Laurent Arnaud · Ronald van Vollenhoven

Advanced Handbook of Systemic Lupus Erythematosus

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Author biographies

Laurent Arnaud, MD, PhD, is a Clinical Professor of Medicine at Strasbourg University School of Medicine, Strasbourg, France, and consultant in the French National Reference Center for Rare Systemic Autoimmune Diseases located in Strasbourg. He received his MD and PhD degrees from Assistance Publique - Hôpitaux de Paris and Université Pierre et Marie Curie, Paris, France, and completed a fellowship program with a specialization in auto-immune diseases, mainly systemic lupus erythematosus, at Hôpital Pitié-Salpêtrière in Paris. He then pursued clinical research in the team of Ronald van Vollenhoven at the Karolinska Institutet, Stockholm, Sweden before moving back to France to take his current position. His main research interests focus around the development and systematic evaluation of biological and immunomodulatory treatments for systemic diseases, with a special focus on systemic lupus erythematosus and the antiphospholid syndrome. With his team, he has also contributed to several research projects in the field of other rare diseases such as for Takayasu's arteritis, relapsing polychondritis, Erdheim-Chester disease and the systemic capillary leak syndrome.

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Ronald F van Vollenhoven, MD, PhD, is the Director of the Amsterdam Rheumatology and Immunology Center ARC and Chief of the Department of Rheumatology and Clinical Immunology at the AMC and of the Department of Rheumatology at VUMC in Amsterdam, the Netherlands.

He received his MD and PhD degrees from the University of Leiden in The Netherlands. After graduating in 1984 he pursued immunology research at Cornell Medical College in New York, followed by residency (specialty training) in Internal Medicine at the State University of New York at Stony Brook, and a fellowship in Rheumatology at Stanford University in Palo Alto following which he received American Board of Internal Medicine certification in both Internal Medicine and Rheumatology.

From 1993 to 1998 Dr. Van Vollenhoven held a faculty appointment as Assistant Professor of Medicine in the Division of Immunology and Rheumatology at Stanford University, and from 1995 he was the Medical Services Chief and Fellowship Director in that division.

In 1998 Dr. Van Vollenhoven moved to Stockholm, Sweden, where he worked as a Senior Physician and Chief of the Clinical Trials Unit in the Department of Rheumatology at the Karolinska University Hospital and Associate Professor of Rheumatology; and in 2010, he was appointed as Professor and Chief of the Unit for Clinical Therapy Research, Inflammatory Diseases (ClinTRID) at the Karolinska Institute.

On January 1st, 2016 Ronald van Vollenhoven assumed his new position as Director of the Amsterdam Rheumatology and Immunology Center ARC, Professor of Rheumatology at the University of Amsterdam and the VU University, and as Chief of Rheumatology at both the AMC and VUMC hospitals in Amsterdam, The Netherlands. He is also chair of the rheumatology research council at Reade, and maintains part of his responsibilities at the Karolinska Institute.

Dr. Van Vollenhoven's research interests focus around the development and systematic evaluation of biological and immunomodulatory treatments for the rheumatic diseases. With his co-workers, he has established the Stockholm registry for biological therapies (the STURE database) for this purpose, which has supported research projects relating to clinical efficacy, pharmacology, outcomes and pharmacoeconomics. He has been principal investigator in many clinical trials of novel therapies in

rheumatic diseases and has contributed to a number of important investigator-initiated trials including the recently published SWEFOT trial. He has published over 300 original papers (H-index: 61), book chapters and reviews, and is editor of the textbook *Clinical Therapy Research in the Inflammatory Diseases* (World Scientific Press, 2015), author of the monograph *Biologic for the Treatment of Rheumatoid Arthritis* (Springer International Publishing, 2015), and associate-editor of *Dubois' Lupus Erythematosus* (Elsevier, 2014). In 2004, Dr. Van Vollenhoven was awarded the Scandinavian Research Foundation Prize for excellence in clinical research in rheumatology, and he is an honorary member of several rheumatological societies. He is the Editor-in-Chief of *Lupus Science & Medicine*, Chair of the EULAR Standing Committee on Clinical Affairs, member of many editorial boards, past-chair of the Swedish Rheumatology Society Professors' Council, co-founder of the IRBIS registry for biologics in SLE, the CERERRA registries collaboration, and the NORD-STAR collaboration for Nordic trials in the rheumatic diseases, and the initiator of the Treat-to-Target-in-SLE initiative. Prof Van Vollenhoven is married and has two children aged 22 and 18. Outside his professional life he is an avid classical pianist.

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Abbreviations

ACE	Angiotensin-converting enzyme
ACLE	Acute cutaneous lupus erythematosus
ACP5	Acid phosphatase 5
ACPA	Anti-citrullinated peptide antibodies
ACR	American College of Rheumatology
AIHA	Autoimmune haemolytic anaemia
ANA	Antinuclear antibodies
AOSD	Adult onset Still's disease
APC	Antigen-presenting cell
APRIL	A proliferation inducing ligand
aPL	Antiphospholipid antibodies
BAFF	B-cell activating factor
BCMA	B-cell maturation antigen
BCR	B-cell receptor
BILAG	British Isles Lupus Assessment Group index
BLyS	B lymphocyte stimulator
BSLE	Bullous systemic lupus erythematosus
CBC	Complete blood count
CCLE	Chronic cutaneous lupus erythematosus
CHLE	Chilblain-like lupus erythematosus
CK	Creatine phosphokinase
CLASI	Cutaneous Lupus Erythematosus Disease Area and Severity Index
CLE	Cutaneous lupus erythematosus
CLIFT	Crithidia luciliae immunofluorescence test
CMV	Cytomegalovirus
CNS	Central nervous system
CRP	C-reactive protein
CT	Computed tomography
CVRF	Cardiovascular risk factors
CVE	Cardiovascular events
CyX	Cyclophosphamide
DHEA	Dehydroepiandrosterone

DHEAS	Dehydroepiandrosterone sulfate
DIL	Drug-induced lupus erythematosus
DLE	Discoid lupus erythematosus
DM	Dermatomyositis
DNASE1	Deoxyribonuclease I
DNASE1L3	Deoxyribonuclease I-like 3
dsDNA	Double-stranded DNA
EBV	Epstein-Barr virus
ECLAM	European Consensus Lupus Assessment Measure
EEG	Electroencephalogram
ELISA	Enzyme-linked immunosorbent assay
EMA	European Medicines Agency
ESR	Erythrocyte sedimentation rate
ESRD	End-stage renal disease
EULAR	European League Against Rheumatism
FACIT	Functional Assessment Chronic Illness Therapy
FcR	Fc receptor
FDA	Food and Drug Adminstration
FSS	Fatigue Severity Scale
GWAS	Genome-wide association studies
HAQ-DI	Health assessment questionnaire disability index
HCQ	Hydroxychloroquine
Hep2	Human epithelial tissue
HHV	Human herpes virus
HLA	Human leukocyte antigen
HR-QOL	Health-related quality of life
IFN	Interferon
IgG/M	Immunoglobulin G/M
IIM	Idiopathic inflammatory myopathy
IL	Interleukin
IRBIS	International registry for biologics in SLE
IRF	Interferon regulatory factor
ITP	Idiopathic thrombocytopenic purpura
JAK	Janus kinase
JIA	Juvenile idiopathic arthritis

LAI	Lupus Activity Index
LEP	Lupus erythematosus profundus
LLDAS	Lupus low disease activity state
LN	Lupus nephritis
MAS	Macrophage activation syndrome
MCTD	Mixed connective tissue disease
MCPs	Metacarpophalangeal joints
MMF	Mycophenolate mofetyl
MRI	Magnetic resonance imaging
MS	Multiple sclerosis
NET	Neutrophil extracellular traps
NK	Natural killer
NPSLE	Neuropsychiatric systemic lupus erythematosus
NSAIDs	Non-steroidal anti-inflammatory drugs
pDC	Plasmacytoid dendritic cells
PIPs	Proximal interphalangeal joints
PKCδ	Protein kinase C delta
PRO	Patient-reported outcome
RA	Rheumatoid arthritis
RIFLE	Response Index For Lupus Erythematosus
RNP	Ribonucleoprotein
RPR	Rapid plasma reagin
SAMHD1	Sterile alpha motif domain and HD domain-containing protein 1
SCLE	Subacute cutaneous lupus erythematosus
SCORE	Systematic COronary Risk Evaluation
SELENA	Safety of Estrogens in Lupus Erythematosus National Assessment
SLAM	Systemic Lupus Activity Measure
SLE	Systemic lupus erythematosus
SLEDAI	Systemic Lupus Erythematosus Disease Activity Index
SLICC	Systemic Lupus International Collaborative Clinics
snRNP	Small nuclear ribonucleoprotein
SPECT	Myocardial perfusion imaging
SPENCD	Spondyloenchondrodysplasia

STING	Stimulator of IFN genes
TACI	Transmembrane activator and calcium-modulator and cyclophilin ligand interactor
TCR	T-cell receptor
TEN	Toxic epidermal necrolysis
TGF	Transforming growth factor
Th17	T helper 17 cell
TIA	Transient ischemic attack
TLR	Toll-like receptor
TNF	Tumor necrosis factor
TRAP	Tartrate-resistant acid phosphatase 5
Treg	Regulatory T cell.
TREX1	Three prime repair exonuclease 1
TTP	Thrombotic thrombocytopenic purpura
UCTD	Undifferentiated connective tissue disease
UV	Ultraviolet
VAS	Visual analog scale
WHO	World Health Organization

Chapter 1

Introduction

1.1 Disease overview

Systemic lupus erythematosus (SLE), the "disease with a thousand faces" [1], is an autoimmune disease characterized by the production of autoantibodies to nuclear antigens in association with a broad spectrum of clinical manifestations. SLE has an estimated prevalence of about 10–150 per 100,000 persons and a female:male ratio of around 9:1 (see section 1.6) [2]. The peak incidence is between the ages of 15 and 40, and SLE is therefore considered to be one of the most common autoimmune diseases of women of childbearing age. However, SLE can affect all age groups, from infants to geriatric patients (see Chapter 7). The exact etiology and pathogenesis of SLE remain unknown, but involves complex multifactorial interactions between genetic, epigenetic, hormonal and environmental factors (Figure 1.1) that eventually result in a loss of self-tolerance. The disease can affect almost any tissue or organ system (see Chapter 3), and has a variable course and severity that can range from mild to potentially fatal. A broad spectrum of autoantibodies can be found in SLE patients, and are often associated with specific clinical features. Antinuclear antibodies (ANA) are found in 98% of patients, but are non-specific. Conversely, antibodies to double-stranded DNA (dsDNA), anti-Sm, or anti-nucleosome are highly specific (see section 4.2). Three main patterns of disease activity have been identified, including a remitting-relapsing disease course characterized by flares and periods of remission, chronically active disease, and long quiescence [3]. Organ damage, which can occur in relation with disease activity or even in

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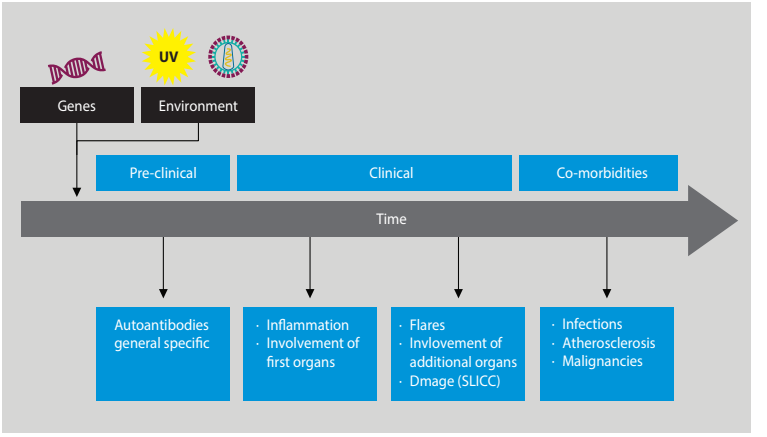

Figure 1.1 Natural history of systemic lupus erythematosus. SLICC, Systemic Lupus International Collaborating Clinics/American College of Rheumatology damage index. Reproduced with permission from © BMJ Publishing Group Ltd & European League Against Rheumatism, 2010. All rights reserved. Bertsias et al [6].

patients without obvious symptoms, is the main predictor of morbidity and mortality. There has been a significant reduction in mortality of SLE patients over the last decades, with many studies reporting 5-year survival rates exceeding 95%. While infections and cardiovascular morbidity are the main causes of death, SLE itself can still cause death today (see Chapter 7).

SLE is more than ever an active area of research and of therapeutic innovation. The identification of several genes involved in the rare monogenic forms of SLE has considerably impacted our knowledge of the pathogenesis of the disease. Further advances have allowed identification of new pathways and expanded the list of potential therapeutic targets. A new treatment for SLE has been approved for the first time in five decades [4], and more than 40 candidate molecules are undergoing preclinical or clinical studies.

However, many pitfalls remain. Measuring disease activity is challenging [5] because current scores either do not capture fully the broad spectrum of disease manifestations, or are too complicated to be used in routine clinical practice. There is still no consensus on the definitions of low disease activity or remission, although recent progress has been

made in these areas [5]. We also need to define better response criteria and relevant end-points, and assess the long-term efficacy of these definitions [7]. Despite significant improvements in the overall prognosis of the disease over the past decades, the burden due to renal damage, infections, and cardiovascular diseases remains unacceptably high [8]. A significant proportion of patients do not respond to treatment with the standard of care [9], particularly those with lupus nephritis but alternative agents available for therapy switching are limited [10]. A consensual definition for refractory lupus nephritis remains to be derived [11]. Further, patients with severe organ manifestations have generally been excluded from the recent trials, and the optimal therapeutic strategies in these patients therefore remain largely unknown, especially in the long-term. An estimated 10–15% of patients with lupus nephritis still progress to end-stage renal disease requiring dialysis and/or renal transplantation, and we are truly lacking drugs that may prevent or eventually reverse fibrosis [12]. Infections are among the most common complications of SLE, and remain one of the first causes of morbidity [13] and mortality [14,15] during the course of the disease. However, current immunization schemes may be insufficient to reach proper immunization [16]. We still need to identify effective pharmacological strategies for the prevention of cardiovascular manifestations, as none of the trials of statins in SLE have met their primary end-points [17]. Pregnancy remains a challenge for SLE patients and their physicians, and the prevention of neonatal lupus is still limited in at-risk patients [18]. Also, we aim at controlling disease activity without toxicity, and have to develop effective steroid-sparing strategies. In the regard, the results of the observational single-center cohort study conducted by Condon and Lightstone [19] are promising. Original treatment strategies, such as preventive treatment or sequential treatment combinations (for instance rituximab followed by belimumab) remain to be assessed [20]. Several studies suggest that treatment response in SLE depends on age, gender, and ethnicity as well as genetic and pharmacokinetic factors [11,21]. The treatment of SLE should therefore slowly evolve from standardized therapy to an individualized therapeutic approach based on individual patients characteristic [11]. Enzymatic phenotyping and metabolite monitoring is increasingly

used; however, we do lack integrative tools that would allow reliable identification of patients with poor long term prognosis and of the most adequate therapeutic strategy at the patient level.

1.2 Epidemiology

There are marked worldwide disparities in the epidemiology of SLE, that are partly due to the heterogeneous definitions and methods used to ascertain cases [22]. The best information on the incidence and prevalence of the disease are originating from Europe, North America, and Asia, with less data available from South America and Africa. SLE is primarily a disease of women of childbearing age, with a typical incidence between 15 and 40 years old [23]. However, the disease can occur at any age (see Chapter 7 for pediatric and late-onset SLE). Due to the role of genetic background (see section 1.4), familial aggregation is observed in about 10% of cases [24], and association with other autoimmune diseases is commonly reported [25]. Mortality in patients with SLE has improved over the past decades but remains considerably higher than in the general population (see section 8.7).

1.2.1 Incidence

The incidence rates of SLE show considerable variation depending on the racial and ethnic background of the population studied. The global incidence of SLE ranges approximately from 1 to 15 per 100,000 person per year [26], with peaks in females aged 30–39 and in males aged 50–59 years [2]. The reported incidence of the disease varies from 0.7 to 7.4 per 100,000 per year in North America [27], 2.2 to 5.0 in Europe [27], and 0.9 to 3.1 in the Asia-Pacific region [28]. Data for south-America [29,30] and Africa are scarce. The commonly belief that SLE is rare in Africa mostly reflects the lack of good quality data [31], and is unsupported by studies of recent migrants [32]. In the UK, the incidence is approximately twofold higher in Blacks, Hispanic, and Asian patients compared with Caucasians [33], and has been reported to be higher in the urban area compared to the rural population [34].

1.2.2 Prevalence

The prevalence rates of SLE range approximately from 15 to 150 per 100,000 [26,33]. These figures have increased during the last decades [33], although this might be due to the better recognition of cases. The prevalence of the disease appears to vary broadly from one continent to another, ranging from 20.6 to 150.0 per 100,000 in North America, 16.2 to 97.0 in Europe [28], and 4.3 to 45.3 in the Asia-Pacific region [28]. In most cohort studies [26], the F/M sex ratio is ≈9:1 (ranges reported: 6:1 to 15:1) but female predominance is less marked in children (≈3:1), especially before puberty [2], as well as in late-onset SLE (see Chapter 7) [35]. The maximum prevalence is observed in patients of 45 to 65 years of age [2,27]. Key messages on the epidemiology of SLE are below (Table 1.1).

Key messages on the epidemiology of systemic lupus erythematosus (SLE)
SLE has been reported on all continents Familial aggregation of SLE cases is observed in ≈ 10% of cases Associations with other autoimmune diseases is frequent
Incidence • Global SLE incidence ranges from ≈ 1 to 15 per 100,000 person per year • Incidence in Europe: ≈ 2.2 to 5.0 per 100,000 per year • Incidence in North America: ≈ 0.7 to 7.4 per 100,000 per year • Incidence in the Asia-Pacific region: ≈ 0.9 to 3.1 • The maximum incidence is observed in females aged 30–39 years and in males aged 50–59 years of age • Incidence of SLE is higher in Blacks, Hispanic and Asian patients compared with Caucasians
Prevalence • Prevalence ranges from ≈15 to 150 per 100,000 • In North America: 20.6 to 150.0 per 100,000 • In Europe: 16.2 to 97.0 per 100,000 • In the Asia-Pacific region: 4.3 to 45.3 per 100,000 • Maximum prevalence is observed in patients of 45 to 65 years of age • In most studies, the female-to-male ratio in women of childbearing age is ≈ 9:1

Table 1.1 Keys messages on the epidemiology of systemic lupus erythematosus.

1.3 Etiology and pathogenesis

The exact etiology and pathogenesis of SLE remain unknown, but has been shown to result from complex multifactorial interactions between genetic, hormonal and environmental factors that eventually result in the loss of self-tolerance (Figure 1.2) [36]. This chapter focuses on the role of the immune system in the pathogenesis of the disease.

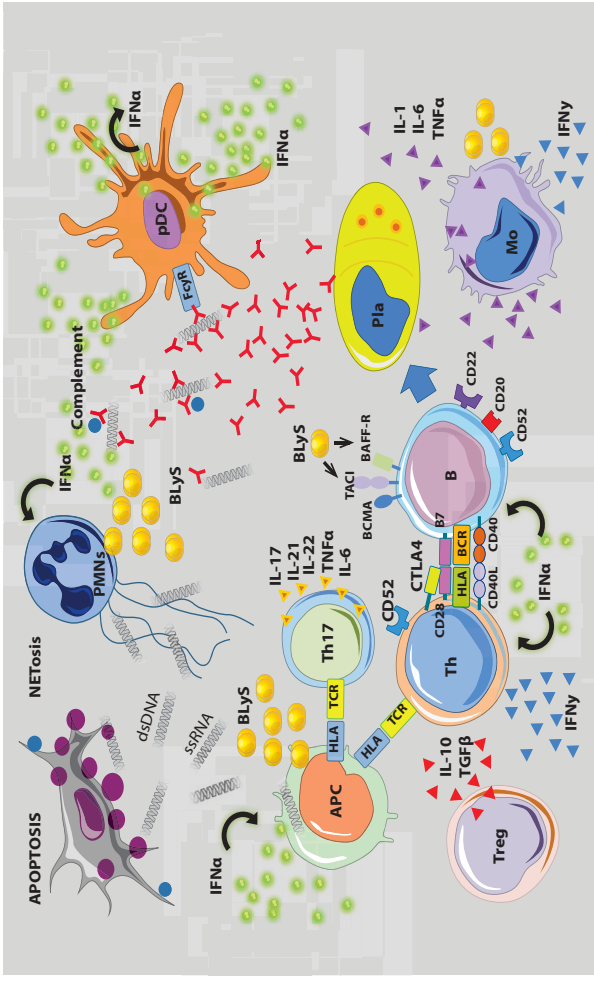

Figure 1.2 Pathogenesis of systemic lupus erythematosus. APC, antigen-presenting cell; BAFF, B-cell activating factor; BCMA, B-cell maturation antigen; BCR, B-cell receptor; BLyS, B lymphocyte stimulator; HLA, human leukocyte antigen; IFN, Interferon; IL, Interleukin; NET, neutrophil extracellular traps; TACI, Transmembrane activator and calcium-modulator and cyclophilin ligand interactor; TCR, T-cell receptor; TGF, transforming growth factor; Th17, T helper 17 cell; TNF, tumor necrosis factor; Treg, regulatory T cell. Elements of this illustration were provided by Servier Medical Art by Servier (http://smart.servier.com/), licensed under a Creative Commons Attribution 3.0 Unported Licence.

The key nuclear self-antigens recognized by the immune system in SLE are released in relation to alterations of cell death pathways, including apoptosis [37] as well as through the neutrophil specific death releasing neutrophil extracellular traps (NETosis) [38], and accumulate due to impaired clearance of necrotic cell-derived material [39]. These self-antigens are presented through restricted human leukocyte antigen (HLA) haplotypes [40] by follicular dendritic cells [41] to autoreactive B cells in germinal centers of secondary lymphoid organs, and activate the differentiation and clonal expansion of CD4+ autoreactive T cells. Activated T helper cells release interferon (IFN)-gamma, and subsequently mature dendritic cells release pro-inflammatory cytokines such as interleukin 1 (IL-1) and tumor necrosis factor (TNF), and activate B cells [42]. The survival of these B cells is promoted by B lymphocyte stimulator (BLyS) [43] produced by neutrophils and monocyte/macrophages as well as by IL-17 producing T-cells [44], and those differentiate into autoantibody-producing plasma cells. CD8+ cytotoxic T cells [45], natural killer (NK) cells [46], and CD4+CD25hiFoxp3+ regulatory T cells [47] fail to regulate these processes efficiently, and contribute to the pathogenesis of the disease.

With immune pressure, the immune response eventually switches, via somatic hypermutation and affinity maturation, from low-affinity immunoglobulin M (IgM) to highly specific high-affinity IgG auto-antibodies directed toward more limited epitopes of the self-antigens [48]. One key-step in the pathogenesis of SLE is that immune complexes containing nuclear self-antigens deposit or form in situ in the tissues, activate complement, and eventually cause tissue damage [49].

Immune complexes containing nuclear self-antigens play a critical role by contributing directly to the activation of innate immune cells, such as plasmacytoid dendritic cells (pDC), via Fc receptor (FcR)-mediated uptake [50]. Following intra-cellular trafficking, nuclear antigens, possibly in conjunction or after pDC priming by infectious triggers [45,51], activate Toll-like receptors (TLRs), particularly TLR-7 and TLR-9, which are able to recognize nuclear materials. The pDC subsequently undergo increased expression of interferon RNA transcripts, that contribute to 'the interferon signature' [52], and release type 1 IFNs that are major boosters of the immune system [41] through an amplification loop of immune responses.

1.4 Genetic susceptibility

SLE has a significant genetic component, as originally suggested by the higher concordance of the disease among monozygotic twin pairs (14–57%) compared with dizygotic twins (3–5%) [53]. Also, studies of familial aggregation show that relatives of SLE patients have a ≈10% risk for the disease [24,54].

Linkage studies, later followed by the candidate-gene approach, and now by genome-wide association studies (GWAS) and whole exome-sequencing, have progressively unveiled the genetic basis of the disease. Up to now, more than 120 genes have been associated with the susceptibility to SLE (Table 1.2). The majority of SLE cases (>99%) involve a complex pattern of inheritance, in which several genes conferring a low-to-moderate magnitude of risk concur to determine the actual disease risk of a given individual (polygenic SLE) [55]. The proteins encoded by these SLE-associated genes contribute to the pathogenesis of SLE through a multiplicity of mechanisms [55], and many of these [56], have been associated with other auto-immune diseases [57]. Conversely, rare monogenic mutations cause SLE or lupus-like phenotypes inherited in a Mendelian pattern [58], but these account for only a small fraction of SLE cases (monogenic SLE).

1.4.1 Human leukocyte antigens

Historically, associations with the HLA have been identified among the strongest genetic risk factors for SLE. This association has been consistently confirmed in the GWAS performed to date. However, the relationship between HLA and SLE is complex, with different alleles and haplotypes at risk that have been reported across different ethnicities, clinical and laboratory profiles [59]. In addition, other genes located within the HLA region, such as the TNF-related genes and the complement system proteins, are also strongly associated with SLE.

1.4.2 Complement deficiencies

The complement pathways play a pivotal role in the pathogenesis of SLE (see Figure 1.3). Homozygous and/or heterozygous deficiencies of the classical complement pathway (C1q, C1r, C1s, C4A, C4B, and C2)

are associated with an increased susceptibility to SLE. The homozygous deficiency of C2 is the most frequently occurring complete complement

ABHD6-PXK*	FAM107A	LPP	SH2B3
ADAMTSL1	FAM98B	LRRC18	SLC12A1
AFF1	FCGR	LRRC18-WDFY4*	SLC15A4
ARID5B	FCGR2B	LRRC34	SLC22A12
ATG16L2	FCHSD2	LYN	SLC22A4
BACH2	FCRL5	MECP2	SLU7
BANK1	GLDC	MED1	SMG7-NCF2*
BC040734	HIC2	MIR146A	SNRPC
BIN1	HIC2-UBE2L3*	MTG1	SNRPC-UHRF1BP1*
BLK	HIP1	MYNN	SPATA8
CADM2	HLA	NA	SPRED2
CAPSL	IFIH1	NCF2	STAT4
CCL22	IKZF1	OLIG3-TNFAIP3*	STXBP6
CD44	IKZF2	PCNXL3	TCF7-SKP1*
CD80	IKZF3	PDHX-CD44*	TET3
CDKN1B	IL10	PHRF1	TLR7-like-TLR8*
CFHR1	IL12A	PLD2	TMEM39A-CD80*
CIITA-SOCS1*	IL23R	PRDM1	TNFAIP3
CLEC16A	IL2RA	PRDM1-ATG5*	TNFSF4
CNTN6	IL4	PRKCB	TNIP1
CREBL2	IL7R	PRPS2	TNPO3
CREBL2-CDKN1B*	IRAK1	PRR14	TRAF1-C5*
CSK	IRAK1-MECP2*	PTPN2	TYK2
CSMD1	IRF5	PTPN22	TYRO3
CXorf21	IRF5-TNP03*	PTPRC	UBAC2
DDX6	IRF7	PTTG1	UBE2E3
DDX6-CXCR5*	IRF8	PXK	UBE2L3
DHCR7-NADSYN1*	ITGAM	RABGAP1L	UHRF1BP1
DRAM1	JAZF1	RAD51B	USMG5
EDEM3	KCNJ3	RASGRP3	WDFY4
EHF	KDM4C	RASSF2	XKR6-FAM167A*
ELF1	KIAA1542	RGS1	ZPBP2
ETS1	LBH	RNF114	
ETS1-FLI1*	LOC100506023	SEC61G	

Table 1.2 List of genes associated with systemic lupus erythematosus (SLE) in genome-wide association studies. *Polymorphism associated with SLE located in the intergenic region. Data from [63–76].

