to 20% of patients [118,119]; thus, ulcerated variceal columns found at follow-up endoscopy should not be injected [94]. EIS induced esophageal strictures are well documented, with a frequency between 2% and 10%, and can present with dysphagia or food bolus obstruction; strictures usually respond to dilation [94,120,121]. Esophageal complications are often treated with proton pump inhibitors, although the usefulness of this practice is questionable [122]. Sucralfate has also been utilized to facilitate esophageal ulcer healing and to lower the risk of rebleeding, although it remains a controversial treatment [123,124].

Bacteremia may occur in up to 35% patients and lead to other complications, such as spontaneous bacterial peritonitis or distal abscesses [111,125–127]. However, the risk of EIS related infectious complications is mitigated by the recommended use of prophylactic antibiotics in cirrhotic patients presenting with AVB.

Chest pain (38%), dyspnea (31%), and pleural effusion (23%) are the most common cardiorespiratory AEs experienced after EIS [128]. The most clinically significant pulmonary AE is delayed perforation with the formation of esophagopleural or esophagobronchial fistulae. Pneumonia, empyema, pulmonary infarction, and atelectasis can also occur. Post-procedure pulmonary function tests often show a transient restrictive deficit [129,130].

The reported frequency of AEs of sclerotherapy varies greatly among series. AEs are undoubtedly related to the experience of operators and the frequency and completeness of follow-up examinations [94]. Mortality as a direct result of post-EIS AEs may occur in 2% of patients and is usually the result of recurrent bleeding, perforation, sepsis, or severe respiratory disorders [116].

EIS Versus Placebo or Non-Active Treatment A meta-analysis of five studies comparing EIS with either sham or non-active treatment found EIS to be associated with significantly increased control of acute bleeding, and a significant reduction in early rebleeding and mortality [131].

EIS Versus Vasoactive Drugs A Cochrane review of 17 trials in 2010 compared vasoactive drugs with emergency EIS in the management of bleeding esophageal varices in cirrhotic patients [88]. No significant difference was found between the two therapies regarding initial bleeding control, rebleeding, or mortality. Treatment with vasoactive drugs was associated with significantly less AEs than EIS. Overall, no convincing evidence was found to favor emergency EIS as the first treatment for bleeding esophageal varices compared with vasoactive drugs [88].

EIS Versus Balloon Tamponade Four trials have compared sclerotherapy with balloon tamponade, showing significantly higher control of bleeding with EIS [19].

Combination Therapy Versus Monotherapy with Vasoactive Agents or EIS Combination EIS and vasoactive therapy appears to improve initial control of bleeding and to decrease treatment failure when compared with either modality alone. A systematic review compared endoscopic treatment (EIS or EVL) alone with combination therapy, and demonstrated increased control of bleeding initially and at day 5 with combination therapy, with a similar serious AE rate in both groups. No survival benefit was seen with combination therapy [132].

One trial [133] and one abstract [134] have been published comparing combined EIS and vasoactive therapy with vasoactive treatment alone, using somatostatin and octreotide, respectively. Combination therapy was associated with increased control of bleeding and increased AEs, with no significant effect on mortality [36]. Higher doses of somatostatin in combination with EIS were also associated with a lower rebleeding rate [135].

Summary of EIS EIS of esophageal varices remains an effective method of controlling acute variceal hemorrhage, although it is associated with significant AEs. EIS has been superseded by EVL and should be considered in cases where band ligation is unsuccessful or not available (Video 5.1) [136]. EIS is more effective than balloon tamponade or placebo, but is not superior to vasoactive agents.

Endoscopic Variceal Ligation

Banding of esophageal varices evolved from the established treatment of ligating hemorrhoids and was first presented in 1986 [137]. In 1989, a seminal study by Stiegmann and Goff reported the successful application of EVL to esophageal varices in 68 consecutive patients, with an 88% success rate in controlling acute bleeding [138]. EVL involves suction of a variceal column into a hollow plastic cylinder attached to the tip of the endoscope, followed by placement of a rubber ring onto the column, which ligates and ultimately strangulates the varix (Figure 5.3) [94,139]. Original devices consisting of single-shot ligators that were time consuming and required the use of an overtube were associated with potentially serious complications. These have now been replaced by multiple-shot devices, which make the procedure much faster and simpler. In addition, the original opaque caps have now been replaced with transparent caps, which significantly improve visibility (visual field with the old caps may be reduced by 30%) [100]. Several commercial, single use, multiband devices are available for EVL, which carry between four and 10 preloaded bands, enabling multiple varices to be easily ligated in a single banding session.

EVL comprises a two step process. Initially, a diagnostic endoscopy is performed, which enables examination of the entire upper gastrointestinal tract and the identification of culprit or high risk esophageal varices; markings on the endoscope enable the distance from the mouth to the varices to be measured. The endoscope is then withdrawn and the ligation device is attached. A second procedure is then performed. Esophageal intubation can be challenging with the ligation device attached, but with flexion of the neck, visualization of the pharynx, gentle scope pressure, and slight torque of the scope shaft left and right, it is successful in the vast majority of cases [94,140]. The scope is advanced to the location of the varices based on the distance measured previously. Once the varix is identified, the tip of the endoscope is pointed toward it and continuous suction applied so the varix fills the cap. Once inside the cap, a "red out" should appear and at this point the band is fired, ligating the varix [94,140]. As the variceal blood supply originates from the gastroesophageal junction (GEJ), variceal ligation is typically performed by applying bands at the GEJ first and working upwards (Video 5.2).

In the setting of active variceal bleeding, the visual field can be significantly impaired by both blood and the banding cap. This significantly increases the complexity of the procedure, making bleeding points difficult to locate and requiring active flushing with water and suction as necessary. Ideally, the rubber band should be delivered on the varix at the site of active bleeding (Video 5.3). Unlike the injection of a sclerosant, which may cause side effects, banding esophageal varices is generally not harmful. If vision is impaired and a point of bleeding cannot be identified, several bands can be placed onto the varices at the GEJ; this may reduce torrential bleeding, enabling visualization of the actual bleeding site and allowing further bands to be accurately placed [94,141].

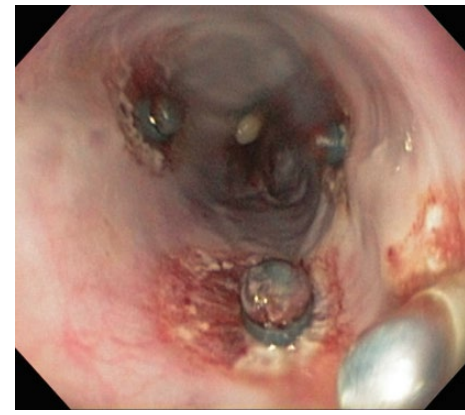

Figure 5.5 Post-band ligation ulcers with only a few retained bands.

Following variceal banding, the ligated tissue undergoes ischemic necrosis, accompanied by variceal thrombosis [142]. The ligated tissue, along with the band, generally falls off within a few days (range 1–10 days), leaving esophageal ulcers (Figure 5.5). The ligation induced ulcers are shallower, have a greater surface area, and heal more rapidly than ulcers caused by EIS [143,144]. Some studies have suggested that the use of a proton pump inhibitor following EVL can reduce the size of post-banding ulcers [145,146], although this practice is not routine.

The most common AEs associated with EVL include chest discomfort and post-banding ulceration; rarer AEs include esophageal strictures and bleeding resulting from a band falling off [29]. To minimize chest pain and band dislodgment, patients are generally maintained on a full liquid diet for the first 12 hours, followed by gradual diet advancement thereafter as tolerated. The incidence of bacteremia and infectious complications are significantly reduced with EVL compared with EIS [139].

The incidence of bleeding from band induced ulcers appears to be higher in patients undergoing EVL for acute bleeding compared with elective EVL for primary or secondary prophylaxis [147].

Patients with more severe liver disease, as evidenced by a higher Child–Pugh score or impaired synthetic function (i.e., hypoalbuminemia and/or coagulopathy), may be more likely to experience post-EVL bleeding [148,149]. In addition, the incidence of bacterial infections is also higher in patients experiencing post-EVL bleeding [148]. The rate of bleeding from post-banding ulcers varies widely among studies, and is reported to be as high as 12% in patients with AVB [147].

Combination Therapy (EVL and Vasoactive Therapy) Versus Vasoactive Therapy Alone One trial has compared combination therapy (EVL and vasoactive therapy) with vasoactive therapy alone. The combination of EVL and terlipressin infusion for 2 days demonstrated superiority to infusion of terlipressin alone for 5 days with regard to reduction of very early rebleeding and treatment failure [150].

Combination Therapy (EVL and Vasoactive Therapy) Versus EVL EVL alone was compared with the combination of EVL and octreotide infusion. Although rebleeding was significantly reduced in the combination therapy arm, there was no significant difference in mortality [151].

EVL Versus EIS

Both EVL and EIS have been shown to be effective in the control of AVB. Four meta-analyses and 10 RCTs have compared EVL and EIS (Table 5.2). In the RCTs, EVL was found to be superior to EIS for eradicating varices more rapidly [97,98,139,152–156], with significantly less recurrent bleeding [98,139,153,155–157]. Three of the RCTs also demonstrated a survival advantage in patients treated with EVL [98,139,158]. EVL was associated with significantly fewer AEs compared with EIS [98,139,154,156–159] (Table 5.3). EVL is equivalent or superior to EIS in achieving initial hemostasis. Three meta-analyses also confirmed the superiority of EVL compared with EIS for all major outcomes (recurrent bleeding, local AEs including ulceration and stricture formation, time to variceal obliteration), [97,160,161] and two showed better survival [97,160]. In addition, one study measuring HVPG before and after endoscopy demonstrated that EIS, but not EVL, may increase portal pressure in AVB [162]. Finally, a meta-analysis found the combination of EVL and EIS was not superior to EVL alone [163].

Thus, EVL should be considered the gold standard endoscopic treatment for the control of acute esophageal variceal hemorrhage, with EIS considered in situations where EVL is technically unsuccessful or not available.

Rescue Therapies for Refractory Esophageal Variceal Bleeding

Despite best practice management, 10–20% of patients with AVB will still experience treatment failure or early rebleeding [30,36,164]. A consensus definition is commonly used to define treatment failure in AVB [85]. Treatment is considered to have failed if the patient dies or if any of the following occurs:

- Fresh hematemesis or nasogastric tube aspiration of ≥100 mL of fresh blood ≥2 hours after the start of a specific drug treatment or therapeutic endoscopy.
- Development of hypovolemic shock.
- A 3 g/dL drop in hemoglobin (or a 9% drop in hematocrit) within any 24-hour period if no transfusion is administered.

It is important to exercise clinical judgment in all cases, as these criteria can potentially be met without continued bleeding.

Any bleeding that occurs more than 48 hours after the initial admission for variceal hemorrhage, provided there has been at least a 24-hour period without bleeding, is considered to represent rebleeding. Rebleeding that occurs within 6 weeks of

Table 5.2 Studies comparing the outcomes of endoscopic variceal band ligation (EVL) versus endoscopic injection sclerotherapy (EIS).

Study, year	Study type	No. patients	Arms	Hemostasis	Rebleeding	30-day mortality
Stiegmann et al. 1992 [139]	RCT	129	EVL vs EIS	86% vs 77% (p >0.05)	36% vs 48% (p = 0.072)	28% vs 45% (p = 0.041)[a]
Laine et al. 1993 [152]	RCT	77	EVL vs EIS	NT	26% vs 44% (difference 17%, CI –4% to +38%)	ND
Gimson et al. 1993 [153]	RCT	103	EVL vs EIS	91% vs 92% (p >0.05)	30% vs 53% (p <0.05)	ND
Laine & Cook 1995 [97]	Meta-analysis		EVL vs EIS	NT	OR 0.52[b] (CI 0.37–0.74)	OR 0.67[b] (CI 0.46–0.98)
Lo et al. 1995 [98]	RCT	120	EVL vs EIS	94% vs 80% (p = 0.23)	33% vs 51% (p <0.05)	Lower with EVL (p = 0.011)
Hou et al. 1995 [157]	RCT	134	EVL vs EIS	100% vs 88% (p >0.05)	19% vs 42% (p <0.01)	ND
Lo et al. 1997 [159]	RCT	71	EVL vs EIS	97% vs 76% (p = 0.009)	17% vs 33% (p = 0.19)	19% vs 35% (p = 0.19)
Baroncini et al. 1997 [154]	RCT	111	EVL vs EIS	NT	ND	ND
Sarin et al. 1997 [155]	RCT	95	EVL vs EIS	80% vs 86% (p >0.05)	6% vs 21% (p <0.05)	ND
Masci et al. 1999 [156]	RCT	100	EVL vs EIS	NT	12% vs 42% (p = 0.001)	NT
Gross et al. 2001 [287]	Meta-analysis[c]		EVL vs EIS	91% vs 81% (p >0.05)	NT	NT
Villanueva et al. 2006 [158]	RCT	179	EVL vs EIS[d]	96% vs 85% (p = 0.02)	NT	Lower with EVL (p = 0.01)
Abraldes & Bosch 2007 [160]	Meta-analysis		EVL vs EIS	RR 0.47[e] (CI 0.27–0.81) (p = 0.007)	NT	RR 0.59[e] (CI 0.35–0.98) (p = 0.04)
Dai et al. 2015 [161]	Meta-analysis	1236	EVL vs EIS	1.06[e] (CI 1.01–1.12)	21.7% vs 33.1%; RR 0.68[e] (CI 0.57–0.81)	22.8% vs. 24.6%; RR 0.95[e] (CI 0.77–1.17)

[a] Survival over 10 months (30-day mortality lower in EVL group compared with EIS group).
[b] Odds ratio favoring EVL over EIS.
[c] Included patients only with ongoing variceal bleeding.
[d] Both groups given combination therapy with somatostatin.
[e] Relative risk favoring EVL over EIS.
CI, 95% confidence interval; ND, no significant difference; NT, not tested; OR, odds ratio; RCT, randomized controlled trial.

the onset of active bleeding is considered "early rebleeding," while rebleeding episodes after 6 weeks are referred to as "late rebleeding" [8]. Approximately 40% of rebleeding episodes will occur within 5 days of the initial variceal bleed [160]. The mortality rate in this group remains high (30–50%) and rebleeding remains a

Table 5.3 Studies comparing adverse events between endoscopic variceal band ligation (EVL) and endoscopic injection sclerotherapy (EIS).

Study, year	Study type	Esophageal strictures	Bacterial infections	Complex ulcers	Significant AE rates	No. treatments required to achieve eradication
Stiegmann et al. 1992 [139]	RCT	0% vs 12% (NS)	2% vs 11% (NS)		2% vs 22% (p <0.001)	Lower with EVL (p = 0.056)
Laine et al. 1993 [152]	RCT	0% vs 33% favoring EVL (p <0.001)	NT	2.6% vs 15% (p = 0.11)		Lower with EVL
Gimson et al. 1993 [153]	RCT				ND	Lower with EVL (p = 0.006)
Laine & Cook 1995 [97]	Meta-analysis	OR 0.10[a] (CI 0.03–0.29)	ND	NT		Lower with EVL
Lo et al. 1995 [98]	RCT	NR	NR	NR	3.3% vs 19% (p <0.01) favoring EVL	Lower with EVL
Hou et al. 1995 [157]	RCT				4% vs 22% (p <0.01)	
Lo et al. 1997 [159]	RCT				5% vs 29% (p =0.007)	
Baroncini et al. 1997 [154]	RCT				11% vs 31% (p = 0.001) favoring EVL	Lower with EVL (p = 0.004)
Sarin et al. 1997 [155]	RCT	0% vs 10%				Lower with EVL (p <0.01)
Masci et al. 1999 [156]	RCT	2% vs 18% (p <0.005)			10% vs 36% (p <0.005) favoring EVL	Lower with EVL (p <0.001)
Villanueva et al. 2006 [158]	RCT				4% vs 13% (p = 0.04)	
Dai et al. 2015 [161]	Meta-analysis	Lower with EVL (NS)	Lower with EVL (p <0.05)	Lower with EVL (NS)	0.28[b] (CI 0.13–0.58)	

[a] Odds ratio favoring EVL over EIS.
[b] Relative risk favoring EVL over EIS.
AE, adverse events; CI, 95% confidence interval; ND, no difference; NR, not reported; NS, not significant (p >0.05).

strong predictor of death from variceal bleeding [132,160]. Treatment options in the setting of rebleeding include a second endoscopy with therapeutic intent, balloon tamponade, esophageal stent tamponade, transjugular intrahepatic portosystemic shunt (TIPS), or a surgical shunt.

Second Endoscopy

Current guidelines state that in the setting of failure of initial combined treatment (endoscopy and vasoactive therapy), it is reasonable to consider a second attempt at endoscopic therapy [52,85,90]. Second endoscopy can occur either before or after a period of balloon tamponade.

Balloon Tamponade

Balloon tamponade with a Sengstaken–Blakemore or Minnesota tube is a temporizing measure that pneumatically compresses the gastric fundus and lower esophagus to achieve hemostasis in 60–90% of refractory variceal bleeding cases [30,165]. In cases of massive bleeding where endoscopic treatment is unavailable, this form of treatment may be life saving. Patients should remain endotracheally intubated and the tube should be deflated within 24 hours to minimize the risk of pressure tissue necrosis. Patients require further endoscopy immediately after deflation.

The Sengstaken–Blakemore tube should ideally be kept in a refrigerator as this eases its passage. Once inserted, the gastric balloon should be inflated with 150–300 mL of air; traction should then be applied and maintained [19]. It is highly effective at stopping bleeding, yet on removal of the balloon 50% of patients will rebleed [166]. Tamponade is also associated with serious AEs in 6–20% of patients, including aspiration, esophageal ulceration, and perforation [2,19]; the latter is associated with very high mortality. Ideally, insertion of the device should be performed by an experienced operator as this is associated with fewer complications [167]. Balloon tamponade only serves as a bridge to definitive therapy, such as an endoscopic procedure, TIPS, or surgery.

Self-Expandable Metal Stents

Case studies have documented the successful use of dedicated covered self-expandable metal stents (SEMSs) in controlling refractory esophageal variceal bleeding [168–171]. Similar to balloon tamponade, this procedure is used as bridging therapy due to a high rate of bleeding with conservative management following stent removal [168]. Insertion of a stent does appear to be efficacious at stopping ongoing bleeding, thereby providing time to perform a definitive interventional or surgical procedure to lower portal pressures. However, no randomized trials have been published comparing this technique with established treatments, such as balloon tamponade. One case report also showed the successful use of SEMSs to treat post-banding ulcer hemorrhage [172].

Transjugular Intrahepatic Portosystemic Shunt

TIPS is a radiologically placed portosystemic shunt that achieves hemostasis in approximately 95% of patients with refractory variceal bleeding [19]. It was first described in 1988 [173,174]. TIPS is only available in specialized centers and involves the creation of a low resistance channel between the hepatic vein and the intrahepatic portion of the portal vein (usually the right branch) using angiographic techniques. The tract is kept patent by the deployment of an expandable metal stent through it, which functions like a side to side portacaval shunt, allowing portal blood to return to the systemic circulation. TIPS does not require general anesthesia for placement [175].

Contraindications to TIPS placement are listed in Table 5.4. The survival benefit of TIPS in patients with severe liver failure (defined as Child–Pugh class C cirrhosis, MELD score >24, serum bilirubin >3 mg/dL) remains unclear [176]. Chronic portal vein thrombosis does not absolutely preclude TIPS insertion, but makes the procedure technically challenging. Acute portal vein thrombus is not a contraindication for TIPS, but it necessitates extensive stenting to prevent shunt occlusion.

Treatment guidelines for AVB have categorized TIPS as second line treatment, applicable for patients in whom combined pharmacological and endoscopic therapy has failed to control bleeding [36,85,177–180]. Its role as salvage therapy stems from the fact that although TIPS is extremely effective in controlling variceal bleeding,

Table 5.4 Absolute and relative contraindications to transjugular intrahepatic portosystemic shunt insertion. Source: Adapted from Boyer and Haskal 2005 [294].

Absolute contraindications	Relative contraindications
Congestive cardiac failure	Portal vein thrombosis
Severe pulmonary hypertension (mean pulmonary pressure >45 mmHg)	Hepatocellular carcinoma (especially if central)
Severe systemic infection or sepsis	Hepatic encephalopathy
Severe tricuspid regurgitation	Severe coagulopathy
Unresolved biliary obstruction	Obstruction of all hepatic veins
	Polycystic liver disease (technically challenging with high risk of hemorrhagic complications)
	Severe thrombocytopenia (<20,000 mm^3)
	Moderate pulmonary hypertension

two early meta-analyses demonstrated that TIPS increased the risk of hepatic encephalopathy without improving survival compared with endoscopic therapy [181,182].

Several uncontrolled series that evaluated the use of TIPS in patients with acute treatment failure [183–187] have confirmed that TIPS is highly successful (90–100%) in controlling bleeding esophageal and gastric varices [188]. Despite the high rate of hemostasis with TIPS, a significant proportion of patients still die of liver and multiorgan failure as a consequence of sepsis, hemodynamic instability requiring inotropes, multiple blood transfusions, repeated endoscopic treatments, and development of hepatic encephalopathy [189]. In patients with a Child–Pugh score >13, early mortality after TIPS is almost inevitable. Thus, a good prognosis following TIPS relies on the general condition of the patient, status of the liver function reserve, associated comorbidities, and timing of the procedure [176].

The role of TIPS in AVB is currently being re-evaluated in the setting of technical advances and new studies. The development of extended polytetrafluoroethylene (PTFE) covered stents has significantly improved stent patency and reduced the incidence of encephalopathy when compared with bare stents [190], which may contribute to improved outcomes. An RCT by Monescillo et al. in 2004 used invasive criteria (HVPG ≥20 mmHg) to select high risk patients who should receive early TIPS using an uncovered stent and compared results to EIS as the control therapy. Early TIPS was associated with reduced treatment failure and in-hospital and 1-year mortality [191]. In addition, a multicenter RCT by Garcia-Pagán et al. in 2010 tested the hypothesis that an early decision to use TIPS made on the basis of clinical criteria can improve the prognosis of high risk patients with variceal bleeding [192]. Patients were randomized to receive either combination treatment (vasoactive drugs and EVL) or TIPS (using expanded PTFE-covered stents). Only patients at high risk of bleeding related mortality (Child–Pugh class B patients with active bleeding at endoscopy or Child–Pugh class C patients with a score <14) were included. The early use of TIPS (within 3 days of admission) was associated with a reduced 6-week mortality rate of 3% (33% with combination treatment) and a 1-year mortality rate of 14% (39% with combination treatment). When TIPS was used as rescue therapy following failure of medical and endoscopic treatment, the mortality rate was high and comparable to previous results. Other beneficial effects of early TIPS

placement included reduced rates of ascites, hepatorenal syndrome, and spontaneous bacterial peritonitis, and significantly reduced hospital and intensive care unit length of stay [180,192]. No increase in the risk of hepatic encephalopathy was noted. The same authors conducted a retrospective review of all patients admitted for AVB and at high risk of treatment failure (defined by Child–Pugh class C with a score <14 or Child–Pugh class B with active bleeding at endoscopy despite vasoactive drug treatment, as in the RCT) at the centers participating in the original RCT in 2010. Patients treated with early TIPS were again found to have a significantly lower incidence of failure to control bleeding or rebleeding than patients receiving standard combination therapy, as well as improved 1-year survival [193].

These studies suggest using simple clinical parameters (Child–Pugh score) and findings at endoscopy to select high risk patients who may benefit from early TIPS. Initial management with vasoactive drugs, antibiotics, and endoscopy with EVL performed within 12 hours of admission would be unchanged in the treatment paradigm. In high risk patients (Child–Pugh class C with a score <14 and Child–Pugh class B patients with active bleeding at endoscopy), TIPS with expanded PTFE covered stents would be offered within 72 hours of admission instead of adopting a conservative treatment strategy with TIPS as late salvage therapy [180].

This treatment strategy has not yet been adopted in management guidelines, and in many centers TIPS remains a salvage therapy for patients with uncontrolled variceal bleeding. Further studies are currently underway evaluating the benefits of early TIPS in high risk patients with AVB. In addition, while these studies are promising, it should be noted that, in both trials, patients in the control arms experienced mortality rates higher than expected with current standards of care for AVB (combination therapy with vasoactive agents, EVL, and prophylactic antibiotics), which potentially overestimates the possible benefit of early TIPS [36]. Another limiting factor in adopting early TIPS is the increase in demand experienced by interventional radiology departments and the limited number of centers that can offer TIPS. In the 2010 RCT [192] and 2013 retrospective review [193] by Garcia-Pagán et al., only 63 of 359 patients and 75 of 659 patients admitted with AVB met the inclusion criteria, respectively. This suggests that, in real life settings, only about 15–20% of patients presenting with AVB may benefit from the early TIPS strategy and, thus, the increase in demand for TIPS may not be as high as imagined [180].

Recently published international guidelines [194] and a meta-analysis [195] both support consideration of early TIPS with PTFE-covered stents within 72 hours (ideally <24 hours) in patients with AVB who are at high risk of treatment failure (Child–Pugh class C with a score <14 or Child–Pugh class B with active bleeding at endoscopy) after initial pharmacological and endoscopic therapy [194]. In this setting, early TIPS is associated with decreased rebleeding, superior 1-year survival, and no increased incidence of hepatic encephalopathy [195].

Surgical Procedures

Since the introduction of TIPS, surgical shunting procedures are now rarely performed and no longer represent a first line rescue therapy. There are, however, two basic types of operations utilized in the setting of refractory variceal bleeding: shunt and non-shunt operations.

Shunt Operations Shunt operations can be categorized as non-selective (if they divert all portal blood flow to the inferior vena cava bypassing the liver, such as the portacaval shunt) and selective (if they are intended to at least partly preserve some portal blood flow to the liver, such as the distal splenorenal shunt or the calibrated small diameter portacaval H-graft shunt) [188]. Selective and non-selective shunts have equivocal clinical outcomes at medium or long term follow-up [2,188].

Similar to TIPS, shunt surgery also significantly increases the incidence of hepatic encephalopathy. In addition, portacaval shunts alter vascular anatomy, which can complicate future liver transplant surgery [2].

Non-Shunt Operations Non-shunt operations include esophageal transection or devascularization of the gastroesophageal junction (GEJ) [188,196]. Data on the efficacy of these treatments are difficult to combine because of differences in patient population and types of operations used, and heterogeneity in supportive management. Portal decompressive surgery and esophageal transection both appear to be highly effective in achieving hemostasis and controlling bleeding, although they are associated with significant mortality (approximately 45–75%) [178,188].

Gastric Varices

Although less common than esophageal variceal hemorrhage, gastric variceal bleeding (GVB) represents a serious complication of portal hypertension [197]. Gastric varices (GVs) develop in approximately 20% of patients with portal hypertension and represent 5–10% of all upper gastrointestinal bleeding episodes in cirrhotic patients [30,198]. They are also commonly seen in patients with non-cirrhotic portal hypertension, especially in patients with splenic vein thrombosis [197]. The risk of first bleeding from GVs is lower than that for esophageal varices, estimated at 4% and 9% within the 1- and 3-year time intervals, respectively [199]. Bleeding rates are higher in patients of Child–Pugh class C with large gastric varices. Hemorrhage from GVs is generally more severe and is associated with higher morbidity, transfusion requirements, and mortality than esophageal varices [200]. GVs can be found alone or in combination with esophageal varices (Figure 5.6). Risk factors for GVB are given in Table 5.5.

GVs are most commonly subtyped according to Sarin's classification [198,200] based on their location in the stomach and

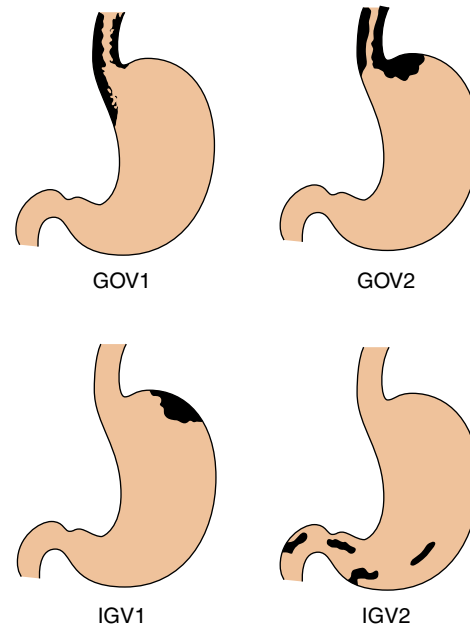

Figure 5.6 Sarin classification of gastric varices. GOV, gastroesophageal varix; IGV, isolated gastric varix. Source: Adapted from Sarin 1997 [293]. Reproduced with permission of American Society for Gastrointestinal Endoscopy.

Table 5.5 Risk factors for gastric variceal bleeding [202]. Source: Adapted from Sarin and Kumar 2014 [202]. Reproduced with permission of Elsevier.

Risk factor	Explanation
Location of gastric varices	IGV1 > GOV2 > GOV1
Size of gastric varices	Large (>10 mm) > medium (5–10 mm) > small (<5 mm)
Severity of liver disease	Child–Pugh class C > B > A MELD score ≥17
Concomitant hepatocellular carcinoma	
Presence of portal hypertensive gastropathy	
Presence of high risk stigmata	Red color signs

GOV, gastroesophageal varix; IGV, isolated gastric varix; MELD, model for end-stage liver disease.

their relationship to esophageal varices (Figure 5.6). Gastroesophageal varices (GOVs) are associated with esophageal varices, which extend along the lesser curve of the stomach (GOV1) or along the fundus (GOV2). Isolated gastric varices (IGVs) are GVs without any associated esophageal varices; these can be localized to the fundus (IGV1) or at ectopic sites in the stomach or the first part of the duodenum (IGV2). GVs may be primary (at initial presentation) or secondary (appearing after obliteration of esophageal varices) [201]. GOV1 represents the most common of all GVs (74%); they are also known as cardial varices. GOV2 and IGV1, which comprise 21% and 7% of GVs respectively, are together referred to as fundal varices. Although less common than GOV1, fundal varices are much more likely to bleed and account for 80% of patients presenting with GVB (Figure 5.7) [197,201].

The diagnosis of GVs is made at endoscopy. Endoscopic ultrasound (EUS) can be used to clarify or further differentiate GVs if required. If only IGV1 are present, exclusion of portal or splenic vein thrombosis as the underlying cause with Doppler ultrasound is imperative [29].

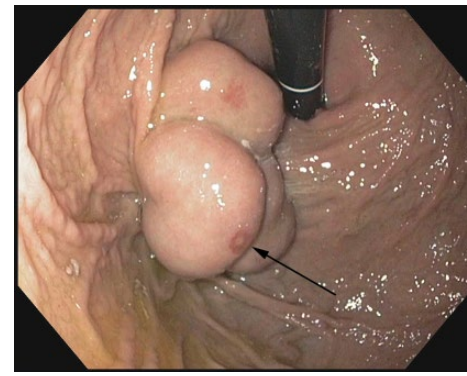

Figure 5.7 Large fundal varices with stigmata of recent bleeding (arrow).

Management Overview

The initial management of GVB is the same as for esophageal variceal hemorrhage, including fluid resuscitation, airway protection, empirical antibiotic prophylaxis, and use of vasoactive agents. Evidence for the use of vasoactive drugs in acute GVB is limited; their efficacy in controlling esophageal variceal bleeding favors their use in the setting of acute GVB [202]. Therapeutic options for acute GVB include balloon tamponade, endoscopic therapies (tissue adhesives such as cyanoacrylate (superglue), thrombin, EIS, EVL), radiological therapies (TIPS or balloon-occluded retrograde transvenous obliteration (BRTO)), and surgical procedures. Evidence in the management of GVB is scarce, with few RCTs and little consensus as to the gold standard treatment.

Balloon Tamponade

Balloon tamponade with pneumatic compression of gastric varices is a temporizing measure or bridge to further definitive

therapy. It can achieve hemostasis in up to 80% of patients with GVB, but rebleeding occurs frequently [201]. The AEs of balloon tamponade are the same as those described previously. The maximum volume of air in the gastric balloon of a Sengstaken–Blakemore or Minnesota tube may be insufficient to adequately tamponade large GVs; a Linton–Nachlas tube has a larger 600 mL gastric balloon and may be more successful in this circumstance [203], although it is not readily available.

Endoscopic Management

Endoscopic therapy remains the initial treatment of choice, and all cirrhotic patients presenting with upper gastrointestinal bleeding should undergo endoscopy within 12 hours of presentation. The endoscopic therapies utilized for GVB often depend on availability and local expertise.

Endoscopic Injection Sclerotherapy

Prior to the introduction of newer techniques, EIS with conventional sclerosants, such as alcohol or sodium tetradecyl sulfate, was used to control acute GVB [201]. EIS was found to be less efficacious for GVB compared with bleeding esophageal varices, with larger volumes of sclerosant required and more AEs described [19,204,205]. Fundal varices, in particular, can be quite large in size, necessitating large quantities of sclerosant, which places the patient at risk of systemic (especially pulmonary) embolization. In addition, AEs, such as fever, chest or abdominal pain, and extensive mucosal ulceration may also be increased [197,202].

In acute GVB, EIS was associated with initial hemostasis rates of 67–100%, although unacceptably high rebleeding rates of up to 90% were noted [202,206]. Approximately 50% of rebleeding episodes resulted from EIS induced ulcers [202]. Overall, the success of EIS is questionable in the management of GVB [205] and it is not a preferred hemostatic method.

Endoscopic Variceal Ligation

While EVL is the gold standard endoscopic therapy for esophageal varices, it is less effective for GVs and potentially harmful. This is due to the fact that GVs are larger and propagate deep in the submucosa, making ligation difficult [207]. One RCT compared EVL with cyanoacrylate injection; EVL was inferior to cyanoacrylate for hemostasis of large GVs (45% versus 87%) and was associated with a higher rebleeding rate (54% versus 31%) [208].

The main indication for EVL in acute GVB is the banding of GOV1 (cardial varices), which are extensions of esophageal varices into the stomach along the lesser curvature (Video 5.4). Studies suggest that EVL of GOV1 varices results in equivalent hemostasis and comparable rebleeding rates to EVL of esophageal varices [197,206].

Endoscopic Variceal Obturation

Obturation is the term used for GVs treated by cyanoacrylate (glue) injection (Figure 5.8), because the varix can be visible as a hardened structure after it has been effectively treated [202]. Endoscopic variceal obturation (EVO) utilizes tissue adhesives such as *n*-butyl-2-cyanoacrylate (BCA), a monomer that rapidly undergoes exothermic polymerization on contact with the hydroxyl ions present in water or blood, and which changes from a liquid to a hard brittle acrylic plastic [201]. This stems the flow of blood within the varix. In EVO, a disposable sclerotherapy injection needle is passed through the working channel of a standard gastroscope and used to puncture the varix lumen (Video 5.5). Cyanoacrylate is then injected into the varix in 1–2 mL aliquots, followed by a flush of saline or sterile water as the needle is withdrawn [209]. Commonly, a mixture of BCA and lipiodol is injected in

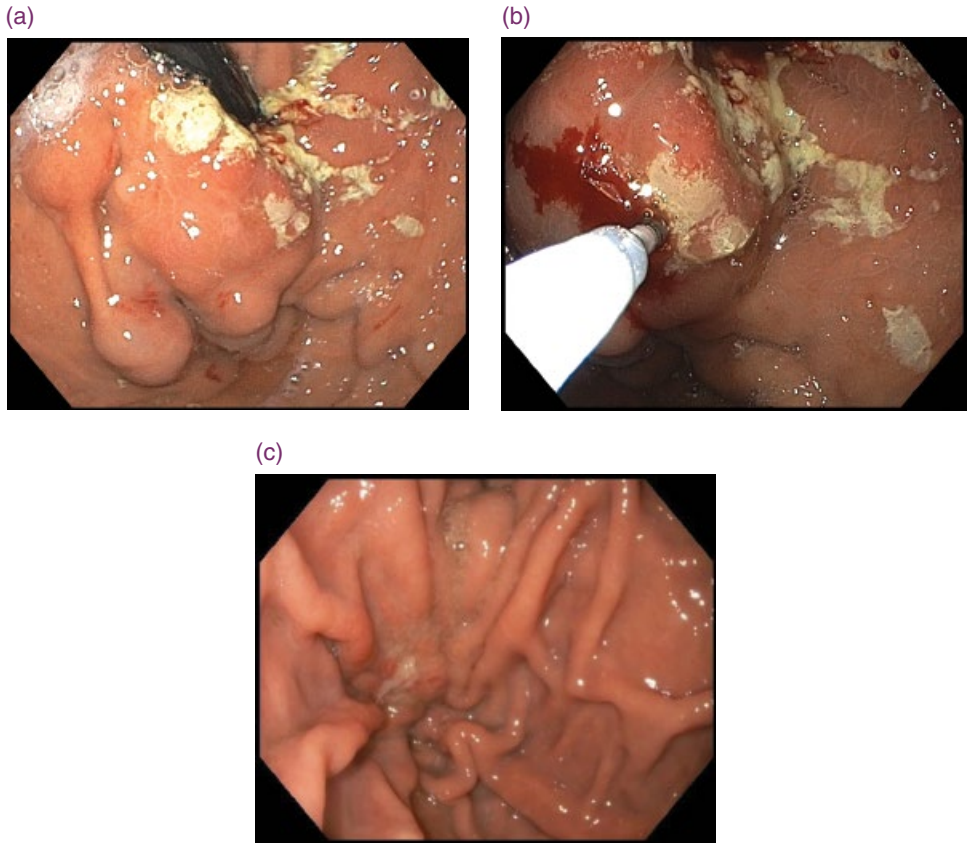

Figure 5.8 (a) Acute bleeding from fundal varices. (b) Cyanoacrylate injection into the fundal varices. (c) Eradicated varices with a small retained glue cast at the injection site at 1 month follow-up.

a 1:1 or 1:1.5 ratio; lipiodol is used to slow down the polymerization of BCA and avoid premature glue solidification in the injection catheter. Following variceal injection, the needle should be withdrawn immediately to prevent adherence to the varix, then flushed again with saline or sterile water. Additional 1 mL aliquots of tissue adhesive can be injected until obliteration of the varices is achieved. EVO can be confirmed by blunt palpation of the varices using the injector with the needle retracted. Successful EVO is characterized by a hardened feel to the varix. On subsequent endoscopy, the patency of the varix can be assessed by either blunt palpation or EUS.

Multiple studies worldwide have reported hemostasis rates of over 90% with EVO for GVB; rebleeding rates vary from 15% to 30% [210–218]. One to three injections are generally needed to achieve variceal obliteration, and higher eradication rates have been noted for GOV1 and GOV2 than for IGV1 [202].

A number of AEs have been documented in association with cyanoacrylate injection. The majority of these AEs relate to post-procedure thromboembolic phenomena, including pulmonary embolism, cerebral stroke, portal vein embolization, splenic infarction, and renal, coronary, or spinal emboli, with rare deaths documented [201]. One case series reported non-fatal pulmonary emboli in 5% of cases [219]. Embolic and thrombotic phenomena are associated with larger volumes of glue injection and thus it is recommended not to exceed 2 mL per variceal column per session [202,219,220]. Other AEs

include needle entrapment in the varix, gastric ulceration, retrogastric abscess, visceral fistula formation, and bacteremia or sepsis [202]. Endoscopic ultrasound (EUS) guided insertion of cyanoacrylate and/or coils is emerging as a promising alternative to standard glue injection, and may enhance safety and efficacy of the procedure [9,220].

EVO Versus EIS

Three studies have examined the efficacy of glue injection in comparison with sclerotherapy. In a non-randomized prospective study of 53 patients with acute GVB, Oho et al. found EVO to be superior to EIS in achieving hemostasis (93% versus 67%) and with improved mortality [221]. In a retrospective study, Ogawa et al. also found significantly better hemostasis in favor of glue injection [222]. An RCT by Sarin et al. demonstrated a trend towards superior hemostasis (89% versus 62%) with glue compared to EIS with alcohol [223], although only a small proportion of patients (n = 17) presented with acute GVB.

EVO Versus EVL

Two studies have found EVO to be superior to EVL in the treatment of GVs. A RCT by Tan et al. demonstrated a lower rebleeding rate in favor of EVO (cyanoacrylate mixed 1:1 with lipiodol) compared with EVL (27% versus 63%) with no difference in long term survival [224]. Another RCT by Lo et al. showed a 1-year rebleeding rate of 15% with EVO versus 60% with EVL, with a significant survival advantage in the EVO group [208].

EVO Versus TIPS

A RCT by Lo et al. comparing EVO with TIPS following initial control of GVB showed similar survival and complication rates in both groups, although TIPS was associated with a lower rebleeding rate (11% versus 38%) [225]. Two retrospective studies have compared EVO to TIPS. Mahadeva et al. demonstrated TIPS to have a lower initial rebleeding rate than EVO (15% versus 30%), but at higher cost and with no difference in survival [226]. Procaccini et al. found equivalent hemostasis rates in both groups, although TIPS was associated with a higher rate of hepatic encephalopathy [227].

Overall, there is good evidence for the efficacy of tissue adhesives in the management of GVB and most guidelines support EVO as first line treatment [10,52,85].

Thrombin Injection

Thrombin is a hemostatic agent first used for the management of GVs in 1947 [228]. Bovine thrombin was originally used, but owing to the increased risk of prion transmission, human thrombin has been adopted. Thrombin induces hemostasis by converting fibrinogen to fibrin clot and also influences platelet aggregation [201,229]. In rare cases where there is a primary clotting disorder resulting in the absence of fibrinogen, thrombin will fail to clot blood. A 5 mL solution of thrombin containing 1000 units/mL of thrombin will clot a liter of blood in under 60 seconds. A standard gastroscope is used for the procedure and no specific preparation is required.

To date no RCTs have investigated the use of thrombin for bleeding GVs and, thus, comparison with EVO is unavailable. Eight non-randomized trials involving more than 200 patients have been published, which demonstrate high rates of hemostasis, low rebleeding rates, and minimal AEs (Table 5.6). The initial study by Williams et al. used bovine thrombin for control of GVB and reported 100% hemostasis with no significant complications and a rebleeding rate of 27% [230]. Similarly, Ramesh et al. reported 92% hemostasis for GVB using bovine thombin, with no rebleeding or AEs during the follow-up period [231]. The largest study evaluating the efficacy of human thrombin in the management of bleeding gastric and ectopic varices was performed by McAvoy et al. in 2012. This study found that human thrombin was safe and effective, with

Table 5.6 Summary of studies using thrombin for the management of gastric variceal bleeding.

Study, year	Type of thrombin used	No. patients (follow-up)	Hemostasis	Rebleeding
Williams et al. 1994 [230]	Bovine	11 (9 months)	100%	27%
Przemioslo et al. 1999 [288]	Bovine	52 (15 months)	94%	18%
Ramesh et al. 2008 [231]	Bovine	13 (25 months)	92%	0%
Yang et al. 2002 [289]	Human	12 (17.8 months)	100%	25%
Heneghan et al. 2002 [290]	Human	10 (8 months)	70%	0%
Datta et al. 2003 [291]	Human	15 (1 month)	93%	27%
McAvoy et al. 2012 [232]	Human	37 (22 months)	100%	10.8%
Smith et al. 2014 [292]	Human	30 (22 months)	90%	35%

100% initial hemostasis and a rebleeding rate of 10% [232].

Overall, thrombin is a promising and efficacious therapy for GVB that is easy to use and has an enviable safety profile. Controlled studies comparing thrombin with other treatment modalities are required before it can be universally recommended.

Rescue Therapies for Refractory Gastric Variceal Bleeding

When patients with GVB experience treatment failure or early rebleeding, a second attempt at endoscopic therapy should be considered [85]. If endoscopic attempts fail to control bleeding, rescue therapy options include radiological procedures (TIPS or BRTO) or surgery.

Transjugular Intrahepatic Portosystemic Shunt

As previously described, TIPS is well studied and validated in the management of esophageal varices. Since GVB is relatively uncommon, there are few studies (and no randomized trials) that assessed its efficacy in the setting of bleeding GVs. One of the largest studies investigating TIPS in acute GVB was performed by Barange et al. [233] in 1999. Thirty-two cirrhotic patients with GVB from GOV1 (68%) and GOV2 (32%) were included, all of whom had been unresponsive to treatment with vasoactive agents, sclerotherapy, and/or balloon tamponade. TIPS resulted in hemostasis in 90% of patients, with a rebleeding rate of 31% at 1 year [233]. Similarly, a study by Chau et al. of 28 patients with acute GVB who had failed vasoactive therapy only showed a hemostasis rate of 96% and a rebleeding rate of 29% with salvage TIPS [184]. A later study by Choi et al. demonstrated a primary hemostasis rate of 92.3% and a rebleeding rate of 8% with TIPS for acute GVB [234].

Despite the lack of randomized trials, TIPS with a PTFE-covered stent remains the treatment of choice for patients with acute GVB who fail first line medical and endoscopic therapy.

Balloon-Occluded Retrograde Transvenous Obliteration

Balloon-occluded retrograde transvenous obliteration is an advanced radiological procedure first described by Kanagawa et al. [235] in 1996 for the management of GVs. Cardiofundal varices usually have unique vascular anatomy, with spontaneous splenorenal or gastrorenal shunts that divert blood flow into the systemic circulation [236]. This provides a pathway for interventional radiologists to access and allow transvenous obliteration of the

varices. With BRTO, the right femoral or internal jugular vein is accessed and a balloon-occlusion catheter is inserted through the left renal vein into the gastrorenal shunt. After balloon inflation, venography is performed to delineate the GVs and collateral veins. The veins draining the GV can be embolized with microcoils or gelfoam, and a sclerosant mixed with a contrast agent is injected into the GV until obliteration [209].

Hong et al. compared BRTO with EVO in patients with acute GVB and/or high risk varices (≥5 mm, presence of red spots, and Child–Pugh class B or C). Hemostasis rates were higher in the EVO group (100% versus 77%), but the rebleeding rate was significantly lower in the BRTO group (15% versus 71%); AEs were similar between groups [237]. Min et al. compared BRTO to both EVO and EVL in 103 patients with acute GVB. No significant differences in either rebleeding or survival rates were found between groups, and BRTO was associated with a rebleeding rate of 7% [238]. A small randomized study by Choi et al. compared BRTO with TIPS for treatment of active GVB. No differences were found between the groups with regard to rates of hemostasis, rebleeding, or encephalopathy [234].

Adverse events of BRTO include hemoglobinuria, abdominal pain, pyrexia, and pleural effusion; hemodynamic shock and atrial fibrillation have been documented to occur rarely [202]. In addition, hepatic portal blood flow and portal pressure have been shown to increase after BRTO. This may improve liver function (50% of patients had an improvement in Child–Pugh score in one study), but may worsen the size of esophageal varices [239–241]. Hepatic encephalopathy may also improve following BRTO, but whether this beneficial effect is sustained long term remains unknown [241].

BRTO may be an alternative to TIPS for the management of acute GVB in the presence of a gastrorenal shunt. The procedure is not commonly performed outside of Asia, but should be considered an option for the treatment of GVB where available.

Ectopic Varices

Ectopic varices are defined as dilated portosystemic collateral veins occurring anywhere in the gastrointestinal tract other than the esophagogastric region [242]. They account for 2–5% of all variceal bleeds, but are the cause of bleeding in 20–30% of patients with extrahepatic portal hypertension [243–245]. The most common sites for ectopic varices include the duodenum, jejunum, ileum, colon, rectum, and surgical stoma sites. Although rare, bleeding from ectopic varices can be massive and life-threatening.

Endoscopy is the most important diagnostic tool and an accurate examination of the duodenum is essential; the door to scope time should be less than 6 hours [52]. In patients with portal hypertension, acute bleeding, and negative findings on upper endoscopy, bleeding from ectopic varices must be considered. Colonoscopy is the principal method used for the diagnosis of colonic and rectal varices, although the diagnostic yield may be increased with EUS [246]. Double balloon enteroscopy may be required to diagnose jejunal and ileal varices. Other methods of diagnosing ectopic varices include technetium-99m red blood cell scintigraphy, video capsule endoscopy, computed tomography (CT) angiography, multislice helical CT, CT enterography, contrast enhanced 3D magnetic resonance angiography (MRA), EUS, laparoscopy, and laparotomy [247].

Management Overview

Bleeding ectopic varices represent a difficult management problem and may require a multidisciplinary team of

endoscopists, hepatologists, surgeons, and interventional radiologists. The diversity of their location, presentation, and complications increases the challenges of successful treatment and precludes development of standardized guidelines. The optimal therapeutic modality depends on a number of factors, including the location of the varices, the patient's clinical condition, locally available expertise and facilities, and the cause of portal hypertension. Management incorporates urgent resuscitation and immediate workup to localize the site/source of bleeding, followed by application of a suitable treatment modality or transfer to a tertiary referral center for specialized therapy [247]. As with other forms of variceal hemorrhage, vasoactive therapy and antibiotics are used, although there are no specific data related to ectopic variceal bleeding.

Endoscopic Variceal Ligation

A small number of case series and single reports detail the successful use of EVL for the treatment of ectopic varices in the rectum and duodenum (Figure 5.9) [248–251]. One study also reported that EVL, together with BRTO, demonstrated efficacy in the management of bleeding duodenal varices [252]. EVL is not appropriate for large varices and case reports have described rebleeding following EVL of duodenal varices; additional treatment following initial hemostasis with EVL may therefore be required [29,253].

Injection Therapies

Injection sclerotherapy and EVO have the greatest body of evidence in the management of ectopic varices and are usually considered to be first line therapy. Most ectopic varices are within the reach of a standard gastroscope or colonoscope [243], and injections using cyanoacrylate (Figure 5.10), thrombin, or sclerosants have successfully controlled bleeding from duodenal, jejunal, colonic, and rectal varices in case reports [254–259].

Transjugular Intrahepatic Portosystemic Shunt

Multiple publications have reported the successful use of TIPS in controlling bleeding ectopic varices, which has typically been employed as a salvage therapy. TIPS has been successful in treating duodenal [260–262], intestinal [263], anorectal [264–266], and stomal [267–270] ectopic varices. Larger case series have also demonstrated TIPS to be a highly effective

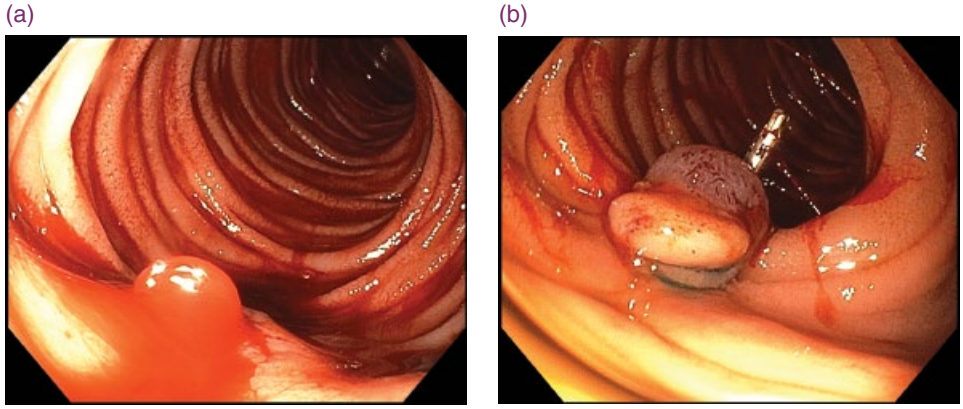

Figure 5.9 (a) Actively bleeding duodenal varix. (b) Hemostasis secured with endoscopic band ligation (EBL); a clip was placed distal to the bleeding point to serve as a visual aid during reinsertion of the EBL loaded endoscope to the bleeding varix.

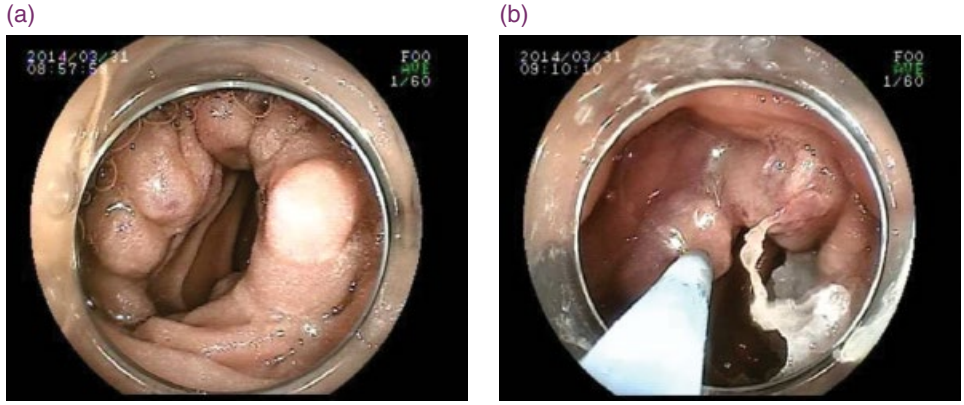

Figure 5.10 (a) Jejunal varices with stigmata of recent bleeding diagnosed by double balloon enteroscopy. (b) Cyanoacrylate injection of the jejunal varices.

modality for controlling bleeding [271–275], although there are multiple reports of ectopic variceal rebleeding despite a reduction in the HVPG to <12 mmHg. Thus, additional treatment modalities, such as angiographic embolization or endoscopic therapy, may be required [274,275].

Radiological Embolization

Several case reports have demonstrated successful hemostasis of ectopic varices with percutaneous transhepatic obliteration (PTO). The goal of PTO is to occlude the feeding veins supplying the varix rather than occluding the varix itself; feeding veins can be reached via percutaneous transhepatic or transjugular routes. PTO has successfully treated duodenal [276], jejunal [277], rectal [278], and peristomal [279] varices. Embolization can be achieved with a variety of agents, including steel coils, thrombin, gel foam, tissue adhesives, collagen, and autologous blood clot. Steel coils are preferred because they result in a permanent focal occlusion, come in a variety of sizes, and allow the occlusion of large veins [247]. Since angiographic embolization does not decompress the portal venous system, high rebleeding rates are noted with monotherapy. Therefore, combination therapy with TIPS is usually recommended.

Two studies have demonstrated that TIPS combined with variceal embolization resulted in superior hemostasis compared with TIPS alone, and should be the preferred salvage procedure if local therapies fail [274,280]. The combined therapy constitutes an effective and minimally invasive management option in patients with bleeding ectopic varices, can be performed in patients unfit for surgery, and does not preclude subsequent liver transplantation if required [280].

Surgery

If endoscopic and/or interventional radiological procedures fail to control bleeding or are not feasible, surgery is a potential option if the expertise is available. Careful patient selection is important based on an assessment of underlying liver function. Surgery is preferred in patients with Child–Pugh class A cirrhosis and in those with extrahepatic portal vein occlusion [281]. Direct surgery or local devascularization of ectopic varices is a useful and minimally invasive procedure that does not involve resection of long segments of small bowel and can be done in the setting of portal vein thrombosis or in a patient with Child–Pugh class B or C cirrhosis [247,282,283]. Other surgical interventions reported to successfully control

bleeding ectopic varices include simple oversewing of duodenal varices through a duodenotomy [284], duodenal dearterialization and stapling [285], and circumferential stapled anoplasty [286]. Major surgical interventions, such as shunt procedures, are now rarely performed.

Conclusion

Variceal hemorrhage is a common medical emergency in patients with cirrhosis, and is associated with high morbidity and mortality. Advances in care, incorporating a multidisciplinary approach, resuscitation, antibiotics, vasoactive therapy, and enhanced endoscopic and interventional radiological techniques, have improved patient outcomes in the setting of acute variceal bleeding.

Videos relating to this chapter are:

Video 5.1 Endoscopic injection sclerotherapy as salvage modality for failed band ligation of bleeding esophageal varices.
Video 5.2 Endoscopic band ligation of esophageal varices with stigmata of recent bleeding.
Video 5.3 Endoscopic band ligation of an actively bleeding esophageal varix.
Video 5.4 Endoscopic band ligation of actively bleeding gastroesophageal varices type I (GOV1).
Video 5.5 Endoscopic cyanoacrylate injection of fundal varices with stigmata of recent bleeding.

All videos cited in this book can be found on the companion website at
www.wiley.com/go/plevris/endoscopyinliverdisease

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6

Prevention of Recurrent Bleeding from Esophageal Varices

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Introduction

Secondary prophylaxis of variceal bleeding refers to the prevention of variceal rebleeding in patients who have survived an initial episode of variceal hemorrhage. Since these patients already have advanced liver disease and portal hypertension, they have a much higher risk of rebleeding and death than patients who have never bled. Therefore, an aggressive treatment approach to prevent variceal rebleeding is justified.

This chapter reviews current recommended therapy for secondary prophylaxis, approach to treatment failures, and new treatments on the horizon.

Natural History, Prognosis, and Rationale for Therapy

Patients who survive the first variceal bleeding episode are at high risk of rebleeding and death. The rebleeding risk in untreated patients approximates 60–70% at 2 years, which is much higher than the risk of first variceal bleeding in the same timeframe in patients with large varices (15–35%) [1]. This increased risk of bleeding is due to the fact that if no treatment is provided, the factors leading to the first variceal hemorrhage will persist. With regard to rationale for therapy, it is worth noting that the factors leading to variceal pressure increase variceal wall tension [2]. Variceal wall tension (WT), as defined by Laplace's law, is determined by the following equation:

$$WT = [(\text{variceal pressure} - \text{esophageal luminal pressure}) \times \text{variceal radius}] / \text{variceal wall thickness}$$

This equation explains why variceal bleeding is more frequent in patients with very high portal pressure (or advanced decompensated cirrhosis as its surrogate), increased size of the varices, and thin varices (reflected endoscopically by the presence of red color signs) (Figure 6.1). It follows that any rational therapy should attempt to modify these three factors.

This has been studied in humans in whom variceal wall tension has been calculated from endoscopic measurements of variceal pressure combined with endosonographic

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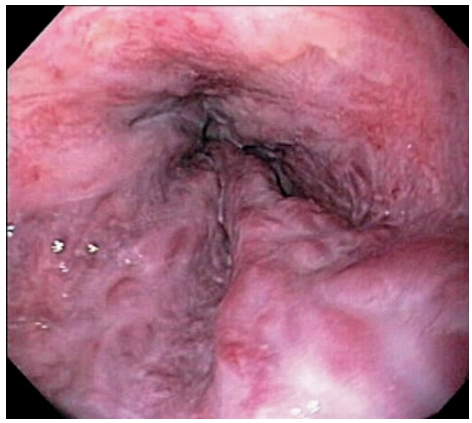

Figure 6.1 Large varices with red signs.

measurements of variceal radius and volume [3]. Non-selective beta-blockers (NSBBs) influence dramatically variceal wall tension as these drugs decrease significantly the portal pressure (the direct determinant of variceal pressure), portal collateral flow, and variceal volume (thus decreasing variceal size), and probably wall thickness as well (because the thin wall of the varices is likely to behave as an elastic structure, where dilation is accompanied by thinning of the vessel wall) [3,4]. Drugs that decrease portal pressure without significantly modifying portal collateral blood flow (vasodilators such as isosorbide mononitrate, angiotensin II inhibitors, and alpha-adrenergic antagonists) cause a less profound decrease in variceal wall tension and have a lesser effect on variceal size [5]. It follows that the threshold for protection from variceal rebleeding established for beta-blockers may not be applicable to drugs acting primarily on portal collateral resistance without reduction in blood flow. This may also explain why one should aim for a much more profound decrease in portal pressure when using a transjugular intrahepatic portosystemic shunt (TIPS) than when using NSBBs, since TIPS causes worsening of the hyperkinetic syndrome, with a resulting increased portal blood inflow. Endoscopic treatments in turn may be highly effective during the acute bleeding episode when successfully obliterating the bleeding point and/or feeding vessel(s), but the effect on preventing bleeding is linked to the ability to eradicate the varices or decrease their size – an effect that is neither constant nor permanent.

With regard to the risk of death, patients who survive a variceal bleeding episode, by definition, have entered the decompensated phase of cirrhosis and, therefore, have a much greater risk of dying than patients with compensated cirrhosis (30–57% versus 3.5% at 1 year) [6]. The potential of reducing this increased mortality risk is limited to trying to ameliorate the cirrhosis, which up to now has been mostly based on treating the underlying cause of portal hypertension (e.g., antivirals for hepatitis B or C related cirrhosis, abstinence from alcohol, and weight reduction). Limitations in current therapies make consideration of liver transplantation mandatory in these patients, especially when the model for end-stage liver disease (MELD) score increases above 12–14 points.

Risk Stratification in Secondary Prophylaxis

The risk of rebleeding and death is not equal in all patients surviving a variceal bleeding episode. Prognostic factors allow for stratifying the risk, which has important connotations in individualizing therapy.

Considering the risk of subsequent bleeding episodes, a very important factor is the time interval from the index bleed. The risk of rebleeding is high during the first 6 weeks; at about 20% between day 5 (end of the acute bleeding episode) and day 42 [7,8]. After 6 weeks, the risk of recurrent bleeding decreases to approximately the same as in patients on primary prophylaxis.

During this initial period after a bleed, circumstances that may have worsened portal hypertension and precipitated the original bleeding (e.g., infections, alcoholic hepatitis, and surgical stress) are still acting and maintaining an increased risk of further hemorrhage. Therefore, treatment to prevent rebleeding should be instituted immediately after the completion of the acute variceal bleeding episode (day 5 following admission for acute variceal bleeding). During the initial 6 weeks when rebleeding episodes are more likely to occur, treatment should be especially well conducted and patients should be instructed to avoid any further risk and to pay special attention to compliance with treatment. Patients referred beyond these 6 weeks have already survived the higher risk period, and have a relatively better prognosis than those seen immediately following the index bleed.

Other risk factors include failure of primary prophylaxis with NSBBs (and probably with endoscopic therapy), lack of adequate hemodynamic response to beta-blockers, and the presence of ascites or hepatic encephalopathy, among others (Table 6.1). It is important to note that the protection against recurrence of bleeding and death conferred by secondary prophylaxis also applies to patients with hepatocellular carcinoma [9]. In this subgroup of patients, not providing secondary prophylaxis independently increases by four times the risk of death after a first variceal bleeding episode. Not surprisingly, other independent predictors of death relate to tumor stage (Barcelona Clinic Liver Cancer classification and malignant portal vein thrombosis) and to liver function (Child–Pugh score) [9].

Therapies for Secondary Prophylaxis of Variceal Bleeding

The available armamentarium for preventing variceal rebleeding includes pharmacological therapy (NSBBs with or without isosorbide mononitrate (ISMN)), endoscopic therapy, combined pharmacological and endoscopic therapy, TIPS, and surgical shunts. These are briefly summarized below.

Non-Selective Beta-Blockers With or Without Isosorbide Mononitrate

Non-selective beta-blockers (e.g., propranolol and nadolol) reduce portal pressure

Table 6.1 Prognostic factors in patients requiring secondary prophylaxis.

Prognostic factors for 6-week mortality	Prognostic factors for late rebleeding (>6 weeks) and mortality
Child–Pugh score (presence of ascites and/or hepatic encephalopathy)	Child–Pugh and MELD scores
MELD score	Alcohol use
Hepatocellular cancer	Renal failure
Bacterial infection	Hepatocellular cancer
Renal failure	Lack of adequate hemodynamic response to NSBBs (↓ ≥ 20% of baseline value or ≤12 mmHg)
Early rebleeding	Failure of primary prophylaxis with NSBBs (clinical non-responders to NSBBs)
	Dose of NSBBs received

MELD, model for end-stage liver disease; NSBBs, non-selective beta-blockers.

in patients with cirrhosis. In patients who are treated for prevention of recurrent variceal bleeding, NSBBs are associated with an absolute risk reduction in rebleeding of about 20% (from 63% in controls to 42% in treated patients) [10]. In addition, NSBBs reduce overall mortality (from 27% to 20%) [10] and bleeding related mortality [11]. The number of patients needed to be treated (NNT) with NSBBs to prevent one episode of rebleeding is 5, and the NNT to avoid one death is 14 [10], indicating that this therapy is highly effective.

ISMN can be administered orally together with an NSBB in order to achieve a greater reduction in portal pressure [12]. This drug combination was found to further reduce the rebleeding risk in one study as compared with propranolol alone [13]. Other studies have shown that the addition of ISMN to NSBBs achieves the target decrease in hepatic venous pressure gradient (HVPG) (≥20% from baseline and/or ≤12 mmHg) in one third of patients deemed "non-responders" to NSBBs and, consequently, reduces the rebleeding risk [14,15].

NSBBs are usually well tolerated, but an average of 18% of patients experience unpleasant side effects that require discontinuation of therapy. However, there have been no deaths associated with the use of NSBBs in clinical trials. Dosing is shown in Table 6.2.

Recently, a concern has been expressed about the possibility that the reduction in cardiac output caused by NSBBs may lead to renal failure in patients with refractory ascites [16]. This has been debated but not proven by research based on outcomes in large patient populations [17]. Nevertheless, it is appropriate to carefully monitor renal function when giving NSBBs. On the other hand, patients with refractory ascites on NSBBs are high risk patients that are often managed by TIPS, thus circumventing the need for NSBBs.

ISMN is usually well tolerated at low doses (10 mg twice daily). The most common side effect is headache, which usually decreases within a few days. Headache is much less common when ISMN is first introduced as a single dose at bedtime and increased to twice daily after 3–4 days (Table 6.2). Simvastatin administration in patients with cirrhosis improves endothelial dysfunction, decreases hepatic vascular tone and fibrogenesis, improves liver

Table 6.2 Standard approach used for the prevention of recurrent variceal hemorrhage.

Therapy	Dosing	Duration
Propranolol Nadolol	Begin with 20 mg orally twice daily Begin with 40 mg orally once daily For both: titrate up to maximum tolerated dose or until heart rate is 50–55 beats/min	Indefinite
Isosorbide mononitrate	Begin with 10 mg orally once daily at bedtime Titrate up to a maximum of 20 mg twice daily; maintain systolic arterial pressure >90 mmHg	Indefinite
Simvastatin	20 mg/day, which is increased to 40 mg if tolerated and there is no increase in AST/ALT after 2 weeks Child C patients: 10 mg/day, which is titrated to a maximum of 20 mg/day	Indefinite
Endoscopic variceal ligation	Sessions to be repeated every 2–4 weeks	Until variceal obliteration has been achieved (usually <5 sessions are needed)

AST/ALT, aspartate aminotransferase/alanine aminotransferase.

function, and has shown to improve survival after variceal bleeding.

Endoscopic Therapy

Endoscopic therapy is aimed at eradicating varices. This locoregional treatment has no beneficial effect in decreasing portal pressure. The two techniques that have been more extensively used are endoscopic injection sclerotherapy (EIS) and endoscopic variceal ligation with elastic bands (EVL). The latter has proven to be superior to EIS [18,19], allowing an effective reduction in the risk of rebleeding with less frequent and less severe adverse events, as well as achieving eradication with a lower number of sessions [18]. Moreover, EIS increased the HVPG in some studies. Because of these drawbacks, EIS has been superseded by EVL, which is currently the endoscopic treatment of choice [8]. Nonetheless, EVL does not confer any survival benefit as compared with EIS. EVL has been compared with NSBB + ISMN in four randomized controlled trials (RCTs) [20–23], with controversial results. A meta-analysis of the studies showed significant heterogeneity [24], but the two treatment modalities were comparable in terms of preventing rebleeding and complications. However, long term follow-up [25] of the study initially reporting superiority of EVL in preventing rebleeding [21] showed that the combination of nadolol + ISMN enhanced long term survival, suggesting that EVL alone should not be used in these patients.

Other studies have evaluated the combined use of EIS plus EVL versus either treatment alone. A meta-analysis of these studies has shown that this combined approach does not reduce rebleeding or mortality, but marginally increases the rate of complications [26], suggesting that there is no indication for its use.

Lifelong endoscopic follow-up is indicated in patients undergoing endoscopic treatment, since variceal recurrence is common after the initial eradication [8]. Outpatient sessions of EVL are carried out under conscious sedation or monitored anesthesia care at 2–4-week intervals until varices are eradicated (or too small to be banded), which is achieved in about 70% of cases following a median of two or three sessions (Figure 6.2). Although EVL is safer than EIS, adverse events are not negligible. The more common adverse events are thoracic pain and dysphagia soon after the procedure, and post-banding esophageal ulcers (9%) that may cause bleeding in about 3–5% of cases (Figure 6.3).

Combination of Endoscopic Variceal Ligation and Non-Selective Beta-Blockers: Current Standard Therapy

Based on meta-analyses of published data [27], current guidelines and expert recommendations [8,28] suggest combination of EVL plus NSBBs as the best available first line treatment for secondary prophylaxis of variceal bleeding.

Studies comparing EVL plus drug therapy versus EVL alone uniformly showed better outcomes for combined therapy [29,30]. More recently, two RCTs compared the combination of EVL plus drug therapy to pharmacological treatment alone (NSBBs + low dose ISMN) [31,32]. Both trials showed a significantly lower rate of variceal rebleeding with the combination of EVL plus drug therapy. However, the risk of rebleeding from any cause was not significantly decreased, as the lower rebleeding risk from varices with EVL was accompanied by an increased risk of bleeding from post-banding esophageal ulcers and from portal hypertensive gastropathy. Similarly, no survival benefit was noted in these studies and in a meta-analysis [27], suggesting that the additional beneficial effect of combination therapy is rather small and that further studies are needed for confirmation.

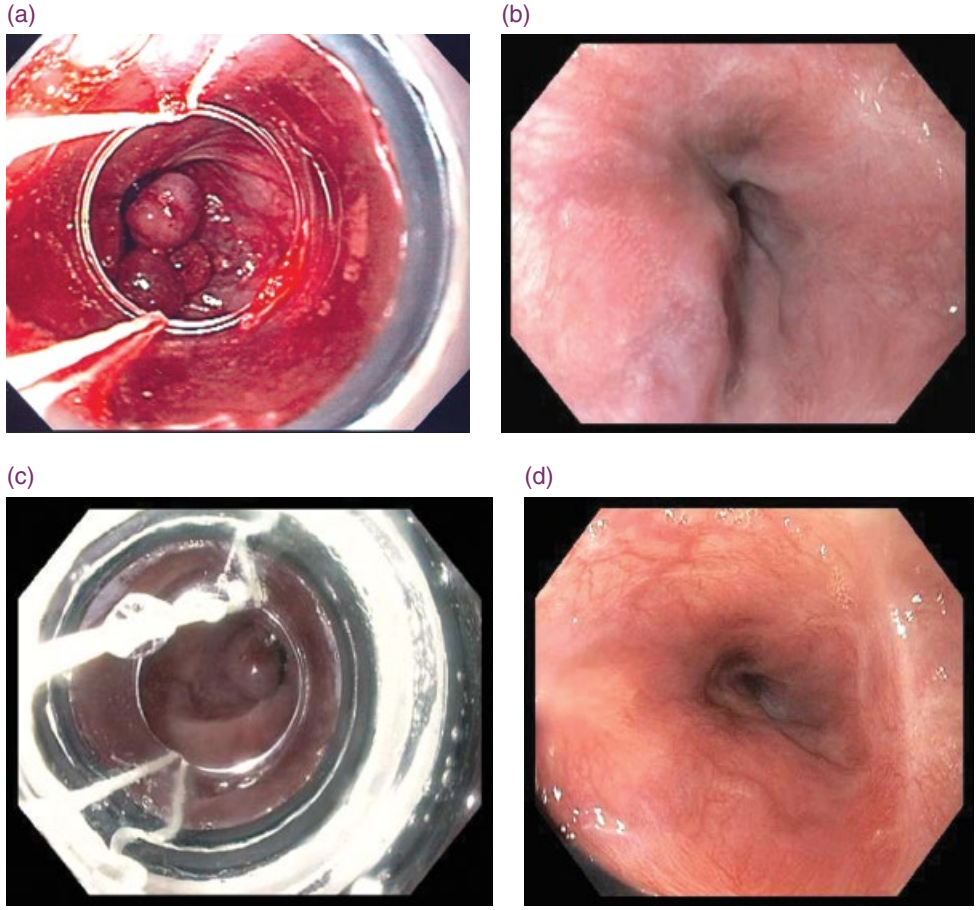

Figure 6.2 (a) Acute variceal bleeding status post band ligation. (b) Residual varices on follow-up endoscopy. (c) Secondary prophylaxis with band ligation (third treatment session). (d) Eradicated varices with post-band ligation scarring.