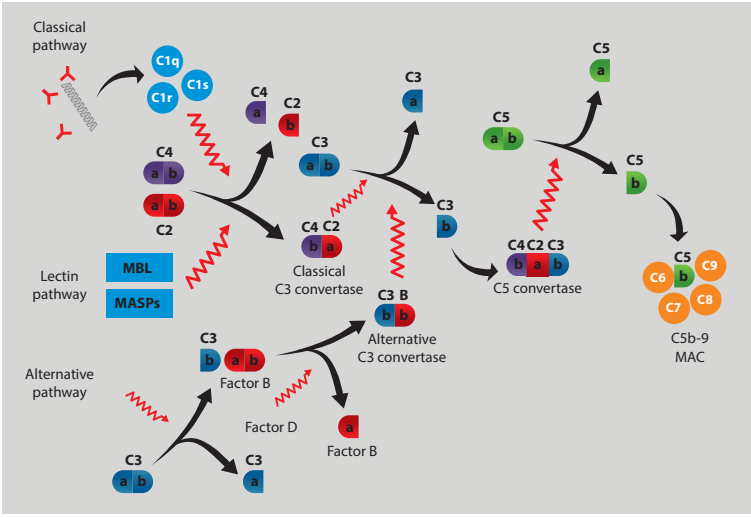

Figure 1.3 Schematic view of the complement pathways. The classical pathway is activated by dsDNA-containing immune complexes. The lectin and the alternative pathways are activated by the surfaces of pathogens.

deficiency in humans, with a prevalence of ≈1 in 20,000 Caucasian patients, and is associated with SLE in 10–30% of cases [60]. Heterozygous C2 deficiency is observed in ≈1% of Caucasian individuals, and in 2.5–5.8% of SLE patients [61,62]. The genetics of C4 is more complex as there are two protein isotypes (C4A and C4B) characterized by a strong inter-individual variations of the copy-number (from 0 to 5 for C4A, and 0 to 4 for C4B) and gene-size (long and short) [77]. The risk of SLE increases among subjects with only two copies of total C4 and decreases in those with more than five copies [77,78]. Homozygous C4 deficiency has been reported in ≈30 cases, in which SLE occur in most patients [60]. About 75 cases of homozygous C1q deficiency have been reported [79], with more than 90% of these patients having SLE or lupus-like syndrome. Deficiencies of C1r and C1s are usually concomitant (≈20 cases reported), and are associated with SLE in 65% of cases [80]. Finally, deficits in complement regulation proteins or in component of non-classical pathways may also increase the risk for SLE [81,82].

1.4.3 Monogenic systemic lupus erythematosus and interferonopathies

Type I IFNs are key regulators of the immune system, as these enhance dendritic cell maturation, T helper cell activation and IFNγ production, B cell Ig class switching, IFNγ production by NK cells, and increase production of BLyS by monocytes. Mutations in the interferon pathways, such as of TLR-7, TLR-9 [83], or of interferon regulatory factors (IRFs; IRF-5, IRF-7 and IRF-8), the transcription factors downstream of TLRs, contribute significantly to the risk to develop SLE [84,85] (see Figure 1.4). Various mutations in TREX1, a DNA-degrading exonuclease [86], result in high levels of IFN-α and have been associated with Aicardi-Goutieres syndrome, a neurological condition characterized by lupus-like

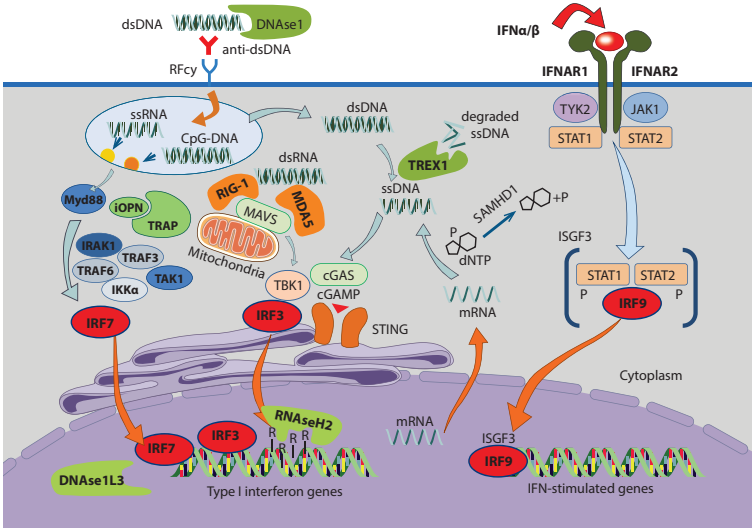

Figure 1.4 Defects in the three prime repair exonuclease 1 (TREX1), the major 3'->5' DNA exonuclease, as well as in the endonucleases DNase (deoxyribonuclease) 1 and DNAse1L3 result in the accumulation of excess nuclear material that triggers interferon production. Tartrate-resistant acid phosphatase 5 (TRAP) is responsible for dephosphorylating osteopontin (OPN). The latter is believed to activate the Myd88 pathway and lead to increased IFN-related genes production. Gain-of-function mutations in IFIH1, which encodes the cytosolic double-stranded RNA sensor MDA5 results in spondyloenchondrodysplasia, a skeletal dysplasia associated with SLE-like manifestations. Mutations in the deoxynucleoside triphosphate triphosphohydrolase SAMHD1 causes deoxyribonucleoside triphosphates (dNTPs) imbalances leading to an impairment of genome stability that triggers interferon production. IFN, interferon; IRF, Interferon regulatory factor; JAK, Janus kinase; SLE, systemic lupus erythematosus. Elements of this illustration were provided by Servier Medical Art by Servier (http://smart.servier.com/), licensed under a Creative Commons Attribution 3.0 Unported Licence.

manifestations, and with familial chilblain lupus. TREX1 mutations have also been found in 0.5–2% of SLE cases [87,88], in which they have been recognized as the most common form of monogenic lupus. Similarly, individuals carrying rare variants of the RNASEH2, a major endoribonuclease involved in the clearance of ribonucleotides, have an increased risk for SLE [89]. Gain-of-function mutations in stimulator of IFN genes (STING) that activate induction of IFN-β have also been associated with a SLE-like phenotype [90]. Mutations in the tartrate-resistant acid phosphatase 5 (ACP5) cause spondyloenchondrodysplasia (SPENCD), a skeletal dysplasia associated with upregulated expression of IFN-stimulated genes and SLE-like manifestations [91]. Mutations of deoxyribonuclease I (DNASE1) [92,93], deoxyribonuclease I-like 3 (DNASE1L3) [94], and sterile alpha motif domain and HD domain-containing protein 1 (SAMHD1) [95] have been also been associated with SLE-like manifestations and raised level of interferons (Figure 1.4). Finally, the recently described mutations in PRKCD [96,97], which encodes the protein kinase C delta (PKCδ), further expand the list of monogenic SLE. Key messages on the genetics of SLE are below (Table 1.3).

Key messages on the genetics of systemic lupus erythematosus (SLE)
Indirect evidence for a genetic background in SLE
• Disease concordance among monozygotic twins is high (14–57%)
• Familial aggregation is observed in ≈10% of SLE cases
Direct evidence for a genetic background in SLE
• Candidate gene, GWAS and exome-wide sequencing have identified ≥ 80 genes associated with SLE
Polygenic SLE
• Familial SLE as well as early-onset juvenile SLE studies have enabled the identification of monogenic causes of SLE
• Identification of these rare inherited conditions is of great interest to our understanding of SLE pathogenesis
• Complement deficiencies, genetic overproduction of interferon-type 1 (interferonopathies) and apoptosis defects are the main situations that can lead to monogenic SLE

Table 1.3 Keys messages on the genetics of systemic lupus erythematosus.

1.5 Environmental factors

SLE onset is generally believed to be triggered by environmental factors interacting with a susceptible genetic background. Certain environmental factors such as ultraviolets (UV), tobacco, silica, solvents and infections have been linked to the development of lupus, but none of these factors have been identified as direct causes of the disease (Figure 1.5). Drug-induced SLE is described later in this chapter.

1.5.1 UV light

The risk of flare in SLE patients and murine models of SLE exposed to UVs is well documented [98]. Some reports suggest that disease activity is increased during the spring and summer [99,100]. However, the relationship between sun exposure and risk of incident SLE remains controversial [98]. A study [101] has reported a twofold increase in the risk of SLE with outdoor work ≥20h per week for at least 2 months in the year preceding the diagnosis. Conversely, another study [102] found no significant association between the risk of SLE and ≥24 months of outdoor sun exposure.

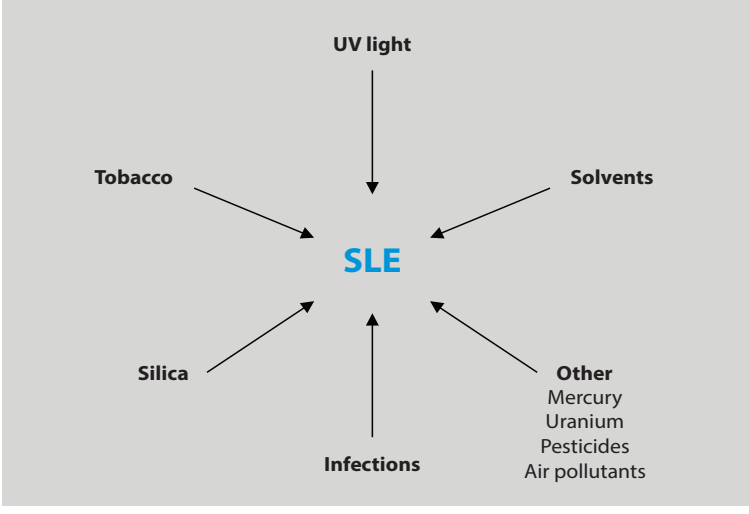

Figure 1.5 Environmental triggers for systemic lupus erythematosus.

1.5.2 Tobacco

Smoking has been associated with an increased risk of incident SLE [103], higher disease severity [104], more frequent anti-dsDNA antibody positivity [105], and decreased response to antimalarials [104]. Passive early-life exposure to cigarette smoke has not be found to be associated with an increased risk of adult-onset SLE [106]. In contrast, low and moderate alcohol consumption has been reported to have a protective effect on the risk of SLE [103].

1.5.3 Silica

Exposure to crystalline silica dust is a widespread occupational hazard, particularly in construction, mining, and ceramic, stone, or tile works [107]. Occupational [101,108–110] exposures to silica, especially if prolonged [109], have been associated with an increased risk of SLE. The risk of SLE has been reported to be increased (although non-significantly) in patients with silicosis [111].

1.5.4 Solvents

Solvents are widely used in both residential and industrial settings, as cleaners and in paints, varnishes, and perfumes [109,110]. Relatively strong associations (ORs: 3 to 10) have been reported between the use of paints, dyes or works such as developing film or nail application and SLE [101]. However, the two studies that assessed these relationships with the most robust methodology found no significant association [109,112].

1.5.5 Infections

Infections may act as environmental triggers for SLE, possibly through molecular mimicry, or because the innate immune responses elicited by viral RNA or DNA may share pathogenic pathways with those elicited by nuclear auto-antigens [45,51]. The viruses that have been suggested to be linked to the pathogenesis of SLE include: Epstein-Barr virus (EBV), cytomegalovirus (CMV), parvovirus B19, and human herpes virus (HHV)-6, -7, and -8. Several studies have reported more frequent seropositivity or viremia in SLE patients compared with controls [114]. However, this

may only reflect functional impairment of immune responses towards viral antigens [45], and is not sufficient to infer causality between viral infection and the risk of incident SLE. A large study of Danish patients [114] has reported no association between Paul-Bunnell heterophile antibody test or hospitalization for infectious mononucleosis and the risk of incident SLE.

1.5.6 Other exposures

SLE has been associated with many other exposures, including uranium [115], mercury [112], pesticides [109,110,112], and air pollutants [116]. Key messages on environmental factors in SLE are below (Table 1.4).

Key messages on the environmental factors in systemic lupus erythematosus (SLE)
General messages • SLE is generally believed to be triggered by environmental factors interacting with a susceptible genetic background • Many environmental factors have been associated with the risk of incident SLE, but causality remains speculative
Reported associations • **Sun (UV light):** the increased risk of flare (especially cutaneous and articular) is well documented but the association with incident SLE remains unclear • **Tobacco:** Smoking has been associated with an increased risk of incident SLE, higher disease severity, higher anti-dsDNA antibody positivity, and decreased response to antimalarials. • **Silica:** Occupational exposures to silica, especially if prolonged, have been associated with an increased risk of SLE • **Solvents:** association with SLE is reported in some studies, but not in those with the best methodological quality • **Other:** SLE has been associated with exposure to uranium, mercury, pesticides, and air pollutants
Association between SLE and infections • Molecular mimicry and activation of innate immunity pathways by viral RNA or DNA may provide a link between infections and SLE • Viruses that have been associated with SLE include EBV, CMV, parvovirus B19, HHV-6, -7, -8

Table 1.4 Keys messages on environmental factors in systemic lupus erythematosus. CMV, cytomegalovirus; EBV, Epstein-Barr virus.

1.6 Hormonal factors

Indirect evidence for the role of sex hormones in SLE arise from the predominance of the disease in women [117], the increased risk of flares (≈25–30%) during pregnancy [118,119], and the decreased incidence of the disease after menopause [2]. In a Swedish study linking multiple national registers, the prevalence of SLE among females ranged from 79–144 per 100,000 versus 12–25 per 100,000 in men [117]. Also, the female-to-male ratio is lower in children than in adults, especially before puberty [2].

Sex hormones such as 17β-estradiol (estradiol), testosterone, progesterone, prolactin, and dehydroepiandrosterone (DHEA) can modulate the incidence and severity of SLE [120]. A meta-analysis of serum concentrations of sex hormones has shown that estradiol was found at significantly higher levels in adult SLE patients compared to controls [120]. In a prospective cohort of ≈238,000 women, the early age at menarche, use of estradiol-containing oral contraceptives, and postmenopausal hormone replacement therapy were associated with an increased risk of incident SLE. Conversely, a randomized trial suggested that estrogen-containing oral contraceptives did not increase the risk of flare among women with stable SLE (Table 1.5) [121]. Some data support the support the notion of a gene-dose effect from the X chromosome in SLE. Trisomy X (47, XXX) [122] and Klinefelter's syndrome (47, XXY) [108] have been associated with an increased risk of prevalent SLE. Conversely, the association between Turner syndrome (45, XO) and SLE is very uncommon [123]. Keys messages on hormonal factors in systemic lupus erythematosus are below (Table 1.6).

Hormone	Women	Men
DHEA/DHEAS ↓	↓	Probably ↓
Progesterone ↓	↓	Unknown
Testosterone ↓	↓	Normal
Estradiol (stimulates) ↓	↓	Normal
Prolactin	↑	↑

Table 1.5 Sex hormone changes in systemic lupus erythematosus patients. *Compared with healthy controls. DHEA/DHEAS, dehydroepiandrosterone/dehydroepiandrosterone sulfate. Reproduced with permission from © John Wiley & Sons, Inc, 2003. All rights reserved. McMurray, May [120].

Key messages on the hormonal factors in systemic lupus erythematosus (SLE)
General messages • Sex hormones such as 17β-estradiol (estradiol), testosterone, progesterone, prolactin and DHEA/DHEAS, may modulate the incidence and severity of SLE
The role of sex hormones in SLE is suggested by: • The higher prevalence of the disease in women, increased risk of flares (≈25-30%) during pregnancy, and decreased incidence after menopause • A meta-analysis showing higher blood levels of Estradiol in SLE patients compared to controls • The documented association between an early age at menarche, the use of oral contraceptive or postmenopausal hormone replacement therapy and the increased risk of incident SLE in a large prospective cohort study • The notion of a gene-dose effect from the X chromosome in SLE (Trisomy X, Klinefelter's syndrome and Turner syndrome)

Table 1.6 Keys messages on hormonal factors in systemic lupus erythematosus. DHEA/DHEAS, dehydroepiandrosterone/dehydroepiandrosterone sulfate

1.7 Drug-induced systemic lupus erythematosus

Drug-induced lupus erythematosus (DIL) refers to an idiosyncratic side-effect of more than 70 drugs and medications (see Figure 1.6) characterized by clinical and serological features similar to SLE, that are temporally related to drug exposure, and resolve after discontinuation of this drug [124,125]. DIL used to be characterized by a strong male

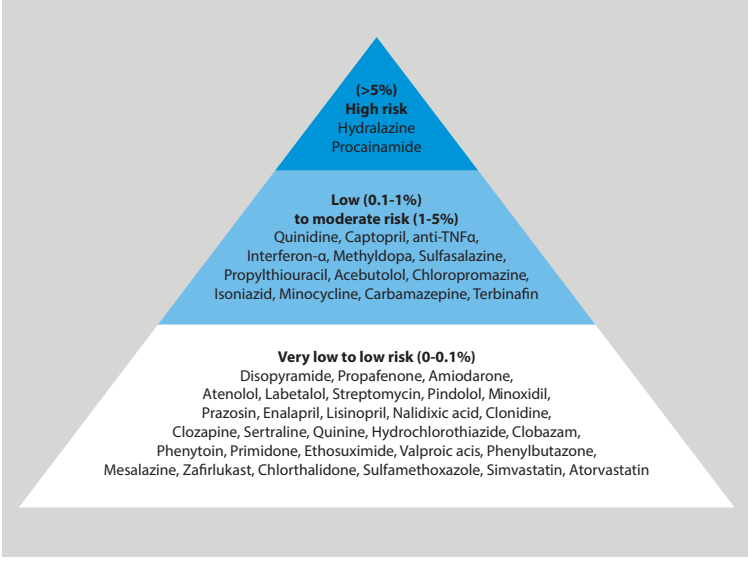

Figure 1.6 Risk levels for drugs at risk of causing drug-induced lupus.

predominance, and most patients were in their fifth decade or older, due to the more frequent long-term treatment with lupus-inducing drugs in this population [126]. While this may still be true at some level, the current epidemiology of DIL is largely unknown because there are no consensual diagnostic criteria and cases are probably under-reported [124]. Therefore, only a careful review of a patient's drug history in correlation with clinical findings as well as the resolution of symptoms, and sometimes auto-antibodies after withdrawal of the drug, remain the standard for identifying DIL [127].

DIL usually occurs after several months or years of continuous therapy with a lupus-inducing drug. In the French nation-wide pharmacovigilance database, DIL accounted for 0.1% of ≈235,000 unexpected and severe drug adverse events recorded over a 10-year period [128]. In most cases, the severity of DIL is mild, but severe cases, including some with fatal outcome, have been reported [125]. Patients commonly present with aspecific SLE symptoms such as arthralgia (the only clinical manifestation in 90% of cases), myalgia, fever, weight loss, and less commonly with rash or cutaneous vasculitis, pleural effusion, pericarditis or hepatosplenomegaly. Conversely, severe organ manifestations such as renal and central nervous system (CNS) involvement are rare, but their presence shall not exclude the diagnosis of DIL.

The spectrum of DIL has strongly evolved over the three past decades, as many of the drugs that were responsible for DIL are barely used nowadays, if at all. The drugs that used to be at highest risk for DIL were procainamide (with a DIL incidence of ≈20% for 1 year of treatment), and hydralazine (DIL incidence of ≈5–8%). Quinidine was at intermediate risk (1–5% of treated patients), but due to the risk in adverse reaction we now use less toxic derivatives. Finally, chlorpromazine and D-penicillamine were also responsible for DIL, although at a lowest incidence of 0.1–1% [124]. Currently, the drugs that are the most commonly associated with DIL are anti-TNF (DIL incidence of 0.2–0.4% [129,130]) and IFNs [130]. Most patients with TNF blocking agent-related DIL have only cutaneous manifestations [130], which is different from what is usually observed in DIL. The other drugs associated with DIL (at a low risk of 0.1–1%) are methyldopa, sulfasalazine, carbamazepine, acebutolol, isoniazid,

captopril, propylthiouracil, terbinafine, and minocycline [124]. For most other reported drugs (Figure 1.6), the risk of DIL is believed to be <0.1% and the level of evidence is low, as the association with DIL has only been reported in case-reports [124]. DIL shares with SLE the typical presence of antinuclear antibodies (ANA) in virtually all patients. Anti-histone IgG antibodies are observed in 40–95% of symptomatic patients with DIL, depending on the lupus-inducing drug while asymptomatic patients tend to have IgM anti-histone antibodies. However, anti-histone antibodies are not specific as they are found in 50–80% of patients with SLE. Anti-dsDNA antibodies are highly specific for SLE and rarely found in DlL, with the exception of DIL due to anti-TNF agents or interferon [131]. Keys messages on hormonal factors in systemic lupus erythematosus are below (Table 1.7).

Key messages on drug-induced lupus (DIL)
General facts • DIL refers to idiosyncratic side-effect of several medications characterized by clinical and serological features similar to SLE, that are temporally related to drug exposure, and resolve after discontinuation of this drug • However, there are no commonly accepted diagnostic criteria for DIL • DIL usually occurs after several months or years of continuous therapy with a lupus-inducing drug • More than 70 drugs and medications have been reported in association with DIL • The epidemiology of DIL is poorly known • The spectrum of DIL has strongly evolved over the past decades, as many of the drugs that were responsible for DIL are barely used nowadays, if at all • Currently, the most common lupus-inducing drugs are anti TNF, interferons, methyldopa, sulfasalazine, carbamazepine, acebutolol, isoniazid, captopril, propylthiouracil, terbinafine and minocycline
Clinical symptoms • In most cases, the severity of DIL is mild, but severe cases have been reported • Patients commonly present with aspecific SLE symptoms such as arthralgia (the only clinical manifestation in 90% of cases), myalgia, fever, weight loss • Less commonly manifestations include with rash (however very common in DIL to TNF blockers) or cutaneous vasculitis, pleural effusion, pericarditis or hepato-splenomegaly • Severe organ manifestations such as renal and CNS involvement are rare, but their presence shall not exclude the diagnosis of DIL
Laboratory features • Antinuclear antibodies (ANA) are virtually observed in all DIL patients • IgG anti-histone antibodies are seen in 40-95% of DIL patients, depending on the drug • Anti-histone antibodies are not specific for DIL as they are found in 50-80% of patients with SLE • Anti-dsDNA antibodies are highly specific for SLE and rarely found in DIL, with the exception of DIL due to anti-TNF agents or interferon (in which diseases their sole presence is insufficient to define DIL)

Table 1.7 Keys messages on hormonal factors in systemic lupus erythematosus.

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Chapter 2

Disease classification

2.1 Historical development

The term 'lupus', Latin for wolf, has been used in medicine for centuries to denote a severe and chronic skin disease leading to scarring. It is now clear that many different pathophysiological entities were included in that term, most importantly infectious ones such as mycobacterial diseases as well as various autoimmune and vascular diseases where the term lupus is still used today. 'Lupus erythematosus' (or 'erythematodes') was used to narrow this down to more specific inflammatory skin conditions where the classical sign of inflammation, redness, was prominent. The term systemic lupus erythematosus (SLE) was first introduced in the late 19th century when it became clear that some individuals who were affected by these characteristically scarring skin diseases were also suffering from severe disease manifestations in the internal organs, most notably in the kidneys. At that time the concept of autoimmunity was not accepted; notably, the great pioneer of immunology Paul Ehrlich had declared that autoimmunity was not possible, nature had an aversion to this, a 'horror autotoxicus'. However, in the middle of the 20th century several important discoveries overturned this dogma. Hemagglutinins found in patients with severe anemia were shown to be autologous anti-erythrocyte antibodies [1], rheumatoid factor was found to bind to naturally occuring IgG antibodies [2], and in patients with SLE, antinuclear [3] and anti-DNA antibodies [4] were demonstrated, followed by many other autoantibodies. These observations placed SLE firmly in the emerging domain of the systemic autoimmune diseases.

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2.2 Classification criteria

For many decades, the distinctions between SLE and other autoimmune diseases remained a matter of the clinician's individually applied diagnostic skills, creating difficulties in the comparability across clinics, specialties, and nations. In order to facilitate such comparisons, the American Rheumatism Association, which later became the American College of Rheumatology (ACR), endorsed the first widely used classification criteria for SLE in 1972 [5]. These first criteria were derived by comparing patients in whom the diagnosis of SLE had been made by an experienced clinician with patients in whom another diagnosis had been made, in most cases rheumatoid arthritis (RA). The resulting criteria were thoroughly revised in 1982 [6] (and underwent a relatively minor modification in 1997 [7]) and they are widely used today. A more recent set of classification criteria was derived by the Systemic Lupus International Collaborative Clinics (SLICC) [8], and a current initiative jointly by ACR and the European League Against Rheumatism (EULAR) is expected to provide yet another set of such criteria in the coming years.

2.3 The American College of Rheumatology classification criteria for systemic lupus erythematosus

The ACR classification of SLE is based on a list of 11 items (or small groups of related items), at least four of which must be documented in a patient for her or him to be classified as having SLE (shown in Table 2.1). These manifestations need not be present at the same time, and for many patients a significant amount of time passes between the first and the fourth manifestation. How to classify patients during this period of time remains somewhat controversial. Conceptually, the problem is that, while in 'real-time' it may be entirely correct to withhold the diagnosis of SLE, in retrospect it is often clear that the patient was already suffering from the disease that was diagnosed later.

Applying the ACR criteria may be challenging in other ways as well. The publications provide some guidance on their interpretation but also leave many matters unresolved. A recurring theme is that the manifestation must not be explained by another disease, a requirement that is

Criterion	Definition
1. Malar rash	Fixed edema, flat or raised, over the malar eminences, tending to spare the nasolabial folds
2. Discoid rash	Erythematosus raised patches with adherent keratotic scaling and follicular pluggin, atrophic scarring may occur in older lesions
3. Photosensitivity	Skin rash as a result of unusual reaction to sunlight, by patient history or physician observation
4. Oral ulcers	Oral or nasopharyngeal ulceration, usually painless, observed by physician
5. Nonerosive arthritis	Involving 2 or more peripheral joints, characterized by tenderness, swelling, or effusion
6. Pleuritis or pericarditis	1. Pleuritis–convincing history of pleuritic pain or rubbing heard by a physician or evidence of pleural effusion OR 2. Pericarditis–documented by electrocardiogram or rub or evidence of pericardial effusion
7. Renal disorder	1. Persistent proteinuria >0.5 grams per day or >than 3+ if quantification not performed OR 2. Cellular casts–may be red cell, hemoglobin, granular, tubular, or mixed
8. Neurologic disorder	1. Seizures–in the absence of offending drugs or known metabolic derangements eg, uremia, ketoacidosis, or electrolyte imbalance OR 2. Psychosis–in the absence of offending drugs or known metabolic derangements eg, uremia, ketoacidosis, or electrolyte imbalance
9. Hematologic disorder	1. Hemolytic anemia–with reticulocytosis OR 2. Leukopenia–<4,000/mm^3 on ≥2 occasions OR 3. Lyphopenia–<1,500/mm^3 on ≥2 occasions OR 4. Thrombocytopenia–<100,000/mm^3 in the absence of offending drugs
10. Immunologic disorder	1. Anti-DNA: antibody to native DNA in abnormal titer OR 2. Anti-Sm: presence of antibody to Sm nuclear antigen OR 3. Positive finding of antiphospholipid antibodies on: i. an abnormal serum level of IgG or IgM anticardiolipin antibodies ii. a positive test result for lupus anticoagulant using a standard method, or iii. a false-positive test result for at least 6 months confirmed by Treponema pallidum immobilization or fluorescent treponemal antibody absorption test
11. Positive antinuclear antibody	An abnormal titer of antinuclear antibody by immunofluorescence or an equivalent assay at any point in time and in the absence of drugs

Table 2.1 1997 update of the 1982 American College of Rheumatology revised criteria for the classification of systemic lupus erythematosus. IgG/M, immunoglobulin G/M. Reproduced with permission from © John Wiley & Sons, Inc, 1982. All rights reserved. Tan et al [6]. Reproduced with permission from © John Wiley & Sons, Inc, 1997. All rights reserved. Hochberg [7].

often not as easy to apply as it may seem. Most manifestations among the eleven, for example photosensitivity, oral ulcers, or seizures do sometimes occur in isolation in otherwise healthy individuals, and are then usually referred to as 'idiopathic' or 'non-specific'. Other manifestations are seen in isolation and often attributed to viral infection, for example pleurisy, and the anti-nuclear antibody test is known to have a relatively high false-positive rate.