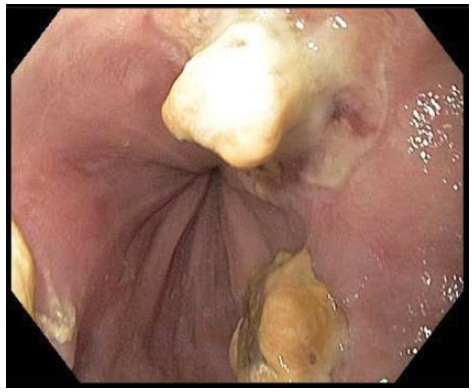

Figure 6.3 Self-limited bleeding from post-banding esophageal ulcers.

Rescue Therapy when Standard Treatment Fails

Transjugular Intrahepatic Portosystemic Shunts

In patients who rebleed despite being on state of the art medical and endoscopic treatment, TIPS is the first option. TIPS is a "calibrated" shunt [33], designed to decompress the portal system to prevent rebleeding and other complications of portal hypertension [34] while attempting to maintain sufficient liver perfusion so as not to cause severe hepatic encephalopathy.

TIPS is carried out by creating a shunt between the right hepatic vein and the right branch of the portal vein using minimally invasive interventional radiology techniques, which avoids the complications of surgery [33]. When using polytetrafluoroethylene (PTFE) covered stents, the rate of primary unassisted patency with TIPS is comparable to that of surgical shunts [35,36].

TIPS is highly effective in reducing the risk of rebleeding, with rebleeding rates of 9–23% in published series (including patients treated using the old bare stents), and is superior to both endoscopic and pharmacological therapy (NSBB + ISMN) for the prevention of rebleeding [37,38]. TIPS is also highly effective in decreasing the risk of bleeding from portal hypertensive gastropathy, as well as in reducing the risk of ascites, spontaneous bacterial peritonitis, and hepatorenal syndrome. However, these beneficial effects are in part counterbalanced by an increase in the risk of hepatic encephalopathy, and TIPS does not provide a clear-cut survival benefit. These findings are mostly derived from initial studies using bare stents, and should be revised in new studies using PTFE covered stents that are more effective in preventing complications from portal hypertension and show much lower obstruction and reintervention rates [35,36], together with trends for less hepatic encephalopathy and improved survival [39,40].

Encephalopathy is more likely in patients over 65 years of age, as well as in those receiving large diameter TIPS (e.g., 12 mm in diameter) that causes total shunting of portal blood flow and an excessive drop in the portal pressure gradient. From a hemodynamic point of view, the optimal TIPS should decrease the portacaval pressure gradient slightly below 12 mmHg (which confers absolute protection from the risk of rebleeding), but not below 9–10 mmHg (which is associated with an increased risk of hepatic encephalopathy). In practice, however, it is difficult to tailor the decrease in portacaval pressure gradient very accurately. About 60–75% of patients may have an adequate decrease in portal pressure with an 8 mm shunt, and about 90% with a 10 mm shunt. Larger shunts are very rarely required. If the portacaval pressure gradient is still above 12 mmHg after TIPS, the administration of propranolol achieves an appropriate final reduction in portal pressure in the majority of patients [41].

Surgical Shunts

In well compensated, Child–Pugh class A patients, shunt surgery is a possible alternative, with comparable outcomes relative to TIPS [42]. The use of surgical shunts has rapidly declined because of limited availability of surgeons with expertise in this type of surgery.

Special Situations

The above recommendations are adequate as a starting point for most patients surviving an episode of variceal bleeding. However, the presence of high risk factors poses the question of whether patients in special high risk situations (see Table 6.1) should receive the same treatment as the more usual patient with a lower risk of failure and death. There is limited objective evidence in such high risk situations and, therefore, the strength of the recommendations is weaker than that for the current standard of care. Nevertheless, as these special situations are quite frequent in clinical practice, potential new approaches that may improve the outcomes of standard therapy are now highlighted.

Hepatic Venous Pressure Gradient Guided Therapy

As previously stated, the pharmacological reduction of HVPG to ≤12 mmHg or by ≥20% of the baseline value nearly abolishes

the risk of rebleeding and significantly reduces mortality [43]. In patients with a good hemodynamic response to NSBBs alone ("responders"), the rebleeding risk is as low as that of patients treated with TIPS [44], so that these patients probably do not require the addition of EVL, a combination that might even result in an increase in adverse events. It should be noted, however, that a portion of patients will lose the hemodynamic response over time, especially with clinical deterioration (signaled by the appearance of new complications from portal hypertension). On the other hand, it is largely unknown whether patients with an insufficient hemodynamic response to pharmacological therapy ("non-responders"), who are also at higher risk of rebleeding (46–65% in a recent survey [44]), would benefit from alternative treatments. The available evidence relies on only a few studies [14,31]. In one study, non-responders to NSBB ± ISMN were referred to EVL [14]; despite the change in therapy, non-responders showed an extremely high rate of rebleeding (87%). In an RCT comparing NSBB + ISMN versus NSBB + ISMN + EVL, the rebleeding rate was similar in non-responders treated only with drug therapy compared with those who also received EVL, suggesting no added benefit from the inclusion of EVL. In addition, current recommended therapy already includes both pharmacological and endoscopic treatments, so other more aggressive therapies, such as TIPS, might be needed in non-responders.

Pre-Emptive TIPS

The potential use of pre-emptive TIPS in secondary prophylaxis of variceal bleeding is increasingly being considered, since the same approach has been shown to be highly effective in the management of acute variceal bleeding in high risk patients [39,45]. However, there are still no randomized trials evaluating pre-emptive TIPS in any high risk situation. The only evidence consistent with its use in these circumstances is the study by Gonzalez et al. [46] in which high risk patients, identified by the total lack of hemodynamic response to NSBBs (<10% decrease in HVPG), received TIPS, while good responders received only NSBBs, and intermediate responders (decrease in HVPG >10% but <20% of baseline value) received NSBB + EVL. The study showed that high risk null responders treated with TIPS fared as well in terms of rebleeding and death relative to the low risk hemodynamic responders [46]. TIPS has not been evaluated in other high risk scenarios, but it is conceivable that it could be a good alternative in the prevention of rebleeding in patients with ascites. These patients could benefit from TIPS with regard to both rebleeding and ascites. Until randomized clinical trials are available, the decision to use pre-emptive TIPS in high risk patients should be made on an individual basis. Clinicians should take into consideration other factors, such as whether the patient is a candidate for liver transplantation, as well as the age of the patient since those over 65 years may have too high a risk of hepatic encephalopathy.

Novel Drug Therapies

Carvedilol is an NSBB with intrinsic anti-alpha-adrenergic activity that has a greater portal pressure reducing effect than other NSBBs [47,48], alone or in combination with ISMN [49,50]. The portal hypotensive effect of carvedilol is especially evident in patients with advanced liver failure, and can be achieved with low doses (6.25–12.5 mg/day) that usually do not cause systemic hypotension and are well tolerated [48,49,51,52]. However, there is limited experience with the use of carvedilol in patients with ascites, in whom there is the concern that the treatment will have potentially negative consequences on sodium retention and renal function.

These factors should be carefully evaluated before making specific recommendations on the use of carvedilol in such patients. The same holds true for another drug combination, nadolol (NSBB) and prazosin (anti-alpha-adrenergic agent) [53].

Another promising approach currently being evaluated in a large RCT is whether the addition of simvastatin (20–40 mg/day) can improve the results of treatment with NSBB and EVL. The rationale for this approach comes from several studies demonstrating that statins improve intrahepatic endothelial dysfunction and lower hepatic vascular resistance in experimental cirrhosis [54,55]. Statins are associated with increased intrahepatic nitric oxide availability, presumably through an increased expression of the transcription factor KLF2 and the ensuing overexpression of endothelial nitric oxide synthase (eNOS), and through enhanced eNOS phosphorylation and activity [56]. In addition, simvastatin has been proven to decrease HVPG in patients with cirrhosis [57,58]. The effect is additive to that of propranolol and is accompanied by improved quantitative liver function [58].

Gastric Varices

Gastric varices are classified in two categories, depending on whether these are in continuity with esophageal varices (gastroesophageal varices (GOVs)) or if they occur in the absence of esophageal varices (isolated gastric varices (IGVs)). GOVs are further subdivided into GOV1, which are considered an extension of esophageal varices along the lesser curve of the stomach (cardial varices), and GOV2, which are esophagogastric varices that extend into the fundus. IGVs are subclassified as occurring in the fundus (IGV1) or elsewhere in the stomach (IGV2) [59]. IGVs are more frequent in patients with prehepatic portal hypertension than in patients with cirrhosis. Patency of the splenic and portal vein should be formally investigated in any patient found to have gastric varices [59,60].

In western countries, GOV1 are treated in the same way as esophageal varices, and separate considerations are given to fundal varices (GOV2 and IGV1) [8]. These differ from esophageal varices in that they are less prone to bleed, but may bleed at relatively low HVPG values, close to the threshold value of 12 mmHg and sometimes even lower. These differential aspects likely reflect the fact that gastric varices typically drain in large splenorenal collaterals (usually associated with less marked increases in portal pressure) and that they may be much larger than esophageal varices (and therefore may reach high variceal wall tension at relatively low portal pressure).

The most important differential aspect in the treatment of gastric varices is that EVL is not an adequate technique (Figure 6.4). In patients with gastric varices, endoscopic variceal obturation using tissue adhesives (cyanoacrylate) has been proven effective [61]. Some centers have used successfully intravariceal thrombin injection for this purpose [61]. These techniques are not devoid of risk, and adverse events include thrombosis

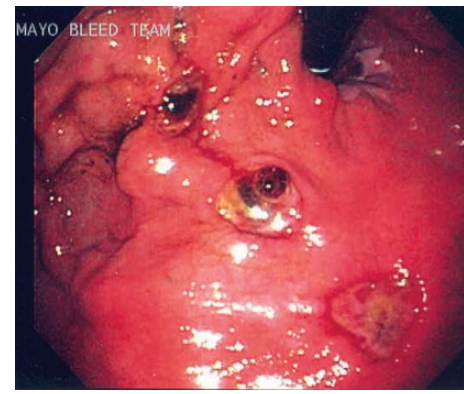

Figure 6.4 Significant bleeding from post-banding ulcers involving fundal varices.

extending to the portal vein, pulmonary embolism, and systemic embolism (e.g., stroke) in patients with intracardiac shunts. Gastric variceal obturation is usually performed during the acute bleeding episode in conjunction with vasoactive therapy, such as terlipressin, somatostatin, or a somatostatin analog. After bleeding has been controlled, the patient is started on an NSBB [61]. There is no consensus on whether further sessions of variceal obturation are required in terms of secondary prophylaxis.

Since gastric variceal bleeding is relatively infrequent, conclusions have to be drawn from small studies in a markedly heterogeneous population [61]. Therefore, it is necessary to establish cooperative studies to provide high quality evidence so that firm recommendations can be made.

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7

Refractory Variceal Bleeding: When First Endoscopy Fails, What Next?

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Introduction

Acute variceal bleeding (AVB) is the most severe and life threatening complication of portal hypertension. Intensive care management, together with the use of combination treatment with endoscopic therapy, vasoactive drugs, and antibiotics, has been able to reduce the 6-week mortality from AVB to about 15% [1]. Current recommendations for AVB entail the combination of a pharmacological vasoactive agent (e.g., terlipressin, somatostatin, somatostatin analog) and endoscopic treatment (e.g., band ligation, sclerotherapy) [2]. Mortality from AVB can occur due to hemodynamic instability and also from complications related to liver insufficiency that require correction of hypovolemic shock, prevention of bacterial infections, and management of hepatic decompensation and renal failure.

Despite standard therapy, up to 10–20% patients present with refractory variceal bleeding and require further intensive management. Mortality after early rebleeding varies between 30% and 50% and accounts for 90% of deaths related to AVB [3,4]. Inability to control bleeding within the first 5 days is considered treatment failure and requires a change in management [2]. This chapter reviews management strategies available if standard therapy (pharmacological plus endoscopic treatment) fails to control bleeding.

Rescue Therapies

Second Endoscopic Treatment

Rebleeding during the first 5 days, if mild and without hemodynamic instability, can be managed by a second endoscopic attempt [2]. This is especially true when the initial endoscopic treatment was not performed under the best circumstances nor by an experienced endoscopist. However, if the patient is hemodynamically unstable or the second endoscopic attempt fails to control bleeding, local treatments, such as balloon tamponade or self-expandable metal stents, should be used.

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Balloon Tamponade

Since the first description of its use in the 1950s, balloon tamponade still remains a valuable procedure and is highly successful in stopping bleeding from varices. The Sengstaken–Blakemore tube has gastric and esophageal balloons together with a gastric suction port and should be used when hemorrhage is due to esophageal varices [5]. The Linton–Nachlas tube consists of a single gastric balloon and has proven more effective than the Sengstaken–Blakemore tube in the control of fundal variceal bleeding [6]. However, if the Linton–Nachlas tube is not available, compression with the maximally inflated gastric balloon of a Sengstaken–Blakemore tube may be used to control gastric variceal bleeding.

Both devices aim to obtain hemostasis by direct compression of bleeding varices and, in experienced hands, are very effective in achieving hemostasis in more than 90% of cases. Within 24 hours, however, the balloon needs to be deflated to minimize pressure tissue necrosis, and that time point represents a critical moment since in about half of patients hemorrhage will recur [7]. Major adverse events (AEs) are commonly associated with inadvertent inflation of the gastric balloon in the esophagus and, unfortunately, this situation is not infrequent. Indeed, fatal AEs (e.g., esophageal rupture) has been reported in 6–20% of patients [8] and the incidence of AEs increases with inexperience [9].

The use of balloon tamponade should be considered as a temporary "bridge" for a maximum of 24 hours [2] until definitive treatment can be performed, and should be placed by skilled and experienced personnel in the intensive care unit.

Self-Expandable Metal Stents

Self-expandable metal stents (SEMSs) are an alternative method to balloon tamponade that compress varices in the lower esophagus to control bleeding [10].

The SX-Ella Danis stent (Ella-CS, Hradec Kralove, Czech Republic) is a covered SEMS dedicated for esophageal variceal tamponade that can be easily placed and removed at endoscopy. The stent can be left in place for up to 14 days. A few uncontrolled trials have evaluated the role of the SX-Ella Danis stent in massive ongoing bleeding [10] or in the setting of active bleeding despite previous therapy [11], and demonstrated that the stent migration rate is low, the technique is safe with a very low rate of AEs, and the efficacy is over 85% for securing hemostasis. A preliminary analysis of a multicenter randomized clinical trial comparing SEMSs to balloon tamponade in refractory esophageal variceal bleeding suggests that SEMSs are at least as effective but safer than balloon tamponade in this setting [12]. Further evidence based data will likely refine and support the role of SEMS in the treatment of refractory variceal bleeding.

Shunting Procedures

Once hemodynamic stability is achieved with either balloon tamponade or SEMS placement, definitive treatment should be performed. Shunting procedures are most effective and represent the gold standard therapy for refractory bleeding.

Surgical Shunt

Although not used as frequently as in previous decades due to the development of less invasive techniques, the use of surgical shunts still represents a valuable treatment strategy in select cases. Nowadays, the main indication for a surgical shunt involves the rare situation in which transjugular intrahepatic portosystemic shunt (TIPS) placement is technically unfeasible (e.g., thrombosis with cavernous transformation of intrahepatic portal vein

branches) and the patient is a good surgical risk (Child–Pugh class A cirrhosis) [2].

Briefly, the surgical shunt consists of diverting blood flow from the portal venous axis to the inferior vena cava, bypassing the liver (portacaval shunt), or more selectively in an attempt to preserve portal blood flow (distal splenorenal shunt and small diameter portacaval H-graft shunt), although selectivity is commonly lost with time. Despite achieving hemostasis in the vast majority of patients, a high rate of complications, such as hepatic encephalopathy and procedure related mortality when performed on an emergency basis in very ill patients [8,13], is the main reason for the scant use of surgical shunts nowadays.

Transjugular Intrahepatic Portosystemic Shunt

When placed as rescue therapy for uncontrolled gastric or esophageal variceal bleeding, TIPS is successful in over 95% of cases [14,15]. With the use of covered expandable polytetrafluoroethylene (e-PTFE) stents as opposed to bare stents, rates of shunt dysfunction, clinical relapse, and the need for reintervention have significantly diminished. Thus, e-PTFE covered stents are currently the preferred stents for use during TIPS placement.

However, the outcome of patients needing a rescue emergency TIPS remains poor (30–50% mortality) [8,16,17]. The long term survival depends on the severity of the underlying liver disease and on the complications associated with uncontrolled hemorrhage, especially renal failure and superimposed bacterial infections, rather than on the variceal bleeding per se. The poor outcome of patients who fail initial treatment and require rescue therapy makes it mandatory to identify such patients, with the aim of testing more aggressive approaches that can prevent treatment failure and, thus, favorably alter patient outcome.

Balloon-Occluded Retrograde Transvenous Obliteration

Balloon-occluded retrograde transvenous obliteration (BRTO) can successfully obliterate cardiofundal varices in patients with spontaneous portosystemic (gastrorenal or splenorenal) shunts through the inflation of a balloon catheter into the shunt followed by injection of a sclerosing agent into the gastric varices. Although high quality trials are still needed, there is evidence reporting the efficacy of BRTO in the management of acute gastric variceal bleeding. A small study of 15 patients with acute cardiofundal variceal bleeding and gastrorenal shunts compared one cohort of eight patients treated with BRTO versus another cohort of seven patients treated with TIPS [18]. There were no differences between the two strategies in terms of rates of hemostasis, rebleeding, hepatic encephalopathy, and survival.

Although further evidence is clearly needed, BRTO may be an alternative in patients who are not candidates for TIPS, such as those with recurrent hepatic encephalopathy.

High Risk Patients: Strategies to Prevent Rebleeding

The identification of factors associated with a poor outcome and high risk of treatment failure using current standard of care is a strategy that could help to individualize treatment and, therefore, improve the outcome of patients with cirrhosis and acute variceal bleeding. Predictors of prognosis include the Child–Pugh class and score, aspartate aminotransferase (AST) levels, shock on admission, presence of portal vein thrombosis, presence of hepatocellular carcinoma, active bleeding at endoscopy on admission, hepatic venous pressure gradient (HVPG) ≥20 mmHg, and a high model for

end-stage liver disease (MELD) score [19–25]. Most of these indicators do not have appropriate external validation and are not systematically used, and studies on the accurate identification of high risk patients are needed to help individualize treatment. Nevertheless, some of these criteria have been proposed already to select high risk patients and, thus far, two strategies are recommended for these patients: intensification of pharmacological therapy and pre-emptive TIPS.

Pharmacological Therapy

The doubling of the somatostatin dose to 500 µg/h produces a bigger reduction in portal pressure than the standard dose of 250 µg/h [26]. These two doses were compared for the treatment of AVB in one randomized controlled trial without finding significant differences in terms of bleeding control or mortality [26]. Active bleeding at endoscopy was the only predictor of failure to control bleeding. In this specific high risk group, somatostatin at 500 µg/h improves bleeding control, reduces blood transfusion needs, and improves survival [27]. Therefore, when active bleeding is found at endoscopy, doubling the somatostatin dose may help to better control bleeding and improve outcome.

A hemodynamic study comparing high dose somatostatin (500 µg/h) with terlipressin showed that the latter further reduced HVPG; a decrease in HVPG of more than 20% was observed in 36% of patients on terlipressin versus 5% of patients on somatostatin [28]. However, specifically designed trials are needed to evaluate whether this higher reduction in HVPG correlates with better efficacy in controlling AVB.

Pre-Emptive TIPS

The TIPS procedure is very effective for the control of acute bleeding and for preventing rebleeding. Therefore, it appears reasonable to place a TIPS in patients at high risk of treatment failure before uncontrolled bleeding or rebleeding occurs. An initial study, selecting high risk patients using the hemodynamic criteria of an HVPG ≥20 mmHg within the first hours after admission, showed that early placement of a TIPS improved survival and reduced treatment failure in comparison with medical and endoscopic treatment [25]. Due to important study limitations (use of sclerotherapy instead of band ligation, discontinuation of vasoactive drugs right after endoscopy, and use of non-covered stents), together with the impracticability of performing HVPG measurement in all patients, the early use of TIPS in this setting was not adopted. These limitations were addressed in a multicenter European randomized controlled trial [29]. In this study, high risk patients were identified based on clinical parameters of Child–Pugh class C (up to 13 points) or class B with active bleeding at endoscopy despite adequate administration of vasoactive agents. Once the AVB episode was controlled, patients were randomized to receive TIPS using e-PTFE covered stents within the first 72 hours after admission or to continue with current standard of care (i.e., non-selective beta-blocker ± isosorbide mononitrate, endoscopic band ligation, and antibiotics). The early TIPS strategy strongly reduced failure to control AVB and rebleeding within 1 year, and reduced mortality without significant changes in the rates of hepatic encephalopathy.

The beneficial effects regarding the early use of TIPS have been confirmed in a retrospective surveillance study from the same centers, which included 75 patients [30].

Preliminary data from two small prospective cohorts using the same high risk criteria have reported similar results in terms of rates of rebleeding, survival, and

hepatic encephalopathy [31,32]. More recently, data form one Parisian center have corroborated the beneficial effect of early TIPS in the prevention of rebleeding in high risk patients [33].

Thus, the available data strongly support the early use of TIPS using e-PTFE covered stents in patients at high risk of treatment failure, because this approach reduces failure to control bleeding and the rebleeding rate (Figure 7.1) [34]. Nonetheless, the main challenge remains that of recognizing more accurate prognostic factors in order to stratify patients according to their real risk. Larger studies are needed to validate high risk criteria and to strengthen the recommendation on the use of early TIPS in this population, as well as to identify new prognostic models that may help refine even more the subgroup of patients who would benefit from early use of TIPS.

Conclusion

Despite the implementation of intensive care management and the use of vasoactive drugs, endoscopic therapy, and antibiotics, mortality from AVB remains significant (up to 20%) and treatment failure occurs in up to 10–20% of patients. A more accurate method of identifying patients with a high likelihood of failure to control bleeding with standard means and who may benefit from alternative treatment measures would improve the overall management and outcome of patients with AVB. Personalized medicine based on risk stratification may lead research studies in the near future.

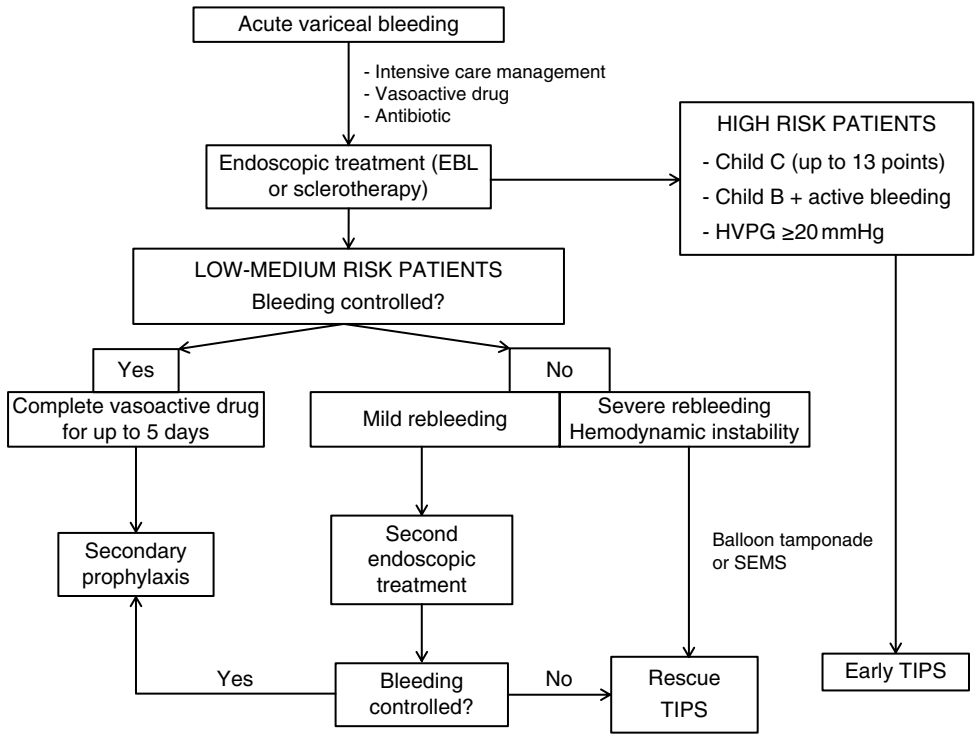

Figure 7.1 Proposed management algorithm for acute variceal bleeding. EBL, esophageal band ligation; HVPG, hepatic venous pressure gradient; SEMS, self-expandable metal stent; TIPS, transjugular intrahepatic portosystemic shunt.

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8

Portal Hypertensive Gastropathy and Gastric Vascular Ectasia

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Introduction

Patients with cirrhosis frequently undergo endoscopy for the diagnosis and/or treatment of varices. Besides the identification of varices, other endoscopic findings related to liver disease include portal hypertensive gastropathy (PHG) and gastric vascular ectasia (GVE). These entities can either remain asymptomatic or result in anemia from gastrointestinal (GI) blood loss. Chronic anemia is present in 21–87% of patients with cirrhosis [1,2], and is due to iron deficiency in most cases [3]. While these conditions may occasionally present acutely, this presentation is relatively infrequent so that other causes of acute GI bleeding should first be ruled out, such as variceal and peptic ulcer hemorrhage [4].

Although PHG and GVE affect the same organ and may present in a similar fashion clinically, it is important to distinguish between the two conditions because they are managed differently (Table 8.1).

Portal Hypertensive Gastropathy

Pathophysiology

Portal hypertension is a sine qua non for the development of PHG. Cirrhosis is the most common cause of portal hypertension in the western world and the available data on PHG relate primarily to cirrhotic patients. The reported prevalence of PHG ranges from 20% to 80%, depending on the severity of liver disease [5,6] and previous therapy with endoscopic band ligation [7–9].

Although portal hypertension plays a central role, the pathophysiological mechanisms underlying PHG have not been completed elucidated. The role of portal hypertension is supported by the correlation between the hepatic venous pressure gradient (HVPG), an estimate of portal pressure, and the presence and severity of PHG [10–12]. Furthermore, patients with PHG have lower systemic and pulmonary vascular resistance, which is associated

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Table 8.1 Comparison of portal hypertensive gastropathy and gastric vascular ectasia.

Characteristic	Portal hypertensive gastropathy	Gastric vascular ectasia
Frequency in liver disease	Relatively common	Uncommon
Presence of portal hypertension	Always	Sometimes
Present in non-hepatic disease	No*	Yes
Lesion distribution in stomach	Mainly proximal stomach	Mainly antrum
Potential gut involvement aside from stomach	Yes†	No
Endoscopic findings	Mosaic mucosal pattern with or without red/brown spots	Angioectatic red spots without background mosaic mucosa
Endoscopic classification	Mild or severe	Linear (watermelon variant) or diffuse
Histological findings	Dilated vessels, no inflammation	Vascular thrombi, fibrohyalinosis, spindle cell proliferation
Mainstay of therapy	Portal pressure reducing agents	Endotherapy
Salvage therapy	TIPS	Antrectomy‡

* Includes portal vein thrombosis as hepatic disease.
† Portal hypertensive enteropathy and colopathy.
‡ In selected patients.
TIPS, transjugular intrahepatic portosystemic shunt.

with portal hypertension, compared with cirrhotic patients without PHG [11]. However, the association between HVPG and PHG is not consistently present in all studies [13,14] and other pathophysiological mechanisms have been proposed, including alteration in gastric mucosal blood flow [14,15], reduction in mucosal prostaglandin production, alteration in microcirculatory responsiveness to nitric oxide [16,17], hypoxia [18,19] and enhanced expression of vascular endothelial growth factor (VEGF) [19].

Portal hypertension leads to increased susceptibility to noxious agents and impaired healing of the gastric mucosa, both in experimental models and in portal hypertensive patients [20–23]. Although an increased prevalence of intestinal metaplasia has been reported in patients with PHG as a consequence of chronic irritation [24], an increased risk in gastric cancer has not been described.

PHG is associated with typical histopathological changes consisting of vascular dilation in the mucosa and submucosa without significant inflammation (Figure 8.1) [25], although biopsies are rarely required for diagnosis. If histological diagnosis becomes necessary, deep biopsies should be obtained since the histopathological features can be patchy and situated predominantly in the submucosa.

Diagnosis

The diagnosis of PHG is typically established at endoscopy. The characteristic findings include a snakeskin mosaic mucosal pattern, with or without red or black-brown spots, localized primarily in the proximal stomach. The extent of the spots overlying the background mosaic mucosa is used to categorize PHG as mild (none to few spots) or severe (many to extensive spots) (Figure 8.2). This simple classification scheme distinguishes between two different risk groups with regard to the incidence of bleeding, which is evidently higher in severe PHG [5,26].

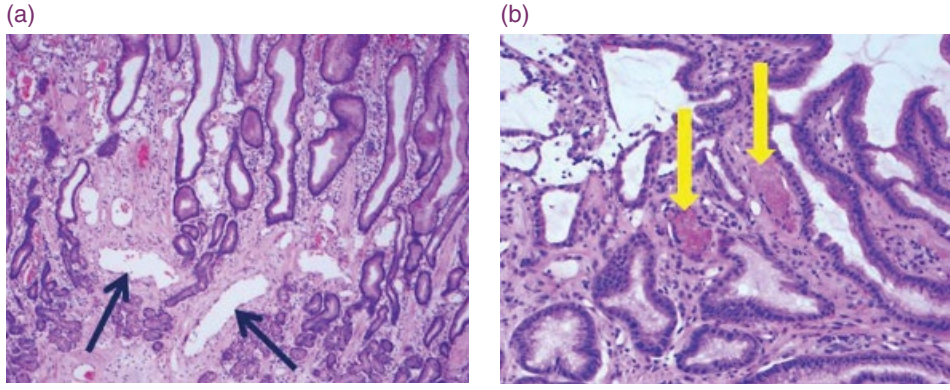

Figure 8.1 (a) Histopathology showing vascular dilation without surrounding inflammation (arrows) in portal hypertensive gastropathy. (b) Histopathology showing typical fibrin thrombi (arrows) in gastric vascular ectasia.

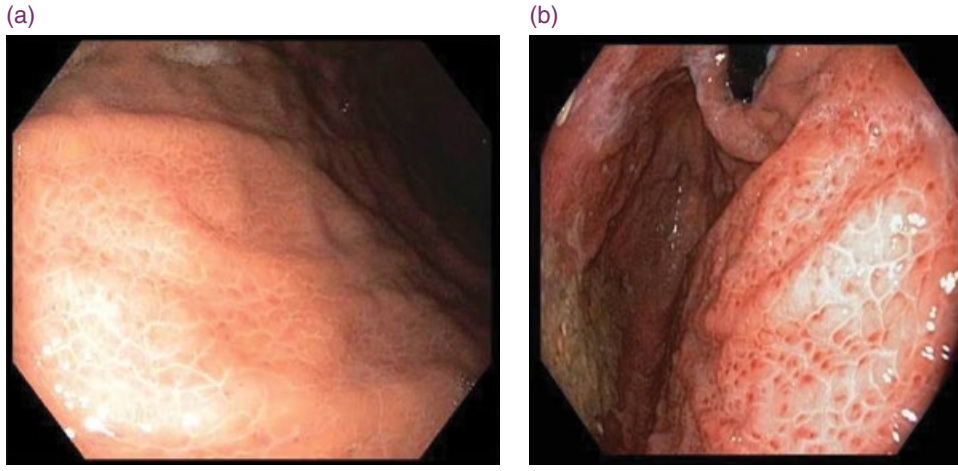

Figure 8.2 (a) Typical mosaic (snakeskin) mucosa without red spots in mild portal hypertensive gastropathy (PHG). (b) Mosaic mucosa with extensive red spots in severe PHG.

Recently, several studies have described polypoid gastric lesions associated with portal hypertension [26–29]. These lesions are more commonly located in the antrum and are histologically distinct from other gastric polyps, with findings of vascular proliferation and increased vascular density [26–28]. They are friable in nature and can excacerbate bleeding in the setting of PHG (Figure 8.3). The effects of portal hypertension can also extend to other parts of the GI tract, such as the small bowel (portal hypertensive enteropathy) [30–37] and colon (portal hypertensive colopathy) [32,38].

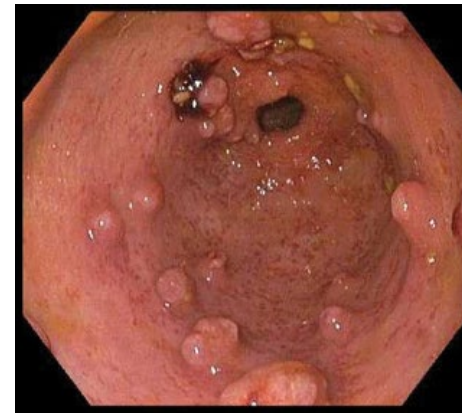

Figure 8.3 Portal hypertensive gastropathy associated gastric polyps.

The diagnosis of PHG primarily relies on endoscopic interpretation of findings and is, therefore, subject to observer variation. Interobserver agreement on the different features of PHG has been evaluated, and the most reliable and best predictive value was obtained when assessing the presence or absence of features instead of grading their severity, which further emphasizes the clinical utility of a simplified classification [26,39]. Of note, the mosaic snakeskin pattern is not specific for PHG. This feature can be found in up to 1.4% of non-cirrhotic patients with conditions such as *Helicobacter pylori* infection and eosinophilic gastritis [40–43].

The use of non-endoscopic modalities for the diagnosis of PHG is mainly anecdotal. Knowledge of the features of PHG during the performance of tests, such as computed tomography (CT) and magnetic resonance imaging (MRI), might be useful in order to avoid unnecessary evaluation in these patients. However, the description of findings associated with PHG – including enhancement of the inner gastric layer in the delayed phase [44], transient gastric perfusion defect sign (in which a lack of perfusion in the arterial phase is observed) [45], and increased spleen volume [46] – is heterogenous. The evaluation of the size of gastroesophageal varices with MRI is not useful for the identification of PHG [47].

Association with Portal Hypertensive Enteropathy and Colopathy

Besides the stomach, congestive mucosal abnormalities due to portal hypertension may be observed in other segments of the GI tract. Lesions that are considered markers of portal hypertensive enteropathy (PHE) include erythema, angioectasias, villous edema, erosions, and varices (Figure 8.4). The extent of small bowel involvement in PHE can be assessed with capsule endoscopy [30,33,35,36,48,49], although its diagnostic utility is limited for gastric lesions [50]. PHE is observed in approximately two thirds of patients with cirrhosis and anemia [36,48,49,51]. In one study involving 60 patients with Child–Pugh class A and B cirrhosis and anemia (hemoglobin <12 g/dL), a variety of lesions were observed in 67% of cases, predominantly distributed in the proximal and mid small bowel [49]. On univariate analysis, PHE was associated with the presence of PHG and increased severity of liver disease, as outlined in previous studies [36,48]. On multivariate analysis, however, only the presence of ascites was an independent predictor of PHE.

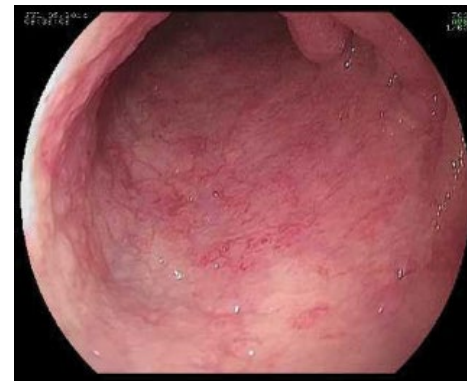

Figure 8.4 Portal hypertensive enteropathy with mucosal edema and ectatic vessels identified during retrograde double balloon enteroscopy.

Portal hypertensive colopathy (PHC) is characterized by the presence of diffuse hyperemia, edema, angioectasias, spontaneous bleeding, and varices (Figure 8.5) [12,38,51,52]. The reported prevalence for PHC ranges from 50% to 65%, depending on the presence or absence of anemia in the study population. Its association with portal hypertensive changes, including PHG and severity of liver disease, is more controversial than in the case of PHE [12,38,51,52].

Relationship of Portal Hypertensive Gastropathy with Variceal Eradication

Endoscopic variceal eradication and beta-blockers are the main pillars of prophylaxis

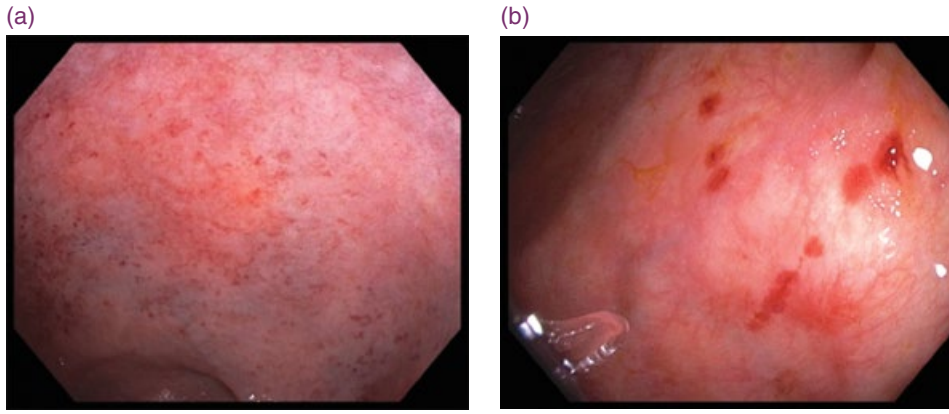

Figure 8.5 (a) Portal hypertensive colopathy with mucosal edema and (b) angioectatic red spots in the transverse colon.

against variceal bleeding. Variceal eradication leads to an increase in portal pressure, which is sustained for a longer period following sclerotherapy compared with endoscopic band ligation (EBL) [53]. An acute increase in portal pressure is associated with functional and structural changes in the gastric mucosa [54].

Although variceal sclerotherapy [9,55–63] and EBL [57,62–64] have been associated with the development or worsening of PHG, the mucosal alterations are usually transient [9,57]. The natural history of these lesions has not been fully elucidated. Some studies suggest no significant impact of endoscopic therapy on the natural history of PHG [8], whereas others report that the development of PHG after variceal eradication follows a more benign course and frequently disappears [9,57]. Nevertheless, patients who have PHG prior to endoscopic therapy may develop worsening lesions that are subject to bleeding during follow-up [9]. Post-endotherapy changes of the mucosa have been described in the small bowel [37], but not in the colon [65,66]. Indeed, the prevalence of PHE increased from 6.6% to 46.7% ($p < 0.001$) in a study of 30 cirrhotic patients who underwent gastric and small bowel biopsies before and after band ligation of varices [37]. At histopathology, an increase in angiogenesis, manifested by a surge in VEGF, vascular ectasia, and blood extravasation, was observed. Furthermore, these findings were clinically relevant, with a decrease in hemoglobin following variceal obliteration.

Management

Patients with PHG but without signs of occult GI bleeding require no specific therapy. These patients are typically diagnosed during screening endoscopy for varices. For primary prophylaxis of large esophageal varices, either EBL or non-cardioselective beta-blockers can be used. In the presence of PHG, especially when severe, prophylaxis with a beta-blocker may be favored unless there is intolerance or contraindication to the medication. As previously mentioned, EBL may worsen or convert PHG from an asymptomatic to symptomatic state in some patients.

In the setting of secondary prophylaxis for variceal bleeding, patients may either develop or demonstrate worsening PHG as a result of repeated EBL sessions. Nevertheless, standard therapy for secondary prophylaxis includes EBL, along with a beta-blocker, which has been shown to reduce the incidence of PHG [64].

Chronic Bleeding

Before establishing PHG as the cause of iron deficiency anemia, other etiologies should be ruled out, particularly when PHG is mild in severity. In addition to iron replacement therapy, specific management of PHG relies on measures that reduce portal pressure. The mainstay of therapy for PHG involves the use of non-selective beta-blockers, as supported by randomized trials (Figure 8.6) [67,68]. Other drugs, such as losartan [69], thalidomide [70], or corticosteroids [71], have been reported for the management of symptomatic PHG, although the evidence supporting their routine use is lacking.

Endoscopic therapy is of limited value in the management of chronic GI blood loss due to PHG. Although a small case series (n = 11) with limited follow-up reported on the utility of argon plasma coagulation (APC), there is under-reporting of studies that show limited to no impact of endotherapy in managing chronic bleeding secondary to PHG. A recent observational report on a small number of patients with bleeding PHC (n = 7) suggested APC to be effective in this setting, although sustained efficacy in the long term remains doubtful [72]. Similarly, the application of hemostatic sprays (Hemospray, Cook Medical, Bloomington, IN, USA) was found to be useful in a small series of patients with acute bleeding from PHG and PHC (n = 4), although it is not likely to be of benefit for the control of chronic blood loss [73].

Patients with ongoing blood loss despite adequate non-selective beta-blockers and iron therapy are considered non-responders and should be managed on an individual basis. Portosystemic shunt therapies, either surgical or through transjugular intrahepatic portosystemic shunt (TIPS) placement, should be considered in patients with severe PHG and frequent blood transfusions. Surgical shunts may be contemplated mainly in patients with reasonable liver function and performance status and in those with non-cirrhotic portal hypertension. Such surgical shunt procedures should be performed by experienced surgeons [74–77]. TIPS placement, the less invasive alternative, has been shown to improve the endoscopic findings of PHG and PHC within 6–12 weeks [78–82] and to decrease transfusion requirements.

Acute Bleeding

Cirrhotic patients who present with acute GI hemorhage should initially be managed as potential variceal bleeders, with the administration of a vasoconstrictor (e.g., somatostatin analog or terlipressin) and antibiotics, maintenance of a restrictive

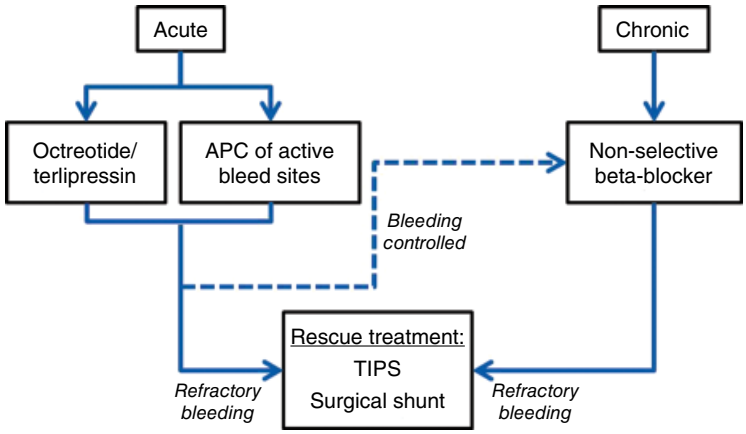

Figure 8.6 Management algorithm for portal hypertensive gastropathy. APC, argon plasma coagulation; TIPS, transjugular intrahepatic portosystemic shunt.

blood transfusion policy, and performance of urgent endoscopy [4,83,84]. Once variceal and other non-variceal bleeding causes (e.g., peptic ulcer) have been excluded, PHG can potentially be identified as the bleeding etiology, particularly if severe and in the presence of stigmata of hemorrhage, such as adherent blood flecks or blood oozing from the congested mucosa. In cases where the endoscopic findings are ambiguous as to the cause of hemorrhage (e.g., small esophageal varices without obvious bleeding stigmata coexisting with severe PHG), the clinical presentation can be helpful in ascertaining the cause of bleeding. A variceal source is more likely in the case of significant hematemesis and hemodynamic instability, whereas acute bleeding from severe PHG is more likely to present as melena without hemorrhagic shock.

The use of a vasoactive agent is recommended for acute hemorrhage from PHG and, per treatment guidelines, should already have been initiated prior to endoscopy in the setting of an acutely bleeding cirrhotic patient. Although the earliest study on medical therapy demonstrated a beneficial effect of beta-blockers for acute bleeding from PHG [85], it is preferable to use a vasoactive agent with a more rapid hypotensive effect on portal pressure. Several studies have demonstrated adequate control of hemorrhage with the use of somatostatin [86], octreotide [86,87], and terlipressin [88] in this setting. Terlipressin is more effective at higher dosage (1 mg/4 h) than lower dosage (0.2 mg/4 h) for acute control of hemorrhage and prevention of rebleeding [88]. In one study, vasopressin offered no advantage over omeprazole, and it should therefore be avoided [87]. Although no trials have specifically evaluated the role of antibiotics in acutely bleeding PHG, it is likely that the benefit observed in the setting of variceal hemorrhage would extend to other types of portal hypertensive bleeding.

There are no established endoscopic therapies for the management of acute bleeding due to PHG. APC may be applied to focal areas of hemorrhage to obtain initial hemostasis. Hemostatic sprays may be more practical when bleeding is diffuse. However, definitive therapy rests primarily on non-endoscopic measures, such as vasoactive agents or shunting procedures (see Figure 8.6).

Therapeutic failure should be defined by the same criteria as in acute variceal bleeding [89]. However, this is a rare event in the setting of PHG and, thus, re-evaluation of the patient is warranted in order to establish whether another source of hemorrhage has been overlooked. In the event that no other source is identified, the patient should be managed in a similar fashion to non-responders with chronic GI bleeding from PHG.

Gastric Vascular Ectasia

Pathophysiology

Gastric vascular ectasia typically causes chronic GI bleeding with iron deficiency anemia. In addition to chronic liver disease, it has been associated with other conditions, such as autoimmune connective tissue disorders, bone marrow transplantation, and chronic renal failure [90–94]. Its prevalence approximates 2% in patients with liver disease and 1% in patients with systemic sclerosis [95], although it has been described in as many as 23% of cases with the latter condition [96].

The pathophysiology of GVE is not completely elucidated. Vasodilating mediators, such as gastrin or prostaglandin E2, have been implicated [97,98]. It has been proposed that liver insufficiency per se (rather than portal hypertension) could lead to the accumulation of vasodilating substances, thereby contributing to the development of GVE [81,99–101]. Other postulated mechanisms, especially when

the disease distribution is limited to the antrum (gastric antral vascular ectasia (GAVE)), are abnormal antral motility [102] and mechanical stress [97], which are supported by the histological finding of fibromuscular hyperplasia [103]. Detailed examination of the microvascular architecture of an antrectomy specimen containing watermelon stomach described ectatic vessels at the surface of the mucosa embedded within an intact capillary bed [104]. It was inferred that repeated high intravascular pressure leads to focal weakening of the capillary structure and dilation once the limits of elastic distensibility are surpassed. The progressive ectatic process, in part, would explain failure to control bleeding long term with endoscopic therapy.

Diagnosis

Gastric vascular ectasia is diagnosed at the time of endoscopy and, unlike PHG, the disease process is limited exclusively to the stomach. Two case series suggest that capsule endoscopy may be more sensitive than conventional endoscopy at detecting GVE due to lack of air insufflation, which could mask the gastric mucosal changes from increased intraluminal pressure. Nevertheless, the use of capsule endoscopy to diagnose GVE remains anecdotal [105,106], and the approach by standard upper endoscopy is preferred due to ease of access and ability to provide therapy.

The angioectatic red spots are typically found in the antrum in the absence of an underlying mosaic mucosal pattern. The arrangement of the red spots in longitudinal stripes is coined watermelon stomach, which is more often seen in patients without liver disease. Often, a cuff of red spots is seen at the cardia in association with GAVE (Figure 8.7). Specific antibody patterns in patients with systemic sclerosis, including the absence of antitopoisomerase I antibodies and the presence of antibodies to RNA polymerase III/speckled antinuclear antibody, have been associated with GAVE [94,95], although this has not been confirmed in all studies [96].

The red spots can also be distributed in a diffuse pattern (diffuse variant GVE) in the antrum, with variable extension toward the more proximal stomach (Figure 8.8). These lesions may be difficult to distinguish from other conditions, such as severe PHG or *Helicobacter pylori* infection [40,41]. GVE of the diffuse variant is more commonly seen in patients with liver disease.

In cases where endoscopic diagnostic differentiation is difficult, biopsies can be

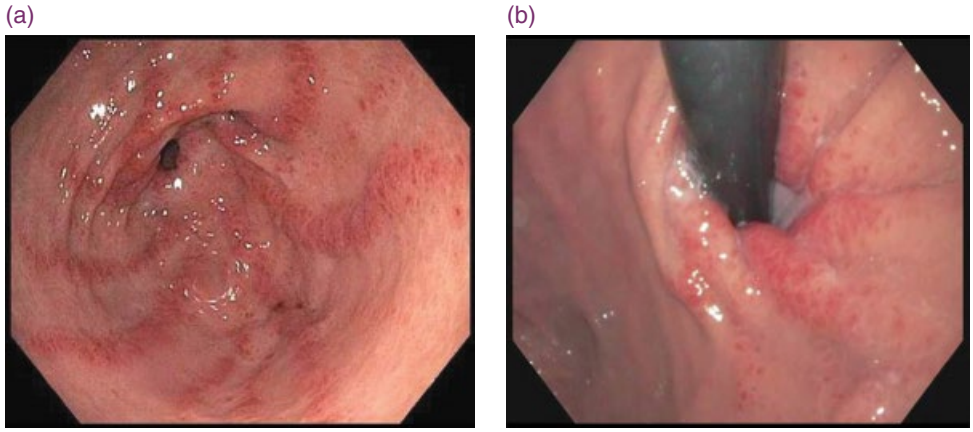

Figure 8.7 (a) Watermelon stomach. (b) Cardia angioectasias associated with watermelon stomach.

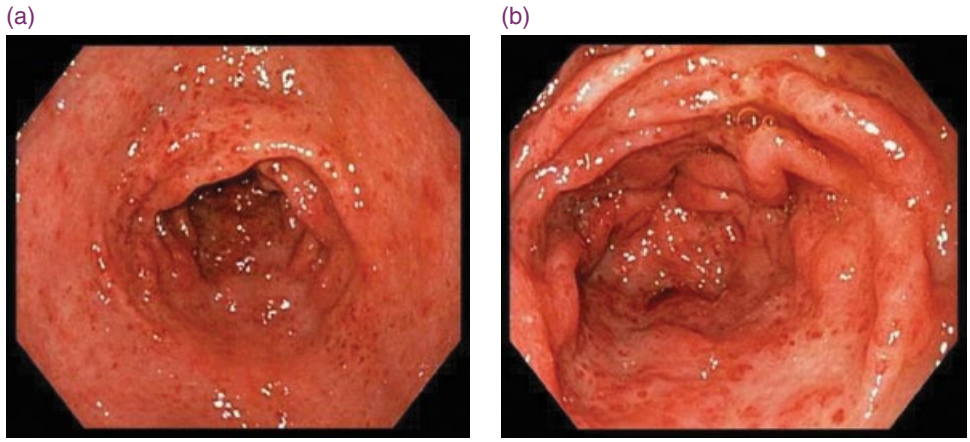

Figure 8.8 (a) Diffuse variant gastric vascular ectasia (GVE). (b) GVE with diffuse red spots in the antrum without background mosaic mucosa.

of benefit, although deep biopsies should be obtained to include the mucosa and submucosa. Histopathological findings of GVE include dilated vessels within the mucosa with regenerative changes, increased lamina propria smooth muscle, and typical fibrin thrombi (see Figure 8.1) [103,107]. The utilization of immunohistochemical staining for platelet markers (e.g., CD61), which specifically stain platelets in the characteristic thrombi, can enhance the utility of histological examination in GVE [108].

Management

The finding of GVE in the absence of bleeding or iron deficiency anemia does not require treatment. Symptomatic GVE is managed primarily by endoscopic means. A trial of drug therapy, such as estrogen/progesterone [109–111], tranexamic acid [112], thalidomide [113], octreotide [114], serotonin antagonist [115], cyclophosphamide [116,117], and corticosteroids [118,119], is generally reserved for GVE that is refractory to endotherapy, although the evidence for pharmacological therapy is limited to case reports. TIPS and beta-blockers are ineffective for the long term prevention of recurrent bleeding from GVE.

Endoscopic treatment of GVE typically requires more than one session to achieve sustained control of bleeding. The goals of endoscopic therapy are to eradicate the vascular lesions, eliminate or minimize the need for blood transfusions, and lengthen the time interval between endoscopic sessions in those who require periodic endotherapy for control of bleeding (Figure 8.9). Although most reports on the use of endotherapy for GVE have focused on thermoablative techniques, cryotherapy and EBL are emerging as first line modalities in selected cases.

Endoscopic Modalities

Argon Plasma Coagulation APC is the most commonly used thermoablative method for the management of GVE (Figure 8.10). APC is preferred over contact thermal modalities, such as bipolar or heat probes, because of ease of use. Discrete lesions can be ablated using focal pulses of energy application, whereas the longitudinal stripes of vascular ectasias (watermelon stomach) are more efficiently treated using the "paint brush" technique (Video 8.1). Suction is applied intermittently to clear the visual field and minimize over-distention of the stomach by argon gas. Aggressive coagulation of lesions close to the pylorus

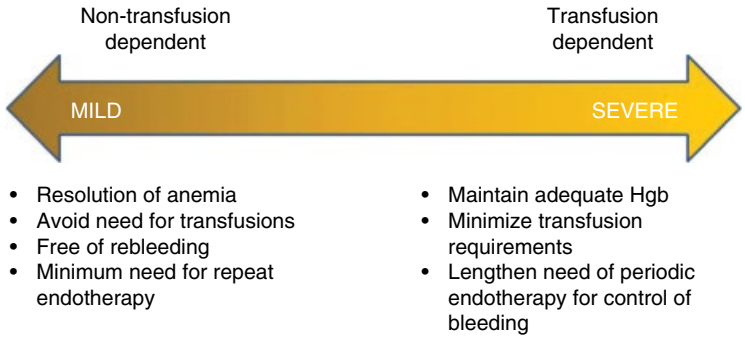

Figure 8.9 Goals of endotherapy for gastric vascular ectasia based on disease severity and transfusion dependency. Hgb, hemoglobin.

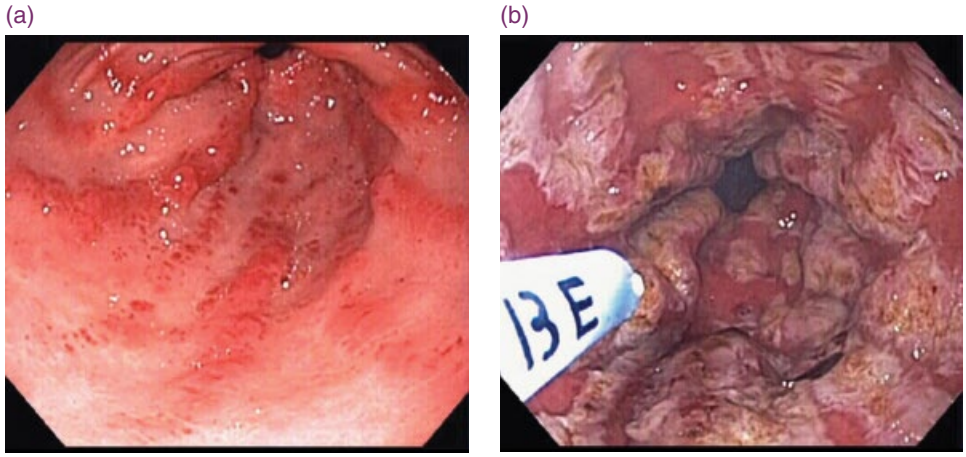

Figure 8.10 Appearnace of watermelon stomach before (a) and after (b) argon plasma coagulation.

may result in pyloric channel stenosis and should be avoided. Ablation using APC, however, can be time consuming if the affected surface area is extensive, as can be seen in diffuse variant GVE. The suggested APC settings are a power of 45 watts and argon flow rate of 1 L/min, although a wide range of treatment settings have been reported (20–80 watts; 0.5–2 L/min flow rate). A proton pump inhibitor is usually prescribed post APC therapy to facilitate healing of the iatrogenic ulcers. The need for repeat therapy is dictated by the clinical response and an initial interval of 4–8 weeks between treatment sessions is reasonable. The treatment interval can be lengthened as the long term objectives of GVE eradication and resolution of symptomatic anemia are achieved.

In the short term, APC has been shown to reduce bleeding and blood transfusion requirements in over 70% of patients with GVE [120–132]. However, the beneficial effects of initial therapy with APC are not sustainable in a significant proportion of patients. In a recent retrospective study encompassing 62 patients with a mean follow-up of 47 months, treatment success following initial APC therapy, defined by an increase in hemoglobin level of 30% above baseline and the resolution of symptoms, was obtained in only 25% of patients [133]. The outcomes may potentially be worse for GVE, since patients with

focal vascular ectasias (angiodysplasias) were also included in the study. Thus, most patients require more than two treatment sessions for long term control of bleeding. Although APC appears effective in both cirrhotic and non-cirrhotic patients with GVE, the latter group tended to require more treatment sessions to achieve a sustained response in one study [129].

APC induced adverse events are uncommon and include iatrogenic ulcer bleeding, antropyloric stricture with gastric outlet obstruction, and perforation. A recognized adverse event of thermal therapy is the formation of hyperplastic/inflammatory polypoid lesions, often with surface erosions, which can aggravate bleeding (Figure 8.11). Whether the use of proton pump inhibitors to promote healing of APC induced ulcers is an inciting factor for the formation of these polypoid lesions is unclear. Due to their friable nature, these polyps usually necessitate resection via snare debulking, with or without submucosal fluid injection (Video 8.2).

Laser Therapy The neodymium-doped yttrium aluminum garnet (Nd:YAG) laser can effectively ablate vascular ectasias and has been shown to reduce rebleeding rates and transfusion requirements in GAVE [90,91,134–140]. Similar to APC, it is a non-contact, probe based technique with reported power settings of 40–90 watts and short pulse durations (0.5–1 seconds). Treatment sessions are generally carried out every 2–4 weeks until eradication of the ectatic lesions has been achieved. Nd:YAG laser ablation is a suitable treatment option, where available, although the technique is rarely used nowadays due to limited availability and high maintenance costs of the laser system.

Radiofrequency Ablation Endoscopic radiofrequency ablation (RFA) is used primarily for the ablation of premalignant mucosal diseases, such as Barrett esophagus, although recent studies suggest RFA may be a viable option for the treatment of GVE. Both over-the-scope (OTS) and through-the-scope (TTS) RFA catheters can be utilized for ablation of GVE. The active component of the OTS RFA catheter (Covidien-Medtronic, Mansfield, MA, USA) consists of a rectangular platform containing an array of electrodes that is mounted at the tip of the endoscope [141,142]. The platform is tiltable to enable contact between the electrodes and the tissue surface. Platforms of various dimensions are available, with the active electrodes ranging from

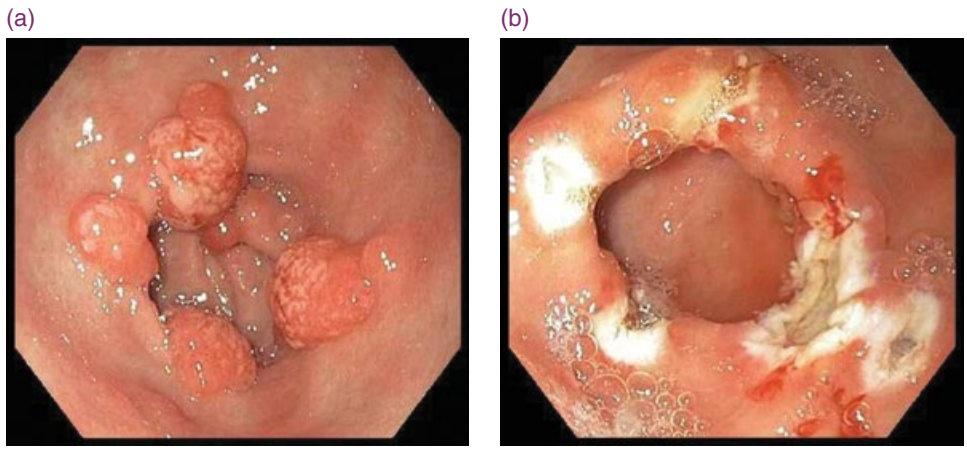

Figure 8.11 (a) Formation of friable hyperplastic polyps following repetitive argon plasma coagulation of gastric vascular ectasia. (b) Snare resection of polyps.

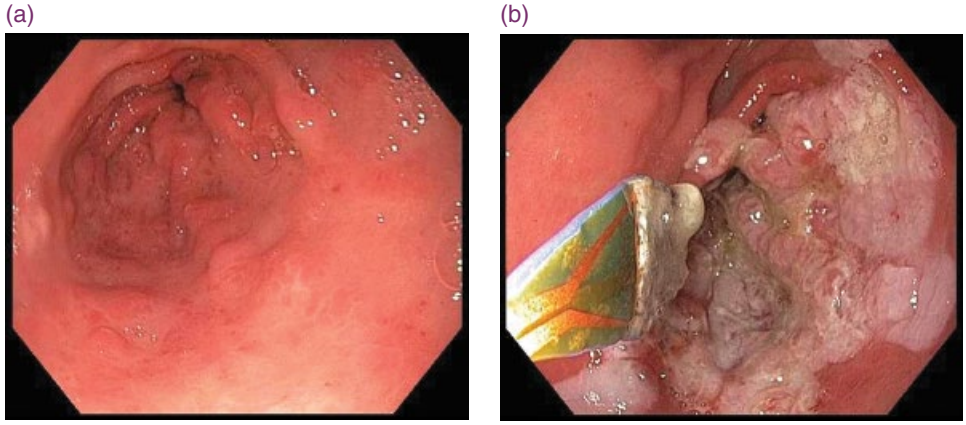

Figure 8.12 (a) Persistent gastric vascular ectasia (GVE) despite multiple applications of argon plasma coagulation. (b) Radiofrequency ablation of GVE using a through-the-scope catheter.

15 to 40 mm in length and from 7.5 to 13 mm in width. Recently, a TTS RFA catheter was introduced that has a smaller treatment surface area (15.7 × 7.5 mm), but which is more convenient to use as it is rotatable and can easily be removed through the working channel of the endoscope for intermittent cleaning of the electrode (Figure 8.12) [143]. Both the OTS and TTS RFA catheters provide a uniform, but relatively superficial, thermal injury using treatment protocols of 2–4 applications per contact site at a default setting of 12 J/cm^2. Following treatment of one area, the catheter is positioned to the adjacent untreated area for ablation, and this process is continued until all the affected areas have been ablated (Video 8.3).

The data on the use of RFA for GVE are limited to a handful of case series and the technique has been applied primarily in patients whose GVE is refractory to other endoscopic modalities. In one prospective, pilot study with limited (6 months) follow-up, 18 of 21 patients (86%) with GAVE refractory to APC became transfusion free after a median of two RFA sessions (range, 1–3 sessions) administered at intervals of 4–6 weeks. Mean hemoglobin increased from 7.8 to 10.2 g/dL in responders (n = 18). Minor adverse events (non-clinically significant bleeding and superficial ulceration) occurred in two patients, which resolved without intervention [142]. As a more serious adverse event, bacteremia causing sepsis following RFA has been described [144].

In contrast to APC, the application of RFA is cumbersome and relatively expensive. Drawbacks of the OTS RFA catheters include potential difficult passage of the devices through the cricopharyngeus, the need for multiple esophageal intubations for removal and cleaning of the electrode, and challenging electrode–tissue contact in some areas, such as the incisura. The availability of the TTS RFA catheter eliminates some of the challenges associated with OTS catheters, although cost may prohibit RFA as initial therapy for GVE. Cost efficacy studies are warranted to assess the role of RFA as primary therapy for GVE or as rescue therapy for refractory cases.

Cryotherapy The application of cryotherapy results in superficial tissue necrosis and ulceration, followed by re-epithelialization of the mucosa [145]. The advantage of cryotherapy is the ability to treat a large surface area by non-contact spray application of a cryogen onto the mucosa (Figure 8.13). Commercially available endoscopic cryotherapy

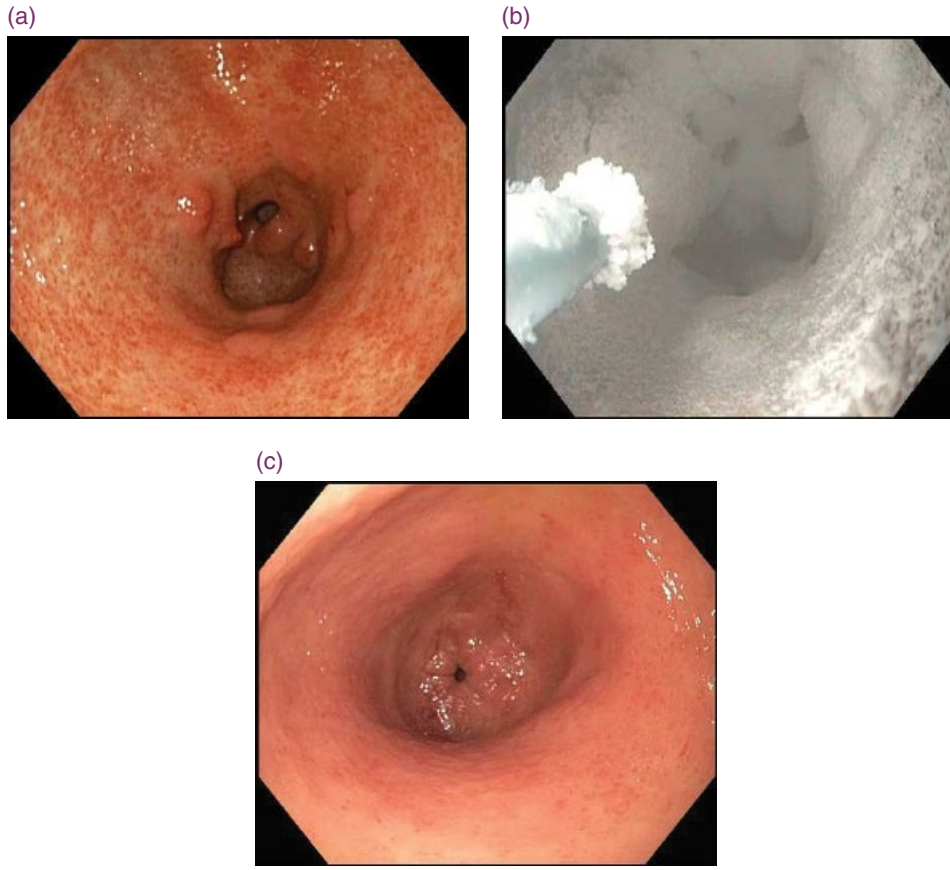

Figure 8.13 (a) Gastric vascular ectasia (GVE), diffuse variant. (b) Cryotherapy. (c) Endoscopic improvement of GVE at the 1-month follow-up.

systems are catheter based and employ either liquid nitrogen (CSA Medical Inc., Lutherville, MD, USA) or compressed carbon dioxide (CO_2) gas (Polar Wand, GI Supply, Camp Hill, PA, USA) as cryogens.

Reports on the utilization of cryotherapy for GVE relate primarily to the CO_2 device. A spray catheter is maintained 1–2 cm away from the targeted mucosa and the cryospray is activated by a foot pedal. The technique is based on the principle of the Joule–Thompson effect, whereby rapid expansion of the CO_2 gas as it exits the catheter results in a rapid drop of the surrounding temperature to –78 °C. A gastric length overtube or a dedicated decompression tube is required to allow escape of the high volume CO_2 gas (~8 L/min) being delivered during the procedure. Application of the cryospray results in whitening (icing) of the mucosal surface, followed by thawing upon termination of spraying (Video 8.4). The cycle of freezing and thawing is typically repeated 3–5 times per treatment session.

In a small pilot study (n = 12), the endoscopic appearance and hemoglobin level improved significantly in half of the transfusion dependent patients following three cryotherapy sessions spaced 3–6 weeks apart. A partial response was obtained in the remaining cases and no treatment related adverse events occurred [146].

Cryotherapy is particularly appealing for the treatment of GVE that is diffuse and extensive due to its ease of use and

ability to rapidly treat a large surface area. Disadvantages of cryotherapy include a cloudy field of view during cryospray and the apparent need for multiple treatment sessions before a sustained hemostatic response is achieved. The best treatment protocol with regard to the optimal cryogen, duration of cryospray, and number of freeze–thaw cycles remains to be determined. Potential adverse events include abdominal distention, treatment induced bleeding, and perforation.

Endoscopic Band Ligation A few studies have reported on the utilization of EBL for the treatment of GVE [147–151]. EBL may be considered for GVE that is refractory to APC or for the nodular/raised-type lesions (Video 8.5). The lesions are suctioned into the band ligation cap until "red-out," followed by band deployment. Bands are placed in a caudad to orad fashion, starting at the prepylorus (Figure 8.14). As many as 12 bands can be placed in a single treatment session. Post-procedural abdominal discomfort and nausea are common but transient, and respond well to liquid analgesics and antiemetics. A liquid diet is recommended for 24 hours post EBL. Follow-up endoscopy is performed in 4–8 weeks after the initial EBL session; post-banding scarring is a typical finding (Figure 8.15).

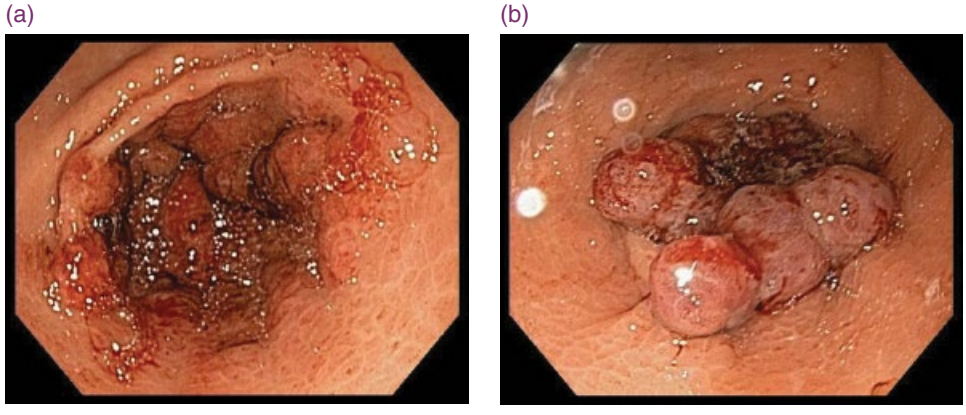

Figure 8.14 (a) Nodular gastric antral vascular ectasia (GAVE). (b) Band ligation of GAVE.

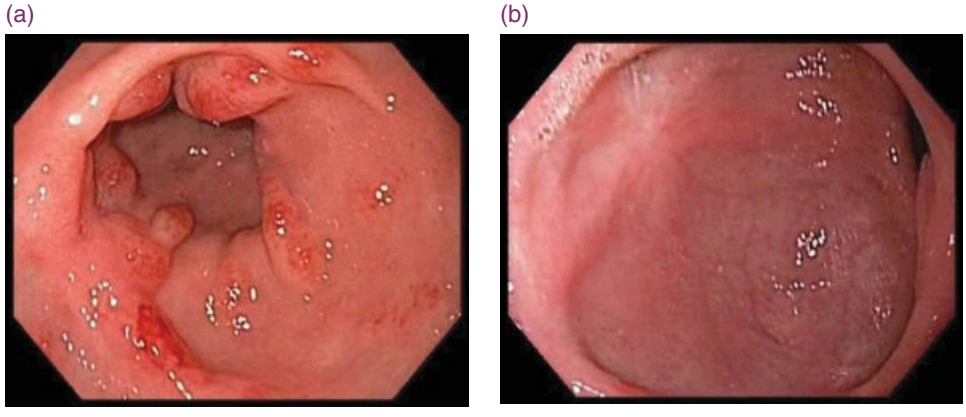

Figure 8.15 (a) Gastric antral vascular ectasia. (b) Post-band ligation scarring at the 6-week follow-up.

Repeat band ligation is dictated by the endoscopic and clinical response.