Some details of each of the 11 criteria are important to keep in mind:

- The malar rash, often referred to as the classical butterfly rash of SLE, must be an indurated inflammatory lesion, and not a simple erythema of the malar eminences.
- The discoid lesion is correctly listed as a possible manifestation of SLE but may very well exist in isolation as the main form of chronic cutaneous lupus.
- Photosensitivity can be understood in different ways. Some individuals react with a strong inflammatory skin reaction to ultraviolet light exposure, and this reaction is highlighted in the criteria. However, others may develop systemic illness following such exposure, in the form of fever and generalized symptoms, and both reactions can occur at the same time; some clinicians feel that the latter reaction should also be considered as photosensitivity for the purpose of classification.
- Oral (and to a lesser extent nasal) ulcers are of course very common in the general population as incidental findings and must therefore be used for classification only when clearly in excess of the 'normal' background occurrence. The typical ulcer of SLE is said to be painless, but in practice both painless and painful ulcers are encountered. It does not appear that this aspect contributes to the accuracy of classification.
- The arthritis of SLE is generally said to be non-erosive, posing a clear distinction with RA. Nevertheless, erosions have been reported in SLE, and a non-erosive but strongly deforming type of arthritis, Jaccoud's arthropathy, can also be seen in SLE.
- Sometimes pleurisy and pericarditis are clearly demonstrated, yet it may be very hard to rule out that they are caused by viral

infection, especially Coxsackie virus (Bornholm disease). In other cases the diagnosis of pleurisy is made purely on clinical grounds, because of typical pain or a friction rub. It remains somewhat controversial what level of evidence is needed to make these diagnoses, and how far one needs go to rule out other causes. An autoimmune inflammation of the peritoneum ('abdominal serositis') is sometimes seen in patients with SLE and most experts feel this should also be included in this category.

- Two distinct neuropsychiatric manifestations are included in the ACR classification criteria for SLE: psychosis and seizures. This is remarkable for several reasons. The occurrence of psychosis as an SLE manifestation is very rare. Seizures as a manifestation of SLE tend to have an unusual course in that they are not rarely seen many years before any other SLE manifestations; and developing seizures later in the course of SLE is unusual. Perhaps most remarkably, none of the many other genuine SLE-related neuropsychiatric manifestations of SLE are included in this set of classification criteria: aseptic meningitis, transverse myelitis, and stroke syndrome are uncommon but well-defined whereas mild cognitive impairment, white substance abnormalities, organic brain syndrome, affective disorders, and cranial and/or peripheral neuropathies are all seen frequently in patients with SLE, but are not part of the classification criteria, either.
- Renal manifestations that are included in the classification criteria are proteinuria and urinary casts. It is again noteworthy that some well-established SLE-related renal findings, such as erythrocyturia or progressively worsening renal function, are not included. Perhaps most odd is that a clear histopathological diagnosis of lupus nephritis is not counted towards the classification criteria.
- The hematological manifestations include hemolytic anemia, leukocytopenia, lymphopenia, and thrombocytopenia. While all of these can be genuine SLE manifestations, modest lymphopenia is commonly seen without clear underlying disease, and is very often present in patients treated with glucocorticoids.

- The 'immunological manifestations' in the ACR classification criteria have undergone some modification since the original version, mostly driven by changes in laboratory technologies and the increasing awareness of the anti-phospholipid syndrome as a distinct disease entity. In the most recent version of the criteria, the presence of anti-DNA, anti-Sm, and/or anti-phospholipid antibodies is considered as one criterion. Some of the tests included in older versions of the criteria, such as the 'LE cell phenomenon' have fallen into disuse.
- The positive antinuclear antibodies (ANA) are very commonly found in SLE but also seen in many other diseases and at a relatively high rate in healthy individuals.

The original derivation of the ACR classification criteria used expert opinion as the gold standard against which to measure its accuracy, and similar approaches were used for some of the updates. In each of these instances, the sensitivity and specificity of the criteria were 80–90%, underscoring on the one hand their robustness, but on the other hand the risk of 'blindly' applying the criteria for diagnostic purposes, as up to one in five patients could be misclassified in either direction.

2.4 Limitations of the American College of Rheumatology classification criteria for systemic lupus erythematosus

The ACR classification criteria for SLE have served the global community of physicians and academicians who deal with SLE rather well. It has been possible to compare studies of various types across centers, countries, and continents. They have also been very useful in education and training. It is also clear that these criteria have increasingly been used as diagnostic criteria, for better or worse. However, some distinct disadvantages of these criteria have also emerged. For example, four mucocutaneous manifestations are included among the 11, lending disproportionate weight to this particular organ system involvement in SLE. The specific definitions of some of the criteria seem too restrictive, as indicated above. The criteria allow the classification of patients as having SLE without any evidence for autoimmunity per se, which seems to go against the generally held conception of SLE as a prototypic autoimmune disease.

Additionally, it was noted in the clinical trial setting that ambiguities in the criteria could result in the incorrect inclusion of individuals with mild undifferentiated connective tissue disease.

2.5 The Systemic Lupus International Collaborative Clinics classification criteria for systemic lupus erythematosus

Partly in response to the limitations of the ACR classification criteria for SLE, the SLICC group, a consortium of 35 SLE experts from 30 centers in Northern and Central America, Europe, and Korea set out in 2002 to redefine classification criteria for SLE [8]. The group recognized that it would not be possible to do so without first defining which patient would be considered truly to have SLE, in other words, the gold standard had to be made explicit. It was decided by consensus to use a two-step approach for this: each member would submit vignettes describing real patients from their own practice or cohort, in whom they as experts had made the diagnosis of either SLE or one of the eight control diseases (other connective tissue diseases, such as dermatomyositis or vasculitis, fibromyalgia, and others). These vignettes would then be studied by the other members of the group and they would indicate whether this was, in their opinion, SLE or not-SLE. If a clear majority concurred, the cases were considered for the further derivation or confirmation steps. Some further adjudication was done for cases where assessments diverged. In the end, around 700 cases where a clear diagnosis by expert opinion was established were used to derive the best possible set of individual items for classification. Most of this was done in an 'unsupervised' manner, but some steps were 'supervised' to ensure face validity. In the end, a set of 16 items was generated, divided into clinical and immunological ones, and applied in the following manner: classification of SLE was to be based on the presence, sequentially or simultaneously, of at least four items, of which at least one must be clinical and at least one must be immunological. Furthermore, a patient with histologically proven membranoproliferative glomerulonephritis in the presence of ANA or anti-DNA could also be classified as having SLE. The SLICC classification criteria for SLE are shown in Table 2.2.

Clinical criteria

1. Acute cutaneous lupus including:

- lupus malar rash (do not count if malar discoid)
  - bullous lupus
  - toxic epidermal necrolysis variant of systemic lupus erythematosus (SLE)
  - maculopapular lupus rash
  - photosensitive lupus rash
    in the absence of dermatomyositis
- or subacute cutaneous lupus (nonindurated psoriaform and/or annular polycyclic lesions that resolve without scarring, although occasionally with postinflammatory dyspigmentation or telangiectasias)

2. Chronic cutaneous lupus including:

- classical discoid rash
  - localized (above the neck)
  - generalized (above and below the neck)
- hypertrophic (verrucous) lupus
- lupus panniculitis (profundus)
- mucosal lupus
- lupus erythematosus tumidus
- chillblains lupus
- discoid lupus/lichen planus overlap

3. Oral ulcers:

- palate
- buccal
- tongue
- or nasal ulcers
  in the absence of other causes, such as vasculitis, Behcets, infection (herpes), inflammatory bowel disease, reactive arthritis, and acidic foods

4. Nonscarring alopecia (diffuse thinning or hair fragility with visible broken hairs)

in the absence of other causes such as alopecia areata, drugs, iron deficiency and androgenic alopecia

5. Synovitis involving two or more joints, characterized by swelling or effusion OR tenderness in 2 or more joints and thirty minutes or more of morning stiffness.

6. Serositis:

- typical pleurisy for more than 1 day
  - or pleural effusions
  - or pleural rub
- typical pericardial pain (pain with recumbency improved by sitting forward) for more than 1 day
  - or pericardial effusion
  - or pericardial rub
  - or pericarditis by EKG
  in the absence of other causes, such as infection, uremia, and Dressler's pericarditis

Table 2.2 1997 update of the 1982 American College of Rheumatology revised criteria for the classification of systemic lupus erythematosus (continues overleaf). EKG, electrocardiogram.
 Tan et al [6].
 Hochberg [7].

7. Renal:

- Urine protein/creatinine (or 24 hr urine protein) representing 500 mg of protein/24 hr or
- Red blood cell casts

8. Neurologic

- seizures
- psychosis
- mononeuritis multiplex
  in the absence of other known causes such as primary vasculitis
- myelitis
- peripheral or cranial neuropathy
  in the absence of other known causes such as primary vasculitis, infection, and diabetes mellitus
- acute confusional state
  in the absence of other causes, including toxic-metabolic, uremia, drugs

9. Hemolytic anemia

10. Leukopenia (<4000/mm^3 at least once)

in the absence of other known causes such as Felty's, drugs, and portal hypertension

or **lymphopenia** (< 1000/mm^3 at least once)

in the absence of other known causes such as corticosteroids, drugs and infection

11. Thrombocytopenia (<100,000/mm^3) at least once

in the absence of other known causes such as drugs, portal hypertension, and TTP

Immunological criteria

1. ANA above laboratory reference range

2. Anti-dsDNA above laboratory reference range, except ELISA: twice above laboratory reference range

3. Anti-Sm

4. Antiphospholipid antibody: any of the following

- lupus anticoagulant
- false-positive RPR
- medium or high titer anticardiolipin (IgA, IgG or IgM)
- anti-β_2 glycoprotein I (IgA, IgG or IgM)

5. Low complement

- low C3
- low C4
- low CH50

6. Direct Coombs test *in the absence of hemolytic anemia*

Table 2.2 1997 update of the 1982 American College of Rheumatology revised criteria for the classification of systemic lupus erythematosus (continued). ANA, antinuclear antibodies; Ig, immunoglobulin; RPR, rapid plasma reagin; TTP, thrombotic thrombocytopenic purpura; Reproduced with permission from © John Wiley & Sons, Inc, 1982. All rights reserved. Tan et al [6]. Reproduced with permission from © John Wiley & Sons, Inc, 1997. All rights reserved. Hochberg [7].

This set of criteria was shown, in the derivation sample of 702 patients, to have excellent sensitivity and specificity, and when compared to the gold standard defined above: the sensitivity was 94% and the specificity 92%, which were both clearly better than the ACR criteria. However, when the same criteria were tested in a similarly large confirmation sample of 690 additional patients, the metric properties were somewhat less – although still very good – and not clearly superior to the ACR criteria (sensitivity 97%, specificity 84%) [8].

The SLICC classification criteria have been widely lauded as an important step forward in the definition of SLE [9,10]. Specifically, it was noted that these criteria seem to 'fit' better with our general understanding of SLE, that is, they have better face validity. For instance, the requirement to have both clinical and immunological features is close to the approach that many would take to the patient with possible SLE. It was also seen as a strength that a clear histological demonstration of class IV lupus nephritis, in the presence of ANA or anti-DNA, is sufficient to make a diagnosis of SLE, again matching well with the approach that many clinicians would take. The SLICC criteria publication also provides detailed instructions on each item to aid the clinician in determining whether the criterion is met [8].

On the other hand, the SLICC criteria also have some disadvantages. Having a larger number of items, they are somewhat harder to memorize. They are not clearly superior to the ACR criteria in terms of their metric properties, and still misclassify about one in 10 patients, in either direction. As such, they should not be used blindly in making or rejecting the diagnosis of SLE.

Overall, it can be said that the SLICC criteria for SLE represent a useful new set for clinical studies of SLE, including clinical trials. Indeed, the European Medicines Agency (EMA) in a recent guidance document for the development of medications for the treatment of SLE explicitly endorsed the SLICC criteria as an alternative to the ACR criteria.

2.6 Sub-classification of systemic lupus erythematosus

Some of the specific manifestations of SLE can be classified further according to criteria that in some instances have been developed within the medical discipline most closely involved in its management, and in other instances by multispecialty task-forces. Lupus nephritis is histologically classified into six subtypes [11,12]. For the precise use of terms in neuropsychiatric SLE a glossary of 23 items was defined, indicating the specific description of each item and what other causes should be considered or ruled out before attributing it to SLE [13].

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Chapter 3

Disease manifestations

3.1 Overview

Although the term 'lupus' has been used since the middle ages to describe skin lesions, the truly systemic nature of the disease was fully recognized only at the turn of the 19th century. SLE is often referred to as "the disease with a thousand faces" [1], due to its highly polymorphic nature that can affect almost any organ system or tissue (Figure 3.1). Its presentation and course are highly variable, with symptoms ranging from minimal to life-threatening. In addition to differences in disease epidemiology

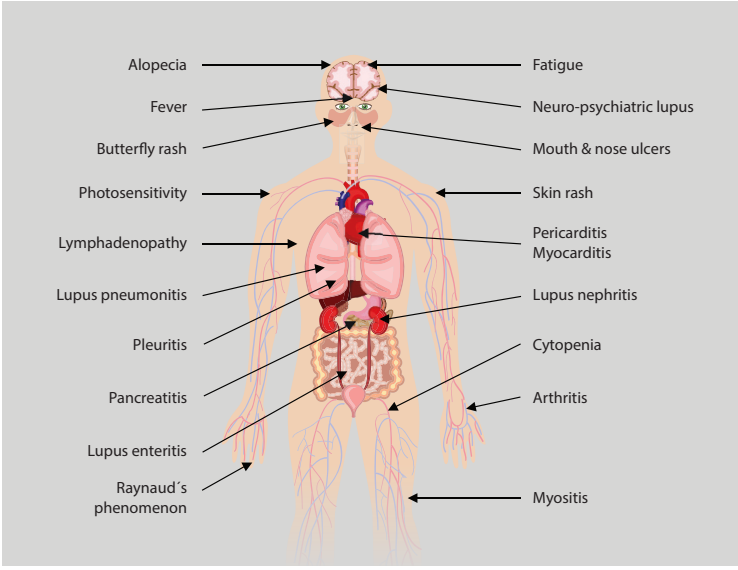

Figure 3.1 Anatomical depiction of disease manifestations of systemic lupus erythematosus. Elements of this illustration were provided by Servier Medical Art by Servier (http://smart.servier.com/), licensed under a Creative Commons Attribution 3.0 Unported Licence.

L. Arnaud and R. van Vollenhoven, *Advanced Handbook of Systemic Lupus Erythematosus*, https://doi.org/10.1007/978-3-319-43035-5_3

(see Chapter 1), marked ethnic variation in organ involvement has also been reported. While the disease is typically characterized by periods of remissions and flares, several patterns of disease activity have been described [2–4] in relation to organ manifestations (Table 3.1) [5].

Manifestations	At onset no. (%)	During evolution no. (%)
Malar rash	401 (40)	579 (58)
Discoid lesions	63 (6)	104 (10)
Subacute cutaneous lesions	27 (3)	56 (6)
Photosensitivity	294 (29)	453 (45)
Oral ulcers	108 (11)	238 (24)
Arthritis	689 (69)	840 (84)
Serositis	172 (17)	364 (36)
Nephropathy	160 (16)	393 (39)
Neurologic involvement	117 (12)	268 (27)
Thrombocytopenia	94 (9)	220 (22)
Hemolytic anemia	38 (4)	82 (8)
Fever	361 (36)	524 (52)
Raynaud phenomenon	184 (18)	339 (34)
Livedo reticularis	47 (5)	137 (14)
Thrombosis	42 (4)	137 (14)
Myositis	38 (4)	86 (9)
Lung involvement	29 (3)	73 (7)
Chorea	9 (1)	16 (2)
Sicca syndrome	47 (5)	161 (16)
Lymphadenopathy	70 (7)	119 (12)

Table 3.1 Clinical features at the onset and during the evolution of the disease in 1000 patients with systemic lupus erythematosus. Reproduced with permission from © Wolters Kluwer Health, Inc, 1993. All rights reserved. Cervera et al [22].

3.2 Constitutional

Approximately 50% of SLE patients report constitutional symptoms during the course of the disease, including fatigue, fever, and unintentional weight loss [6], and those are common presenting manifestations.

Fatigue is the most prevalent complaint in patients with SLE [7]. It is highly multifactorial [8] and can be related to: global disease activity, disease complications (such as anemia), damage (such as cardiac or renal failure), side effects of treatments (such as corticosteroids), chronic pain, fibromyalgia, poor quality of sleep, and depression (Figure 3.2). More than 15 different instruments have been used to measure fatigue in SLE [9], among which the Fatigue Severity Scale (FSS) [10] and the Functional Assessment Chronic Illness Therapy (FACIT) [11] are most commonly used. Fever is common at SLE presentation [12], as well as during disease flares and complications such as the hemophagocytic syndrome. Differential diagnosis of fever in SLE is crucial for the optimal management of these patients. This is particularly true as disease activity and infections are the two most common causes of fever in SLE. Fever due to SLE is not accompanied by chills, an important feature in the

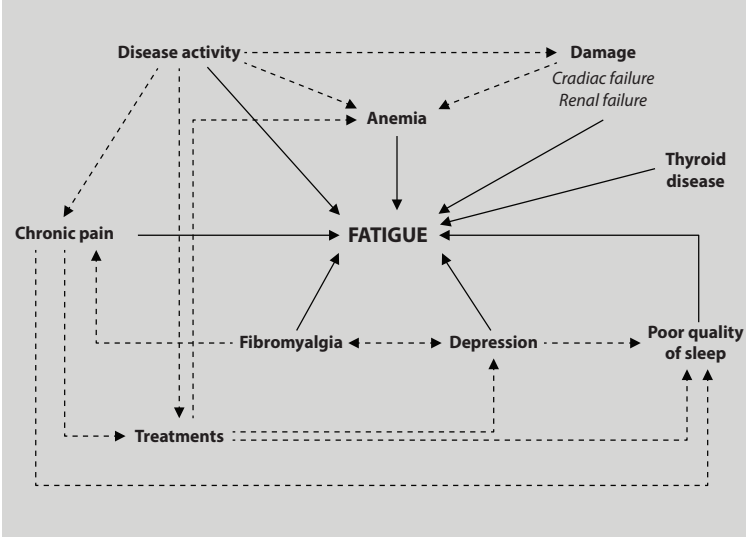

Figure 3.2 Causes of fatigue in patients with systemic lupus erythematosus.

differentiation from bacterial infections. Also, those with SLE-related fever are more likely to have lower serum complement C3 and a higher Systemic Lupus Erythematosus Disease Activity Index (SLEDAI) [12]. On rare occasions, fever in SLE may be due to malignancy or a medication [12]. Careful history taking, use of C-reactive protein (CRP) or procalcitonin [13], and specific scores [14] may help differentiate between causes of fever in SLE (see section 7.6 for infections in SLE).

3.3 Musculoskeletal

Involvement of the musculoskeletal system is among the most frequent manifestations of SLE. Arthritis and arthralgia are seen in up to 65% of patients at presentation and in 85% during the course of the disease [11]. While all joints can be involved, the involvement is typically polyarticular and symmetric, with a predilection for the wrist, metacarpophalangeal joints (MCPs), proximal interphalangeal joints (PIPs), and knees (see Figure 3.3).

Joint inflammation may be migratory or persistent. In some patients, severe arthralgia may contrast with the lack of objective findings. However, a majority of SLE patients with hand arthralgia show US signs of synovitis or tenosynovitis suggestive of subclinical disease [15].

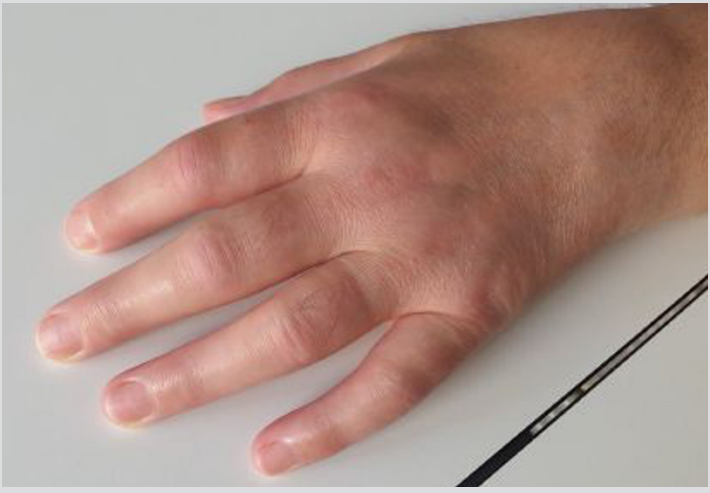

Figure 3.3 Arthritis of left wrist, metacarpophalangeal and proximal interphalangeal joints in a patient with systemic lupus erythematosus.

Arthritis in SLE is typically considered to be non-erosive. However, recent studies using more sensitive imaging methods such as ultrasound [15] or magnetic resonance imaging (MRI) [16,17] have revealed a high frequency of erosions, nevertheless of unclear clinical significance. While rheumatoid factor is found in 10–20% of SLE cases, the presence of anti-citrullinated peptide antibodies (ACPA) is observed in 5–10% of SLE cases [18–21], and is strongly associated with an erosive arthritis overlapping with RA that is termed 'rhupus' [23,24]. Jaccoud arthropathy, a deforming non-erosive arthropathy characterized by ulnar deviation of the second to fifth fingers with MCP subluxations that can be passively reduced, and occasional involvement of the knees or the feet, is seen in 3–8% of patients with SLE [25,26]. Independent risk factors for the development of Jaccoud arthropathy are prolonged disease activity in the musculoskeletal domain and overall longer disease duration [27].

SLE is the primary cause of corticosteroid-induced osteonecrosis of femoral head [28], which can be unilateral or bilateral [29]. Conversely, symptomatic knee osteonecrosis is a relatively rare complication of the disease [30]. Osteonecrosis may be silent or may clinically present with gradual onset or sudden pain, and magnetic resonance imaging (MRI) represents the 'gold standard' for the early detection of the complication. In a recent meta-analysis [31], osteonecrosis in SLE was associated with doses of ≥20 mg prednisone equivalent per day.

Muscular involvement in SLE ranges from common myalgia to symptomatic myositis with proximal muscle weakness. An inflammatory myositis related to SLE (5–10% of patients, possibly more in pediatric patients [32]) or an overlap syndrome [33] should be differentiated from drug-induced myopathies (statins, glucocorticoids, or antimalarials), as well as from other causes of myolysis such as endocrinopathies, and myasthenia gravis [34]. Anti-ribonucleoprotein (RNP) antibodies are more prevalent in SLE patients with myositis than without [35,36]. The clinical and laboratory features (including the increased levels of creatine phosphokinase [CK] [36]) are similar between SLE-related myositis and other forms of myositis [35]. Conversely, CK are generally normal in corticosteroid-induced myopathy. Further electromyographic studies, muscular MRI, and muscle biopsy can help to distinguish between the

various causes of muscle involvement in SLE patients. The main histological finding in SLE-related myopathy is interstitial myositis [36,37], with lymphocytic or plasma-cell infiltration in the perifascicular and perimysial areas. In case of corticosteroid-induced myopathy, the main histological finding is type II myofiber atrophy without inflammation, while acid-phosphatase–positive autophagic vacuolar myopathy is suggestive of antimalarial-induced myopathy [38].

3.4 Dermatologic

Cutaneous lupus erythematosus (CLE) includes a broad range of skin manifestations [39]. These lesions are generally classified as LE-specific or non LE-specific [38]. Currently, CLE is subdivided [40] into acute CLE (ACLE), subacute CLE (SCLE), and chronic CLE (CCLE) while non LE-specific lesions are further sub-divided into vascular (livedo, Raynaud's phenomenon, leukocytoclastic vasculitis) and non-vascular (papular mucinosis, amicrobial pustulosis) lesions. Diagnosis of LE-specific lesions currently relies on their clinical course, clinical aspects, histopathological features and disease evolution [41].

3.4.1 Histopathology of cutaneous lupus erythematosus

The different subtypes of CLE share some histological features, but also exhibit subset-specific findings. Histopathology and immunopathology may be helpful in the diagnosis of CLE but have less utility in determining the clinical subtype [40]. Typically shared histological patterns include perivascular and periadnexal lymphocytic infiltrate while the presence of changes in the dermoepidermal junction (the interface dermatitis) and the intensity and pattern of mucin deposition depends on the exact nature of the lesions [42]. All forms of LE may show a deposition of immunoglobulin (commonly IgG) and complement fractions (usually C3) at the dermoepidermal junction of lesional skin (the 'lupus band') as well as, although less frequently, in non-lesional skin [41].

3.4.2 Acute cutaneous lupus erythematosus

ACLE is associated with SLE in 90–95% of cases [41]. The typical localized form of ACLE is known as the 'malar rash', which has a 'butterfly'-like

distribution that spares the nasolabial folds. The rash usually begins with small erythematous macules and papules involving the malar areas and/or the bridge of the nose, sometimes with a fine scaling. A generalized form of ACLE is possible, and has a predilection for the sun-exposed areas of the forehead, V-area of the neck, the upper limbs, the trunk and the dorsum of the hands (in the interphalangeal regions). Other ACLE lesions comprise superficial ulcerations of the oral and/or nasal mucosa and alopecia with thinning or broken hairs. In general, ACLE lesions do not result in scarring.

3.4.3 Subacute cutaneous lupus erythematosus

SCLE lesions initially present with erythematous macules or papules that evolve either into scaly papulosquamous (psoriasiform) or annular/polycyclic plaques. SCLE is associated with SLE in 50% of cases [41], and patients with SCLE commonly have anti-Sjögren's-syndrome-related antigen A (anti-Ro/SSA) antibodies [43]. Papulosquamous lesions often appear as red scaly patches. Annular lesions have a typical ring-shaped appearance, with a little scaling on the edge of the lesions. SCLE has a characteristic distribution in the sun-exposed areas such as the upper chest and back, the shoulders, the extensor surface of the arms, and less commonly the face. Healing without scarring or atrophy is typical, but hypopigmentation may occur.

3.4.4 Chronic cutaneous lupus

CCLE comprises discoid lupus, lupus tumidus, chilblain-like lupus, and LE profundus also termed lupus panniculitis [39]. Discoid lupus erythematosus (DLE) is the most common type of CCLE, and is associated with SLE in 20% of cases [41]. DLE lesions begins with flat or slightly elevated erythematous macules or papules with a scaly surface. These lesions commonly evolve into larger, confluent, discoid plaques with follicular plugging, and adherent scaling [40]. Other rare presentations of DLE include the hypertrophic (verrucous) and the telangiectoid variants. DLE is most commonly observed on the cheeks, nose and ears, scalp, but also on the anterior V of the neck and dorsum of the hands. In most cases, the lesions resolve leaving pigmentation as well as definitive atrophic dermal scarring that can cause great esthetic prejudice (Figure 3.4). Scalp lesions may lead to scarring alopecia. Chilblain-like

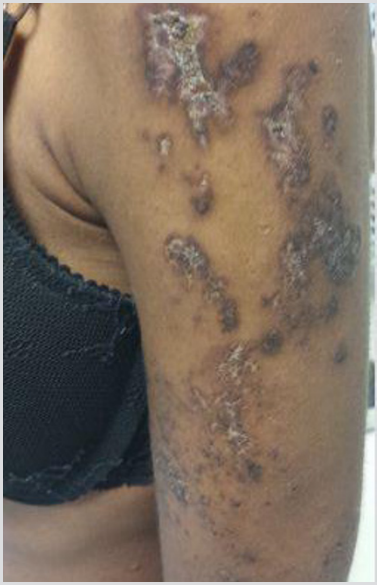

Figure 3.4 Discoid lupus with definitive atrophic dermal scarring in an afro-Caribbean patient.

lupus erythematosus (CHLE) is a rare variant of CCLE, and is associated with SLE in about 20% of cases [41]. The lesions are characterized by symmetrically distributed, well-circumscribed, prurigineous or sometimes painful purple plaques of the hands, feet, ears, nose, elbows, and knees, that mimic those of frostbite (chilblain) but persist out of the cold season and have a typical lupus histology [44].

Lupus erythematosus profundus (LEP, or lupus panniculitis), is characterized by chronic single or multiple sometimes painful subcutaneous nodules or plaques of panniculitis typically located on the shoulders and thighs, but also on the trunk and buttocks. LEP lesions resolve leaving typical deep atrophic scars (Figure 3.5). In most cases, the patients also have CLE overlying the panniculitis lesions. In the absence of such other lesions, it is recommended to formally confirm the LEP diagnosis with a deep biopsy, because a LEP can have a presentation similar to that of subcutaneous lymphoma. Lupus erythematosus tumidus (LET) is characterized by highly photosensitive, swollen, urticarial-like erythematous

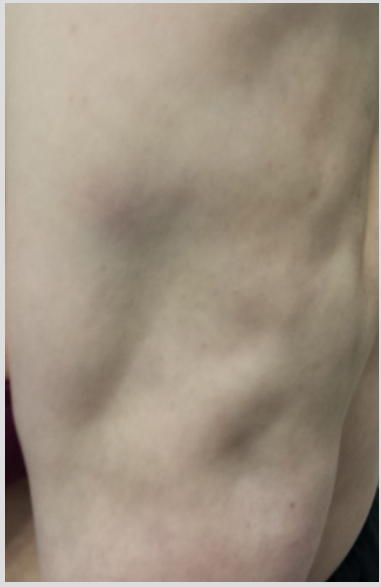

Figure 3.5 Typical deep atrophic scars following lupus panniculitis in the posterior port of the arm

lesions in the absence of clinically visible epidermal involvement [45,46]. The lesions are mostly located on the face, upper back, V-area of the neck, extensor side of the arms, and shoulders. Histologic analysis of skin lesions is necessary to confirm the diagnosis and shows the typical lymphocytic perivascular and periadnexal dermal infiltrate of CLE, but with no or minimal epidermal and dermoepidermal junction changes [47], and with a typically abundant interstitial dermal mucin deposition [48].

3.4.5 Bullous lesions

Bullous systemic lupus erythematosus (BSLE) is rare and encompasses several entities [49,50] that are often caused by autoantibodies to the dermoepidermal junction, mainly against type VII collagen. Reported clinico-histopathological patterns [49] include toxic epidermal necrolysis (TEN)-like lesions (with sheet-like skin detachment such as in the classical Lyell syndrome, but with sun-exposure, mild mucosal involvement, and dermal mucin deposition that allows differential diagnosis),

vesiculo-bullae and/or crusting on typical lesions of SCLE or chronic cutaneous lupus erythematosus, and tense vesicles and/or blisters with an underlying neutrophilic dermatosis.

3.4.6 Assessment of cutaneous activity

Several global disease activity scores have been established for SLE (such as the Systemic Lupus Erythematosus Disease Activity Index 2000 [SLEDAI-2K], British Isles Lupus Assessment Group index 2004 [BILAG 2004] or Systemic Lupus Activity Measure [SLAM]). While those include dermatological items, they are not really suitable for specifically judging activity of the different CLE subtypes. Therefore, two scoring systems have been specifically derived for CLE: the Cutaneous Lupus Erythematosus Disease Area and Severity Index (CLASI) [51] and its revision by another team, the Revised CLASI (RCLASI) [52]. Key messages on cutaneous lupus are below (Table 3.2).

Key messages on cutaneous lupus erythematosus (SLE)

General comments

Cutaneous lupus erythematosus (CLE) may be one of the clinical components of SLE, or a fully autonomous entity. Based on the clinical, histopathological and evolution profile, three main subtypes of CLE have been defined: acute, subacute and chronic CLE

Acute cutaneous lupus erythematosus (ACLE)

- ACLE is associated with SLE in more than 90–95% of case and often seen in patients with active SLE
- The typical localized form of ACLE is known as the 'malar rash' or 'butterfly rash', and usually begins with small erythematous macules and papules, sometimes associated with fine scales involving the malar areas and/or the bridge of the nose
- Other area that may be involved are: the forehead, the V-area of the neck, the upper limbs, the trunk and the dorsum of the hands, oral and/or nasal mucosa and the scalp
- ACLE lesions do not result in scarring

Subacute cutaneous lupus erythematosus (SCLE)

- SCLE is associated with SLE in 50% of cases
- Patients with SCLE commonly have anti-Ro/SSA antibodies.
- There are two main presentations of SCLE:
  - Scaly papulosquamous (psoriasiform)
  - Annular/polycyclic plaques
- SCLE has a characteristic distribution in sun-exposed areas
- Healing without scarring or atrophy is typical, but hypopigmentation can occur

Chronic cutaneous lupus (CCLE)

- CCLE comprises 4 subtypes:
  - Discoid lupus (DLE), characterized by coin-shaped (discoid), confluent, plaques with follicular plugging, adherent scaling, and definitive atrophic dermal scarring.
  - Lupus tumidus (LET)
  - Chilblain-like lupus (CHLE)
  - LE profundus/lupus panniculitis

Table 3.2 Key messages on the epidemiology of cutaneous lupus erythematosus.

3.5 Renal lupus

Lupus nephritis (LN) is one of the most common organ-threatening manifestation of SLE [53], and occurs in 30–70% of SLE patients, especially within 5 years following the diagnosis of SLE [54]. Anti-dsDNA antibodies have been shown to contribute to the pathogenesis of lupus nephritis through the formation of immune complexes and complement activation, that trigger downstream inflammatory and fibrotic processes [55]. LN can result in end-stage renal disease (ESRD) in up to 10–15% of patients [56]. Among SLE patients who progress to ESRD, ≈80% have SLE as the main cause of ESRD [57]. The high prevalence of renal disease in SLE warrants routine monitoring of proteinuria and renal function tests in all SLE patients. Risk factors for renal disease in SLE include male sex, young age (<33 years), and non-Caucasian ethnicity [58]. The presence of proteinuria (>0.5 g/day), active urinary sediment (with red blood cell, granular, tubular, and/or mixed casts), with or without elevated plasma creatinine, is strongly evocative of LN in SLE patients [59]. Because there are multiple histologic subtypes of LN, with different prognosis and optimal treatment [60], the adequate classification of LN requires a renal biopsy. Prompt diagnosis and treatment of LN is recommended, a rapidly rising serum creatinine being an indication for an urgent renal biopsy. The latest revised classification of LN, the 2003 International Society of Nephrology/Renal Pathology Society (ISN/RPS ISN/RPS) classification [61] divides patterns of glomerular injury into six classes (see Table 3.3 and Figure 3.6). Biopsies from most patients with LN reveal an immune complex-mediated glomerular disease that may combine with tubulointerstitial and vascular lesions [61]. Histologic overlap is relatively common [62,63], with mixed proliferative LN including features of classes III or IV and V combined. Also, subdividing proliferative LN into class III, IV-S and IV-G has been shown to provide less clinically discriminant prognostic information than baseline chronicity index [60]. Tubulointerstitial disease (tubular lesions and/and interstitial infiltrate) is commonly reported in LN [64], and is an important prognostic factor [65]. Vascular changes [66] may include immunoglobulin microvascular casts, acute thrombotic microangiopathy,

Class	Terminology	Description
I	Minimal mesangial lupus nephritis	Mesangial accumulation of immune complexes identified by immunofluorescence, or by immunofluorescence and electron microscopy, without concomitant light microscopic alterations
II	Mesangial proliferative lupus nephritis	Any degree of mesangial hypercellularity without identification of any subendothelial deposits
III	Focal lupus nephritis	Segmental endocapillary proliferative lesions or inactive glomerular scars, with or without capillary wall necrosis and crescents, with subendothelial deposits involving less than 50% of all glomeruli. Further subdivision based on whether lesions are active (A) and/or chronic (C)
IV	Diffuse lupus nephritis	This class is subdivided into diffuse segmental lupus nephritis (class IV-S) when >50% of the involved glomeruli have segmental lesions, and diffuse global lupus nephritis (class IV-G) when >50% of the involved glomeruli have global lesions. Further subdivision based on whether lesions are active (A) and/or chronic (C)
IV	Membranous lupus nephritis	Global or segmental continuous granular subepithelial immune deposits
VI	Advanced-stage lupus nephritis	≥90% global glomerulosclerosis without evidence of ongoing active glomerular disease

Table 3.3 Classification of glomerular involvement in lupus nephritis. Adapted from © Elsevier, 2004. All rights reserved. Weening et al [61].

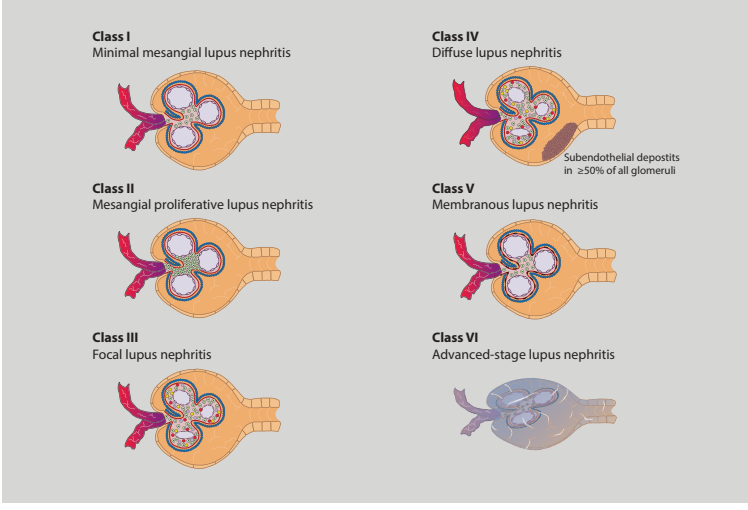

Figure 3.6 Classification of glomerular involvement in lupus nephritis. Elements of this illustration were provided by Servier Medical Art by Servier (http://smart.servier.com/), licensed under a Creative Commons Attribution 3.0 Unported Licence.

chronic vascular lesions, vasculitis, or microvascular thrombi associated with antiphospholipid antibodies (aPL) [67].

Patients with severe LN having normal or well-preserved renal function at biopsy are significantly more likely to attain a remission with therapy and have an excellent long-term prognosis [68]. LN activity is monitored by following changes in proteinuria, C3 and anti-dsDNA levels, and by the estimated glomerular filtration rate as well as by conducting an interval examination of the urine sediment. The spot protein-to-creatinine ratio may be inaccurate in the quantification of proteinuria in LN and should be preferred to 24h proteinuria only for screening [69]. Achievement of a proteinuria <0.7–0.8 g/day at month 12 is a major predictor of good long-term renal outcome [70,71]. Recent data suggest that microscopic hematuria should not be considered in the definition of treatment response [70]. Repeated renal biopsy may be discussed after 3–6 months, to assess treatment response at the histology level [72].

Despite marked improvements in the survival of patients with severe lupus nephritis over the past 50 years, the rate of complete clinical remission after therapy is <50% [68]. Therefore, the optimal therapy remains to be elucidated. Pejorative prognostic factors in LN include the older age at diagnosis, non-Caucasian ethnicity, higher baseline proteinuria and renal biopsy chronicity scores [58]. The percentage of patients who progress to end-stage LN typically varies from 5 to 20 %, depending on the series [59].

3.6 Neuropsychiatric

Neuropsychiatric SLE (NPSLE) is among the most challenging manifestations of SLE. NPSLE can affect both the peripheral and the central nervous systems, and involvement of the latter remains a major cause of morbidity and mortality in SLE patients [73]. The current classification of NPSLE [74] distinguishes 19 main manifestations (Figure 3.7), that span the central, peripheral, and less commonly autonomic nervous systems.

The exact incidence of NPSLE manifestations is difficult to estimate as many of these symptoms are non-specific for SLE [75]. NPSLE manifestations with the highest incidence include cerebrovascular disease and seizures, while severe cognitive dysfunction, acute confusional state,

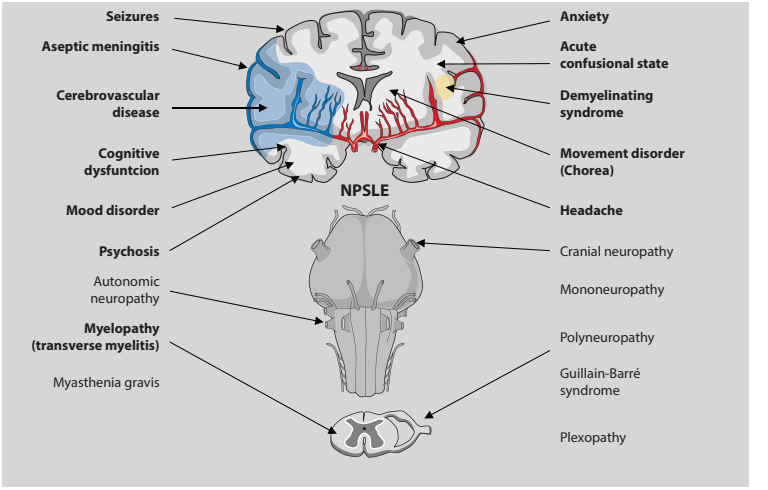

Figure 3.7 The 19 main manifestations of neuropsychiatric systemic lupus erythematosus. CNS manifestations are denoted in dark red, while PNS manifestations are shown in dark blue. Elements of this illustration were provided by Servier Medical Art by Servier (http://smart.servier.com/), licensed under a Creative Commons Attribution 3.0 Unported Licence.

psychosis, and peripheral nervous disorders are less common [76]. The main differential diagnoses of NPSLE include trauma, infection, hypertensive emergencies, metabolic changes including uremia, drug effects, epilepsy, migraine, psychiatric disorders, multiple sclerosis, posterior reversible encephalopathy, and previous nervous system disorders [77]. The investigations of choice will vary with the presentation. Typical investigations for CNS involvement include brain MRI, cerebrospinal fluid analysis where appropriate, and occasionally electroencephalogram (EEG) and neuropsychological tests in case of seizure and cognitive dysfunction, respectively [76]. MRI shows lesions in only ≈60% of patients with CNS involvement, the most frequent pattern being small hyperintense T2-weighted focal lesions in subcortical and periventricular white matter. However, similar lesions are also observed in a significant proportion of SLE patients without NPSLE, and have unclear significance [76]. Therefore, a normal MRI is not sufficient to rule out central manifestations of NPSLE, and presence of lesions is not sufficient to define NPSLE. Nerve conduction studies are performed for peripheral neuropathy. Despite the recent derivation of diagnostic scoring systems [78,79], NPSLE remains essentially a diagnosis of presumption and exclusion [77].

In NPSLE, cerebrovascular disease mostly results of ischemic stroke and/or transient ischemic attack (TIA), whereas CNS vasculitis is rare [76]. Main risk factors are presence of high disease activity, aPL, heart valve disease, arrhythmia, systemic hypertension, and age [76]. The acute management of SLE stroke or TIA is similar to that of the general population [76].

Seizures are an important manifestations of SLE (5–10% of patients), and are included in the 2012 Systemic Lupus Collaborating Clinics (SLICC) classification criteria [80]. Seizures are more common during the first year after SLE diagnosis [81], and recurrence occurs in 10–55% of patients [81,82]. The risk of seizure at or after diagnosis of SLE is mostly associated with disease activity, use of corticosteroids, and prior psychosis [82]. Most patients have tonic-clonic seizures, but other types of seizures are not uncommon [81].

Cognitive dysfunction is common in SLE (up to 60% of patients in some studies) [83], and may range from minor abnormalities to severe decline. Functional MRI studies have shown extensive disruptions in the normal modulation of brain function in relation to task demands [84]. Psychosis is a rare NPSLE manifestation (1–5% of patients), and usually occurs early in the course of the disease (within the first year in 80% of the cases) [85]. It is mostly associated with clinical features (90% of patients have skin manifestations) and biological markers of SLE disease activity [85]. Long-term outcome is generally favorable after immunosuppressive treatment, but time to remission is usually long [85].

Aseptic meningitis is a rare manifestation of SLE (1–5%) [73,86] that should be considered once infections have been ruled out. Altered mental status, plasma leukocytosis, neutrophilia, cerebral spinal fluid (CSF) pleiocytosis and hypoglycemia have been reported to be more prominent in SLE patients with septic meningitis compared with aseptic meningitis, but none of this features is specific and throughout search for infections should always be considered [86]. Besides, aseptic meningitis can be induced by ibuprofen in SLE and this treatment should therefore be avoided [75].

The association between SLE and headache is controversial [87]. Headache is frequent in SLE, but overall, is not associated with global disease activity or specific autoantibodies [87]. The entity 'lupus headache' has traditionally been defined as a severe, disabling, persistent

headache that is not responsive to narcotic analgesics [74]. However, this is not specific as severe migraine with or without lupus may share these characteristics [87]. Persistent headache in SLE should always suggest the possibility of cerebral venous thrombosis, in patients with aPL.

Other less common manifestations include chorea, which is the most frequent type of movement disorder in SLE, and has been associated with aPL [88], and involvement of the peripheral nervous system including cranial neuropathies, polyneuropathy and less commonly mononeuropathy (single, multiplex), acute inflammatory demyelinating polyradiculoneuropathy, myasthenia gravis, or plexopathy.

3.7 Cardiac manifestations

Cardiac manifestations are among the most common manifestations of SLE (Figure 3.8) [6]. Any part of the heart can be affected [89], including the pericardium, myocardium, the valves, the conduction system, and the coronary arteries (ischemic cardiovascular manifestations are specifically described in Chapter 7). Pericarditis is the most common cardiac manifestation of SLE [80] and part of the classification criteria [80]. The exact frequency of pericarditis varies depending on whether only symptomatic pericardial involvement is considered as well as on the methods used to document the involvement [90]. Pericarditis is a common presenting manifestation of SLE [91], and is usually associated with active disease in other organs. Overall, symptomatic pericarditis is observed in ≈20–40% of SLE patients during the course of the disease [92]. Pericardial effusions causing tamponade occur only in a minority of patients, but can be life-threatening [93]. As in other causes of pericarditis, a pericardial rub at chest auscultation, and diffuse ST segment elevations, PR segment depression, and low voltages on electrocardiogram are diagnostic of pericarditis. C-reactive protein (CRP) levels may be significantly increased in lupus pericarditis in the absence of an infection [94]. Echocardiography is the method of choice for the investigation of pericardial involvement in SLE, but MRI can be useful in case of pericarditis without effusion [95].

Acute myocarditis occurs in 5–10% of SLE patients. Signs and symptoms of myocarditis in SLE are similar to those due to myocarditis of

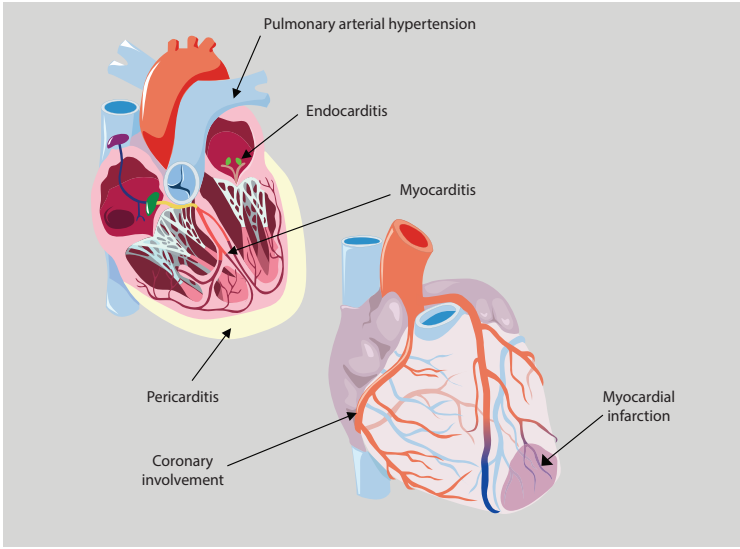

Figure 3.8 Main cardiac involvements in systemic lupus erythematosus. Elements of this illustration were provided by Servier Medical Art by Servier (http://smart.servier.com/), licensed under a Creative Commons Attribution 3.0 Unported Licence.

other causes, and the main complications are conduction abnormalities, arrhythmias and heart failure [96]. Therefore, any of these complications, as well as electrocardiographic abnormalities involving ST and/or T waves, increased troponin level without evidence of ischemic coronary involvement, or unexplained cardiomegaly should suggest the possibility of a myocarditis in a patient with SLE. Echocardiography typically shows global hypokinesis, but MRI allows differential diagnosis with other mechanisms of heart involvement, such as ischemic heart disease [97,98]. An important differential diagnosis of cardiac failure in SLE is antimalarial cardiopathy, although onset of the latter is usually not sudden [99].

Valvular abnormalities such as valve vegetations, thickening or dysfunction are frequently reported in SLE patients with aPL [100] or with antiphospholipid syndrome [6], but are generally not associated with SLEper se. Importantly, only a minority of patient (≈5%) with aPL-related valvular disease develop severe manifestations that require surgical treatment [6]. Key messages on the cardiac manifestations of SLE are as follows (Table 3.4).

Key messages on the cardiac manifestations of systemic lupus erythematosus (SLE)
General comments Cardiac manifestations are among the most common manifestations of SLE Any part of the heart can be affected
• Pericarditis is the most common cardiac manifestation of SLE (≈ 20–40% of SLE patients) • Pericarditis is a common presenting manifestation • Tamponade is rare but can be lethal • CRP levels are may be significantly increased in lupus pericarditis, in the absence of an infection • Acute myocarditis occurs in 5–10% of SLE patients • The main complications are conduction abnormalities, arrhythmias and heart failure • MRI allows differential diagnosis with other mechanisms of heart involvement • Cardiac toxicity of antimalarials should be considered in case of cardiac failure in SLE patients • Valvular abnormalities are reported in SLE patients with antiphospholipid antibodies • ≈5%) with aPL-related valvular disease require surgical treatment

Table 3.4 Key messages on the cardiac manifestations of systemic lupus erythematosus.
aPL, antiphospholipid antibodies; CRP, C-reactive protein; MRI, magnetic resonance imaging.

3.8 Pulmonary

The main pulmonary manifestation of SLE is pleuritis. Other manifestations such as pulmonary arterial hypertension, interstitial lung disease, lupus pneumonitis, pulmonary hemorrhage, and the shrinking lung syndrome are uncommon manifestations of SLE. Pulmonary embolism is mostly associated with the antiphospholipid syndrome [6].

Pleuritis is the most common pulmonary manifestation in SLE [6,92] and part of the classification criteria [80]. It is often associated with disease activity in other organs [101,102], including with pericarditis in 10–20% of cases [102]. Concomitant anti-Sm and anti-RNP seropositivity, greater cumulative damage, longer disease duration, and younger age at SLE disease onset have been associated with a higher rate of pleuritic involvement in SLE [103]. Most patients report pleuritic chest pain but isolated cough and dyspnea is described. Pleuritis may be unilateral or more typically bilateral, and its abundance is usually moderate in SLE. Clinical assessment of pleural manifestations should search for a history of pleuritic chest pain, rubs on pulmonary auscultation, and areas of decreased breath sounds or dullness to percussion. As in other form of serositis in SLE, CRP levels are significantly increased in lupus pleuritis [94]. A thoracentesis should be performed when there is a concern for infection. The pleural fluid is usually exudative. Antinuclear antibody testing in pleural fluid is not

routinely performed, but negativity for ANAs or specific autoantibodies has been shown to argue against the diagnosis of lupus pleuritis [104].

Interstitial lung disease is far less common in SLE than in other connective tissue diseases [105], and is generally not attributable to the disease itself [106]. Lupus pneumonitis is a rare entity (1–5% of patients) with severe prognosis [107]. It is characterized by fever, cough, dyspnea, hemoptysis and hypoxemia, and may therefore be difficult to distinguish with severe infection or acute respiratory distress syndrome (ARDS). Chest imaging usually reveals bilateral opacities and high resolution CT-scan reveals patchy consolidations surrounded by ground glass appearance [107]. Pulmonary hemorrhage is a life threatening complication of SLE that mostly occurs in patients with severe, multi-organ involvement, with high disease activity [108]. It is thought to result from vasculitis of the pulmonary vessels. This complication is typically marked by hemoptysis and confirmed by bronchoscopy, but the diagnosis should be considered in case of severe respiratory failure with unexplained pulmonary infiltrates and anemia, even in the absence of hemoptysis [108]. Pulmonary hypertension is a rare but severe complication of SLE [109,110] that may be secondary to chronic pulmonary emboli or may result from the disease itself. Pulmonary arterial hypertension in SLE has been associated with pericardial effusion and anti-RNP antibody [111]. Finally, the shrinking lung syndrome is a very rare manifestation of SLE characterized by restrictive defects on pulmonary function testing due to diaphragm dysfunction in the setting of a normal lung parenchyma [112]. Key messages on the pulmonary manifestations of SLE are below (Table 3.5).

Key messages on the cardiac manifestations of systemic lupus erythematosus (SLE)
General comments
Pleuritis is the most common pulmonary manifestation in SLE
C-reactive protein levels are significantly increased in lupus pleuritic
A thoracentesis should be performed when there is a concern for infection.
Other less common manifestations
Interstitial lung disease
Lupus pneumonitis
Pulmonary hemorrhage
Pulmonary Arterial Hypertension
Shrinking lung syndrome

Table 3.5 Key messages on the pulmonary manifestations of systemic lupus erythematosus.

3.9 Gastrointestinal

A vast majority of gastrointestinal manifestations observed in SLE patients are unrelated to the disease [113]. Pancreatitis is a rare (<5%) but life-threatening complication of SLE. It is mostly observed at initial presentation, especially in children, or during the first years of the disease, and is generally associated with high disease activity [114]. Traditional predisposing factors should be searched for, particularly hypertriglyceridemia or use of azathioprine [115].

Lupus enteritis is a rare cause of abdominal pain in patients with SLE [116]. Clinical symptoms include abdominal pain, vomiting, diarrhea, and fever. Imaging studies such as abdominal ultrasound or CT scan commonly reveals a bowel wall edema (or 'target sign', see Figure 3.9) along with ascite, mesenteric abnormalities and less frequently bowel dilatation [116]. Digestive vasculitis is confirmed in only a minority of cases [116], and the disease may rarely evolve to intestinal necrosis and perforation, mostly if untreated. Cases of acute acalculous cholecystitis have been reported, including in children. Protein-losing enteropathy characterized by profound edema and severe hypoalbuminemia secondary to excessive

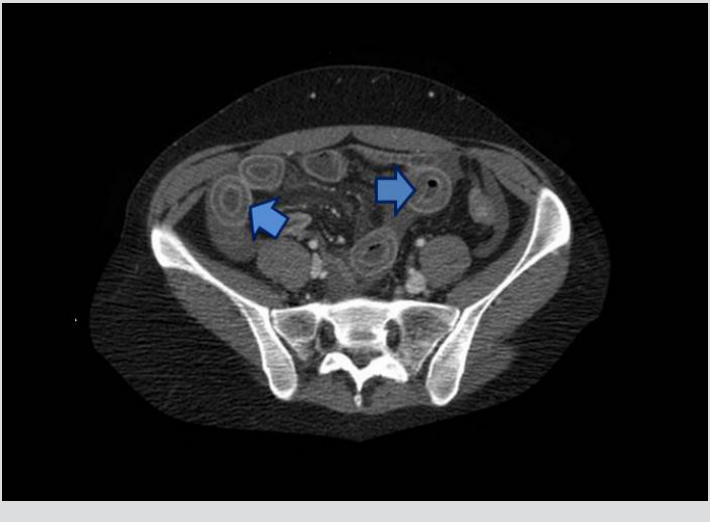

Figure 3.9 Bowel-wall thickening and enhancement (target sign) in a systemic lupus erythematosus patients with lupus enteritis.

loss of serum protein from the gastrointestinal tract is very rare [117,118]. SLE-related intestinal pseudo-obstruction is a rare but well-recognized clinical syndrome characterized by the presence of clinical features of intestinal obstruction without an identifiable organic obstructive lesion with intestinal hypomotility and esophageal aperistalsis [119]. Mesenteric ischemia can occur in the context of antiphospholipid syndrome [6].