EBL has been compared with APC, although the assignment of the treatment option was not randomized and approximately half of the patients had failed prior APC. A larger proportion of patients who had EBL were free of rebleeding (56–92% versus 23–32%) [147,151] and required fewer treatment sessions (1.9 versus 4.7; $p = 0.05$) [147] and blood transfusion requirements (–12.7 versus –5.2; $p = 0.02$) [147] than the APC group. These findings require prospective validation.

Miscellaneous Endoscopic Therapies The use of coagulation snares swept over the mucosal surface [152] and endoscopic mucosectomy [153] have been described to be effective in case reports. Sclerotherapy and heat probe ablation are less efficient than the previously described treatment options [154]. A recent systematic review highlighted the various medical and endoscopic therapies that have been applied for the management of GVE, but no recommendations could be made in the absence of robust evidence based data [155]. This review underscored the need for well designed randomized controlled trials to assess the efficacy and adverse events of endotherapy in patients with GVE.

Surgical Therapy

In patients with frequent transfusion requirements and severe bleeding that is refractory to endoscopic and pharmacological therapy, salvage surgery consisting of an antrectomy and Billroth I anastomosis may be considered [156–159], although this should be assessed on an individual basis. In cirrhotic patients, the surgical option is associated with high postoperative morbidity and mortality due to the significant medical comorbidities that usually accompany the disease [160]. There are case reports documenting that GVE is reversible following liver transplantation, but the evidence is insufficient to specifically recommend this therapy for refractory GVE [40,41].

Conclusion

Portal hypertensive gastropathy and GVE are two distinct entities with regard to management, yet they share overlapping features in terms of presentation and association with liver disease. Endoscopic assessment is critical in differentiating between the two conditions. PHG is a consequence of portal hypertension and, therefore, amenable to therapies that target portal pressure, such as beta-blockers and TIPS. In contrast, GVE may or may not be associated with portal hypertension, and the mainstay of treatment is endotherapy. Several endoscopic modalities have been utilized with variable success, and well designed trials are needed to determine the optimal endoscopic technique(s) for the treatment of GVE. Moreover, a better understanding of the pathophysiology of GVE will lead to a rational development of treatment options.

Videos relating to this chapter are:

Video 8.1 Argon plasma coagulation of watermelon stomach.
Video 8.2 Management of polypoid lesions secondary to thermal therapy of gastric vascular ectasia.
Video 8.3 Radiofrequency ablation of gastric vascular ectasia.
Video 8.4 Cryotherapy of diffuse and extensive gastric vascular ectasia.
Video 8.5 Endoscopic band ligation of gastric vascular ectasia.

All videos cited in this book can be found on the companion website at
www.wiley.com/go/plevris/endoscopyinliverdisease

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9

Portal Hypertensive Enteropathy and Obscure Gastrointestinal Bleeding

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Introduction

Although variceal bleeding is the most feared complication of portal hypertension (PH), still carrying significant mortality and morbidity, patients with PH can have chronic intestinal blood loss, often caused by mucosal changes induced by PH [1,2]. The spectrum of portal hypertensive gastrointestinal vasculopathy includes changes in the stomach (portal hypertensive gastropathy (PHG)) and in the colon (portal hypertensive colopathy (PHC)), which can be easily identified by upper endoscopy and colonoscopy, respectively. These changes are often present with a hepatic venous pressure gradient (HVPG) of ≥10 mmHg [2,3]. When the cause of bleeding cannot be ascertained after a negative initial evaluation with bidirectional endoscopy and radiological small bowel imaging, it is defined as obscure gastrointestinal bleeding (OGIB) [4–7]. The latter can be subclassified into two clinical forms: (i) occult OGIB, manifested by the absence of evident bleeding with recurrent iron deficiency anemia and/or a recurrent positive fecal occult blood test; and (ii) overt OGIB, manifested by recurrent passage of visible blood with melena and/or hematochezia [8].

Historically, the diagnostic workup of patients with OGIB has been challenging and time consuming, even more so when there is a background of cirrhosis and PH. In these patients, PH can induce significant mucosal changes in the small bowel, defined as portal hypertensive enteropathy (PHE). PHE is characterized by the development of several red spots (Figure 9.1), patchy mucosal hyperemia (Figure 9.2), diffuse small bowel mucosal edema (so-called herring roe appearance) (Figure 9.3), spontaneous bleeding from the mucosa (Figure 9.4), and/or small bowel varices (Figure 9.5) [9]. Currently, data about PHE are scarce; furthermore, its true prevalence in liver cirrhosis is still unknown and, until recently, the endoscopic features were not well described, mostly due to the limitations imposed by conventional endoscopy. However, the introduction of new endoscopic methods, including capsule endoscopy (CE) and deep enteroscopy (e.g., double balloon enteroscopy), has led to better characterization and more frequent detection of these abnormalities.

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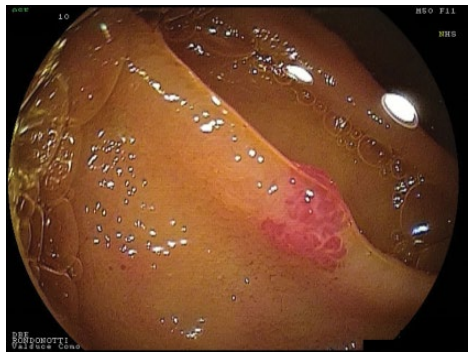

Figure 9.1 Arteriovenous malformation type of lesions seen at double balloon enteroscopy in the jejunum of a patient with portal hypertension.

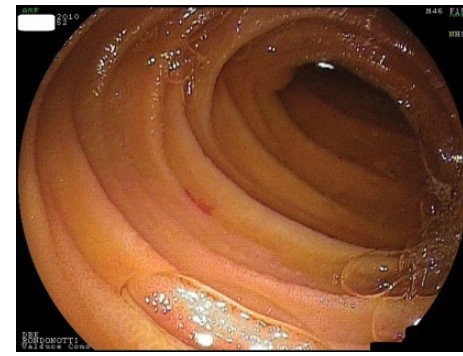

Figure 9.2 Patchy mucosal hyperemia seen during double balloon enteroscopy.

(a) (b)

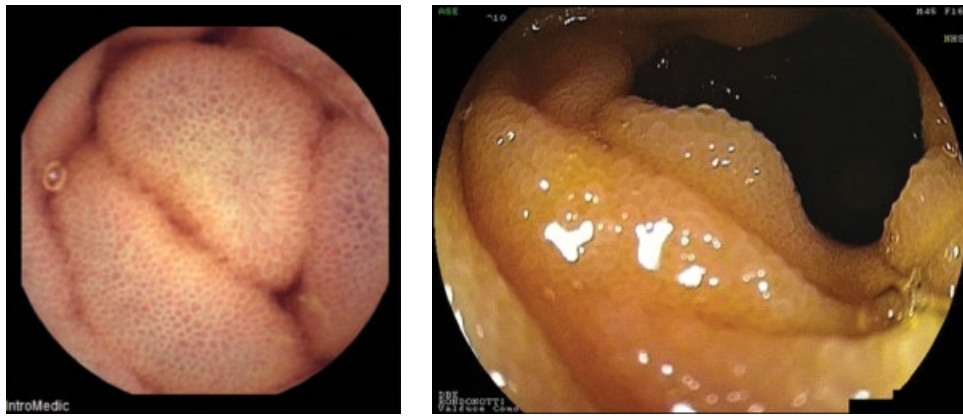

Figure 9.3 "Herring roe" mucosa seen on (a) capsule endoscopy and (b) double balloon enteroscopy.

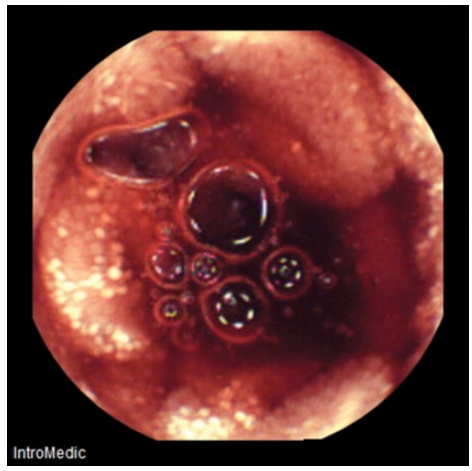

Figure 9.4 Spontaneous bleeding and lymphangiectasic villi in a patient with cirrhosis and portal hypertension.

Nevertheless, whether it is necessary to routinely perform pan-endoscopy in patients with PH (e.g., patients with advanced liver disease with no evidence of OGIB), is still a matter of debate.

Epidemiology of Obscure Gastrointestinal Bleeding in Patients with Portal Hypertension

Iron deficiency anemia is the most common cause of anemia worldwide, occurring in 2–5% of adult men and postmenopausal women in the developed world, and is a common reason for referral

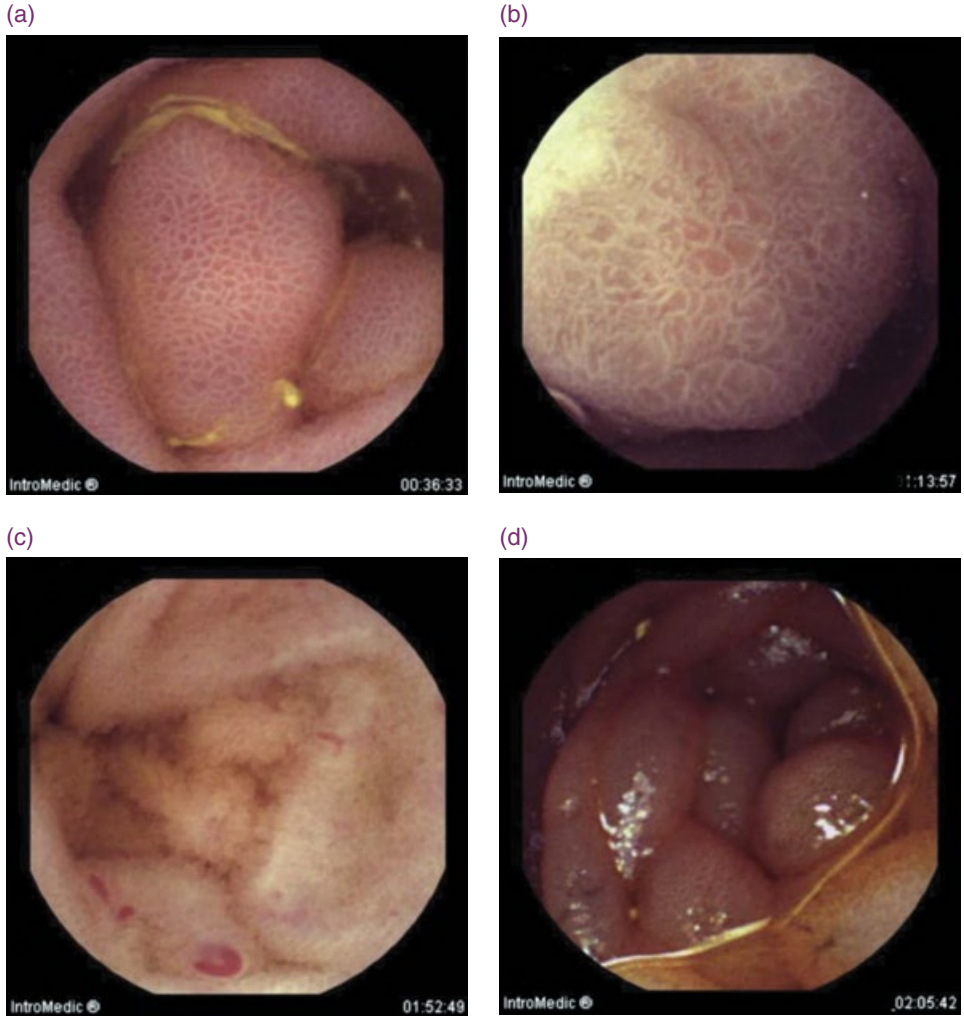

Figure 9.5 (a, b) "Herring roe" mucosa; (c) ectatic villi; and (d) small bowel varices. Source: Koulaouzidis et al. 2012 [9]. Reproduced with permission of Elsevier.

to gastroenterologists (4–13% of referrals) [10,11]. In patients with PH, anemia is found more frequently than in the general population; hence it is estimated that about 75% of patients with cirrhosis exhibit varying degrees of anemia [12]. Anemia in this subgroup of patients is multifactorial. For instance, in severe hepatocellular disease, decreased synthesis of liver produced plasma proteins leads to reduced serum levels of several blood clotting factors [13], whereas splenomegaly may lead to secondary hemolysis [14]. Alcohol – a common etiological factor of chronic liver disease – is "toxic" to the bone marrow [15]. Moreover, patients with high alcohol intake often develop multiple nutritional deficiencies, a common manifestation of which may be anemia caused by vitamin deficiency [16]. Finally, anemia is a recognized complication of the treatment of chronic hepatitis C; in this context, anemia is predominantly caused by drug induced hemolysis in ribavirin based therapies [17]. As a consequence, the natural history of PHE and its incidence,

prevalence, and manifestations, and the factors that influence the involvement of specific intestinal segments have not been firmly established [18].

These issues can explain why an accurate estimation of the prevalence of OGIB in patients with PH is difficult. Additionally, in patients with cirrhosis, bidirectional gastrointestinal endoscopy depicts mild/subtle lesions and the causal relationship of these lesions with anemia – hence the proportion of patients who have OGIB due to small bowel mucosal changes – is often difficult to establish. Until recently, the small bowel was relatively inaccessible and data were limited to anecdotal reports pointing to the small bowel mucosa as a potential source of bleeding in patients with cirrhosis. Correct identification of patients with PH who suffer an episode of OGIB is crucial for their subsequent diagnostic workup and management. When OGIB is suspected in patients with PH, the small bowel becomes the target for further diagnostic procedures [6]. Unfortunately, studies focusing on the small bowel in patients with OGIB in the general population seldom report relevant comorbidities. Nevertheless, in 2010, Akyuz et al. [19] studied 444 patients with cirrhosis and reported that OGIB occurred in about 4.5% of patients with PH. In a retrospective review of 595 patients who underwent CE for OGIB, Sidhu et al. [20] found similar results, that is, 20 patients (3.4%) with established chronic liver disease who presented with OGIB; they confirmed that angiodysplasia was the commonest pathology seen. Timely examination with CE had a positive impact on patient management. Tang et al. [21] in 2004 reported 4/46 patients (8.7%) with small bowel varices of various etiologies diagnosed by CE. Fresh blood adjacent to the varices was documented in three patients.

Small Bowel Evaluation in Patients with Portal Hypertension and Obscure Gastrointestinal Bleeding

Capsule Endoscopy

Gastrointestinal bleeding in patients with advanced liver disease can cause hepatic decompensation and have an impact on mortality. Hence, an early and aggressive diagnostic panenteric workup, including the small bowel, is important if bidirectional endoscopy is negative [22]. However, until just over a decade ago, the small bowel was relatively inaccessible to clinicians [23].

Most of the studies on the mucosal changes seen in PHE are based on examination at upper endoscopy [24], push enteroscopy [25], and retrograde ileoscopy during colonoscopy [26], and therefore included findings only seen in the duodenum, proximal jejunum, and terminal ileum, respectively. These reports estimated the overall prevalence of PHE to be 10–15% [1,27]. With the advent of wireless CE, the prevalence significantly changed, mostly because of its capability to provide clear details of the mucosal surface throughout the small bowel and to identify even tiny or subtle mucosal changes. CE detected mucosal changes compatible with PHE in about two thirds of cirrhotic patients undergoing this examination [28]. CE is non-invasive and performed without medication or air insufflation, thus it is the best suited modality to investigate the state of the small bowel vascular bed in patients with cirrhosis and PH [1].

Wireless CE has a favorable safety profile, especially in patients with comorbidities, such as liver disease, frailty, and/or heart disease [29]. Furthermore, it is more likely to allow inspection of the mucosa of the entire small bowel, even compared with device assisted enteroscopes [23,30]. In patients with cirrhosis and PH, CE has been proved to be feasible

and safe. Akyuz et al. [19] showed that CE in patients with cirrhosis has a comparable completion rate (90.5% versus 83.5%) and a similar retention rate (0% versus 1.4%) compared with non-cirrhotic patients.

No scoring system of prognostic value has been validated to date on the basis of CE findings. A PHE classification was proposed by De Palma et al. [28] in 2005, one of the first groups to study the prevalence of small bowel mucosal abnormalities in PH. They aimed at determining whether these findings are associated with the severity of liver disease, esophageal varices, PHG, PHC, and/or other clinical characteristics. Over a 3-year period, CE was performed in 37 patients with cirrhosis of different etiologies and PH who also had anemia with negative bidirectional endoscopy, and in 34 control patients evaluated for irritable bowel syndrome, within 2 weeks after conventional endoscopic procedures. The incidence of PHE was 68%; interestingly, 10.8% had active bleeding at CE. Mucosal changes were commonly found in cirrhotic patients compared with controls (67.5% versus 0%; $p < 0.001$). Such changes included red spots in 62.2%, angioectasias in 24.3%, and varices in 8.1% of patients. A comparison of patients with and without PHE showed that grade ≥2 esophageal varices, PHG, PHC, and Child–Pugh class C cirrhosis were all significantly associated with PHE, whereas no differences were noted with regard to etiology, gender, and history of variceal hemorrhage.

More recently, Abdelaal et al. [31] proposed a similar classification to evaluate PHE severity. They suggested that PHE related small bowel mucosal changes be classified into four main types; (i) red spots; (ii) angioectasias; (iii) small bowel varices (all of the above vascular type lesions); and (iv) inflammatory like lesions. Subsequently, they attempted to validate this system by using transient elastography, an ultrasound based technology that measures liver stiffness. To this effect, they studied 31 patients with cirrhosis and PH and 29 controls with OGIB. Not surprisingly, they found that mucosal lesions were significantly more common in cirrhotic than in control patients (67.7% versus 6.9%; $p < 0.001$). Small bowel changes in PH were more common in patients with high liver stiffness and/or high Child–Pugh score, large esophageal varices, PHG, and a history of endoscopic variceal sclerotherapy and/or ligation. Furthermore, they found that patients with higher transient elastography values, high Child–Pugh score, larger varices, and prior endoscopic variceal therapy had a significantly higher PHE score.

Riccioni et al. [32] sought to compare the findings of CE with HVPG, platelets <100,000/μL, esophageal/gastric varices, PHG, spleen length >13 cm, portal vein diameter >1.2 cm, and intra-abdominal collaterals in patients with cirrhosis and chronic anemia. Twelve patients (mean age 56.3 years) with PH (Child–Pugh score 5–12) and chronic anemia (mean hemoglobin 9.2 g/dL: range 7–10 g/dL) were submitted to CE. Interestingly, no significant correlation was found between the presence or the stage of small bowel lesions and the level of HVPG, the number of indirect signs of PH, and/or the type of intra-abdominal collaterals. Conversely, in another CE study, Takahashi et al. [33] showed that among all small bowel lesions identified, small bowel edema had the strongest correlation with HVPG (measured within 3 days of CE). The investigators categorized pathology according to its location in the duodenum, jejunum, or ileum. Mucosal edema was evaluated using a four grade CE scoring index. HVPG and edema scores increased with Child–Pugh scores. Red spots and angiodysplasias did not correlate with HVPG.

Similarly, in a retrospective study, Aoyama et al. [22] characterized small bowel lesions depicted by CE in patients with PH with compensated cirrhosis and associated anemia. Small bowel

abnormalities were found in 67% of patients, such as erythema (53%), erosions (17%), angioectasias (15%), small bowel varices (7%), and mucosal or villous edema (7%). Interestingly, most lesions were located in the proximal or middle part of the small bowel. Factors associated with PH related lesions were Child–Pugh score (class B), presence of ascites, and PHG. The authors concluded that CE should be considered in the above subgroup of cirrhotic patients who also show evidence of gastrointestinal blood loss and/or anemia that cannot be attributed to varices or PHG.

With the advent of CE, mucosal changes due to PHE are more frequently recognized in clinical practice, but the exact impact and relevance of these findings is still unclear. In fact, the prevalence of PHE related mucosal lesions in patients with cirrhosis and anemia and in those with cirrhosis without anemia is remarkably similar. Urbain et al. [34] reported that the hemoglobin values were not significantly different when comparing patients with and without small bowel lesions related to PH. Furthermore, small bowel findings, such as active bleeding, occurred in 7–10% of patients with cirrhosis regardless of the presence of anemia, although such data are from a small single center cohort. At the present time, no firm conclusions can be drawn about the definitive role of PHE in the genesis of OGIB in cirrhotic patients.

Ileoscopy, Push Enteroscopy, and Device Assisted Enteroscopy

Prior to the advent of device assisted (single balloon, double balloon, spiral) enteroscopy, conventional push enteroscopes or pediatric colonoscopes were used for per oral enteroscopy, and this significantly limited the ability of clinicians to examine the small bowel beyond the level of the ligament of Treitz. The data on PHE obtained by device assisted enteroscopy are fewer than those obtained with CE. This is partly due to the higher expertise required, and the limited availability and invasiveness of the procedure. Therefore, especially in the western world, device assisted enteroscopy is used more for its therapeutic than diagnostic capabilities [23].

Misra et al. [26], by intubating the terminal ileum of 44 patients with cirrhosis and PH, found that ileal varices and/or PHE in the terminal ileum were present in 36% of cirrhotic patients, but not in a single control patient ($p < 0.01$). Portal hypertensive ileopathy was observed in 39% patients with colopathy and in only 9.5% of patients without colopathy ($p < 0.05$). In 2004, Desai et al. [25] presented case controlled data from 40 consecutive patients with PH and 43 controls (with non-ulcer dyspepsia) who underwent push enteroscopy with jejunal, duodenal, and gastric biopsies. PH jejunopathy was seen in 15% of patients in the PH group but none in the control group. All patients with jejunopathy had PHG and five also had PH duodenopathy. The presence and degree of vascular dilation were similar in both groups.

Higaki et al. [35] compared features from endoscopic small bowel images and biopsy specimens obtained during double balloon enteroscopy of 21 patients with cirrhosis and PH. They classified the endoscopic findings in the small bowel of patients with PH into two categories: villous abnormalities and vascular lesions. Erythema and angioectasias were observed in 24% and 5% of patients, respectively. In 38% of patients, the small bowel mucosa was edematous, and the intestinal villi of these patients were swollen and rounded, resembling herring roe (Figure 9.3). The overall appearance and the prevalence of these findings were similar to those obtained from CE studies. Advanced cirrhosis and the presence of PHG and PHC were associated with PHE changes. Furthermore, patients with the

herring roe appearance had a significantly increased spleen volume and decreased platelet count ($p < 0.05$).

Kodama et al. [36] performed double balloon enteroscopy in 15 patients with PH and 49 controls without liver disease. A total of 24 and 90 antegrade and/or retrograde procedures were performed in PH and control patients, respectively. Fourteen of the PH patients exhibited villous abnormalities, including edema (73%), atrophy (40%), and reddening of the villi (47%). Vascular lesions, such as angioectasia like abnormalities (67%), dilated/proliferated vessels (93%), and varices (7%), were observed in all patients with PH. Definitive or suspected bleeding sources were identified in nine of 13 patients with both PH and OGIB, which was similar to the incidence found in controls with OGIB. Interestingly, the frequency of post-procedure fever (>37.5 °C) was higher in patients with PH in comparison to controls (29% versus 2%; $p < 0.01$). Lastly, Lopez et al. [37] reviewed intraoperative enteroscopy data from 16 consecutive patients referred with occult OGIB in whom upper endoscopy, push enteroscopy, and colonoscopy had failed to identify the source of bleeding. They found the bleeding source in 14/16 patients; PHE and varices were diagnosed in one patient.

Therapy

Pharmacologically mediated regression of PHE lesions in humans is still under investigation. Beta-blocker and/or terlipressin seem to be a reasonable first choice for primary prophylaxis and PHE related OGIB. Animal and human studies have evaluated the effectiveness of sorafenib, losartan, and octreotide [38–43]. In experimental models, increases in portal pressure trigger the production of vascular endothelial growth factor (VEGF) which, in turn, induces endothelial nitric oxide synthase upregulation in the intestinal microcirculation. Inhibition of VEGF signaling reverts splanchnic neovascularization in animals with established PH [43]. Thalidomide is reported to have achieved control of anemia in a patient with PHE [44].

As in esophageal/gastric varices, endoscopic therapy is considered the modality of choice when medical measures fail. Deep enteroscopy, such as double balloon enteroscopy, appears to be the best option to approach a variceal bleeding source in PHE induced OGIB for either thrombin or cyanoacrylate injection [45].

Matsushita et al. [46] aimed to assess the effects of transjugular intrahepatic portosystemic shunt (TIPS) on small bowel mucosal changes detected by CE in cirrhotic patients with PH. They studied 15 cirrhotic patients with PH who underwent CE before and 2 weeks after TIPS. They defined as small bowel mucosal changes mucosal edema, angioectasias, red spots, and/or small bowel varices. They noted that, pre-TIPS, small bowel edema was detected in all patients; following TIPS insertion, small bowel edema, angioectasias, and red spots were attenuated in the majority of patients. Moreover, small bowel varices, as seen in four patients pre-TIPS, disappeared post-TIPS.

In a case series [47], the endoscopic treatment of jejunal varices via device assisted enteroscopy has been reported to be technically feasible and effective. Nevertheless, this approach is cumbersome, time consuming, and, although it can solve the acute variceal bleeding, it cannot reverse the underlying PH. Therefore, systemic therapies (e.g., TIPS) are preferable when available.

Portal Hypertensive Colopathy

Although colonic mucosal changes due to PH can be identified through a routine colonoscopy – and for this reason PHC

should not be considered, by definition, a cause of OGIB – PHC is often overlooked in patients with PH. This may be due to the subtle or patchy nature of PHC. PHC related colonic changes include hemorrhoids, anorectal varices, and more subtle mucosal changes, such as diffuse hyperemia and mucosal edema resembling chronic inflammation, angiodysplasia like lesions, and a severe acute colitis like appearance with spontaneous mucosal bleeding [48].

The prevalence of hemorrhoids in patients with PH varies greatly (20–60%), but seems to be comparable with that observed in age matched controls. On the other hand, anorectal varices are identified more frequently in patients with PH (up to 89.3%), but their prevalence was significantly different from that of the control group in the report by Ghoshal et al. [49]. Similar to the small bowel, all studies highlight the high prevalence of PHC in patients with PH, but do not clarify whether there is a relationship between these abnormalities and clinically relevant parameters, such as the etiology of liver disease, Child–Pugh class, history of variceal bleeding, platelet count, and presence of PHG.

Conclusion

Chronic blood loss is a common feature in cirrhotic patients with PH [50]. Several lesions attributed to PH can cause chronic blood loss and the majority can be easily identified by upper endoscopy and colonoscopy. OGIB in cirrhosis can be due to PHE and/or PHC. To identify PHE, CE is the best diagnostic tool but the exact impact of small bowel lesions is often difficult to establish in the setting of cirrhosis and OGIB; the role of CE is more relevant in ruling out other causes of bleeding than to confirm PHE. Deep enteroscopy has a possible role in cirrhosis only in selected patients in whom causes of upper and lower gastrointestinal bleeding have been excluded, and a definitive source has been identified that can be treated endoscopically.

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10

Endoscopic Management of Upper Gastrointestinal Pathology in the Patient with Liver Disease

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Introduction

Endoscopy plays an important part in the management of patients with liver disease. Apart from its role in the treatment of variceal hemorrhage and portal hypertensive gastropathy, endoscopy aids in the diagnosis and management of various conditions, including Barrett's esophagus, gastroesophageal reflux disease, peptic ulceration, celiac disease, and upper gastrointestinal (GI) malignancy. In this chapter, we highlight the impact of liver disease on the incidence, diagnosis, and endoscopic management of common upper GI pathologies.

Barrett's Esophagus

Prevalence

Barrett's esophagus (BE) is found in 2% of the general adult population and in 3–5% of patients with gastroesophageal reflux disease (GERD) [1,2]. BE has the same prevalence in liver disease patients as in the general population [3,4]. Zaman and colleagues [3] assessed the prevalence of GI pathology in 120 liver transplant candidates in Oregon, USA who were undergoing endoscopic screening and found 2% of them had BE. Tyberg and colleagues have also assessed the prevalence of BE in patients with cirrhosis in New York and found the prevalence to be equivalent to that of the general population at 2–4% [4]. In addition, they found no relationship between the prevalence of BE and the etiology of cirrhosis.

Diagnosis and Surveillance

The 2014 British Society of Gastroenterology (BSG) guidelines define BE on endoscopy as evidence of more than 1 cm of histologically confirmed metaplastic columnar epithelium in the lower esophagus above the esophagogastric junction (Figure 10.1) [5]. Endoscopic screening for BE should be considered in those with chronic GERD symptoms and at least three risk factors, including age >50 years, white race, male sex, and obesity [5].

Endoscopic surveillance of BE requires four-quadrant biopsies every 2 cm within the columnar segment, together with targeted biopsies of any visible lesion. The length of the Barrett segment and the presence of dysplasia are important

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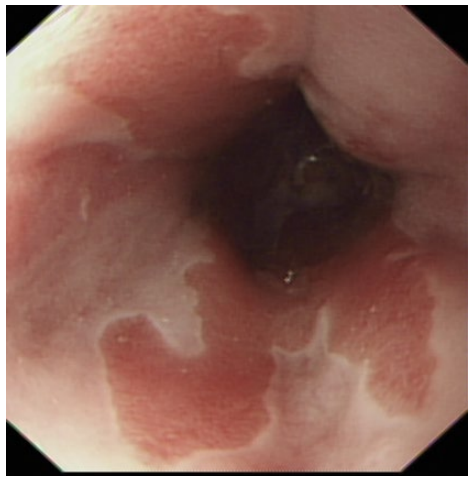


Figure 10.1 White light image of Barrett esophagus.

factors that will influence the timing of repeat endoscopy and therapy.

Diagnosis and surveillance of BE in the setting of cirrhosis is not well studied, and there is a recognized diagnostic challenge in cirrhotic patients with portal hypertension, with or without esophageal varices. These patients are less likely to have surveillance biopsies undertaken because of the perceived higher risk of bleeding and limited life expectancy. In addition, if dysplasia or adenocarcinoma is detected, the risks associated with endoscopic, oncological, or surgical treatment in cirrhotic patients are significant.

The risk of developing adenocarcinoma in patients with BE was reported to be 1.2 per 1000 patients in a Danish study [6]. This incidence was shown to increase to 5.1 per 1000 patients in those with dysplasia. There is some debate about the impact of cirrhosis on the risk of development of esophageal cancer. A French study recognized that cirrhosis and esophageal carcinoma have common etiological factors [7]. In this retrospective study of 958 cases of esophageal carcinoma, only 2.7% of cases were in cirrhotic patients. A large cohort study of 11,605 cirrhotic patients from Denmark suggested no increased risk of esophageal cancer in patients with cirrhosis [8]. However, a smaller case–control study from Italy reported that cirrhosis was associated with an increased risk of esophageal cancer, with an odds ratio of 2.6 [9].

Other Diagnostic Modalities

Image Enhanced Techniques

Chromoendoscopy uses topical dyes to improve the detection of intestinal metaplasia and has been shown to improve the diagnostic yield of dysplasia. Chromoendoscopy has a negative predictive value of 98% for detecting high grade dysplasia [10]. This may have a particular role in identifying dysplasia in patients at risk from multiple repeated biopsies, such as patients with liver disease, with the caveat that further management of identified pathology may itself be problematic. The dyes used in chromoendoscopy include methylene blue, indigo carmine, and acetic acid [5].

Virtual chromoendoscopy includes narrow band imaging (NBI), i-Scan, and Fujinon intelligent chromoendoscopy. NBI has been most widely studied, with a meta-analysis reporting sensitivity and specificity of 96% and 94%, respectively, in BE (Figure 10.2) [11]. Autofluorescence imaging also has been used in conjunction

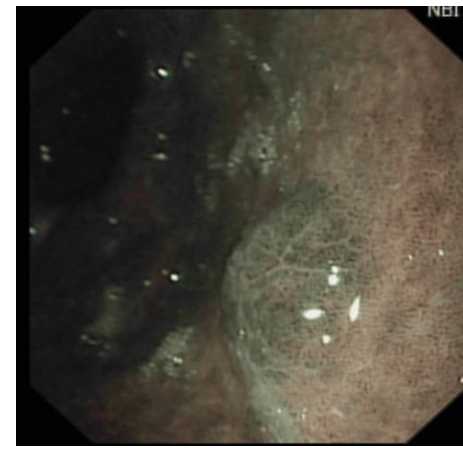


Figure 10.2 Narrow band imaging highlighting a nodular lesion in Barrett esophagus.

with white light endoscopy and NBI as "endoscopic trimodal imaging." Studies suggest there may be a role for the latter in reducing the number of biopsies required when used in low risk patients; however more studies are required before firm recommendations can be made [12].

Although additional data are required, these modalities may be a useful non-biopsy approach to assess and carry out surveillance of BE in patients with cirrhosis, with or without portal hypertension or coagulopathy.

Biomarkers

Patients who progress from BE to adenocarcinoma have been shown to have p53 alterations. One of the normal p53 alleles is inactivated by mutation and the other is lost by a mechanism called loss of heterozygosity. Immunostaining of p53 can be used as an adjunct to histopathological analysis since it may improve the diagnosis of dysplasia [5,13]. Another biomarker found to be a predictor of progression is cyclin D1 [14]. Aneuploidy, which can be diagnosed from systemic flow cytometry, has been shown to have a 5-year cumulative esophageal carcinoma incidence of 28% [15]. Apart from p53, no other biomarkers have been found useful for the diagnosis of dysplasia. However, more robust evidence is required before recommending the routine use of biomarkers in this situation.

Management

Although the management of BE is problematic in the setting of cirrhosis, it is important to determine its presence in patients being considered for liver transplantation, because there can be rapid progression of premalignant and malignant lesions in the setting of immunosuppression. Once a patient is diagnosed with BE, it is important to commence proton pump inhibitor (PPI) therapy. An observational study by Kastelein et al. reported a >75% reduction in the risk of neoplastic progression in BE if long term PPIs are prescribed [16].

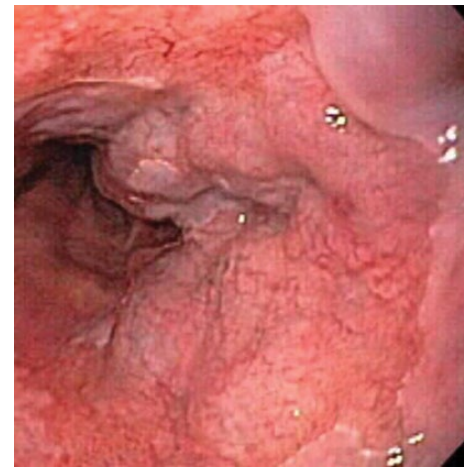


Figure 10.3 Esophageal varices within Barrett esophagus.

In the BE patient with liver disease, surveillance strategies will depend on the risks of repeated multiple esophageal biopsies. In patients with esophageal varices, the risks of biopsy surveillance clearly outweigh the benefits (Figure 10.3). In patients without esophageal varices, surveillance biopsies should be considered on an individual basis.

Once low grade dysplasia (LGD) has been diagnosed and confirmed by two independent pathologists, the updated BSG guidelines recommend repeat endoscopy every 6 months as long as LGD persists [5]. However, a recent randomized trial comparing endoscopic surveillance with radiofrequency ablation (RFA) of BE in patients with LGD suggested a benefit in favor of RFA [17]. In this study, 136 patients were randomized to undergo either biopsy surveillance or RFA. After 2 years of the planned 3-year study, 20.6% of patients randomized to the surveillance group progressed to high grade dysplasia (HGD) (n = 9) or esophageal adenocarcinoma (n = 5). Only one patient in the RFA group progressed to esophageal adenocarcinoma ($p < 0.01$) and the remaining

patients achieved complete eradication of dysplasia or intestinal metaplasia. Despite these promising initial findings, more data are required before a definitive change to the current guidelines can be made.

Once HGD has been confirmed, expert high resolution endoscopy is recommended to identify any visible mucosal lesions. If no visible lesion is identified within the Barrett segment, RFA is usually recommended to treat the entire BE. If visible lesions are identified at endoscopy, endoscopic mucosal resection (EMR) is generally employed to target removal of the lesions. Once resected and confirmed as HGD (or a T1a cancer), RFA therapy of the remaining Barrett segment is usually undertaken [5]. RFA has a better safety and side effect profile compared with photodynamic therapy and argon plasma coagulation (APC), and is therefore presently considered the optimal ablative therapy.

Surgery should be considered if a T1b (or more advanced) cancer is diagnosed. In a series of 36 patients with intramucosal carcinoma and HGD who underwent surgical resection, no operative mortality was reported [18]. However, 11% of these patients had major complications. In one study, Ivor Lewis esophagectomy had a mortality rate of 2–10% and a morbidity rate of 30–40% [19]. This study included 19 cirrhotic patients and complications in this subgroup occurred in 83% of cases.

In cirrhotic patients, EMR can be associated with a high risk of bleeding. RFA is also associated with an increased bleeding risk in the setting of cirrhosis, and most studies excluded cirrhotic patients [20,21]. Therefore the endoscopic treatment options for BE in cirrhotic patients are limited. One possible option is to reduce portal pressure by the insertion of a transjugular intrahepatic portosystemic shunt (TIPS). Moulin et al. reported a successful case of TIPS for portal decompression prior to palliative laser therapy of esophageal adenocarcinoma [22]. Another option in cirrhotic patients with esophageal varices and BE is band ligation without resection. One pilot study showed that this method was safe and effective at eradicating short segment BE [23]. Another case report highlighted the successful ablation of a 5 cm segment of BE in a patient with esophageal varices [24].

Gastroesophageal Reflux Disease

Gastroesophageal reflux disease is frequently found in patients with cirrhosis. In 2007, Schecter et al. reported GERD in 37% of cirrhotic patients [25]. These authors found that cirrhosis, with or without the presence of varices, was associated with an increased incidence of GERD. Cirrhosis in and of itself has been shown to be an important factor in the incidence of esophageal dysmotility, as well as that of acid and bile reflux. Zhang et al. reported that the incidences of bile reflux and reflux esophagitis were significantly higher in cirrhotic patients than in controls [26]. This study confirmed a higher incidence of reflux esophagitis in the setting of severe liver disease using pH monitoring, manometry, and endoscopy (Table 10.1). Reflux esophagitis was classified endoscopically using the Los Angeles classification (Table 10.2).

Table 10.1 Incidence of reflux esophagitis and bile reflux in patients with Child–Pugh class A–C cirrhosis. Source: Adapted from Zhang et al. 2011 [26].

Group	Reflux esophagitis: no. (%)	Bile reflux: no. (%)
Class A (n = 28)	8 (28.57)	12 (42.86)
Class B (n = 27)	11 (40.74)	15 (55.56)
Class C (n = 23)	10 (43.48)	16 (69.57)
Total (n = 78)	29 (37.18)	43 (55.13)

Table 10.2 Los Angeles classification for reflux esophagitis. Source: Adapted from Lundell et al. 1999 [62].

Grade	Mucosal findings
A	One or more mucosal breaks no longer than 5 mm, none of which extend between the tops of the mucosal folds
B	One or more mucosal breaks of more than 5 mm long, none of which extend between the tops of two mucosal folds
C	Mucosal breaks that extend between the tops of two or more mucosal folds, but which involve less than 75% of the esophageal circumference
D	Mucosal breaks that involve at least 75% of the esophageal circumference

Table 10.3 Marsh grade and related histological changes. Source: Adapted from Oberhuber et al. 1999 [63].

Grade	Histological features
0	Normal mucosa
1	Increased number of intraepithelial lymphocytes, exceeding 20 per 100 enterocytes
2	Proliferation of crypts of Lieberkuhn
3a	Partial villous atrophy
3b	Subtotal villous atrophy
3c	Total villous atrophy
4	Hypoplasia of small bowel architecture

Celiac Disease

The prevalence of celiac disease in the general population is 0.5–1% [27]. Diagnosis involves serological testing for tissue transglutaminase antibody and confirmation with duodenal biopsy. The Marsh classification is routinely used to classify small bowel histology in celiac disease (Table 10.3). In general, standard duodenal biopsies in patients with liver disease are not associated with an increased bleeding risk. At endoscopy, a scalloped mucosal appearance of the duodenum suggestive of celiac disease may be seen (Figure 10.4).

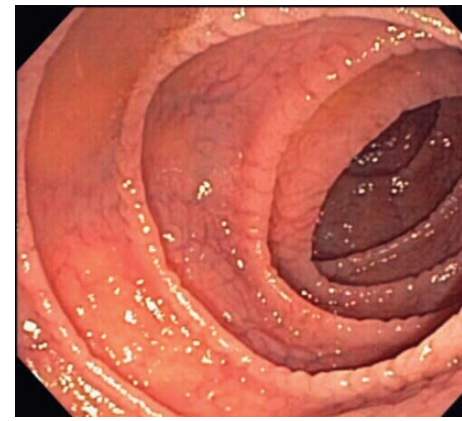


Figure 10.4 Scalloping of the duodenal folds as can be seen in celiac disease.

Celiac disease itself can be associated with liver test abnormalities. These typically present as elevated transaminase levels and usually resolve with a gluten-free diet [28,29]. Data suggest that up to 40% of adult patients with celiac disease present with abnormal liver function tests [30]. Celiac serology should, therefore, be routinely performed in patients with abnormal liver function tests [31]. In fact, 10.7% of patients presenting with elevated transaminases have celiac disease in the absence of other known underlying liver disorders [31]. The prevalence of celiac disease is 3.4% in patients with autoimmune hepatitis and 5.3% in patients with cryptogenic cirrhosis. Celiac disease is also associated with primary biliary cirrhosis (PBC) and primary sclerosing cholangitis (PSC); 6% of patients with celiac disease were found to have PBC and 2–3% had PSC [32,33].

Similar to the general population, once celiac disease has been diagnosed in a cirrhotic patient, a standard gluten-free diet should be initiated. One small study encompassing four untreated celiac patients with advanced liver disease on the liver transplant waiting list showed that all

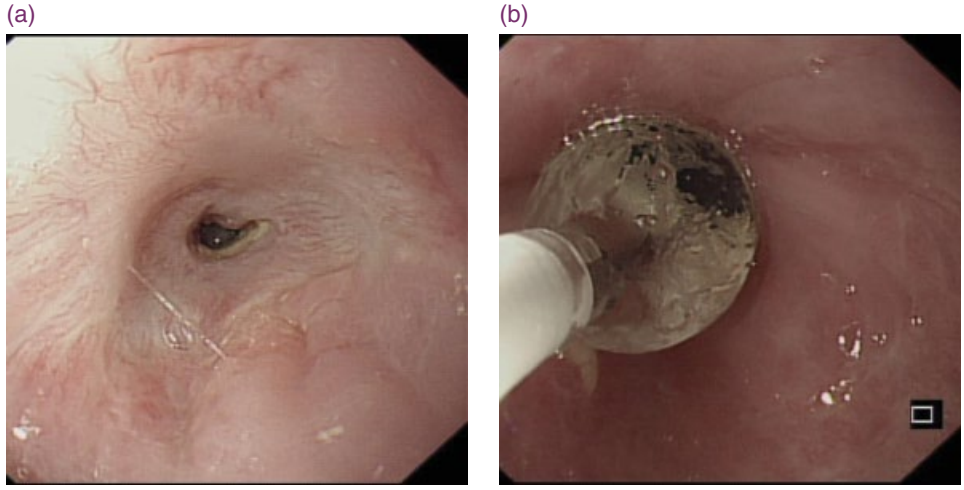


Figure 10.5 (a) Peptic stricture. (b) Balloon dilation of a peptic stricture.

cases had some degree of liver function improvement when a gluten-free diet was adopted [28]. Diagnosing and treating celiac disease also improves nutrient absorption, and decreases the risk of GI malignancy and osteoporosis [34,35].

Esophageal Strictures

Esophageal strictures can be peptic, post-operative, post-radiotherapy, corrosive, or malignant in nature. Peptic strictures are the most common, accounting for 70–80% of all strictures, and are usually secondary to chronic reflux esophagitis. Ruigomez et al. reported the stricture occurrence to be 1.1 per 10,000 person years, with a recurrence rate of 11.1 per 100 person years [36]. There is no documented evidence regarding the incidence of esophageal strictures in the setting of liver disease. However, there are many studies describing the incidence of esophageal strictures caused by endoscopic sclerotherapy. Schmitz et al. reported that 25% of patients undergoing sclerotherapy for varices developed strictures requiring dilation [37]. The use of endoscopic band ligation for varices has led to much fewer symptomatic strictures.

It is common practice to undertake endoscopic balloon dilation for the management of esophageal strictures (Figure 10.5); procedure related risks include bleeding and perforation. Perforation risk approximates 2.6%, with mortality of 1% [38]. Major bleeding occurs in less than 1% of treated patients [39].

Three types of dilators are available: bougies, wire guided polyvinyl dilators, and through the scope (TTS) balloon dilators. The latter are more commonly used. Contraindications to dilation include advanced coagulopathy, suspected or confirmed perforation, severe ulceration or mucosal inflammation, and inability to safely advance the dilator through the strictured area. Unlike balloon dilation, the wire guided bougies or dilators also exert longitudinal force, although there are no proven differences in efficacy between these methods for treating benign esophageal strictures. It is likely that dilation induced bleeding and overall complication risks would be higher in cirrhotic patients with portal hypertension and esophageal varices. However, there are limited data in this clinical situation.

Ramage et al. carried out a double blind, randomized controlled trial of endoscopic steroid injection therapy for recalcitrant

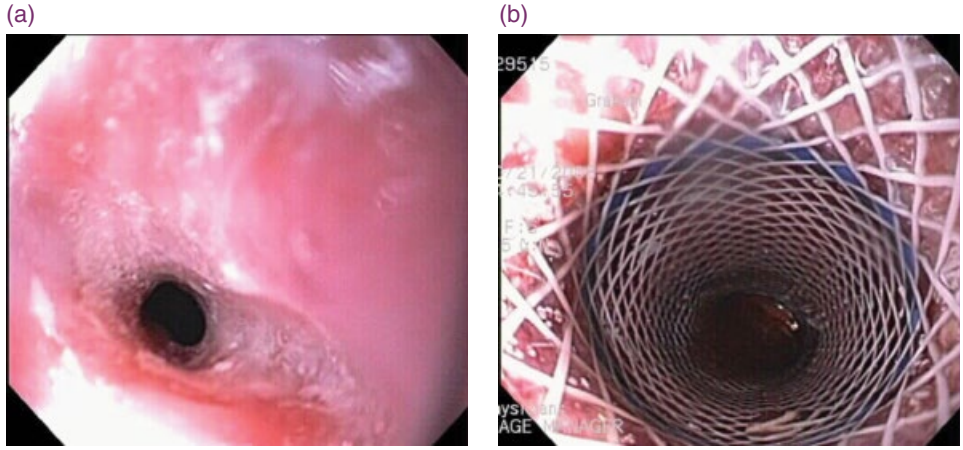


Figure 10.6 (a) Recurrent esophageal stricture. (b) Self-expandable plastic stent placement across the stricture.

esophageal peptic strictures [40]. They reported that steroid injection therapy, in addition to acid suppression, significantly reduced the overall number of dilations required and increased the mean time interval between dilations. At the 1-year follow-up, 13% of those who had received steroid injections required dilation compared with 60% of those receiving placebo injection [40]. However, none of the 30 patients enrolled in this study were documented to have cirrhosis.

When faced with a cirrhotic patient with a symptomatic stricture, it is important to weigh the risks and benefits of endoscopic intervention. In a cirrhotic patient without esophageal varices who has a stricture that significantly impacts his or her nutritional status and overall health, cautious balloon or wire guided Savary dilation is reasonable. In the presence of esophageal varices, band ligation (± TIPS) in an attempt to eradicate the varices prior to dilation may be considered.

Self-expandable stents are approved for use in the palliation of malignant esophageal strictures, but can also be considered for the management of complex and refractory benign esophageal strictures. A meta-analysis assessing the efficacy of self-expandable removable plastic esophageal stents in benign refractory strictures showed modest benefit for long term symptom relief (Figure 10.6) [41]. The stricture etiologies included peptic, radiation, corrosive, and post-surgical. At follow-up, 57% of patients were free of dysphagia, although perforation and stent migration occurred in 1% and 19%, respectively. The overall mortality was 0.6%. In this meta-analysis, no patients were documented to have liver disease. The high complication rates associated with stent placement for benign strictures suggest that further research and modifications are required before stents can be widely used in this situation.

Biodegradable stents were evaluated in 21 patients with refractory benign strictures [42]. Stent insertion was successful in all patients; 9.5% of patients suffered stent migration. At 3 months post-procedure, the stent was found to be almost completely fragmented. At a median of 53 weeks' follow-up, 45% of patients had complete resolution of dysphagia and none had suffered major complications. Minor complications, including post-procedural pain and self-limited bleeding, were reported in four patients. There are no specific published data on the use of esophageal stents for the management of

strictures in patients with liver disease. Similar to the approach to stricture dilation, stent placement in this setting should be assessed on an individual basis, with careful consideration of the risks and benefits of the procedure.

Peptic Ulcer Disease

Peptic ulcer disease is commonly found in cirrhotic patients. In a study by Kim et al., 24% of cirrhotic patients had peptic ulcers [43]. In this study, the severity of cirrhosis correlated positively with the incidence of peptic ulcer; 22% of patients with Child–Pugh class A cirrhosis had peptic ulcer disease compared with 31% in patients with Child–Pugh class C cirrhosis. The etiology of peptic ulcer disease appears to be different in cirrhotic patients compared with the general population. For example, the incidence of *Helicobacter pylori* infection is significantly lower in cirrhotic patients with peptic ulcers compared with the overall population with ulcer disease [43]. In cirrhotic patients, it is likely that increased gastrin levels, impaired gastric mucosal defence, and decreased prostaglandins E2 levels contribute to the formation of peptic ulcers.

Non-bleeding ulcers are generally managed the same way in cirrhotic and non-cirrhotic patients. Acid suppressive therapy is the mainstay of treatment along with *H. pylori* eradication, when present. Repeat endoscopy in 8–12 weeks is recommended for those with gastric ulcers to document healing.

Non-Variceal Upper Gastrointestinal Bleeding

Peptic Ulcer Bleeding

Although the majority of GI bleeding in cirrhosis is attributable to esophageal varices, Rudler et al. reported that 30% of cirrhotic patients had bleeding secondary to peptic ulcers [44]. In all patients presenting with upper GI bleeding, it is useful to calculate the Glasgow–Blatchford score on admission and the Rockall score after endoscopy for risk stratification [45]. Although neither score was designed to specifically assess variceal bleeding, both scores incorporate liver disease as a risk parameter for poor outcome. In the patient diagnosed with a bleeding ulcer, the Forrest classification is useful during endoscopic assessment (Table 10.4).

The management of peptic ulcer bleeding in a cirrhotic patient is similar to that of ulcer bleeding in a non-cirrhotic patient. After resuscitation, early endoscopy is undertaken. Endoscopic therapy is indicated for ulcers with high risk stigmata, including Forrest grade IA, IB, and IIA lesions (Figure 10.7). There is controversy

Table 10.4 Forrest classification of peptic ulcer bleeding. Source: Adapted from Heldwein et al. 1989 [64].

Grade	Endoscopic findings	Risk of rebleeding
IA	Active hemorrhage – spurting vessel	85–100%
IB	Active hemorrhage – oozing bleeding	10–27%
IIA	Visible vessel – recent hemorrhage	50%
IIB	Adherent clot – recent hemorrhage	30–35%
IIC	Hematin covered flat spot	<8%
III	Clean base ulcer	<3%

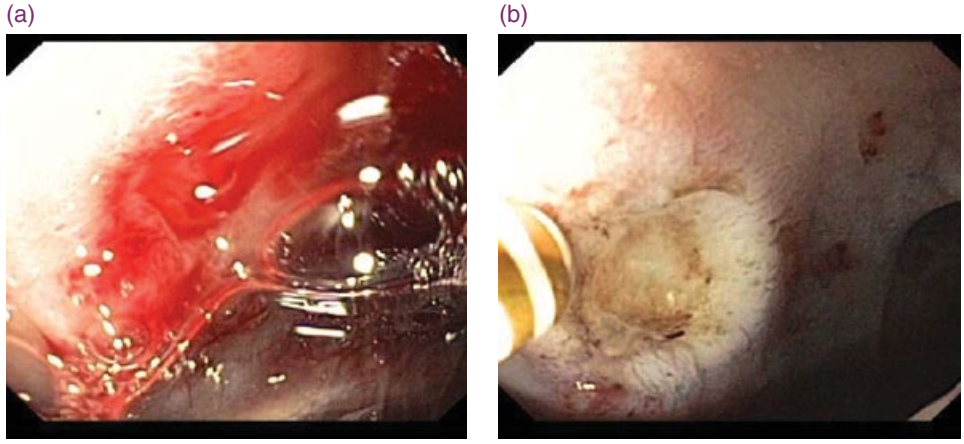


Figure 10.7 (a) Bleeding duodenal ulcer. (b) Hemostasis achieved with bipolar coagulation.

about endoscopic therapy of ulcers with adherent clots (IIB lesions), although the general consensus is to wash vigorously in an attempt to dislodge the clot and treat any underlying stigmata. For ulcers with high risk stigmata, dual endoscopic therapy is recommended, which includes dilute epinephrine injection and contact thermal therapy (e.g., heater probe) or hemoclips. Epinephrine injection alone is insufficient as definitive therapy [45]. In addition to endoscopic therapy, intravenous PPIs are recommended, and omeprazole 80 mg IV bolus followed by a continuous infusion of 8 mg/h for 72 hours is a typical regimen. Angiographic embolization is utilized as rescue therapy for recurrent peptic ulcer bleeding, particularly if surgery is likely to be associated with a high risk of mortality [45].

Most randomized controlled trials on peptic ulcer bleeding have excluded cirrhotic patients and therefore data assessing the efficacy and outcome of standard treatments in cirrhotic patients are few. However, a recent retrospective study by Venkatesh et al. found that mortality in patients with peptic ulcer bleeding and concomitant cirrhosis was significantly higher compared with the non-cirrhotic group (5.5% versus 2%, respectively) [46]. A multivariate analysis in this study showed that the presence of cirrhosis independently increased mortality. In addition, decompensated cirrhotic patients had a higher mortality compared with compensated cirrhotic patients and the hospitalization costs were higher in the decompensated group. Not surprisingly, cirrhotic patients were subjected to less surgical intervention compared with the control group.

Gastric Antral Vascular Ectasia

Gastric antral vascular ectasia (GAVE), or watermelon stomach, is more often associated with chronic GI bleeding and recurrent iron deficiency anemia than acute bleeding. Approximately 30% of all GAVE cases are associated with cirrhosis and the condition accounts for less than 4% of non-variceal bleeding [47,48]. GAVE can often be confused with portal hypertensive gastropathy. However, these two entities are distinct histologically and clinically. GAVE typically occurs in the distal stomach, appearing in a linear pattern with red spots on endoscopy. Histology shows thrombi, spindle cell proliferation, and fibrohyalinosis, and 31% of patients with GAVE have also been found to have portal hypertension [49]. Therapy includes endoscopic coagulation

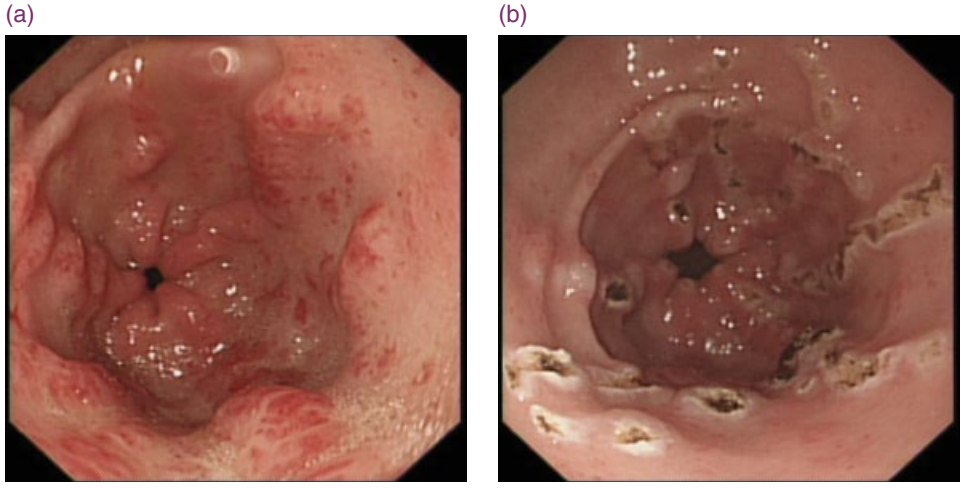


Figure 10.8 (a) Gastric antral vascular ectasia. (b) Treatment with argon plasma coagulation.

with a contact thermal probe or APC (Figure 10.8). In a study of 29 patients with GAVE, 87.5% of patients were successfully treated with APC therapy [50]. Patients who do not respond to endoscopic therapy may be considered for antrectomy, depending on the severity of bleeding, underlying liver disease, and other comorbidities. TIPS is not effective for GAVE.

Portal Hypertensive Gastropathy

Portal hypertensive gastropathy (PHG) has the characteristic endoscopic appearance of "snakeskin" mucosa. PHG typically presents with iron deficiency anemia, but may occasionally cause acute bleeding. The prevalence of PHG appears to correlate with the severity of cirrhosis – 13% in Child–Pugh class A compared with 87% in class C patients [51]. PHG may be misdiagnosed as GAVE because the clinical presentation is similar. It is important to distinguish between the two entities as the approach to therapy is different. PHG is mainly proximally distributed in the stomach. Biopsy typically shows dilated capillaries and venules with no inflammation. If chronic anemia, or occasionally significant clinical bleeding, occurs from severe PHG, treatment is directed at reducing portal pressure. Interventions therefore include non-selective beta-blockers, such as propranolol or carvedilol, TIPS, and in severe cases, liver transplantation.

One study reported on APC therapy every 2–4 weeks in 29 patients with PHG and showed an 81% reduction in blood transfusion [50]. It is likely that these patients had GAVE rather than PHG. Data are limited but TIPS may be an option in patients with severe, transfusion dependent bleeding despite beta-blocker therapy.

Mallory–Weiss Tear

Mallory–Weiss tears account for 5% of all non-variceal bleeds [52]. On endoscopy, they have the appearance of a longitudinal ulcer at the esophagogastric junction. Typically the tear heals spontaneously within 24–48 hours and the risk of rebleeding is low. Depending on the presence of high risk stigmata, such as active bleeding or a non-bleeding visible vessel, endoscopic therapy may be required. Patients with liver disease and portal hypertension are at an increased risk of a major bleeding episode, resulting in an increased need for endoscopic

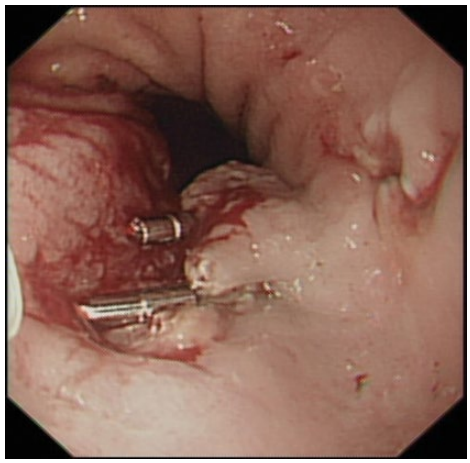


Figure 10.9 Bleeding Mallory–Weiss tear treated with endoscopic clips.

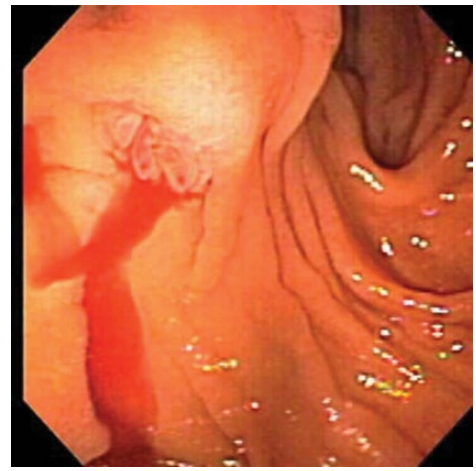


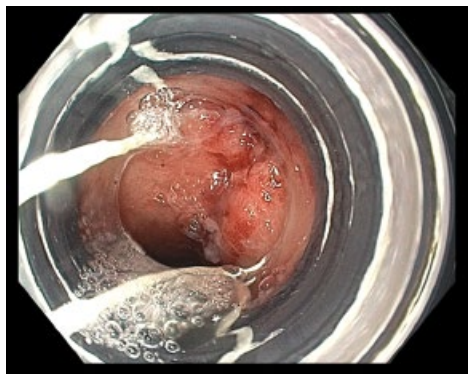
Figure 10.11 Active bleeding exiting the major papilla (hemobilia).

intervention [53]. When feasible, the application of endoscopic clips is preferred in closing a large bleeding tear as clips do not extend tissue injury (Figure 10.9). However, band ligation is more appropriate when the tear overlies gastroesophageal varices. The band ligation cap also facilitates access to a tear straddling the cardia side, which can be brought into the cap via suction (Figure 10.10).

Hemobilia

Even though bleeding from the hepatobiliary tract is a rare cause of upper GI blood loss, it should be considered in patients with a history of hepatic injury, liver biopsy, TIPS insertion, biliary stent placement or a background of hepatobiliary malignancy. The diagnosis of hemobilia may be confirmed at endoscopy by the appearance of blood or clots exiting the major papilla (Figure 10.11). Therapy is generally outside the realms of endoscopy, with angiographic embolization (or surgery) as the primary intervention. On occasion, biliary stent tamponade may be effective, depending on the underlying cause of the hemobilia.

(a)



(b)

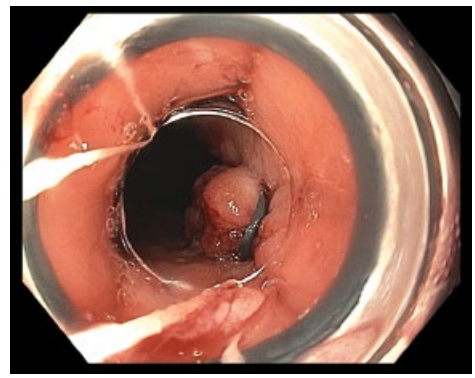


Figure 10.10 (a) Mallory–Weiss tear. (b) Treatment with band ligation.

Upper Gastrointestinal Tumors

Neoplasms in the upper GI tract account for less than 3% of upper GI bleeds [52]. Endoscopic therapy includes epinephrine injection, thermal contact probes, APC, and laser therapy. The risk of rebleeding is high and endoscopic management is generally recognized as a temporary measure. Ultimate management includes staging and consideration for surgical resection and/or chemoradiotherapy, although the severity of the liver disease may preclude aggressive intervention.

Cirrhosis is associated not only with an increased risk of hepatocellular carcinoma but several extrahepatic cancers. In a Danish nationwide cohort study, there was a 59-fold increased risk of hepatocellular cancer and a 10-fold increased risk of cholangiocarcinoma. There was also a significant increased occurrence of breast, lung, upper GI, and colonic cancers, which was felt to be related to alcohol and tobacco use [8]. With regard to the upper GI carcinomas, there was a ninefold increase in esophageal carcinoma, 0.4-fold increase in gastric carcinoma, and 6.5-fold increase in laryngeal carcinoma.

When diagnosed with GI carcinoma, a background of cirrhosis and portal hypertension will be a major factor influencing the management plan. Esophagectomy for esophageal cancer in cirrhotic patients is associated with morbidity of 80% and mortality of 17–30% [19]. Complications include pulmonary sepsis and fistulae. Surgery for gastric cancer in cirrhotic patients is also associated with complications of infection, hemorrhage, and hepatic encephalopathy in the postoperative period. There is a significant increase in mortality and morbidity rates at 10% and 40%, respectively [54]. Resectional surgery for GI cancer in patients with Child–Pugh class B or C cirrhosis is associated with unacceptable postoperative mortality rates. In cirrhotic patients where surgical resection is not possible, alternative endoscopic interventions can be considered, although the bleeding risk is increased by the presence of portal hypertension. To reduce this risk, TIPS has been performed before undertaking laser therapy or EMR in select cases. Guglielmi et al. reported a case where TIPS was performed, allowing subsequent successful EMR of an early gastric carcinoma [55].

TIPS has also been performed prior to intra-abdominal and cardiothoracic surgery, allowing selected cirrhotic patients to undergo relatively major surgery with acceptable rates of short term mortality and morbidity [56]. However, more data are required before TIPS can be recommended routinely prior to endoscopic procedures or surgery.

Novel Endoscopic Intervention for Non-Variceal Bleeding

Hemospray® (TC-325, Cook Endoscopy, Bloomington, IN, USA) is a novel hemostatic agent licensed for endoscopic hemostasis of non-variceal upper GI bleeding in Europe and Canada. Following endoscopic spray application of the powder to an actively bleeding lesion, water is rapidly absorbed to form a mechanical barrier leading to hemostasis. Early clinical studies revealed the hemostatic spray to be effective in the management of bleeding peptic ulcers and other sources of GI bleeding (Figure 10.12) [57,58].

Chen et al. reported the successful use of Hemospray® in cancer related upper GI bleeding in a cohort of patients from Canada [59]. Recent evidence suggests a role in managing problematic non-variceal diffuse portal hypertensive bleeding, although further data are required to assess the risks and benefits of Hemospray® in this situation [60]. A small study recently reported benefit from another hemostatic spray, Endoclot® (Endoclot Plus, Santa Clara, CA, USA), as adjunct therapy to standard endoscopic approaches in severe

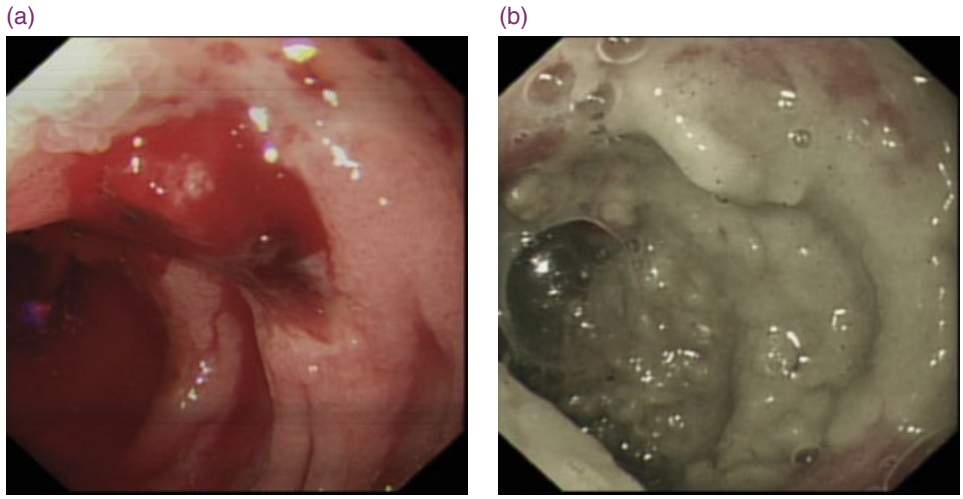


Figure 10.12 (a) Active duodenal ulcer bleeding. (b) Hemostasis achieved following application of a hemostatic spray.

upper GI bleeding [61]. These endoscopic hemostatic sprays appear to be promising therapeutic agents in the management of GI bleeding, but robust comparative data with established endoscopic techniques are required to determine their ultimate role.

Conclusion

Liver disease has been shown to have an influence on the presence of GERD, peptic ulcer disease, celiac disease, and upper GI malignancy. The diagnosis, surveillance, and management of upper GI pathology in the patient with liver disease can potentially be a challenge due to bleeding risks, and therefore the decision regarding surveillance and endoscopic management needs to be individualized. In particular, the management of BE and upper GI malignancy in the cirrhotic patient can be challenging.

The endoscopic management of non-variceal bleeding lesions in the setting of cirrhosis generally involves conventional therapies, including epinephrine injection, contact thermal coagulation, APC, hemoclips, and band ligation. The novel endoscopic hemostatic powders appear promising, but require further study.

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11

Colonoscopic Screening and Surveillance in the Patient with Liver Disease (Including Post-Transplant)

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Introduction

Patients with liver disease and expected long term survival warrant standard health maintenance screening to promote health. On the other hand, patients with advanced cirrhosis who are not candidates for transplantation may have limited survival and may thus not be suitable for routine health screening. This may be especially true for screening with finite risks. Finally, in liver patients who are candidates for transplantation, health screens serve not only to preserve health but also to select patients without serious extrahepatic disease that would limit life expectancy or complicate the post-transplant course. Colonoscopy for colorectal cancer (CRC) screening or surveillance for adenomatous polyps falls into this category of health screens that warrants selective and thoughtful application in patients with liver disease. Some liver diseases, such as primary sclerosing cholangitis (PSC) with associated colitis, are known risk factors for CRC and deserve special consideration [1,2]. This chapter outlines and discusses the colonoscopic screening and surveillance guidelines that apply to patients with liver disease, including post-transplant patients.

Screening Colonoscopy in Average Risk Populations

Colorectal cancer is the third most common cancer in the USA and the second leading cause of cancer death [3]. CRC screening and surveillance are effective and have consistently been shown to reduce CRC related morbidity and mortality. Prevention and early detection of CRC in screening populations have led to decreased incidence and death rates. In the recent report to the nation on the status of cancer covering 1975–2006, overall cancer death rates continued to decline in the USA among both men and women, and in all major racial and ethnic groups; this decline was most prominent for CRC [4]. This has been attributed to risk factor modification and a higher use of screening resources [5]. The US Multi-Society Task Force (MSTF) on CRC, the US Preventive Services Task Force (USPSTF), and the American College of Gastroenterology (ACG) have all formulated colon

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cancer screening guidelines [6–8]. While there are variations between the guidelines, there is general consensus that one of the various screening strategies should be employed in all patients. The USPSTF is the only guideline that advocates an age limit to screening (Table 11.1). While the most rigorous data from randomized controlled trials exist for fecal occult blood testing and flexible sigmoidoscopy, there is a growing body of case–control data suggesting that screening colonoscopy reduces CRC mortality [9–17]. In the USA, colonoscopy has become the dominant form of CRC screening in average risk individuals, although overall screening rates remain low relative to other types of cancer screening [18]. In the UK, 2-yearly fecal occult blood testing from the age of 50 years (Scotland) or 55 years (England) followed by colonoscopy for positive testing is the dominant form of CRC screening.

Surveillance for Colorectal Neoplasia

The main benefit of colonoscopy is the detection and removal of adenomatous polyps, thereby preventing CRC. Based on the National Polyp Study, patients with adenomatous polyps have a reduced incidence of CRC after polypectomy. Patients found to have adenomas are at increased risk for developing metachronous adenomas or cancer compared with patients without adenomas [19]. Therefore, once adenomas are detected, patients are advised to have colonoscopic surveillance and the US MSTF on CRC has proposed post-polypectomy surveillance intervals based on polyp number and characteristics. Recommended screening and surveillance intervals are based on evidence showing that periodic examinations reduce the number of cancers and

Table 11.1 Colorectal screening recommendations for average risk individuals* (aged 50–75 years).

	American College of Gastroenterology (ACG)† [7]	US Preventive Services Task Force (USPSTF)‡ [8]	US Multi-Society Task Force (MSTF) [6]
Cancer prevention tests (can detect both polyps and cancer)			
Colonoscopy	Every 10 years (preferred)	Every 10 years	Every 10 years
Sigmoidoscopy	Every 5–10 years	Every 5 years Every 10 years if with annual FIT	Every 5 years
Computed tomographic colonography	Every 5 years	Every 5 years	Every 5 years
Double contrast barium enema	Not recommended	Not considered	Every 5 years
Cancer detection tests			
Fecal immunochemical test (FIT)	Annual (preferred)	Annual	Annual
Highly sensitive guaiac based fecal occult blood test (gFOBT)	Annual	Annual	Annual
Stool DNA	Every 3 years	Every 1–3 years	Interval uncertain

* An average risk individual is a person without a family history of colorectal neoplasia.
† The ACG recommends screening the African American population at age 45 years.
‡ Screening for individuals aged 76–85 years can be considered on an individual basis but is not routinely recommended, while individuals older than 85 should not undergo screening.