3.10 Hematological

The main hematological manifestations of SLE include neutropenia, lymphopenia, thrombocytopenia, autoimmune haemolytic anaemia (AIHA), thrombotic thrombocytopenic purpura (TTP), hemophagocytic syndrome, and autoimmune myelofibrosis. Some of these manifestations are included in the classification criteria for SLE [80] (see Table 3.3). However, none of these manifestations are specific. It is therefore crucial to distinguish SLE-related hematological manifestations from the consequences of immunosuppressive agents, or signs of a co-existing hematological disease. A recent meta-analysis did not find evidence for a significant association between an isolated reduction in white blood cells of a whole (with normal absolute lymphocyte and neutrophil count) and occurrence of infections. However, the study reported an association between absolute lymphocyte or neutrophil count and the risk of major infections [120].

Lymphopenia ($<1.5\times10^9$ lymphocytes/L on two or more occasions [79]) is the most frequent white cell abnormality in SLE, being reported in up to 93% of cases [120]. Lymphopenia is commonly observed at presentation and often persists during course of the disease, where it may fluctuate with disease activity. Lymphopenia is usually moderate, and severe lymphopenia ($<0.5\times10^9$ lymphocytes/L) is rare (5–10% of cases). Glucocorticoids and immunosuppressive drugs may also contribute to lymphopenia in SLE.

Neutropenia is usually defined as an absolute neutrophil count <1000 cells/mm^3, and is believed to be due to antibodies directed against neutrophil cell surface antigens. Mild neutropenia is a common finding in SLE (20–40% of patients), but severe neutropenia is rare (<5%) [120]. The exact definition of neutropenia is complicated by the common finding of benign ethnic neutropenia in a significant proportion of patient of Arab and African origins [121].

Thrombocytopenia (platelet count <100 000/mm^3 without any other identifiable cause [80]), is observed in 10–20% of SLE patients [6], but is also a common manifestations of patients with the antiphospholipid syndrome [100]. Thrombocytopenia can be due to an idiopathic thrombocytopenic purpura (ITP)-like thrombocytopenia related to SLE, but also to an adverse effects of treatments, due to hypersplenism (for reasons other than SLE), to thrombotic thrombocytopenic purpura (TTP), or be a consequence of a bone marrow involvement, such as in the hemophagocytic syndrome or myelofibrosis (in which cases other cytopenias are also observed). Thrombocytopenia that occurs early in the course of SLE has been associated with a more severe and active disease [122]. In a recent retrospective study of 230 SLE patients with thrombocytopenia, there were no significant differences in clinical or other laboratory findings according to the severity of thrombocytopenia, except for hemorrhagic complications and mortality [123], a finding reported across most studies [122,124].

Autoimmune haemolytic anaemia (AIHA) is observed in 5–15% of patients with SLE [125]. As in any other condition, diagnosis of AIHA in SLE is based on the presence of positive haemolytic markers (such as decreased haptoglobin, and increased lactate dehydrogenase and indirect bilirubin), presence of significant reticulocytosis, and a positive direct antiglobulin test, mainly of the warm-type IgG in SLE. AIHA is mostly observed at SLE onset [126] and is part of the classification criteria for SLE [80]. The association with thrombocytopenia is common, and suggests a shared pathogenic mechanism [125,127]. Causes of non-regenerative anemia in SLE include chronic inflammation, renal disease, iron deficiency due to gastrointestinal loss, and pure red cell aplasia, which is associated with SLE [128] and with parvovirus B19 infection in SLE patients [129].

Thrombotic thrombocytopenic purpura (TTP)-like thrombotic microangiopathy (TMA) is a rare (<5%) but severe hematological manifestations of SLE [130]. TTP is diagnosed based on the characteristic association of thrombocytopenia, mechanical hemolytic anemia with schistocytes, acute renal failure, central neurological manifestations, and occasionally fever. Independent risk factors for the development of TTP in SLE include high SLE disease activity index scores and coexisting nephritis [131].

SLE patients with TTP may have less clinically apparent manifestations of TTP [130] and worse survival [132] compared with other etiologies of TTP. Specifically, presence of a concurrent infection or of neurological impairment have been associated with a worse survival [131,133]. In case of renal impairment, renal pathology usually reveals signs of thrombotic microangiopathy with or without signs of lupus nephritis. Pathogenesis of TTP in SLE involves the widespread formation of platelet aggregates within the microcirculation due to the abnormal persistence of von Willebrand factor (vwf) multimers. The physiological cleavage of these multimers is impaired due to the reduced activity of a disintegrin-like and metalloproteinase with thrombospondin type 1 motif-13 (ADAMTS13). The decrease in ADAMTS13 activity is due to autoantibodies neutralizing ADAMTS13 in a large proportion of SLE patients with acquired TMA associated with severe ADAMTS13 deficiency [134].

Hemophagocytic syndrome (or macrophage activation syndrome [MAS]) is a rare but potentially lethal complication of SLE [135]. In a recent French nationwide study of 81 MAS episodes [136], MAS was the first manifestation of SLE in ≈45% of patients. MAS can be related to SLE disease activity or secondary to an infection (documented in ≈40% of cases). The main clinical features of MAS are fever, thrombocytopenia $<100\times10^9$/, neutropenia, anemia <8 g/dl, splenomegaly and increased transaminases, CRP, and ferritin. A recently described feature of SLE-MAS is the frequent increase of procalcitonin (85%), even in the absence of an infection. Reported visceral complications include myocarditis, acute lung injury, seizures, and pancreatitis leading to intensive care unit (ICU) hospitalization in ≈30% of cases. Relapses occur in <20% of patients. Due to prompt management, the death rate in the French series was <5%.

Finally, cytopenia may result from autoimmune myelofibrosis (AIMF), which is an extremely uncommon entity in association with SLE (less than 40 reported cases in the literature) [137]. Most patients present with either bicytopenia or pancytopenia, and bone marrow biopsy shows fibrosis with increased reticulin fibers and fibroblasts [138]. Mutational analysis for the genes involved in the pathogenesis of primary myelofibrosis is negative, and the prognosis is much more favorable. Key messages on the hematological manifestations of SLE are below (Table 3.6).

Key messages on the hematological manifestations of systemic lupus erythematosus (SLE)
Hematological manifestations in SLE can be due to: • Disease itself (SLE-related hematological manifestations) • Consequences of immunosuppressive agents • Co-existing hematological disease Proper distinction between these categories is crucial
The main hematological manifestations associated with SLE are: • Leucopenia • Neutropenia • Lymphopenia • Idiopathic thrombocytopenic purpura (ITP)-like thrombocytopenia • Autoimmune haemolytic anaemia • Thrombotic thrombocytopenic purpura • Hemophagocytic syndrome (or macrophage activation syndrome) • Autoimmune myelofibrosis

Table 3.6 Key messages on hematological manifestations of systemic lupus erythematosus.

3.11 Ocular manifestations

Ocular manifestations are fairly common in SLE. These may be the presenting features of the disease and may occasionally lead to permanent blindness. Almost any part of the eyes and visual pathways can be affected, including the eyelid, ocular adnexa, sclera, cornea, uvea, retina, and optic nerve [139–141]. The most common manifestation is keratoconjunctivitis sicca, which is association with secondary Sjögren's syndrome. The most vision-threatening complications are retinal vasculopathy (also inappropriately termed retinal vasculitis) and optic neuritis/neuropathy. Retinal vasculopathy is mostly observed in patients with aPL [142], and is typically characterized by microthrombosis and immune complex mediated vasculopathy rather than a true vasculitis [143]. Optic nerve diseases are rare manifestations of SLE and consist of optic neuritis and ischemic optic neuropathy. Presenting visual acuity in SLE-associated optic neuritis is poor and the prognosis of the complication has been reported to be less favorable than in idiopathic cases [140]. The neuromyelitis optica spectrum disorders are characterized by a combination of optic neuritis, transverse myelitis, and a high association with aquaporin-4 antibodies and have been reported in SLE patients [144]. Ischemic optic neuropathy is due to an ischemic process that affects the small vessels supplying both the optic nerve head and the retrobulbar portion, and usually presents as an acute loss of vision with an altitudinal visual field defect with or

without optic disc edema [140]. Prompt diagnosis and treatment of eye involvement is crucial in SLE as the most severe of these complications are often associated with end-organ damage [140].

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Chapter 4

Diagnosis

The diagnosis of systemic lupus erythematosus is based on clinical and laboratory criteria.

4.1 Clinical assessment

The great variability in the expression and severity of SLE (see Chapter 3) constitutes a diagnostic challenge for the clinician [1]. SLE may involve any organ or system, in any combinations. Therefore, many symptoms are not specific to just SLE, and it is therefore important to make proper distinction between SLE and other etiologies (see Chapter 1). The most common presenting manifestations are arthritis, malar rash, and constitutional symptoms such as malaise, fatigue, fever, and weight loss [1].

Classification criteria (see Chapter 2) have been developed and updated throughout the years, as a mean to categorize patients for study purposes [2]. However, these are not diagnostic criteria and have been shown to overemphasize cutaneous manifestations and lack sensitivity in early SLE [3]. Also, it may take several months or years from the first sign of SLE until the patient fulfills the classification criteria, and therefore those criteria are not valid for incident SLE.

In the absence of proper diagnostic criteria, SLE is generally recognized based on clinical and laboratory criteria, after exclusion of alternative diagnoses. A list of clinical manifestations compatible with the diagnosis of SLE is shown in Table 4.1. Of note, there are patients who do not fulfill the classification criteria for SLE, but nevertheless have the disease. This includes patients presenting with an inadequate number of criteria, or those who have manifestations of SLE that have

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Main clinical features compatible with the diagnosis of systemic lupus erythematosus		
Abdominal pain	Myositis	Psychosis
Alopecia	Nausea or vomiting	Pulmonary hemorrhage
Arthralgia	Nasopharyngeal ulcerations	Pulmonary hypertension
Arthritis	Oral ulcerations	Purpura
Butterfly rash	Organic brain syndrome	Raynaud's phenomenon
Chilblain-like lesions	Optic neuropathy	Ring-shaped cutaneous lesions
Cranial neuropathies	Panniculitis	Seizures
Discoid rash	Pericarditis	Splenomegaly
Fatigue	Peripheral neuropathies	Transverse myelitis
Fever (in the absence of infection)	Photosensitivity	Urticaria
Hepatomegaly	Pleuritis	Vasculitis
Lymphadenopathy	Pneumonitis	Weight loss
Myocarditis	Proteinuria on urinary dipstick	

Table 4.1 Main clinical features compatible with the diagnosis of systemic lupus erythematosus.

not been included in the classification criteria. The initial evaluation of a patient for SLE requires a careful history and physical examination, along with adequate laboratory testing (see Section 4.2). Demographic characteristics should be taken into account since the disease occurs primarily, in young women of childbearing age. However, SLE cannot be excluded based solely on age or racial background (see Chapter 7 for pediatric and late-onset SLE).

4.2 Laboratory testing

SLE is an autoimmune disease characterized by a broad spectrum of clinical manifestations, in association with antibodies against various nuclear components. In patients with a clinical suspicion of SLE, additional laboratory testing is indicated (Table 4.2). Also, routine laboratory tests are helpful in organ systems that cannot be assessed clinically.

4.2.1 Antinuclear antibodies

Presence of antinuclear antibody (ANA) at a titer ≥1/80 is the most sensitive diagnostic criteria for SLE, as it is observed in virtually all patients with the disease. ANA can be detected in the blood several years before the diagnosis [4]. Although extremely rare, ANA-negative lupus

Routine laboratory tests at initial evaluation of systemic lupus erythematosus
Full blood count
Liver function tests
Electrolytes, urea, creatinine
Prothrombin time
Partial thromboplastin time
C-reactive protein
Urine Protein to Creatinine Ratio (and 24h-proteinuria if abnormal ratio)
Urinalysis
Antinuclear antibodies
Anti-double stranded antibodies
Anti-ENA antibodies (anti-Sm, anti-RNP, anti-SSA, anti-SSB)
CH50, C3, C4
Lupus anticoagulant
Anti-cardiolipin antibodies (IgG and IgM)
Anti-β2-glycoprotein-1 antibodies
Coombs test
Additional testing: fasting lipid panel, thyroid function tests, HIV, HBV and HCV serologies

Table 4.2 Routine laboratory tests at initial evaluation of systemic lupus erythematosus.

exist; however, the diagnosis of SLE should generally be questioned in the absence of ANA. The ANA test is not specific for SLE, and positivity can be observed in healthy individuals (commonly at low titers <1:80), transiently during infections, with use of drugs and medications (see section 1.7 for drug-induced lupus) as well as at significant titers in other connective tissue diseases. The most common screening test for ANA is immunofluorescence on human epithelial (HEp2) tissue, although an enzyme-linked immunosorbent assay (ELISA) test, bead-based tests, and solid phase assays are also available. Immunofluorescence ANA testing should include the determination of both the titer and pattern of the fluorescence. Low titers (1:40 to 1:80 or 5–10 IU) are not uncommon in healthy individuals, especially in women >40 years of age or elderly subjects. Therefore, a titer of >1:80 is taken as significant for the diagnosis of connective tissue diseases by most laboratories. Reliable identification of ANA immunofluorescence patterns is difficult and requires an experienced laboratory. A homogeneous/peripheral pattern usually reflects antibodies to histone/dsDNA/chromatin, whereas the many other specificities that may be observed in SLE patients (anti-SSA, SSB, RNP, Sm) show speckled patterns of various sizes and densities. ANA-positive samples should be subjected to more specific assays for the

diagnosis of SLE, such as search for anti-double stranded DNA (dsDNA) antibodies and antibodies against extractable nuclear antigen (ENA).

4.2.2 Anti-dsDNA, anti-histone and anti-nucleosome antibodies

Anti-dsDNA antibodies are detectable in 60-80% of patients with SLE [5]. Therefore, a diagnosis of SLE cannot be excluded solely by the absence of anti-dsDNA antibodies. These antibodies are highly specific (≈95–98%) for the disease [5], and are included in the classification criteria [2]. The direct pathogenic role of anti-dsDNA antibodies is shown by the fact that DNA/anti-dsDNA complexes activate complement and are nephritogenic [6]. The most common methods to detect anti-dsDNA are the ELISA, the Crithidia luciliae immunofluorescence test (CLIFT), and the Farr immunoprecipitation assay. Of the three tests, the ELISA is the most sensitive but has limited specificity, CLIFT has moderate sensitivity and good specificity, while the Farr assay is highly specific but less sensitive [7]. High levels of anti-dsDNA antibodies, often with hypocomplementemia, are generally believed to correlate with clinical activity in SLE and are associated with proliferative lupus nephritis. However, whether it is indicated to treat patients with increasing anti-dsDNA antibody titers in the absence of clinical activity remains controversial [8]. However, these patients should probably be monitored more closely, especially if they have hypocomplementemia. Anti-single stranded DNA (ssDNA) have a very limited diagnostic value due to their low specificity [9] and are not used in routine clinical practice.

Around 50–80% of patients with SLE have anti-histone antibodies. These antibodies are barely used anymore as they are not specific for SLE and cannot reliably distinguish drug-induced lupus erythematosus (see section 1.7) from SLE as it was claimed initially [10].

Conversely, anti-nucleosome antibodies have a good sensitivity (≈60%) and high specificity (≈90%) for SLE [11], and are correlated with lupus nephritis [11]. Most autoantigens recognized by anti-nucleosome antibodies are conformational epitopes and these antibodies do not react with DNA or histones alone [6]. Anti-nucleosome antibodies may be useful markers for diagnosis and activity assessment of anti-dsDNA-negative SLE [6].

4.2.3 Anti-ENA antibodies

Antibodies to Ro (SS-A) and La (SS-B) are found in SLE (15–30%) but also in Sjögren's syndrome (50–70%), and are important diagnostic markers when anti-dsDNA are absent. They are statistically associated with sicca syndrome, subacute cutaneous lupus (see section 3.4), and neonatal lupus (see section 7.4). Anti-RNP antibodies react with proteins that form U1snRNP. They are observed in ≈30% of SLE patients and also observed typically at high titer in mixed connective tissue disease (MCTD). Anti-SSA, anti-SSB, and anti-RNP antibodies have been associated with the occurrence of neonatal lupus. Anti-Sm antibodies are directed against proteins that constitute the common core of small nuclear ribonucleoprotein (snRNP). These are found in 10–30% of cases, depending on the demographic and ethnic characteristics of the study populations [12], and are highly specific for SLE. Anti-C1q antibodies are found in 40–60% of lupus patients but are not specific. However, they appear to correlate with global and renal disease activity [6].

4.2.4 Other specificities

Other less frequent auto-antibodies include anti-ribosomal P (anti-Ribo P) antibody, which give a finely granular cytoplasmic pattern in immunofluorescence. Anti-Ribo P have a low sensitivity (5–10% of SLE patients) but a high specificity for SLE. The association of anti-Ribo P antibodies with specific features of SLE (such as neuropsychiatric, renal, or hepatic involvements) is controversial [13]. Finally, anti-dense fine speckled 70 (DFS70) antibodies were reported to be negatively associated with the presence of auto-immune diseases but are also observed in some patients with SLE [14].

4.2.5 Complement levels

Homozygous and/or heterozygous deficiencies of the classical complement pathway (C1q, C1r, C1s, C4A, C4B and C2) are associated with increased susceptibility to SLE (see section 1.4). Furthermore, consumption of complement factors reflecting classical pathway activation (see Figure 4.1) by immune complexes in SLE is reflected by decreased levels of individual proteins such as C3 and C4 as well as by a decrease

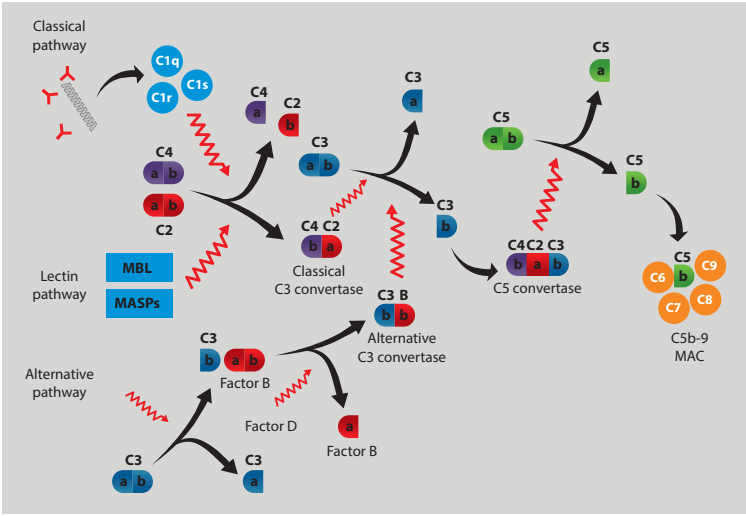

Figure 4.1 Schematic view of the complement pathways. The classical pathway is activated by dsDNA-containing immune complexes. The lectin and the alternative pathways are activated by the surfaces of pathogens.

in total complement hemolytic activity (CH50). Hypocomplementemia is not specific to SLE and can be found in any disease with circulating immune complexes. Also, consumption of C3 and C4 is not seen in all patients with active SLE, and is mostly observed in patients with active lupus nephritis and hematological manifestations. Also, because C3 and C4 are acute phase proteins, their levels may be normal during inflammatory processes, despite ongoing complement consumption.

4.2.6 Antiphospholipid antibodies

Anti-phospholipid antibodies (aPL) are associated with thrombotic and pregnancy complications [15]. Testing for lupus anticoagulant (LA) is generally recommended in all SLE patients, as well as patients who have unexplained prolonged aPTT during a routine laboratory testing [16], as abnormal LA finding is the laboratory test result that confers the strongest risk for thrombosis [17,18]. The assay has been standardized [16] and is currently based on a mixing test of the patient plasma with normal plasma from healthy donors, with coagulation times measured using both diluted russell viper venom time (dRVVT) and another aPTT

test performed using silica as an activator. Once a patient has been identified as positive for LA, it important to repeat the testing at least 12 weeks after the initial evaluation, in accordance with the definition for the antiphospholipid syndrome (APS) [19]. Anticardiolipin antibodies (aCL) are seen in 16–60% of patients with SLE. These antibodies react primarily to membrane phospholipids such as cardiolipin and phosphatidylserine. Presence of moderate to high levels of IgG or IgM aCL in serum or plasma (i., >40 IgG phospholipid units (GPL)/mL or IgM phospholipid units (MPL)/mL or >99th percentile) on two or more occasions at least 12 weeks apart is included in the definition for APS [19]. Laboratory testing for anti-β2-glycoprotein-1 antibodies is not standardized and their prevalence in SLE may therefore vary across different studies.

4.2.7 Standard laboratory testing

Routine laboratory testing includes the erythrocyte sedimentation rate, which is usually raised in SLE patients, but does not correlate well to disease activity. The C-reactive protein (CRP) is usually normal or only slightly elevated during SLE flares SLE, except in case of serositis [20], hemophagocytic syndrome [21], as well as during infections. Also, procalcitonin (PCT) can be used in the early differentiation between bacterial infection and flare in febrile SLE patients, with raised levels being strongly suggestive of bacterial infection in the absence of hemophagocytic syndrome [22]. Leucopenia, lymphopenia, neutropenia, thrombocytopenia, and anemia may be related to disease activity, treatments, or additional hematological diseases. Serum albumin, creatinine, urine protein/creatinine ratio and urinalysis provide information on the presence of renal involvement.

4.3 Imaging

The diagnosis of SLE is generally based on compatible clinical and laboratory criteria, after exclusion of alternative diagnoses (see Section 4.1). Nevertheless, imaging is routinely performed during the diagnostic phase of SLE as well as complications to decide whether those are related or not to SLE, and is largely guided by specific symptoms (see Table 4.3).

Imaging type	Imaging technique
Joint involvement imaging	Plain X-ray radiograph Doppler ultrasound Joint MRI Fluorescence optical imaging
Thoracic & cardiovascular imaging	Chest X-ray CT-scan CT angiography (coroscan) Angio CT-scan Electron beam CT Echocardiography cardiac MRI Carotid ultrasound
Abdominal imaging	Abdominal CT-scan (including angio CT-scan) Abdominal echography Abdominal MRI Renal ultrasonography
CNS imaging	Brain CT-scan Brain MRI
Other imaging	FDG PET-CT scan Functional brain MRI Brain SPECT

Table 4.3 Main imaging techniques that can be used in systemic lupus erythematosus.

Plain radiographs of hand, feet, or any swollen joint are performed as part of the diagnostic procedure for early arthritis, in order to rule out features that would be more evocative of rheumatoid arthritis [23,24]. In case of Jaccoud arthropathy, the x-rays show metacarpophalangeal (MCP) subluxations with reducible deformities without erosions [25,26] while presence of the latter would be evocative of 'rhupus' [23,24,27] or of any other erosive arthritis (Figure 4.2). Magnetic resonance imaging (MRI) and bone scintigraphy can be useful for the diagnosis of osteonecrosis.

Chest X-ray is mostly used for the diagnosis of pleuritis or to rule out pneumonia in case of fever. Thoracic computed tomography (CT)-scan is routinely used to search for pulmonary embolism, in case of serositis, pneumonia, interstitial lung disease, and pulmonary hemorrhage. Diagnostic thoracentesis under ultrasonographic guidance may help to differentiate between pleural effusions from SLE and those from other causes [28]. Echocardiography is used to assess pericardial

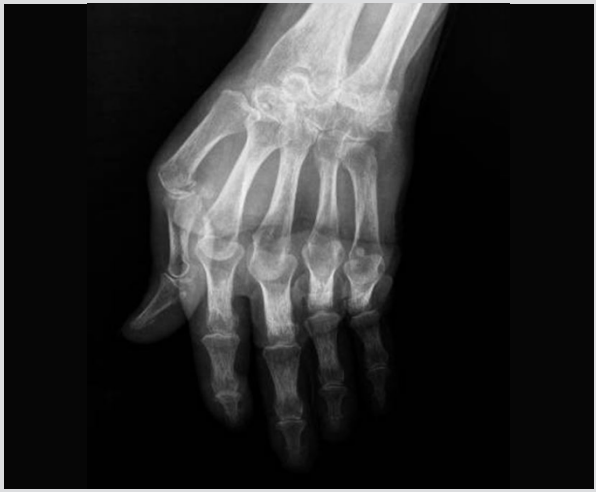

Figure 4.2 Erosive carpitis suggestive of 'rhupus'.

effusion, pulmonary hypertension, Libman-Sacks endocarditis, and the left ventricular function.

Myocardial perfusion imaging (SPECT) has largely been replaced by cardiac MRI, which is particularly interesting when myocarditis is suspected [29]. Electron beam CT and CT angiography (coroscan) can be used to quantify coronary artery calcification as a measure of coronary atherosclerosis [30]. Carotid ultrasound allows for assessment of intima-media thickness and plaques [31].

Abdominal CT-scan and echography are mostly used in case of abdominal pain, to rule out complications such as mesenteric artery thrombosis or lupus enteritis (see Chapter 3). Renal ultrasonography is mostly used to rule out an obstructive cause in case of renal failure or before kidney biopsy.

Brain MRI (Figure 4.3) is usually performed when neuropsychiatric SLE is suspected (see Chapter 3), keeping in mind that its sensitivity is low (30–40%), and that the diagnostic ability to differentiate SLE-related from non-SLE-related neuropsychiatric involvement has not been adequately established [8]. Brain MRI is also performed in case of stroke or of central nervous system (CNS) vasculitis.

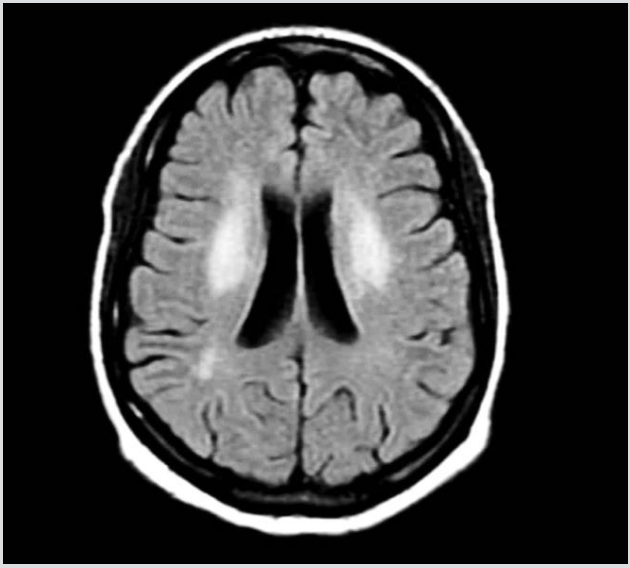

Figure 4.3 Fluid-attenuated inversion recovery (FLAIR)-weighted brain magnetic resonance imaging showing bilateral hypersignal of the corona radiata and left subcortical right parietal lesion in a patient with active neuropsychiatric systemic lupus erythematosus.

4.4 Differential diagnosis

Due to the highly polymorphic nature of the disease, the list of possible differential diagnoses is broad, and will vary with the presentation of each case (see Table 4.4). These include drug-induced lupus (see section 1.7), other connective tissue and systemic diseases, infections, fibromyalgia, rare enzymatic deficiencies such as prolidase deficiency [32,33], and closely-related immune system dysregulations such as in the autoimmune lymphoproliferative syndrome [34].

Main differential diagnoses of systemic lupus erythematosus (SLE)	
Drug-induced lupus	Arthralgia is the only clinical manifestation in 90% of cases. Myalgia, fever, weight loss are common (as well as rash in anti-TNFα and terbinafine-induced LE)
Rheumatoid arthritis	Important distinguishing features are the absence of joint erosion on plain radiographs in SLE, as well as in the reducible joint subluxation, if any. Significant erosions with positive ACPA constitutes 'rhupus'
Sjögren's syndrome	Patients with Sjögren's syndrome have keratoconjunctivitis sicca and xerostomia, and lymphocytic infiltrate on salivary gland biopsy, which is not typical of SLE. Interstitial lung disease is relatively common in Sjögren's syndrome and rare in SLE
Idiopathic inflammatory myopathy (IIM)	Clinical findings characteristic of SLE such as oral ulcers, nephritis, and hematologic abnormalities are absent in IIM. Dermatomyositis (DM) and SLE share a very similar pathology on skin biopsy and are virtually impossible to distinguish. The 'Lupus band' may be seen in both SLE and DM patients. However, the rash typically involves the interphalangeal area in SLE and is located over the dorsal aspect of the knuckles in DM. Muscle biopsy may help to distinguish SLE from IIM. Patients with DM or polymyositis may express IIM-specific antibodies
Undifferentiated connective tissue disease (UCTD)	Patients with UCTD do not fulfill classification criteria for SLE, but may evolve towards criteria-defined SLE
Mixed connective tissue disease (MCTD)	Renal or CNS involvement is highly uncommon in patients with MCTD, and these patients do not have anti-dsDNA antibodies
Adult onset Still's disease (AOSD)	Fever, arthritis, hepatosplenomegaly, and lymphadenopathy can be observed in both AOSD and SLE, but ANA are typically negative in AOSD and the WBC show leukocytosis with neutrophilia in AOSD while SLE patients have commonly lymphopenia and frequent neutropenia
Multiple sclerosis (MS)	Optic neuritis and myelitis are observed in SLE, and up to 10–20% of MS patients have positive ANA. Extra-neurological symptoms such as arthritis and photosensitivity points towards SLE. Oligoclonal band analysis is positive in up to 50% of patients with CNS lupus. The ESR is commonly raised in SLE but not in MS. MRI changes are neither invariable nor specific. Skin biopsy (staining for Ig and complement deposition, the 'lupus band') can be extremely helpful to confirm lupus
Infections (HCV, HIV, lyme's disease, parvovirus B19)	Fever, arthritis, hepatosplenomegaly, and lymphadenopathy can be observed in both SLE and infections
Medium and small vessel vasculitides	Fever, arthritis, myalgia, neurological, and kidney involvement are seen in SLE, but patients with vasculitis are generally ANA-negative, and may have positive ANCA
Endocarditis	Should be considered in all patients with arthritis and fever. These patients can be ANA-positive. Diagnosis should be excluded based on blood cultures and echocardiography

Table 4.4 Main imaging techniques that can be used in systemic lupus erythematosus (continues over the page). ACPA, anti-citrullinated peptide antibodies; ANA, antinuclear antibodies; ANCA, Anti-neutrophil cytoplasmic antibodies; ESR, erythrocyte sedimentation rate; HCV, hepatitis C virus; HIV, human immunodeficiency virus;

Fibromyalgia	Patients with SLE may have arthralgias, myalgias, and fatigue, but other disease manifestation or organ-system involvement are not seen in fibromyalgia. Patients with fibromyalgia may have positive ANA (as in the general population) but are typically negative for anti-dsDNA. Patients with SLE may have overlapping fibromyalgia
Rosacea	The malar (butterfly) rash of SLE can be difficult to distinguish from rosacea. Fine scaling and pigment changes favor the diagnosis of SLE while papules, pustules, and bepharitis are more suggestive of rosacea. Other SLE symptoms are not observed in rosacea
Lymphoma	Should be considered in patients with lymphadenopathy, hepatomegaly and/or splenomegaly, and lymphopenia
Juvenile idiopathic arthritis (JIA)	A diagnosis of JIA is made after other causes of arthritis have been excluded. Clinical findings (eg, rash, systemic illness) help differentiate JIA from SLE
Prolidase deficiency	Prolidase deficiency is an autosomal recessive inherited disease that begins in childhood and is characterized by typically severe and chronic skin lesions (such as ulcers of the lower extremities) and telangiectasias of the face and hands, recurrent infections, dysmorphic facial features, hepatosplenomegaly, cytopenias, hypergammaglobulinemia, and hypocomplementemia
Autoimmune lymphoproliferative syndrome (ALPS)	ALPS is characterized by lymphoproliferation (leading to hepatosplenomegaly and lymphadenopathy) and autoimmunity (mainly cytopenias), which can mimic SLE. One prominent finding is an elevated level of CD4- and CD8-negative T lymphocytes (double-negative T cells) in the blood

Table 4.4 Main imaging techniques that can be used in systemic lupus erythematosus (continued).

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Chapter 5

Treatments

5.1 Goals of treatment and treatment strategies

As with all chronic diseases, the treatment of systemic lupus erythematosus (SLE) must be a balanced consideration of multiple disease-related and patient-specific aspects. SLE is associated with symptomatology and may also engender significant functional impairment and restrictions of activities. SLE also has the potential to cause severe and irreversible damage in the affected organs and tissues, and preventing such damage must be an important consideration as well. From these disease characteristics follow the treatment goals for SLE. First, the patient's symptomatic suffering must be alleviated. Patients generally see this as the most obvious and clear goal of the treatment and will seek medical care primarily to obtain such relief. However, the very important second goal must be to prevent, as much as possible, the accumulation of damage caused by the disease or by its treatment. These two goals are not always aligned. Simple analgesics and non-steroidal anti-inflammatory drugs (NSAIDs) may provide some symptomatic relief but there is no evidence that they prevent any damage. Thus, the approach to SLE must always be based on multiple goals and this can be regarded as part of the more extensive framework articulated by Fries [1] who identified the five dimensions of treating chronic illnesses as the 'five D's':

- death: preventing mortality
- discomfort: relieving symptoms
- disability: preventing functional decline
- drug side effects: minimizing toxicities due to the treatment
- dollar cost: finding an appropriate health-economic balance

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In the case of SLE, mortality that is directly attributable to the disease is uncommon but remains a concern in patients with the most severe forms of the disease. In addition to mortality caused by the disease itself, the treatments given to combat it may contribute to short-term mortality (for example, immunosuppression leading to fatal infections) and long-term morbidity (for example, treatments that accelerate arteriosclerosis), and more effective therapies used in a judicious manner might therefore improve outcomes.

In addition to the goals of limiting discomfort and disability the therapeutic discussions around SLE are frequently dominated by considerations of risks from the treatments. This is most clearly the case for corticosteroids. These medications, which will be discussed in more detail below, can be highly effective but are often associated with significant adverse health consequences, posing major challenges to the clinician. The final consideration is one of costs. In the treatment of SLE, older established medications such as corticosteroids are very inexpensive but newer approved biologic agents (belimumab) or unapproved but plausible therapies can pose large problems in terms of cost to the patient, the insurer, or to society.

Treatment of SLE can be divided into treatments aiming for immediate control of the disease process (treatment when SLE is first manifest, treatment of a flare, or the first step in an induction-maintenance treatment approach) and those aiming to keep the disease under control and prevent flares (maintenance treatment); in clinical practice, the same medications are often used for both purposes and the two intentions may overlap to a considerable degree. Nevertheless, it is useful to distinguish these two objectives.

5.1.2 Treatment strategies

There is no clear and generally accepted treatment strategy for SLE. For most practicing specialists, it is obvious that they will treat the lupus manifestations as they occur, and attempt to minimize exposure to toxic drugs when the clinical situation allows it. Thus, one might explain to the patient with SLE-related pleurisy and arthritis that because of the active disease she will now have to take a moderately

high dose of glucocorticoids to reduce the inflammation, and that once this has been accomplished the dosage of the glucocorticoids will be reduced so as to minimize side effects; and that she will have to take an antimalarial to prevent a new flare.

The development of more specific treatment strategies in other medical fields prompted an interest in examining these for lupus as well. Most importantly, in rheumatoid arthritis (RA) several trials demonstrated that a 'tight-control' strategy was superior to management as usual [2,3]. The basic idea of a 'tight-control' strategy is to set a treatment goal, to assess it at pre-specified time intervals, and to intervene if the treatment goal has not been achieved. This approach was codified in formal internationally agreed-upon 'treat-to-target' recommendations and has been included in most international guidance documents for RA. A logical question was whether the same could be true for SLE as well. In 2014, an international task force published 'treat-to-target' recommendations for SLE [4]. First of all, it was recognized that there is currently no formal evidence that a 'treat-to-target' approach in SLE is superior to management as usual. On the other hand, the experiences in other disease areas suggest that such might be the case, and this task force recommended that a certain number of principles should be applied to SLE as well. Among these were the fact that treatment targets should be chosen such as remission, the absence of flares, the minimization of damage, and the best possible quality of life.

5.2 Local measures and nonsteroidal medications

Some very mild manifestations of SLE may not require any medical treatment at all. Other manifestations of a limited nature could be treated with simple local means. Mild skin rashes may respond to topical corticosteroids, and a single incidentally inflamed joint or tendon can of course be injected with corticosteroids. Mild headaches, myalgias, and other painful symptoms of a limited degree may not require anything other than simple analgesic medications used as needed.

NSAIDs are widely used for non-specific pain, myalgias, and arthralgias, and even for more decidedly inflammatory disease manifestations such as arthritis and pleurisy. The intermittent use of NSAIDS at low

dosages that are often available without prescription can have a positive practical role in patients with milder SLE, as it is enabling to the patient and most often not harmful, but a few points must be kept in mind: ibuprofen, which is included in many over-the-counter medications, can rarely cause aseptic meningitis as an idiosyncratic reaction, and this is seen more often in individuals with SLE [5]; with other NSAIDs this risk appears to be lower. The potential of NSAIDs for causing gastric or duodenal complications (gastritis, duodenitis, and peptic ulcers) is greater when combined with corticosteroids, and so for patients with SLE who are on continuous low-dose corticosteroids (as many are) the use of NSAIDs should be viewed with more caution than in other cases.

Full-dose continuous NSAID treatment may be considered in patients with SLE who suffer from arthritis or pleurisy. In both cases such treatment can be rapidly effective and it may be possible to discontinue the medication after 4–6 weeks once the 'flare' has subsided. Needless to say, all the usual potential toxicities and contraindications will apply. In SLE, it is particularly important to consider the possible presence of renal disease and of coagulation abnormalities (anti-phospholipid syndrome), and interactions with other medications. As mentioned above, the concomitant use of NSAIDs and corticosteroids greatly increases the risk for gastric or duodenal side effects. In such cases, the combined use with a proton-pump inhibitor (or H2-antagonist) is logical. The cyclooxygenase-2 specific agents have not been formally tested in SLE nor used widely for such patients but the lower risk of upper gastrointestinal side effects would be an advantage.

5.3 Antimalarials

The use of antimalarial agents for the treatment of various lupus-related manifestations was mentioned in articles dating back to the early 1900s. During the Korean war in the 1950s, the antimalarial quinacrine was used widely for malaria prophylaxis and was found to be effective against various cutaneous lupus manifestations. Later studies confirmed that the antimalarials chloroquine and hydroxychloroquine were effective treatments for SLE, and particularly the latter is now considered the cornerstone of medical treatment for all but the mildest forms of SLE.

Evidence for the benefit of hydroxychloroquine in SLE comes from several trials, of which the flare-prevention study by the Canadian Hydroxychloroquine Study Group has been the most widely noted [6]. In this study, patients with SLE who were in a stable remission on hydroxychloroquine were randomized to continue the treatment or to continue with a placebo. The latter group had a significantly greater number of flares in the subsequent study period.

This result has been widely regarded as proof that hydroxychloroquine prevents SLE flares, although it must be recognized that when seen from a strictly pharmacological perspective, the withdrawal of an agent can be associated with events that would not have occurred if the treatment had not been given in the first place (for example, the sudden withdrawal of a beta-blocker can lead to a catecholamine-related syndrome even in someone who has never experienced this before). Another trial showed modest efficacy for hydroxychloroquine against SLE-related arthritis [7]. Additional benefits for hydroxychloroquine have been suggested in non-randomized comparisons, and based on these, multiple potential benefits of hydroxychloroquine are sometimes given as established facts [8], including a favorable effect on mortality, various SLE manifestations, coagulopathies, and others.

Practical use: hydroxychloroquine, chloroquine, quinacrine.

5.3.1 Hydroxychloroquine

The most widely used antimalarial is hydroxychloroquine (HCQ). It is generally available in 200 mg tablets and given as a single daily dose. To achieve the target dose of 5.0–6.5 mg/kg/day, different dosages can be taken on different days of the week. HCQ is a slow-acting agent: some patients report improvements after 4-6 weeks, but full effect is not expected until after 6 months of treatment. Recent studies have suggested that pharmacological monitoring of HCQ treatment can be useful, in part to detect insufficient compliance, but also to achieve optimal dosing [9,10]. However, this is not yet widely used in practice.

HCQ is generally well-tolerated, but some patients may experience hypersensitivity reactions or gastrointestinal discomfort. The most

notable potential side-effect is retinal toxicity: the deposition of HCQ in the retina causing irreversible damage in distinct areas, leading to scotomas, and most seriously, damage to the macula; in extreme cases this can lead to the classical 'bull's eye' appearance on fundoscopy. It is clear that retinal toxicity is very rare, and that the most severe retinal toxicity can be prevented by monitoring. Exactly how best to do this has remained unclear. A current recommendation in many countries is that monitoring through ophthalmological examination (including fundoscopy) should be done at baseline and then yearly. In some countries the follow-up control examinations are only started after five years of continuous treatment, in view of the fact that it is the cumulative dose of antimalarials that is associated with the risk. It must also be recognized that antimalarials can be associated with depositions in the cornea which, although much less dangerous than the ones in the retina, may cause some visual symptoms – and considerable concern on the part of the patient.

Deposition of hydroxychloroquine in the inner ear is a possibility and some cases of auditory loss following very high dosages have been reported – whether this can occur at the relatively low dosages used in the treatment of SLE is unclear.

5.3.2 Chloroquine

Chloroquine is used less commonly than hydroxychloroquine but has a similar pharmacology. It is believed to be somewhat more likely to cause retinal toxicity but retains an overall favorable benefit-to-risk ratio. The usual dosage is 160–250 mg daily.

5.3.3 Quinacrine

Quinacrine has been used primarily for cutaneous lupus. Whether it is effective for SLE in general remains unclear. The usual dosage is 100 mg daily. It is generally a safe drug, but with chronic use it frequently causes a yellowish discoloration of the skin and mucous membranes, which may not be reversible. In individuals with glucose-6-phosphatase dehydrogenase deficiency quinacrine may cause severe hemolytic anemia.

5.4 Systemic corticosteroids (glucocorticoids)

Systemic corticosteroids remain one of the most important therapeutic interventions for patients with all but the mildest forms of SLE. Corticosteroids are generally prescribed at the time of active disease, and in most situations the clinician's intent is to taper and stop the corticosteroids once the disease is under control. Paradoxically, numerous observational studies have shown that at any given point in time half of patients with SLE or more are taking corticosteroids, suggesting that either the intent to taper and stop is not followed through, or that disease activity recurs in a majority of cases when this is attempted.

Corticosteroids have powerful dose-dependent anti-inflammatory effects. For moderate to severe active lupus manifestations, such as severe polyarthritis, pericarditis, pleurisy, widespread acute cutaneous lupus and others, 0.5–1 mg/kg/day of prednisone (or the equivalent dose of another corticosteroid) is recommended. For severe manifestations I recommend a divided daily dose initially, in recognition of the relatively short serum half-life of prednisone. The second dose of the day should be taken in mid-afternoon, as later dosing may cause insomnia.

The duration of initial treatment should be 2–4 weeks, which is usually sufficient to bring the active lupus manifestations under control. Subsequently, a tapering schedule can be instituted. There is no generally agreed-upon tapering schedule; my own recommendation is to taper rapidly at first and then more slowly, aiming to reach 10 mg daily after 3 months and to stop – if possible – after 6 months.

For the most severe lupus manifestations, such as life-threatening CNS disease, extreme cytopenias, alveolitis or myocarditis, 'pulse' corticosteroids are usually given. Methylprednisolone 1000 mg as a daily intravenous infusion for three consecutive days is commonly used, followed by prednisone 1 mg/kg orally as above. There is in vitro evidence that these extremely high doses achieve a unique effect on T lymphocytes and/or engage cytoplasmic corticosteroid receptors, and clinicians have consistently observed very rapid improvements following such dosing. This very high-dose but short-term use of corticosteroids may be associated with some notable risks, including psychosis and avascular necrosis. In addition, too rapid intravenous administration has been associated

with severe cardiac arrhythmias; infusion over at least one hour is recommended. Sometimes doses of 250–500 mg are used as 'pulses' , but there are no studies that have systematically compared the efficacy or safety of these variations in dosing.

5.5 Immunosuppressive agents

Several conventional immunosuppressive medications are used widely in the treatment of SLE. None of these were developed primarily for this indication, and data on their efficacy derive from clinical studies that do not always achieve the same standards as those that are required for regulatory approval. Nonetheless, the cumulative knowledge on some of these agents is considerable.

5.5.1 Cyclophosphamide

Originally a chemotherapeutic, the alkylating agent cyclophosphamide (CyX) has been used for decades in the treatment of severe SLE. It has a strong, dose-dependent, non-specific immunosuppressive effect believed to result from its cytotoxic effect on rapidly dividing activated lymphocytes and/or on granulocyte precursors. In lupus nephritis, randomized trials at the National Institutes of Health (NIH) showed that the addition of CyX to corticosteroids achieves better long-term results than corticosteroids alone (see below) [11–13]. A single randomized trial in SLE in the central nervous system (CNS) also favored the addition of CyX [14]. For the treatment of other severe SLE manifestations (alveolitis, myocarditis, enteritis, extreme cytopenias) the use of CyX has remained largely empiric. Although CyX is considered a slow-acting agent, clinicians have often been impressed how sometimes dramatic improvements were seen within days of administering this agent, and the pharmacokinetics and dynamics of CyX also do allow for this possibility.

CyX can be dosed intravenously and orally, but in SLE the former has been used by far the most widely. The original studies with CyX used the 'NIH dosing regime', 0.75–1 gram per square meter body surface area, given monthly for 6 months. In the original protocols each dose was increased further if nadir leukopenia (leukocytes <2000/mm3 ten days after the infusion) was not achieved. It is my impression that, insofar as

clinicians use the monthly CyX dosing regime, these dosing recommendations are not followed to the letter, and most often doses in the range of 750–1000 mg are given without further upward adjustments. In lupus nephritis, more recent studies have focused on lower doses (see below).

CyX has many potential toxicities. The intravenous administration is often associated with nausea and sometimes vomiting, which can be alleviated considerably by the prophylactic use of anti-emetics. Hypersensitivity reactions are uncommonly seen. In the weeks following infusion a state of immunosuppression ensues, and patients must be warned to seek medical attention if they develop fever or focal signs of infection. Antibiotics should be administered if a bacterial infection is suspected. Herpes zoster is not uncommon and can be treated with antiviral medication. Cytopenias are to some extent expected following the administration of CyX, but severe leukopenia, anemia, or thrombocytopenia may also occur on occasion. Hemorrhagic cystitis can occur and many clinicians recommend the use of the bladder-protectant mesna, although there is no formal evidence demonstrating its value. However, this medication can be associated with hypersensitive skin reactions, and in the clinical setting it is hard to know which of the two medications caused the reaction. Longer term, the use of CyX is associated with several important risks: interstitial cystitis and bladder cancer, much more so with oral dosing of CyX than with intravenous therapy; an increase in the risk for leukemia and lymphoma, albeit very small; and premature ovarian failure leading to infertility [15]. The latter is of course a major concern for patients of reproductive age who still wish to have children. The risk appears to be quite limited in patients under 30 years of age but increases steeply thereafter [16,17]. If minimization of this risk is essential, it has been suggested to administer CyX during the menses (when the ovaria are less vulnerable), or hormonally to stop the menstrual cycle [18,19].

5.5.2 Azathioprine

Azathioprine is an immunosuppressant that has been used for decades in the treatment of SLE. It has a slow onset of action and is therefore mostly used as a maintenance drug after induction with more rapidly

acting medications, and for steroid-sparing purposes in patients on chronic corticosteroids or with frequently recurring flares. It is usually dosed at 100–150 mg daily. Azathioprine can cause gastrointestinal disturbances and the patient must be monitored for elevated liver enzymes and bone marrow suppression.

5.5.3 Methotrexate

Methotrexate is an antimetabolite and the cornerstone of treatment for RA. In SLE it can be used for patients with predominant arthritis but also for skin manifestations, serositis, and other symptoms. Like azathioprine it is most often used when chronic treatment is needed, in order to achieve better disease control and to be steroid-sparing. The usual target dose is 20–25 mg once weekly, and folic acid supplementation is added to decrease the risk for side effects. Gastrointestinal intolerance, discomfort in the mouth (mucositis) and mild hair loss are common side effects, and the patient must be monitored for hepato- and myelotoxicity.

5.5.4 Cyclosporin A

The calcineurin inhibitor cyclosporin A is an immunosuppressant used widely in transplantation. It has been used in SLE in a similar manner as azathioprine and methotrexate, and in lupus nephritis with nephrotic syndrome it has a special place on account of its antiproteinuric effect (a direct effect on the renal tubuli). The main drawback of cyclosporin A is its long-term renal toxicity and risk for hypertension. Another calcineurin inhibitor, tacrolimus, has only been studied in small groups of patients with SLE with variable results, but a larger recent study suggests that it may be useful as part of a combination therapy approach [20].

5.5.5 Mycophenolate mofetyl

Mycophenolate mofetyl (MMF) is used very widely in transplantation medicine and has over the past 15 years become an important immunosuppressive in SLE as well. Several trials demonstated very good efficacy in lupus nephritis [21–26]. A large randomized trial intended to demonstrate that it was superior to CyX for the treatment of lupus nephritis failed its primary objective [27], but in doing so confirmed that it was

as effective as the latter. In the maintenance phase of treating lupus nephritis MMF is at least as effective as azathioprine [28,29]. The role of MMF in non-renal lupus has not been studied as well, but it again appears to be at least as good as, if not better than, azathioprine. MMF is usually dosed at 1000–1500 mg twice daily; an interesting feature is that its metabolites can be measured and used to adjust doses, but it is not clear that this leads to better results in SLE. MMF can be associated with hypersensitivity reactions, gastrointestinal disturbances, and other side effects, and the patient must be monitored for hepato- and myelotoxicity.

5.6 Biologic agents

Over the past two decades, the treatment of autoimmune diseases such as RA, Crohn's disease, psoriasis, and multiple sclerosis has been revolutionized by the introduction into the therapeutic armamentarium of biological medications, large protein molecules derived with hybridoma and/or DNA recombinant methodologies and designed specifically to target a signaling molecule in the inflammatory pathways or a cell surface marker. Having had an enormous and mostly favorable impact in those diseases it was logical to expect a similar revolution in the treatment of SLE, but unfortunately this has not yet materialized. Some biologics that were approved in other diseases were tested in SLE, in the form of case series or small trials, but of these 'off-label' agents only one, the B-cell-depleting agent rituximab, has been used more widely and studied in larger numbers of patients, and another, the T-cell costimulation-modulator abatacept, is still being studied. Despite two decades of clinical development, only one biological medication has specifically been approved for SLE: belimumab.

5.6.1 Belimumab (anti-BLyS monoclonal antibody)

Belimumab is currently the only biological medication approved for the treatment of SLE. It was the first new medication in decades to receive formal approval by both the United States Food and Drug Administration (FDA) and by the European Medicines Agency (EMA), and is used increasingly in many countries.

Belimumab is a genetically engineered fully human monoclonal antibody that binds the B-cell-stimulating cytokine Blys (BAFF). Once bound, Blys can no longer engage its receptor and B-cell activation is diminished. It has been speculated that autoreactive B cells (the B cells that eventually become plasma cells that produce auto-antibodies such as anti-DNA) are more critically dependent on Blys and are therefore more effectively down-regulated by belimumab than normal B cells. And indeed, after administration of belimumab to individuals with SLE, a relatively rapid decrease of the levels of anti-DNA is seen, as well as a somewhat slower decrease in the number of B cells – but without outright B-cell depletion.

The clinical effects of belimumab were ascertained in two large clinical trials, named BLISS-52 [30] and BLISS-76 [31]. These two Phase III trials had very similar designs, differing only in the length of follow-up, 52 and 76 weeks respectively. In both trials, patients with SLE who had moderately high disease activity, defined as Safety of Estrogens in Lupus Erythematosus National Assessment (SELENA)- SLE Disease Activity Index (SLEDAI) score (S-SLEDAI) of six or greater despite receiving conventional therapy, were randomized to receive one of two dosages of belimumab or placebo as 4-weekly infusions. The primary outcome of the trials was a pre-specified 'SLE responder index' (SRI) ascertained at week 52 and defined such that the patient was consider an SRI-responder if the S-SLEDAI had improved by at least four points while no new lupus manifestations had been recorded in the British Isles Lupus Activity Group (BILAG; not a single one at the A level and not more than one at the B level) and while the physician's assessment did not show a worsening. The 'point' of this complex outcome measure was that the patient had to have an improvement as the result of the treatment (the improved S-SLEDAI) but could not have a worsening that the S-SLEDAI failed to capture (hence the other two requirements).

Both trials demonstrated that the higher dose of belimumab was associated with a greater percentage of SRI responders at 52 weeks. In BLISS-52 the difference was greater: 58% versus 44%, while in BLISS-76 it was 43% versus 34%, but in both trials the difference was statistically significant, providing the formal evidence that the treatment was

effective. Further investigation of the trial results led to a number of important findings:

- The difference between belimumab and placebo was gradual, generally requiring 6 months of treatment to be fully evident; however it must be considered that these trials were 'pragmatic' and that during the trial adjustments of corticosteroid dosages and even of some other medications were allowed based on the clinical course.
- The lower dosage of belimumab, 1 mg/kg, generally had intermediate results, but in BLISS-52 it, too, achieved statistical significance for the primary and many secondary outcomes. The precise dose-response characteristics of belimumab remain unclear.
- A mild steroid-sparing effect was noted as a secondary outcome and confirmed in a more recent post-hoc analysis [32].
- A reduction in flares was also noted as a secondary outcome.
- A reduction in the incidence of renal abnormalities was seen in a post-hoc exploratory analysis [33]. Inasmuch as patients with active and severe nephritis were not included in the BLISS trials, this analysis is so far the only evidence that belimumab may be safe and effective in such patients. A randomized trial directly analyzing this question is currently underway.
- Several base-line markers for a higher likelihood of response were identified in pre-specified analyses: the presence of anti-DNA antibodies, hypocomplementemia, the baseline use of glucocorticoids, and a baseline S-SLEDAI of 10 or greater all increased the difference between belimumab and placebo [34]; consequently, the EMA and other authorities recommended the use of belimumab primarily for patients with a combination of these characteristics.

The safety profile of belimumab, as it emerged from the clinical trials, was favorable. No relevant differences were seen in the occurrence of infections, malignancies, or cardiovascular events. A small increase in the number of suicide-related adverse events (such as suicidal ideation) was noted. It has been reported that some patients develop renal flares during belimumab treatment [35] but in the BLISS trials, the number was lower than those who developed renal flares under placebo treatment [33].