Table 11.2 United States Multi-Society Task Force 2012 surveillance recommendations [6]. Source: Adapted from Snover et al. 2010 [142].

Colonoscopy findings	Surveillance recommendation* (years)
No polyps	10
Small (<10 mm) hyperplastic polyps in rectum or sigmoid	10
1–2 small (<10 mm) tubular adenomas	5–10
3–10 tubular adenomas	3
>10 adenomas	<3
Advanced adenoma	3
Sessile serrated polyp(s) <10 mm with no dysplasia	5
Sessile serrated polyp(s) >10 mm	3
Or	
Sessile serrated polyp with dysplasia	
Or	
Traditional serrated adenoma	
Serrated polyposis syndrome†	1
Piecemeal resection of large adenoma or sessile serrated adenoma	3–6 months

* Assumes baseline colonoscopy was complete and that all visible polyps were completely removed.
† Based on the World Health Organization definition of serrated polyposis syndrome [142] with one of the following criteria: (i) at least five serrated polyps proximal to sigmoid, with two or more >10 mm; (ii) any serrated polyps proximal to sigmoid with a family history of serrated polyposis syndrome; and (iii) >20 serrated polyps of any size throughout the colon. Advanced adenomas are defined as >10 mm, or polyps of any size with villous histology or high grade dysplasia.

cancer related mortality. Risk stratification of patients based on the findings at baseline colonoscopy has been imperative in formulating these guidelines (Table 11.2) [6]. While these screening and surveillance guidelines relate to healthy, average risk individuals they, along with screening outcome studies, provide a reference perspective for patients with liver disease.

Bowel Preparation in Patients with Liver Disease

The quality of colon preparation is a major determinant of colonoscopy outcome. A suboptimal preparation increases the chances of missed lesions, particularly flat or sessile polyps, and it is associated with increased procedural risks and an escalated cost of colonoscopy, especially if a repeat procedure is needed to accomplish adequate inspection or if the surveillance interval has to be shortened. In one study, cirrhosis was identified as an independent predictor of an inadequate colon preparation. Other factors include a later colonoscopy starting time, failure to follow preparation instructions, inpatient status, procedural indication of constipation, use of tricyclic antidepressants, and male gender [20].

In addition to potentially being a risk factor for poor preparation, underlying liver disease may increase the risk of select preparation regimens. Dietary restriction is an established beneficial adjunct to bowel preparation agents used for bowel

cleansing. Clear liquid and low residue diets over 1–4 days are incorporated into the bowel preparation regimen for all patients, including liver disease patients. Since clear liquids are often high in sodium, patients must be educated about the potential consequences of sodium overload, especially in the setting of cirrhosis and ascites [21].

Several approved bowel preparation agents include polyethylene glycol (PEG) with electrolytes, which is an osmotically balanced electrolyte lavage solution. They are relatively safe in liver disease patients including those with ascites who cannot tolerate significant fluid overload [21,22]. Compared with standard 4 L PEG regimens, 2 L PEG regimens combined with bisacodyl or magnesium citrate and low volume (2 L) PEG-3350 combined with bisacodyl have been demonstrated to have comparable efficacy in terms of colonic cleansing and improved overall patient tolerance. These regimens are therefore a more acceptable alternative to the 4 L PEG regimens; however, there is a paucity of safety data in liver disease patients [21]. Sulfate-free PEG (SF-PEG), a lavage solution without sodium sulfate, was developed as an attempt to improve the smell and palatability of PEG solutions. The improved taste is the result of a complete absence of sodium sulfate that results in a lower luminal sodium concentration and, therefore, the mechanism of action is dependent on the osmotic effects of PEG. There also is a decrease in potassium concentration and increase in chloride concentration in these preparations [23,24]. SF-PEG is comparable to PEG in terms of safety, effectiveness, and tolerance, and is more palatable. SF-PEG therefore is an acceptable alternative to PEG in liver disease patients [25].

Other preparations include sodium phosphate and magnesium based regimens. Sodium phosphate is a low volume hyperosmotic solution that works by drawing plasma water into the bowel lumen to promote colonic cleansing. This results in fluid and electrolyte shifts that can result in hyperphosphatemia, hypernatremia, hypokalemia, and worsening kidney function [26]. Because of its osmotic mechanism of action, sodium phosphate can result in potentially fatal fluid and electrolyte shifts in patients with advanced liver disease [25,27]. Use of sodium phosphate is therefore contraindicated in advanced hepatic dysfunction and ascites and due to reports of renal and electrolyte disorders in high risk patients, these preparations have been removed from the market in the USA [21]. Magnesium based bowel preparations can lead to life threatening hypermagnesemia; this has especially been reported in elderly patients, including those without pre-existing renal disease [28].

The timing of PEG administration has proven to be an important determinant of bowel preparation quality. The standard 4 L PEG dosing given the day before the procedure is an established safe and effective regimen. However, PEG taken in divided doses (2–3 L the evening before and 1–2 L the morning of the procedure) has been demonstrated to be more effective and better tolerated than the standard 4 L dose given the day before the procedure [29]. These so-called split dose regimens have proven to be superior to single dose regimens in multiple studies [30]. As cirrhosis may be a risk factor for inadequate bowel preparation, split dose regimens are preferred, and given the early satiety often associated with ascites, the split dose regimen is likely to be better tolerated than the 4 L single dose regimens.

Sedation in Patients with Liver Disease Undergoing Colonoscopy

Sedation in liver disease patients can be challenging and requires an endoscopist or anesthesiologist with expertise and

experience with this patient group. Understanding the altered pharmacodynamics in advanced liver disease is vital. An increased volume of distribution, decreased protein binding, and changes in hepatic conjugation, oxidation, and shunting can all lead to altered hepatic metabolism of sedatives [31].

The American Society of Anesthesiologists (ASA) has defined a continuum of four levels of sedation from minimal sedation or anxiolysis to moderate sedation to deep sedation, and finally general anesthesia [32]. In general, most endoscopic procedures are performed with the patient under moderate sedation, a practice that was formerly referred to as "conscious sedation." At this level, the patient is still able to make purposeful movements in response to verbal or tactile stimulation and maintains cardiorespiratory function. During colonoscopy, the goal of sedation is to relieve anxiety and discomfort, allow safe completion of the examination, and diminish the patient's memory of the event [32].

Informed consent obtained for colonoscopy should include a discussion regarding sedation and anesthesia. Liver disease patients should be educated about additional risks that may ensue due to their liver condition. The suitability of such a patient to undergo the planned sedation is assessed on a case by case basis. Particular attention should be given to other comorbidities, previous sedation experience, a complete list of medications including over the counter medications, and allergies. An ASA physical status classification scale assessment should be performed and the duration of fasting should be determined before sedation. The ASA guidelines state that a minimum of 2 hours should pass after clear liquid intake and 6 hours after a light meal before the administration of moderate sedation or anesthesiologist directed sedation [32,33]. A targeted physical examination, including vital signs with heart rate, blood pressure, baseline oxygen saturation, and a limited neurological examination should be performed to assess the mentation of the patient, especially in patients with a history of encephalopathy.

Successful colonoscopy may be performed in selected groups of patients without sedation or sedation only if needed during the procedure [34]. Patients likely to tolerate colonoscopy with minimal to no sedation include older patients, men, patients who are not anxious, or patients without a history of abdominal pain. In general, diagnostic and uncomplicated therapeutic colonoscopy can be successfully performed with moderate sedation in most liver patients. Deep sedation or general anesthesia may be needed for those who have been difficult to manage with moderate sedation or who are anticipated to have a poor response to sedatives. This includes patients who are on chronic opioids, benzodiazepines, alcohol, or other psychotropic medications [32].

The choice of sedatives for moderate sedation generally consists of benzodiazepines used with or without an opiate. Midazolam and diazepam are the two most commonly used benzodiazepines with comparable efficacy [35]. Midazolam is preferred due to its rapid onset of action, amnestic properties, and short duration of action, and it appears to be well tolerated without major complications in liver disease patients [36]. However, caution is advised for its use in patients with advanced liver disease as these patients are likely to be sensitive in their response to midazolam or other benzodiazepines. Midazolam is protein bound and metabolized in the liver by cytochrome P3A4. No dosage adjustment is recommended if a single dose is being used, but for multiple doses accumulation can occur with prolongation of its action, thus dose reduction is advisable [37,38]. In patients with cirrhosis, the clearance of midazolam is impaired and the elimination half-life is doubled [38].

Most opiates are metabolized by the liver. Fentanyl is preferred over meperidine (pethidine) due to a more rapid onset of action and clearance and a lower incidence of adverse effects. Dosing caution is advised in patients with advanced liver disease but it can be used safely in patients with minor liver dysfunction. As with all sedative regimens, the dosage should be titrated to reach the desired clinical effect with careful monitoring of the patient [39]. The half-life of fentanyl is shorter than most opiates and does not appear to be affected by cirrhosis [40].

Propofol (2,6-diisopropylphenol) is classified as an ultrashort acting hypnotic agent that provides sedative, amnestic, and hypnotic effects with no analgesic properties. Propofol is 98% plasma protein bound, and is metabolized primarily in the liver by conjugation to glucuronide and sulfate to produce water soluble compounds that are excreted by the kidney. Propofol is well tolerated, with some studies showing no major complications in liver disease patients [36]. The presence of cirrhosis does not significantly affect the pharmacokinetic profile of propofol likely due to the short half-life [33]. In a randomized control trial, sedation with propofol was suggested to have a faster recovery time and a shorter time to discharge relative to midazolam. It was also reported that subclinical hepatic encephalopathy in patients with compensated liver cirrhosis was not exacerbated by propofol use [41]. More recently published data have assessed the safety of propofol in patients with advanced liver disease including Child–Pugh class C cirrhosis patients undergoing colonoscopy. It was found to be safe and effective, and no cases of overt hepatic encephalopathy were reported [42]. There is no reversal agent for propofol, which has limited its use in some healthcare settings, and it is advisable that it be limited to use by practitioners with training in advanced airway management. Dose related propofol side effects include hypotension, respiratory depression, and bradycardia [43]. The presence of an anesthesia specialist is mandatory for ASA physical status III, IV, and V patients.

Colonoscopic Findings in Liver Disease

Patients with liver disease, particularly patients with portal hypertension, may have unique colonoscopic findings. The spectrum of findings ranges from colonic manifestations of portal hypertension such as portal hypertensive colopathy and anorectal or colonic varices to findings unrelated to liver disease including colonic angiodysplasias, mucosal inflammation, ulcers, diverticulosis, and colorectal polyps. Only 18–26% of cirrhotic patients have a normal colonic examination [44,45]. Furthermore, these colonic alterations can potentially influence the effectiveness of colorectal screening.

Colonic manifestations of portal hypertension are often detected as incidental findings during screening or surveillance colonoscopy [46]. Portal hypertensive colopathy can manifest with a variety of endoscopic appearances. These findings may be non-specific such as mucosal edema, erythema, altered vascular pattern, granularity, friability, spontaneous bleeding of the colonic mucosa, and vascular lesions of the colon reminiscent of chronic inflammatory colitis [47,48]. Lesions such as vascular ectasias, angiodysplasias, arterial spiders, and diffuse cherry red spots can also be present [49]. Arterial spider like lesions have a hallmark appearance of a central arteriole from which numerous small vessels radiate. The lesion blanches with pressure from a forceps biopsy. Additionally, the angiodysplasia like lesions have an irregular margin with a fern like pattern and sometimes a pale halo around them. Cherry red spots like lesions are defined by the presence of a red spot in the colonic mucosa, similar to

that seen in the gastric mucosa of patients with portal hypertensive gastropathy [49]. The mean reported prevalence of portal hypertensive colopathy in patients with cirrhosis is 24%, with a range from 3% to 84% [49–52]. This wide range may be due to lack of consensus on its endoscopic appearance.

Rectal varices are present at colonoscopy in approximately 40% of patients with cirrhosis and they tend to be more frequent in patients with advanced portal hypertension [53]. Some series have reported a much higher prevalence [50]. Colonic varices can be seen in 7.6–31% of patients with liver cirrhosis [44,49]. In addition, hemorrhoids are present in 22–79% of cirrhotic patients [54,55]. They tend to occur independently of anorectal varices and their presence is unrelated to the degree of portal hypertension [53]. Several investigators have found no association between colorectal manifestations of portal hypertension, etiology of liver disease, Child–Pugh score, and previous history of hepatic decompensation [49,55,56].

Diverticulosis appears to occur with the same prevalence in patients with liver disease compared to the general population. However, there is a report of an increased incidence of diverticulitis in post-transplant liver patients due to the impact of immunosuppression [57]. These patients are also noted to have a higher morbidity and mortality with or without surgery. Therefore, a pre-transplant diagnosis of diverticulosis may be useful in facilitating an early diagnosis if diverticulitis develops post-transplant [57].

The prevalence of colon polyps in cirrhotic patients is 38–42% and these are predominantly adenomatous [49]. Whether cirrhosis or portal hypertension are risk factors for adenomas is not clear but it has been speculated that alterations in the colonic mucosal microvasculature in portal hypertensive colopathy could be associated with mucosal proliferation [49]. As in healthy populations, the prevalence of neoplastic polyps in liver disease patients has been noted to increase with age [36]. A strong correlation of neoplastic polyps with rectal varices has also been observed in liver disease patients, however the etiology of this association is unclear [36].

Conventional adenomatous polyps include tubular, tubulovillous, and villous adenomas. They account for 70–80% of colorectal neoplasms [58]. Serrated polyps include hyperplastic polyps (HPs), sessile serrated polyps (SSPs), and traditional serrated adenomas (TSAs). HPs are considered benign while SSPs and TSAs are precursors of colorectal malignancy [59]. TSA is defined by the presence of serrations in ≥20% of the lesion crypts in association with surface epithelial dysplasia and they are relatively uncommon [60]. SSPs are more common and defined by a serrated pattern throughout the entire length of the crypts. There is an absence or rarity of undifferentiated cells in the lower third of the crypts. Dilation, branching, or broad bases in basal crypts that grow parallel to the muscularis mucosae, creating the distinctive L shape, boot shape, or inverted T shape, are additional supportive criteria [59,61].

The well established adenoma to carcinoma molecular pathway characterized by chromosomal instability is responsible for the development of most conventional adenomatous polyps. The chromosomal instability pathway is characterized by widespread imbalances in aneuploidy and loss of heterozygosity. This leads to the progressive accumulation of a characteristic set of mutations in oncogenes, such as K-ras, and tumor suppression genes, such as adenomatous polyposis coli (APC) and p53 [62]. On the other hand, the serrated polyp carcinoma pathway accounts for 20–30% of CRC [58]. It involves mutation of the *BRAF* oncogene and an epigenetic mechanism characterized by abnormal hypermethylation of CpG islands (CIMP) located in the promoter regions of tumor suppressor genes. This hypermethylation silences some tumor suppressor genes;

silencing of the DNA mismatch repair gene *hMLH1* appears to play a significant role in advanced lesions. These molecular changes lead to the development of a sessile serrated polyp with dysplasia that can evolve into colorectal tumors characterized by a microsatellite instability molecular phenotype similar to the molecular mechanism of the Lynch syndrome [63]. Because of the phenotypical microsatellite instability in the later stages of this pathway, it has the potential to progress more rapidly to cancer compared with the chromosomal instability pathway.

Serrated polyps are common. In unselected patients with polypectomy, HPs, SSPs, and TSAs have a reported prevalence of 20–30%, 2–9%, and 0.3%, respectively [58]. Of all removed serrated polyps, HPs account for 70% while SSPs and TSAs are reported to have a prevalence of 25% and <2%, respectively [64]. Hyperplastic polyps and TSAs are most frequently found in the left colon while SSPs are more common in the right colon [65]. It is vital to identify these lesions during colonoscopy and for the pathologist to correctly categorize them so appropriate surveillance intervals are applied. Table 11.2 shows updated MSTF guidelines for colon polyp surveillance including those for serrated polyps. SSPs are associated with synchronous CRC, especially if the polyps are large (≥1 cm), multiple, or if they are in the proximal colon [64]. These lesions are also thought to be responsible for a considerable number of interval cancers [58]. SSPs have an endoscopic appearance characterized by a flat morphology and are often noted to have a rim of residual debris and a mucous cap. Sometimes the only clue to their presence is a focal loss of the normal vascular pattern. The subtlety of all of these findings contributes to the difficulty in distinguishing these lesions from the surrounding normal colonic mucosa. Because of the altered vascular pattern and edema in patients with portal hypertensive colopathy these subtle serrated lesions may be more difficult to identify (Figure 11.1). Therefore, vigilant inspection is required, especially in patients likely to be transplant candidates given the potentially more rapid evolution of these lesions and the increased cancer risk due to the requiste post-transplant immunosuppression.

Risks of Colonoscopy and Polypectomy in Liver Disease

Colonoscopy, despite its diagnostic and therapeutic benefits of screening and surveillance, can lead to rare but potentially serious and life threatening complications. Transient and minor symptoms have been reported in up to 33% of patients after colonoscopy [66]. The most commonly reported minor complications are bloating (25%) and abdominal pain and/or discomfort in 5–11% [67]. Colonoscopy does not worsen the general clinical state of liver patients. However, compared with patients with compensated cirrhosis, patients with ascites and/or peripheral edema are at a higher risk of post-procedure fluid retention [45].

The most serious complication of colonoscopy is perforation, and variable rates have been reported in several large studies ranging from 0.003% to 0.3%. However, perforation rates of less than one in 500 for all colonoscopies or one in 1000 for screening colonoscopies are considered to be acceptable [68]. There is no evidence that advanced liver disease increases the risk of perforation.

Bleeding can occur after a diagnostic colonoscopy although it is rarely of clinical significance, with a reported incidence of between 0.001% and 1.24% [69]. The risk of bleeding from colonoscopy with polypectomy is significantly higher [70]. Over 85% of the serious colonoscopy complications are reported in patients

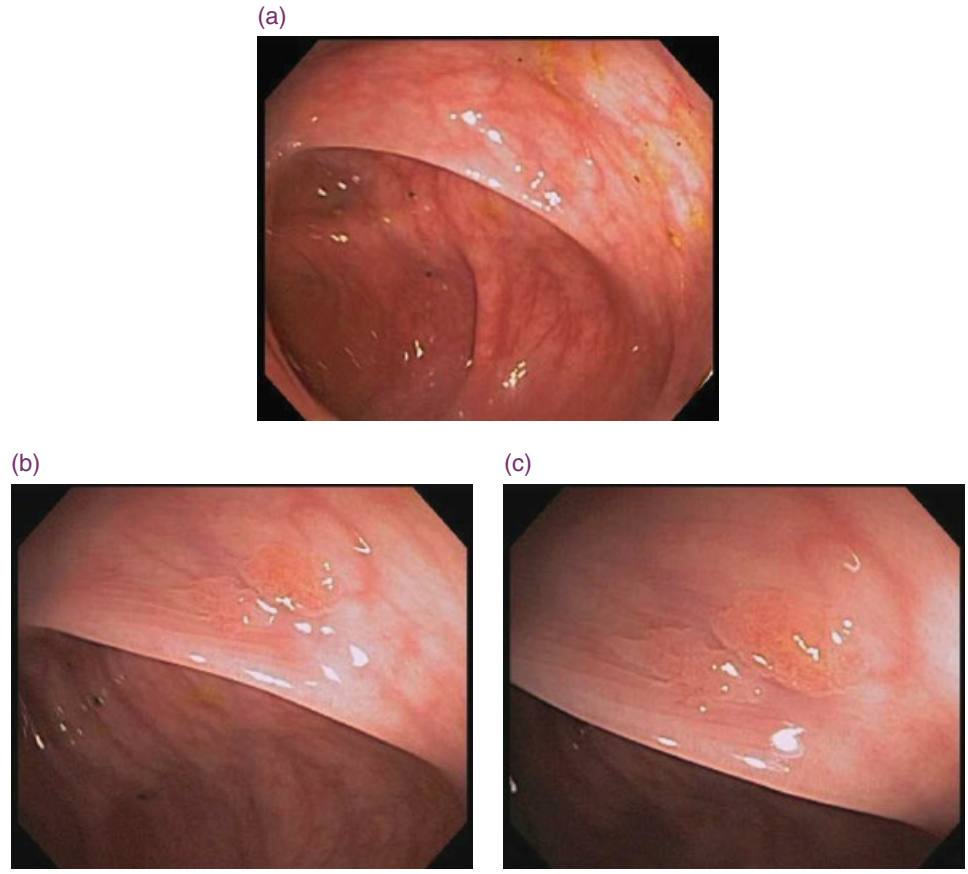

Figure 11.1 Endoscopic image of a sessile serrated adenoma in a patient with portal hypertensive colopathy. (a) The lesion is not visible and there are diffuse background changes with blurring of the normal vascular pattern. (b) Closer inspection reveals subtle nodularity of the mucosa. (c) Further close-up reveals an obvious lesion.

undergoing colonoscopy with polypectomy [71]. Post-polypectomy bleeding can be immediate or may occur up to 2 weeks after the procedure and occurs in 0.2–0.6% of patients [72]. It has been suggested that post-polypectomy bleeding rates of less than 1% would be considered consistent with quality care [68]. Significant risk factors for immediate post-polypectomy bleeding include old age (≥65 years), comorbid cardiovascular/chronic renal disease, polyp size (>1 cm), number of polyps removed, gross morphology of polyps (such as pedunculated polyps) or laterally spreading tumor, polyp histology, poor bowel preparation, cutting mode of electrosurgical current, inadvertent cutting of a polyp before current application, anticoagulant use, and combination antiplatelet agents [72,73]. Colonoscopists are often reluctant to perform endoscopic polypectomy in patients with liver disease, especially liver cirrhosis, because of the perceived increased risk of post-polypectomy bleeding. There is a paucity of data and further studies evaluating the risks of post-polypectomy bleeding specific to these patients are warranted.

In a retrospective study of 30 patients with compensated liver cirrhosis who underwent polypectomy, the incidence and predictors of immediate post-polypectomy

bleeding and delayed post-polypectomy bleeding were investigated [74]. Only two of the 66 (3.03%) removed polyps displayed mild oozing and were controlled using hemoclips. Delayed polypectomy bleeding did not occur in any of the patients. The size and the gross morphology of the polyps were associated with immediate post-polypectomy bleeding, while platelet count and Child–Pugh score did not have an impact [74].

The mechanisms of coagulopathy and thrombocytopenia in cirrhosis are often complex and multifactorial. Hypersplenism, decreased production of thrombopoietin, diminished production of most coagulation factors, malnutrition, and vitamin K malabsorption due to cholestasis are a few of the contributing factors. Advanced liver disease and the presence of cirrhosis is, however, associated with a reset equilibrium of prothrombotic and antithrombotic factors that leads to a fragile balance making patients more susceptible to both bleeding and thrombotic events [46,75]. Therefore, the prothrombin time (PT) and international normalized ratio (INR), which reflect only the altered levels of coagulation factors, have poor clinical relevance to bleeding risk in cirrhotic patients. There is currently no reliable way to assess this altered balance. Colonoscopy with or without mucosal biopsy is considered to be associated with a low bleeding risk; however polypectomy with snare electrocautery is associated with an increased bleeding risk [46,76,77].

Routine laboratory screening tests such as coagulation studies, hemoglobin level, and chemistry tests are not generally recommended before colonoscopy [78]. However, for patients with liver disease, it is recommended to check coagulation profile and complete blood count. In general, platelet counts <80,000/μL and PT prolongation ≥3 seconds above the normal limit may need to be corrected prior to endoscopic procedures with a high risk of bleeding [79,80]. It is important to note that the benefit of correcting an elevated INR in the setting of cirrhosis is uncertain and routine use of plasma cannot be recommended [81–84]. Likewise, administration of one standard unit of adult platelet concentrate corresponds to $(300 \pm 33) \times 10^9$ platelets, which leads to a small increase in the platelet count and is not a guarantee of normalization of homeostatic imbalances. The required threshold of platelet counts >50,000–77,000/μL is based largely on in vitro studies identifying normal thrombin production with these levels but there is an absence of rigorous outcome based clinical studies [85–87].

Factor VII is a vital determinant of PT prolongation and is significantly decreased in liver disease patients. Recombinant activated factor VII transfusion is safe and effective in correcting clotting in these patients, thus reducing the risk of bleeding from several invasive procedures [88,89]. However, its role in reducing bleeding complications secondary to invasive interventions such as polypectomy remains to be determined. Factor VII is expensive and this is a limiting factor to widespread use [82].

Mortality secondary to colonoscopy itself is very low and it appears very safe in patients with cirrhosis. Most deaths are related to comorbidities including cirrhosis [90,91]. A review in 2010 on 30-day mortality for all patients undergoing colonoscopy found a 0.07% risk of all-cause mortality (116/176,834) and 0.007% risk of colonoscopy specific mortality (19/284,097) [66].

Risk of Septicemia After Colonoscopy in Patients with Ascites

Bacteremia or septicemia can occur after colonoscopy due to mucosal disruption and can lead to the translocation of indigenous colonic bacteria. However, it is only

rarely clinically significant. Infectious complications such as acute febrile illness, abscess, or other infections are rare [92]. Colonoscopy with or without biopsy and/or polypectomy is considered a low risk endoscopic procedure in terms of its ability to cause post-procedural bacteremia. On average, approximately 4.4% of patients have transient bacteremia after colonoscopy, with reports ranging from 0% to 25% [93,94]. The use of prophylactic antibiotics in patients with cirrhosis undergoing colonoscopy therefore remains a subject of controversy requiring further elaboration. The American Society for Gastrointestinal Endoscopy currently does not recommend the administration of prophylactic antibiotics in cirrhosis due to a paucity of data to guide recommendations for these patients [92,95]. However, clinical considerations must be individualized. Potential indicators of a greater risk for infectious complications include ascites with low ascitic fluid protein, recent gastrointestinal bleeding, hospitalized patients, presence of active colitis, prior history of spontaneous bacterial peritonitis, or bacteremia following colonoscopy [93,96–99]. While cirrhotic patients with ascites may be at a higher risk for infection, the magnitude of the risk is not clear [95]. There have been case reports of septicemia and peritonitis in cirrhotic patients undergoing colonoscopy with or without biopsies and polypectomies [93,96,100,101]. This has been attributed to the reduced ability to clear the transient bacteremia in addition to multiple other factors. Portal systemic shunting that bypass hepatic Kupffer cells, a compromised immune system, and concomitant use of immunosuppressive agents in many of these patients are a few of the explanations offered [102,103]. Whether these isolated case reports translate into absolute risk is not clear.

Prospective assessment of the risk of bacteremia in cirrhotic patients undergoing lower intestinal endoscopy was undertaken for 58 consecutive cirrhotic patients in Spain [104]. Six cultures were positive from six patients, four were obtained post-endoscopy and two were obtained before colonoscopy, but the corresponding post-endoscopy cultures in the latter two samples were negative. All organisms recovered were normal skin flora. All patients, including those with positive cultures, remained asymptomatic 72 hours post-procedure. The authors concluded that lower intestinal endoscopy did not induce bacteremia in cirrhotic patients with or without ascites [104]. On the basis of limited data routine antibiotic prophylaxis prior to colonoscopy in patients with cirrhosis or ascites cannot be recommended.

Colorectal Neoplasia in Primary Sclerosing Cholangitis

Primary sclerosing cholangitis is strongly associated with inflammatory bowel disease (IBD). Ulcerative colitis (UC) is present in 70–90% of patients with PSC [105] and up to 14% of PSC patients are reported to have Crohn's colitis [106]. Conversely, PSC has been diagnosed in 2.4–7.5% of patients with UC and 3.4% of Crohn's disease (CD) patients [105,107]. PSC patients with CD almost always have colonic involvement. IBD can be diagnosed at any time during the course of PSC, and PSC can occur at any time during the course of IBD [105,108]. In general, however, IBD is diagnosed several years earlier than PSC. Many PSC patients without clinical symptoms of IBD have colonoscopic and histological findings compatible with IBD, and the subclinical phase can last several years before the onset of symptoms of active colitis. The characteristics of UC in patients with PSC are different from those in patients without PSC. The colitis is usually substantial yet its clinical course is quiescent, while rectal sparing and backwash ileitis are common endoscopic findings [106].

While chronic UC is associated with an increased risk of colorectal neoplasia, there appears to be a more profound increased risk of CRC in patients with PSC and associated UC [109–112]. A fourfold increase of CRC in patients with PSC and UC has been demonstrated compared with those with UC alone [113]. The cumulative incidence of CRC or dysplasia in PSC/UC patients versus UC alone is 9% versus 2% after 10 years and 20–31% versus 5% after 20 years of disease duration, respectively [114]. The risk of colon cancer has also been studied in patients with PSC and CD involving the colon, and to date the risk of colon cancer in patients with PSC and CD is unclear [115]. The small sample size limits the ability to definitively conclude the magnitude of any association. To highlight the importance of CRC screening and surveillance in PSC/IBD patients, it has been demonstrated that the frequency of CRC development within 2 years of concurrent diagnosis is the same as CRC development within 8–10 years from diagnosis of IBD alone. Notably, more than 50% of patients have stage 3 or 4 CRC at the time of diagnosis [116]. Guidelines from the American Association for the Study of Liver Diseases suggest a complete colonoscopy with biopsies is recommended in patients with newly diagnosed PSC and no previous history of symptoms of IBD [117]. As IBD in PSC can be clinically asymptomatic and focal, a full colonoscopy is required to establish the diagnosis of IBD and to screen for CRC. If the initial colonoscopy with biopsies is negative for IBD, a surveillance colonoscopy should be considered every 5 years [118]. In PSC patients with UC a surveillance colonoscopy at 1–2-year intervals from the time of diagnosis of PSC is recommended. Patients with PSC who have CD are recommended to be surveyed similarly to patients with UC [117,119,120]. The role of chromoendoscopy, narrow band imaging, and confocal endomicroscopy to augment the diagnostic ability of white light colonoscopy to detect neoplasia is evolving [121].

Chronic inflammation appears to be the primary mechanism for carcinogenesis in these patients. Interestingly, CRC in PSC exhibits a tendency to occur more commonly on the right side of the colon, with up to 76% of reported CRC in PSC/IBD patients having a lesion proximal to the splenic flexure [122,123]. An increased concentration of cytotoxic secondary bile acids in the proximal colon is a potential but unproven factor contributing to this distribution [122]. Cytotoxic injury to colonic mucosa by the secondary bile acids, such as deoxycholic acid and lithocholic acid, causes hyperproliferation that can lead to neoplasia [124]. Secondary bile acids have also been implicated in the development of sporadic colonic adenomas and colon cancers. PSC/IBD patients should have a vigilant and thorough examination of the entire colon and especially the right side of the colon to optimize the detection of neoplasia.

Liver transplantation for PSC patients is highly successful, with a 5-year survival rate of approximately 85%. The survival outcomes for live donor transplant are thought to be comparable [117]. Disease recurs in up to 20–25% of patients 5–10 years after the transplant procedure [125,126]. Approximately 60% of patients with pre-existing IBD will experience active inflammatory bowel disease after transplantation despite the use of immunosuppressive agents [127]. It is critical to appreciate that patients with PSC and UC undergoing liver transplantation remain at a higher risk for the development of CRC compared with PSC patients without transplantation (odds ratio 4.4; 95% confidence interval 0.9–12.8) [128]. The risk is higher with longstanding UC and pan-colitis [128,129]. Post-transplant PSC patients with UC should therefore continue to undergo annual surveillance with colonoscopy [117].

Liver Transplantation

Pre-Transplant Screening in Liver Transplant Candidates

Indications for mandatory pre-transplant colon cancer screening remain controversial. The advent of model for end-stage liver disease (MELD) scoring has led to an increasing number of advanced liver disease patients being placed on transplant waiting lists. The challenge remains to balance the need of an urgent transplant with the possibility of a healthy, long term survival of the recipient after the transplantation. There are extensive and detailed cardiac, pulmonary, and renal evaluations that are warranted as a means of excluding comorbidity, infection, or malignancy, which may compromise the success of transplantation [36]. In addition, since these patients are exposed to lifelong immunosuppression, any undetected precancerous or malignant colonic neoplasms may have an increased risk of progressing to overt malignancy, thereby emphasizing the need for pre-transplant detection and removal of such lesions [130–133]. Currently, the decision to perform a pre-transplant screening colonoscopy is primarily driven by the local policies of individual centers. Some centers recommend flexible sigmoidoscopic screening only, especially in younger patients without risk factors [134], while others screen patients over the age of 45–50 years with full colonoscopy [135,136]. Balancing the risks and potential benefits often favors proceeding with screening. Comorbidities secondary to liver disease such as coagulopathy, ascites, and renal insufficiency can pose an increased risk of morbidity and mortality in this patient population [36]. Despite the potential increase in risks, colonoscopic evaluation can help management decisions in potential transplant candidates both before and after transplantation [137].

Post-Transplant Screening and Surveillance

One of the leading causes of mortality in post-transplant patients is primary malignancies. An increased risk of developing de novo cancer is an established complication of organ transplantation and the associated immunosuppression. The cumulative prevalence of malignancy has been shown to increase with the duration of follow-up and the intensity of immunosuppression [138]. CRC is more frequent in liver transplant recipients than in an age and sex matched population [139]. This increased incidence is noted in the overall post-liver transplant recipients, including the subgroup of non-PSC post-transplant patients, when compared with the general population. In a single center post-transplant Dutch population study by Haagsma et al., a significantly increased relative risk (RR) of 12.5 was observed for colon cancer [27]. Rates as high as 6.5% has been reported in patients with UC and PSC who underwent liver transplantation [139].

Several possible mechanisms for an increased incidence of colorectal neoplasia post-transplant have been suggested. Liver transplant patients can have predisposing conditions such as IBD or precursor lesions such as adenomatous/serrated polyps before transplantation that can eventually lead to CRC. Immunosuppression can impair immunosurveillance, an important protective mechanism for cancer development. Immunosuppressive agents themselves could alternatively act as direct carcinogens [140]. Several post-transplant malignancies are related to viral infections. It has been hypothesized that JC virus (a type of human polyomavirus) reactivation in colorectal mucosa/adenomas in post-transplant patients secondary to immune suppression induces CRC development, however the clinical significance of this remains uncertain [141]. Despite these

concerns, under current guidelines, non-PSC liver transplant recipients are not recommended to undergo an intensified screening or surveillance protocol compared with the general population [130].

Conclusion

Colorectal cancer screening with colonoscopy has increased over the last decade in part due to emerging data on reducing CRC mortality. Evidence supporting screening and surveillance colonoscopy in liver disease patients, including those with cirrhosis, has largely been extrapolated from the literature and outcomes in patients without liver disease. Patients with PSC and IBD clearly represent a select group with an elevated cancer risk that warrants annual pre- and post-transplant surveillance. In non-PSC patients, routine pre-transplant evaluation with colonoscopy has become the standard in most transplant centers. More intensive post-orthotopic liver transplantation screening and surveillance may be indicated but remains poorly defined. A high quality colonoscopic examination is important in improving outcomes and several issues – including the challenges of colon preparation, altered colonic mucosa in the setting of portal hypertension, and altered coagulation parameters – all require special consideration in patients with advanced liver disease.

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12

Endoscopic Retrograde Cholangiopancreatography and Cholangioscopy in Hepatobiliary Disease

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Introduction

There are a myriad of conditions affecting the biliary tract in patients with chronic liver disease, such as primary sclerosing cholangitis (PSC) and secondary sclerosing cholangitis (SSC). However, patients with cirrhosis are also prone to suffer from common conditions such as choledocholithiasis, bile duct injuries, and primary or secondary hepatobiliary tumors (Table 12.1; Figures 12.1, 12.2, and 12.3) [1–10]. Hepatocellular carcinoma (HCC) may result in biliary strictures due to compression, tumor invasion, or hemobilia (Figure 12.4). Hemobilia is also a complication associated with local radiological or surgical therapy for HCC. Other non-biliary tract conditions, such as portal hypertension with or without chronic liver disease, may result in portal biliopathy, a condition that can present as obstructive jaundice due to external biliary compression from hemobilia or by the enlarged collateral veins. Nevertheless, the most common biliary problem seen in patients with chronic liver disease is choledocholithiasis. Although in patients with intact liver function the decision to perform an invasive procedure such as endoscopic retrograde cholangiopancreatography (ERCP) is usually straightforward, this is a difficult decision in patients with liver dysfunction and coagulopathy. In this chapter we will present a practical approach to ERCP and cholangioscopy in patients with chronic liver disease, and highlight key aspects of patient preparation, intra-procedural steps, and post-procedure care.

General Aspects of Endoscopic Retrograde Cholangiopancreatography and Cholangioscopy

Patient Preparation

The pre-endoscopic preparation of patients with chronic liver disease undergoing ERCP and/or cholangioscopy should be

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Table 12.1 Biliary tract disorders in chronic liver disease.

Benign	Malignant
Gallstones	Hepatocellular carcinoma (HCC)
Primary sclerosing cholangitis (PSC)	Cholangiocarcinoma (CCA)
Secondary sclerosing cholangitis	Metastatic disease:
Bile duct injuries	Stomach
Postoperative strictures:	Pancreas
Post-cholecystectomy	Small bowel
Post-OLT	Colon
IgG4 cholangiopathy	Rectum
AIDS related cholangiopathy	Lung
Parasite infestation:	Breast
Ascaris lumbricoides	Uterus
Liver flukes (e.g., *Fasciola hepatica*)	Kidney
Tuberculosis	Multiple myeloma
Sarcoidosis	Lymphoma:
Congenital:	Infiltrating liver
Congenital liver fibrosis	Portal lymph nodes
Caroli syndrome and disease	Histiocytosis X
Cystic fibrosis	
Congenital bile duct cysts	
Tumors:	
Adenomas	
Benign intraductal papillary mucinous neoplasms	
Biliary papillomatosis	

structured and detailed as these procedures are associated with specific risks (Table 12.2). For example, sphincterotomy in patients with cirrhosis and cholestatic disorders is associated with a higher risk of bleeding [11]. Thus, a multidisciplinary team approach involving the endoscopist, anesthesiologist or internist, radiologist, and surgeon is mandatory in the majority of patients with chronic liver disease submitted for ERCP and/or cholangioscopy. In the authors' endoscopy unit we have designed and followed a specific preoperative preparation checklist for every endoscopy that is summarized with the mnemonic ASSCOPE (Box 12.1). By having such a checklist the team can be reassured that no surprises arise on the day or moment of endoscopy.

Physical Examination

Patients with chronic liver disease are generally frail, have multiple comorbidities, and the pancreatobiliary interventions are usually complex and associated with multiple dilations and stenting. The focus of the physical exam should be on: (i) the oropharynx and airway (Mallampati score); (ii) the skin (evaluate for ecchymosis, suggesting vitamin K deficiency) or signs of chronic liver disease (e.g., palmar erythema, spider angioma, Dupuytren contractures) suggesting liver dysfunction; and (iii) the abdomen (evaluating for ascites, which would impair proper patient positioning on the endoscopy table). In most institutions, ERCP is generally performed in the prone position, which is more challenging in the presence

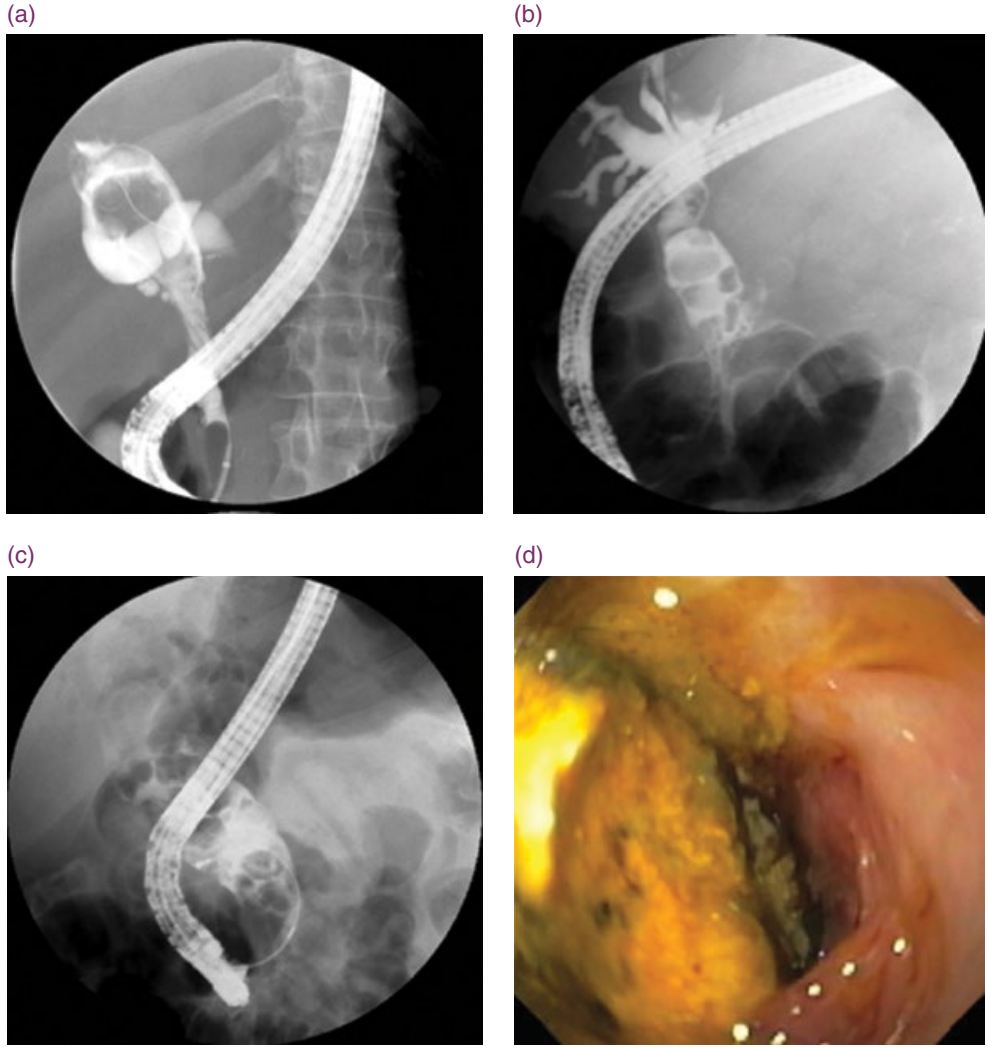


Figure 12.1 Complex stone disease in a patient with sclerosing cholangitis and liver cirrhosis. (a) The proximal bile duct is massively dilated and contains at least one giant stone. (b) Detailed cholangiography showing multiple large stones. (c) The common bile duct is also strictured distally, complicating management of the proximal stones. (d) Direct cholangioscopy allows for direct visualization and targeted destruction of bile duct stones.

of ascites [12]. In the presence of significant ascites we recommend that a pre-endoscopic paracentesis be done, even if the procedure will be performed in the supine or left lateral decubitus position. When the patient is lying on the operating table, the ascites compresses the diaphragm and the tidal volumes are decreased, leading to decreased respiratory capacity.

Laboratory Tests

ERCP should be regarded as one of the most invasive endoscopic procedures alongside other high risk interventions

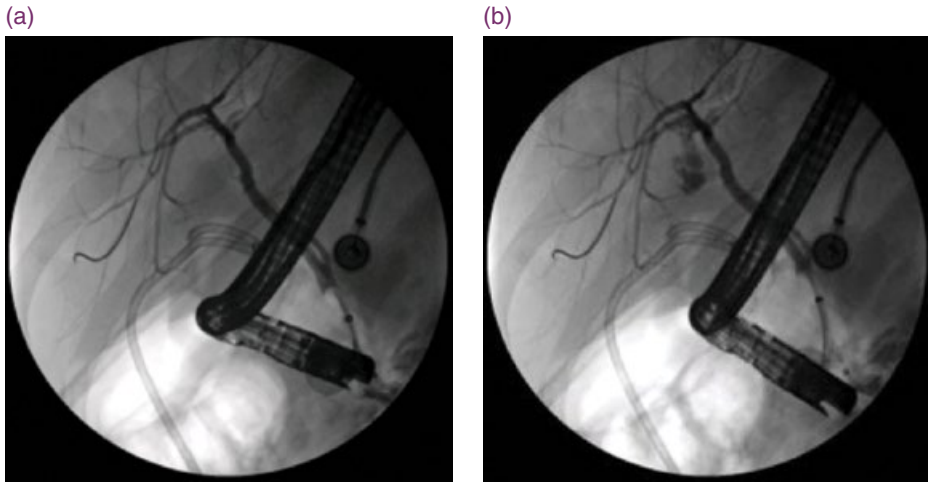


Figure 12.2 Postoperative bile duct leak of Luschka in a patient with Child–Pugh class A cirrhosis. (a) Clinically, a leak was evident because of abdominal pain and bile exiting the percutaneous drain. However, the initial cholangiography did not demonstrate this leak. (b) It is imperative to perform an occlusion cholangiogram (i.e., by inflating the balloon catheter while injecting contrast into the bile ducts) to demonstrate small or complex leaks, such as this bile leak.

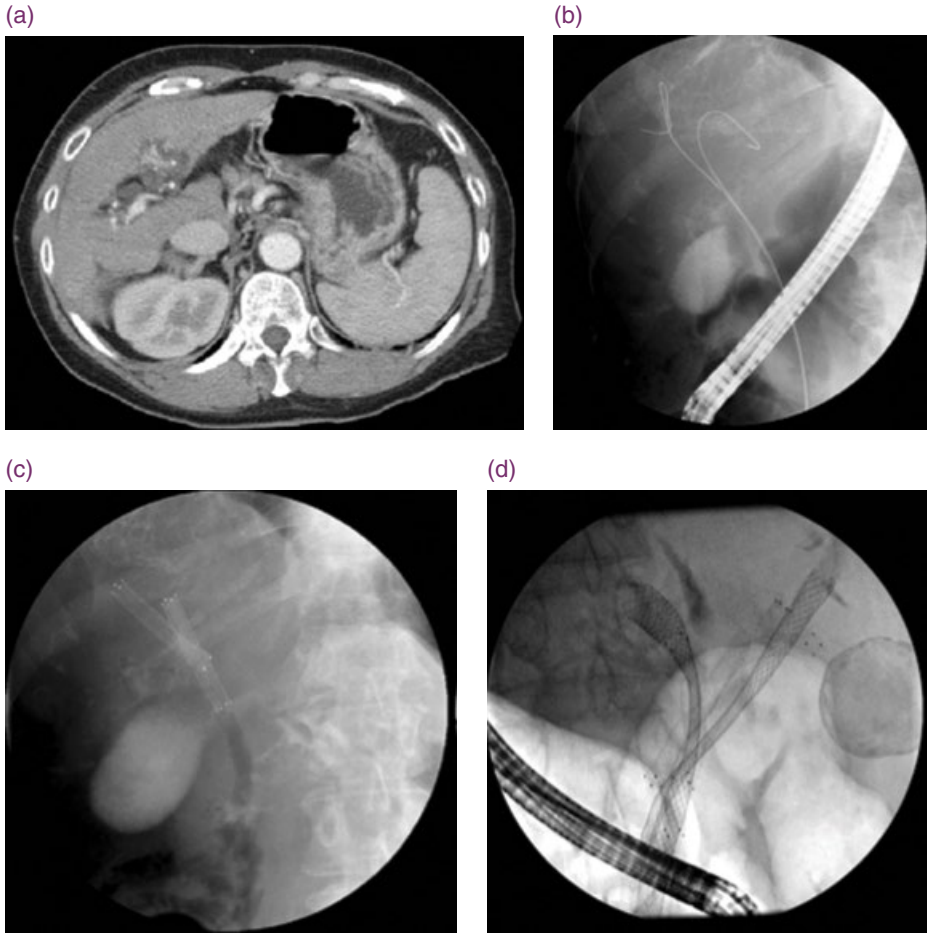


Figure 12.3 Hepatobiliary tumors. (a) Liver cell cancer causing hilar obstruction. (b) The use of multiple wires is essential to keep access to the obstructed bile ducts. (c) Double metal stenting in a hepatobiliary tumor causing obstruction. (d) Multiple (i.e., four) stenting in a patient with complex hepatocellular cancer causing multiple bile duct strictures.

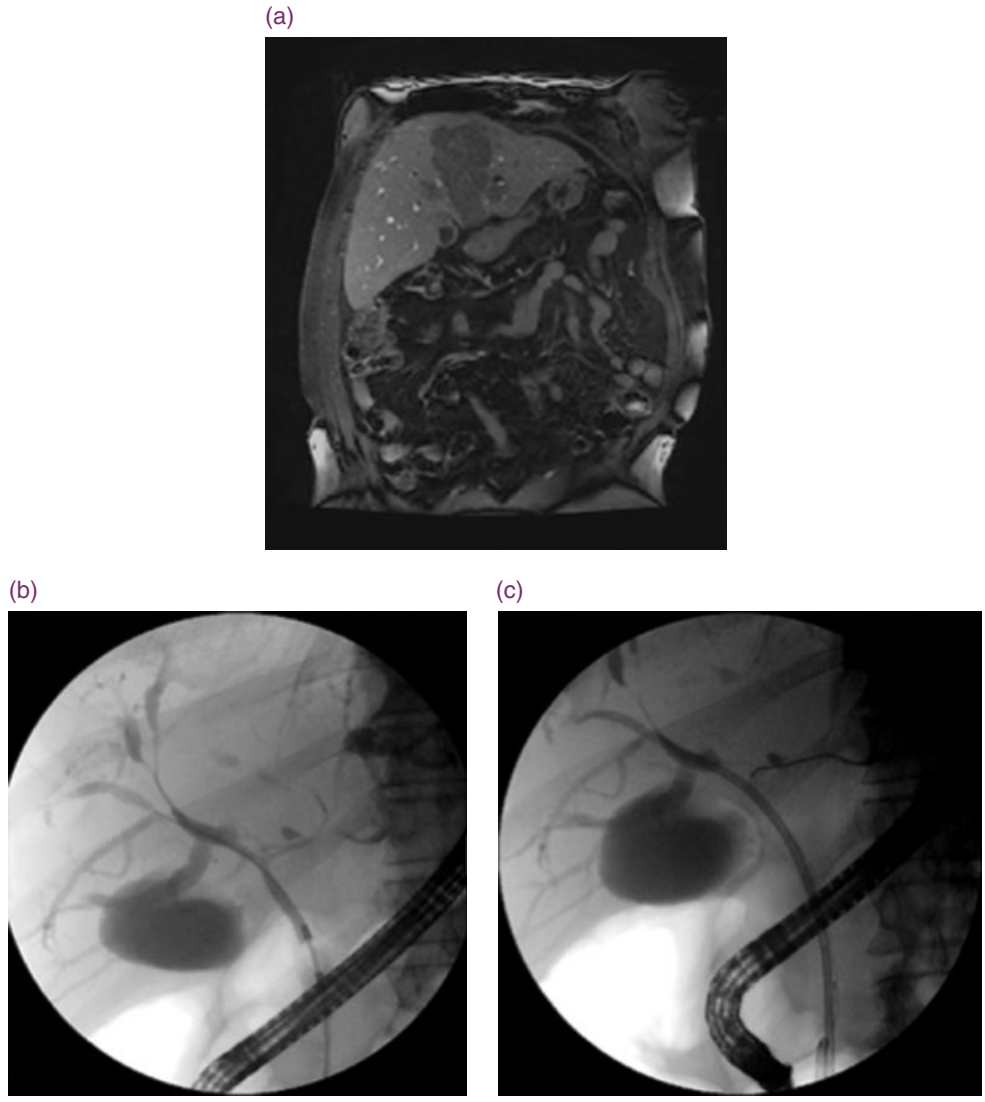


Figure 12.4 Large hepatocellular carcinoma in a patient with cirrhosis due to hepatitis C. (a) A large mass compressing the bile ducts. (b) Multiple compressions appear similar to sclerosing cholangitis. (c) An attempt at decompressing the bile ducts using long plastic stents.

such as sphincterotomy and balloon dilation. Therefore, a precise knowledge of the coagulation status and platelet count is essential (Table 12.2). The ideal platelet count to permit an ampullary incision (i.e., sphincterotomy) is not known. However, the risk of bleeding is highest when the platelet count is lower than 50,000/μL. In addition, the minimum accepted platelet count for the adequate formation of a coagulum is 44,000/μL [13]. A preoperative laboratory check is mandatory as many patients have coagulopathy due to vitamin K malabsorption or impaired liver synthesis of coagulation factors [1]. Oral or intravenous replacement of vitamin K is useful in patients with bile duct obstruction. In patients with underlying parenchymal destruction due to cirrhosis, vitamin K may not lead to any improvement in the

Table 12.2 General considerations for endoscopic retrograde cholangiopancreatography (ERCP) in patients with chronic liver disease.

Conditions	Clinical and laboratory workup	Measures to be taken
Coagulopathy: Bile duct obstruction Impaired liver synthesis	INR >1.5 Total/direct bilirubin, alkaline phosphatase >3×; albumin <28 g/L; PT <50% (>6 seconds), INR >1.5	If sphincterotomy is anticipated give IV vitamin K Bring INR <1.5; Give fresh frozen plasma (FFP) and recombinant factor VIIa
Thrombocytopenia	<40,000/μL	Consider platelet transfusion, especially if sphincterotomy is planned or performed
Ascites	Tense, distended, and tender abdomen	Give IV antibiotics Pre-ERCP paracentesis Left lateral or supine position
Sedation	If encephalopathic, coagulopathic, or with kidney failure	Have an anesthesist provide sedation or general anesthesia

INR, international normalized ratio; IV, intravenous; PT, prothrombin time.

Box 12.1 The Mönkemüller and Weber ASSCOPE pre-endoscopic mental checklist

- **A** Anticoagulation and antibiotic management
- **S** See the patient (bedside exam; make sure the patient is not unstable, with no tense ascites, an adequate airway, adequate vital signs, no rash, no contagious disorders, and stable enough to be transported to the endoscopy suite)
- **S** Sedation (moderate versus general anesthesia)
- **C** Consent (obtain permit/consent from patient and or responsible party/family member)
- **O** Order any necessary pre-procedural tests: blood counts, electrolytes, coagulation studies, and pregnancy test, as appropriate
- **P** Preparation: is there an indication for special/additional prep, such as moderate or severe constipation or prior poor prep? Nothing by mouth except meds after midnight for all procedures
- **E** Equipment: what specialized equipment is needed, such as carbon dioxide for cholangioscopy, ultraslim gastroscope, or special stents and wires? Always carry a fully covered metal stent if performing sphincterotomy in cirrhotic patient

prothrombin time or international normalized ratio (INR). We prefer to guide the endoscopic intervention based on INR values instead of prothrombin time (PT). Although there are no large studies evaluating a "safe" INR to perform ERCP in these patients, we do not advocate performing sphincterotomy in patients with an INR >2.0 (other more conservative experts limit sphincterotomy to INR <1.5). The use of platelets and fresh frozen plasma (FFP) has never been proven to correct coagulopathy, but can be helpful during an acute episode of bleeding [11]. However, personal experience has led us to use judicious administration of these blood products in the perioperative period in an attempt to decrease the risk of bleeding in patients with a high INR (i.e., INR >3.0). Nevertheless, the decision to intervene should be on a case

by case basis and dictated by the severity of the patient's clinical status, comorbidities, and the need for urgent decompression. ERCP has been performed in extremely sick patients with chronic liver disease and coagulopathy presenting with cholangitis without biliary sphincterotomy but with stent insertion and biliary decompression, which has resulted in marked improvement of the patient's condition and no bleeding complications.

Sedation and Patient Position

In most US-based institutions, ERCP is performed with patients under general anesthesia or monitored anesthesia care under the direct supervision of an anesthetist, whereas in Germany conscious sedation with propofol administered by a trained medical personnel and physician is widely accepted as standard of care. The majority of ERCP procedures are performed under general anesthesia with patients in the prone position; this allows easier passage of the duodenoscope through the pharynx and lowers the risk of aspiration. A left lateral or prone position has an advantage as it enables effective control of secretions by allowing drainage from the oropharynx with gravity rather than requiring frequent suction. However, the prone position is not always optimal, especially in patients with tense ascites, abdominal distention or tenderness, indwelling percutaneous catheters or recent abdominal surgery. In addition, patients with limited neck mobility may not be able to accommodate the endotracheal tube. While there has been no formal evaluation of the use of ERCP in the left lateral position, a left lateral or supine position can be used depending on the clinical circumstances [12]. However, there are conflicting data on the clinical safety of the supine position. While it has been considered safe and preferable, some studies have reported more cardiopulmonary adverse events in patients placed in the supine position [14]. The supine position is technically feasible but more demanding and can be less comfortable for the endoscopist as he or she has to turn his or her back away from the operating table (and patient) to successfully achieve cannulation. This 90 degree body rotation sometimes impairs the endoscopist's view of the endoscopy monitor and may require the use of a second monitor, which may not be available in every endoscopy unit.

General Endoscopic Retrograde Cholangiopancreatography Techniques in Patients with Chronic Liver Disease

Cannulation of the Biliary Tract

Before ERCP is started, careful attention should be given to removing any external wires, artifacts, metal, or objects that may confuse or obscure the operating field (Figure 12.5). The presence of these objects may lead to confusion and misrepresentation of subtle findings of strictures, leaks, and other bile duct defects. The majority of ERCPs in patients with chronic liver disease have a therapeutic intent. Thus we always use a sphincterotome and guidewire to cannulate the bile ducts in these patients. Furthermore, some studies show that ERCP wire guided cannulation is associated with fewer complications than traditional biliary catheter cannulation [15].

Table 12.3 lists the equipment and accessory considerations for ERCP in patients with chronic liver disease. The amount of contrast injected will depend on the clinical indication and the underlying biliary disease. After deep cannulation of the biliary tract, enough contrast should be injected to identify the stricture or leak and to define the management strategy. In patients with suspected bile duct stones, we recommend the use of diluted contrast to avoid obscuring the stones if the contrast is too dense. In addition, gentle injection of contrast is mandatory, first

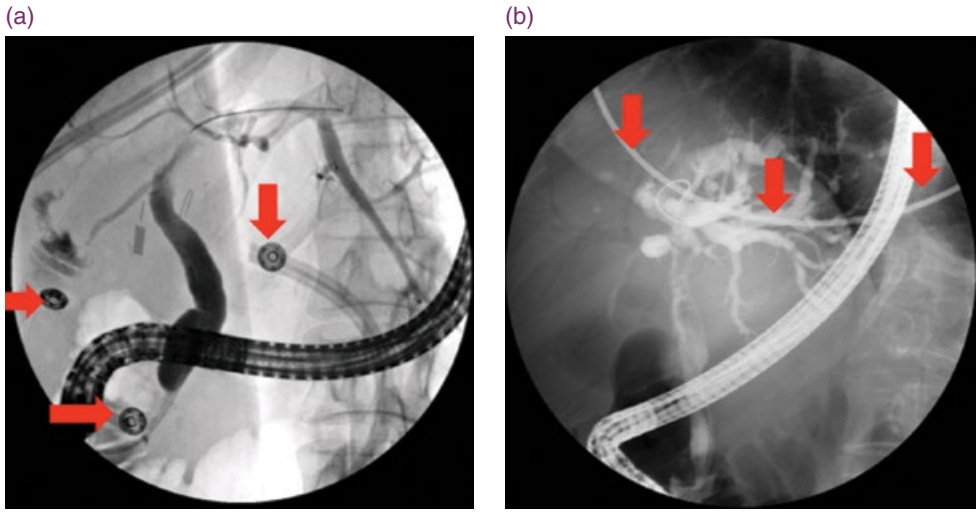


Figure 12.5 Preparation of the operating field. (a) Before embarking on ERCP careful attention should be given to remove any items with radiopaque material that may obscure or interfere with the operating field (red arrows show electrocardiogram strips). (b) The presence of these objects may lead to confusion and misrepresentation of findings of strictures, leaks, and other bile duct defects (red arrows indicate a bra).

Table 12.3 Equipment and accessory considerations for endoscopic retrograde cholangiopancreatography in patients with chronic liver disease.

Equipment	Considerations
Cannulation	Standard
Wire	Hydrophilic, soft tip, operator preferred shape (straight versus angled shape)
Contrast	Diluted; given gently from distal to proximal bile duct
Sphincterotomy	If necessary. Consider the use of pulse cut (Endocut) instead of blend current Consider EPBD in Child–Pugh class C patients
Stent placement	Consider <10 Fr stent placement without prior endoscopy unless proximal lesion For multiple stenting, endoscopic sphincterotomy is necessary
Stent type	Plastic: consider silicon pigtail shape to avoid trauma of the contralateral duodenal wall Consider insertion of uncovered SEMS in patients with prolonged life expectancy fcSEMS is an alternative option for benign conditions (strictures affecting bile duct bifurcation require bilateral drainage)

EPBD, endoscopic papillary balloon dilation; fcSEMS, fully covered self-expanding metal stent; SEMS, self-expanding metal stent.

filling the distal bile duct and gradually injecting towards the bifurcation and intrahepatic ducts. In patients with PSC and those with strictures of the proximal parts of the bile ducts, extreme care should be taken regarding the amount and force of contrast injection as this may lead to bacteremia and sepsis. It is important to avoid overinjection of contrast to prevent acute cholangitis in cases where local drainage is not adequate. On the other hand, forceful injection, including the use of an inflated balloon ("occlusion cholangiogram"), is mandatory when a bile leak

is suspected and not found on initial cholangiography (Figure 12.2).

Endoscopic Sphincterotomy and Endoscopic Papillary Balloon Dilation

Patients with cirrhosis have a significantly higher risk of post-sphincterotomy bleeding than non-cirrhotic patients. Advanced Child–Pugh stage, higher model for end-stage liver disease (MELD) score, and coagulopathy are well known risk factors for post-sphincterotomy bleeding. There are some precautions and alternative methods that have been shown to decrease this risk. Endoscopic papillary balloon dilation (EPBD) may be a safer option than endoscopic biliary sphincterotomy for the treatment of bile duct conditions in patients with advanced cirrhosis and coagulopathy because it is associated with a reduced risk of bleeding (Table 12.4) [16]. While there is no difference in the incidence of bleeding in patients with Child–Pugh class B cirrhosis between biliary sphincterotomy and EPBD, patients with Child–Pugh class C cirrhosis are at a substantially higher risk of bleeding if undergoing biliary sphincterotomy as compared with EPBD (35.7% and 0%, respectively) [16]. Interestingly, EPBD of the intact papilla is still rarely used in most western countries, whereas this technique is more widespread in eastern countries [17,18]. Parlak and colleagues reported less bleeding in cirrhotic patients undergoing sphincterotomy with an electrosurgical generator applying alternating current in pulse cut mode as opposed to patients who underwent sphincterotomy via a blended current [19]. In cases of post-sphincterotomy bleeding, injection of saline/adrenaline or fibrin glue, clipping, or the insertion of plastic or covered self-expanding stents may lead to hemostasis. When performing ERCP with sphincterotomy in patients with chronic liver disease, we always have a fully covered self-expanding metal stent available as these types of stents have a larger diameter and when inserted into the bile duct across the bleeding sphincterotomy site their expansion forces generally lead to hemostasis (Figure 12.6).

Biliary Stents

The preferred stents for use in the majority of biliary tract diseases in patients with chronic liver disease are plastic (polyethylene or Teflon) (Figure 12.7) [20,21]. Whereas large diameter (i.e., 10 or 11.5 Fr) stents are nearly always preferred due to their longer patency rates, occasionally only smaller diameter (7 Fr) stents can be inserted, especially in patients with primary or secondary sclerosing cholangitis and those with cholangiocarcinoma with very tight and complex strictures. Occasionally, multiple 5 Fr pancreatic plastic stents are needed when treating multiple, complex strictures in PSC or SSC (Figure 12.8). In situations with complex strictures or tortuous bile ducts we favor the use of double pigtail stents, as these appear to adapt better to the shape of the bile duct strictures (Figure 12.9). In addition, the exposed endoluminal part of the stent is curved (due to the pigtail shape), potentially leading to less mucosal contact and damage inside the duodenum (Figures 12.3 and 12.4). In the event of endoscopic inaccessibility of complex hilar strictures, percutaneous transhepatic cholangiopancreatography is mandatory (Figure 12.10).

Self-Expandable Metal Stents

The major disadvantage of plastic stents is their high rate of occlusion (about 75% within 90 days of placement) [20,21]. Thus, if the patient is expected to survive for more than 3 months, but less than 6–9 months, the use of self-expanding metal stents

Table 12.4 Therapeutic options in various hepatobiliary disorders associated with chronic liver disease.

Disease	Condition	Therapeutic options
Primary sclerosing cholangitis	Dominant stricture (<1.5 mm)	Biopsy or brush cytology ± FISH or digital imaging to exclude cholangiocarcinoma Consider cholangioscopy if possible Balloon dilation with/without stent placement
Bile duct injury	Type A	Stent insertion with or without EST
	Type B	EST and stent placement to bypass leak Consider PTCD (± rendezvous procedure) if ERCP fails (25%)
	Type C	Consider Bismuth classification prior to ERCP Balloon dilation Plastic stent (multiple) insertion
	Type D	Consider EUS/ERCP rendezvous procedure if expertise are available
Biliary stones	No coagulopathy (Child–Pugh A and B)	Same as low risk patients
	Coagulopathy	Consider EPBD instead of EST
Hepatocellular carcinoma	Type 4	EST with or without stent insertion
	Type 3	Brush cytology or digital imaging for diagnosis Consider cholangioscopy if possible Balloon dilation with/without stent placement Consider SEMS for type 3b
	Type 2	Stenting is controversial
	Type 1	No role for stenting
	Hemobilia	Plastic stent insertion Consider fcSEMS
Cholangiocarcinoma	In CBD tumors with life expectancy >6 months	Plastic (preferably), uncovered SEMS if life expectancy between 3 and 9 months
	In CBD tumors with life expectancy <6 months	Plastic stent insertion
	Hilar lesions	Unilateral uncovered SEMS usually sufficient Bilateral plastic or uncovered SEMS if possible or required
	Unresectable CBD (± hilar) tumors	Photodynamic therapy
	Stent occlusion	If plastic, consider scheduled stent exchange after 2–4 months If SEMS consider plastic stent insertion or ablation (APC, RFA)

APC, argon plasma coagulation; CBD, common bile duct; EPBD, endoscopic papillary balloon dilation; ERCP, endoscopic retrograde cholangiopancreatography; EST, sphincterotomy; EUS, endoscopic ultrasound; fcSEMS, fully covered self-expanding metal stent; FISH, fluorescence in situ hybridization; PTCD, percutaneous transhepatic cholangiogram and drainage; RFA, radiofrequency ablation; SEMS, self-expanding metal stent.

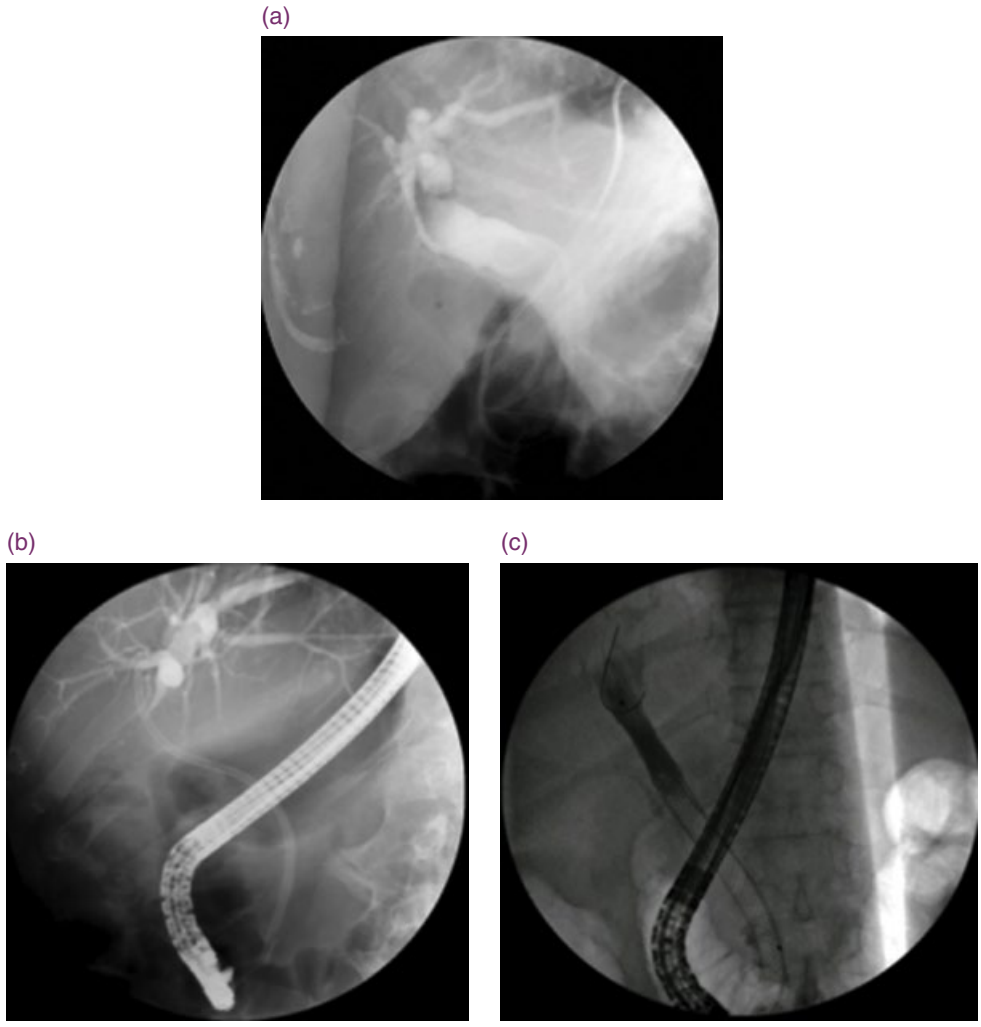


Figure 12.6 Plastic versus metal stents in chronic liver disease. (a) Dilated bile duct with ampullary swelling impeding adequate drainage. (b) Prophylactic insertion of a plastic stent. (c) Post-sphincterotomy bleeding in liver cirrhosis.

(SEMSs) is advocated (Figure 12.11) [20,21]. Most SEMSs for malignant biliary strictures are made of nitinol, a superelastic nickel-titanium alloy with thermal shape memory (a property of reassuming a predetermined shape through heating) (Figure 12.7). As these stents are placed through the working channel of the endoscope, fluoroscopy is always needed. Ideally, SEMSs should be clearly visualized during fluoroscopic placement. The radio-opacity of some metal stents is enhanced by incorporating other metals into the body or the ends of the stent (Figure 12.7). Fully covered SEMSs offer the potential advantage of preventing tissue ingrowth and are particularly useful in the setting of post-sphincterotomy bleeding (Figure 12.6). Whereas the use of SEMSs is clearly indicated for distal and hilar strictures, the use of double metal stenting into each intrahepatic bile duct is less well studied (Figure 12.11). Fully covered SEMSs are not indicated for

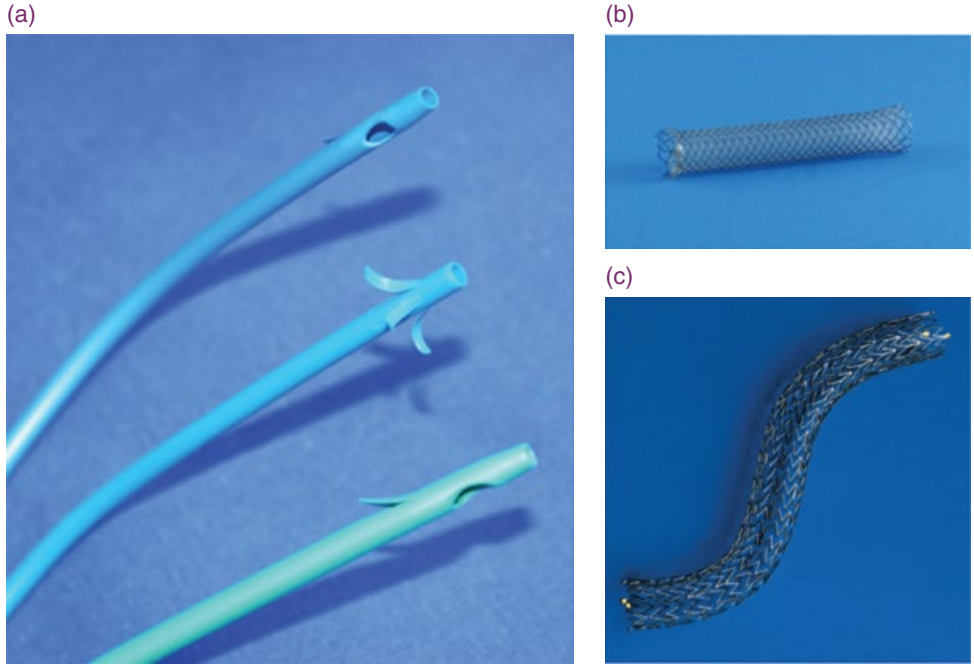


Figure 12.7 Types of stents. (a) The preferred stents for the majority of biliary tract diseases in patients with chronic liver disease are plastic (polyethylene or Teflon). (b, c) Metal stents are reserved for malignant strictures, post-sphincterotomy bleeding, and occasionally for benign bile duct strictures. The radio-opacity of some metal stents is enhanced by incorporating other metals into the body or to the ends of the stent.

proximal biliary obstruction because they may occlude the contralateral biliary system or biliary side branches [21]. In addition, fully covered SEMSs should be avoided in the presence of patent cystic duct as the large diameter stent may occlude it, resulting in cholecystitis.