5.6.1.1 Belimumab: appraisal

Currently, belimumab remains the only approved biologic agents for the treatment of SLE and one of only a few medications specifically approved for this disease. However, the use of belimumab remains somewhat limited when regarded against the totality of patients with SLE. There seem to be several reasons for this. Belimumab is perceived as a weak agent with an effect size in the order of 10–15%. Being an intravenous and costly treatment, some have expressed doubt that this is 'worth it'. However, it should be recognized that a small effect size may reflect a weak effect overall, but is also consistent with a strong effect in a subset of patients, such as was demonstrated for anti-DNA positive patients with hypocomplementemia (Figure 5.1) [34]. The small effect size in the BLISS trials must also be seen in the light of a trial where other treatments could be adjusted, so that patients who were doing well might have their corticosteroid doses lowered, and a small effect size may be an underestimate of the true effect due to the limitations of the outcomes that were used.

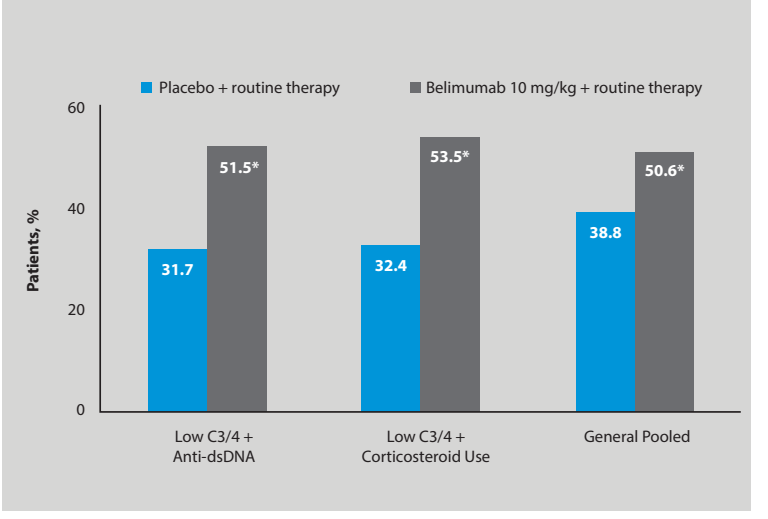

Figure 5.1 Predictors for response to belimumab treatment. In posthoc analyses based on the BLISS trials it was found that for patients who at baseline had anti-DNA antibodies, low complement and/or the use of corticosteroids, the percentage who responded to treatment differed more from placebo than for the overall patient population. Adapted from © BMJ Punlishing Group Ltd & European League Against Rheumatism, 2012. All rights reserved. Van Vollenhoven et al [34].

Another limitation for the use of belimumab may be the fact that the formal approval text does not match the way that most clinicians choose treatments for patients with SLE. A single occurrence of high disease activity in a patient who has a mild disease course overall would normally trigger corticosteroid treatment followed by a taper rather than starting a slow-acting immunomodulatory agent, whereas the patient who stands to benefit the most from belimumab is probably the patient whose disease course has been characterized by frequent flares and chronically grumbling disease, the failure to respond to conventional immunosuppressives, and a persistent need for corticosteroids at harmful dosages – irrespective of whether (s)he does or does not have high disease activity at this particular point in time.

Thus, it is this author's opinion that the parameters under which belimumab was approved by the regulatory authorities, and which determines both market access and marketing, is at odds with the optimal use of the drug and appears to limit the practical use of this potentially beneficial medication.

5.7 Unapproved and experimental therapies

As indicated above, several currently available biologic agents have been tried in SLE, often in small numbers of patients and without the benefit of controlled trials.

5.7.1 Rituximab

The B-cell depleting anti-CD20 monoclonal rituximab has been studied very widely in SLE. Many uncontrolled observational studies suggested that rituximab was effective, particularly in patients with severe SLE who had failed treatment with conventional medications [36–44]. However, two large RCTs intended to support the regulatory approval of rituximab were reported as negative [45,46]. These contradictory results have been reviewed many times, and this in turn has been reviewed [47]. One possible interpretation of the totality of the evidence is that rituximab does not have a role in treating the more commonly encountered SLE manifestations (general symptoms, joints) but that it does have efficacy in some patients with severe SLE, particularly in severe lupus nephritis,

severe hematological lupus, severe and acute cutaneous lupus, and possibly in severe CNS lupus. A recent study demonstrates that insofar as rituximab is used off-label, these are the kinds of patients that it is used for [48]. The currently ongoing clinical trial RING will address whether this use in refractory lupus nephritis is appropriate.

Preliminary signs of clinical efficacy in very small numbers of patients were seen with several anti-TNF agents and the anti-IL-6 agent tocilizumab. The T-cell costimulation modulator abatacept was studies in several clinical trials that were mostly negative [49–51].

Recent studies using biological inhibitors of the interferon type 1 pathways have shown promise and are being studied in larger trials [52–54], and there are many other treatments currently in earlier-phase trials.

5.8 Overall treatment principles

5.8.1 Treatment of active lupus and lupus flares

When SLE is first diagnosed it usually requires treatment, and the same is true when a worsening occurs in a previously stable situation, also known as a 'flare'. In both these situations, the treatment must be such that it can achieve control over the inflammatory process in a reasonably expeditious manner, and of course the more severe the manifestation, the more rapidly and effectively this has to be accomplished. For mild lupus manifestation local treatments (corticosteroid creams) or non-steroidal anti-inflammatory agents may be sufficient, but in all other cases, corticosteroids need to be used to achieve disease control in a matter of days or weeks. Choosing the correct doses of corticosteroids in each clinical situation, guided by the dosages given above, remains as much an art as a science in treating SLE.

For the most severe lupus manifestations, for example inflammation in the central nervous system, the heart, or the lungs it is recommended, along with corticosteroids, to treat with strong immunosuppressives, most often cyclophosphamide intravenously, even though formal evidence that this is beneficial is only available for lupus nephritis (see below) and to a limited degree for CNS lupus. In uncommon cases, where very severe and active lupus cannot be controlled by these interventions, the use of unapproved and experimental agents can be considered. In practice,

most experience in this setting exists with the use of rituximab, intravenous immunoglobulins (IVIG), and plasmapheresis. In my opinion, the uncontrolled evidence for rituximab in this setting is sufficiently compelling to support its use; the same may be said for IVIG; but results with plasmapheresis have remained less convincing.

Irrespective of this, it is also possible already at this stage to add an antimalarial (assuming the patient is not already taking one), immunosuppressive, or even belimumab. It is important to understand that all these therapies are not likely to improve the immediate efficacy of the corticosteroids; the main reason to add them is as part of a longer-term strategy, in order to be able to maintain disease control while attempting to taper and stop the corticosteroids later on. This may not always be necessary: if a patient has mostly inactive disease, interrupted by a flare only very rarely, and these flares can easily be controlled by a short course of corticosteroids, then initiating another agent may not be in the patient's best interest. But when a second-line agent is needed, the ones most commonly used in this setting are an antimalarial, azathioprine, and methotrexate, while the role of belimumab in this setting remains incompletely defined.

5.8.2 Chronic treatment of lupus

If it becomes clear that the patient has chronically active SLE or frequently recurring flares (or both) it follows that treatment based on corticosteroids is insufficient, and other alternatives must be vigorously explored according to the treat-to-target principle. All such patients should be taking an antimalarial, barring any contraindications. Often an immunosuppressive is needed as well, and while azathioprine and methotrexate are used most widely for this purpose, other immunosuppressives and belimumab can all be reasonable choices. These treatments will always remain empiric on the individual patient level and must be assessed for efficacy after 3–6 months (while of course also monitoring for toxicities based on each drug's characteristics).

5.8.3 Treatment of lupus nephritis

The treatment of lupus nephritis is a special case in the treatment of SLE for several reasons:

- This organ system may be affected by severe SLE in the absence of most other lupus manifestations, and the patient may not experience symptoms until a late stage.
- Lupus nephritis has been studied at the pathophysiological and histological levels in more detail than any other lupus manifestations, and is understood rather compellingly as the result of the accumulation of immune complexes in the glomeruli.
- The treatment of lupus nephritis has been studied in clinical trials in more detail and with more success than the treatment for other lupus manifestations or SLE in general.
- The treatment of lupus nephritis is often based on histopathological and immunological assessment of a renal biopsy.

Lupus nephritis of the histological classifications I and II does not require treatment. In contrast, classes III, IV and V do require treatment in order to control the nephritic and/or nephrotic symptoms and to prevent progression to renal failure; class VI is usually managed as a pre-dialysis state.

For active lupus nephritis class III and IV a distinction is made between induction and maintenance therapies. For induction of a therapeutic response, a combination of high-dose daily oral corticosteroids and an immunosuppressive are used. For many decades initial corticosteroid doses of 1 mg/kg/day (prednisone or equivalent) or even higher were recommended, but two recent studies suggest that a lower starting dose may be equally efficacious with less toxicity. The starting dose is usually maintained for one month and subsequently tapered over the course of 3–6 months to a low level (5–10 mg daily). There is no agreed-upon tapering schedule and no agreement among experts on whether further tapering and stopping should always be attempted and how soon. The corticosteroid treatment can be initiated by administering very large 'bolus' doses, for example, methylprednisolone 1000 mg intravenously daily for three days; in one controlled trial this led to better long-term outcomes [55].

In addition to the corticosteroids an immunosuppressive should also be administered. CyX was used almost exclusively for this purpose for many years, but more recent studies have shown that mycophenolate mofetyl (MMF) is equally efficacious. Two different dosing regimens for CyX exist: the original regimen as used in trials at the National Institutes of Health (NIH) and the EuroLupus regimen. Induction with the former consists of six 4-weekly infusions of CyX at 750–1000 mg/m2 body surface area while the EuroLupus regimen consists of six 500 mg infusions biweekly. Especially in the NIH dosing regimen the white blood cell and neutrophil counts must be monitored and dosing may need to be adjusted based on the results. The EuroLupus protocol has largely replaced the NIH dosing following the demonstration that it achieved similar efficacy with considerably fewer side effects [56,57]. Some experts nonetheless feel that the NIH regimen may be appropriate in patients with the most severe forms of nephritis or in those who already failed the other alternatives. As discussed above, induction with MMF 1–1.5 gram twice daily appears equally effective to CyX and is widely used for this purpose.

For maintenance treatment of lupus nephritis, several alternatives can be considered. After induction with CyX according to the NIH protocol, early studies used 3-monthly infusions of CyX (at the same dose) as maintenance. It appeared that this approach, while often effective, contributed much to long-term toxicities and it has mostly fallen into disuse, and most often, after six months of CyX, maintenance is done with AZA. In the EuroLupus protocol the switch from CyX to AZA is done after 3 months. Recent studies have shown that MMF can also be used as maintenance therapy, with equivalent or even slightly better results. Following induction with MMF the simplest maintenance treatment is continuation with the same.

In addition to corticosteroids and immunosuppressives, patients with lupus nephritis can be treated with various other medications, depending on the specific situation. If proteinuria is present, angiotensin-converting enzyme (ACE) inhibitors or ACE-receptor blockers can be used. Hypertension, hyperlipidemia, or hypercoagulability associated with nephritis must of course also be treated in their own right.

Treatment of lupus nephritis class V is less well studied than classes III and IV. Some patients require only simpler interventions such as low-dose corticosteroids and medications targeting the proteinuria such as ACE inhibitors. The long-term outcome of the renal function in class V nephritis is mostly good and it is not clear that adding immunosuppressives to corticosteroids improves this. However, the proteinuria may be hard to control, and in such cases cyclosporin-A may be useful, having not only an immunosuppressive effect but also a direct antiproteinuric effect on the tubuli.

5.9 Adjunctive and preventive measures

The use of corticosteroids, antimalarials, and immunosuppressives is only the basis of the treatment of SLE. For each individual patient many other interventions can be considered, which follow from the individual disease manifestations and the risks that apply to the patient's situation. Examples of the former are analgesics (pain), antidepressants (mood disturbance), anxiolytics (anxiety), histamine-2 antagonist and proton pump-inhibitors (upper gastrointestinal symptoms) and others; and an example of the latter is the use of calcium and vitamin D supplements to decrease the risk of corticosteroid-induced osteoporosis. It has been proposed that vitamin D is also beneficial for treating SLE itself [58,59], but this has remained controversial, and two randomized trials have suggested that it is not [60,61].

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Chapter 6

Therapies in late-stage clinical development

6.1 Advances in the treatment of systemic lupus erythematosus

We need better treatments for SLE. This statement remains true despite considerable advances that have been made over the past several decades, both in terms of the best use of existing agents, such as the development of less toxic but equally effective dosing schedules with cyclophosphamide [1]; the introduction of conventional medications from other medical disciplines into the treatment armamentarium for lupus, such as mycophenolate mofetil for lupus nephritis [2]; the off-label use of biological agents such as rituximab [3]; the development of novel therapeutic strategies including treating-to-target [4]; and last but not least, the emergence, through an extensive clinical trials program, of an entirely new approved medication for SLE, the B-lymphocyte stimulator (BLyS)-antagonist belimumab [5,6].

Why then are newer and better treatments still needed? Unfortunately, the fact remains that despite all the advances mentioned above, patients with SLE are not doing as well as one might wish. Recent studies clearly illustrate the current situation. Several SLE registries demonstrate that remission – the complete absence of disease activity – is only infrequently achieved by patients with SLE, and even when achieved, it is rarely sustained [7–10]. A survey of patients with SLE in Sweden, where access to health-care is generally good and approved medications are always available, demonstrated that overall quality-of-life in patients with SLE was reduced to an average level similar to advanced chronic obstructive lung disease or HIV infection [11]. Thus, while some patients with SLE

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do indeed enjoy a good therapeutic result with long-lasting remission and limited need for medications, for many other patients the reality of living with lupus is having a chronic disease with persistent low-level symptomatology punctuated by unpredictable moderate or severe flares and with the need for long-term medical treatments, some of which may be associated with considerable toxicities and risks. Moreover, long-term follow-up studies of lupus patients have repeatedly demonstrated a worrisome increase in cardiovascular morbidity and mortality [12]. For example, after many years of disease, for female patients a 2.4-fold increased risk for cardiovascular death was demonstrated [13]. It is not clear whether this risk is imparted by the disease itself or by the treatments used to control it (most importantly, corticosteroids) and a reasonable hypothesis is that both contribute.

The development of new therapeutics for SLE has been slow and mostly disappointing, with a long series of failed clinical trials, and only one fully successful clinical development program that resulted in the above-mentioned biological treatment for lupus being approved by regulatory authorities. Importantly, there may have been very different reasons why so many drug development programs failed, and it is not always possible, even in retrospect, to be certain what the most important factors were. A brief review of the most important failed developments demonstrates the variability (Table 6.1). Thus, while many drugs are said to have failed, the reasons for these failures ranges from the simple fact that the drug may, in truth, not have had a benefit for patients with SLE, to the disturbing possibility that a drug that did have potential benefit in lupus had to be abandoned because the trials were not done in an optimal manner. Naturally, it is hoped that failed trials lead to insights that will ensure better and more successful studies in the future [26].

6.2 B-cell modulating agents

SLE, being characterized in part by the ubiquitous production of autoreactive antibodies such as ANA, anti-DNA, anti-Sm and so on, can be thought of as a disease of dysregulated B-cell activity. This view is not uncontroversial, because it could equally well be argued that the regulatory mechanisms that are needed to control B-cell activity and prevent

Agent	Results in phase II and III	Most likely explanation for failure of the program
Prasterone (DHEA)	Two phase III trials missed the primary endpoint by a small margin [14,15]	Trials were underpowered and/or patient inclusion criteria should have been more focused
Abetimus sodium (LJP396)	A biological effect (lower anti-DNA antibodies) was achieved but several large trials failed to achieve clinical endpoint (prevention of renal flare) [16,17]	The proposed mechanism of action may not be causally linked to the desired clinical effect
Rituximab	Despite encouraging uncontrolled results, two phase III trials, one in non-renal lupus and in lupus nephritis, failed to achieve the primary endpoint [18,19]	The trial in non-renal SLE, having no suggestion of efficacy, may have failed because that patient population does not benefit from the drug; while the trial in lupus nephritis showed a non-significant trend and may have been underpowered
Abatacept	A phase III trial in non-renal lupus, a phase III trial in lupus nephritis, and an investigator-initiated trial in lupus nephritis all failed to achieve the primary endpoint [20–22]	Secondary and post-hoc analyses of these trials suggested that for non-renal lupus a focus on severe musculoskeletal SLE could have been more successful, while in renal lupus the choice of outcomes might have influenced the result; a third trial in lupus nephritis is underway
Tabalumab	Two phase III trials in non-renal lupus failed unequivocally to achieve the primary endpoint, although in each of these two trials a positive result or trend was obtained with one of the two tabalumab dosing arms [23,24]	The overall results were consistent with a lack of effect but also with a weakly positive effect that failed to achieve convincing statistical significance
Epratuzumab	Two phase III trials in non-renal lupus failed to achieve the primary endpoint [25]	Many questions remain unanswered about this agent, including the precise mechanism of action and its biological relevance; it is possible that a better understanding of the drug and its effects could have led to a more successful clinical trial design

Table 6.1 Most important failed developments in systemic lupus erythematosus.

the appearance of abnormal autoantibodies are defective, rather than the B cells themselves. Nevertheless, it has been an attractive proposition therapeutically to target the B lymphocytes in the hope of reducing or completely eliminating the abnormal antibodies and thereby achieving clinically meaningful improvements in the manifestations of the disease. Targeting the B-cells can take many forms, including the complete elimination of B-cells using cell-specific monoclonal antibodies, the blocking of B-cell specific cytokines, or down-regulating B-cells by other means.

6.2.1 B-cell cytokine antagonists

Indirectly targeting B cells by blocking the activity of B-cell-specific cytokines is an attractive proposition and follows logically from the dramatic successes of anti-cytokine therapies in the treatment of rheumatoid arthritis (RA) and other autoimmune diseases. Indeed, the only successfully developed new drug for SLE belimumab targets the B cells by blocking the BLyS cytokine or B-cell activating factor (BAFF). Reductions in several autoantibodies, including anti-DNA, were seen in patients treated with the anti-BLyS monoclonal antibody belimumab [27]. These changes may be biomarkers for the clinical improvements that are seen with belimumab therapy, even though a clear one-on-one relationship between the two has not been demonstrated.

Unfortunately, other B-cell modulating agents have fared less well in clinical development. Tabalumab is an anti-BLyS monoclonal antibody with strong similarity to belimumab. The one biologically relevant difference appeared to be that it binds both soluble and membrane-bound BLyS, while belimumab only binds the former. As indicated above, two large phase III trials with tabalumab failed [23,24] and the development of this drug has been halted for now. More recently, it was announced in a press release that a phase III clinical trial of blisibimod, a modular biologic agent with similarity to the immunoglobulin structure and specificity for BLyS, had failed as well. More information on this trial is awaited.

Another B-cell specific cytokine is 'a proliferation-inducing ligand' (APRIL). The receptor-construct atacicept combines the normally-occurring receptor TACI with an immunoglobulin frame. The resulting molecule, Taci-Ig or atacicept, has been studied in patients with SLE. Results have been mixed, with some positive signals but also trials that failed on account of limited efficacy or potential toxicity [28–31].

6.2.2 B-cell-depleting agents

On the assumption that B-lymphocytes are responsible for much of the clinical phenotype of SLE it could be reasonable to deplete B lymphocytes in patients with the more severe forms of the disease. Starting around the beginning of the millennium many case reports and case series were published on the possible efficacy of rituximab in SLE [3,32–35], the

anti-CD20 molecule that does indeed deplete B cells and is used clinically for the treatment of non-Hodgkin lymphoma, RA and, more recently, vasculitis. As indicated above, and as discussed in more detail elsewhere in this book, the results in observational settings with this agent have been encouraging, but two phase III trials failed [18,19], possibly for two different reasons. The current status of rituximab in lupus remains therefore that of an interesting but unapproved treatment. Meanwhile, the anti-CD20 molecule ofatumumab has been approved for hematological indications, primarily chronic lymphocytic leukemia, and could theoretically be used for SLE. I am personally aware of a small number of patients who had been treated with rituximab, developed hypersensitivity reactions to that drug, and were then retreated with ofatumumab, in some cases with apparent success. There does not appear to be a formal development of this biological as a treatment for SLE. Another anti-CD20, ocrelizumab, was tested in SLE but the development was halted when severe infections had occurred in several patients [36]. The same molecule was more successful in trials for multiple sclerosis and is now registered for that indication.

6.2.3 Other B-cell modulating agents

Epratuzumab is an anti-CD22 monoclonal antibody. It is believed that binding to the CD22 molecule on the surface of the lymphocyte sends a down-regulatory signal, although the exact mechanism(s) are not completely clear. As indicated above, two large phase III trials with epratuzumab failed [25], and it appears that this development has ended.

Bortezomib is a proteasome inhibitor used for the treatment of multiple myeloma. Thus, it is not so much a B-cell treatment as a treatment targeting the differentiated end-result of the B lymphocyte: the plasma cell. Recently, it was reported that in 12 patients with severe SLE, improvements were seen following treatment with bortezomib [37], and a single case report illustrated the possibility of pharmacological monitoring with this agent [38].

6.3 Interferon antagonists

Work by many researchers, including the group of Rönnblom in Uppsala, has identified the interferon (IFN) system as a critical pathway in the

immunopathogenesis of SLE [39–45]. Based on this, several specific interferon antagonists have been put into clinical trials in an attempt to control the immunological activation in this disease. A phase II clinical trial with the anti-interferon monoclonal antibody rontalizumab failed to demonstrate overall efficacy but, unexpectedly, seemed to benefit patients with a low interferon signature [43]. More recently, a large clinical trial was done with the anti-IFNα monoclonal antibody sifalimumab [46]. In this multi-center trial, 431 patients with active SLE were randomized to one of four arms, and treated with three different dosages of sifalimumab or placebo, all added to stable conventional background therapy. After 24 weeks the patients were assessed using the SLE response index (SRI) and based on this result, the authors conclude that the drug was more effective than placebo in achieving the pre-specified primary outcome; and multiple secondary outcomes were also achieved.

More recently, a large phase II clinical trial was reported of anifrolumab in SLE [47]. Anifrolumab is a monoclonal antibody that targets the IFN receptor, thereby exerting a broader blocking effect on the IFN system than sifalimumab (or rontalizumab). In this trial, 305 patients with moderately or highly active SLE were randomized to receive placebo or one of two dosages of anifrolumab (300 mg or 1000 mg) every 4 weeks for 48 weeks. The primary endpoint, the SRI response at week 24 with sustained reduction of oral corticosteroids, was achieved by 17% of patients on placebo versus 34% of patients on the 300 mg dose and 29% on the 1000 mg dose of the active drug; the difference achieved statistical significance for the 300 mg dose. Many secondary outcomes, including the response after 48 weeks of treatment, also favored the active treatment arms, and the safety profile was good.

I recently commented on the Khamashta trial [48] and the same can be said for the more recent Furie trial: the positive outcome of these trials must be regarded as important steps in identifying what could potentially become a new class of therapeutic agents for SLE. However, some hurdles still remain to be taken. The precise role of anti-IFN therapies will have to be defined further. The recent trials seemed to achieve the most striking results in patients with active cutaneous lupus, and it might therefore be that this particular subset of patients stands to gain the most from this

novel target. Some caution is also needed. Antagonizing the IFN system, with its important roles in protection from viral infection and potentially even from malignancies, may be associated with as yet unknown short-term and long-term risks; so far, the trials with anti-IFNs have shown a remarkably benign side effect profile, but vigilance will have to be maintained throughout the development of these agents and beyond.

6.4 Other investigational agents

Rigerimod is a 21 amino acid polypeptide that was derived from the anti-snRNP autoantibody sequence with a single modification in one of the amino acids (a serine phosphorylation in position 140 of the original sequence). This molecule exerts immunosuppressive and immunoregulatory effects in vitro [49], in a lupus animal model [50], and in a small early-phase human study [51,52]. More recently, a phase II trial showed encouraging results [53]. In this trial, 149 patients with moderately active SLE were randomized to receive one of two regimens of rigerimod versus placebo. At week 12, 36% of patients on placebo achieved a response, whereas 53% of patients who had received rigerimod 200 ug subcutaneously every 4 weeks achieved the response, a statistically significant difference. Somewhat counterintuitively, for patients who received rigerimod every other week the results were intermediate. A phase III trial is currently being planned.

Edratide is another immunoregulatory peptide. Originally designated hCDR1, it is a 19 amino acid polypeptide based on the sequence of the heavy chain of a human monoclonal anti-DNA antibody. This antibody carries the 16/6 idiotype, which has been associated with autoimmunity and was found to correlate with SLE severity [54]. Edratide exhibits many immunoregulatory and immunosuppressive activities in vitro [55–57], in an animal model of SLE [58], and in an early human trial [59]. Recently, a clinical trial with edratide was published. The primary endpoint of the trial was not achieved, but favorable trends and a good preliminary safety profile suggest that development can be continued [60].

6.5 Conclusion

The number of agents under development for SLE is large (Table 6.2). Unfortunately, in vitro studies, animal models, and early-phase clinical

trials have a poor track record of predicting which drugs will be successful in the later stages of development. Nonetheless, observing the many developments that are taking place gives reason for optimism, and it can be hoped that new treatments for SLE will make the future brighter for patients afflicted with this disease.

Molecule	Mechanism of action	Development status
Anifrolumab	Anti-IFN receptor monoclonal antibody	Phase II trial met its primary endpoint [47]
Atacicept	Anti-Blys/anti-APRIL fusion protein	Mixed results with positive signals but also trials that failed on account of limited efficacy or potential toxicity [28–31]
Belimumab	Anti-BLyS monoclonal antibody	Currently approved for SLE
Bortezomib	Proteasome inhibitor	Improvements were seen in SLE patients following treatment with bortezomib (open label trial) [37]
Edratide	Immunoregulatory peptide	Phase II trial did not meet its primary endpoint, but some encouraging trends were seen [60]
Epratuzumab	Anti-CD22 monoclonal antibody	Two large phase III failed [25]
Ocrelizumab	Anti-CD20 monoclonal antibody	Tested in SLE but the development was halted when severe infections had occurred in several patients [36]
Ofatumumab	Anti-CD20 monoclonal antibody	Approved for hematological indications, primarily chronic lymphocytic leukemia
Rigerimod (IPP-201101, Lupuzor)	Polypeptide derived from the anti-snRNP autoantibody sequence	Phase II trial showed encouraging results [53]
Rituximab	Anti-CD20 monoclonal antibody	Two phase III trials failed [18,19]
Rontalizumab	Anti-interferon monoclonal antibody	A phase II clinical trial failed to demonstrate overall efficacy but, unexpectedly, seemed to benefit patients with a low interferon signature [43]
Sifalimumab	Anti-IFNα monoclonal antibody	Phase II trial met its primary endpoint [46]
Tabalumab	Anti-BLyS monoclonal antibody binds both soluble and membrane-bound BLyS	Two large phase III trial with tabalumab failed [23,24]

Table 6.2 Main agents under development for systemic lupus erythematosus.

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Chapter 7

Specific issues

7.1 Pediatric systemic lupus erythematosus

Maximum age limits ranging from 14 to 20 years of age have been inconsistently used to define childhood-onset systemic lupus erythematosus (SLE) [1], and this variation has strongly impaired the comparability of previous pediatric SLE studies. Therefore, and despite many recent advances, including the recognition of greater role of genetic background [2], the epidemiology, optimal management and long term outcomes of pediatric lupus remain poorly known.

It is commonly reported that ≈10–20% of patients with SLE initially present during childhood, but a population-based study has shown that children represented less than 2% of prevalent SLE cases [3]. Among Medicaid [4], the US federal entitlement program for low-income children and parents, the prevalence and annual incidence of pediatric SLE were respectively of 9.73 (95% CI 9.38–10.08) and 2.22 cases (95% CI 2.05–2.40) per 100,000 enrolled-children between 3 and 18 years of age. The diagnosis of SLE is uncommon before the age of 10 and very rare before the age of 5 years. Notably, the disease weakly predominates in females before puberty, with a female to male ratio of 4:3, and the sex ratio subsequently increases to reach approximately the same as in adults for SLE presenting in the pubertal age. The incidence and severity of childhood-onset SLE varies among different ethnic groups [5]. As in adults, the disease has been reported to be more frequent in Afro-American and Asian pediatric patients than in Caucasians [6].