Plastic Versus Self-Expandable Metal Stents

Plastic stents are the most common used types of stents. These are indicated for most types of benign strictures and leaks. Plastic stents have the important advantage of lower initial costs and they can be changed several times. However, plastic stents have shorter patency rates and are associated with obstruction rates of 30–70% within a period of 3–6 months, with replacement being recommended every 3 months to prevent complications related to obstruction. The obstruction occurs due to the biofilm formed by bacterial colonization and duodenal reflux [21]. SEMSs are mainly indicated for the treatment of malignancy, especially when the life expectancy of the patient is expected to be more than 3 months but less than 9–12 months. Uncovered SEMSs have the advantage of being larger in diameter and consequently prolonged patency, with fewer interventions being needed because of obstruction. However, these stents are very difficult to remove. Some studies have compared plastic and metallic stents with regard to cost, complications rate, and survival. In one recent meta-analysis [20] involving seven randomized controlled trials, 724 participants were randomized

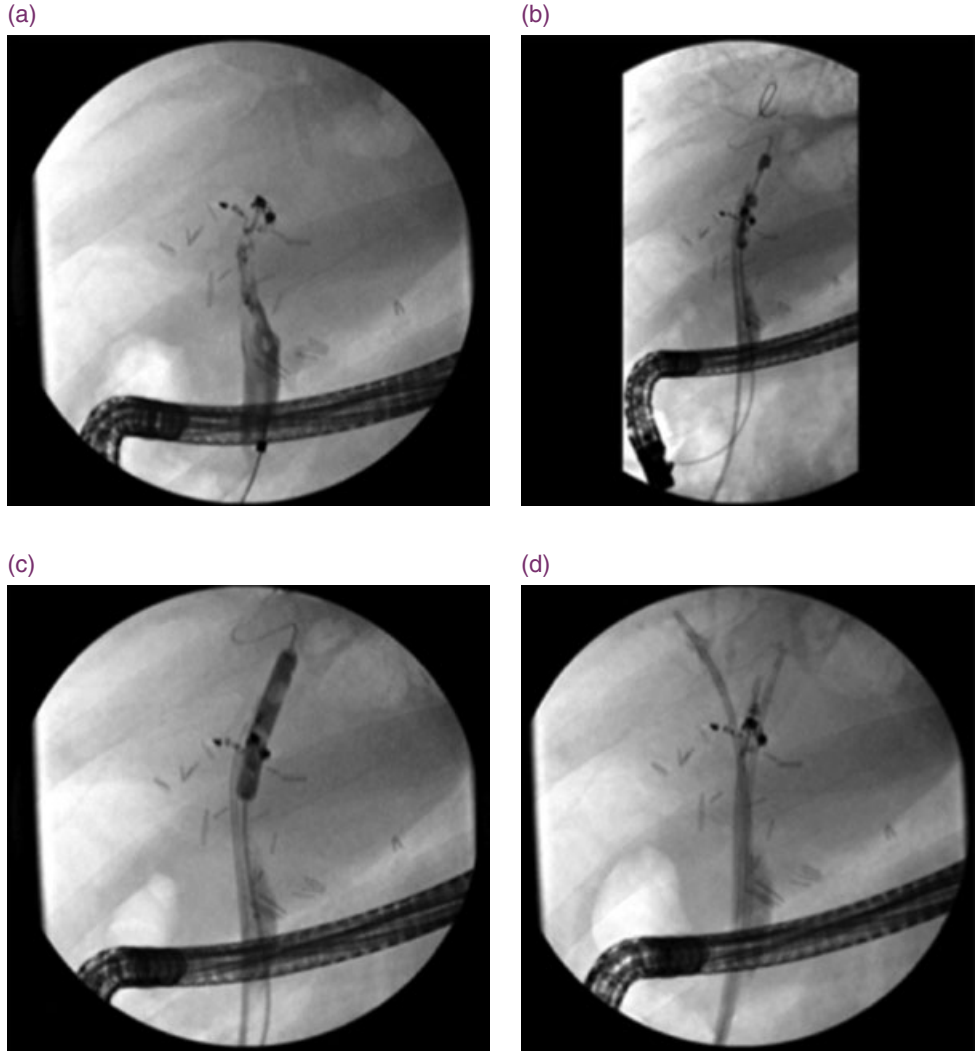


Figure 12.8 Complex ischemic, secondary sclerosing cholangitits with liver cirrhosis. (a) This patient developed ischemic cholangiopathy after an episode of hemorrhagic shock due to a ruptured pseudoaneurysm of the hepatic artery. (b) Insertion of multiple wires is mandatory to secure access to all patent bile ducts. (c) The strictures are dilated with a biliary balloon catheter. (d) Occasionally, the use of multiple 5 Fr pancreatic plastic stents is needed when treating multiple, complex strictures.

to either SEMSs or plastic stents. No significant difference between the two stent types in terms of technical success, therapeutic success, 30-day mortality, or complications was observed. The plastic stent patency rates ranged from 62 to 165 days, and metal stent patency rates from 111 to 273 days. Metal stents were associated with a significantly smaller relative risk of stent occlusion after 4 months than the plastic stents. The overall risk of recurrent biliary obstruction was also significantly lower in patients treated with metal stents [20].

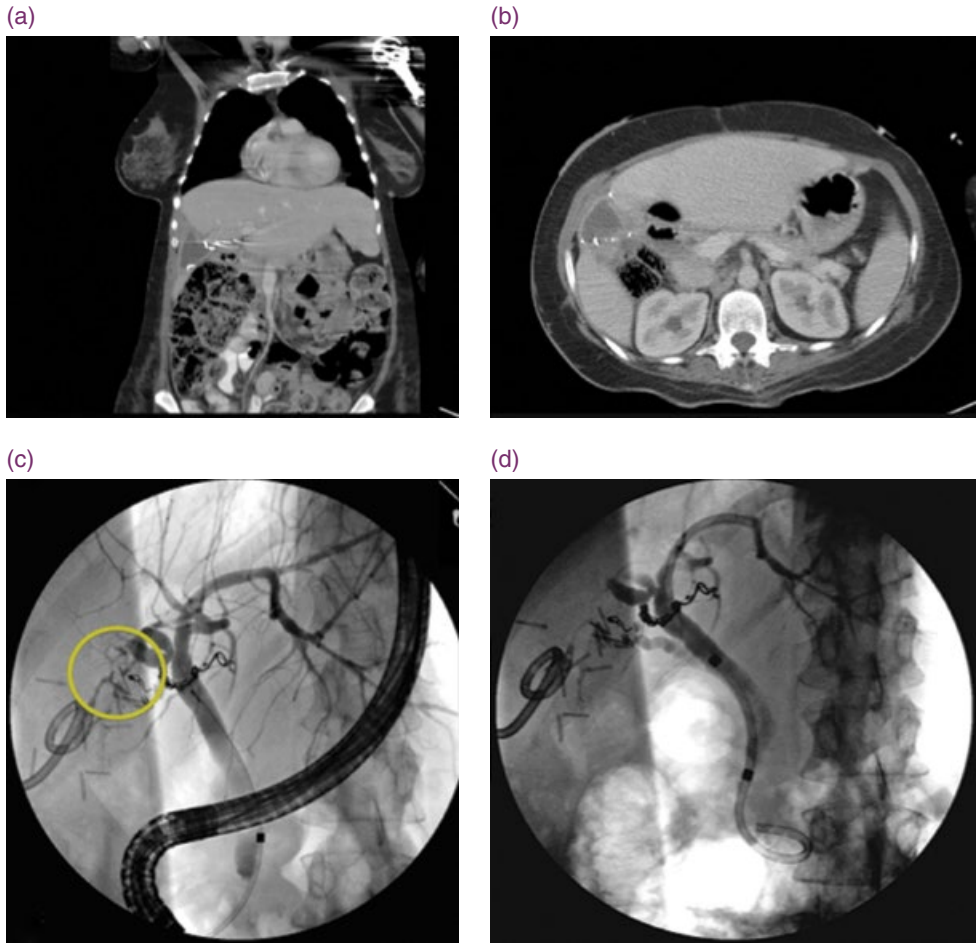


Figure 12.9 Bile leak after partial right-sided hepatectomy. (a) Computed tomography (CT) scan showing the biloma. (b) CT, sagittal view. (c) A small bile leak became apparent during cholangiography. (d) A double pigtail stent was inserted.

Diseases Associated with Biliary Obstruction or Damage in Chronic Liver Disease

Biliary Stones

Patients with chronic liver diseases have a higher incidence of hepatobiliary lithiasis than healthy individuals and not uncommonly require cholecystectomy and biliary manipulation for the treatment of gallbladder stone diseases (Figure 12.1) [22,23]. Chronic liver diseases associated with lithogenesis are primary and secondary sclerosing cholangitis, oriental cholangiohepatitis, and Caroli disease and syndrome (Figures 12.12 and 12.13) [22,23]. Furthermore, liver cirrhosis of any etiology is associated with a higher incidence of bile duct stones [22]. Conte et al. [23] found that cirrhosis is a risk factor for gallstones in males and suggested that an increase in estrogen level could play a role. In patients with cirrhosis, most gallstones are black pigment stones and they are formed by supersaturation of calcium bilirubinate in bile [24].

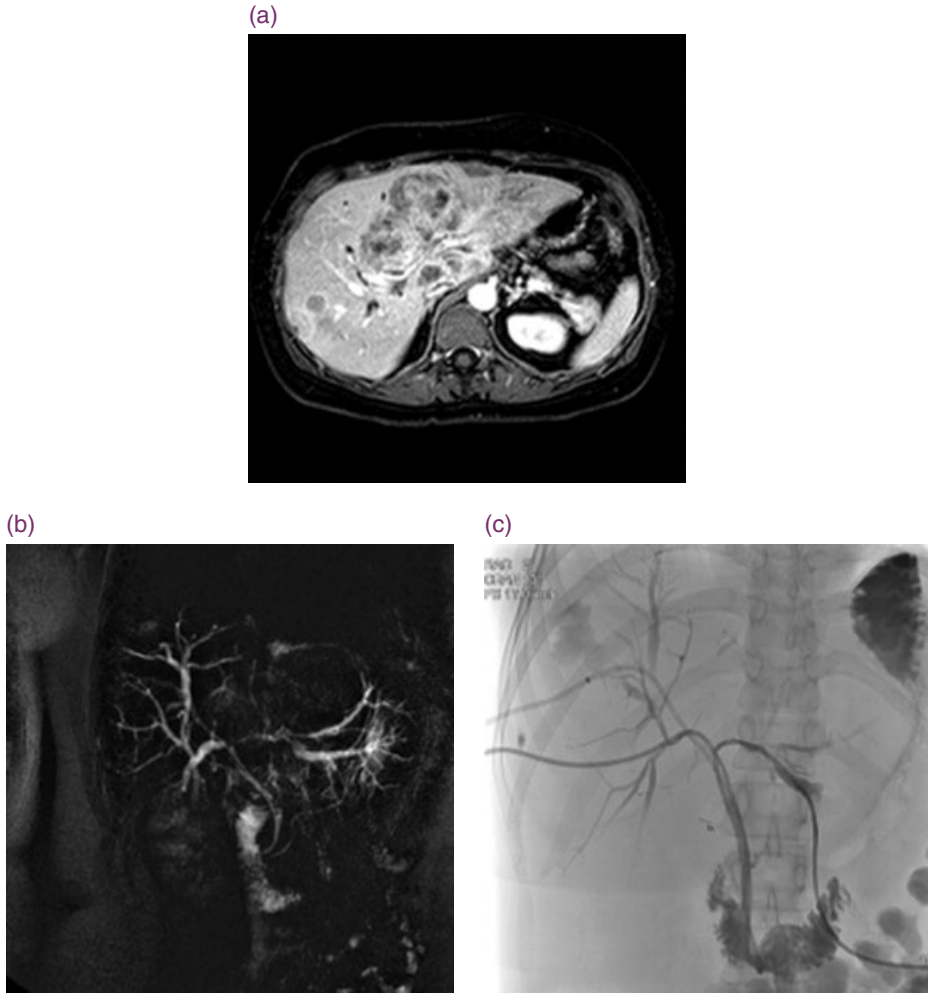


Figure 12.10 Large hepatocellular carcinoma leading to obstruction of the intrahepatic bile ducts. (a) Magnetic resonance (MR) image showing the carcinoma. (b) MR cholangiography showing complex strictures. (c) In the event of endoscopic inaccessibility of complex hilar strictures, percutaneous transhepatic cholangiopancreatography is mandatory.

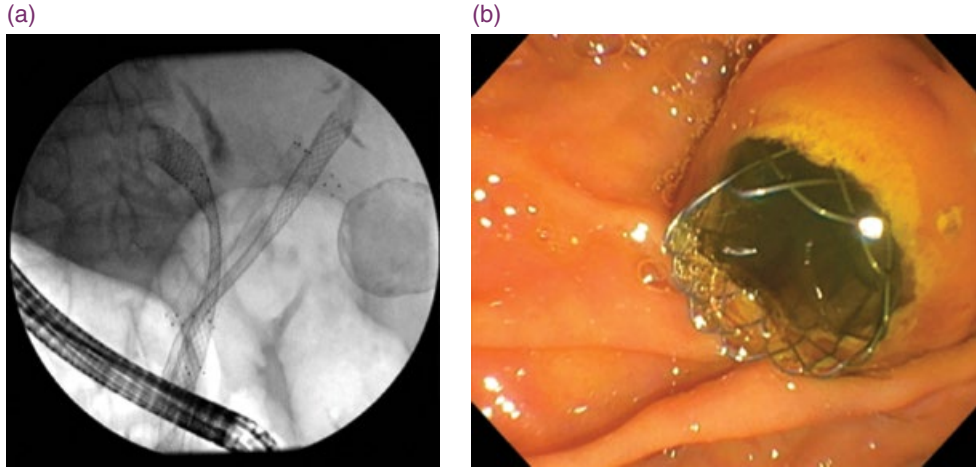


Figure 12.11 Metal stents for bile duct obstruction. (a) Whereas the use of self-expanding metal stents is clearly indicated for distal and hilar strictures, the use of double metal stenting into each intrahepatic bile duct is less well studied. (b) Endoscopic view of a metal stent exiting the papilla of Vater.

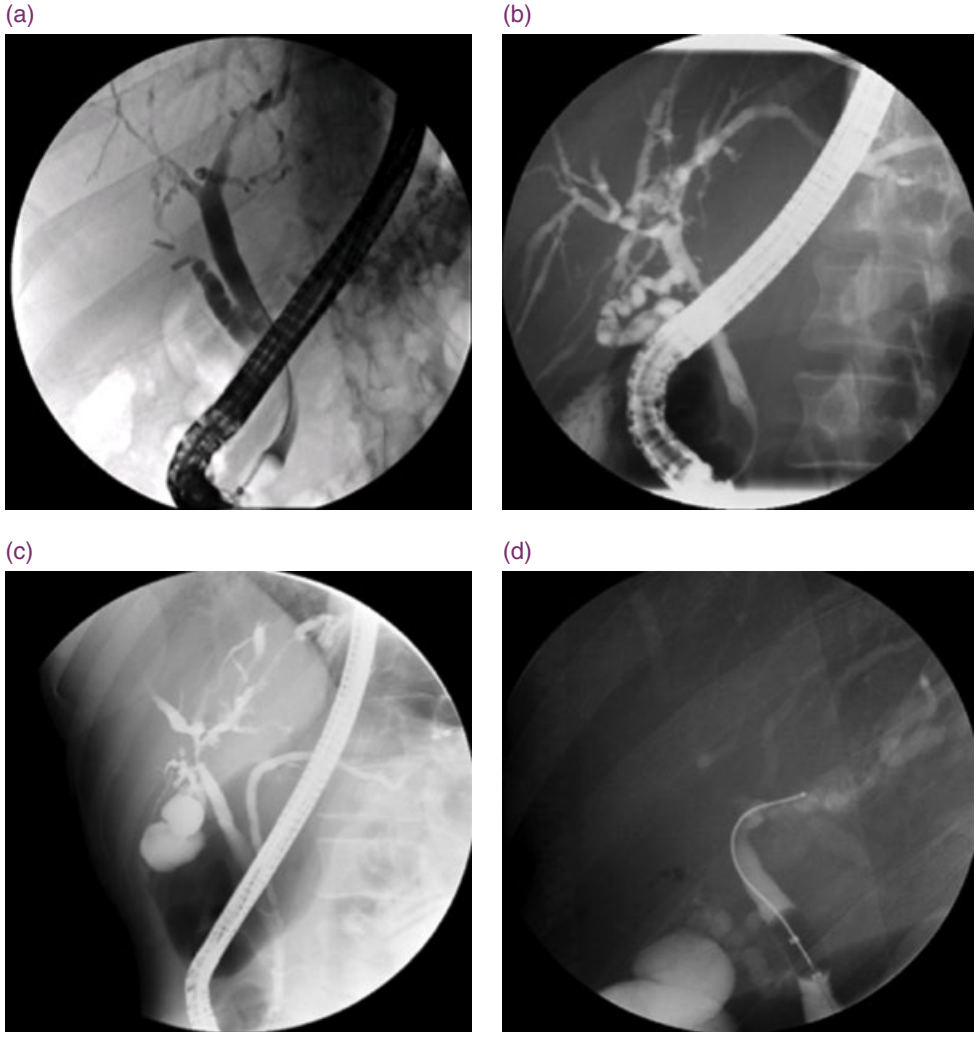


Figure 12.12 Spectrum of primary sclerosing cholangitis (PSC). (a) Classic intrahepatic PSC. (b) Intra- and extrahepatic PSC. (c) Cholangiocarcinoma. (d) Selective cannulation of the left hepatic bile duct in PSC using a balloon catheter and biliary wire.

The prevalence of cholelithiasis has been reported to vary according to the severity of cirrhosis, with the highest prevalence in advanced cirrhosis [22,25]. Stones in patients with PSC, SSC, and oriental cholangiohepatitis tend to be of hard consistency, making them more difficult to crush and retrieve. Patients with PSC, SSC, Caroli disease, and oriental cholangioghepatitis also develop intrahepatic stones (Figure 12.13).

Endoscopic management of choledocholithiasis in this population is more difficult because of underlying coagulopathy and an increased risk of post-sphincterotomy bleeding. In a retrospective study evaluating the efficacy and safety of ERCP in liver cirrhosis patients with common bile duct stones, the rates of bile duct clearance and complications were compared between cirrhotic and non-cirrhotic patients [26]. Although the success rate of

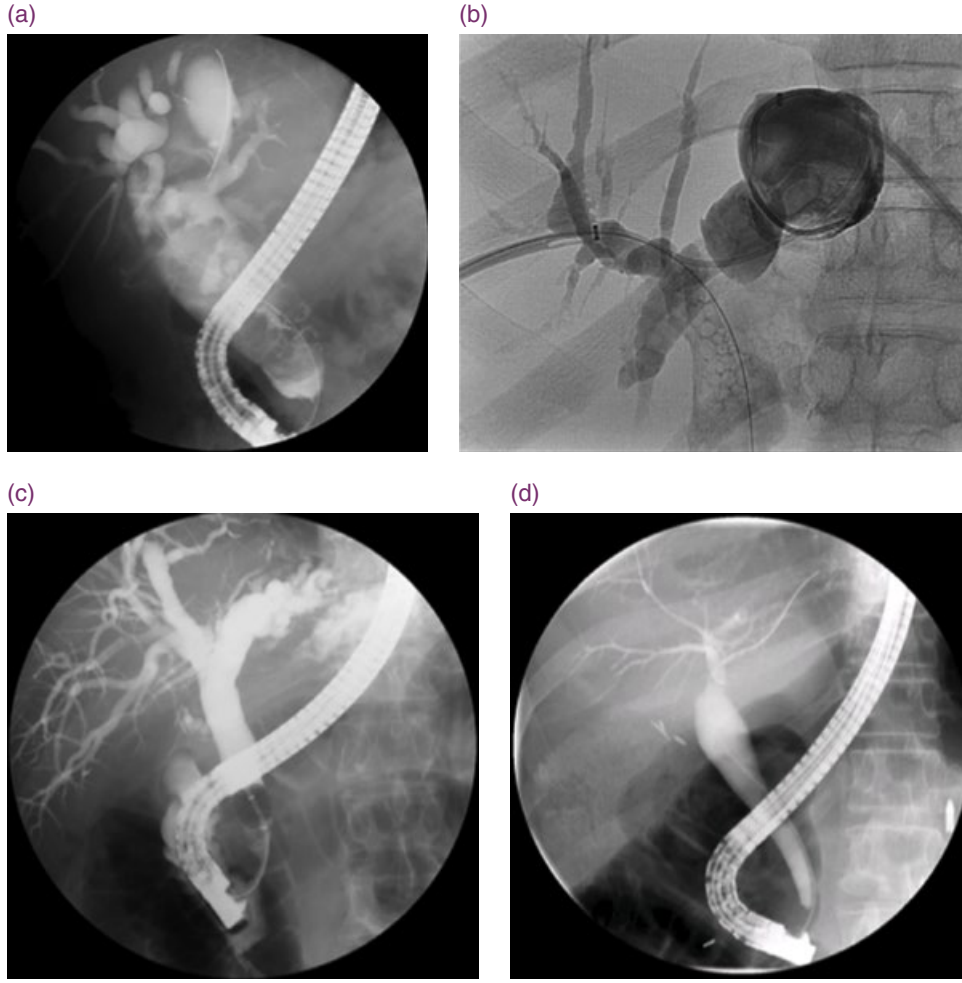


Figure 12.13 Spectrum of Caroli disease. (a) Intra- and extrahepatic dilation. (b) Intrahepatic dilations with multiple stones. (c) Selective left-sided involvement. (d) Disease limited to the common bile duct.

selective biliary cannulation was 95.6% in patients with liver cirrhosis versus 97% in non-cirrhotic patients, the bile duct clearance rate was lower (87%) in cirrhotic patients versus 96% in non-cirrhotic patients. The post-sphincterotomy bleeding rate associated with ERCP in Child–Pugh class C patients (25%, 2/8) was significantly higher than that in non-cirrhotic patients (3%; $p < 0.01\%$). There was no significant difference between these two groups in the rate of post-ERCP pancreatitis and cholangitis, suggesting that ERCP is safe and effective for Child–Pugh class A and B cirrhotic patients with common bile duct stones but that the hemorrhage risk of ERCP is higher in Child–Pugh class C patients [26].

Management of bile duct stones in patients with chronic liver disease does not differ from that in patients without liver damage. The key aspect when dealing with biliary stones in these patients is to attempt clearance during one session, as repeating ERCP is not desirable due to higher morbidity.

Primary Sclerosing Cholangitis

Primary sclerosing cholangitis is characterized by chronic inflammation and fibrosis of the intrahepatic and/or extrahepatic biliary ducts, leading to cholestasis, cirrhosis, and cholangiocarcinoma (CCA) (Figure 12.12). Although in the past ERCP was frequently used to evaluate symptomatic patients with suspected biliary obstruction or CCA, magnetic resonance cholangiopancreatography (MRCP) has largely replaced ERCP as the primary diagnostic tool [27]. A strategy of initial MRCP followed, if necessary, by ERCP is currently the safest approach in the workup of patients with suspected PSC [27]. Among cases with suspected PSC and normal cholangiography, liver biopsy is recommended to rule out small duct PSC. Small duct PSC is associated with longer survival and lower cumulative risk for CCA than large duct PSC.

The main indication for ERCP in PSC is the evaluation and treatment of single or multiple bile duct strictures. Single or dominant strictures have the highest risk of harboring CCA and develop in about 50% of patients. In a patient with stable PSC, the occurrence of clinical deterioration with worsening pruritus, jaundice, or bacterial cholangitis warrants evaluation with ERCP to exclude CCA. Other indications for ERCP in PSC are progressive biliary dilation on imaging, rising biochemical indices, and/or constitutional symptoms such as weight loss. The use of biopsy plus diagnostic brushing has a sensitivity of 60–100% and a specificity of 85–89% [28]. Recently, two advanced cytological techniques (digital image analysis and fluorescence in situ hybridization (FISH)) have been used for the detection of malignancy in PSC-related strictures and have proved to be more sensitive and equally specific to conventional cytology [29]. In addition, ERCP and/or cholangioscopy permits therapeutic interventions with balloon dilation or stent placement as appropriate [30]. The ideal endoscopic technique to deal with strictures in PSC has not been established, but small, nonrandomized studies suggest that balloon dilation alone and dilation with stent placement are equally efficacious, although the latter may be associated with more complications than balloon dilation alone [31]. Hence, stenting is usually reserved for strictures that are refractory to dilation. The required duration of stenting varies between 6 and 8 weeks to avoid cholangitis, although some patients require stenting with periodic exchange for as long as 6–12 months before the stricture resolves. When performing ERCP in patients with PSC we always use prophylactic antibiotics and often keep patients on antibiotics for 5–7 days after the procedure (pre-emptive use of antibiotics). Complications from endoscopic therapy occur in up to 20% of PSC patients, and include pancreatitis, cholangitis, biliary tract perforation, and hemorrhage [32].

Hepatobiliary Injury

The most common causes of bile duct injury in patients with chronic liver disease are iatrogenic and these occur most commonly after surgery (Figure 12.2). Patients with cirrhosis have a 10-fold increased risk of dying after surgery than patients without cirrhosis. The second most common cause of bile duct injury is radiological (Figure 12.14), such as bile duct damage during transhepatic arterial chemoembolization (TACE) (Figure 12.15), radiofrequency ablation (RFA) (Figures 12.16 and 12.17), and selective internal radiation therapy (SIRT). The incidence of bile duct injury in patients with chronic liver disease who have undergone cholecystectomy is between 0.1% and 0.6%, being more prevalent after laparoscopic cholecystectomy. The diagnosis of bile duct injury is based on clinical features and cross-sectional imaging techniques.

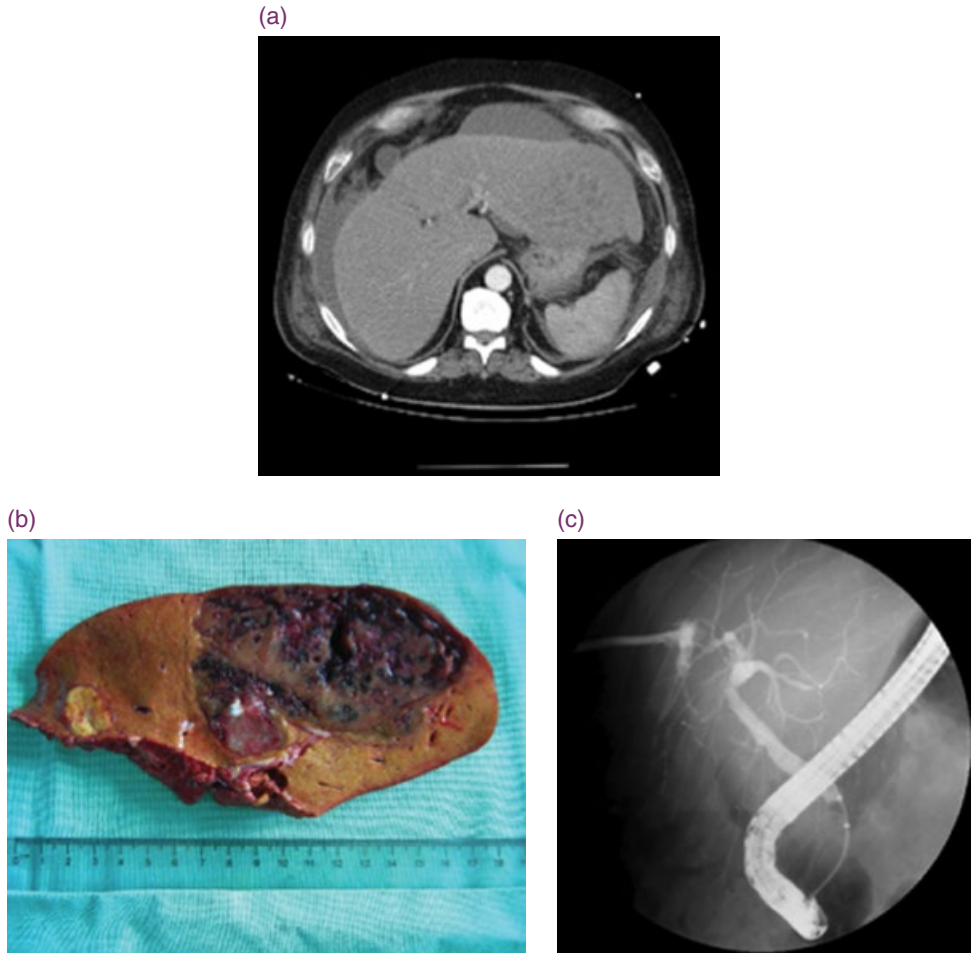


Figure 12.14 Hepatocellular carcinoma treated with radiological ablation therapies. (a) Computed tomography showing the cirrhotic liver and large tumor. (b) Resected tumor showing post-radiation necrosis. (c) Post-interventional cholangiogram showing bile leakage and accumulation into the necrotic area.

The finding of a fluid collection on imaging or the presence of bile in a draining catheter placed by surgeons suggests bile duct leak. However, there is usually a delay in diagnosis of bile leaks, with patients presenting with either prolonged draining of bile through surgically placed draining catheters or with signs and symptoms of biliary peritonitis. If bile leaks are diagnosed early they do not represent a major problem for the patient as ERCP is quite effective in dealing with them. However, prolonged leaks lead to peritonitis and sepsis, and are associated with high mortality, especially in patients with chronic liver disease. Ligation or transection of the bile duct is usually not resolved endoscopically and these patients must undergo surgery.

Hemobilia is another common manifestation of bile duct injury and should be suspected in any patient presenting with abdominal pain, gastrointestinal bleeding (or anemia), and jaundice. Endoscopic treatment of hemobilia is challenging (Figures 12.15 and 12.18). First, the ongoing

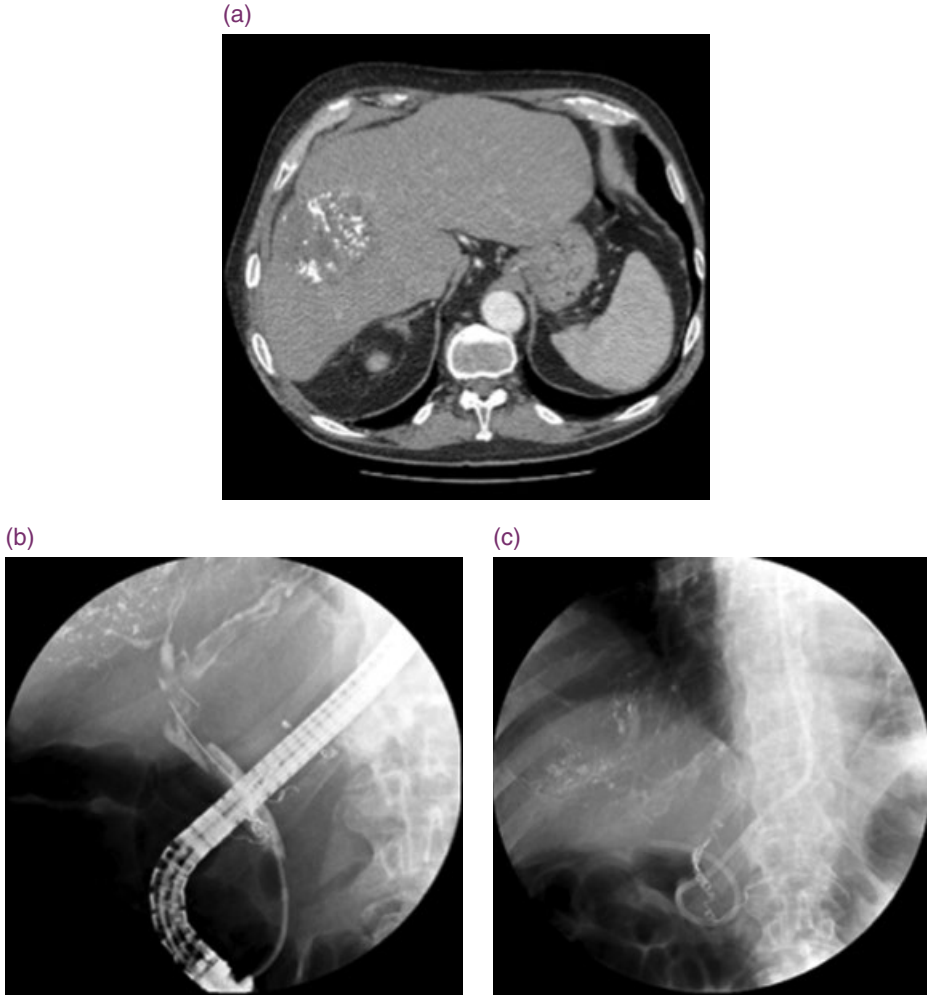


Figure 12.15 Hemobilia after transhepatic arterial chemoembolization (TACE). (a) Computed tomography showing the tumor treated by TACE. (b) Cholangiogram showing multiple filling defects inside the bile ducts (hemorrhage and blood clots). (c) In the presence of massive amounts of blood clots, a nasobiliary drain is an adequate initial decompression therapy. During subsequent endoscopic retrograde cholangiopancreatography, stenting may become necessary to enable bile flow.

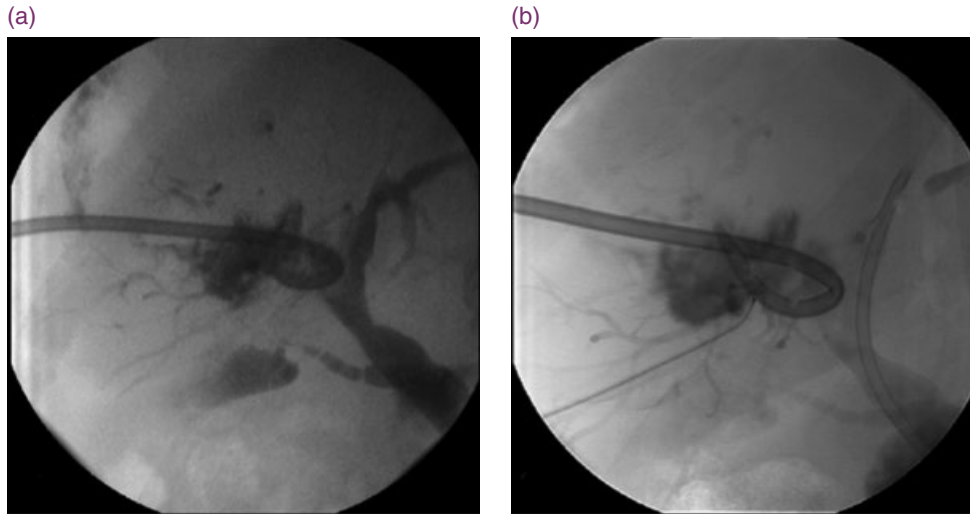


Figure 12.16 Bile duct injury after radiofrequency ablation of liver cancer. (a) Large, right-sided bile leak. (b) Initial drainage of the biloma and abscess is achieved with a percutaneous drain.

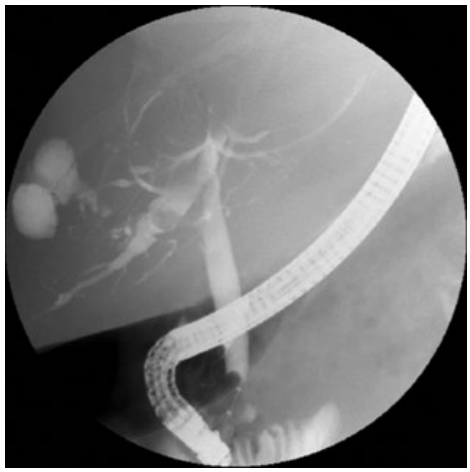
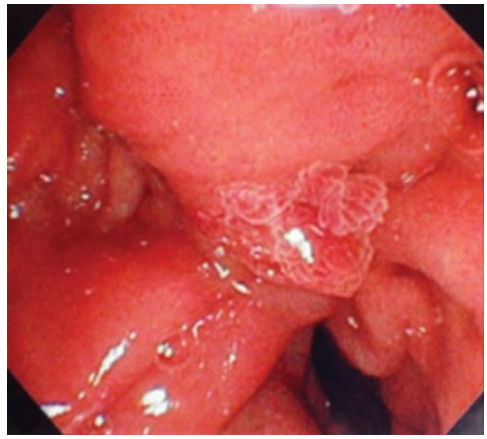


Figure 12.17 Hemobilia and biloma after radiofrequency ablation of liver cancer.

bleeding and clot formation may occlude the plastic or metal stent inserted endoscopically. Thus, some experts recommend first using nasobiliary drainage until the hemorrhage has been controlled and then placing an endoscopic stent if needed (Figure 12.15). Second, patients with hemobilia may bleed for several reasons, such as mucosal injury, portal hypertensive biliopathy, or frank arterial spurting from a damaged artery or aneurysm. Thus, patients with chronic liver disease and hemobilia should be jointly evaluated by surgeons, endoscopists, and interventional radiologists.

(a)



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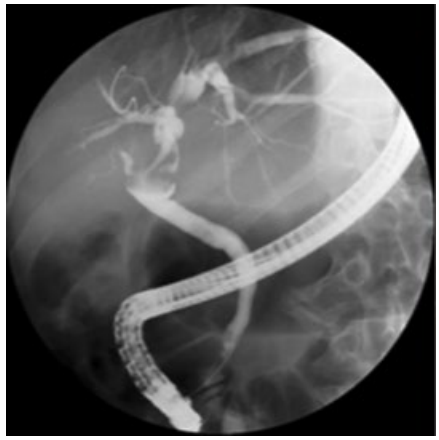

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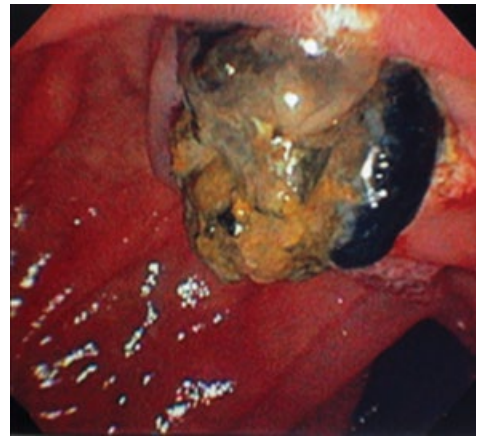

Figure 12.18 Hemobilia in liver cancer. (a) The papilla is massively enlarged due to compression of blood clots from hemobilia. (b) Large intrabiliary blood clots. (c) Coagulum exiting the papilla of Vater.

Hepatobiliary Malignancy

Hepatocellular Carcinoma

The most common tumor developing in patients with chronic liver disease is HCC (Figures 12.3, 12.4, 12.10, and 12.14). Although jaundice is the presenting symptom of HCC and occurring in up to 40% of patients, this is usually due to diffuse tumor infiltration, liver damage, and underlying cirrhosis [33]. HCC may lead to bile duct obstruction in around 10% of patients. Such cases are clinically classified as "icteric type hepatoma" or "cholestatic type of HCC" [33]. Indeed, identification of this group of patients is important as they may benefit from endoscopic bile duct drainage. The mechanisms of bile duct involvement in HCC are many and include: (i) tumor invasion; (ii) metastasis of tumor fragments attaching to various parts of the luminal biliary tract; (iii) extraluminal tumor and lymph node compression and encasement of the biliary tract; and (iv) hemobilia. In addition, patients with HCC are also prone to developing complications resulting from radiological interventional therapies such as TACE, RFA, and SIRT (Figures 12.16 and 12.17). Hemobilia is particularly problematic to diagnose and treat. The prognosis of this cholestatic type of HCC is closely related to the degree of liver dysfunction, the stage of disease, and the location and extension of tumor thrombi in the bile duct [33,34]. In 1994, Ueda et al. [34] classified HCC affecting bile duct into four types:

1) Type I: tumor affecting the secondary branch of the biliary tree.
2) Type II: tumor extending to the first branch of the biliary tree.
3) Type III: IIIa – tumor extending to the common hepatic duct (CHD); IIIb – an implanted tumor growing in the CHD.
4) Type IV: floating tumor debris from the ruptured tumor in the CBD [34].

They also found that patients with tumors type I, IIIb, and IV had a relatively better prognosis than those with other types [34].

Ultrasonography and computed tomography (CT) are helpful in showing hepatic tumors and dilated intrahepatic and/or extrahepatic ducts containing dense material corresponding to tumor debris [35]. Even though MRCP is useful in detecting biliary obstruction, it is relatively ineffective for interpretation of icteric type HCC [33,35]. The differentiation of hilar HCC from CCA by MRCP may be quite difficult [36]. Thus, direct cholangioscopy can be useful in differentiating obstruction resulting from an intraluminal mass, infiltrating ductal lesions, or extrinsic mass compression. Jan and Chen [37] found the main choledochoscopic findings of HCC were a yellowish, intraluminal, nodular mass and tumor thrombus in the CBD. These features may allow differential diagnosis from hilar papillary type CCA [37]. Factors associated with improved survival are lower total bilirubin level, earlier TNM (tumor, node, metastasis) stage, absence of portal vein invasion, successful biliary drainage, and the patient being able to receive chemotherapy or TACE [33,38].

The beneficial effect of ERCP guided biliary drainage for the survival of HCC patients with obstructive jaundice has been proven, thus every attempt should be made to ensure adequate decompression of the biliary tract [33]. However, ERCP and stenting has proven to be beneficial only in the presence of bile duct dilation on CT or ultrasonography [33]. Thus, a detailed study of the imaging tests is mandatory to plan the endoscopic intervention.

Hilar strictures below the bifurcation are the easiest to treat, whereas those extending into the intrahepatic bile ducts or involving large segments of the liver may be impossible to stent (Table 12.4). Although western endoscopists prefer to use metallic stents in patients with HCC,

eastern endoscopists preferentially use plastic stents. Because the life expectancy of these patients is short, it makes sense to use SEMSs. However, in the current era of TACE, SIRT, RFA, and advanced chemotherapeutic agents, the life expectancy of patients with HCC is increasing and, therefore, SEMSs may become occluded several times during the patient's follow-up. Läuffer et al. [39] reported one patient who underwent combination therapy with surgical segment III drainage, TACE, and radioembolization with yttrium-90 resin particles and in whom endoscopic stenting was performed. With these combined procedures, relief of jaundice and a survival time of 32 months were achieved [39].

Tumor progression and hemobilia are a common occurrence in HCC and often lead to occlusion of metal stents. Thus, a strategy of repeated plastic stenting appears more logical and clinically intuitive. It is important to determine the site, extent, and nature of the obstruction, as well as liver function and the presence of portal thrombus, before embarking on ERCP with stenting. Patients with tumor involvement of both the right and left intrahepatic ducts have poor survival and endoscopic drainage should be avoided as it may lead to cholangitis and more complications.

Cholangiocarcinoma

The second most common biliary tumor affecting patients with chronic liver disease is CCA, which arises from the bile ducts (Figures 12.19 and 12.20) [40]. CCA accounts for 2–3% of all malignant neoplasia diagnoses, with an incidence of about 2.1 per 100,000 [40–45]. The majority of CCAs occur in patients over the age of 65 years (60%), with a slight male predominance [40–42]. Predisposing conditions for CCA include the presence of PSC, intrahepatic stones, choledocholithiasis, choledochal cysts, liver parasites, and previous exposure to the contrast agent thorium dioxide [41]. There are three main types of CCAs based on their anatomical location. The most common type is the perihilar variant (pCCA) (50%), followed by the distal type (dCCA) (40%) and intrahepatic type (iCCA) (10%). The classic clinical presentation of CCA consists of jaundice, pruritus, pale stools, dark urine, cholestasis, and cholangitis [40–42]. However, other clinical symptoms are also common, including weight loss, malaise, and anorexia. Unfortunately, more than half of the patients presenting with CCA present with non-resectable disease and have a poor prognosis [40,43,44]. Despite current treatments, including chemotherapy, followed by radiotherapy and surgery, the average survival rate for CCA is still very low [40–45].

Therapy for CCA should be based on the tumor's size, location, and type. Small dCCA and pCCA tumors should be treated using radical surgical resection [40,45]. Mass tumors located inside the liver, large or metastatic extrahepatic tumors, and recurrences after attempted curative surgery may be treated with chemotherapy (e.g., gemcitabine and cisplatin) [41–43]. If the lesions are causing biliary luminal obstruction with resulting jaundice, endoscopic therapy using stents (plastic or metal) or ablative methods such as photodynamic therapy (PDT) or RFA are excellent palliative options [40–45]. Importantly, these therapies should be initiated before the onset of cholangitis and liver failure.

Endoscopic Retrograde Cholangiopancreatography ERCP is performed in CCA for both diagnostic and therapeutic purposes (Table 12.4; Figures 12.19 and 12.20). Differentiation between malignant and benign strictures in cases of the hilar or sometimes distal type can be difficult but it is important for the planning of treatment as well as tumor staging. Diagnosis can be made during ERCP through a combination of cytological sampling (e.g., brushing) and

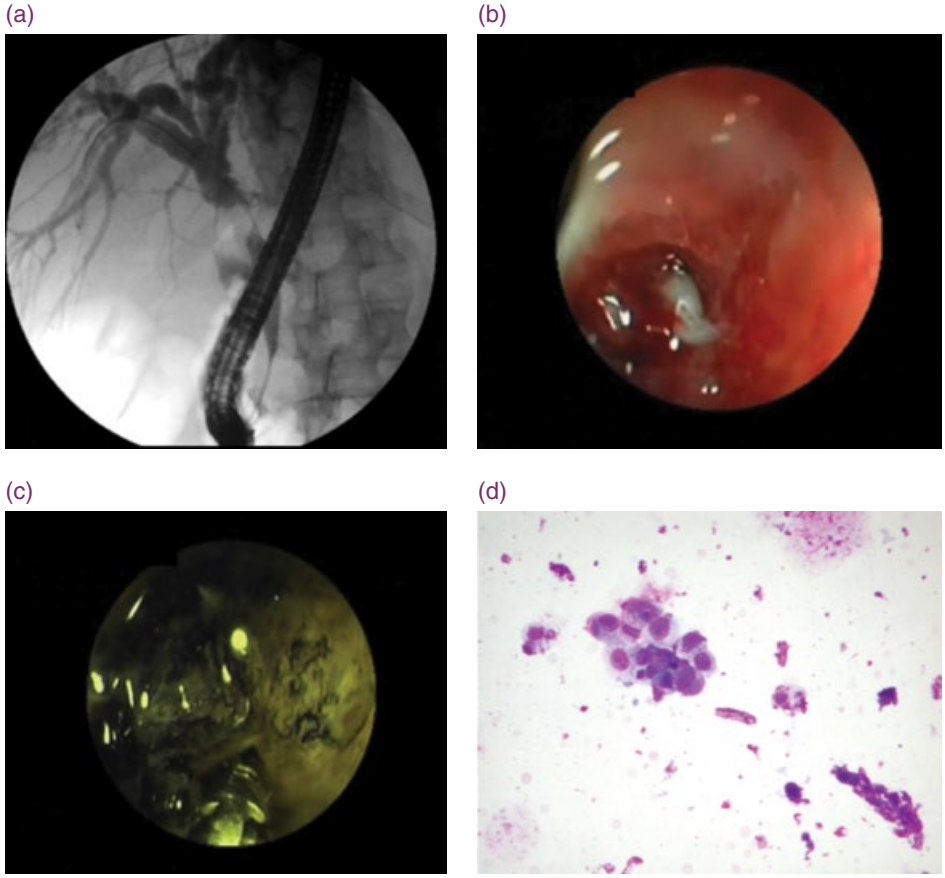

Figure 12.19 Cholangiocarcinoma (CCA). (a) Cholangiogram showing a stricture due to CCA. (b) Direct cholangioscopy demonstrating tight stenosis. (c) Hypervascularity and tortuous vessels characteristic of neoplasia are demonstrated using flexible spectral imaging color enhancement. (d) Histocytological sampling confirms CCA.

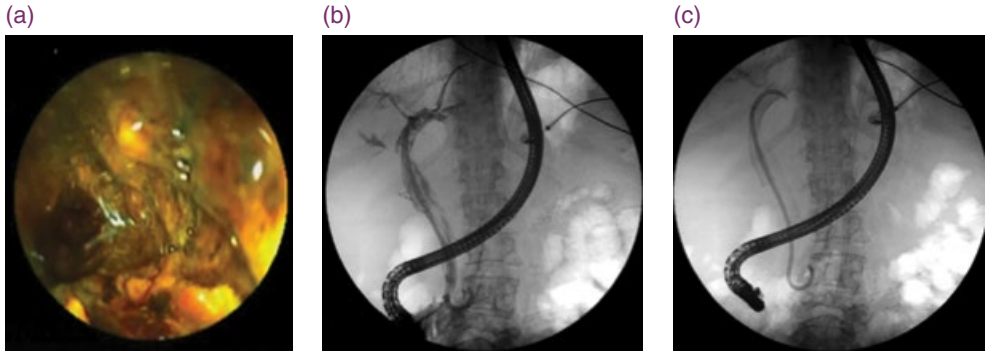

Figure 12.20 Cholangiocarcinoma. (a) The metal stent is partially occluded by the tumor. (b) Cholangiogram showing placement of a plastic double pigtail stent (i.e., stent in stent technique) to relieve the obstruction. (c) Plastic stent in situ.

biopsies, with a sensitivity of 40–70%. Newer cytological techniques such as digital image analysis and FISH may improve the accuracy. Endoscopic ultrasound and fine needle aspiration biopsy can be used as alternative techniques where expertise exists.

Malignant biliary obstruction is the most frequent indication for endoscopic decompression. Endoscopic drainage may be employed as a definitive or temporary method. Temporary biliary decompression is indicated before surgery in the following situations: patients with acute cholangitis, for the prevention of cholangitis after endoscopic biliary contrast injection, or if surgery will be delayed due to unfavorable clinical conditions. Excluding these situations, endoscopic biliary drainage is controversial if done before surgery since it may increase the risk of postoperative infection [40–45]. However, preoperative unilateral drainage of the future remnant lobes has been reported to be effective in most cases with hilar CCA, being rarely complicated with segmental cholangitis [40–45]. Definitive endoscopic biliary drainage is indicated in patients with advanced and unresectable tumor or for non-surgical candidates with poor health conditions. Resectability may be ascertained by surgical exploration or by radiographic findings, such as vascular encasement, involvement of adjacent organs, retropancreatic and paraceliac nodal metastases, non-regional liver metastasis, or distant metastasis.

Biliary stenting has been shown not only to improve jaundice but also quality of life, potentially also with increased survival (6.5 months versus 1.8 months) [40–45].

The type and number of stents used for biliary drainage in CCA is debatable. The decision to stent, including the number and caliber of the stents, is based on several variables including volume of liver requiring drainage, type of stenosis, patient condition and life expectancy, and local expertise. Nonetheless, a key aspect to remember during endoscopic drainage of non-resectable CCA is to relieve enough liver segments [40–45]. In most cases of hilar or Bismuth type II stenosis, a single stent placement bridging the tumor is sufficient. In Bismuth type III and IV tumors some experts recommend draining all obstructed segments, while other experts agree on draining only one side of the liver or the dominant segments [41–45]. Whereas Naitoh et al. [41] concluded that bilateral stenting was more effective than unilateral stenting, Maguchi et al. [42] showed similar outcomes in stent patency and complication free survival in patients undergoing unilateral drainage as compared with those undergoing bilateral drainage. Interestingly, drainage of a mere one third of the entire liver volume is considered to result in the resolution of jaundice [41,42]. In this regard, a single stent for the dominant segment may be adequate for ameliorating jaundice in most cases of hilar strictures. However, injecting contrast medium into undrained ducts is often associated with cholangitis. To prevent this complication, preceding CT or MR cholangiography can be used to delineate biliary anatomy, and selective guide wire cannulation of the targeted bile duct can be accomplished even without contrast injection. Bilateral stenting, particularly the bilateral placement of SEMSs, is technically difficult and the left system should be drained first because it is more difficult and usually produces more effective drainage than a right system stent. This is due to the longer length of the left main duct before branching, leading to larger volumes of the liver being drained. However, this affirmation is questioned by many others. Other experts carefully measure the volume of the obstructed liver segments and focus on draining the large and non-atrophic areas, regardless of location. Liberato and Canena [43] retrospectively reviewed the outcomes of patients undergoing endoscopic biliary drainage for hilar CCA. The authors

divided the patients with HCC into four groups based on unilateral or bilateral plastic stent or SEMS placement [43]. Repeat endoscopic biliary drainage for stent occlusion was required more frequently in unilateral plastic stenting than in bilateral plastic stenting (80.9% versus 34.2%; p <0.001) as well as in unilateral SEMSs than in bilateral SEMSs (31.4% versus 11.9%; p = 0.036). The median stent patency period was 17 weeks for unilateral plastic stenting, 18 weeks for bilateral plastic stenting, 24 weeks for unilateral SEMSs, and 29 weeks for bilateral SEMSs. Kaplan–Meier analysis showed a significant difference in the cumulative stent patency period between unilateral and bilateral plastic stenting (p = 0.0004; hazard ratio (HR) = 2.24) as well as between unilateral and bilateral SEMSs (p <0.0001; HR = 3.69). Multivariate analysis revealed SEMS placement and bilateral deployment to be the only independent prognostic factors associated with longer stent patency [43]. However, reintervention ("re-do") for stent dysfunction is more complicated in bilateral metal stenting than in unilateral metal stenting.

Some patients may require bilateral stenting for adequate amelioration of jaundice and cholangitis. In case of need for complete drainage, two or more guidewires can be placed simultaneously with the same technique. When more than one stent is placed, all strictures should be balloon dilated to 6 mm to facilitate the placement of stents.

Endoscopic Versus Percutaneous Transhepatic Approach Although preferable and widely accepted, endoscopic drainage is usually not superior to the percutaneous radiological approach (Figure 12.10). Available evidence suggests that the percutaneous method, with either external drainage or internal drainage, with antegrade stenting is more effective. In a Dutch study published in 2010, Kloek et al. reported a higher technical success rate (100% versus 81%), fewer infectious complications (9% versus 48%; p <0.05), and fewer drainage procedures (1.4 versus 2.8; p <0.01) in the percutaneous group compared with the endoscopy group in patients with resectable hilar CCA [44]. A Korean study comparing SEMSs deployed by either percutaneous or endoscopic means in patients with unresectable hilar CCA further affirmed that the technical success rate in the percutaneous SEMS group was higher than that in the endoscopic SEMS group (92.7% versus 77.3%) [45]. Nonetheless, ERCP is still the recommended first line drainage approach for patients with inoperable Bismuth type I and II (extrahepatic) CCA. Although the percutaneous approach is more invasive than the endoscopic one, it is indicated in cases where ERCP drainage will be less successful such as in Bismuth type III and IV tumors. Rescue percutaneous drainage should be considered in previously failed attempts at endoscopic drainage. In addition, the percutaneous approach can be used initially for the rendezvous procedure or to facilitate later endoscopic internalization. The selection criteria for endoscopic or percutaneous drainage depend on anatomical factors determined by MRCP, the estimated number of stents required for appropriate biliary decompression, and locally developed algorithms and expertise. Of interest, patients with potentially resectable CCA may be submitted directly to surgery, without preoperative drainage.

Photodynamic Therapy In recent years, PDT delivered through the duodenoscope or percutaneously has emerged as a good palliative measure in some patients with pCCA and dCCA [40,46]. PDT is applied during ERCP directly into the malignant bile duct stricture(s). Because the procedure is performed during ERCP, its ability to reach "unreachable" or even "peripheral" lesions makes it an attractive palliative alternative for managing patients with CCA

[40,46]. However, PDT should be considered only for: (i) patients with "unresectable" disease; (ii) disease confined to the extrahepatic bile duct; (iii) patients with resectable disease who are poor surgical candidates; and (iv) patients stable enough to undergo ERCP [40,46]. In addition, the presence of cirrhosis and significant liver disease is a relative contraindication to PDT. It should be emphasized that patients with CCA and cirrhosis already have a decreased quality of life and depriving them of sunlight, as is necessary in this treatment, may have detrimental emotional and social effects. Thus, we offer PDT judiciously to this group of patients.

PDT application is a two step process. First, the photosensitizer drug is administered intravenously. During the next 24–48 hours the photosensitizer (e.g., porfimer sodium) concentrates in areas of rapid cell multiplication, such as tumors, and incorporates itself into the tissue. The second step is the application of laser light at a specific wavelength (i.e., 630 nm, which is also present in the spectrum of sunlight). The light exposure starts the cell destruction process by transforming the drug from its neutral ground state into its activated state. In the presence of oxygen, cytotoxic singlet oxygen species (i.e., oxygen radicals) are then formed, destroying the dysplastic or rapidly multiplying cells to which the porfimer sodium molecules are bound, thereby inducing apoptosis and tumor necrosis to a depth of 4–6 mm [40,46]. Thus, tumor mass outside the bile duct is not amenable to therapy. However, the main goal of PDT for CCA is not to destroy the entire tumor mass but to reopen the bile duct lumen and improve the flow of bile. Due to the massive edema and necrosis induced, nearby tumor feeding vascular channels are occluded, indirectly accelerating the necrotic process by cutting off the supply of vital nutrients.

Other cells multiplying rapidly, such as intestinal and skin cells, can also take up the photosensitizer. As long as these cells are not exposed to light, no oxygen radical formation, and hence no photosensitivity, occurs. This highlights the importance of patient education about PDT. The patient's eyes and skin react to light sources containing 630 nm wavelength, such as sunlight, after receiving the intravenous photosensitizer. The photosensitivity can range from mild skin burning to severe eye and skin reactions.

Cholangioscopy

Despite advances in radiological and endoscopic techniques, the diagnosis and management of biliary tract problems remains challenging. Intuitively, direct visualization of a lesion is likely to provide inherent benefit, as has been witnessed for other disease processes throughout the luminal gastrointestinal tract. Direct cholangioscopy is the direct visualization of the extra- and intrahepatic bile ducts using fiberoptic or videoendoscopic imaging methods [30,46,47]. Besides characterization of the mucosa and tissue sampling, in some patients direct visualization allows targeted therapy and wire or catheter guidance (Figures 12.21 and 12.22).

In the past, cholangioscopy was seen as an extravagant and difficult technique to master. Using a fiberoptic or video assisted mother–baby cholangioscope provided direct visualization and potential for tissue acquisition and therapy of the bile duct, but this system was difficult to use as it required two endoscopists (dual operator system). The choledochoscope was also small (outer diameter 2.4–3.4 mm) and very fragile with a limited range of motion (two way tip deflection), a small working channel of only 1.2 mm, and a limited lifespan [47]. The development of ultraslim endoscopes has allowed direct transoral or transnasal cholangioscopy to now be possible and has revolutionized the approach to biliary tract diseases (Figures 12.21 and 12.22) [48–50]. In addition, through-the-duodenoscope

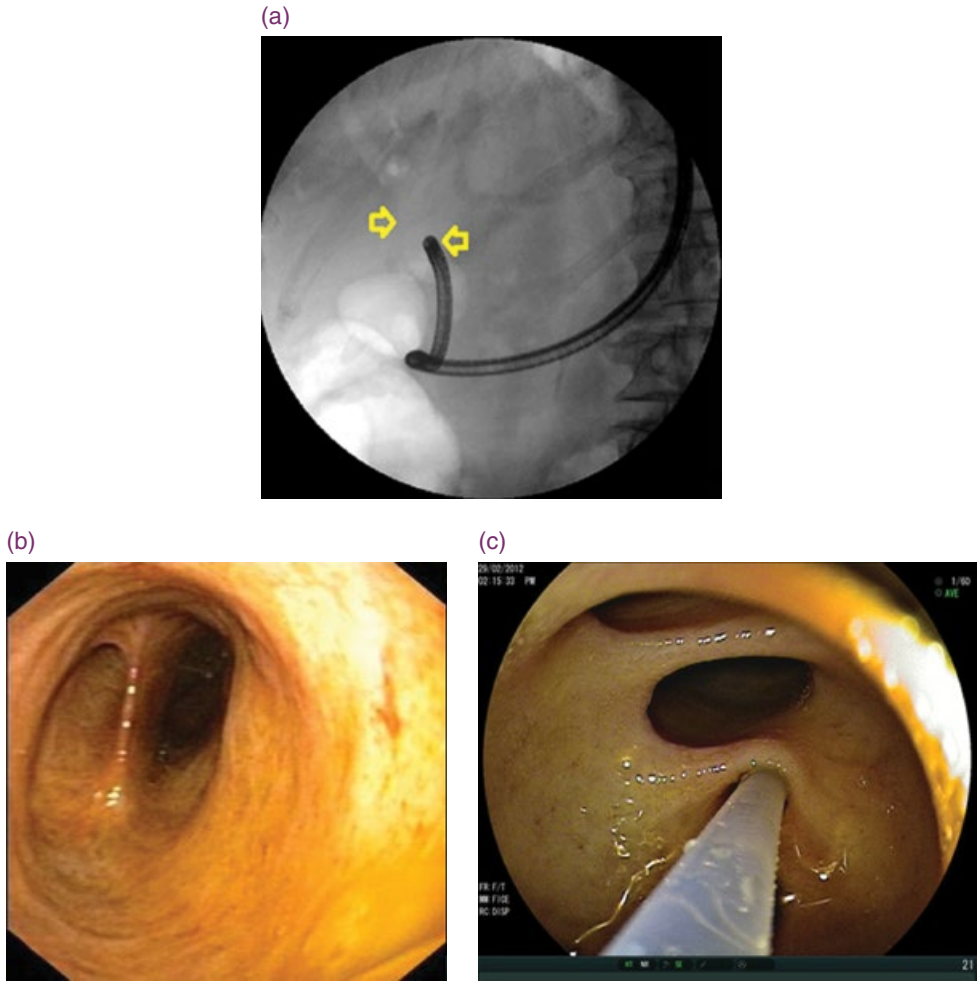

Figure 12.21 Direct cholangioscopy. (a) X-ray image demonstrating the location of the cholangioscope within the bile ducts. The arrows show aerobilia. Cholangioscopy should always be performed using either saline solution or carbon dioxide, never with air due to the risk of an air embolism. (b) Inside the bile ducts. (c) Cholangioscopy allows for direct and selective cannulation of the bile duct branches.

systems such as SpyGlass™ (Boston Scientific Corp., Natick, MA, USA), using fiberoptic technology, have improved visual access to the bile ducts (Figures 12.23 and 12.24) [47–52]. The SpyGlass™ system is comprised of a disposable 10 Fr, 230 cm long catheter with four lumens: two for irrigation, one for the optical fiber, and one for the instrumentation (diameter of 1.2 mm). The optical fiber is a reusable, 0.77 mm, 6000 pixel fiberoptic bundle that is introduced through the catheter [47]. The SpyGlass™ catheter has a four way tip deflection itself, which can be combined with movements of the duodenoscope to achieve great maneuverability. However, limitations exist and are related to the size and configuration of the bile duct investigated as well as by anatomical variation of the upper gastrointestinal tract that do not allow for proper duodenoscope position.

SpyGlass™ may be more suitable to reach deeper stenosis of the bile duct. However, the visual quality is not as good as that of videoendoscopy. The use of an ultrathin upper endoscope (4.9–5.9 mm)

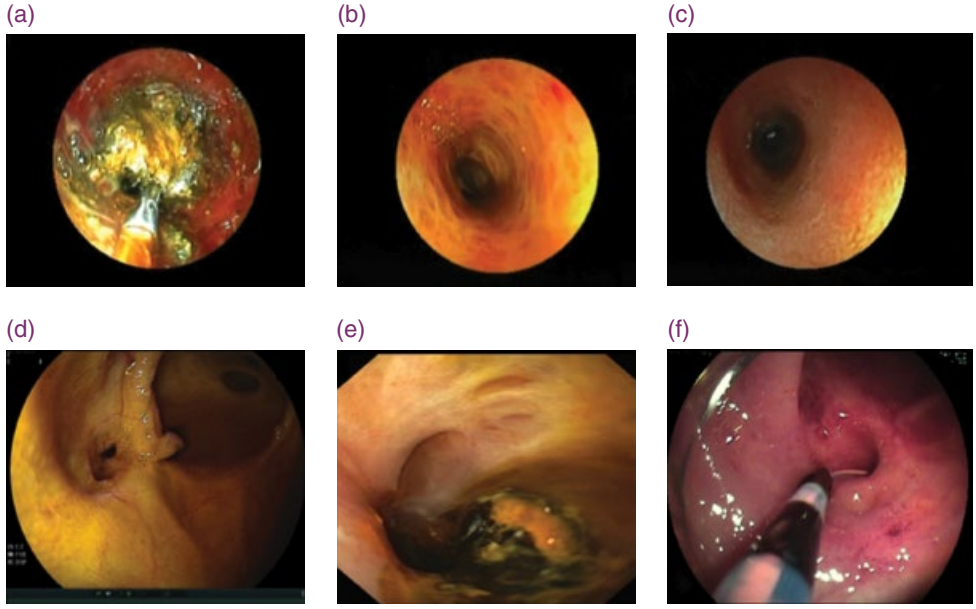

Figure 12.22 Direct cholangioscopy in chronic liver disease. (a) Lithotripsy of a large stone in Caroli syndrome. (b) Mucosal inflammation of the bile duct in primary sclerosing cholangitis (PSC). (c) Edematous mucosa in portal hypertensive cholangiopathy. (d) Stenotic bile duct branch in PSC. (e) Fibrotic bile ducts in secondary sclerosing cholangitis. (f) Selective wire insertion into a stenotic bile duct in a patient with sclerosing cholangitis.

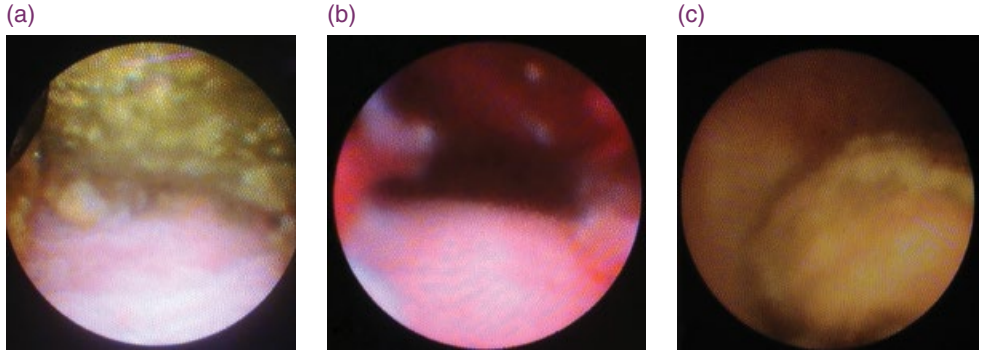

Figure 12.23 Cholangioscopy with SpyGlass™. (a) Stone inside the common bile duct in a patient with cholangitis. (b) Fibrotic and inflamed mucosa of the bile duct in primary sclerosing cholangitis. (c) Cholangiocarcinoma.

typically used for transnasal endoscopy has provided the quality of images we have grown accustomed to (Figure 12.22). Such an endoscope has a larger working channel (2 mm) providing a full range of endoscopic accessories for endobiliary interventions. It could be an effective and safe approach for patients with difficult to manage biliary disease as well as providing superior imaging quality; in addition, only a single operator is needed. This type of cholangioscopy is performed by direct introduction of the cholangioscope into the bile duct or by using commercially available balloon catheters to anchor the endoscope into the bile duct, and can only

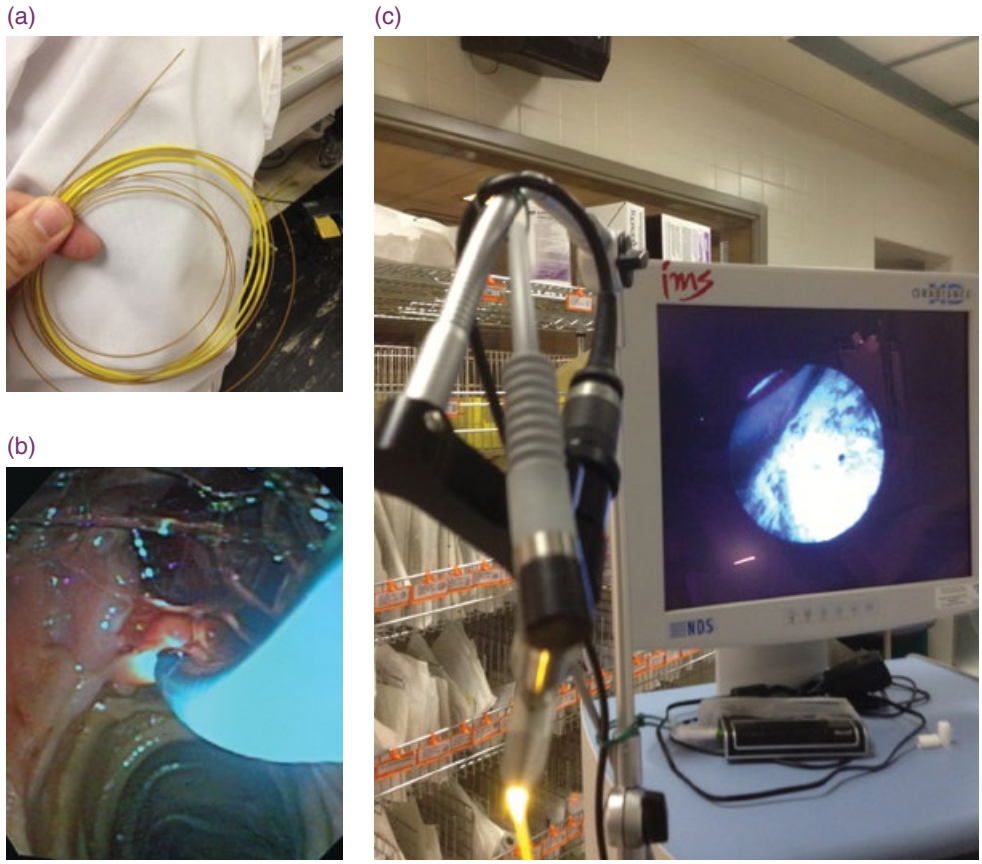

Figure 12.24 Partially disposable cholangioscopy SpyGlass™ system. (a) The optical fiber. (b) Image produced by the cholangioscopy system. (c) The monitor.

be performed if the bile duct entrance and the bile duct are dilated [47,51].

Cholangioscopy can be utilized as a diagnostic and therapeutic tool. The most frequent use is to assess indeterminate strictures and to manage difficult biliary stones. A number of studies have demonstrated the utility of direct cholangioscopy for better targeted biopsies to evaluate indeterminate biliary strictures [47–50]. Combined with cholangiographic images obtained during ERCP, cholangioscopy increases diagnostic sensitivity significantly. This is called ERCC (endoscopic retrograde cholangioscopy and cholangiography) [51]. Cholangioscopy enables the distinction of stones from tumors and is also useful in assessing the extent of the disease and in identifying synchronous lesions which would be missed on classic cholangiography. Targeted biopsies in the presence of visible neovascularization seen on cholangioscopy yield diagnostic accuracy of 96% in detecting malignancy [47]. Direct cholangioscopy has been compared with conventional ERCP with brush cytology in patients with PSC. Cholangioscopy with tissue sampling has proved to be more sensitive (92% versus 66%) and specific (93% versus 51%) than ERCP in detecting CCA in PSC [47–50]. Other indications for diagnostic cholangioscopy include the assessment of ductal abnormalities, choledochal cysts, and filing defects. Cholangioscopy has also been used for evaluation of IgG4 related

cholangiopathy and the evaluation of ductal strictures and ischemia after liver transplantation and tumor staging.

One of the first therapeutic uses reported for cholangioscopy was electrohydraulic lithotripsy of large bile duct stones [47]. Direct visualization of stones reduces the risk of bile duct injury and differentiates stones, air bubbles, tumors, and blood clots. Other potential therapeutic uses include ablative therapies for tumors such as PDT, argon plasma coagulation, and RFA as well as selective guidewire placement, control of bleeding, and reopening of occluded metal stents. Many uses for biliary therapy can be foreseen, dependent on the available technology and tools compatible with the current working channel.

There are scant data on the use of cholangioscopy in patients with chronic liver disease [37,52,53]. Nonetheless, it is safe to assume that direct cholangioscopy offers the same advantages in patients with liver disease as in those without chronic liver damage. A key technical aspect to remember when performing direct cholangioscopy is to always utilize carbon dioxide insufflation instead of air, as there have been reports of both nonfatal and deadly air embolism resulting from air insufflation into the bile ducts. In addition, all patients undergoing direct cholangioscopy should always receive prophylactic antibiotics, as water and carbon dioxide insufflation within the bile ducts can promote bacterial translocation into the systemic circulation.

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13

Endoscopic Ultrasound in the Diagnosis of Hepatobiliary Malignancy

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Introduction

Cholangiocarcinoma (CCA) is a rare, but increasingly common, malignancy with features of biliary tract differentiation arising along the intrahepatic and extrahepatic biliary tree, excluding the gallbladder and ampulla [1]. The disease can be defined anatomically as: (i) intrahepatic CCA presenting as mass lesions within the hepatic parenchyma; (ii) perihilar CCA presenting with bile duct obstruction and defined as a cancer between the cystic duct and the secondary bifurcation of the right and/or left hepatic ducts; and (iii) distal cholangiocarcinoma which is below the cystic duct. The underlying tumor biology, typical late presentation, and challenges of diagnosis all contribute to the poor prognosis of CCA. While surgical resection offers the only opportunity for cure, the 5-year survival following resection of perihilar CCA is only 20-40%, depending on the tumor stage [2–5]. There is increasing use of neoadjuvant therapy followed by liver transplantation for unresectable perihilar CCA that has not metastasized, with 5-year survival now approaching 75% [6–8]. Improved diagnostic and staging modalities are desperately needed to accurately stage CCA and thus identify patients most likely to benefit from aggressive medical and surgical therapy. This information is necessary, especially when considering the higher risk of liver transplantation, in order to justify the use of extremely scarce donor organs as well as other resources.

Limitations of CCA diagnosis and staging have driven the development of new technologies. Endoscopic ultrasound (EUS) provides unprecedented imaging and tissue acquisition. However, the role of EUS in CCA is debated, particularly as pertains to primary tumor fine needle aspiration (FNA). EUS guided biopsy may permit an otherwise unattainable diagnosis. However, primary tumor biopsy risks needle tract seeding, tumor upstaging, and potential conversion of an otherwise resectable tumor to unresectable status. Therefore, while EUS findings may guide management and improve outcomes, ill-advised use can compromise patient care and outcome. In the first part of this chapter, we draw upon published EUS data from which we consider the role of EUS in patients with suspected or known extrahepatic CCA.

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In addition to CCA, the differential diagnosis of a hepatic mass includes hepatocellular carcinoma (HCC) and hepatic metastases. As a diagnosis of HCC is commonly made by a combination of the presence of underlying cirrhosis, elevated tumor markers, and classic radiographic characteristics, EUS has not often been used in the diagnostic workup for suspected HCC. On the other hand, although less data exist, EUS has been increasingly used to detect and diagnose hepatic metastases when performed for the staging of intra-abdominal and intrathoracic malignancies. The second part of this chapter will discuss the role of EUS and FNA in hepatic metastases.

Endoscopic Ultrasound in Cholangiocarcinoma

Published Data

Published data on the use of EUS in CCA must be carefully analyzed. While some studies included only patients with a suspected or confirmed CCA, others evaluated a broader group of patients with a "biliary stricture," "jaundice," or "pancreatic head mass" [9–14] (Table 13.1). The inclusion of a diverse study population helps establish the role of EUS among patients with general symptoms or presentations. However, these reports often lack sufficient disease specific enrollment and other details to clarify the role of EUS in CCA (Tables 13.1 and 13.2). In addition, most EUS studies included patients with CCA located throughout the extrahepatic biliary tree, or the tumor site was not specified. This pooling of data irrespective of tumor subtype has not helped our understanding of the utility of EUS in patients with distal or perihilar CCA – which vary in clinical presentation, diagnostic approach, and management. Furthermore, existing reports excluded patients with intrahepatic CCA, thereby providing no information as to the role of EUS in this patient cohort.

Stricture/Tumor Detection

Most EUS CCA studies failed to distinguish patients with CCA from other tumor types involving the biliary tree, including pancreatic carcinoma and metastatic biliary deposits. With regard to imaging detection alone (excluding FNA biopsy results), EUS identified 156 of 162 (96%) strictures or tumors [9,11–13]. In the two studies that clearly limited findings to CCA patients alone, the EUS imaging detection rate was 87 of 93 (94%) [13,14]. One study analyzed the rate of detection based on tumor location and found that proximal tumors were identified less often than distal tumors: 25 of 30 (83%) versus 51 of 51 (100%; $p < 0.01$), respectively [14].

Performance of Endoscopic Ultrasound Fine Needle Aspiration and Diagnostic Sensitivity

Potentially the most important, yet highest risk, aspect of EUS in CCA pertains to primary tumor FNA (Figure 13.1). Despite clinical or radiographic suspicion of CCA, the tumor related desmoplasia and tendency for longitudinal rather than radial growth negatively impact tissue acquisition. This often results in a delayed or failed tissue diagnosis [15]. Endoscopic retrograde cholangiography (ERC) with brush cytology and intraductal biopsy is routinely employed for diagnosis and provides high specificity, but suffers from a low diagnostic sensitivity of approximately 20–60% [16–18]. These findings have driven the pursuit of new technologies such as digital image analysis and fluorescence in situ hybridization that detect malignancy/neoplasia by assessing nuclear DNA content and aneusomy, respectively [19–21]. Although use of

Table 13.1 Endoscopic ultrasound (EUS) literature: study design, inclusion criteria, enrollment, and tumor site.

Study, year	Design	Inclusion criteria	Total enrollment	Study population	Primary stricture/ tumor site	Number per site
Mohamadnejad et al. 2011 [14]	Retrospective	Known cholangiocarcinoma	81	81	Proximal Distal	30 51
Rosch et al. 2004 [13]	Prospective	Indeterminate biliary stricture or pancreatic head mass	50	50	Hilar CBD	4 8
Eloubeidi et al. 2004 [12]	Prospective	Bile duct stricture Suspected cholangiocarcinoma[a]	28	25[b]	Proximal Distal	15 13
Lee et al. 2004 [11]	Retrospective	Known or suspected bile duct stricture Prior intraductal tissue sampling, if any, negative Prior CT and/or MRI failed to demonstrate the cause	42	40[c]	CHD CBD	1 39
Byrne et al. 2004 [10]	Retrospective	Bile duct mass or stricture with biliary EUS FNA	35	31[d]	CHD CBD	3 32
Fritscher-Ravens et al. 2003 [9]	Prospective	Clinical suspicion of hilar cholangiocarcinoma ERC with non-diagnostic tissue sampling Fit for hepatic resection	44	44	Hilar	44
			280	271	"Perihilar"[e] "Distal"[f]	97 (40%) 143 (60%)

[a] Patients ultimately found to have pancreatic cancer or nodal metastasis were excluded.
[b] Three patients were excluded because the tumor could not be visualized with linear imaging.
[c] Two patients were excluded because of inadequate follow-up.
[d] Four patients were excluded because of the absence of a diagnostic gold standard.
[e] "Perihilar" represents tumors designated as hilar, common hepatic duct, or proximal.
[f] "Distal" represents tumors designated as distal or common bile duct.
CBD, common bile duct; CHB, common hepatic duct; CT, computed tomography; ERC, endoscopic retrograde cholangiography; FNA, fine needle aspiration; MRI, magnetic resonance imaging.

Table 13.2 Tumor type and endoscopic ultrasound (EUS) stricture/tumor detection.

Study, year	Benign versus malignant		Details regarding malignancy	Primary stricture/ tumor detection with EUS (grouped data)	Primary stricture/ tumor detection with EUS (CCA patients alone)
Mohamadnejad et al. 2011 [14]	Malignant Benign	81 0	CCA (n = 81)	NA	76 of 81 (94%)[a]
Rosch et al. 2004 [13]	Malignant Benign	28 22	CCA (n = 12) Pancreatic (n = 16)	47 of 50 (94%)	11 of 12 (92%)
Eloubeidi et al. 2004 [12]	Malignant Benign	21 4	CCA (n = 21)	25 of 28 (89%)	~
Lee et al. 2004 [11]	Malignant Benign	24 16	CCA/pancreatic (n = 23) Metastatic (n = 1)	40 of 40 (100%)	~
Byrne et al. 2004 [10]	Malignant Benign	14 17	CCA/pancreatic (n = 11) Metastatic (n = 3)	(Preselected)[b]	~
Fritscher-Ravens et al. 2003 [9]	Malignant Benign	36 8	CCA (n = 30) Metastatic (n = 6)	44 of 44 (100%)	~
Summary	Malignant Benign	204 (73%) 76 (27%)	CCA (n = 144–178)[c]	156 of 162 (96%) (excluding preselected)	87 of 93 (94%)

[a] Tumor detection varied by site: proximal 25/30 (83%) versus 51/51 (100%).
[b] The cited study included preselected patients whose enrollment necessitated EUS visualization and FNA. Therefore, the findings do not apply in terms of stricture/tumor detection.
[c] Patients with CCA cannot be reliably distinguished because the studies combine data from patients with other pathologies (e.g., pancreatic carcinoma, metastatic biliary lesions). Therefore, some of the following analyses are based on grouped data.
CCA, cholangiocarcinoma; FNA, fine needle aspiration; NA, not available.

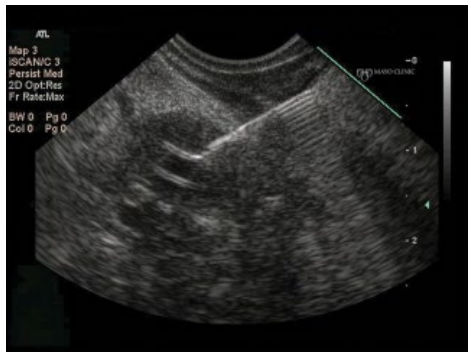

Figure 13.1 Endoscopic ultrasound guided fine needle aspiration of a common hepatic duct cholangiocarcinoma.

these molecular markers increases tumor detection by approximately 10–30%, the combined sensitivity remains less than 70% in most series [19–21].

For primary tumor EUS FNA, the reported sensitivity was 29–89% depending on the manner in which the cytology interpretations were analyzed (Tables 13.3 and 13.4) [9–14]. When studies accepted either a "positive" or "suspicious" cytological interpretation as being indicative of malignancy, the cumulative diagnostic sensitivity was 124 of 169 (73%) [9–12,14]. When studies required a "positive" cytological interpretation, the diagnostic sensitivity was only 63 of 106 (59%) [9–13]. Limited data suggest a higher diagnostic sensitivity when sampling distal versus proximal CCA; 38 of 47 (81%) versus 16 of 27 (59%) (p = 0.04) [14]. Conversely, another study reported a sensitivity of 32 of 36 (89%) for hilar strictures/tumors [9]. The sensitivity of EUS FNA after a negative or unsuccessful endoscopic retrograde

Table 13.3 Details regarding performance of endoscopic ultrasound (EUS) fine needle aspiration (FNA).

Study, year	Number of FNAs performed	Onsite review available	Cytological interpretations indicative of a positive FNA test result
Mohamadnejad et al. 2011 [14]	Median of five passes (range 1–12)	Yes	Positive or suspicious
Rosch et al. 2004 [13]	Two or more passes with material sufficient for assessment[a] Mean of 2.8 passes (range 2–4)	No	Only positive
Eloubeidi et al. 2004 [12]	Five or more passes unless onsite review confirmed malignant cells Median of three passes (range 1–7)	Yes	Dual analyses[b]
Lee et al. 2004 [11]	Until adequate cellularity or five or more passes Mean of 2.8 passes	Yes	Dual analyses[b]
Byrne et al. 2004 [10]	Range of 2–7 passes	Yes[c]	Dual analyses[b]
Fritscher-Ravens et al. 2003 [9]	Two or three passes	No	Dual analyses[b]

[a] Based on gross inspection by the endosonographer who deemed the material sufficient when visible material was identified.
[b] Data provided when considering "positive" for malignancy as the only indicator of a positive test result. Authors also provided data when considering either a "positive" or "suspicious" interpretation as indicative of a positive test result.
[c] Onsite cytopathology review available in 32 of 35 patients.

Table 13.4 Diagnostic sensitivity of endoscopic ultrasound fine needle aspiration.

Study, year	"Positive" or "suspicious" interpretation equates to positive for malignancy	Only "positive" interpretation equates to positive for malignancy
Mohamadnejad et al. 2011 [14]	54/74 (73%)[a]	NA
Rosch et al. 2004 [13]	NA	3/11 (27%)
Eloubeidi et al. 2004 [12]	18/21 (86%)	17/21 (75%)
Lee et al. 2004 [11]	11/24 (47%)	7/24 (29%)
Byrne et al. 2004 [10]	9/14 (64%)	6/14 (43%)
Fritscher-Ravens et al. 2003 [9]	32/36 (89%)	30/36 (83%)
	124/169 (73%)	63/106 (59%)

[a] The diagnostic sensitivity was significantly greater when sampling distal versus proximal cholangiocarcinoma; 38 of 47 (81%) versus 16 of 27 (59%); p = 0.04.
NA, data were not provided.

cholangiopancreatography (ERCP) is suggested by two studies reporting sensitivities of 77% and 89%, respectively [9,14].

Tumor Seeding

The enhanced diagnostic capability of primary tumor FNA must be balanced against the risk of tumor seeding; also sometimes referred to as needle tract seeding or implantation metastasis. The reported risk of clinically evident tumor seeding following EUS FNA of all sites is only 1/10,000-40,000 [22,23]. However, there are many limitations in assessing the incidence of tumor seeding and the cited

rates likely greatly underestimate the true occurrence. The inevitable mortality among patients with unresectable cancers makes it difficult to document tumor seeding as patients typically succumb before developing clinical evidence of tumor seeding. In addition, for patients undergoing attempted curative resection, preoperative biopsy likely deposits cancer cells that are undetected within the surgical specimen or deposited outside the field of resection. The resulting occult reservoir of tumor cells may lead to disease progression that is falsely attributed to incomplete resection or tumor recurrence rather than growth of residual needle tract cancer cells. Limited data suggest that tumor seeding correlates with important clinical outcomes including tumor stage, prognosis, resectability, resection margin status, recurrence, and survival [23–34]. Others report a lack of correlation between tumor seeding and clinical outcomes [35–38].

The potential for tumor cell displacement during FNA has been previously demonstrated [39]. In a prospective study of 140 patients undergoing EUS, the luminal fluid that is routinely aspirated through the accessory channel was collected and submitted for cytological analysis. Luminal fluid cytology was positive for malignancy in 48% of patients with a luminal cancer, which may be expected given the inherent tumor shedding that occurs within the gastrointestinal lumen. More concerning was the detection of positive cytology within post-FNA luminal fluid in three of 26 patients (12%) with pancreatic cancer. In patients with extraluminal cancers such as pancreatic cancer, we would not anticipate finding malignant cells within the gastrointestinal luminal fluid. This finding suggests the process of FNA may withdraw malignant cells from a pancreatic cancer into the gut lumen. This is likely an analogous method to that by which needle tract seeding occurs.

This hypothesis is supported by a study that examined the rate of newly occurring peritoneal carcinomatosis following EUS versus percutaneously guided FNA among matched cohorts with pancreatic cancers [40]. One patient developed peritoneal carcinomatosis in the EUS FNA group compared with seven patients in the percutaneous FNA group (2.2% versus 16.3%; $p < 0.025$). This study suggests a difference in tumor seeding rates between techniques and a potentially greater risk of seeding than previously recognized. Similarly, a recent meta-analysis of eight published series identified tumor seeding in 2.7% of patients following percutaneous biopsy of HCC [41].

We evaluated the incidence of tumor seeding in patients with hilar CCA who underwent primary tumor transperitoneal FNA [42]. The study included 191 patients with locally unresectable disease who underwent neoadjuvant chemoradiotherapy with the intent to proceed to liver transplantation if the operative staging showed no evidence of metastasis. Unlike operative resection where patients typically proceed directly to definitive therapy after diagnosis, this protocol involves a prolonged waiting period after diagnosis and completion of neoadjuvant therapy in order for a donor organ to become available. This waiting period has provided a unique opportunity to observe the impact of FNA biopsy. Since our practice is to avoid FNA in this setting, all biopsies were obtained at the referring institution. Among the 16 patients who underwent transperitoneal FNA (13 percutaneous, three EUS), six were positive for malignancy, nine were negative, and one patient had an equivocal test result. During operative staging, peritoneal metastasis was found in five of six (83%) versus none of nine (0%) patients with preoperative positive versus negative FNA, respectively. Peritoneal metastasis was discovered in only 14 of the remaining 175 (8%) patients who did not undergo

transperitoneal biopsy, versus five of six (83%; p = 0.0097) with a positive preoperative FNA.

Our findings highlight the risk of FNA induced tumor seeding, but also raise questions. It is unclear what factors led to the initial FNA. We cannot exclude that clinical or tumor related features suggested more advanced disease that may have diminished concern for tumor seeding leading to FNA. Although precise staging comparison was not possible, the study groups had similar CA19-9 levels, frequency of mass detection, tumor size, and histology. In addition, all patients were considered transplant candidates at the time of staging laparotomy. Nevertheless, an element of bias cannot be excluded. The interval from enrollment to staging in patients with a positive transperitoneal biopsy was 76 (54–249) days. Although this was not significantly different than that of the other groups, the stated interval did not include the time from biopsy until referral, which is sometimes delayed. Given the rate of malignant progression, it is unknown whether FNA induced tumor seeding would advance to grossly identifiable peritoneal disease within this timeframe.

Based on our experience, we consider primary tumor FNA to be a contraindication to transplantation for CCA. There are limitations to our approach partly due to the inherent difficulty of tissue diagnosis in this setting. Our approach mandates an exhaustive effort to establish the diagnosis of CCA by other means and to exclude other causes of biliary strictures. We recognize that caution is needed when proceeding to surgery without a tissue diagnosis given that 10–20% of patients with presumed CCA are found at surgery to have benign disease or an alternate tumor type [43–46]. The diagnostic challenges lead some to adopt less stringent markers such as CA19-9 levels and/or imaging criteria alone to provide a presumptive diagnosis in the proper clinical setting. While reliance on these softer surrogate markers may be appropriate in select patients, their use risks a false positive diagnosis that may lead to unnecessary, inappropriate, and often high risk surgery. Thorough counseling is essential so that patients understand the potential for major operative intervention, even transplantation, for benign disease. Patients are more apt to accept this approach when understanding the diagnostic hurdles, the need to avoid delays in oncological therapy, and the risks and implications of tumor seeding.

Staging and Resectability

Patient selection is a key component for the delivery of stage appropriate management of CCA. Several staging systems are utilized for CCA [4,47,48]. These systems differ in intended application and provide varying accuracy in terms of prognostic determination, assessing resectability status, and guiding the extent of resection. While unique criteria exist, certain features are common to each staging system, including the proximal and distal tumor extent and presence or absence of nodal metastasis, vascular infiltration (Figure 13.2), lobar atrophy, and distant metastasis. Improved imaging guided preoperative staging can reduce the need for staging laparoscopy and decrease the rate of tumor upstaging at laparoscopy.

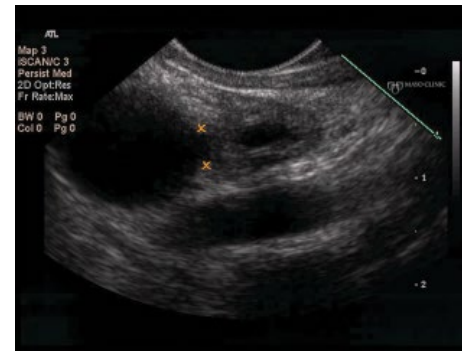

Figure 13.2 Tumor infiltration of the portal vein.

The CCA staging accuracy of EUS cannot be reliably determined due to the paucity of data. Published reports highlight a few patients with key staging information provided by EUS. However, this was not the intended purpose nor was the methodology sufficient to determine EUS staging accuracy. One study attempted to more fully address this issue [14]. Among 81 patients enrolled, 75 were evaluated for surgery. Among the 15 patients eventually deemed unresectable, EUS identified unresectable disease in a greater number than computed tomography (CT) and MRI; eight of 15 (53%) versus five of 15 (33%) and none of 15 (0%), respectively. Among this group, EUS identified six sites of disease not seen by CT/MRI, including infiltration of the portal vein (n = 2), hepatic artery, celiac lymph node, liver metastasis, and peritoneal spread. Sites identified by CT/MRI not seen by EUS included portal vein invasion (n = 2) and celiac lymphadenopathy. Finally, there were four sites of disease confirmed at surgery that were not detected with EUS or CT/MRI, including the hepatic artery, portal vein, celiac node, and longitudinal bile duct extension. Other patient data were not included in this report, thereby prohibiting us from determining the accuracy of EUS for staging and determining resectability.

Nodal Staging and Features of Malignant and Benign Lymph Nodes

Nodal metastasis of CCA is a poor prognostic indicator [49,50], with distant lymphadenopathy precluding curative resection. However, the impact of locoregional nodal metastasis is debated. At a minimum, its occurrence contraindicates liver transplantation and in some centers precludes attempted curative resection. Few studies have adequately addressed the issue of EUS nodal staging accuracy [14,51]. Other studies simply noted if any nodes had been seen [9,11] or completely neglected this issue [10,12,13].

The utility of EUS FNA for nodal staging was evaluated in 47 patients with locally unresectable hilar CCA who were being considered for liver transplantation [51]. EUS identified regional lymph nodes in all the patients, leading to FNA of 70 lymph nodes, with nodal metastasis identified in eight patients. The finding of malignant lymph nodes obviated the morbidity and expense of unwarranted chemoradiation and brachytherapy as well as staging laparotomy in anticipation of transplantation. CT and/or MRI detected malignant nodes in only two of the eight patients. Among the 22 patients with benign lymph nodes at FNA, 20 (91%) were confirmed negative at the time of exploratory laparotomy. EUS failed to detect malignant perigastric lymphadenopathy in two patients. This study demonstrated enhanced nodal staging provided by EUS FNA and the significant impact of this information on patient care. Important data were also collected concerning the EUS features of benign and malignant lymph nodes in patients with CCA (Figures 13.3 and 13.4). We found that historically adopted EUS imaging features, including long axis length, roundness, echogenicity, and homogeneity, individually and collectively provided poor predictive value (Table 13.5). Therefore, in CCA patients we biopsy all

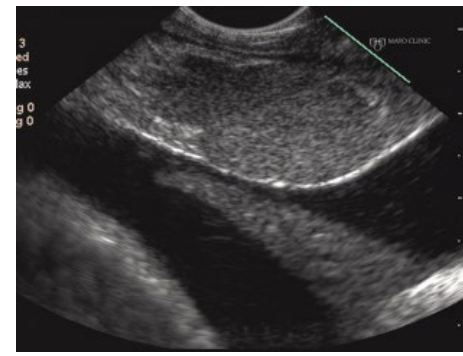

Figure 13.3 Endoscopic ultrasound image of a biopsy proven malignant lymph node.

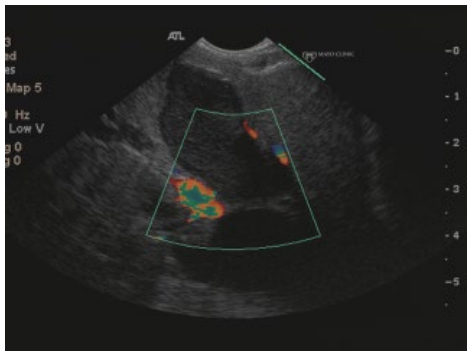

Figure 13.4 Endoscopic ultrasound image of an established benign lymph node.

Table 13.5 Endoscopice features of malignant and benign lymph nodes.

Mean	Malignant lymph node	Benign lymph node	P value
Long axis (mm)	1.61 ± 0.61	1.47 ± 0.78	0.68
Roundness score	2.5 ± 1.55	2.9 ± 0.81	0.32
Echogenicity score	4.0 ± 0.63	3.78 ± 0.71	0.48
Homogeneity score	3.0 ± 1.1	3.32 ± 0.84	0.41

visualized lymph nodes irrespective of their morphological or echo features.

Another study compared EUS nodal staging with a surgical or tissue gold standard among 45 patients and found an EUS sensitivity of only two of 23 (9%) [14]. The low sensitivity in this report may be accounted for by the investigators' practice of sampling only malignant appearing lymph nodes in contrast to our approach of sampling all nodes regardless of appearance.

Potentially Confounding Variables and Complications

Primary sclerosing cholangitis (PSC) is a major risk factor for CCA. Although precise PSC data were generally omitted, among the five studies providing such information, only 10 of 228 (4%) patients had PSC (Table 13.6). PSC is often associated with multiple biliary strictures, more pronounced desmoplasia, and diffuse benign lymphadenopathy. These features hinder EUS imaging and FNA, and therefore the low rate of PSC among study patients likely artificially improved the EUS imaging and FNA results.

Table 13.6 Potentially confounding variables and complications in endoscopic ultrasound (EUS).

Study, year	PSC present	Stent present at time of EUS	Complications related to EUS
Mohamadnejad et al. 2011 [14]	2 of 81 (2%)	64/74 (86%)[a]	1 (hemobilia)
Rosch et al. 2004 [13]	NA	NA	0
Eloubeidi et al. 2004 [12]	1 of 28 (4%)	27/28 (96%)	0
Lee et al. 2004 [11]	3 of 40 (8%)[b]	40/42 (95%)[c]	0
Byrne et al. 2004 [10]	0 of 35 (0%)	NA	NA
Fritscher-Ravens et al. 2003 [9]	4 of 44 (9%)[d]	44 of 44 (implied)	0
Summary	10/228 (4%)	131/146 (90%)	

[a] The diagnostic sensitivity of EUS fine needle aspiration (FNA) was 45 of 64 (70%) versus nine of 10 (90%) for patients with and without a stent, respectively.
[b] There was no evidence of PSC at the time of EUS. Cholangiographic features of PSC subsequently developed in three patients.
[c] Stent data were given for the initial 42 patients evaluated, but not specifically for the 40 patients ultimately included in the overall analyses.
[d] EUS FNA was falsely negative in the four patients with PSC.
NA, data were not provided; PSC, primary sclerosing cholangitis.

At the time of EUS, 131 of 146 (90%) patients had an indwelling biliary stent (Table 13.6). The presence of a biliary stent can hinder imaging due to artifacts associated with the stent itself as well as stent induced sludge. However, this is seldom a concern except for the smallest of biliary or pancreatic lesions. These problems may be overcome by imaging from various locations, by minimizing insufflation of air (which often passes through the stent into the duct), or by initial stent removal. At times, the presence of a stent can even facilitate the detection of a diminutive mass since the stent typically courses through the lesion thereby indicating its location.

The only complication reported following EUS FNA of CCA was hemobilia in one patient [14]. This patient was observed for 24 hours without the need for intervention.

Endoscopic Ultrasound and Hepatic Lesions

Traditionally, hepatic lesions were biopsied via the percutaneous route due to ease of access and the belief that the liver could not be visualized adequately by EUS. It is now recognized that the left lobe and hilum can be visualized from the gastric body and antrum, while portions of the right lobe can be accessed from the duodenal bulb. Although percutaneous biopsy remains the main method for tissue acquisition of hepatic masses, EUS FNA is increasingly used, particularly in patients who have an incidentally discovered liver lesion during EUS staging of an intra-abdominal or intrathoracic tumor.

Characteristics of Malignancy

Several studies have evaluated EUS characteristics that have helped to distinguish benign from malignant hepatic lesions. Nguyen et al. noticed that all 15 liver masses detected in their study were round with regular borders and lacked internal vascular structures by Doppler [52]. Similarly, another study found that malignant lesions, as compared with benign lesions, more commonly had regular outer margins (60% versus 27%, respectively; $p = 0.02$) and the detection of at least two lesions (38% versus 9%, respectively; $p = 0.03$) [53]. There was no significant difference in echogenicity and size of malignant and non-malignant masses. Finally, tenBerge et al. did not find any EUS characteristics that were predictive of malignancy, including the size, shape, echogenicity, and border of the lesion [54].

We have reported a scoring system using EUS criteria that we derived and validated to help distinguish between benign and malignant solid hepatic lesions [55]. Using this scoring system (Figure 13.5) we were able to diagnose malignant masses with a sensitivity of 85%, specificity of 82%, and positive predictive value of 88%.

Performance and Impact

Of 350 total patients from seven studies that focused on EUS FNA of hepatic lesions, 261 (74.6%) were positive for malignancy, 62 were negative for malignancy (17.7%), and the remaining 27 (7.7%) were either non-diagnostic, suspicious, or atypical for malignancy [52–54,56–59]. Combining the two prospective studies, the sensitivity, specificity, positive predictive value, and negative predictive value of malignancy were 96%, 100%, 100%, and 75%, respectively [52,56].

Three studies have evaluated the impact of the EUS FNA results on patient management [52–54]. A positive EUS FNA of a hepatic lesion upstaged the tumor in 16–57% of cases, while surgery was appropriately avoided in 27–50% of patients in these studies. An additional retrospective, single center study commented that the EUS FNA results influenced management in nine patients, with

Benign:	1. Hyperechoic (Distinctly) 2. Geographic shape (Distinctly)	
		Points
Malignant:	1. Two components	
	With isoechoic/Slightly hyperechoic center	4
	Without isoechoic/Slightly hyperechoic center	2
	2. Post-acoustic enhancement	3
	3. Distorts adjacent structures	
	Distinctly	2
	Slightly	1
	4. Hypoechoic	
	Distinctly	2
	Slightly	1
	5. Size ≥10 mm	1

Benign (either criterion)	Malignant (≥3 points)	Interpretation
Yes	No	Benign
Yes	Yes	Indeterminate
No	Yes	Malignant
No	No	Indeterminate

Figure 13.5 Scoring system of endoscopic ultrasound criteria derived to distinguish malignant from benign solid hepatic lesions.

four receiving palliative chemotherapy, one treated with transarterial chemoembolization, and four switching from curative to palliative therapy [58].

Comparison of Endoscopic and Percutaneous Fine Needle Aspiration

Although interpretation is limited by the bias of the publications focusing on EUS FNA, several studies have commented on the malignant hepatic lesions diagnosed via EUS FNA in patients who previously had non-diagnostic percutaneous biopsies. tenBerge et al. reported 26 and six cases where ultrasound- or CT guided FNA, respectively, were non-diagnostic for malignancy [54]. Out of those cases, EUS FNA was able to confirm malignancy in 23 (89%) and five (83%). Another study mentioned that CT guided biopsy was unable to make a malignant diagnosis in three patients, which were later confirmed by EUS FNA, but they also noted that two of three false negative EUS FNAs required diagnosis by percutaneous biopsies [53].

As tissue acquisition for easily accessible lesions should still be performed via the percutaneous route, these studies provide evidence for the use of EUS FNA as a complementary test in patients who either had a prior non-diagnostic percutaneous FNA or are found to have an incidental hepatic lesion while undergoing EUS staging. This also highlights the importance of performing a thorough evaluation of the liver during each EUS performed for tumor staging, as important lesions may be encountered that affect patient management but may not be seen on radiographic imaging.

Complications

Six complications (3.6%) were encountered in a retrospective, international questionnaire completed by 21 centers for a total of 167 cases, including abdominal pain (n = 2), fever (n = 2), bleeding (n = 1), and death (n = 1) [54]. The cause of death in the one patient was biliary sepsis, which was thought to be related to EUS FNA proximal to an occluded biliary stent. Self-limited bleeding was described in a patient undergoing EUS for a gastric subepithelial tumor. The patient was observed for 2 days and did not require a blood transfusion. The two patients with abdominal pain were observed for 6 hours as outpatients, while the two patients with post-procedural fevers were hospitalized but did not require antibiotics. Another two cases of self-limited bleeding that did not require transfusions or interventions were described as the only adverse event following EUS FNA of 41 liver lesions (4.9%) [56]. This risk related to EUS FNA of hepatic lesions is higher than the risk associated with EUS FNA of other sites, which was confirmed by a meta-analysis that found that hepatic EUS FNA had the second highest morbidity rate (2.33%), only exceeded by FNA of ascites [60].

Conclusion

It is essential, whenever possible, to obtain a definitive tissue diagnosis to help guide the care of patients with CCA and hepatic metastases. The growing use of EUS for CCA diagnosis and staging is largely driven by the inherent limitations of endoscopic bile duct sampling. Although the findings of EUS often facilitate patient care, the specific role in managing CCA is often debated. Some routinely perform bile duct EUS FNA for primary tumor diagnosis. We strongly discourage this practice due to the potential for tumor seeding and secondary impact on transplant candidacy or outcomes following resection for patients with resectable disease. The high false negative rate of primary tumor FNA must also be considered, as a negative test result often leaves great uncertainty among patients and care providers.

We view published CCA data as being most supportive of EUS when evaluating lymphadenopathy in patients being considered for liver transplantation. FNA verification of malignant lymphadenopathy avoids unnecessary neoadjuvant therapy and staging laparotomy, and thus impacts quality of life and cost. EUS is indicated regardless of CT and/or MRI findings, because non-invasive imaging lacks sufficient sensitivity for lymph node detection and poorly discriminates benign from malignant lymph nodes. Thorough sampling is necessary irrespective of nodal appearance, because of the poor predictive value of EUS imaging alone. Patients with a negative FNA must undergo staging laparotomy to verify N0 status. Additional study is needed to determine the role of EUS for obtaining other staging information in patients being considered for liver transplantation. More data are also needed to determine the true impact of EUS staging information in patients being considered for non-transplant forms of operative intervention. Finally, existing reports provide no information pertaining to the use of EUS for intrahepatic CCA.

EUS also has a role in detecting and diagnosing hepatic metastases in patients undergoing tumor staging of gastrointestinal and mediastinal malignancies. EUS FNA of hepatic lesions has been shown to have an impact on patient management by upstaging the tumor and/or avoiding unnecessary high risk surgeries. Therefore, we encourage endosonographers to thoroughly evaluate as much of the liver as possible when performing EUS for tumor staging.

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14

Endoscopic Ultrasound Guided Biliary Drainage

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Introduction

Improvements in echoendoscope design, imaging quality, and accessories have collectively led the evolution of endoscopic ultrasonography (EUS) from a diagnostic to a therapeutic modality [1]. As a result, EUS is now a well established technique for tissue sampling, fine needle injection, and drainage of fluid collections and abscesses adjacent to the gastrointestinal (GI) tract. Widespread adoption of minimally invasive surgery and radiological procedures has naturally led to the increased use of EUS in treatment and/or palliation of GI and pancreaticobiliary diseases, including EUS guided biliary drainage (EGBD).

In patients with normal, non-obstructed, upper GI anatomy, selective bile duct cannulation by experts at endoscopic retrograde cholangiopancreatography (ERCP) is successful in over 90% of cases. When bile duct access is not possible due to failed cannulation, altered upper GI tract anatomy, distorted ampulla, gastric outlet obstruction, periampullary diverticulum, or in situ enteral stents, EGBD has been increasingly used as a minimally invasive alternative to surgery or radiology [2–13].

EGBD can be performed by one of three methods. First, a rendezvous technique may be considered whereby a wire is placed into an intrahepatic or extrahepatic bile duct, passed through the papilla, and retrieved by a duodenoscope for biliary interventions. Second, direct transluminal stenting using a transgastric or transduodenal approach may be performed without accessing the papilla [14,15]. A third approach that has not been extensively reported is EUS guided antegrade transpapillary biliary stent placement [16,17].

Techniques

Rendezvous Technique

A linear echoendoscope is used to achieve initial biliary access within a segment of the dilated bile duct proximal to the site of obstruction. The tip of the echoendoscope is positioned in the gastric fundus or duodenal bulb when accessing the intrahepatic and extrahepatic bile duct, respectively. A 19 or 22 gauge fine needle aspiration (FNA) needle is used to puncture the bile duct with access confirmed by contrast

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injection and fluoroscopic imaging. A 0.035, 0.025, or 0.018 inch guidewire is then advanced into the bile duct. The smaller 0.018 inch wires need to be exchanged for larger wires before stent placement. The echoendoscope and needle are angled to facilitate antegrade guidewire passage through the site of obstruction and across the papilla and coiling of the wire within the duodenum is preferred to enable the rendezvous technique. The echoendoscope is withdrawn leaving the guidewire in place. A side viewing endoscope is passed to the papilla and a snare or biopsy forceps is used to grasp the guidewire and withdraw it through the endoscope with subsequent stent placement (Figure 14.1) [18].

Direct Transluminal Technique

In transluminal cases, the entire procedure is performed using the echoendoscope. After the bile duct is accessed as described above, the puncture tract is dilated with a dilating catheter or dilation balloon and a variety of devices are used to facilitate stent placement. These devices are selected

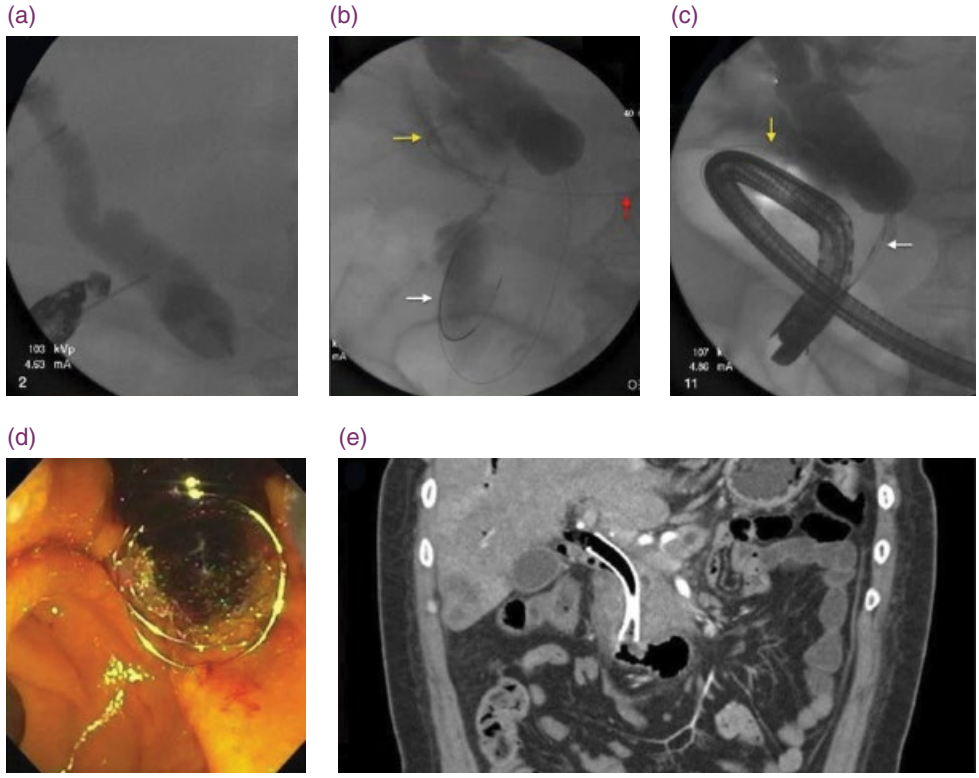

Figure 14.1 Endoscopic ultrasound guided biliary drainage using the rendezvous technique. (a) The common bile duct (CBD) was punctured with a 19 gauge needle under endosonographic guidance, and antegrade cholangiography revealed a dilated CBD with distal obstruction. (b) Antegrade passage of the guidewire can be seen passing via the stomach (red arrow), duodenal bulb (yellow arrow), through the papilla, and coiled in the distal duodenum (white arrow). (c) The wire was grasped through a duodenoscope and a sphincterotome was passed over the wire (white arrow). The wire was withdrawn from the duodenal bulb (yellow arrow) and readvanced in a retrograde fashion to facilitate transpapillary stent placement. (d) Dark bile flowing through transpapillary self-expandable metallic biliary stent. (e) Coronal computed tomography image showing a self-expandable metallic stent placed across a distal biliary stricture due to a pancreatic mass.

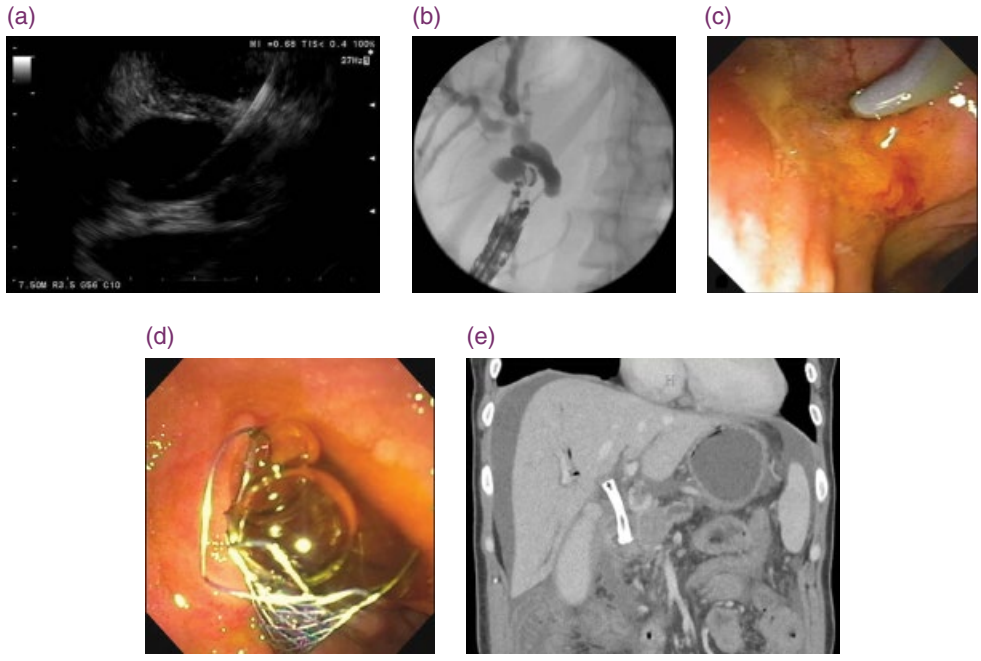

Figure 14.2 Endoscopic ultrasound guided biliary drainage (EGBD) using the direct transluminal technique. (a) Endosonographic image showing the needle and guidewire within the common bile duct (CBD). (b) Antegrade cholangiography demonstrating intra- and extrahepatic biliary dilation with an abrupt cut-off in the mid CBD. A prophylactic pancreatic stent placed at failed endoscopic retrograde cholangiopancreatography remains in situ. (c) The choledochoduodenostomy (CDS) was dilated with a dilating bougie catheter (4–7 Fr). (d) A large volume of bile flowing through the fully covered self-expanding metallic biliary stent that was placed across the CDS. (e) A coronal computed tomography image 4 weeks after EGBD reveals an optimal stent position and absence of biliary ductal dilation.

based on the patient's anatomy and features of the obstructing stricture. Stent insertion is then performed via an antegrade approach (Figure 14.2) [18,19].

Antegrade Stenting Technique

The EUS guided antegrade stenting technique involves the following steps. The dilated biliary ductal segment is punctured with an FNA needle and contrast is then injected through the needle to provide a cholangiogram. A hydrophilic guidewire is advanced through the needle and manipulated across the stricture. The FNA needle is removed, and the tract is dilated over the wire to 7 or 8.5 Fr using an ERCP catheter (e.g., Soehendra Biliary Dilation Catheter®, Wilson-Cook Medical, Winston-Salem, NC, USA). With the dilation catheter tip within the bile duct, the hydrophilic wire is then exchanged for a stiffer instrumentation guidewire (e.g. 0.035 inch Jagwire™, Boston Scientific Corp., Natick, MA, USA). Antegrade stent placement is performed by advancing the stent through the therapeutic channel of the echoendoscope over the guidewire, and the stent is then deployed across the stricture transpapillary or transanastomotic.

Outcomes

Despite growing international experience and peer reviewed publications of EGBD in recent years, concern still remains about the safety and efficacy of these techniques compared with the standard, widely available, alternative procedures.

Data involving mainly small series from expert centers suggest that EGBD can be performed with high therapeutic success (87%) but is associated with a 10–20% morbidity (most mild to moderate) and rare serious adverse events [20]. Artifon et al. [21] published the first prospective randomized trial comparing EGBD with percutaneous transhepatic biliary drainage (PTBD) in 25 patients (13 EUS choledochoduodenostomy (EUS-CDS) and 12 PTBD) with malignant biliary obstruction and failed ERCP. The two groups were similar before EGBD in terms of quality of life, total bilirubin (16.4 versus 17.2 mg/dL; $p = 0.7$), alkaline phosphatase (539 versus 518 IU/L; $p = 0.7$), and gamma-glutamyl transferase (554.3 versus 743.5 U/L; $p = 0.56$). All procedures were technically and clinically successful in both groups. At the 7-day follow-up, there was a significant reduction in total bilirubin in both groups (EUS-CDS: 16.4 to 3.3; $p = 0.002$; PTBD: 17.2 to 3.8; $p = 0.01$), although no difference was noted between the two groups (EUS-CDS to PTBD: 3.3 versus 3.8; $p = 0.2$). There was no difference between the complication rates in the two groups ($p = 0.44$): EUS-CDS (2/13, 15.3%) and PTBD (3/12, 25%). Cost was similar between both groups (EUS-CDS: US$5673 versus PTBD: $7570; $p = 0.39$). Therefore, this randomized study showed that EUS performed via the transluminal approach (choledochoduodenostomy) had a similar success rate, complication rate, and cost as compared with PTBD. Although this small, prospective, single center study provides hope that EGBD may be an acceptable alternative to PTBD, large prospective studies performed by experts may also provide valuable insight into procedure related complications, efficacy, and modifications employed to improve patient outcomes.

Shah and colleagues reported their extensive experience with EGBD in patients with surgical anatomy or failed ERCP [13]. A total of 70 patients had attempted EUS guided cholangiography and this was successful in 68 (97%) patients; 66 patients had cholangiographic findings requiring interventions. EGBD using the rendezvous technique was attempted in 50 patients and was successful in 37 (74%) and failed in 13. Direct EUS guided interventions (hepatogastrostomy, choledochoduodenostomy, antegrade stenting) were attempted in the remaining 16 patients and were successful in 13 (81%). A total of six complications occurred, most of which were managed conservatively. One perforation occurred that required subsequent surgical intervention and was related to sphincterotomy after successful rendezvous ERCP.

Park and colleagues reported their experience in a large prospective cohort who underwent EGBD by one experienced operator at a large, busy, tertiary center in Korea [22]. These authors have previously reported a relatively high adverse event rate of 20% for EGBD [7] and in the more recent study they aimed to evaluate whether a modified technique of "enhanced guidewire manipulation" could improve the safety and efficacy of EGBD [22]. The modified approach by Park et al. included: (i) optimizing the angle of bile duct puncture with the EUS needle; (ii) the use of smaller diameter wires to avoid wire shearing; (iii) introducing a 4 Fr catheter to manipulate the direction of the wire towards/through the distal stricture/ampulla; and (iv) a preference for puncturing a segment 2 intrahepatic duct to allow advancement of the wire towards the hilum [22]. In this study, 45 patients with benign or malignant biliary obstruction underwent same session EGBD after failed ERCP. Technical success, which was defined as successful stenting or balloon dilation along with the flow of contrast medium and/or bile through the stent, was achieved in 41 (91%) patients. Functional success, defined as a decrease of cholestatic indices to less than 75% of the pretreatment value within 1 month of

the procedure, was achieved in 39 (95%) of these patients. A total of five (11%) adverse events occurred in four patients: one each of pancreatitis, focal bile peritonitis, limited pneumoperitoneum, intraperitoneal stent migration, and biloma. The latter complication was managed by a EUS guided approach with stent-in-stent placement. In all, three patients experienced mild complications and one patient experienced a moderate complication per the American Society for Gastrointestinal Endoscopy (ASGE) lexicon's severity grading system [23]. Technical success and complications in this study were similar to other reports.

As stated above, the primary intent of the Park's study [22] was to evaluate whether "advanced guidewire manipulation" may decrease an adverse event rate of 20% (n = 11) that the authors reported in a prior study of 55 patients who underwent either EUS guided hepaticogastrostomy or EUS-CDS [7]. To evaluate whether the authors successfully met their goal, it is important to evaluate potential reasons for complications in these 11 patients (graded as mild in seven and moderate in four). Interestingly, nine of these 11 patients underwent fistula dilation using a needle knife and its use was independently associated with the occurrence of adverse events (odds ratio 12.4; p = 0.01). In the more recent study [22], fistula dilation with a needle knife was used in only five patients. Therefore, we recommend that the use of needle knife cautery for tract creation/dilation during EGBD should be avoided when possible.

Gupta et al. reported a multicenter experience of long term outcomes of EGBD in 246 patients [24]. The intrahepatic approach was used in 60% of the cases. Successful biliary drainage was achieved in 87% of cases, with a similar success rate in extrahepatic and intrahepatic approaches (84.3% versus 90.4%; p = 0.15). A higher clinical success rate was noted in malignant diseases compared with benign diseases (90.2% versus 77.3%; p = 0.02). Complications for all techniques included pneumoperitoneum 5%, bleeding 11%, bile leak/peritonitis 10%, and cholangitis 5%, without a significant difference between the intrahepatic and extrahepatic approaches and between benign and malignant diseases.

It is important to note that results of the above discussed studies come from tertiary centers where all procedures were performed by high volume, highly qualified interventional endoscopists. Similarly, previous series describing EGBD were performed at tertiary centers by highly skilled endoscopists. We believe these procedures are ideally performed by one or more experienced endoscopists trained in both ERCP and EUS and carried out at institutions where surgery and radiology backup are available should complications arise.

Comparison of Different Techniques

Rendezvous Versus Direct Transluminal Techniques

The rendezvous (REN) approach is the preferred approach for many endoscopists as it avoids the need for a permanent bilioenteric fistula and the need to dilate the fistulous tract, which may lead to complications such as bleeding, pneumoperitoneum, and pneumomediastinum. However, this approach may not be possible if the wire cannot pass through the ampulla due to difficult angulation or a tight distal biliary stricture. It is not well known how REN and transluminal (TL) techniques compare in terms of efficacy and adverse events. Khashab et al. compared outcomes of REN and TL techniques in a study of 35 patients who underwent EGBD (REN 13, TL 20) for malignant distal biliary obstruction and failed ERCP [18]. Technical success was achieved in 33 (94%)

patients and clinical success was attained in 32/33 (97.0%) patients. The mean post-procedure bilirubin level was 1.38 mg/dL in the REN group and 1.33 mg/dL in the TL group ($p = 0.88$). Similarly, the length of hospital stay was not different between both groups ($p = 0.23$), and there was no significant difference in adverse event rate between the REN and TL groups (15.4% versus 10%; $p = 0.64$). Long term outcomes were comparable between both groups with one stent migration in the REN group at 62 days and one stent occlusion in the TL group at 42 days after EGBD. The authors concluded that EGBD is safe and effective when performed by experienced operators. Stent occlusion was not common during long term follow-up. Both REN and TL techniques seemed to be equally effective and safe. The latter approach was a reasonable alternative to the REN technique and when aggressive wire manipulation was not warranted.

There are at least three potential disadvantages to the EUS guided biliary REN approach that deserve discussion. First, REN completion even by experts is successful in only 75% of cases and requires an accessible papilla, which may not be possible in patients with altered upper GI anatomy or gastric outlet obstruction [13]. In the study by Park et al. [22], a REN approach (or antegrade transpapillary stenting) was not feasible in 11 (24%) patients and failed in an additional nine (20%). A second difficulty with REN biliary drainage is prolonged procedural times, which are due to several factors including: (i) the requirement for wire manipulation to steer it through the distal stricture and towards the ampulla; (ii) the need to exchange the echoendoscope to a duodenoscope; and (iii) a requisite for subsequent retrograde biliary cannulation. A final shortcoming of REN EGBD is the risk of acute pancreatitis due to manipulation of the papilla [4,9,13].

Since REN EGBD either fails or is not possible in at least 25% of patients, is associated with prolonged procedure times, and still may lead to pancreatitis and other complications, it is essential that endoscopists strive to perfect and minimize the risks associated with EUS guided TL stenting in order to provide a complete armamentarium for patients with malignant and benign biliary strictures or obstruction. However, adoption of bilioenteric fistula tract stenting by some endoscopists has been slow due to concern about potential associated risks, particularly bile leakage and pneumoperitoneum. Nonetheless, our experience suggests that TL stent insertion is safe when biliary drainage is successfully achieved [10,11,25] but, importantly, risks formation of a bile leak if biliary obstruction is not relieved. Several safeguards may assure successful and safe TL stent placement. First, the TL tract should not be dilated until an acceptable guidewire position for stent placement has been achieved. Second, the tract should be dilated only to a diameter to allow stent insertion while avoiding overly aggressive dilation that may predispose to a biliary leak [10]. Third, cautery assisted tract dilation should be avoided if possible given the potential for complications, particularly bleeding and bile leak. Fourth, fully covered metallic stents and carbon dioxide insufflation should be used to minimize the risk of bile leak and pneumoperitoneum, respectively. We agree with the assertion of many experts that REN EGBD should preferentially be attempted first, but believe that a TL approach is an acceptable, efficacious, and safe alternative, provided the above safeguards are followed.

Intrahepatic Versus Extrahepatic Access Routes

Endoscopic ultrasound guided biliary drainage using either a REN or TL technique requires needle puncture via an intrahepatic or extrahepatic route in a

non-obstructed patient with normal upper GI anatomy. However, it is not yet established which access route is optimal for either technique. In cases of REN EGBD, Dhir and colleagues found that an extrahepatic REN approach (using a transduodenal puncture) was associated with significantly shorter procedure times and less post-procedure pain, bile leak, and air under the diaphragm [26]. In addition, they found that success is likely higher with extrahepatic REN as was confirmed by Park et al. (93% versus 50%) [22]. Similarly, in cases of direct TL EGBD, an extrahepatic route (choledochoduodenostomy) is likely safer than an intrahepatic route (hepatogastrostomy) [7]. Therefore, it appears that an extrahepatic access route during EGBD is preferable and safer to an intrahepatic route whether EGBD is performed using the REN or direct TL technique.

Dhir and colleagues compared success and complication rates in 68 patients undergoing EGBD via different methods [27]. EGBD was successful in 65 patients (95.6%). There was no significant difference in the success rates of the different techniques. Complications were seen in 14 patients (20.6%) and mortality in three patients (4.4%). Complications were significantly higher for the intrahepatic route compared with the extrahepatic (transduodenal) route (30.5% versus 9.3%; $p = 0.03$). There was no significant difference in complication rates among TL and transpapillary stent placements, or direct and REN stenting. Logistic regression analysis showed transhepatic access to be the only independent risk factor for complications ($p = 0.03$). The authors concluded that EGBD can be carried out with high success rates regardless of the choice of access route, stent direction, or drainage route. However, complications are significantly higher with the intrahepatic access route. They recommended that the extrahepatic (transduodenal) route should be chosen for EGBD and REN stent placements when both routes are available.

Why does it appear that the intrahepatic route leads to an increased risk of complications? First, an intrahepatic route involves needle puncture into the peritoneal cavity, which risks pneumoperitoneum and peritoneal bile leakage. Second, movement of the liver during respiration may lead to both stent migration with resulting bilomas and increased trauma to the bilioenteric tract (which increases the risk for post-procedure pain and bile leak). Finally, smaller caliber intrahepatic ducts may not allow placement of wider 8–10 mm metallic stents, which can theoretically predispose to pneumoperitoneum and bile leakage due to incomplete sealing of the bilioenteric fistula. Extrahepatic access, on the other hand, has many advantages including close proximity of the duodenum to the dilated bile duct, retroperitoneal location of the bile duct, and a relatively fixed bile duct with minimal respiratory influence. Further prospective studies comparing the safety of these different techniques are needed.

Endoscopic Ultrasound Guided Biliary Drainage in Patients with Pre-Existing Duodenal Stents

Patients with gastric outlet obstruction resulting from duodenal tumor compression and/or infiltration present a particular challenge during ERCP, especially in the presence of a duodenal self-expandable metal stent (SEMS). While ERCP can be accomplished by fenestration of a duodenal stent in some cases, alternative approaches for biliary access and drainage are needed when the papilla is unable to be reached or visualized [10]. Khashab et al. performed EGBD in nine patients with a pre-existing duodenal SEMS and an inaccessible ampulla [10]. The bile duct was accessed via a transgastric ($n = 3$) or transduodenal ($n = 6$) approach, requiring needle passage

through the interstices of the duodenal stent in five patients. Biliary access was achieved using a 19 gauge FNA needle via an extrahepatic (n = 7) or intrahepatic (n = 2) approach. Catheter dilation was performed following guidewire passage through the site of obstruction and papilla. Dilation included the gastric or duodenal wall, intervening tissues between the lumen wall and bile duct, the site of obstruction, and the duodenal stent interstices. Inserted biliary SEMSs were fully covered or uncovered, measured 10 mm in diameter, and ranged from 40 to 80 mm in length. Antegrade bypass stent insertion (direct transluminal access) was required in two patients because of inability to advance the guidewire antegrade through the obstruction and to the duodenum, thereby prohibiting transpapillary drainage. All patients had clinical resolution of their jaundice. There were no complications of significant bleeding or leakage from the gastric, duodenal, or hepatobiliary area reported following the procedure in any patient. One patient developed pancreatitis and cholecystitis following fully covered transpapillary SEMS placement [10]. Therefore, our experience suggests the safety of EGBD in this patient population (Figure 14.3).

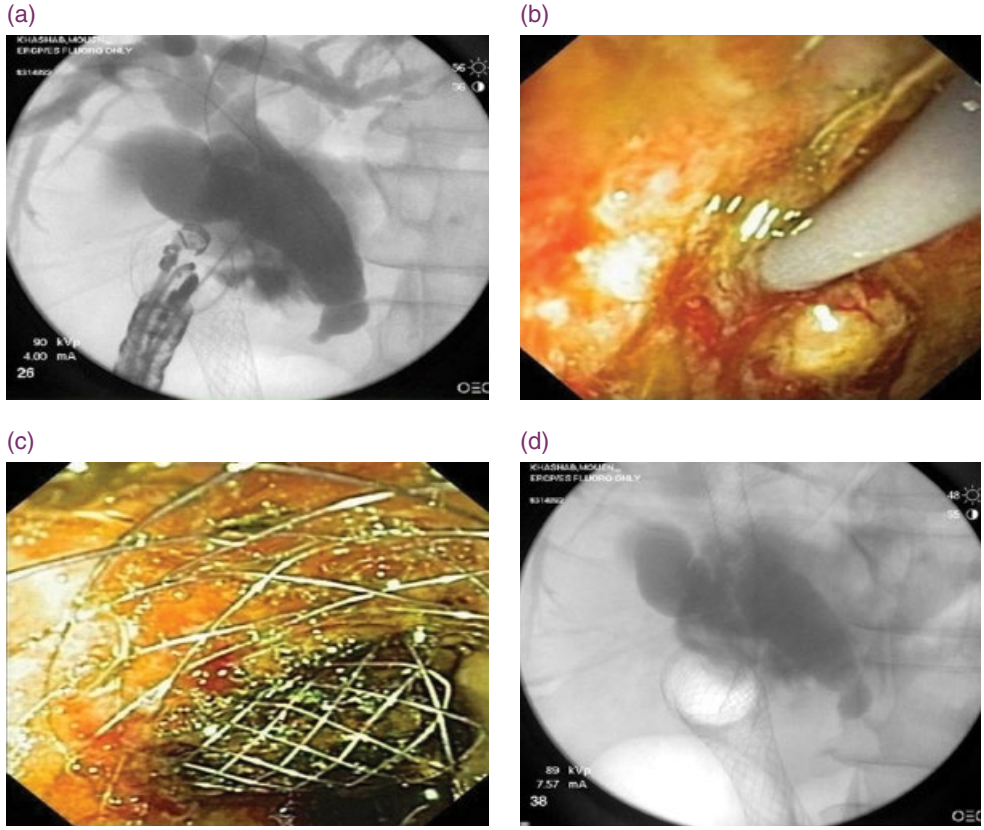

Figure 14.3 Endoscopic ultrasound guided biliary drainage using a direct transluminal technique in a patient with a pre-existing duodenal stent. (a) The bile duct was punctured with a 19 gauge needle and dye was injected. Antegrade cholangiography revealed a dilated bile duct with a tight distal stricture. A 0.035 inch hydrophilic wire was advanced to the proximal biliary system. (b) Choledochoduodenostomy using a 7 Fr Soehendra dilator. (c) A fully covered biliary self-expandable metal stent (SEMS) was placed with its distal end in the duodenal bulb exiting through the enteral stent mesh. (d) Fluoroscopy confirmed the position of the biliary SEMS and enteral stent.

Endoscopic Ultrasound Guided Biliary Drainage in Patients with Hepaticoduodenostomy

Patients with isolated right intrahepatic ductal (IHD) obstruction are traditionally not considered as candidates for EGBD. Park and colleagues evaluated the technical feasibility and safety of EUS guided hepaticoduodenostomy (EUS-HD) in patients with isolated right IHD obstruction [28]. EUS assisted cholangiography of the right IHD was performed in six patients, with successful antegrade bypass stenting in two patients, antegrade transanastomotic stenting in one patient, antegrade transanastomotic balloon dilation in one patient, and a cholangiogram as a roadmap in one patient. Biliary decompression was unsuccessful in one patient because of failed guidewire manipulation for antegrade stenting or balloon dilation. For this patient, subsequent PTBD was performed on a different day. Therefore, the technical success rate of EUS-HD assisted cholangiography and biliary decompression was 100% (6/6) and 83% (5/6), respectively. There were no procedure related complications. Further larger studies assessing the safety and efficacy of EUS-HD are needed.

Endoscopic Ultrasound Guided Biliary Drainage Versus Percutaneous Transhepatic Biliary Drainage

As mentioned above, there has been growing global experience with EGBD in recent years. Data from multiple centers support the efficacy and safety of EGBD [20]. However, comparative outcome data against competing procedures (e.g., PTBD) are limited. These data are essential to decide whether patients who fail ERCP are best managed with EGBD or PTBD. There has been only one small randomized controlled trial comparing EGBD and PTBD in 25 patients with malignant biliary obstruction and failed ERCP [21]. This study concluded that both procedures had equivalent efficacy, safety, and cost. The primary limitation of this study was that only direct procedural costs were calculated. This likely overestimated the cost effectiveness of PTBD, which is associated with increased downstream costs due to the requirement for frequent reinterventions. Therefore, a key aspect of such a comparative analysis is to take the index and subsequent required interventions into consideration in order to avoid bias and get a more comprehensive assessment of healthcare cost.

One of the advantages of EGBD is the possibility of accessing the biliary ductal system from multiple routes. The dilated intrahepatic biliary radicals can be accessed from the liver via the distal esophagus or stomach, or the common bile duct can be punctured from the proximal duodenum (and occasionally from the gastric antrum) [27]. This choice of access routes allows for successful endoscopic biliary drainage even in patients with duodenal obstruction or duodenal bypass surgeries. Other advantages include the feasibility of EGBD even in patients with ascites and liver metastasis, in addition to avoidance of percutaneous catheters, their associated complications (e.g., skin irritation, leak), and their perceived invasiveness and negative impact on quality of life. Moreover, EGBD can be performed during the same endoscopy session after failed ERCP, which avoids the need for repeated interventions and allows for timely biliary drainage in which bilirubin levels decrease more rapidly, thus enabling more rapid initiation of chemoradiation if needed [13,22]. EGBD also maintains bile within the GI tract to ensure proper digestion and absorption of nutrients.

Timing of Endoscopic Ultrasound Guided Biliary Drainage

We recommend obtaining consent for possible EGBD at the time of ERCP in patients at high risk for failed biliary cannulation (e.g., altered anatomy, prior failed ERCP, periampullary cancer with duodenal invasion on imaging, enteral stent covering the ampulla). This approach mandates a lengthy conversation with the patient about the real potential for failed cannulation and available alternatives such as surgery or percutaneous drainage. It also requires the endoscopist to ensure that adequate time, skilled staff, and appropriate backup are available for EGBD and its possible complications. Nevertheless, consenting for EGBD at the time of ERCP avoids the need for repeated endoscopic interventions and allows for timely biliary drainage and commencement of chemoradiation if needed.

A final consideration about EGBD is when to perform the procedure in a patient with a benign or malignant biliary obstruction. Hara and colleagues recently conducted a prospective study of EUS-CDS for primary therapy of malignant biliary obstruction (i.e., not after failed ERCP) in 17 patients [29]. Both technical and clinical success were achieved in 94% of patients, without severe complications. Although such an approach may avoid post-ERCP pancreatitis, we believe that the current role of EGBD should be for salvage therapy in patients who fail ERCP.

Current Limitations and Recent Advances

The current linear array echoendoscopes have an elongated tip that is sometimes not conducive for traversing strictured gut lumens. Also, once guidewire access is obtained, the scope design limits adequate endoscopic visualization which makes stent deployment and other endotherapy technically challenging. A forward view echoendoscope is currently under development to overcome this technical challenge. This new device has a blunt tip, similar to a standard gastroscope, and preliminary data for performing interventions appear promising [30].

Another hindrance to the progress of therapeutic EUS in general is the absence of dedicated accessories. Currently, most interventions are being performed using ERCP accessories, some of which are not conducive for use with a curvilinear echoendoscope. A proprietary, novel, lumen apposing metal stent (LAMS) (Axios®, X-Lumena, Mountain View, CA, USA) was recently developed and has successfully been tested in experimental [31] and clinical [32,33] settings. Axios® is a fully covered, saddle shaped, 10–15 mm diameter nitinol stent with bilateral anchor flanges. Its design is meant to hold tissue layers in apposition, allowing fistula formation between non-adherent extraintestinal fluid collections or bile duct and the GI lumen. The Axios® delivery catheter is attached to the echoendoscope working channel in the same way as EUS needles, allowing precise step by step deployment. The goals of the Axios® LAMS are to provide larger caliber stents for drainage than plastic pigtail stents and to minimize the risk of leakage by its tissue apposition and anti-migration properties. Preliminary data on the use of this novel stent for gallbladder drainage are promising [32,33]. The role of Axios® in EGBD is yet to be determined as it is not suitable for the drainage of intrahepatic biliary ducts due to its wide diameter. In addition, the potential risk of cholecystitis after choledochoduodenostomy and Axios® placement is a concern as its wide flanges may possibly result in cystic duct obstruction.

Conclusion

In conclusion, EGBD is a safe and effective procedure after failed ERCP whether it is performed via the rendezvous or direct transluminal technique. An extrahepatic access route is preferable and is associated with a decreased incidence of adverse events. EGBD is perceivably less invasive than PTBD and limited available data suggest equivalent efficacy and safety. Indications and methods for EGBD are yet to be standardized and, thus, the approach should be individualized for each patient based on the endoscopist's experience and the patient's anatomy. Further prospective, multicenter, controlled studies are needed to further delineate appropriate indications, predictors of success and complications, optimal approach, and clinical outcomes compared to other drainage procedures.

Conflicts of Interest

Dr Mouen A. Khashab is a consultant for Boston Scientific and Olympus America and has received research support from Cook Medical. Dr Shyam Varadarajulu and Dr Robert H. Hawes are consultants for Boston Scientific and Olympus America.

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15

Hepatobiliary Endoscopy in the Patient with Liver Disease and Altered Anatomy

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Introduction

Since the advent of the Billroth procedure in the late 19th century, surgeons have attempted to intervene on foregut disease while maintaining gastrointestinal continuity. Initial indications for such surgical manipulations were dominated by sequelae of peptic ulcer disease, and while these have been somewhat obviated by medical therapies, more complex gastroenteric manipulations are becoming commonplace with rising numbers of liver transplantations, pancreatic head resections, and bariatric surgeries. These individuals may develop biliary disease amenable to endoscopic retrograde cholangiography (ERC); however, their altered anatomy poses specific anatomical and technical challenges to even the most experienced therapeutic endoscopist. This chapter will provide an overview of the pertinent literature and the typical surgically altered gastrointestinal anatomy that may be encountered when attempting ERC in this patient population. We will review techniques and devices helpful to optimize success.

General Considerations

Altered anatomy biliary procedures may involve traversing long segments of small bowel prior to visualization of the papilla or bilioenteric anastomosis. Therefore, before attempting these procedures, thorough pre-procedure planning and review of available operative notes and imaging are critical to optimizing patient selection and the chance for a successful outcome. This includes an understanding of both the basic surgical techniques underlying each procedure as well as the actual operative details for the particular patient. Moreover, optimizing available equipment and recognizing their limitations may be the difference between access and failure.

Anatomical Descriptions

After a distal resection of the stomach, the continuity of the gastrointestinal tract is restored by either a gastroduodenal anastomosis (Billroth I or B1), a gastrojejunal anastomosis (Billroth II or B2), or a Roux-en-Y (RY) gastrojejunal anastomosis.

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The initial Billroth procedure was effective and left the proximal duodenum and pancreaticobiliary system unaltered, however it was soon found to carry an appreciable risk of anastomotic leak, presumably from the disparity in size between the hemi-resected stomach and proximal duodenum (Figure 15.1a). This prompted the development of the Billroth II procedure in which the proximally resected end of the duodenum is oversewn and the stomach remnant anastomosed in an end to side fashion with the proximal jejunum (Figure 15.1b). In both Billroth scenarios the major and minor papillae remain intact, and usually a duodenoscope will be sufficiently long to bring these into endoscopic view, albeit in a reversed orientation. While Billroth procedures for ulceration and antral lesions are becoming

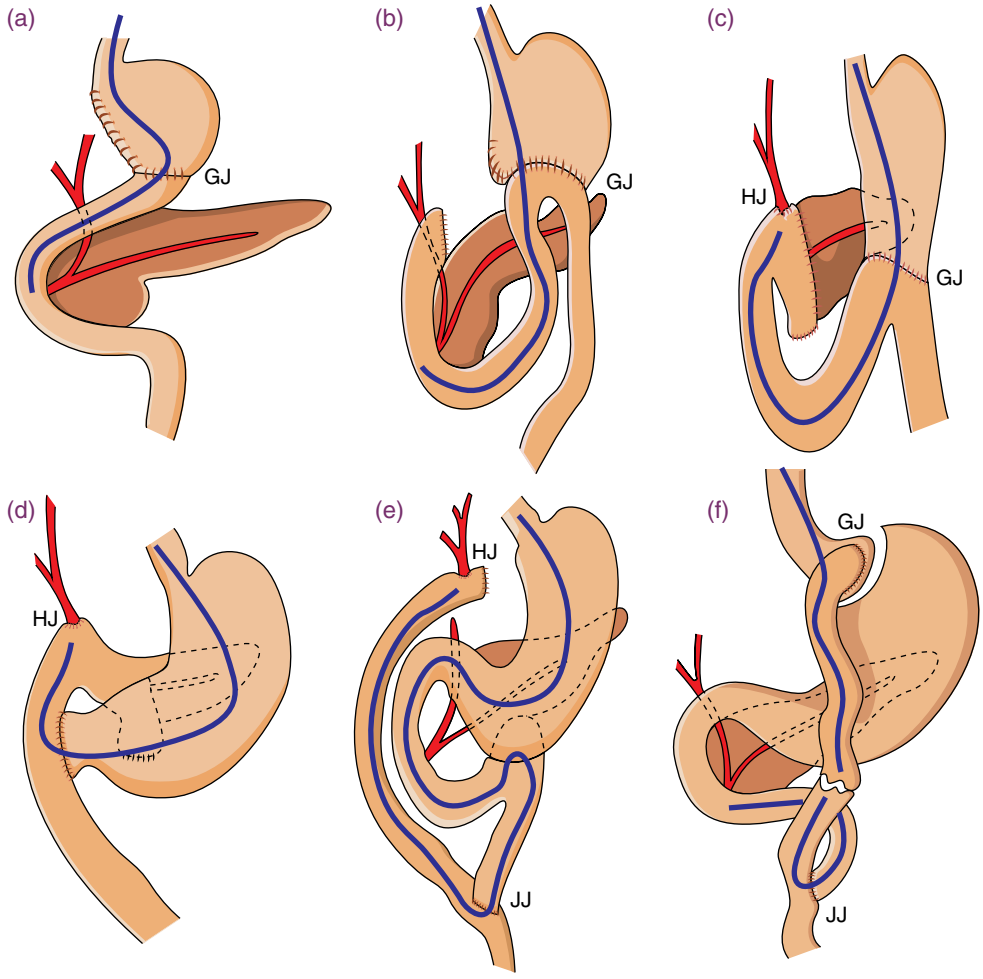

Figure 15.1 Schematic representations of various surgically altered anatomies (a) Billroth I with pyloric resection and gastrojejunostomy (GJ) upstream of the ampulla. (b) Billroth II with pyloric resection and GJ downstream of the ampulla. (c) Traditional Whipple anatomy with resection of the pylorus. (d) Pylorus sparing Whipple anatomy. (e) Short limb Roux-en-Y anatomy in a liver transplant patient. (f) Long limb Roux-en-Y anatomy in a gastric bypass patient. GJ (gastrojejunostomy), JJ (jejunojejunostomy), HJ, hepaticojejunostomy; hashed line represents a surgical anastomosis; ≈ represents long limb; blue line represents an endoscope. Source: Redrawn figures courtesy of Stuart K. Amateau. Reproduced with permission.

less frequent due to improved medical therapy, a large number of older patients are still alive who had these operations. Moreover, many of the basic principles underlying altered anatomy ERC stem from this population, and frequently the available corpus of data consist of Billroth II in comparison with other techniques.

RY anastomoses represent the basic operative configuration underlying a constellation of surgeries including gastrectomy for malignancy (RY reconstruction), as an adjunct to pancreaticoduodenectomy (Whipple) to allow continuity for the remnant pancreatic duct, and to allow for bile duct enterostomy (hepaticojejunostomy (HJ)) in the setting of biliary tree resection, duodenectomy, or liver transplantation (Figure 15.1c, d, e). With the obesity epidemic, RY gastric bypass (RYGB) surgery has blossomed due to its combined restrictive and malabsorptive properties (Figure 15.1f). All the RY procedures involve a jejunal anastomosis, creating a Y shaped configuration of small bowel. Named after the pioneering surgeon of the same name, the Roux limb is then considered the portion of bowel upstream, in terms of enteral continuity, of this jejunal anastomosis. The terms afferent and efferent limbs or loops are then applied to the portions of bowel within which the biliary and pancreatic juices flow, with the upstream limb considered the afferent limb and the limb downstream of the jejunal anastomosis the efferent limb. In some RY procedures the afferent limb and the Roux limb are separate entities and in others they are one and the same. While this can readily become confusing, in terms of endoscopic approach of the biliary system, there are two major anatomical considerations when reviewing operative histories: native versus anastomotic biliary orifice and length of the Roux limb, usually estimated by the surgeon within their operative report.

With total gastrectomy or partial gastrectomy (antrectomy) with RY reconstruction, the stomach remnant is brought together with a portion of jejunum in end to side fashion (gastrojejunostomy). Bowel beyond this anastomosis forms a Roux limb, which itself is anastomosed with the duodenal and proximal jejunal stump at a jejunojejunal anastomosis. Of note, there are instances where the jejunostomy is created in end to side fashion, resulting in what appears endoscopically as three limbs, although one is found to be short and blind. The duodenal stump, in this case the afferent pancreaticobiliary limb, typically involves an unmanipulated pancreaticobiliary system with native ampulla. In such surgeries, the Roux limb is relatively short, typically measuring 45–50 cm. RYGB surgery is usually a relatively simple variation of the RY reconstruction to allow for increased malabsorption; the Roux limb, and thus access to the pancreaticobiliary limb, is significantly longer. An RY configuration is also utilized in orthotopic liver transplantation when neither donor duct to recipient duct nor biliary to duodenal anastomosis (choledochoduodenostomy) are feasible due to anastomotic tension that has been linked to leak and dehiscence. Unlike with standard RY reconstruction, the duodenum is left in continuity and is considered the afferent limb, and a loop of jejunum is mobilized to allow HJ anastomosis and is itself anastomosed with the jejunum (jejunojejunostomy). This biliary loop is traditionally short; however this is not a rule and long limb exceptions should be anticipated.

In conventional pancreaticoduodenectomy the antrum and duodenum are resected in concert with the head of the pancreas, allowing mobilization of the remnant pancreas and transection of the common bile duct proximal to the head of the pancreas. A pancreaticobiliary limb is then fashioned with an end to side HJ as well as a direct pancreaticojejunostomy to what becomes a relatively short limb upstream of the gastrojejunal anastomosis.

Of note, the HJ is usually 3–5 cm downstream of an end to side or end to end pancreaticojejunostomy. In this scenario, there is no so-called afferent limb. A pylorus preserving Whipple involves the transection at the duodenal bulb rather than the antrum with end to side anastomosis with the jejunum, and is otherwise no different from an endoscopist's perspective. In terms of endoscopic approach to the biliary system, both forms of Whipple are favorable with short limbs and HJ anastomoses.

Rarely, the endoscopist will be asked to intervene in biliary disease in an individual who has undergone a now antiquated weight loss procedure such as a biliopancreatic diversion (BPD) or the duodenal switch. The traditional BPD consists of a partial gastrectomy with the formation of a gastroileostomy and long Roux limb of ileum. The afferent pancreaticobiliary limb may be of extreme length and an ileoileostomy is created only several centimeters upstream of the ileocecal valve. A duodenal switch is a slight variation of the BPD in which a sleeve gastrectomy is formed, maintaining an intact pylorus which is then anastomosed to the ileum. Neither procedure allows a biliary approach per os and therefore typically requires at least adjunct surgical exposure, although retrograde enteroscopy access has been described.

Indications

Given the significantly increased technical skill and time required for ERC in patients with altered anatomy, pre-procedure therapeutic indication should be clear with diagnostic biliary evaluations largely replaced by magnetic resonance cholangiopancreatography (MRCP) protocoled reconstruction or computed tomography cholangiography. ERC in this population is particularly useful for the management of biliary obstruction secondary to stones and/or strictures. In comparison to intact anatomy ERC, where successful endoscopic cholangiography with relief of obstruction is technically achieved in over 90% of cases, estimates from several large multicenter studies evaluating enteroscopy assisted ERC in patients with Roux anatomy suggest a much lower overall technical success ranging between 60% and 80% regardless of method of enteroscopy utilized [1,2]. Success rates for procedures where a duodenoscope is utilized for B2 anatomy are comparable with intact anatomy endoscopic retrograde cholangiopancreatography (ERCP) [3]. Moreover, frequently, the surgeon will utilize a pediatric feeding tube as a scaffold for anastomotic healing – something the endoscopist may be asked to subsequently remove.

Patient Positioning and Preparation

Formal recommendations regarding pre-procedure patient preparation have not been proposed. However, given the typically extended length and complexity of these procedures, general anesthesia with endotracheal intubation is the norm. This latter aspect also protects against aspiration regardless of position, which is a concern with the use of over-the-scope assist devices that provide a means for fluid reflux by capillary action. The patient may be positioned on a fluoroscopic gurney in primarily a semiprone position, although the left lateral or supine position with concomitant abdominal counterpressure may be necessary to achieve afferent limb access and/or improved biliary orifice visualization. Prior to biliary cannulation, fluoroscopy may provide several useful clues. This includes the orientation and positioning of the endoscope, in particular when guidance is necessary for entering the biliary/afferent limb toward the right upper quadrant [4]. An enterogram

performed through the enteroscope working channel using an infusion of dilute contrast may also assist in biliary limb identification. Further, fluoroscopy assists in the reduction of loops. For overtube assisted enteroscopy, fluid insufflation is utilized during intubation to avoid small bowel overdistension and the potential for poor coupling of the balloon overtube and/or enteroscope to small bowel during enteroscope reduction. Where available, carbon dioxide insufflation is preferred over air insufflation to minimize gas retention during this particularly lengthy procedure and this may reduce post-procedural pain [5].

Selection of Endoscopes, Device Accessories, and General Technique

Each of the three major endoscope manufactures provide a platform for deep enteroscopy: Fujinon's (FujiFilm Endoscopy, Wayne, NJ, USA) dedicated double balloon enteroscopes to be used with a Fujinon processor and balloon overtube; Olympus' (Olympus America, Center Valley, PA, USA) enteroscope to be used in concert with an Olympus single balloon overtube; and Pentax's (Pentax Medical, Montvale, NJ,USA) enteroscope to be used in combination with Smart Medical's through-the-scope balloon system (NaviAid^{TM}). Smart Medical has also recently developed a double balloon system with a balloon fashioned to the distal end of any endoscope with a therapeutic working channel to accommodate their through-the-scope balloon. At the time of publication, Olympus' Spirus rotational assist device is only selectively available and the device may be utilized in concert with the company's enteroscope or with Pentax's enteroscope.

As enteroscopes have functional lengths of up to 2.3 m, length has become a limiting factor for suitable devices. Unfortunately, the development of enteroscopy specific devices has been limited and therefore many of the tools utilized for enteroscopy assisted ERC are ones designed similarly to those for duodenoscope assisted ERCP and do not account for forward viewing endoscopes and tangential views and lack of elevator (Box 15.1). Although device selection is relatively limited, most therapeutic biliary interventions can be achieved once access is obtained except for metal biliary stenting. A recently developed addition to the short limb armamentarium is the multibending, backward oblique viewing duodenoscope (Olympus TJF-Y0011). This endoscope combines upward angulation of the distal bending segment with downward angulation of the proximal bending segment to allow a swan neck configuration and has been demonstrated to facilitate biliary cannulation in patients with B1 anatomy [6].

A combination of factors underlies the choices as regards which device accessories are utilized for each altered anatomy ERC. As will be discussed below, each anatomical variation poses its own challenges, however two anatomical considerations dominate device selection: distance of the biliary orifice from the pylorus (or gastrojejunal anastomosis) and the structure of the biliary orifice (native (Figure 15.2) or hepaticojejunostomy (Figure 15.3)). Preference should always be given to the use of a duodenoscope if technically feasible given the additional maneuverability offered by the elevator and improved visualization of native papilla. Anatomical configurations with short limbs allow for the use of a standard or pediatric colonoscope, permitting the use of most standard ERCP accessories. The choice of enteroscope compatible devices is relatively limited but does include sphincterotomes, wires, cannulae, and dilating and extraction balloons (Box 15.1).

Box 15.1 Purpose-built devices and endoscopes

Available enteroscopes

- Fujinon EN-450T5 (WL 2000 mm/D 9.4 mm/WC 2.8 mm)
- Fujinon EN-450P5/20 (WL 2000 mm/D 8.5 mm/WC 2.2 mm)
- Fujinon EC-450BI5 (WL 1500 mm/D 9.4 mm/WC 2.8 mm)
- Olympus SIF-Q180 (WL 2000 mm/D 9.8 mm/WC 2.8 mm)
- Pentax VSB-3430 K (WL 2200 mm/D 11.6 mm/WC 3.8 mm)

Available assist devices

- Olympus single balloon overtube ST-SB1
- Olympus Spirus rotational overtube (currently not available)
- Smart Medical NaviAid G-Eye
- Smart Medical NaviAid AB (3500 mm long/3.7 mm/40 mm)
- Smart Medical NaviAid ABC (2000 mm long/3.7 mm/60 mm)

Available enteroscopy length ERCP devices

- Sphincterotome
  Pull type and needle-knife (Cook)
- Cannula (320 cm) (Cook and Olympus)
- Guidewires
  About 550–600 cm wire (Cook and Olympus)
- Extraction balloons (multiple sizes)
- Retrieval basket (6 wire) (Olympus)
- Dilators
  Graded passage (Cook)
  Balloon (6 mm biliary) (Cook) or controlled radial expansion dilators
- Stents (5 and 7 Fr conventional biliary)
- Dilators, extraction balloon, biopsy forceps as "push catheters"
- Biopsy forceps and colon brush (non-wire guided)
- Distal attachment EMR cap (Olympus)

Specialized endoscopes

- Olympus MD duodenoscope (TJF-Y0011)
- Olympus M gastroscope (GIF-2T260M0)

D, endoscope diameter; EMR, endoscopic mucosal resection; ERCP, endoscopic retrograde cholangiopancreatography; WC, working channel diameter; WL, working length of endoscope.

Techniques

Endoscopic Retrograde Cholangiography in Billroth Anatomy

Limited data exist specifically evaluating technique and performance of ERC in B1 anatomy as it closely resembles intact anatomy and the surgical reconstruction is less frequently seen. The challenge in B1 anatomy is that of the cannulation position rather than access to the biliary orifice [7]. A large retrospective case series involving B1 reconstruction described increased difficulty with biliary cannulation due to the straightened, foreshortened duodenum and associated loss of stability when attempting to bring the ampulla into

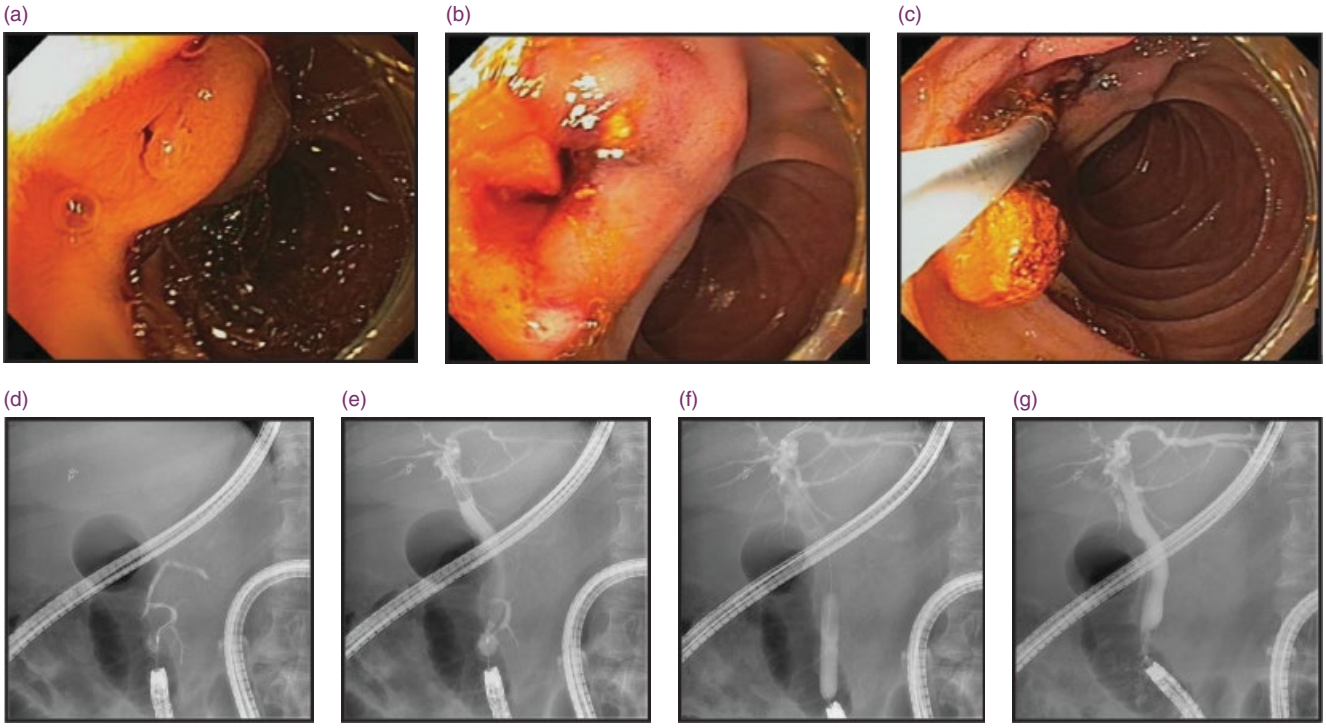

Figure 15.2 Example of enteroscopy assisted endoscopic retrograde cholangiography in a long limb native papilla in a Roux-en-Y gastric bypass patient. Endoscopic views of the native papilla on the left wall before (a) and after (b) sphincterotomy and papillary balloon dilation with subsequent extraction of a stone by balloon sweep (c). Corresponding fluoroscopic views demonstrating (d) unintentional cannulation of the ventral pancreatic duct, (e) successful cannulation of the bile duct with filling defect/stone at the hilum with mild upstream dilation, (f) balloon dilation at the ampulla of the biliary orifice, and (g) cholangiogram following stone recovery without evidence of a further filling defect.

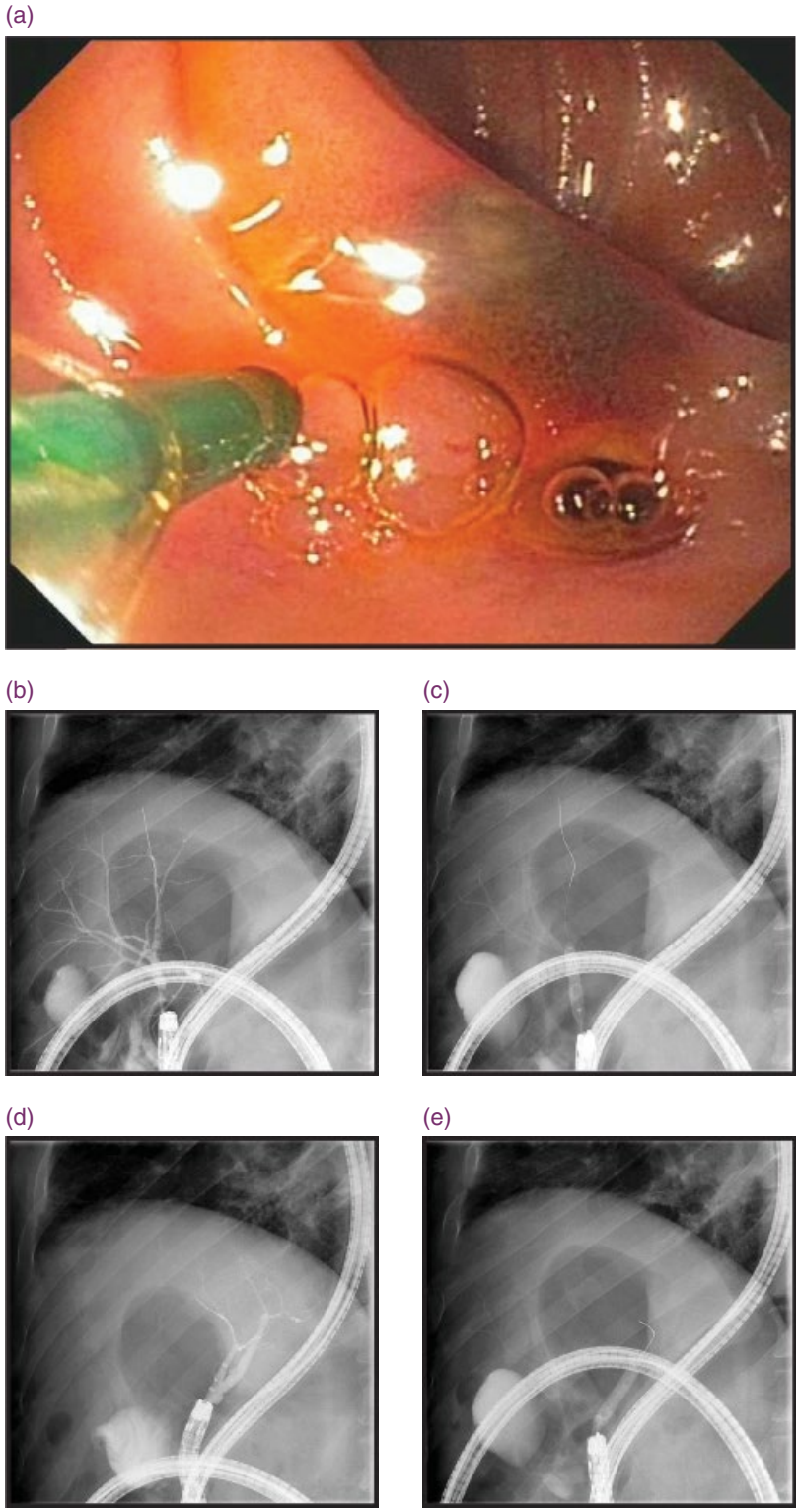

Figure 15.3 Example of enteroscopy assisted endoscopic retrograde cholangiography in short limb hepaticojejunostomy (HJ) in a Roux-en-Y patient after liver transplant. (a) Endoscopic view demonstrating side by side (dual anastomosis) HJ with dilation of the stenosed right intrahepatic anastomosis and a patent left intrahepatic anastomosis. (b) Right intrahepatic cholangiogram demonstrating normal upstream ductal caliber with a narrowing at the anastomosis, and (c) subsequent balloon dilation with demonstration of a "waist" at narrowing. (d) Left intrahepatic cholangiogram demonstrating mild ductal dilation, and (e) subsequent balloon dilation.

position [8]. This differs from a previous case series reporting little difference in technical success with B1 anatomy and mirrors our experience in these patients [9]. A relatively novel multibending duodenoscope with the capability of a backward oblique viewing position has been suggested to improve stability and position, in particular in those with B1 anatomy. As part of a retrospective analysis this multibending duodenoscope successfully completed two previously failed cannulations in patients with B1 gastrectomy [6].

The challenge in patients with B2 anatomy, despite a relatively short limb compared with patients with RY anatomy, relates to the angulation of the afferent limb gastrojejunal anastomosis and the reversed biliary anatomy effectively placing the orifice in the 5 o'clock rather than 11 o'clock position. Often, sphincterotomy using rotatable sphincterotomes can be performed but its extent can be limited. Alternatively, following cannulation, a biliary stent followed by needle-knife sphincterotomy can be performed. Further, if sphincterotomy extension is difficult due to endoscope position, papillary balloon dilation can be performed to widen the orifice for stone extraction.

Although it is generally preferred to use a diagnostic duodenoscope, given its more flexible and slimmer caliber, there is debate as to whether to begin the procedure with a forward viewing or side viewing endoscope to facilitate recognition and navigation of the afferent limb [10,11]. Although reaching the papilla may be easier with forward viewing endoscopes, technical success of duct cannulation may be compromised due to a suboptimal view and position at the ampulla and the lack of an elevator. A retrospective comparison of the two techniques demonstrated a trend of higher success of cannulation with forward viewing endoscopes than side viewing ones (87% versus 68%) with no technical difference in successful sphincterotomy when compared with those with successful cannulation (83% versus 80%) [12]. In this older series, along with others that utilized a now antiquated device with a long distal end, there were significant rates (up to 6%) of jejunal perforation with the duodenoscope [13]. Our opinion is that orientation for sphincterotomy direction and completeness is more consistent with a duodenoscope. Often, duodenoscope shortening into the acutely angled limb will facilitate intubation rather than attempting forward pressure alone with inherent gastric looping. The largest preliminary case series of B2 anatomy ERCP with a duodenoscope demonstrates a much lower perforation rate of 1.3% in over 500 serially recorded patients, with success rates of both reaching the papilla (89%) and subsequent cannulation (93%) closer to those seen in patients with intact anatomy [3]. Similar results have been reported in smaller series utilizing a duodenoscope [14–16]. Interestingly, in a case series preferentially utilizing a forward viewing endoscope, 10 failed cases were reattempted using a duodenoscope and were successfully completed suggesting superiority of the duodenoscope in this patient population [11].

Device Assisted Endoscopic Retrograde Cholangiography in Billroth Anatomy

Billroth II anatomy typically involves a relatively short biliary afferent limb, allowing for the use of either a gastroscope or duodenoscope and obviating the need for a long balloon assist device to reach the papilla. With the advent of short 152 cm enteroscopes, there is the possibility of easier biliary limb intubation as well as improved endoscopic stability and positioning and the ability to use standard ERCP accessories. A single balloon Olympus enteroscope (not yet commercially available; SIF-Y0004) as well as a double balloon Fujinon iteration (EC-450BI5) have been both demonstrated to be technically feasible in B2 and other surgically altered anatomy. While the short double balloon enteroscope has a working channel of 2.8 mm, the short single balloon enteroscope has a therapeutic channel allowing for the complete armamentarium of devices including self-expandable metal

stents [17,18]. Whether a colonoscope, short enteroscope, or standard gastroscope is utilized, all forward viewing endoscopes lack an elevator thus increasing the difficulty for biliary cannulation, in particular with native papilla. Stability of the papilla may, however, be improved with a rigid distal cap fitted to the end of the endoscope [19,20].

Specialized Technique in Billroth II Procedures

Entering the afferent loop may be difficult with a duodenoscope and when the lesser curve remnant is short, leading to a tight angulation with the anastomosed loop. Beyond changing patient position, the stoma can be first cannulated with a superstiff guidewire or device such as a sphincterotome that serves as a stiffener for the shaft over which the endoscope may pass. Similar techniques have been described with biopsy forceps and polypectomy snares, although these seem less effective [11,14]. Since the papilla is in a reverse position within the endoscopic field, the available cannula and sphincterotome, which assumes an upward curve, may not be ideal. Therefore, many authorities suggest the use of a straight catheter to improve rotation toward the biliary direction [11,21]. There have been several reports of inverted and/or sigmoid sphincterotomes specifically fashioned for B2 cannulation and sphincterotomy, however none of these are commercially available [11,16,22]. Moreover, current sphincterotomes are rotatable and appear useful for such access.

Clinical Data Predating Single Balloon Enteroscopy for Endoscopic Retrograde Cholangiography in Roux-en-Y Anatomy

Prior to the development and commercial availability of the first balloon enteroscope by Fujinon in 2001, several small case series documented the feasibility and technical difficulty with short and long limb ERC. Based on the formative work of Gostout and Bender in 1988, the technique typically involved use of pediatric or push enteroscopes to approach the biliary orifice for placement of a superstiff long guidewire within the afferent (biliary) limb with subsequent exchange for a duodenoscope [23]. Regardless of the biliary orifice, whether intact or surgically altered, performance characteristics were suboptimal with technical success defined as biliary cannulation ranging between 60% and 70%, with reaching the papilla as the limiting factor [16,23–27]. The largest of these case series demonstrated a successful approach to the biliary orifice in long limb patients in 84% of procedures using either a pediatric colonoscope or an enteroscope alone, with 86% of those undergoing successful ERC intervention [28]. Another relatively small series evaluated 15 cases, all with long limb and intact papilla, with the majority being gastric bypass patients, which described the use of an inflated occlusion balloon within the biliary limb to serve as an anchor over which a duodenoscope was passed; ultimately therapeutic ERC was successful in 67% of cases [27]. More recently, an experience comparing single balloon enteroscopy (SBE) with the use of standard and pediatric colonoscopes in short limb anatomy demonstrated no statistical difference in biliary cannulation or therapeutic success, unless specifically comparing SBE with the pediatric colonoscope [29]. This suggests that an initial attempt with an adult colonoscope might be reasonable before attempts with overtube assisted enteroscopy devices in such individuals.

Overtube-Assisted Enteroscopy for Endoscopic Retrograde Cholangiography in Roux-en-Y Anatomy

There exists a reasonable corpus of data evaluating various ERCP devices and techniques in RY altered anatomy due to an increase in these surgeries being

performed. Most of the earlier data, however, are small, proof of concept, case series [30–35], with subsequent larger case series evaluating the performance of ERC using various overtube assisted techniques such as long double balloon enteroscopy (DBE), short DBE, SBE, rotational enteroscopy (Spirus), and the additional technique of laparoscopic assisted ERC (Tables 15.1 and 15.2). Many of these reports stratify the procedures into short (<50 cm) and long (>50 cm) limb as well as

Table 15.1 Studies involving device assisted enteroscopy for endoscopic retrograde cholangiography (ERC) after Roux-en-Y; short limb (minimum of 20 cases).

Study, year	Technique(s)	Cases (n)	Papillae	Success rate (enteroscopy/ERC)*	Complications
Azeem et al. 2013 [29]	SBE/colon	58/141	HJ	91/71%; 85/60%	0
Tomizawa et al. 2014 [54]	SBE	22	HJ	68/73%	0
Osoegawa et al. 2012 [44]	sDBE	47	Mixed	96/89%	3.5%
Chua & Kaffes 2012 [42]	SBE/DBE	3/23	HJ	67/100%; 75/80%	3.8%
Raithel et al. 2011 [46]	DBE	86	HJ	74/87%	9.6%
Sanada et al. [47]	DBE	54	HJ	68/100%	NA
Shimitani et al. [48]	sDBE	103	Mixed	97/100%	5%

* Successful ERC rates for those in whom enteroscopy was successful.
DBE, double balloon enteroscopy; HJ, hepaticojejunostomy; LA, laparoscopic assisted ERC; NA, not available; sDBE, short DBE; SBE, single balloon enteroscopy.

Table 15.2 Studies involving device assisted enteroscopy for endoscopic retrograde cholangiography (ERC) after Roux-en-Y; mixed or long limb (minimum of 20 cases).

Study, year	Technique(s)	Cases (n)	Papillae	Success rate (enteroscopy/ERC)*	Complications
Choi et al. 2013 [41]	LA/DBE	42/26	Intact	97/100%; 78/56%	14.5/3.1%
Shah et al. 2013 [2]	SBE/DBE/SE	69/74/72	Mixed	Oa 71/88%; SBE 69/87%; DBE 74/85%; SE 71/88%	12.4%
Siddiqui et al. 2013 [49]	sDBE	79	Mixed	81/90%	5.1%
Schreiner et al. 2012 [1]	LA/SBE/DBE	24/6/26	Mixed	100/100%; 72/59%† (54% SBE/83% DBE)	8.3/3.1%
Lennon et al. 2012 [55]	SBE/SE	54	Mixed	48/100%; 40/88%‡	3.5%
Saleem et al. 2010 [52]	SBE (GB/HJ)	41/15	Mixed	Oa 70/91%; diagnostic rate GB 47%; HJ 78%	0%
Pohl et al. 2009 [45]	DBE	25	HJ	84/100%	0%
Emmett & Mattat 2007 [43]	DBE	20	Mixed	85/94%	0%

* Successful ERC rates for those in whom enteroscopy was successful.
† Combined SBE/DBE.
‡ Cannulation rather than enteroscopy success.
DBE, double balloon enteroscopy; GB, gastric bypass; HJ, hepaticojejunostomy; LA, laparoscopic assisted ERC; NA, not available; Oa, overall; sDBE, short DBE; SBE, single balloon enteroscopy; SE, Spirus enteroscopy.

into hepaticojejunostomy and intact papilla. The technique used for enteroscopy access will not only determine the options for ERCP accessories but also, interestingly, may predict the indication for ERC. For instance, a postoperative HJ stricture requiring intervention for jaundice and cholangitis occurs in up to 12–28% of individuals, and there is an increase in ascending cholangitis in those with both a short limb and HJ [36–38]. In the setting of RYGB, rapid weight loss after bariatric surgery stimulates cholesterol cholelithiasis in nearly a third of patients, many of whom subsequently require endoscopic and/or surgical intervention for common duct obstruction [39]. For years, the percutaneous and/or surgical approach was the standard of care. However, with an ever expanding endoscopic toolbox and increase in deep enteroscopy experience, endoscopic intervention has demonstrated low morbidity and, once the papilla is reached, a technical success reaching that of ERC in intact gastrointestinal anatomy, and may be considered first line therapy depending on center experience [40].

Double Balloon Enteroscopy Assisted Endoscopic Retrograde Cholangiography

The majority of the available larger case series in Roux limb anatomy ERC involve evaluation of the double balloon enteroscope. In these studies the overall success rate of reaching the biliary orifice is typically over 70% [1,2,41–49] and successful biliary intervention rates in those with completed enteroscopy range from 80% to 100%. Given the limitation of accessories compatible with long enteroscopes and difficulties with device advancement through the working channel, the use of a short double balloon enteroscope with a 152 cm working length (which allows for conventional ERCP accessories) has demonstrated improved performance characteristics, regardless of limb length or the presence of native papilla. The largest series (n = 98) in short limb patients have demonstrated enteroscopy success in 97% and therapeutic success in 100% of cases [48]; the enteroscopy and therapeutic success rates were 81% and 91%, respectively, in the largest series (n = 79) in long limb patients [49].

The most comprehensive evaluation of enteroscopy assisted ERC involves cases compiled from eight major US referral centers utilizing DBE, SBE, or rotational enteroscopy in a number of anatomical alterations [2] and integrated selected data from another larger series [1]. This was a non-randomized case series that based overtube enteroscopy technique on institutional preferences. Overall, the enteroscopy success rate was 71% of whom 88% of patients underwent successful therapeutic ERC. Though DBE suggested a higher enteroscopy success of 74% compared with SBE and rotational enteroscopy (69% and 72%, respectively), this did not reach statistical significance. ERC success for DBE, SBE, and rotational enteroscopy was 85%, 87%, and 90%, respectively. Evaluations of each device in the setting of RYGB or other RY anatomy were also without significant individual differences, nor were there differences in ERC success regardless of technique utilized.

Single Balloon and Rotational Enteroscopy Assisted Endoscopic Retrograde Cholangiography

Smaller case series exist for single balloon or rotational enteroscopy [50–53]. Excluding case reports and series with less than 15 procedures, two published studies describe the performance of SBE specifically in short limb RY anatomy with HJ [29,54]. These two studies varied in successful enteroscopy rates, with one group approaching 70% and the other achieving over 90%; however, both demonstrated low rates of successful biliary therapies (73% and 70%, respectively). These rates are lower than seen in case series utilizing

DBE in similar anatomical configurations, perhaps secondary to the increased stability offered by the second balloon; however, prospective, randomized, comparative data are lacking. Four other larger cases series evaluated the performance of SBE to assist in long limb ERC, including the two previously cited studies [1,2,52,55]. All four studies demonstrated similar efficacy in enteroscopy and therapeutic ERC intervention.

Studies of rotational enteroscopy in patients with RY anatomy are of small sample size and report therapeutic success rates of 55–80% [2,55–57]. The largest datasets are within the multicenter group's publication as well as the study comparing rotational enteroscopy with SBE [2,55]. Current efforts to explore the efficacy of rotational assisted ERC are on hold as the device is currently not available from the manufacturer.

Alternative Methods of Biliary Intervention in Long Limb Altered Anatomy

The typical clinical pathway for altered anatomy patients requiring ERC is usually determined by local and regional expertise. At our center, we preferentially first perform a transoral attempt given its lower morbidity compared with surgical and interventional radiology options. If unsuccessful in the setting of RYGB, then a combined surgical/endoscopic approach is preferred. If the altered anatomy is not due to a RYGB then percutaneous techniques are pursued. For palliation of malignant biliary obstruction in the setting of long limb anatomy with a failed device assisted approach, we would also consider endoscopic ultrasound (EUS) guided biliary drainage [58,59].

Surgical approaches broadly include the creation of a gastrostomy or jejunostomy tract for subsequent transabdominal passage of a duodenoscope through a mature tract, as well as a combined laparoscopic assisted ERC which allows for a concomitant transabdominal approach to the biliary orifice using a duodenoscope. Since this technique was first described in 1998 [60], numerous investigators have demonstrated variations in obtaining the gastrostomy and these include laparoscopic, open, EUS guided, enteroscopy guided, and radiological placement of the gastrostomy [61–63]. In the largest series of per gastrostomy ERC, surgical gastrostomy was performed for 30 RYGB patients requiring ERC, 26 of whom underwent tandem ERC, with 100% technical success. It is noted, however, that a 13% complication rate was experienced, which mostly involved the gastrostomy tract itself.

A slight variation of this technique involves the laparoscopic placement of a trocar allowing access to the remnant stomach for transabdominal introduction of a duodenoscope. Published data on this technique demonstrate excellent technical success rates of greater than 90% with no to low morbidity [1,64–67]. A large case series was a retrospective cohort study comparing combined laparoscopic ERC with device assisted ERC (SBE and DBE), which examined the superiority of successful approach to the ampulla (100% versus 72%, respectively), the cannulation rate (100% versus 59%, respectively), and therapeutic success (100% versus 59%, respectively) [1]. These investigators also performed a cost analysis suggesting significant savings when the laparoscopic approach is reserved for failed per oral enteroscopy techniques in long limb surgical anatomy patients. While percutaneous access of the gastric remnant has previously been performed via surgical laparoscopy or percutaneous gastrostomy, there are emerging endoscopic techniques for gastrostomy creation to allow a single setting endoscopic approach for biliary access. These include establishing the percutaneous tract by deployment of a self-expanding stent followed by tandem antegrade access [68]. There are limited

data demonstrating the feasibility of EUS guided biliary access in those with gastric bypass and other long limb altered anatomy [69–71]. The largest such report involves a retrospective analysis of 95 consecutive patients with failed ERC who subsequently underwent EUS guided access at a large tertiary care center; included in these were 17 patients with post-surgical anatomy, of whom nine (53%) had successful interventions and were spared either percutaneous access or surgery. Another possible means of accessing the ampulla in surgically altered anatomy involves reaching the bile duct by means of DBE, after which the enteroscope may be exchanged for an ultraslim cholangioscope passed through the lumen of the overtube, allowing for direct cholangioscopy and appropriate intervention [72].

An available through-the-scope compliant balloon has been designed specifically for deep enteroscopy. It permits endoscope tip stabilization during loop reduction and serves as an a through-the-scope balloon for anchor and exchange and demonstrates potential in the field of enteroscopy [73]. No published data exist, however, demonstrating feasibility in long limb ERC. Complicating the matter, the current iteration of the device requires a 3.7 mm working channel, obviating adjunct use with current enteroscopes with the exception of the Pentax model. That said, the device offers promise and may add to the relatively limited armamentarium at the endoscopist's disposal for altered anatomy ERC.

Limitations and Complications

By far the most common limitation of altered anatomy ERC is failure to reach the desired orifice, which in some larger series may be as high as 30% in both short limb and long limb configuration [1,2,42,47,52]. Various techniques have been proposed, yet not established by significant data or experience, as adjunct maneuvers to increase successful intubation. These include the use of water infusion rather than air to decrease expansion of the small bowel and promote traction to permit deeper intubation. Further, use of demarcating already accessed limbs with either submucosal tattoos or placement of a guidewire can be helpful. While data are scattered, larger series suggest an equal risk of post-procedural pancreatitis as compared with standard ERCP rates (approximately 3–5%) [1,2,46,48]. Intestinal perforation, be it a microperforation from sphincterotomy or a macro-perforation from endoscope trauma, is the most feared clinical complication of overtube assisted ERC and is estimated to occur in 1–2% of cases in expert hands [2].

Conclusion

With both the proliferation of surgical expertise as well as the increasing number of indications for small bowel and pancreaticobiliary manipulation, in particular RYGB for obesity, endoscopists are confronted with an ever growing population of individuals with altered anatomy requiring biliary intervention. The introduction of overtube assisted deep enteroscopy has revolutionized ERC in patients with long limb surgical bypass. It has increased success rates compared with conventional push enteroscopy techniques and with an acceptable morbidity, especially when considering higher morbidity with interventional radiologic and especially surgical techniques. It still does not meet the threshold we have come to accept at high volume centers for biliary access in normal anatomy but with improvements in accessories and, more importantly, the advent of endoscopes and/or overtubes that are designed for ERCP, the success rate for these interventions should increase. Overall, the technical approach varies based on the

specific anatomy. When technically feasible, the use of an endoscope that permits the use of conventional length ERCP accessories will optimize success. Alternative biliary access procedures such as EUS guided drainage hold promise in this difficult patient population. It is clear that ERC or EUS guided interventions in long limb surgical anatomy cases should be performed by skilled therapeutic endoscopists who will tailor their tactics to their personal and institutional expertise.

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16

Management of Post-Liver Transplant Hepatobiliary Complications

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Introduction

The biliary system remains the most common site for complications following liver transplantation and remains a major source of morbidity and mortality. The most common biliary complications are bile leaks and anastomotic strictures. Less common biliary complications include bile duct stones/sludge/casts, papillary stenosis/dysfunction, and hemobilia, with many patients presenting with multiple concurrent biliary issues [1]. Following liver transplant, endoscopy via endoscopic retrograde cholangiopancreatography (ERCP) is the primary modality used for managing biliary complications, especially in patients with duct to duct biliary anastomosis. Once considered impossible, the role of ERCP in patients with Roux-en-Y anatomy has been clarified more recently, with successful intervention using deep enteroscopy techniques in defined clinical scenarios [2]. This chapter focuses on the role of endoscopy in the management of biliary complications following liver transplantation.

Liver Transplant Anatomy

A clear understanding of the post-transplantation biliary anatomy is paramount in the treatment of biliary complications. Biliary reconstruction occurs during the reperfusion phase of the liver transplant procedure. The biliary system can be reconstructed with a duct to duct (choledochocholedochostomy) or Roux-en-Y (choledocho- or hepaticojejunostomy) anastomosis. The type of anastomosis depends on a variety of factors including: (i) etiology of the cirrhotic stage liver disease (e.g., primary sclerosing cholangitis (PSC) versus others); (ii) type of transplantation (deceased donor versus living donor); (iii) history of previous liver transplant or biliary surgery; and (iv) technical factors (e.g., duct number, size, and orientation). Most transplant centers prefer the duct to duct anastomosis as it is technically simpler, allows preservation of the sphincter of Oddi, and facilitates endoscopic access to the biliary system should complications arise [3]. Roux-en-Y anastomoses are typically performed in

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patients with diseased (e.g., PSC) or absent (e.g., biliary atresia) native bile ducts, prior liver transplant or biliary surgery, or in situations of size discrepancy between the donor and recipient ducts. The Roux-en-Y anastomosis is more technically demanding, equating to a longer surgical procedure. Additionally, endoscopic treatment of biliary complications after a Roux-en-Y liver transplant is also technically challenging. Most recently, hepaticoduodenostomy has been described in PSC patients [4]. Endoscopic access is much easier in this latter situation.

Diagnosis of Biliary Complications

The clinical presentation of biliary complications is variable but often heralded by non-specific symptoms or signs such as general malaise, mild abdominal discomfort, anorexia, and jaundice with subsequent pruritus. Patients with biliary strictures often present with asymptomatic cholestasis although some present with florid shock due to ascending cholangitis. Comparatively, abdominal pain, fever, and signs/symptoms of peritoneal inflammation are the predominant features in patients with bile leaks. The time of presentation following liver transplantation is also important as bile leaks typically occur in the immediate post-transplant period while biliary strictures develop over weeks to months following transplant. In many instances, biliary complications following liver transplant are initially suspected in patients with abnormalities on routine post-transplant laboratory studies (e.g., total and/or direct bilirubin, alkaline phosphatase) and confirmed on subsequent imaging.

Multiple imaging modalities can be considered when assessing a post-transplant patient with suspicion for a biliary complication. The most common include transabdominal ultrasound (US) with Doppler studies, magnetic resonance imaging (MRI) and cholangiopancreatography (MRCP), and ERCP. Other tests used less frequently include hepatobiliary iminodiacetic acid (HIDA) scan, computed tomography (CT) scanning, percutaneous transhepatic cholangiography (PTC), and endoscopic ultrasound (EUS). Transabdominal US with Doppler is typically the initial imaging test of choice as it allows evaluation of the hepatic vasculature, parenchyma, and biliary tree; however, the chosen imaging modality should be based on the clinical suspicion for a given complication. US is often insufficient in the diagnosis of biliary strictures as bile duct dilation may be difficult to appreciate or absent in the transplanted liver, even in the presence of moderate stenosis. In contrast, cholangiography via MRCP, PTC, or ERCP is often essential for the diagnosis of biliary strictures or leaks which may not be appreciated on transabdominal US. More commonly, MRCP and/or ERCP are utilized, with data suggesting comparable accuracy for the diagnosis of bile leaks (95%) and strictures (90%) [5]. MRCP has demonstrated ≥90% sensitivity, specificity, positive predictive value, and negative predictive value, without the invasive risks carried by ERCP [6,7]. Additionally, pre-procedural MRCP can aid the interventionalist in localizing the lesion of interest and in planning the needed biliary intervention, as well as limiting unnecessary ERCPs (Figure 16.1). In the setting of non-diagnostic MRCP, ERCP should still be considered in patients with high suspicion for biliary pathology, especially microlithiasis, recurrent PSC, and ampullary stenosis/dysfunction. PTC is reserved for cases where ERCP is unsuccessful although historically was considered necessary, and is performed primarily in some centers in patients following Roux-en-Y liver transplant. ERCP in this setting is being performed with increasing success, further limiting the utility of PTC [2,8]. In patients with an external biliary drainage catheter

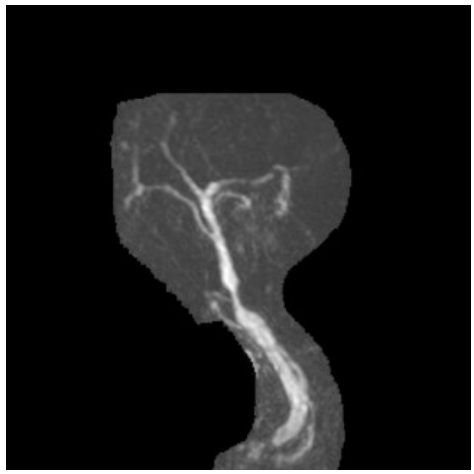

Figure 16.1 A 1 cm long, moderate grade stricture within the biliary duct at the level of the biliary anastomosis identified on magnetic resonance cholangiopancreatography.

in place, percutaneous therapy can be easily performed and negates the need for additional liver puncture.

Biliary Strictures

Biliary strictures, along with bile leaks, represent the most common biliary complication following liver transplantation, with the majority of strictures (75%) occurring at, or near, the biliary anastomosis [1]. The overall incidence of biliary strictures is 5–15% after deceased donor liver transplant and 28–32% after living donor liver transplant [9]. Strictures can occur anywhere within the biliary tree, can be anastomotic or non-anastomotic, and can arise singularly or in multiples. Similar to other biliary complications, early strictures (<4 weeks) are often related to technical issues, while late strictures occur as a result of vascular compromise [10]. Biliary strictures most commonly occur within 5–8 months following liver transplant but can occur at any time, with anastomotic strictures appearing slightly later than non-anastomotic ones.

Anastomotic biliary strictures occur at the anastomotic site between the donor and recipient bile duct with or without dilation of the proximal donor ducts. Anastomotic strictures characteristically appear as a thin, short, localized narrowing at or near the anastomosis on cholangiography (Figure 16.2). Early anastomotic strictures frequently occur due to technical issues related to the operation while late onset strictures are secondary to fibrotic healing following ischemia [11]. Temporary anastomotic biliary narrowing can be secondary to edema in the immediate post-transplant period (≤30 days) and is often treated with a similar, but less aggressive approach (e.g., smaller diameter balloon dilation, fewer stents) than for an anastomotic stricture. Additionally, size mismatch between the donor and recipient bile ducts can be mistaken for an anastomotic biliary stricture leading to unnecessary procedures/interventions. This makes review of the operative report and any early postoperative cholangiograms essential.

Endoscopic intervention remains first line therapy following identification of a stricture in patients with duct to duct anastomoses. Patients with anastomotic strictures can generally be managed endoscopically with balloon or rigid catheter dilation followed by biliary stent placement across the stricture. Balloon dilation alone can be considered; however, data suggest improved stricture resolution using combination therapy (40% versus 75%) [12,13]. The current endoscopic approach for anastomotic strictures is balloon dilation of the stricture (6–10 mm depending on size of the upstream duct) followed by placement of at least two large bore (10 Fr) plastic biliary stents initially. The use of multiple plastic biliary stents increases the success rate up to 80–90% [14–16]. Similar to the management of strictures in non-transplant patients, additional biliary stents are placed and exchanged approximately every 3 months

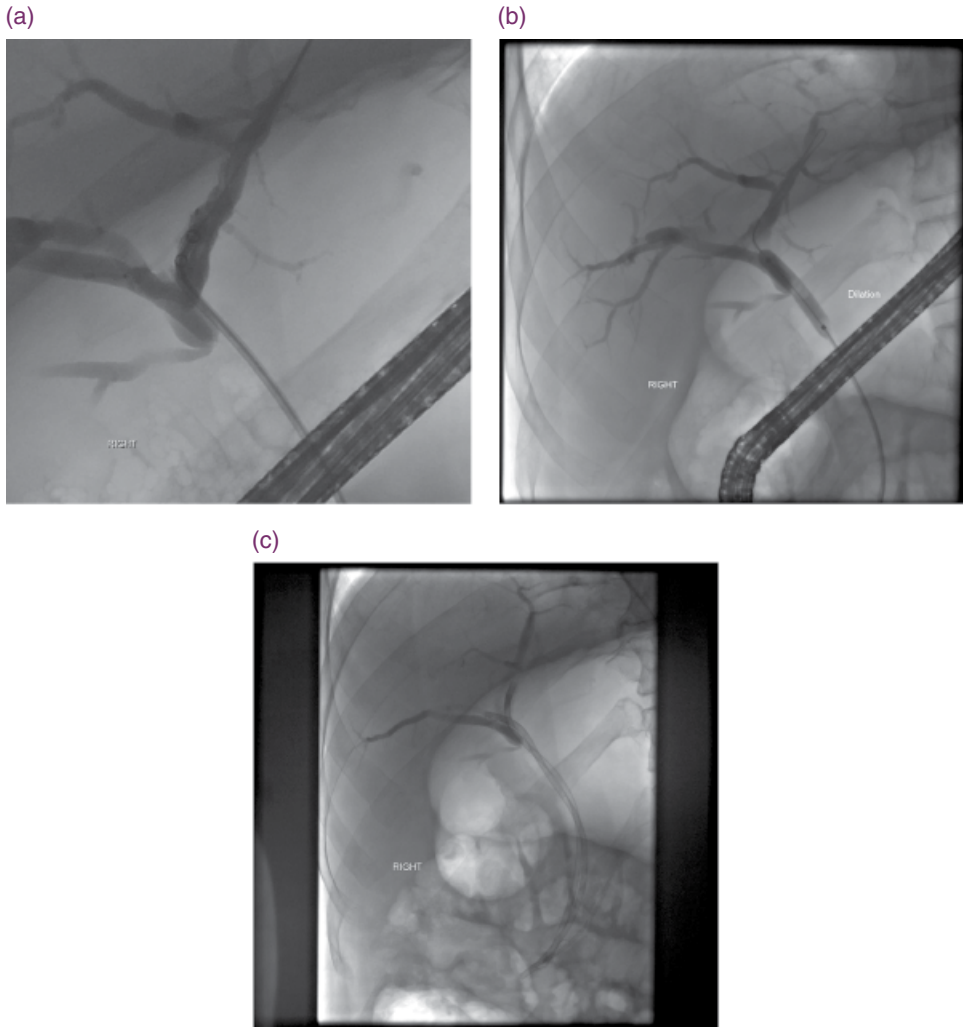

Figure 16.2 (a) Anastomotic strictures of the right anterior and right posterior hepatic ducts in a patient with a hepaticojejunostomy after living donor right liver transplant. (b) Balloon dilation of the anastomotic stricture in the right anterior duct. (c) Placement of two 8.5 Fr, 15 cm plastic biliary stents into the right anterior and posterior hepatic ducts.

until stricture resolution, with many patients requiring several interventions [17]. The number of stents inserted depends on the capacitance of the donor and recipient ducts. The use of biliary self-expandable metal stents (SEMSs) has also been explored in the treatment of post-transplant anastomotic strictures with varying results. A recent systematic review including nearly 800 patients compared the use of multiple plastic biliary stents to biliary SEMSs and found no clear advantage for the use of SEMSs in this setting [18]. Additionally, a 15% migration rate was noted in patients treated with biliary SEMSs. Following initial stricture resolution, patients require ongoing surveillance to assess recurrence. Recurrence of an anastomotic stricture occurs most in patients with delayed presentation and in those with very tight initial strictures [9]. In contrast, patients with an early presentation

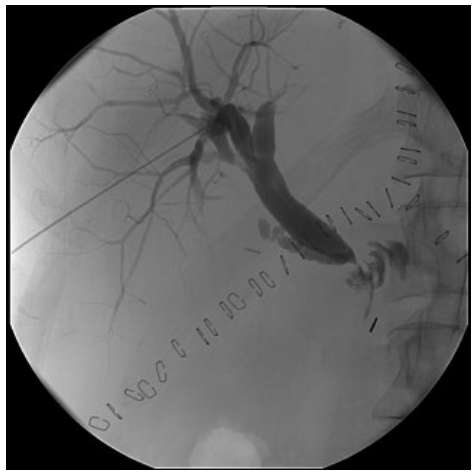

Figure 16.3 Percutaneous tube cholangiogram revealing a stricture at the hepaticojejunal anastomosis in a patient previously transplanted for primary sclerosing cholangitis.

tend to have a good response to short term stenting and are less likely to develop stricture recurrence [19]. Repeat endoscopic intervention is highly successful in patients with stricture recurrence [15].

Patients with Roux-en-Y biliary reconstruction also develop anastomotic strictures between the donor bile duct and recipient jejunum (Figure 16.3). The treatment algorithm is similar but requires access to the anastomosis using a forward viewing endoscope; most commonly a colonoscope or a balloon assisted enteroscope. Given the difficulty of performing ERCP in the setting of altered anatomy, endoscopic intervention is not routinely successful. When endoscopic therapies are unsuccessful, percutaneous management is attempted prior to surgical revision of the anastomosis. In extreme cases, liver retransplantation may be necessary when all other measures fail.

In comparison to anastomotic strictures, non-anastomotic strictures tend to be multiple, longer in length, intrahepatic, or in the donor duct proximal to the anastomosis [20]. In recent years, the incidence of non-anastomotic strictures has increased. Experts have implicated the acceptance of older donors, donors with extended criteria, and donors after cardiac death [21]. Non-anastomotic strictures are generally secondary to vascular issues, either hepatic ischemia or hepatic artery compromise. The most severe non-anastomotic strictures occur in cases of early hepatic artery thrombosis as collateral blood flow has yet to develop, thus leading to biliary necrosis [22]. The severity of non-anastomotic strictures has been correlated to the time of manifestation from transplant, with the worst strictures occurring early on [23]. This scenario can further progress to ischemic cholangiopathy and the development of biliary cast syndrome, as discussed later in this chapter. Other etiologies for non-anastomotic strictures include recurrence of the primary liver disease (e.g., PSC), cytomegalovirus infection, or post-transplant lymphoproliferative disorder. The cholangiographic appearance is similar to that of PSC with involvement of the proximal bile duct and intrahepatic branches. Early diagnosis and intervention are key to a successful outcome. Although managed in a similar fashion to anastomotic strictures, non-anastomotic strictures are more difficult to treat, with success rates ranging from 50% to 75% [24]. The lower success rates are expected given that many patients have diffuse involvement of the biliary tree, making endoscopic intervention complex. Non-anastomotic strictures are treated with sphincterotomy, balloon dilation, and placement of large bore plastic biliary stents (size limited by the diameter of the intrahepatic ducts), although adequate treatment in the setting of multiple strictures is rarely feasible. Due to the accumulation of sludge, and possibly casts, above the stricture, rapid stent occlusion is common. These patients frequently require more interventions to achieve success with endoscopic therapy when compared with anastomotic strictures [25]. Surgical revision is necessary in many cases as endoscopy is insufficient. A Roux-en-Y

hepaticojejunostomy is performed in patients with prior duct to duct biliary anastomosis. Refractory non-anastomotic strictures in patients with a Roux-en-Y biliary anastomosis are treated by re-anastomosing the bile duct to an area of improved perfusion [23]. Due to the difficulty in successfully treating patients with non-anastomotic strictures, data suggest that up to 50% will require retransplantation or die from this complication [26].

Bile Leaks and Bilomas

Biliary tract leaks occur in approximately 10% of patients following liver transplant [27]. Leaks can occur early (<4 weeks) or late following transplant, and can arise from the anastomosis, cystic duct remnant(s), duct of Luschka, T tube insertion/removal site, or the cut liver surface when partial liver grafts are utilized (i.e., pediatric split livers and living related donors). The majority of bile leaks within 4 weeks after transplant occur at the anastomosis, cystic duct remnant, or T tube site (if present) and are secondary to ischemia or technical issues related to the operation [25]. In contrast, late bile leaks are almost always related to removal of the T tube. Due to this finding, many transplant centers have abandoned routine T tube placement due to the high rate of post-transplant leak. Anastomotic leaks occur most commonly in the setting of duct to duct anastomosis, but can occur following Roux-en-Y anastomosis (Figure 16.4). Non-anastomotic bile leaks should raise concern for vascular insufficiency and the possibility of hepatic artery compromise [28,29].

Biliary leaks can be successfully treated with endoscopic therapy in more than 85% of cases [30]. Endoscopic treatment initially includes biliary sphincterotomy with or without placement of a single large diameter (≥10 Fr) plastic biliary stent as these techniques promote preferential drainage of bile into the small intestine [31].

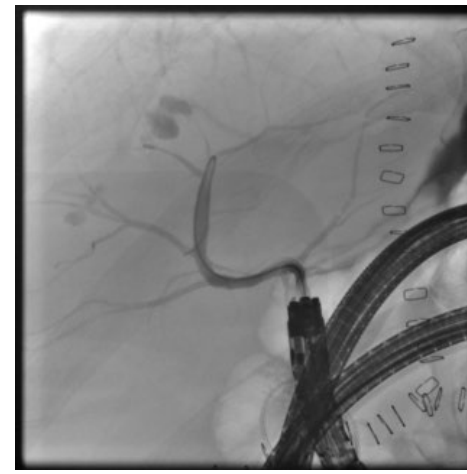

Figure 16.4 Cholangiogram demonstrating two separate bile leaks from the right intrahepatic ducts. Additionally, contrast extravasation is seen from a disruption of the proximal jejunal limb.

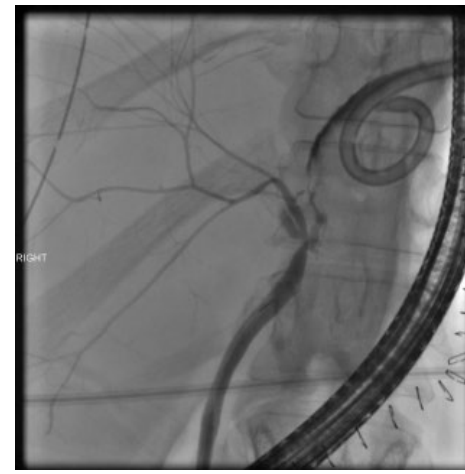

Figure 16.5 Contrast injection demonstrates a mild anastomotic stricture with a bile leak adjacent to the anastomosis.

In patients with a concurrent biliary stricture, successful drainage is predicated on traversing the stricture during stent placement (Figure 16.5). Gentle stricture dilation may be necessary in some cases prior to stent placement. In bile leaks unresponsive to initial endoscopic therapy, ERCP with placement of additional plastic biliary stents may be successful in providing adequate biliary drainage

although the number and size of the stents is contingent on the size of the donor and recipient bile ducts. Repeat ERCP with biliary stent exchange, if necessary, should be performed every 2–3 months until resolution. The use of temporary biliary SEMSs is successful in this regard and can be considered in lieu of plastic stents; however, clinically relevant biliary strictures can occur following SEMS removal in 25–35% of cases [32]. Historically, placement of a nasobiliary tube was an additional endoscopic option for the treatment of bile leaks but this has fallen out of favor and is now rarely performed. Although nasobiliary tubes allow for easy cholangiographic evaluation and can be removed without an additional endoscopic procedure, patients are reluctant to maintain a tube exiting their nose for a prolonged time period and the tube may be inadvertently dislodged. In addition to endoscopic therapy, concurrent placement of a percutaneous abdominal drain may be necessary in patients with a large amount of ascites.

The evaluation and therapy of patients with indwelling cystic ducts or T tubes is generally straightforward. A T tube cholangiogram can localize the leak without the need for ERCP. Additionally, small leaks may resolve by leaving the T tube in place and open to divert bile flow. Certain patients will require concomitant placement of an internal transanastomotic biliary stent, with nearly 100% success in leak resolution [5].

Patients presenting with peritoneal signs should be promptly evaluated by a surgeon given the high risk for rapid decompensation, with surgery more likely in patients with non-anastomotic bile leaks, bile peritonitis, or larger leaks when endoscopic therapy has failed or has a low chance of success. Percutaneous transhepatic biliary drainage is indicated in stable patients when endoscopy is unsuccessful.

Following liver transplant, bile duct rupture and subsequent extravasation of bile into the liver parenchyma or peritoneal cavity can lead to biloma formation. Necrosis of the bile duct has been proposed as the inciting event in development [25]. Post-transplant bilomas most commonly occur in the perihepatic area, outside the liver parenchyma, and occur in approximately 10% of patients following liver transplant [33]. The most commonly identified infective organisms are enterococci, coagulase negative staphylococci, and *Candida* species [33]. These lesions are frequently small and may resolve without invasive measures (i.e., close observation, antibiotics). However, percutaneous drainage is often necessary for larger bilomas not communicating with the bile duct, while sphincterotomy with or without endoscopic placement of a biliary stent into the extrahepatic bile duct may be required for resolution of those with bile duct communication [34]. Percutaneous drainage of larger bilomas with concurrent antibiotic therapy may be necessary to prevent abscess formation in post-transplant patients on immunosuppression. Surgery is reserved for patients with peritoneal signs or if the bile leak cannot be controlled effectively with the above measures. Similarly, percutaneous drainage of free bile may need to be performed as an adjunct to endoscopic therapy. The decision is based upon size/volume and presence of infection.

Bile Duct Filling Defects

Common bile duct filling defects occur relatively frequently (~6%) after liver transplantation with the differential diagnosis including bile duct stones, sludge, blood clots, and biliary casts [35]. Bile duct stones are the most commonly identified filling defect after transplant, occurring in up to 18% of post-transplant patients, with most stones seen in association with distal strictures [1]. Other proposed mechanisms of stone formation after transplant include supersaturation of

bile, biliary reflux, and biliary duct contamination. Endoscopists must maintain a low threshold for the evaluation and intervention of biliary filling defects as patients on immunosuppression may present in an atypical manner, with the propensity to decompensate rapidly. Stones, sludge, or other biliary debris can generally be removed with a very high success rate (~100%) using sphincterotomy and balloon/basket extraction, although those associated with biliary strictures may require stricture dilation before attempts at clearance [36]. The endoscopic techniques and accessories used are similar to those utilized in non-transplant patients, including the use of mechanical/electrohydraulic lithotripsy when standard measures fail. In rare cases where stone extraction is unsuccessful, a plastic biliary stent can be placed to maintain adequate bile flow and bridge to subsequent interventions for reattempts at stone clearance.

Biliary cast syndrome is an infrequent complication that occurs in 2.5% of patients following liver transplantation [37]. Casts appear as dark, hardened material made of organic debris that take the shape of the bile ducts that they occupy (Figure 16.6) [38]. Bilirubin is the primary component of biliary casts with collagen, blood vessels, and cholesterol as secondary components. The inclusion of blood vessels and collagen within the cast composition, along with concurrent biliary strictures, suggest that cast formation occurs secondary to bile duct ischemia leading to ischemic cholangiopathy (Figure 16.7) with bile duct necrosis, cast formation, and ductal scarring/stenosis [39]. Acute cellular rejection has also been proposed as an etiological risk factor for the development of biliary casts. Patients typically present with evidence of biliary obstruction including fever, jaundice, imaging evidence of biliary ductal dilation, and elevation in serum markers of cholestasis. Successful clearance of biliary casts is challenging. Multimodality therapy using endoscopic and percutaneous approaches is successful in 60% of cases, but multiple ERCPs are often needed for complete cast clearance and for the treatment of associated strictures [39]. Endoscopic techniques often require a combination of sphincterotomy, balloon/basket extraction, stent placement, and mechanical/electrohydraulic lithotripsy. Recent data suggest

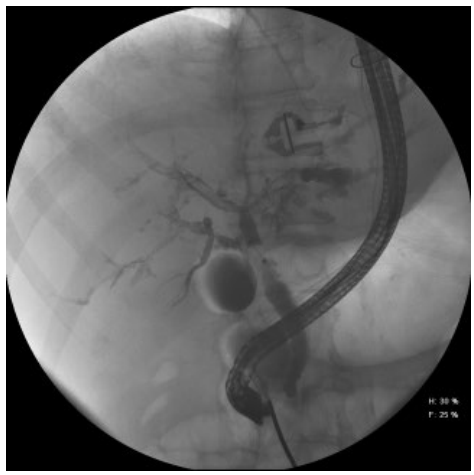

Figure 16.6 Cholangiogram demonstrating a dilated extrahepatic duct with diffuse, irregular filling defects throughout the intrahepatic ducts, consistent with cast syndrome.

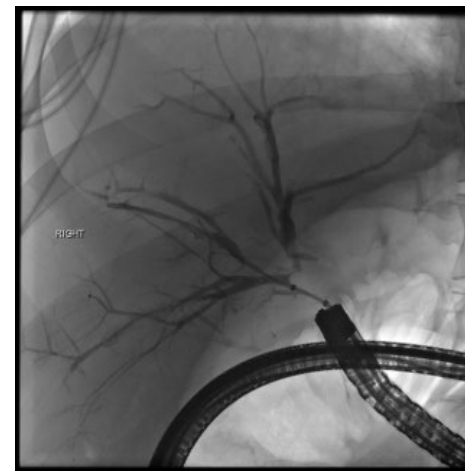

Figure 16.7 Evidence of ischemic cholangiopathy of the right hepatic ducts in a patient with prior hepatic artery thrombosis.

up to 50% of patients relapse following initial cast clearance and require additional interventions [40]. Surgical intervention is reserved for patients when endoscopic and/or percutaneous measures are unsuccessful. Biliary cast syndrome can cause significant liver injury ultimately leading to retransplantation in up to 20% of cases [37].

Sphincter of Oddi Dysfunction and Papillary Stenosis

Ampullary complications occur in up to 7% of patients following liver transplantation with duct to duct anastomosis and can be secondary to mechanical obstruction or physiological dysfunction (Figure 16.8) [41–43]. The etiology of ampullary dysfunction has been attributed to denervation of the ampullary portion of the native bile duct, although this phenomenon is more likely multifactorial (edema, papillary stenosis, etc.) [25]. Post-transplant sphincter dysfunction should be suspected in patients with cholestasis, diffuse biliary ductal dilation, and absence of right upper quadrant (RUQ) pain, as RUQ pain secondary to sphincter dysfunction is atypical following transplant. Patients rarely undergo sphincter of Oddi manometry, but instead undergo empirical biliary sphincterotomy to allow drainage and decompression of the biliary tree.

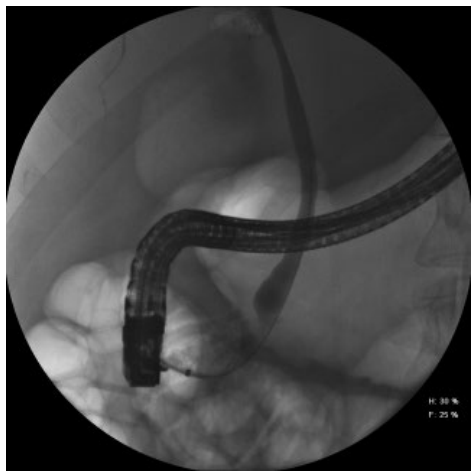

Figure 16.8 Cholangiogram demonstrating post-transplant benign papillary stenosis.

Special Clinical Scenarios

Living Donor Liver Transplantation

Due to the shortage of donor livers, living donor liver transplantation (LDLT) has become an acceptable therapeutic alternative for patients with end-stage liver disease. LDLT involves transplantation of a single donor lobe (usually the right) into the recipient, with the creation of a biliary anastomosis joining the donor's right hepatic duct and the recipient's common bile duct. Alternatively, a Roux-en-Y hepaticojejunostomy can also be performed. A recent meta-analysis has determined that the complication rate is not influenced by the technique of biliary reconstruction (duct-to-duct versus Roux-en-Y hepaticojejunostomy) [44]. Despite advances in surgical techniques and immunosuppressive regimens, biliary complications remain a major cause of morbidity and mortality for LDLT recipients [44].

When compared with cadaveric liver transplants, biliary complications following LDLT occur more commonly and can afflict both the donor and recipient [27,45]. The biliary complication rate following LDLT ranges from approximately 25% to 35% in recent literature [46]. The two most common biliary complications following LDLT are bile leaks, which tend to occur early in the postoperative period (initial 3 months), and anastomotic strictures, which tend to occur later in the postoperative course. Many case series demonstrate a slightly higher rate of biliary leaks compared with stricture formation, likely secondary to the high risk of leak from the cut surface of the liver [47]. Bile leaks from

the cut surface of the liver are frequently managed with percutaneous drainage whereas anastomotic leaks are more likely to require surgical intervention [48]. In many cases, an early bile leak will subsequently lead to stricture formation at the same location. In addition to other factors, the methods for surgical reconstruction and the number and size of reconstructed bile ducts are considered risk factors for biliary complications following LDLT [49]. Given the technical demands of LDLT it is not surprising that a recent meta-analysis has shown that increased operative experience with LDLT can reduce the biliary complication rate further in this population [50]. Endoscopic therapy of LDLT strictures with duct to duct anatomy is difficult and requires understanding of the surgical anatomy. The anatomy varies by the donor's right hepatic duct anatomy. There may be one, two, or even three anastomoses; because of overlying ducts joining at the hepatic hilum, the use of rotatable C-arm fluoroscopy is essential in these cases.

Donor safety during LDLT is of paramount concern and must be considered before, during, and after the procedure. Fortunately, donor mortality remains low, with reported rates up to 0.3% in published series [51,52]. In contrast, donor morbidity rates vary markedly, likely related to the operative experience amongst individual transplant centers and variance in defining what constitutes a surgical complication. Donor morbidity ranges from 3.2% to 47.3% [51,53,54] with donor complications most commonly including biliary strictures and leaks [44]. Strictures tend to occur at the liver hilum while bile leaks can occur anywhere. Endoscopic therapies are similar to those described for liver transplant recipients. Unique to living donor liver transplant, bile leakage can also occur at the cut surface of the liver, from the bed of the resected specimen, and be managed with endoscopic biliary drainage [55].

Roux-en-Y Anatomy

In patients with a Roux-en-Y biliary anastomosis, the choledochojejunostomy or hepaticojejunostomy was traditionally considered inaccessible by endoscopic methods for the treatment of post-transplant complications. Recent advances in endoscopic equipment and procedural techniques have made endoscopic access to the bilioenteric anastomosis attainable, yet still challenging. Successful ERCP in this setting has been performed using colonoscopes (pediatric and adult) and dedicated enteroscopes (single balloon, double balloon, and spiral overtube) [2,8,56–58]. Forward viewing endoscopes have proven moderately successful, but significant limitations have impeded routine success. For example, the adult colonoscope can accommodate a multitude of standard accessories and has a large working channel capable of delivering a 10 Fr plastic stent, but has limited flexibility in areas of tight angulation (e.g., near the bilioenteric anastomosis). In contrast, balloon assisted enteroscopes are longer, more flexible, and can be fixed in the small bowel with the aid of an overtube, but are limited by the lack of available accessories and an inability to deliver endoprostheses larger than 7 Fr diameter. Additionally, all forward viewing endoscopes lack an elevator – a key component to biliary cannulation and intervention during standard ERCP.

With the increasing prevalence of metabolic syndrome and non-alcoholic steatohepatitis (NASH), it seems likely that therapeutic endoscopists will increasingly encounter patients with previous long limb Roux-en-Y gastric bypass (RYGB) who have subsequently undergone liver transplantation for NASH cirrhosis [59]. Access to the biliary tree in patients with RYGB anatomy can be facilitated by dedicated enteroscopes, but the above limitations also apply [58]. Percutaneous access to the stomach via gastrostomy using

radiological [60], surgical [61], and endoscopic [62] methods have been described, all allowing passage of a duodenoscope for conventional ERCP.

Pediatric Patients

Post-transplant biliary complications in the pediatric population are similar to those encountered in adults, although certain caveats are important to note. Due to the scarcity of whole cadaveric livers for adult transplantation, pediatric liver transplantation generally involves split cadaveric, living related donor, or reduced size grafts [63]. Similar to adults, the biliary complication rate is highest in pediatric LDLT [64]. Pediatric surgeons have traditionally utilized a bilioenteric anastomosis; however, duct to duct anastomosis can also be performed with technical variant grafts [64,65]. This is important in the management of post-transplant biliary complications as bilioenteric anastomoses are inherently more difficult to access endoscopically and may require percutaneous intervention [66,67].

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Endoscopic Confocal and Molecular Imaging in Hepatobiliary Disease

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Introduction

Since its introduction in 2004, confocal laser endomicroscopy (CLE) has been studied for a broad variety of gastrointestinal diseases. By enabling the endoscopist to examine suspicious tissue microscopically in vivo and in real time, CLE has not only provided an innovative practice for everyday patient care, but has also given insight into previously unknown aspects of the etiopathogenesis of certain diseases, such as inflammatory bowel disease [1].

By using molecular staining for CLE visualization (i.e., the fluorescent labeling of single molecules), the limits of early diagnosis and characterization of lesions have been moved from the interpretation of sheer morphological findings to the analysis of molecular alterations within tissue. Consequently, a suspicious lesion's molecular characteristics could also be screened for prognostic markers or therapeutic targets on day one of diagnosis, leading to the immediate employment of tailored therapies. During ongoing treatment, surveillance using this technique could possibly aid in detecting tumor escape and new mutations/molecular alterations. Additionally, after endoscopic interventions such as endoscopic submucosal dissection (ESD) or endoscopic mucosal resection (EMR), resection margins could be examined for residual tumor cells.

For neoplastic lesions of the gut, CLE has already been widely employed. A multitude of studies have been conducted due to relatively good accessibility via gastroscopy and colonoscopy [2]. Since the introduction of CLE probes fitting through the working channel of an endoscope, the hepatobiliary system has been an important target for endomicroscopy as well, and the development of probes fitting through needles during endoscopic ultrasound examinations might allow even further implementations of CLE [3].

Current Tools

Confocal Laser Endomicroscopy

Currently, there are two CLE systems in clinical use. In one system, the confocal endomicroscope is integrated into the tip of an endoscope (eCLE) (Pentax Corp., Tokyo, Japan). A blue laser excites fluorophores at

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a wavelength of 488 nm, and fluorescence is detected at 505–550 nm. A high spatial resolution of 0.7 µm is achieved and the imaging plane depth can be moved from the epithelial surface to 250 µm within the tissue. The field of view has an edge length of 475 µm (1024 × 1024 pixels). Image acquisition takes place at a rate of approximately 1 frame per second (fps). A rigid scanner with the same optical properties is available, approximately the size of a pen (Optiscan, Melbourne, Australia) connected to an optical unit, and used primarily in the laboratory. However, in principle, this system could be compatible for use during surgery or laparoscopy, and prototypes using different wavelengths for excitation and emission have been assessed in clinical trials.

In the second system, the endomicroscope is embedded in a flexible probe that fits through the working channel of conventional endoscopes or through endoscopic retrograde cholangiopancreatography (ERCP) catheters (pCLE) (CholangioFlex™, Mauna Kea Technologies, Paris, France). This allows not only for spontaneous ad hoc endomicroscopy upon identifying suspicious tissue, but also for introducing the endomicroscope into the bile or pancreatic duct due to its flexible design. The image acquisition rate of the pCLE system is faster (approximately 12 fps), but the spatial resolution is somewhat lower. The imaging plane for each probe is fixed, but it can be changed by using different probes. The field of view also depends on the probe used, ranging from 240 to 600 µm. The CholangioFlex probe has a field of view of 325 µm with a spatial resolution of 3.5 µm on an imaging plane 50 µm below the tissue surface.

For laboratory research, a system using wavelengths in the near-infrared range (660 nm) is available, in addition to imaging in the blue range. A dual band scanner even allows for bicolor imaging in a laboratory setting [4].

Fluorescent Dyes and Molecular Probes

In both systems, the tissue needs to be stained with fluorescent dyes for microscopic visualization. Currently, the most commonly used fluorescent agent is fluorescein (5 mL, 10% IV), a non-toxic substance widely employed for ophthalmological angiography. Fluorescein can be injected intravenously and leads to good depiction of vessels and histological architecture for excitation/emission spectra around 500 nm. These spectra limit its use to imaging of structures close to the tissue surface, as longer wavelengths are needed for deeper tissue imaging.

Acriflavine is another fluorescent dye of similar excitation and emission spectra. Unlike fluorescein, acriflavine stains nuclei and can therefore complement staining on this wavelength. However, concerns have been raised regarding its carcinogenic potential, although the substance has been used as a component of disinfectants in the past.

For molecular staining, derivatives of fluorescein (e.g., fluorescein isothiocyanate (FITC)) and other fluorophores, such as dyes of the Alexa Fluor® family (Abcam, Cambridge, UK), can be conjugated with a variety of different agents, such as antibodies, affinity peptides, activatable probes, or physiological substances [5]. The choice of a particular agent is dependent on the intent of the procedure. For diagnostic purposes alone, knowledge of the agent's exact target structure is not necessarily required, as long as sensitivity and specificity are high. To screen for potential therapeutic targets, however, knowledge of the agent's target structures is crucial. By fluorescently labeling targeted sites, these drugs can be assessed in vivo within the targeted tissue [6,7]. By specifically highlighting dysplasia, affinity peptides could be an important asset to endoscopic screening [8]. Activatable probes, whose fluorescence is intensified only in the presence of activators such as certain

proteases, could allow the visualization of the cells' proteome in vivo [9], and metabolic substrates, such as labeled folate [10] or 5-aminolevulinic acid [11], can be used for imaging. All these new approaches could expand the horizon in terms of both diagnosis and therapy and are being intensively studied, although mainly in experimental settings currently for the assessment of safety and feasibility.

Bile Duct

Diagnosis and discrimination of biliary diseases often prove difficult, and the yield of histopathology is often limited – especially regarding cholangiocarcinoma and its precursors, where sensitivity rates for conventional brushings have been reported to be lower than 50% [12]. However, it is crucial to detect malignant lesions in an early stage, as therapeutic options and prognosis are limited at an advanced stage of disease. As a means of further characterizing indeterminate lesions, optical biopsy using pCLE could complement conventional brush cytology or forceps biopsy to improve detection rates and differentiation of lesions.

In one study, endomicroscopy of lesions suspicious for cholangiocarcinoma was performed during ongoing cholangioscopy in 14 patients [13]. A CholangioFlex CLE probe was inserted through the instrumentation channel of a cholangioscope and placed directly onto a suspicious lesion. Fluorescein was injected intravenously, as continuous water flow needed to be maintained during the examination. Images of benign lesions showed a reticular pattern of thin, dark grey lines on a lighter background, whereas in malignant lesions thick, irregular, white lines crossed a darker background. In video mode, erythrocytes could be visualized within the white lines. These findings were interpreted as neoangiogenesis, as fluorescein was administered intravenously and therefore contrasted the vessels. CLE analysis showed a sensitivity, specificity, and overall accuracy for the diagnosis of malignant lesions of 83%, 88%, and 86%, respectively. Pathology, on the other hand, showed values of 50%, 100%, and 79%, respectively.

Another study examined pCLE during ERCP in 14 patients with indeterminate strictures of the bile duct [14]. In this study, a lower accuracy for the determination of strictures was observed using predetermined criteria. In a study of 37 patients, sensitivity and specificity rates of 83% and 75%, respectively, were reached using CLE during ERCP [15].

In the Miami classification of probe based CLE, efforts were made to standardize the interpretation of biliary CLE (Box 17.1) [16]. These criteria were then tested in a blinded study with a larger patient cohort (112 pCLE videos of 47 patients with biliary or pancreatic strictures), showing sensitivity values of up to 97% when combining multiple criteria for evaluation, whereas tissue sampling showed a sensitivity of only 48%. In contrast, specificity was 33% for CLE imaging versus 100% for tissue sampling [17]. Even though specificity of biliary CLE is still low at the moment, suboptimal sensitivity as one of the biggest problems of the current toolset for diagnosing cholangiocarcinoma

Box 17.1 Miami classification of biliary lesions: probe based confocal laser endomicroscopy features suggestive of malignancy. Source: Adapted from Wallace et al. 2011 [16] and Meining et al. 2012 [17].

- Thick white bands (>20 µm)
- Thick dark bands (>40 µm)
- Dark clumps
- Epithelial structures

could be drastically improved with pCLE. This is likely due to the fact that tissue sampling only yields small specimens from within the biliary tree, whereas pCLE imaging can visualize larger areas via multiple optical biopsies. Interobserver reliability was also examined in 42 patients and showed significant kappa values for agreement, especially regarding thin and thick dark bands, thin white bands, and visualization of epithelium [17].

The Paris classification has been developed as a modified version of the Miami classification, aiming to further increase diagnostic accuracy [18]. However, more studies are needed to confirm the benefit of these additional criteria.

The criteria used for biliary pCLE have not yet been fully correlated to standard histological findings, as side by side comparison is difficult to perform. Erythrocytes could be identified within thick white bands, which could therefore represent vessels. The often tortuous, saccular, and overall irregular architecture of these bands could correspond to the irregular vascularization of cancerous tissue. The thin dark bands constituting the reticular pattern of healthy mucosa, on the other hand, might resemble lymphatic ductules, as suggested by similar findings in tissue specimens of intact rat bile ducts [14].

All in all, pCLE may have an important role in the characterization of indeterminate biliary lesions, allowing for both direct analysis in vivo and the implementation of targeted biopsy protocols. However, the reliability of pCLE has yet to be assessed under inflammatory conditions (e.g., primary sclerosing cholangitis) where this novel approach to surveillance of the biliary tract might crucially improve tumor screening. Molecular CLE has not yet been broadly introduced for biliary disease, and experimental studies are eagerly awaited. For molecular imaging of the pancreas, a first study visualizing epidermal growth factor receptor (EGFR) and survivin via needle based CLE during endoscopic ultrasound examinations in a porcine model has been conducted successfully [19]. FITC labeled antibodies against EGFR and survivin were injected into different areas of the porcine pancreas under endosonographic guidance. After 30 minutes, needle based CLE was performed and molecular expression could be visualized in vivo for both targets.

Liver

By employing rigid CLE probes that are identical in construction to current eCLE systems (Optiscan) during minilaparoscopy, it was possible to acquire images of the liver parenchyma and other organs in vivo. The CLE devices were modified to accommodate the sterile environment required for laparoscopy, using a camera sleeve and sterile, stainless steel shaft to mantle the CLE probe and its connection cable to the optical unit. In a first study, blue laser light was used for tissue excitation, similar to conventional eCLE [20]. The confocal probe was introduced through a second trocar under laparoscopic guidance in 25 patients with liver disease. The imaging plane was translated up to 250 µm under the surface of the organ, and serial images were acquired after intravenous administration of fluorescein. CLE images were then compared with histopathological findings in targeted biopsies. Although hepatocytes and liver architecture could be visualized, as well as alterations such as fibrosis and steatosis, image quality did not match that of conventional pathology, unlike in gastrointestinal CLE imaging. This might be in part due to the limited penetration depth of blue laser light and the thickness of the liver capsule. Additionally, the parenchymal structure of the liver strongly differs from the layered architecture of gastrointestinal mucosa and might not be as easily accessible.

As a consequence, a second study used a prototype CLE unit that employs a

longer excitation wavelength (780 nm) with deeper tissue penetration (up to 350 µm) [21]. In this study, indocyanine green (ICG) was chosen as the fluorescent dye since its excitation and emission spectra were suitable for the near-infrared range of the laser. Image quality proved to be significantly better than the shorter wavelength system and hepatocytes could be clearly visualized, including subcellular details such as nuclei (visible as negative spaces without ICG uptake) (Figure 17.1). However, owing to the fluorescent dye used, only parenchymal cells were stained and inflammatory or tumor cells could not be discerned. Criteria for normal liver

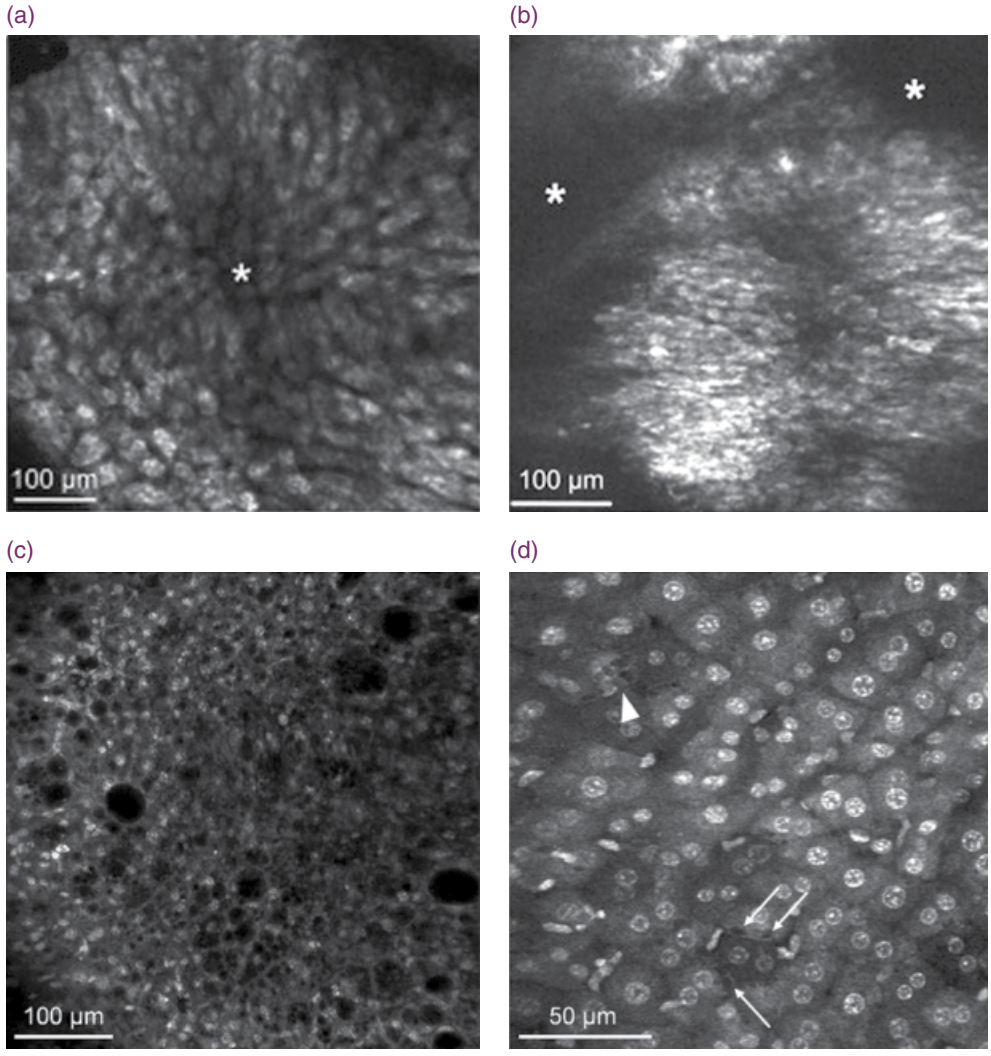

Figure 17.1 (a, b) Confocal laser endomicroscopy (CLE) of the human liver. (a) Normal histoarchitecture of a liver lobule is clearly visible in a healthy liver (* central vein); (b) whereas dark zones (*) separate liver nodules in a patient with liver fibrosis. (c) Lipid vacuoles can be clearly visualized in a mouse model of steatosis. (d) In another mouse model, apoptosis was induced and could be monitored using CLE. One cell (arrowhead) already underwent apoptosis, with only fragments are left. A second cell is currently in the process of fragmentation (thin white arrows). Source: Goetz et al. 2010 [21]. Reproduced with permission of Elsevier.

tissue can be established similar to conventional histological findings; the hexagonal architecture of the liver lobules and their sinusoidal architecture could be visualized. In fatty liver disease, multiple bright inclusions inside the hepatocytes could be discerned, whereas fibrosis was identified by increased negative space (black bands) between the liver lobules representing unstained fibrous tissue (Figure 17.1b). In cirrhosis, the parenchymal architecture was irregular and small areas of parenchyma could be visualized within dark fibrous tissue, whereby cirrhotic scars remained dark after injection of ICG. Using the acquired image data, steatosis and fibrosis could be predicted in 22 patients with accuracies of 81% and 90%, respectively.

In the future, this technique could help target biopsies and allow the in vivo diagnosis of inflammatory or neoplastic diseases, especially in combination with molecular agents (e.g., targeting lymphocytes or tumor cells). ICG itself could be used as a marker for the differentiation of hepatocellular carcinoma (HCC) due to its biliary excretion mode. This was studied in 170 patients undergoing surgery for HCC using a macroscopic fluorescence detection system. In this study, differentiated HCC showed fluorescence after the administration of ICG, whereas undifferentiated HCC showed no uptake of the dye in the tumor itself, but only in the surrounding healthy liver tissue [22]. This technique could be helpful for guiding resection and detecting additional lesions. Another study evaluated its use for detecting extrahepatic metastasis of HCC in 17 patients, with promising results [23].

In animal models, CLE has been studied for a wide array of liver diseases. Inflammation, steatosis, perfusion anomalies, and fibrosis were visualized and compared to ex vivo findings in mice suffering from cytokine induced hepatitis, in an obesity model, or after ligation of the common bile duct [24,25]. Liver metastases or peritoneal carcinomatosis have been found in several studies on tumor xenografts. Metastases often shared the molecular characteristics of the primary xenografted tumors and could therefore be imaged using the same molecular agents [7,26,27]. An advantage of CLE compared with conventional histology is the possibility of real-time imaging. In an animal study, apoptosis of hepatocytes was induced and could then be continuously visualized for several hours using the rigid CLE system (Figure 17.1d) [28]. In this study, nonselective dyes, such as acriflavine and fluorescein, were used for morphological imaging. For perfusion imaging, FITC labeled dextrans were administered, and for functional molecular imaging, caspase activation was assessed using a fluorescein labeled polycaspase inhibitor.

The number of possible implementations of CLE in both clinical and laboratory setting is high, and CLE might serve as a unique tool to improve understanding and diagnosis of liver diseases. However, as of today, the number of studies conducted in humans is still small and the current toolset for imaging does not yet cater to all imaging needs. Therefore, further studies and developments are needed before broad clinical application can follow.

Perspective on Future Applications

With the introduction of needle based CLE during endoscopic ultrasound examination [3], a new diagnostic field is emerging. Cysts and masses can be examined microscopically in vivo, and a first study has already reported on visualization of porcine pancreatic tissue at a molecular level using antibodies against EGFR and survivin [19]. This "seeing needle" technique can be particularly helpful as a navigation aid when locating focal lesions, but still has to be evaluated for the puncture of liver lesions.

Other new techniques might also increase the accessibility of thus far inaccessible

structures: natural orifice transluminal endoscopic surgery (NOTES) allows direct access to the peritoneal cavity and, consequently, CLE imaging of intraperitoneal organs [29]. This might also provide an alternate access path for confocal liver imaging. When resecting suspicious lesions, CLE could be used to screen for potential residual cells or local recurrence, as already demonstrated following endoscopic mucosal resection of superficial gastric lesions [30]. Furthermore, CLE (especially with molecular dyes) could allow the visualization of microscopic metastatic spread in the liver, in the form of peritoneal carcinomatosis, or even in lymph nodes via needle based CLE.

For gastrointestinal diseases, numerous studies have been conducted using molecular fluorescent agents (reviewed in detail in [5] and [31]). For hepatobiliary disease, however, studies using molecular staining are scarce. This is largely attributed to the comparatively low accessibility that might favor the initial assessment of newly developed techniques to take place in a more controllable examination environment – as is the case during gastroscopy or colonoscopy. However, results should most likely be transferable, and molecular hepatobiliary CLE should, in principle, be feasible. This new imaging technique could not only impact on the diagnosis of neoplastic or inflammatory lesions, but also on treatment and prediction of response to therapy, leading to customized treatment protocols and individualized disease management from day one of diagnosis. For this purpose, therapeutic antibodies or other targeted drugs can be used as molecular agents, as already studied for colorectal cancer and inflammatory bowel disease [7,32]. With multicolor CLE using different wavelengths at the same time, molecular imaging could be performed targeting several structures at once, or combining molecular image data with functional or perfusion imaging [4]. This approach might not only influence clinical care, but also basic science, as it allows unique insights into the living organism without altering physiological conditions.

Conclusion

In conclusion, CLE could play an important role in the future management of hepatobiliary disease. A first implementation with immediate benefit for the patient could be in the diagnosis of indeterminate biliary strictures, where the sensitivity of CLE surpasses that of histopathology. With a microscopic view into the liver parenchyma during ongoing (mini)laparoscopy, in vivo diagnosis of liver diseases can be performed, and functional or perfusion CLE imaging could complement histoarchitectural findings. By employing needle based CLE or CLE during NOTES, even more structures can be accessed by this novel imaging technique, further expanding its field of application. With the implementation of molecular CLE, both clinical and basic science could gain a unique tool for targeted visualization, leading to individualized therapy and a better understanding of the underlying disease.

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18

Laparoscopy in Patients with Hepatobiliary Disease

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Introduction

Laparoscopy in the patient with hepatobiliary disease has two distinct roles: the assessment of the existence and extent of a disease process, and the performance of specific interventions. Direct real-time visualization and assessment of the liver, gallbladder, and peritoneum, as well as ultrasonographic assessment of the biliary tree, liver parenchyma, and vasculature add considerably to the armamentarium of today's hepatobiliary surgeon and allow for the planning of appropriate interventions. The ability to not only assess but also intervene laparoscopically in such patients is continually evolving. Over the last two decades, cases of increasing complexity have been shown to be amenable to a laparoscopic approach. This chapter will focus on the role of laparoscopy in the assessment and staging of patients with hepatobiliary disease, as well as its role in facilitating intervention and resection for both benign and malignant disease.

Assessment and Staging

Laparoscopic Staging

Advances in radiology have provided many non-invasive tools – such as multidetector computed tomography (CT) scanning, magnetic resonance imaging (MRI), and combined CT with positron emission tomography (CT/PET) scanning – that have had a considerable impact on the assessment of disease extent, particularly with respect to cancer. Unfortunately, these modalities may underestimate the extent of disease, with small volume metastatic disease being appreciated only at surgical exploration. For over 100 years, laparoscopy has been suggested as a means for identifying such small volume disease. A significant amount of data have been produced to suggest that the use of laparoscopy and laparoscopic ultrasound in the staging of gastrointestinal malignancies has an impact on overall management [1–7]. Staging laparoscopy in suspected malignant disease is a quick,

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safe, but invasive investigation. The aim of this is to mimic staging at open exploration while minimizing morbidity and enhancing recovery, and thus allowing for quicker administration of adjuvant therapies if indicated.

Proponents believe that laparoscopic staging should be viewed as complementary and not as a replacement for other staging modalities, such as CT, MRI, or PET scanning. The advantages of laparoscopy are that it allows the surgeon to visualize the primary tumor, determine vascular involvement, identify regional nodal metastases, detect small volume peritoneal/liver metastases, and determine resectability, as well as obtaining tissue for histological diagnosis. The addition of direct contact laparoscopic ultrasonography (LUS) provides the ability to further assess the local stage of disease and to evaluate the liver for metastases.

Laparoscopic Staging Technique

Laparoscopic staging may be performed immediately before a planned open or major laparoscopic procedure or on a separate occasion. Laparoscopic staging is performed under general anesthesia with the patient positioned supine on the operating table. A warming blanket is placed underneath the patient, who is secured appropriately to the table with padding over the pressure points. As with all laparoscopy, some thought should go into the operating room setup to allow the surgical team to work comfortably. High definition camera systems are now common and provide excellent visualization of the peritoneal cavity. The laparoscopic monitor and stack should be positioned beyond the patient in the direction the surgeon is working. The laparoscopic ultrasound monitor can be placed beside this. Facilities are available for "picture in picture" – the ultrasound monitor view being placed on the same screen as the laparoscopic image – although this may obstruct the laparoscopic view. High definition recordings of the laparoscopic camera feed can be undertaken and facilities for recording video images of the ultrasonography are useful.

The following operative equipment is considered necessary for the procedure (Figure 18.1):

1) A 30° angled laparoscope, either 5 or 10 mm in diameter.
2) A range of 5 mm laparoscopic instruments, including a Maryland dissector, blunt tip dissecting forceps, cup/biopsy forceps, atraumatic grasping forceps, liver retractor, and scissors.
3) A 5 or 10 mm suction/irrigation device.
4) A laparoscopic ultrasound probe (optional).

For hepatobiliary disease, a standard approach involves establishing a pneumoperitoneum (12 mmHg) via a 10 mm infraumbilical port placed under direct vision. An additional 10 mm port is placed in the epigastrium to the left of the midline, well below the costal margin. A 5 mm port is usually placed on the right side to allow the use of a grasper. These positions allow easy access to the liver, gallbladder, and portal pedicle. An alternative approach, particularly in patients with previous midline incisions, is to place the initial port in either the right or the left upper quadrant of the abdomen. Laparoscopic access using an optical trocar combines the advantages of the Hasson and Veress techniques, and is becoming an increasingly accepted technique [8]. Pneumoperitoneum is achieved with carbon dioxide, with an intraperitoneal pressure of 10–12 mmHg considered optimal. However, in patients with cardiopulmonary compromise, a lower maximum pressure may be chosen. A 30° laparoscope is inserted through the umbilical port, and a careful inspection of the intra-abdominal organs and peritoneum performed. Additional trocars are inserted

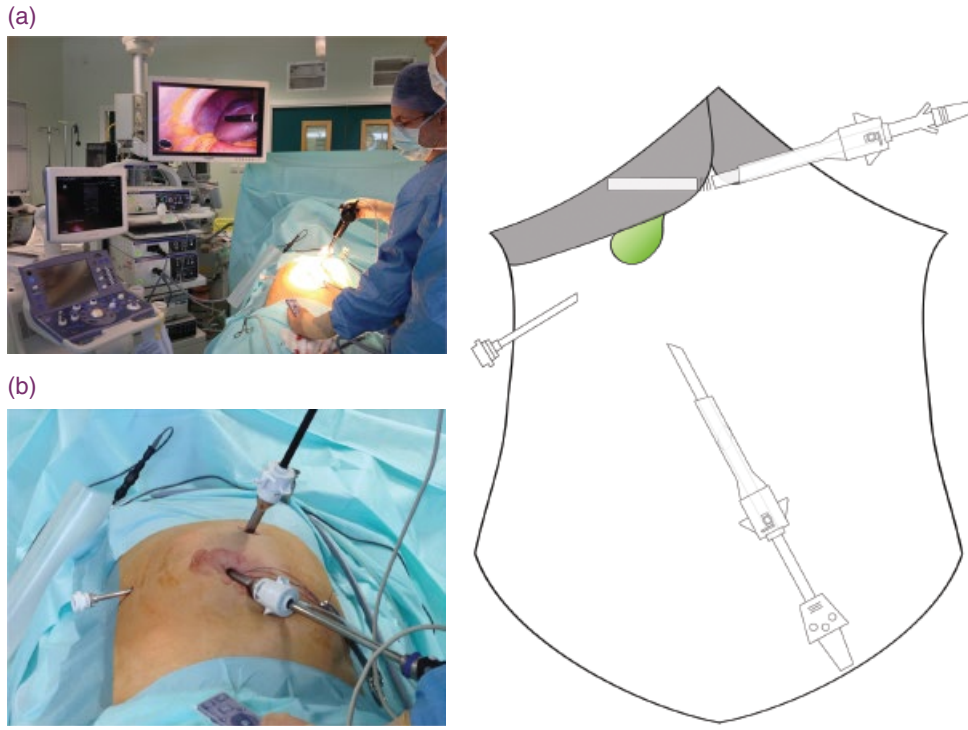

Figure 18.1 (a) Correct theatre setup for the use of laparoscopic ultrasound, placed via an epigastric port, to visualize the gallbladder (b). Alternatively, the port may be placed from the right side.

under direct vision. Placement depends on the site of the primary tumor and the findings at initial inspection (e.g., whether obvious metastatic disease is present). In general, ports are placed along the planned open incision line. Particular attention is paid to the falciform ligament, liver (including the under surface), diaphragm, hepatoduodenal ligament, and lesser omentum. The greater omentum is retracted superiorly to allow the small bowel mesentery and ligament of Treitz to be directly visualized. Any abnormal lymphadenopathy can be identified and any suspicious node can either be excised or biopsied. As in open surgery, care must be taken not to crush the node and possibly disseminate tumor cells during this procedure.

To facilitate hepatic examination, the patient is placed in a 20° head up position with 10° of left lateral tilt. The anterior and posterior surfaces of the left lateral segment of the liver are examined, followed by examination of the anterior and inferior surfaces of the right lobe. Despite the absence of tactile sensation, indirect palpation of the liver surface may be achieved by using two instruments. A blunt suction device is particularly useful in compressing the liver tissue in order to detect small metastases. Improved visualization of diaphragmatic and posterior surfaces may be achieved by placing the camera alternatively in the right upper quadrant port. Any suspicious areas can be biopsied at this point. Thorough hemostasis can easily be obtained with electrocautery or use of argon beam diathermy. If using electrocautery, it is important to avoid direct coupling or capacitance coupling, which can lead to visceral injury. Direct coupling, when current flows directly from one instrument to the other,

may occur when the instruments are too close together, especially if one is just outside the field of view. Capacitance coupling occurs when two conductors have an insulator sandwiched between them. The high frequency alternating current in the active conductor generates a magnetic field, which then induces current in the second conductor. Mixing of metal and plastic instruments and ports can lead to capacitance coupling and, at least in theory, severe burns. The incidence of complications is reduced by limiting the gain of electrocautery to 30 watts, and possibly by using plastic rather than metallic ports.

Returning the patient to a supine position, elevating the left lobe of the liver, and incising the gastrohepatic omentum exposes the caudate lobe of the liver, the inferior vena cava, and the celiac axis. If present, an aberrant left hepatic artery should be identified and preserved. The lesser sac can be entered by dividing the gastrocolic omentum. By elevating the stomach, the "gastric pillar" can be clearly identified, which contains the left gastric artery and vein. Followed down, this structure leads to the celiac axis, and any suspicious nodal tissue can be biopsied. The hepatic artery also is identified and followed to the hepatoduodenal ligament. The anterior aspect of the pancreas, hepatic artery, and left gastric artery are also seen. Any suspicious periportal, hepatic, or celiac nodes can be biopsied. In general, the duodenum is not mobilized. However, for patients with pancreatic or common bile duct tumors, close attention is paid to the presence or absence of tumor infiltration in the angle between the duodenum and the lateral aspect of the common bile duct because this may indicate significant vascular involvement.

Performing peritoneal lavage cytology may increase the diagnostic yield for laparoscopic staging. In general, the specimens are taken at the start of the laparoscopy to avoid potential contamination following tumor manipulation or dissection. Between 200 and 400 mL of normal saline is instilled into the peritoneal cavity. The abdomen is agitated gently before aspiration from the right upper quadrant, left upper quadrant, and pelvis.

Laparoscopic Ultrasound

Laparoscopy, by its nature, is a two dimensional modality, with the result that appreciation of deep or subsurface lesions in solid organs is often suboptimal. LUS can partially overcome this deficiency. Transducers in clinical use employ either curved or linear array technology, and have a high frequency performance with a range in the region of 6–10 MHz. This allows for high resolution images to be obtained that can detect lesions of ≥0.2 cm in size. In the field of hepatobiliary surgery, LUS plays a role in liver parenchymal evaluation, assessment of biliary calculi, facilitating resection of liver tumors, partial liver transplantation, and ablation of liver tumors. In addition, Doppler flow capability allows for accurate vessel identification and facilitates assessment of the tumor–vessel interface. The LUS probe is inserted via a 10–12 mm port, and particular attention must be paid to port placement.

In relation to the detection of bile duct stones, a large series reported identification of the common hepatic duct and the common bile duct (CBD) in 93% and 99% of cases, respectively. Sensitivity and specificity for identifying bile duct stones were 92% and 100%, respectively (Figure 18.2) [9]. A normal CBD diameter at LUS was also an excellent negative predictor of CBD stones. The same authors later concluded that LUS could replace intraoperative cholangiography (IOC) [10]. Others feel IOC and LUS should be seen as complementary rather than competitive tests [11]. LUS may facilitate a policy of selective cholangiography. The use of LUS has not yet been proven to reduce the incidence of biliary tree injuries.

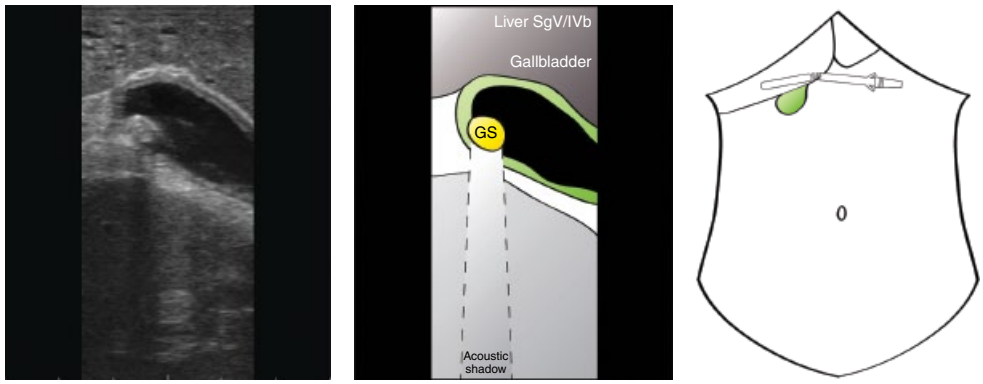

Figure 18.2 Laparoscopic ultrasonographic evaluation of benign biliary disease. In this example, the correct positioning of the laparoscopic ultrasound probe is demonstrated to identify the obvious gallstone (GS).

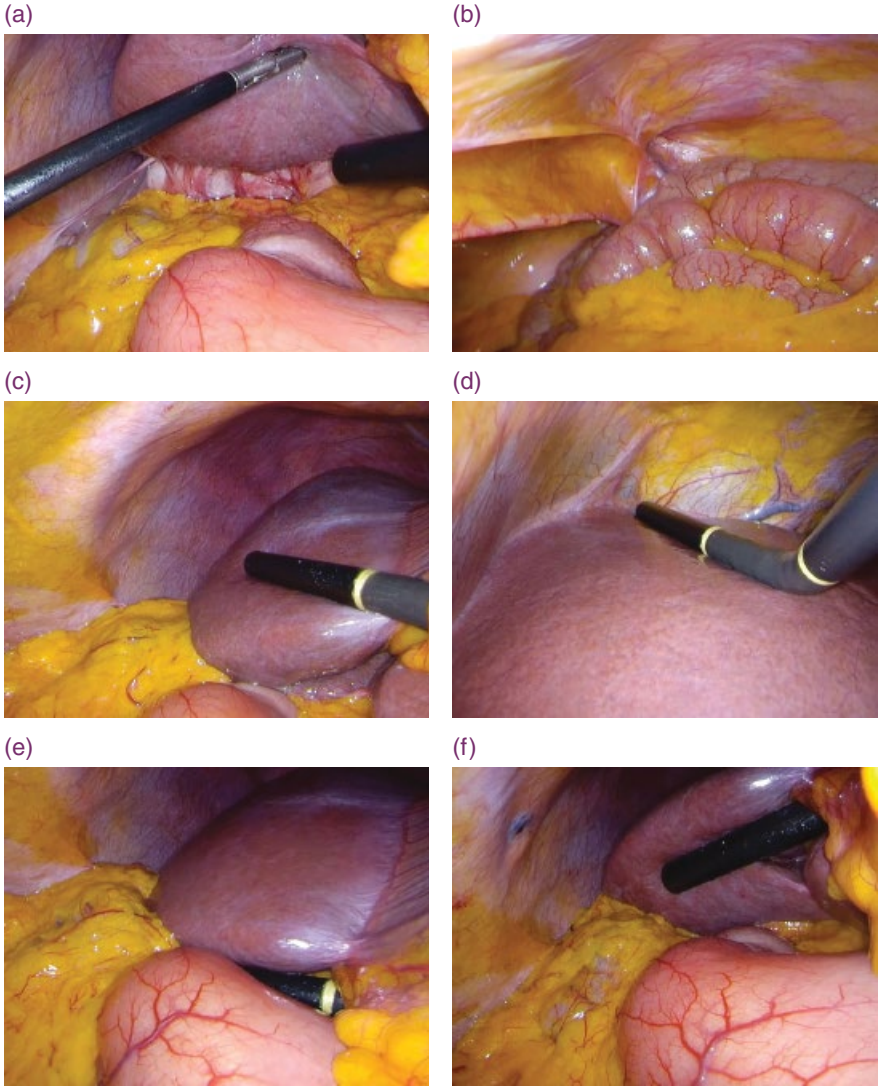

Figure 18.3 (a–f) Full evaluation of the right and left lobes of the liver with laparoscopic ultrasound, together with appreciation of the peritoneal surfaces while performing a staging laparoscopy.

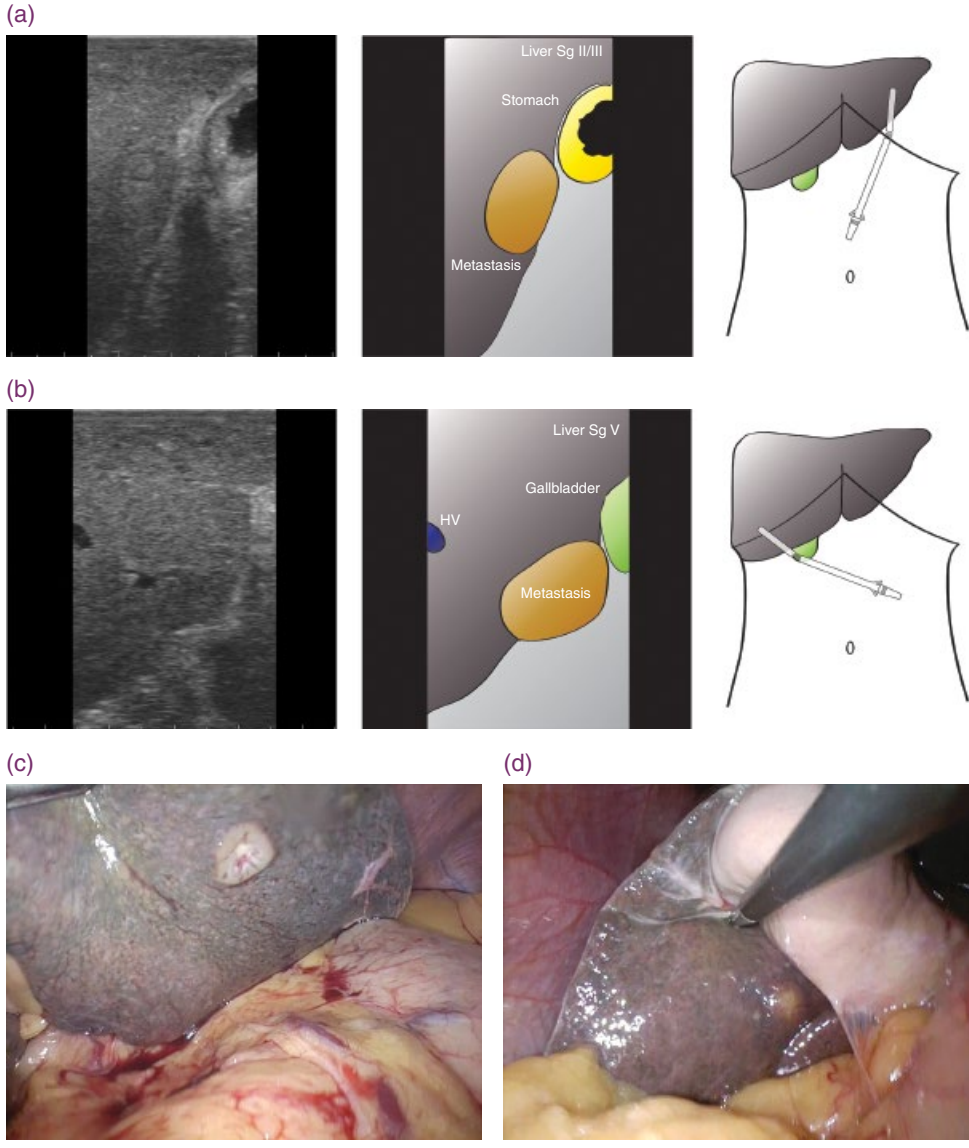

Figure 18.4 Intraoperative laparoscopic evaluation of metastatic deposits in the liver. (a) Liver segments II/III, with schematic representation. (b) Liver segment V, with schematic representation. (c, d) Views on laparoscopy of (a) and (b), respectively.

LUS is an invaluable tool for examination of the liver (Figure 18.3). Initially, the transducer is placed over the left lateral segment, allowing assessment of segments I, II, and III. It is important that the probe is placed in direct contact with the liver surface to maximize acoustic coupling. Examination of the right lobe commences with the probe on the dome of the liver. The vena cava is visualized at the back and the probe is moved forward slowly to identify the hepatic and portal veins. Within the liver, these can be identified by virtue of their surrounding fibrous sheath. The

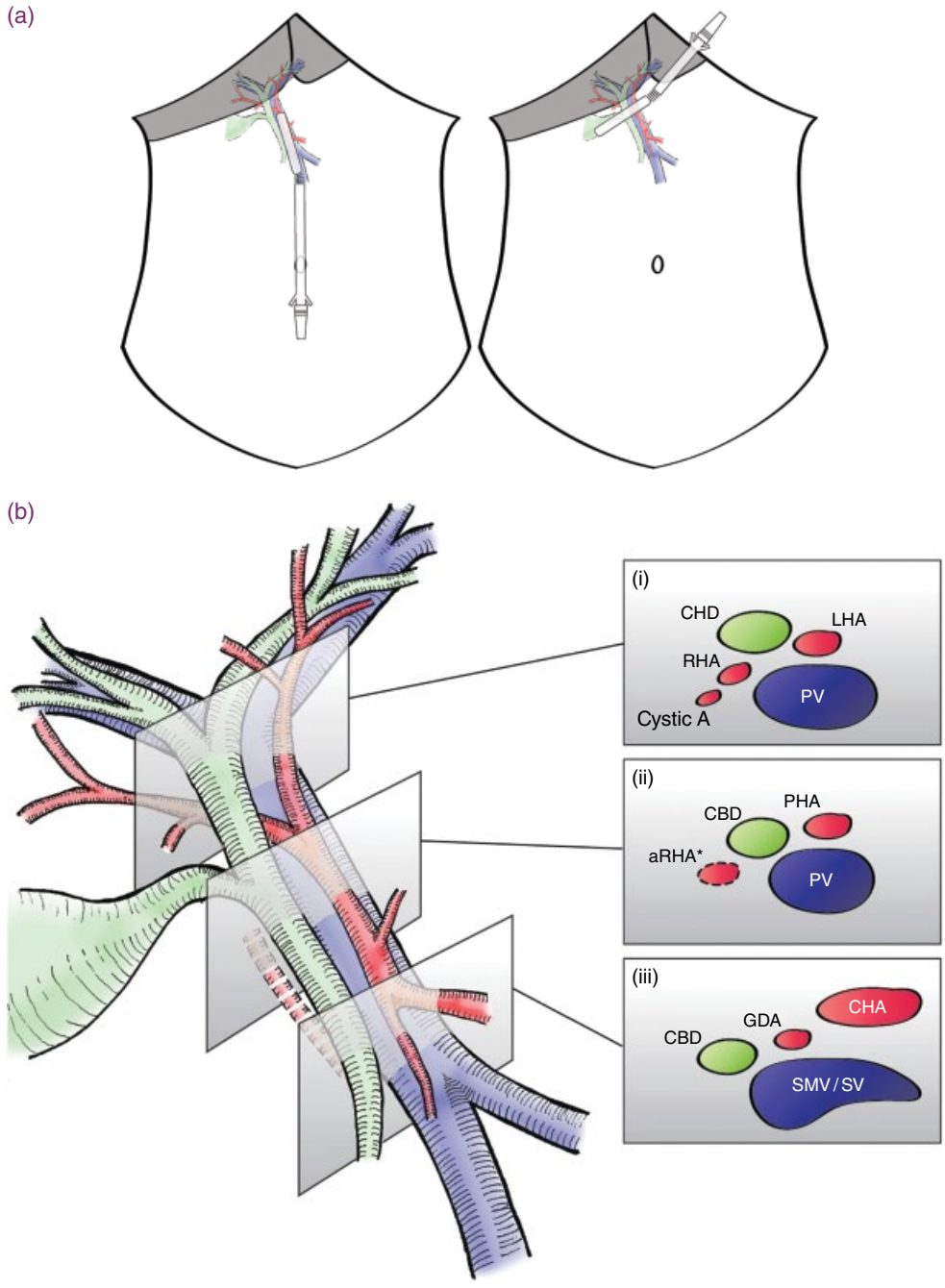

Figure 18.5 (a) Laparoscopic ultrasonographic evaluation of the portal triad. (b) Schematic representation of the expected images at varying points along the hepatic portal pedicle as seen on laparoscopic ultrasonography. (c) If there is any doubt about the structures involved when assessing the portal pedicle, Doppler flow can be evaluated, as shown, to determine the nature of the structures involved. aRHA, accessory right hepatic artery; CBD, common bile duct; CHA, common hepatic artery; CHD, common hepatic duct; GDA, gastroduodenal artery; LHA, left hepatic artery; PHA, proper hepatic artery; PV, portal vein; RHA, right hepatic artery; SMV/SV, splenic mesenteric vein/splenic vein.

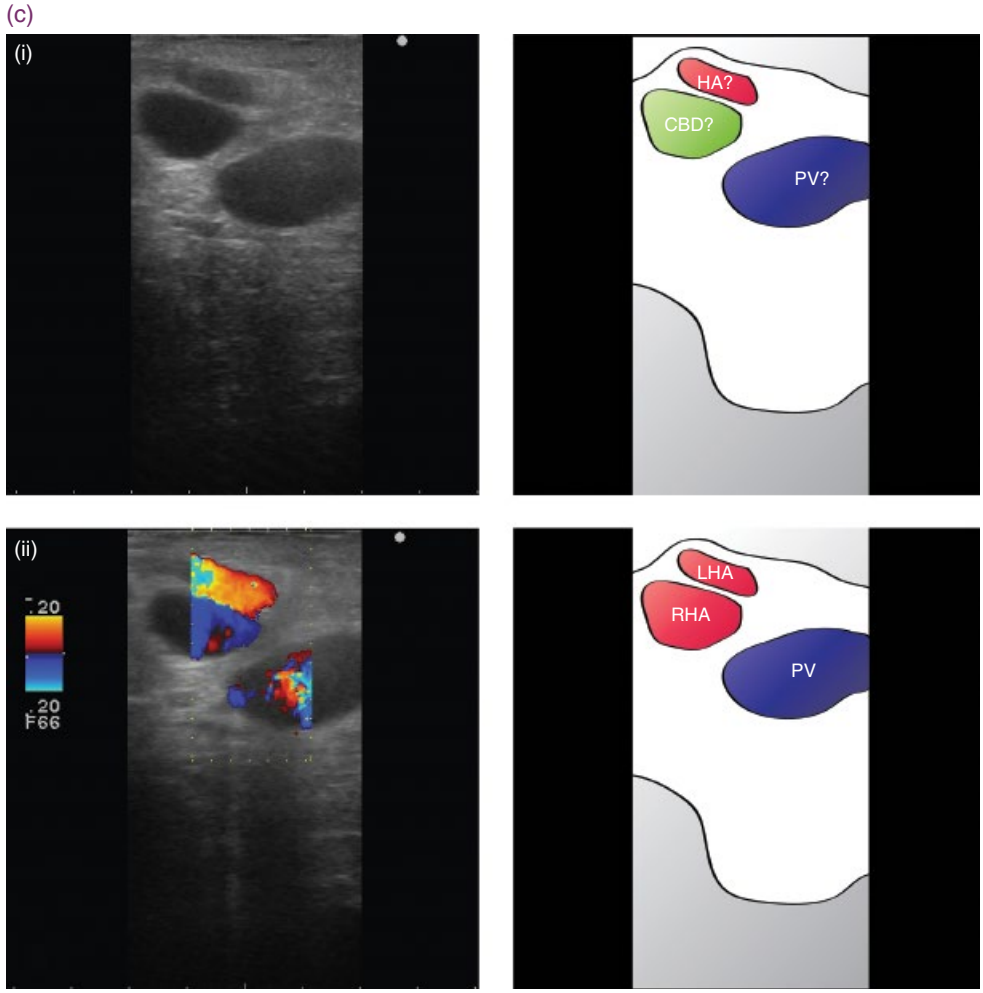

Figure 18.5 (Continued)

remaining hepatic segments (IV–VIII) are examined by rotating the probe over the rest of the liver. Suspicious lesions can be biopsied either by fine needle aspiration (FNA) or by percutaneously inserted core biopsy needles under LUS guidance. With the probe over segment V, the gallbladder is assessed, and with transverse placement of the probe over the hepatoduodenal ligament, the common hepatic duct, CBD, and hepatic arteries, along with the portal vein, can be identified (Figures 18.4 and 18.5). The portal vein can be followed to its confluence with the splenic and superior mesenteric vein. The superior mesenteric artery also can be seen and its relationship to a pancreatic tumor, if present, determined. The pancreas can be examined, and any lesion identified.

LUS plays a crucial role in procedures other than the assessment and staging of tumors. In open surgery, it is estimated that intraoperative ultrasonography (IOUS) routinely identifies 30–35% more hepatic lesions than routine preoperative imaging [12]. In experienced hands, there is no reason to doubt that a similar gain can be made when used laparoscopically. Such a gain could

potentially alter the intraoperative management and approach, as has been shown in open resections since IOUS was first introduced in the early 1980s [13–15].

Laparoscopic Intervention in Patients with Hepatobiliary Disease

Benign Hepatobiliary Disease

Laparoscopic Cholecystectomy

The use of laparoscopic cholecystectomy remains the most efficient method of treating symptomatic gallbladder stones, being a significant advance over open cholecystectomy.

Laparoscopic Common Bile Duct Exploration

Common bile duct stones are identified in 10–15% of patients undergoing surgery for symptomatic cholelithiasis [16]. Despite evidence supporting the fact that the majority of CBD stones will pass spontaneously within 6 weeks of being identified [17], their removal is mandated in many cases owing to risks of acute suppurative cholangitis, obstructive jaundice, hepatic abscess, and acute pancreatitis, as well as clip disruption in the immediate postoperative period.

With regard to CBD exploration for bile duct stones, there now appear to be two similarly effective and relatively safe options available – endoscopic retrograde cholangiopancreatography (ERCP) or laparoscopic CBD exploration. In older patients with comorbid disease who are poor operative candidates, bile duct exploration by ERCP is usually preferred. The benefits are clear for this patient subgroup [18] and, with advancing population age, ERCP with definitive endoscopic sphincterotomy will continue to be a useful procedure. What remains less clear is the management of younger and fit patients who present with simultaneous symptomatic gallbladder and bile duct stones. These patients have lower morbidity and mortality than their older counterparts irrespective of whether they undergo a laparoscopic or endoscopic method of bile duct exploration. In addition, a single laparoscopic approach to undertake cholecystectomy, together with CBD exploration, is intuitively an ideal approach. Early proponents of the one stage laparoscopic approach reported equivalent success rates and patient morbidity for the two management options, but a significantly shorter hospital stay with the single stage laparoscopic treatment. It was proposed that in fit patients (American Society of Anesthesiologists (ASA) physical status I and II), single stage laparoscopic treatment was the better option and preoperative endoscopic sphincterotomy should be confined to poor risk patients (e.g., those with cholangitis or severe pancreatitis) [19]. Despite anecdotal reports of long term complications possibly associated with sphincterotomy, the decision about which method of bile duct exploration to undertake is usually based on local experience and expertise and the preference of the individual center concerned.

Technique With experience and theater organization, laparoscopic bile duct exploration need not add a lot of time. In straightforward cases, an additional 10–30 minutes is required for cholecystectomy alone, even for a transductal exploration. If a transcystic approach is achieved, very little time is added to the hospital stay and it has been shown to be safe and effective [20]. However, it must be emphasized that, as with most innovations, early proponents and enthusiasts will endeavor to accentuate and promote the maximum benefits and these times may not be applicable to all theater situations.

The patient is placed in a supine position and a pneumoperitoneum created as described above. Five ports are used

with a 10 mm, 30° scope at the umbilicus. Surgeons will vary their port placement but it seems necessary in all cases that the epigastric port be placed 2 cm to the right of midline so that it is directly in the line of the CBD. Dissection is commenced around the Calot triangle as for a standard laparoscopic cholecystectomy. The gallbladder is partially dissected from its bed and used for retraction. To prepare for IOC, a clip is placed on the gallbladder and a small cut is made proximal to this in the cystic duct, allowing passage of a 4–6 Fr catheter through the cystic duct into the CBD. Digital fluoroscopy allows imaging of the biliary tree and, if needed, the anterior surface of the supraduodenal CBD is then dissected out cautiously, being careful to avoid any choledochal arteries. The bile duct is opened with a longitudinal incision of 0.5 cm or more, depending on the size of the stone, using an endoknife. Stones are retrieved by spontaneous evacuation while incising the bile duct, and subsequently a 6–10 Fr catheter is passed through the CBD, with lavage using normal saline. Choledochoscopy can be performed using a 5.5 mm (15 Fr) flexible or rigid choledochoscope inserted via a right upper quadrant port site, along with continuous saline infusion through the choledochoscope, which dilates the duct and clears debris. With this technique, CBD stones can be directly visualized and basket or balloon extraction performed until complete clearance of CBD stones is achieved. It is vital to explore the proximal duct as far as the right and left intrahepatic bile ducts, and inferiorly as far as the papilla. A mechanical lithotripter can be used to break impacted stones. The choledochotomy is closed using absorbable suture (4-0 Vicryl®; Ethicon Inc., Somerville, NJ, USA). T tube drainage appears to result in significantly longer operating time and hospital stay as compared with primary closure, without any evidence of benefit after laparoscopic CBD exploration. Based on currently available evidence, there is no justification for the routine use of T tube drainage after laparoscopic CBD exploration in patients with CBD stones [21].

Laparoscopic Deroofing of Simple Liver Cysts

Non-parasitic simple cysts of the liver are estimated to occur in 5% of the population, sometimes as part of the polycystic disease complex. The vast majority of these are unilocular, do not communicate with the biliary tree, have serous content, and present no malignant potential. Unless symptomatic, they virtually never require treatment. When indicated, the aim of treatment in patients with single cysts is to either destroy the epithelial lining with sclerotherapy or to create a communication between the cyst lumen and the peritoneal cavity by fenestration. The latter lends itself in the majority of cases to a laparoscopic approach. Only the protruding part of the cyst wall should be excised and there is no need to enter the liver parenchyma. The procedure consists of establishing a pneumoperitoneum with care, incising the cyst with scissors or electrocautery, and widely excising the roof. Care is taken to visualize the remaining cyst lining and if a biliary communication is suspected, an intraoperative cholangiogram should be performed. Fluid will continue to be produced by the remaining cyst lining, but will be reabsorbed by the peritoneum, and the cyst cavity will collapse.

The traditional view of liver cysts in segment VII or VIII is that open fenestration may be required given the limited access afforded by laparoscopy. However, as experience with laparoscopic mobilization of the liver increases, adequate deroofing is now usually achievable by laparoscopy, although the risk of cyst recurrence may be increased. A greater omental flap to prevent local cyst recurrence after laparoscopic deroofing is dispensable and has been shown to be

a potential source of additional complications [22].

Postoperative complications are reported to occur with rates ranging from 20% to 69% [23], and the most widely reported adverse events include hemorrhage and biliary leak. These are likely to occur as a result of re-expansion of previously compressed structures. Attempts to prevent these complications from occurring include the use of an endovascular stapler along the edges of the cyst at the time of fenestration and IOC.

Loehe et al. have described a comparison of pre- and postoperative symptoms. Abdominal pain was improved in 91% and disappeared in 68% of patients. During follow-up, 9% of patients required further care, and by 5 years only 2% had persistent subjective symptoms [24]. In data extracted from the Lothian surgical audit, four patients with simple cysts and eight with polycystic liver disease, out of a population of 102 patients, required further surgery. All patients with simple cysts had comparable quality of life after surgery. Patients with recurrent symptoms after surgery for polycystic liver disease had a significantly better quality of life following laparoscopic deroofing than after resection [25].

Malignant Hepatobiliary Disease

Laparoscopic Biliary and Gastric Bypass

Since the majority of patients with primary hepatobiliary malignancy have unresectable disease at the time of presentation, palliation to minimize symptoms and maximize quality of life has a major role in the care of these patients. Palliation most commonly is required for one of three problems: biliary obstruction, gastric outlet obstruction, and relief of pain.

For those patients with unresectable disease, progressive jaundice constitutes an immediate limitation to their survival, in addition to causing significant loss to their quality of life secondary to pruritus, malaise, and cholangitis [26]. The available literature suggests that non-surgical palliation can be achieved with a similar technical success to that of surgical bypass, at cheaper cost, and with a trend toward a lower risk of short term complications [27]. However, surgical bypass appears to provide better long term palliation in patients, both in terms of prevention of recurrent jaundice and by including a prophylactic gastrojejunostomy to prevent future gastric outlet obstruction. Therefore, in patients with malignant biliary obstruction, a biliary endoprosthesis should, perhaps, be reserved for those patients with a shorter expected survival time. The cut-off point in survival time that determines which of these two treatment modalities should be used has often been quoted as 6 months [28,29]. Other determinants of poor survival rates include the presence of peritoneal or liver metastases and a low Karnofsky index of performance [30]. These factors should be considered in selecting the appropriateness of cases for bypass procedures versus endoscopic stenting.

While both cholecystoenteric and choledochoenteric bypasses have been performed laparoscopically, the latter is more challenging. A sufficient length of common duct needs to be exposed, and a difficult intracorporeal anastomosis between the small bowel and the common duct must be performed. Cholecystojejunostomy is the more commonly performed laparoscopic procedure but patient selection is critical. A low insertion of the cystic duct into the CDB or tumor impingement within 1 cm of the duct is a predictor of early technical failure. The anastomosis can be performed with either a stapled or handsewn technique. In patients who have experienced a prior cholecystectomy or have a diseased gallbladder, blocked cystic duct, low insertion of the cystic duct, or tumor encroachment on the cystic duct or gallbladder,

a cholecystojejunostomy is not possible. In these cases, either a laparoscopic choledochojejunostomy is performed or the procedure is converted to an open standard surgical bypass.

Rhodes et al. presented in 1995 one of the first series of patients who underwent laparoscopic palliation for advanced pancreatic carcinoma [31]. From the 16 patients, seven underwent laparoscopic cholecystojejunostomy, five had laparoscopic gastroenterostomy, three had both procedures, and in one patient laparoscopic palliation failed. The median operating time was 75 minutes, the hospital stay was 4 days, the morbidity was 13%, and the median survival in 10 patients was 201 days, with the remaining patients still alive at the time of publication [31]. A randomized trial by Naverra et al. reported that patients undergoing laparoscopic gastrojejunostomy had significantly less intraoperative blood loss and resumed oral intake sooner than those patients undergoing an open palliative antecolic gastrojejunostomy [32].

A technique for a transumbilical single incision laparoscopic gastrojejunostomy has been reported [33]. While this is technically feasible, the benefits compared with the conventional laparoscopic approach remain to be determined.

The true incidence of symptomatic gastric outlet obstruction (GOO) remains unclear. Historically, it was considered that more than 25% of patients would develop GOO during the course of their illness and, therefore, prophylactic gastric bypass was recommended at the time of exploratory laparotomy. However, as the need for open exploration for staging purposes has decreased, the need for prophylactic bypass in the majority of patients has been questioned. For example, GOO is a late complication of advanced pancreatic cancer affecting 10–20% of patients who survive more than 15 months [34–36]. However, fewer than 3% of the patients who develop GOO require surgical bypass [18,37,38]. Most importantly, 60% of patients with advanced pancreatic cancer have delayed gastric emptying with no evidence of gastric or duodenal obstruction. This may be explained by tumor infiltration of the celiac plexus causing gastric stasis, nausea, and vomiting [39]. Espat et al. examined 155 patients with unresectable, histologically proven pancreatic adenocarcinoma who underwent laparoscopic staging in a prospective but non-randomized study [34]. Following laparoscopy, 40 patients had locally advanced unresectable disease and the remainder had metastatic disease. At follow-up, only 2% of patients required a subsequent open operation for biliary drainage or GOO. This low incidence of patients requiring operation for symptomatic GOO is consistent with the data seen from the non-operative control groups in randomized trials of endoscopic biliary drainage versus surgery. A laparoscopic gastroenterostomy is a relatively straightforward procedure. In a series of laparoscopic gastrojejunostomies reported by Nagy et al. [40], the laparoscopic method was successful in 90% and there was no postoperative morbidity or mortality associated with the surgical technique.

Technique The patient is placed supine on the operating table in 10° of reverse Tredelenberg position with 10° of left lateral tilt. The placement of trocars is similar to that for the standard staging procedure. However, in order to accommodate a linear stapler, the right upper quadrant 10 mm trocar is converted to a 12–15 mm size. Following exploration, the ligament of Treitz is identified and a loop of jejunum approximately 30 cm distal to the ligament of Treitz is brought in an antecolic position to the gallbladder. Using an intracorporeal suturing technique, the jejunum is approximated to

the gallbladder by two 3-0 coated, braided Lactomer™ (Polysorb™, Covidien Ltd., Dublin, Ireland) sutures. The distended gallbladder may be decompressed using a Veress needle attached to a suction device. There is usually minimal biliary spillage owing to the raised intra-abdominal pressure as a consequence of the pneumoperitoneum. Small incisions (10 mm) are made in the gallbladder and jejunum using either scissors or other devices, such as ultrasonic shears. Hemostasis is achieved with electrocautery. Any spillage can be dealt with by a suction device placed through the left upper quadrant port. An endoscopic 30 mm linear stapler using 3.5 mm staples is introduced through the right upper quadrant port, and the "jaws" are manipulated into the gallbladder and jejunum in a standard fashion. Often, this is difficult because of the proximity of the port site to the gallbladder. An articulating stapler facilitates this maneuver. The stapler heads are approximated and the instrument is fired. After removing the stapler, the anastomosis is inspected, hemostasis is confirmed, and the gallbladder interior is aspirated and irrigated with saline. The resulting enterotomy can be closed by using either a completely intracorporeal or laparoscopically assisted approach. Using an intracorporeal technique, the defect is closed with a continuous seromuscular, 3-0 coated, braided Lactomer suture, with knots tied using an intracorporeal technique. An alternative method is to create a completely handsewn anastomosis using the same suture. If a running suture is used, the assistant should maintain tension on the suture with an atraumatic grasping forceps following the placement of each stitch. Knots can be tied using either intracorporeal or extracorporeal techniques.

The technique for fashioning a gastrojejunostomy is similar. In this case, a proximal loop of jejunum is brought in an antecolic position to the stomach. The left upper quadrant 5 mm laparoscopic trocar is converted to a 12 mm trocar. Two 3-0 coated, braided Lactomer sutures are used to approximate the jejunum to the stomach. Enterotomies are made in both the stomach and jejunum. In cases in whom there has been a significant period of gastric obstruction, the gastric wall may be hypertrophied, making creation of the gastrotomy difficult. Confirmation that one is inside the stomach is required before placement of the stapler. When this is achieved, a 30 mm linear stapler is inserted through the 12 mm left upper quadrant port and manipulated into both enterotomies. The instrument is positioned and fired. The stapler is removed and reloaded, returned into the anastomosis, and redeployed. This creates an anastomosis approximately 5 cm in length. The anterior defect can be closed in a fashion similar to the cholecystojejunostomy. Any defects in the anastomosis can be repaired with individual 3-0 sutures.

The ideal palliative procedure for biliary or gastric obstruction should be effective in relieving jaundice or GOO, have minimal morbidity, be associated with a short hospital stay, have a low symptomatic recurrence, and maintain quality of life. Laparoscopic procedures have the potential to achieve these goals, although data do not support prophylactic bypass procedures in patients who do not otherwise require surgery.

Laparoscopic Liver Resection

The Louisville Statement [41] summarizes very well the current world position on laparoscopic liver surgery, addressing issues such as indications, efficacy, safety, patient selection, and certification and training. Evolving mainly in France [42–45], the introduction of laparoscopic liver surgery has been gradual, with rates of laparoscopic resection, even in highly specialized centers, not surpassing 30–50% of all liver resections in most cases [46–48]. The most suitable lesions for laparoscopic resection are less than 5 cm in size and

located in the left lateral section or anterior in the right lobe (i.e., segments II–VI). Although laparoscopic major right and left hepatectomies have been widely reported, it is quite clear that these should only be undertaken in a unit and by a surgeon already familiar with, and expert in, smaller peripheral segmentectomies. While most practitioners have borrowed techniques from open hepatectomy (e.g., the use of laparoscopic ultrasonic aspirator, clips, and ties, and reservation of stapler devices for larger vessels), there is no doubt that the increased availability and reducing costs of specialized laparoscopic instruments allowing for electrosurgical dissection or stapler hepatectomy have aided in the development of this niche practice. Although these instruments may facilitate an easier laparoscopic transection, it is commonly accepted that they are no replacement for the advanced laparoscopic skills that may be required in an emergency, such as laparoscopic suturing and other techniques of laparoscopic hemorrhage control, thus avoiding the need to convert to an open procedure (which may result in a catastrophic hemorrhage from a major vascular structure).

Relative contraindications to laparoscopic liver resection include lesions near the inferior vena cava, hilum, or distal hepatic veins; lesions in segments I, IVa, VII, or VIII; moderate to severe portal hypertension, coagulopathy, or thrombocytopenia; previous upper abdominal operations; and laparoscopic approaches that would require a larger parenchymal resection than an open approach. Absolute contraindications include gallbladder or hilar cholangiocarcinoma and a patient unable to tolerate an open resection or pneumoperitoneum. With respect to oncological outcome, it has been shown that, in appropriately selected patients, outcomes comparable with open surgery are achievable with respect to margin status, disease recurrence, and survival [49–51].

Technique The two most widely practiced laparoscopic liver resections are the left lateral sectionectomy and the resection of lesions lying within segments IVb, V, and/or VI.

For left lateral sectionectomy, the patient should be positioned in the lithothomy position (with slight reverse Trendelenburg positioning depending on the surgeon's preference), both arms tucked in at the sides, with the primary operator standing between the legs. Ports may be triangulated around the initial subumbilical cut-down or, as in our institution, a 5 cm single access port may be placed in the midline, midway between the xiphisternum and umbilicus. While the ergonomics of this latter technique may be cumbersome to begin with, once mastered it provides a very satisfactory access for all instruments, including articulating stapling devices, as well as for specimen extraction. For laparoscopic resection of lesions from segments VI and VII, the ideal position is the left lateral decubitus position, with the surgeon and assistant standing on the left side of the table, on the opposite side to the monitors and scrub nurse. Again, a reverse Trendelenburg position may facilitate dropping the small bowel into the pelvis as well as aiding in maintaining a decreased central venous pressure.

Following careful inspection of the entire peritoneal cavity for any potential contraindications to resection (e.g., carcinomatosis, cirrhosis, and gross portal hypertension depending on the individual patient's circumstance), a complete intraoperative ultrasound of the liver is performed, as described earlier in this chapter. The round ligament may be divided close to the anterior abdominal wall and used as a "retractor" during the assessment and transection phases. If a Pringle maneuver is anticipated, the pars flaccida can be divided following anterior retraction of the left lateral segment, and a tape placed around the hilum and secured.

For any resection, as in the open technique, the transection line is first marked with monopolar diathermy based on the extent of resection required, the intraoperative ultrasound findings, and anatomical landmarks. Both the LigaSure™ (Covidien, Dublin, Ireland) vessel sealing device and the Harmonic® (Ethicon Endo-Surgery Inc., Cincinnati, OH, USA) scalpel have been shown to be effective in laparoscopic liver transection. However, for larger vessels and indeed deeper parenchyma in general, a stapling device is recommended.

As an example, we describe here a standard left lateral sectionectomy. This is the easiest laparoscopic liver resection to perform and begins with mobilizing the left lateral segment following division of the round and falciform ligaments. It is useful to leave the left triangular ligament intact to facilitate retraction until the end. The lesser sac is opened along the length of the liver between the left lateral lobe and the caudate lobe, along with the division of any accessory left hepatic artery at this time. Attention is then turned to parenchymal transection, using initially either the LigaSure or Harmonic scalpel, facilitated by retraction of the round ligament to the right and the specimen-side to the left, until the portal pedicles of segments II and III are seen. These can be divided using a stapling device, which can be used repeatedly up to and including the left hepatic vein. Hemostasis may be additionally secured with bipolar diathermy and/or clips. The left triangular ligament may then be taken down and the specimen removed through a variety of incisions, depending on surgeon preference (including an extended subumbilical port site if using a single port access or Pfannensteil incision), ensuring in all potential malignancies that a bag is used. A drain is not routinely employed for left lateral sectionectomies but may be used for larger resections. Many larger resections may be facilitated by using a laparoscopic cavitron ultrasonic surgical aspirator (CUSA) device.

It is universally accepted that conversion of a laparoscopic liver resection should not be seen as a complication [35]. Apart from anatomical difficulties and adhesions, bleeding is cited as the most common reason for conversion. Experience has shown, however, that efforts to salvage hemorrhage laparoscopically (assuming an adequate skill set) are often preferable to emergency conversion, as this may often take longer and allow for shock to overtake matters in urgent situations. Nevertheless, laparoscopic liver resection in appropriately selected cases is safe, has all the attendant benefits of laparoscopy employed elsewhere (shorter hospital stay, decreased pain scores, and equivalent outcomes), and will continue to evolve with the increasing need for liver surgery into the future.

Conclusion

Laparoscopy has revolutionized management of HPB disease. In diagnosis, laparoscopy together with LUS continues to have benefits over cross-sectional imaging alone in its ability to diagnose peritoneal disease and directly sample material for pathological examination. We continue to see a role for this, even as the resolution of imaging improves and alternative approaches such as endoscopic ultrasound become more widespread.

Laparoscopic cholecystectomy is currently standard of care and most HPB procedures that were previously only performed through an open incision can now be performed laparoscopically. The learning curve associated with laparoscopy is now shorter, given the fundamental importance of laparoscopy in surgical training. Laparoscopic left lateral sectionectomy is standard of care although we await randomized controlled trial data

to support this. Laparoscopic atypical resection for both colorectal liver metastases and hepatocellular carcinoma is commonly performed, particularly for easily accessible lesions. Laparoscopic major hepatectomy is widely reported and it will be interesting to chart its development over the next few years. Robotic approaches to minimally invasive surgery are widespread and we now enter an era in which we will see a melding of laparoscopic and robotic techniques, combined with the delivery of intraoperative imaging and liver function assessment.

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