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SLE is generally reported to be more severe in pediatric patients than in adults [2], and the former have been shown to accrue both earlier and more substantial disease damage over time than adults [7]. Constitutional symptoms, such as fever, lymphadenopathy, and weight loss are among the most common presenting manifestations of the disease in children [8], and may result in a substantial diagnostic delay if proper investigations for SLE are not conducted in time. Among the most common other presenting manifestations of pediatric SLE are malar rash, photosensitivity, and arthritis, while discoid lupus is reported to be rare in children [9]. In some cases, pediatric SLE can be difficult to distinguish from juvenile dermatomyositis. Non-classical manifestations of SLE including abdominal involvement with pancreatitis [10] or lupus enteritis [11] are common presenting manifestations in children [12], which is not the case in adults. Cytopenias, renal disease and neurologic involvements have been reported to be more common in pediatric than in adult SLE [8], with at least one of the latter two being reported in a majority of children with SLE [13]. Diffuse proliferative glomerulonephritis represents one of the most significant determinants of prognosis and mortality in pediatric SLE [5]. CNS involvement is reported in up to 30% of pediatric SLE, and occurs mostly during the first year following SLE diagnosis [13].

As in adults, no laboratory feature is specific to SLE in children. Hypergammaglobulinemia, elevated erythrocyte sedimentation rate (ESR) and moderately elevated C-reactive protein (CRP) levels are commonly reported [12], while antinuclear antibodies are reported in virtually all pediatric SLE patients. Anti-dsDNA antibody positivity appears to be more common than in adults [12], while patterns of auto-antibodies have been shown to differ significantly among ethnicities [14].

In both adults and children, the diagnosis of SLE relies upon a combination of clinical and laboratory findings. A recent study [15] has suggested that the SLICC criteria [16] (see Chapter 8) performed better in terms of sensitivity and accuracy in pediatric SLE as compared with the previous 1997 ACR criteria. However, one should be reminded that these classification criteria were derived to identify homogeneous

groups of patients for clinical studies, and therefore that diagnosis of SLE at the patient-level should not solely rely upon fulfillment of those criteria. Given the highly polymorphic presentation of the disease and the high frequency of atypical manifestations [12] in children, the diagnosis of SLE should be promptly considered in any febrile children or adolescent with any unexplained organ involvement, especially when associated with an increased ESR or with cytopenias.

There is a current lack of pediatric-specific controlled trials, and treatment strategies are therefore generally guided by adult data. Some studies have reported a higher use of corticosteroids and immunosuppressive agents in pediatric SLE [6,8,12) compared to adults. This may be related to the generally higher disease activity observed in children with SLE. Of note, a specific effort to cover the field of pediatric SLE has been shown in the recent European League Against Rheumatism (EULAR) recommendations for the management of lupus nephritis, which suggest that pediatric lupus nephritis should generally be managed in the same as is done for adults [17]. Consensus treatment plans for induction therapy of newly diagnosed proliferative lupus nephritis in pediatric SLE have also been recently derived [18]. Data suggest that cyclophosphamide, mycophenolate mofetil [19,20], and rituximab can be administered to children [21], and that specific pharmacological monitoring [22] and ovary protection when cyclophosphamide is used [23] may prove useful in this context. Of note, the risk of gonadic toxicity due to cyclophosphamide is mostly a concern in women of reproductive age and increases strongly after 30 years of age. The use of biphosphonates remains controversial in children, owing to concerns for the sustained fixation on the growing bone. Statins have not been shown beneficial for the prevention of cardiovascular risk in a randomized control trial in pediatric SLE [24].

While treatment strategies are mostly guided by adult data, physicians involved in the care of pediatric lupus are confronted with many specific challenges, ranging from the severity of the disease with increased early organ-damage, to the side-effects of treatments such as delayed puberty, growth retardation, osteoporosis, and changes in the physical appearance. Furthermore, the psychosocial consequences

of living with a chronic disease add to the burden of the disease, and include poor compliance [7]. Recognition of these specific issues as well as a carefully planned transition to adult care are among the issues that need to be addressed in pediatric SLE.

The prognosis of pediatric SLE has markedly improved during the last decade [25]. However, the most recent studies report 10-year survival rates lower in children than in adults [26]. Studies have identified a possible increase in the overall risk of malignancies in pediatric SLE, which appears to be driven by hematologic cancer risk [27], as well as a high incidence of severe infections [28]. Table 7.1 below has the key messages from this section on pediatric SLE.

Key messages on pediatric systemic lupus erythematosus (SLE)
Pediatric SLE represents 5–20% of SLE cases Pediatric SLE is generally reported to be more severe than in adults Pediatric SLE patients have been shown to accrue both earlier and more substantial disease damage over time than adults
Common presenting manifestations of pediatric SLE include: • Constitutional symptoms, such as fever, lymphadenopathy, and weight loss • Malar rash (discoid lupus is rare in children) • Arthritis • Atypical symptoms, such as abdominal pain due to pancreatitis The frequency of renal lupus and CNS involvement is increased compared with adults
Specific issues to address in pediatric lupus: • Side-effects of treatments such as: delayed puberty, growth retardation, osteoporosis, and changes in physical appearance and behavior • Psychosocial consequences of living with a chronic disease that affects physical appearance, physical function and quality of life • Poor therapeutic compliance • Need for carefully planned transition to adult care
There is a current lack of pediatric-specific controlled trials Treatment strategies are generally guided by adult data
The prognosis of pediatric SLE has improved during the last decade The 10-year survival rates remain lower in children than in adults

Table 7.1 Keys messages on pediatric systemic lupus erythematosus. CNS, central nervous system.

7.2 Late-onset SLE

While SLE is mostly observed in reproductive-age women, onset of the disease beyond 50 years of age occurs in 3–18% of patients [29]. This exerts a strong modifying effect on the clinical presentation, disease course, response to treatment, and prognosis of SLE.

Most of the literature show that the female to male sex ratio declines with aging in SLE, and is ≈3:1 in late-onset SLE [3]. Because late-onset SLE commonly affects patients with several treated co-morbidities, the possibility of drug-induced lupus should always be considered in these patients (see Chapter 1).

In comparison with younger patients, late-onset SLE patients are often reported to have a more insidious onset of disease and a less common occurrence of severe manifestations (Table 7.2) [30]. The atypical presentation is responsible for a longer diagnostic delay compared to adult-onset SLE [31]. Literature reviews and meta-analyses suggest that serositis are more frequently observed in late-onset SLE, while malar rash, photosensitivity, arthritis, lupus nephritis and neuropsychiatric manifestations occur less commonly than in adult-onset SLE [26,29,30,32,33]. Of note, Sjögren's syndrome is more frequent in late- rather than in early-onset SLE [30]. Therefore, some features observed in late-onset SLE patients, including the higher frequency of interstitial lung disease, may be influenced by the association with Sjögren's syndrome. Nevertheless, and despite the apparent reduced severity of the disease, >50 years of age at disease onset has been reported as an independent risk factor for damage accrual and mortality [32,33].

The frequency of ANA positivity increases with age in the general population without autoimmune disease [34]. Also, the serological manifestations of SLE also change with aging, with anti-RNP, anti-Sm, and low CH50 occurring less frequently in late-onset SLE [30,32]. Conversely, positivity of rheumatoid factor is more frequent [33].

Differential diagnosis (see Chapter 4) of late-onset SLE mostly includes other connective tissue diseases and vasculitides such as polymyalgia rheumatica and temporal arteritis, Sjögren's syndrome, and late-onset RA, various infections (endocarditis, tuberculosis), metabolic conditions (gout, chondrocalcinosis), or neoplasia, including paraneoplastic polyarthritis.

	Early-onset SLE (age<50 y)	Late-onset SLE (age ≥50 y)
Epidemiology		
• Frequency (compared to all SLE cases)	82–97%	3–18%
• F/M sex ratio	Higher F/M sex ratio (from 9 to 14.4)	More frequent occurrence of pericarditis, pleurisy, pulmonary involvement
Clinical features		
• SLE manifestations	More frequent occurrence of malar rash, photosensitivity, alopecia, purpura/cutaneous vasculitis, Raynaud' phenomenon, neuropsychiatric features, lymphadenopathy, lupus nephritis	More frequent occurrence of pericarditis, pleurisy, pulmonary involvement
• Associated Sjögren's manifestations (sicca syndrome)	Less frequent	More frequent
Serological data	Increased frequency of anti-RNP antibodies, anti-Sm antibodies, low CH50	Increased frequency of rheumatoid factor positivity
Disease course	Usually more severe	Usually milder
Treatment	Depends on the type and severity of disease manifestations	Depends on the type and severity of disease manifestations. Extra care needed regarding drug interactions and drug side effects in the elderly
Survival[a]	95% at 5 years 95% at 10 years 92% at 15 years	84% at 5 years 71% at 10 years 59% at 15 years

Table 7.2 Comparison of late-onset systemic lupus erythematosus (SLE) and earlier-age onset SLE characteristics. [a]Data from Boddaert et al [2]. Data were not adjusted for the age at SLE onset. Reproduced with permission from © Adis Data Information BV 2012. All rights reserved. Arnaud et al [29].

The milder severity of the disease usually translates into a reduced need for use of corticosteroids and cytotoxic agents during the course of the disease [30,33]. However, due to comorbidity, polymedication and drug-interactions, and physiological changes such as decreased renal clearance, adverse events of treatments are more frequent in late-onset SLE [33]. Antimalarial agents such as hydroxychloroquine have progressively become one of the cornerstones of SLE treatment, but should be contraindicated in case of previous retinopathy, including age-related macular degeneration. Non-steroidal anti-inflammatory drugs (NSAIDs) should be used with great caution in the elderly, especially in those with

a history of cardiac or renal disease, where it is crucial to monitor renal function regularly, to use a gastroprotective treatment, and to check for drug interactions such as those with oral anticoagulants. Corticosteroid-related side effects induce substantial morbidity and prevention of osteoporosis and of other metabolic complications should be considered in late-onset SLE patients. Finally, data on efficacy of biologics in late-onset SLE are lacking, making it difficult to generalize results in the elderly. Table 7.3 features the key messages on late-onset SLE.

Key messages on late-onset systemic lupus erythematosus (SLE)

Late-onset SLE represents 3-18% of SLE cases
The female to male sex ratio declines with aging in SLE, and is ≈ 3:1 in late-onset SLE
The possibility of drug-induced SLE should always be considered in older patients

Typical manifestations of late-onset SLE include:

- Increased frequency of:
  - Interstitial lung disease
  - Serositis
  - Sjögren's syndrome
- Decreased frequency of:
  - Malar rash and photosensitivity
  - Arthritis
  - Lupus nephritis
  - Neuropsychiatric manifestations

Late-onset SLE is generally reported to be less severe than in other age-groups
Late-onset SLE patients have been shown to accrue more damage over time, and to have increased mortality

Positivity of rheumatoid factor is more frequent in late-onset SLE, as in the general population. Our recommendation is to consider ANA titers ≥ 1:160 as significant, unless diagnosis of late-onset SLE is supported by strong clinical evidence

Differential diagnoses of late-onset SLE mostly include:

- Other connective tissue diseases and vasculitides (polymyalgia rheumatic, temporal arteritis, Sjögren's syndrome and late-onset rheumatoid arthritis)
- Infections (endocarditis, tuberculosis)
- Metabolic conditions (gout, chondrocalcinosis)
- Neoplasia, including paraneoplastic polyarthritis

Specific issues to address in treatment of late-onset SLE:

- Due to comorbidity, polymedication, drug-interactions, and physiological changes such as decreased renal clearance, adverse events of treatments are more frequent in late-onset SLE
- Antimalarial agents such as hydroxychloroquine are contraindicated in case of previous retinopathy, including age-related macular degeneration
- NSAIDs should be used with great caution in the elderly
- Corticosteroid-related side effects induce substantial morbidity and prevention of osteoporosis and of other metabolic complications should be considered in late-onset SLE patients
- Data on efficacy of biologics are lacking in late-onset SLE, making it difficult to generalize results to the elderly

Table 7.3 Keys messages on late-onset systemic lupus erythematosus.

7.3 Management of pregnancy

Pregnancy has always been challenging for SLE patients and their treating physicians. Both maternal and fetal outcomes may be unfavorable if the disease is not managed carefully. SLE is usually not associated with infertility unless the patient has been treated with cyclophosphamide [35]. However, a population-based study has shown that women with SLE have fewer live births than the general population [36].

Systemic lupus per se is not a contraindication for pregnancy but conception should be avoided in case of concomitant severe pulmonary hypertension, heart or renal failure, because of the high risk of maternal morbidity and mortality. In general, a multidisciplinary team consisting of a rheumatologist or an internist and an obstetrician with significant experience on high-risk pregnancies manages the care of pregnant patients with SLE. Patients should be informed that pregnancies in SLE should be carefully anticipated, and that pre-pregnancy multidisciplinary counseling is important to determine the risk of both maternal and fetal complications. Additionally, presence of anti-phospholipid antibodies or antiphospholipid syndrome will significantly impact the course of the pregnancy, and should therefore be accounted for.

Main maternal complications in SLE patients include disease flare, arterial hypertension, especially in patients with previous renal involvement, spontaneous abortion, preeclampsia, eclampsia, premature rupture of membranes and thromboembolism. Adverse fetal outcomes mostly include intrauterine growth retardation, intrauterine fetal death, premature birth, neonatal lupus, and perinatal mortality [37–39].

Lupus flare during pregnancy occurs in about 20–60% of patients, mostly during the first or second trimester, but also during the postpartum period [37,38]. The recent PROMISSE cohort study [38] has reported flare rates of only 2.5% in the second trimester and of 3% in the third, which emphasizes the importance of pre-pregnancy counseling. Of crucial importance, the frequency of flares has been shown to vary with disease activity during the previous 6 to 12 months [37,38] before and at [40,41] conception, and also with discontinuation of treatments such as hydroxychloroquine [42]. Among women with significant organ-specific lupus activity during the 6 months before conception, the

risk for the same type of disease activity during pregnancy is 7–32-fold higher than in those without that type of activity immediately before conception [43].

While most SLE flares occurring during pregnancy are mild and usually treated easily with limited doses of corticosteroids, complications due to flares can cause significantly increased morbidity and mortality in patients as well as in the fetus. Recent studies have reported a high degree of adverse pregnancy outcomes in non-white patients [38,44]. Predictors of adverse pregnancy outcomes include presence of lupus anticoagulant, use of antihypertensive treatments, disease activity according to Physician global assessment score, and low platelet count [38]. In a recent multi-center study [38], the rate of adverse pregnancy outcomes among women without any of these risk factors at baseline was 7.8%. Conversely, for those who were either LA-positive or were LA-negative but non-white or Hispanic and using antihypertensive drugs, the rate was 58% and fetal or neonatal mortality was as high as 22%.

A specificity of pregnancy in SLE patients is that some signs and symptoms of normal pregnancy must be differentiated from those of SLE flare, which can prove challenging. For instance, fluid accumulation in the lower limbs can be clinically difficult to distinguish from arthritis. Physiological proteinuria increases with rates ≥300 mg/24 hours considered pathological. Distinction between preeclampsia and lupus nephritis can be highly challenging, and renal biopsy needed to distinguish between the two conditions [45]. Preeclampsia is generally associated with pure proteinuria while active urine sediment is usually reported in lupus nephritis. Also, proliferative lupus nephritis is often associated with hypocomplementemia and increased titers of anti-DNA antibodies while complement levels are usually not decreased in preeclampsia. Both previous lupus nephritis and active lupus nephritis at conception are predictors for adverse maternal outcomes [38,40] and fetal outcomes in most studies but not all [40]. However, the prognosis of lupus nephritis occurring during pregnancy is poorly known, but failure to achieve a 50% reduction in urine protein levels within six months, longer total duration of renal flare, and acute kidney injury at renal flare is associated with poorer renal prognosis (40). Thrombocytopenia can

be physiological (>100G/L), or related to HELLP (hemolysis, elevated liver enzyme levels, and low platelet counts) syndrome, or be associated with antiphospholipid antibodies, thrombotic thrombocytopenic purpura, or immune peripheral thrombocytopenia of lupus flare. Assessments generally recommended for the care of pregnancy in SLE are shown in the following Table 7.4. Because of the limited number of therapies approved during pregnancy, the clinical management of SLE patients can be challenging. Additionally, vomiting due to morning sickness may prevent absorption of medications. Also, several of the drugs used to treat systemic lupus, such as methotrexate, cyclophosphamide and mycophenolate mofetil [46] are teratogenic, including when used in men [47], and should therefore be discontinued before the pregnancy. Continuing hydroxychloroquine is suggested based on safety data [48] and risk of flare after discontinuation [42]. Glucocorticoids should be continued in pregnant women without changing their doses. Also, starting low-dose glucocorticoids (eg, 5–10 mg per day of Prednisone-equivalent) is a

Key messages on suggested assessments in pregnancy during systemic lupus erythematosus (SLE)
Preconception counseling visit: • Detailed assessment of co-morbidities, if any • Full history of the disease • Search for a contra-indication to pregnancy • Assessment of thrombo-embolic risk • Review of all treatments (teratogenicity) • Physical examination, including blood pressure evaluation • Laboratory works: complete blood count (CBC), renal function tests, including determination of the glomerular filtration rate, urinalysis, and urine protein/urine creatinine ratio, hepatic function tests, including transaminases, anti-dsDNA antibodies, complement (CH50, C3 and C4), test for anti-SSA and -SSB antibodies, tests for Lupus Anticoagulant, anticardiolipin and anti-β2GPI antibodies
Then, during pregnancy (every month to trimester, according to local or national practice): • Complete blood count (CBC) • Renal function tests, including determination of the glomerular filtration rate, urinalysis, and Pu/Cr creatinine ratio • Hepatic function tests, including transaminases • Anti-dsDNA antibodies • Complement (CH50, C3 and C4) tests • Specific placental Doppler echocardiography in presence of aPL • Specific fetal echocardiography in case of anti-Ro/SSA and anti-La/SSB antibodies

Table 7.4 Keys messages on suggested assessments in pregnancy during systemic lupus erythematosus.

common practice to prevent flares if patients without any corticosteroid treatment [49]. If needed, cautious use of azathioprine is possible [50,51]. Cyclosporine does not appear to be a major human teratogen, but may favor the development of hypertension and preeclampsia in pregnant women, and induces fetal immunosuppression. Although few congenital malformations or neonatal infections have been reported, women should be counseled to avoid pregnancy for 12 months after rituximab exposure [52]. Very limited data are available about the potential risk of belimumab during pregnancy [53], but animal models show that the drug can cross the placenta [54].

Unless contra-indicated for a specific reason, all SLE patients should receive low-dose aspirin during pregnancy, as this treatment reduces the risk of preeclampsia [55]. According to US recommendations [56], patients with antiphospholipid antibodies and no previous history of thrombosis are generally treated with low-dose aspirin and prophylactic doses of heparin or low-molecular-weight heparin, while patients with antiphospholipid syndrome and a previous history of thrombosis are generally treated with low-dose aspirin and full doses of heparin or low-molecular-weight heparin [56], as oral anticoagulants are contraindicated during pregnancy.

Prednisone at doses lower than 20 mg/day and hydroxychloroquine can be used safely during breastfeeding because only small amounts are secreted in breast milk and are unlikely to cause any adverse effects in breastfed infants. When the mother receives more than 20 mg/day of prednisone equivalent, breastfeeding should be avoided during the first 3–4 h following the dose [57]. Breastfeeding during treatment with azathioprine is generally safe [58] but cases of transient neutropenia have been reported. Conversely, breastfeeding is contraindicated in patients treated with methotrexate [59], cyclosporine [60] or cyclophosphamide. Excretion of mycophenolate mofetil in human milk has not been studied, and therefore breastfeeding should be contraindicated. Table 7.5 is below with the key messages on the use of immunosuppressive drugs during pregnancy and breastfeeding.

Key messages on use of immunosuppressive drugs during pregnancy and breastfeeding		
Drugs	**Pregnancy**	**Breastfeeding**
Prednisone <20mg/day	Pregnancy possible	Breastfeeding possible
Prednisone ≥20mg/day	Pregnancy possible, but oral clefts have been reported with first trimester exposure	Breastfeeding should be avoided during the first 3–4h following prednisone intake
Hydroxychloroquine	Pregnancy possible and generally safe	Breastfeeding possible
Azathioprine	Pregnancy possible but intra-uterine growth retardation, neonatal cytopenias and infections have been reported	Breastfeeding possible (cases of transient neutropenia reported)
Methotrexate	Pregnancy contraindicated. The drug should be discontinued >1-3 months prior to conception and supplementation with folic acid started	Breastfeeding contraindicated
Mycophenolate mofetil	Pregnancy contraindicated Known teratogenic drug The drug should be discontinued >6 weeks prior to conception	Breastfeeding contraindicated (no data available)
Cyclosporine	The drug can be used, but extra maternal and fetal monitoring is needed	Breastfeeding contraindicated
Cyclophosphamide	Pregnancy contraindicated	Breastfeeding contraindicated
Rituximab	Pregnancy contraindicated The drug should be discontinued >12 months prior to conception	Breastfeeding contraindicated
Belimumab	Pregnancy contraindicated until further notice	Breastfeeding contraindicated until further notice

Table 7.5 Key messages on use of immunosuppressive drugs during pregnancy and breastfeeding.

7.4 Neonatal lupus

Neonatal lupus erythematosus (NLE) refers to a clinical spectrum of cutaneous [61,62], cardiac [63–65], and other systemic abnormalities such as cytopenia, hepatic or neurological manifestations [66] caused by the passive transplacental passage of maternal anti-Ro/SSA, anti-La/SSB, and less commonly anti-U1-ribonucleoprotein (U1-RNP) antibodies. International efforts [64,65,67–69] have attempted to improve the understanding of the risk factors [70], clinical characteristics, and

management of this rare condition, which occurs in 1–2% in anti-SSA/SSB positive women at first pregnancy, but has a recurrence rate of approximately 20%.

Cutaneous lesions are the most common manifestations of neonatal lupus, being reported in 15–25% of cases [64,65,67–69]. These may be present at birth, but most commonly appear between 4 and 6 weeks of age [61,62,71]. Cutaneous manifestations of neonatal lupus can be subtle and mistaken for another neonatal rash. However, the identification of cutaneous neonatal lupus is particularly important, since it predicts a 6–10-fold increase in the risk of a subsequent child developing cardiac neonatal lupus [61]. Typical skin lesions are characterized by multiple round or annular macules [61,62] commonly localized to sun-exposed areas, particularly on the head (the classic erythematous involvement of periorbital areas is termed 'raccoon eyes'), neck, and extensor surfaces of arms. However, involvement of other body parts is common, and more atypical manifestations, including discoid lupus, mucosal ulcerations, telangiectasia, scales, bullous lesions may be seen [62]. A skin biopsy is usually not required to establish the diagnosis, but histologic findings are similar to those of subacute cutaneous lupus (see Chapter 3). The rash usually heals within 15–17 weeks and without treatment [71], as maternal antibodies passively transferred to the child disappear, but low-potency topical corticosteroids may be effective, if needed.

Cardiac neonatal lupus is observed in 15–20% of cases before birth, and typically includes congenital heart block, and less commonly endocardial fibroelastosis and dilated cardiomyopathy [63]. The pathogenesis of the disease involves the expression of the SSA/SSB antigens on the fetal cardiocytes, leading to local inflammation and production of profibrotic cytokines which will impair the conduction system [72]. There is evidence that the antibodies against Ro52 antigen can cause this complication but not those against the Ro60 antigen (72). The heart block is most frequently detected in utero by prenatal ultrasound, between 18 and 24 weeks of gestational age. In the majority of cases, complete block requires a pacemaker implantation [73]. The rate of pacemaker implantation is 70–79% by 10 years of age [65,67]. Unlike the benign cutaneous complications of neonatal lupus, cardiac manifestations are associated

with a risk of fetal or neonatal death of ≈17% [64,65,67]. Third-degree AV block is the most severe manifestation of cardiac neonatal lupus as it is irreversible, but heart blocks are not always complete, and first- or second-degree blocks may show spontaneous resolution during the first few months of life. Presence of complete heart block has been shown as an important predictor of growth restriction that persists for several years after birth, despite pacemaker treatment [74].

The use of fluorinated steroids to reverse the block remains controversial, as their efficacy to prevent disease progression or death is not supported by most recent data [75]. On the contrary, data from a multinational effort have shown that in mothers at high risk of having a child with cardiac neonatal lupus, the use of hydroxychloroquine protected against recurrence of the disease in a subsequent pregnancy [76].

Liver involvement of neonatal lupus usually presents with transient and asymptomatic elevated liver function tests [77], although jaundice has been reported. Occasional hepatomegaly or less commonly splenomegaly is observed. The anomalies generally resolve within the first months of life, without sequelae.

Hematological involvement of neonatal lupus is characterized by a generally transient and asymptomatic neutropenia, thrombocytopenia, and more rarely by a hemolytic anemia, pancytopenia or aplastic anemia [77,78].

Neurologic manifestations of neonatal lupus are uncommon and include non-specific white matter changes on brain imaging, calcification of the basal ganglia, myasthenia-like syndrome, and macrocephaly due to hydrocephaly [79].

The diagnosis of neonatal lupus should be considered in all children born from mothers with anti-SSA or anti-SSB antibodies, or if the child develops clinical and/or biological manifestations that are compatible with the disease. Confirmation of the disease relies on presence of specific autoantibodies in the sera of babies and mothers. Table 7.6 shows the key messages on neonatal lupus.

Key messages on neonatal lupus
Pathogenesis and risk factors: • Neonatal lupus is caused by the passive transplacental passage of maternal anti-SSA/SSB, and less commonly anti-U1-RNP antibodies • In anti-SSA/SSB positive women, the risk of neonatal lupus is 1–2% at first pregnancy, and 20% in subsequent pregnancies
Cutaneous manifestations: • Most common manifestations of neonatal lupus • Can be present at birth, but generally appears between 4 and 6 weeks of age • Typical skin lesions are characterized by multiple round or annular macules similar to subacute cutaneous lupus, but more atypical manifestations can occur • Skin biopsy is usually not required to establish the diagnosis • The rash usually heals without treatment within 4 months, but low-potency topical corticosteroids may be effective if needed
Cardiac neonatal lupus: • Typically includes congenital heart block, and less commonly endocardial fibroelastosis and dilated cardiomyopathy • Heart block is most frequently detected in utero by prenatal ultrasound, between 18 and 24 weeks of gestational age • In the majority of cases, complete block requires a pacemaker implantation • Cardiac manifestations are associated with a risk of fetal or neonatal death of about 17% • The use of fluorinated steroids to reverse the block is controversial • Hydroxychloroquine may protect against recurrence in subsequent pregnancies
Other manifestations (less common): • Liver involvement: transient and asymptomatic elevated liver function tests, occasional hepatomegaly or splenomegaly • Hematological involvement: generally transient and asymptomatic neutropenia, thrombocytopenia, and more rarely hemolytic anemia, pancytopenia or aplastic anemia • Neurologic manifestations: non-specific white matter changes on brain imaging, calcification of the basal ganglia, myasthenia-like syndrome and macrocephaly with hydrocephaly

Table 7.6 Key messages on neonatal lupus.

7.5 Cardiovascular risk

SLE patients are generally considered at early and increased risk of cardiovascular events (CVE) and cardiovascular mortality compared to the general population [80]. This results from a complex interplay between several pathophysiologic mechanisms such as the classic cardiovascular risk factors (CVRF), the disease per se, possibly disease activity, the impact of treatments, the role of damage such as renal failure, and in some cases, the presence of antiphospholipid antibodies (Figure 7.1). All causes of mortality except cardiovascular mortality have decreased in SLE in the past decades [81].

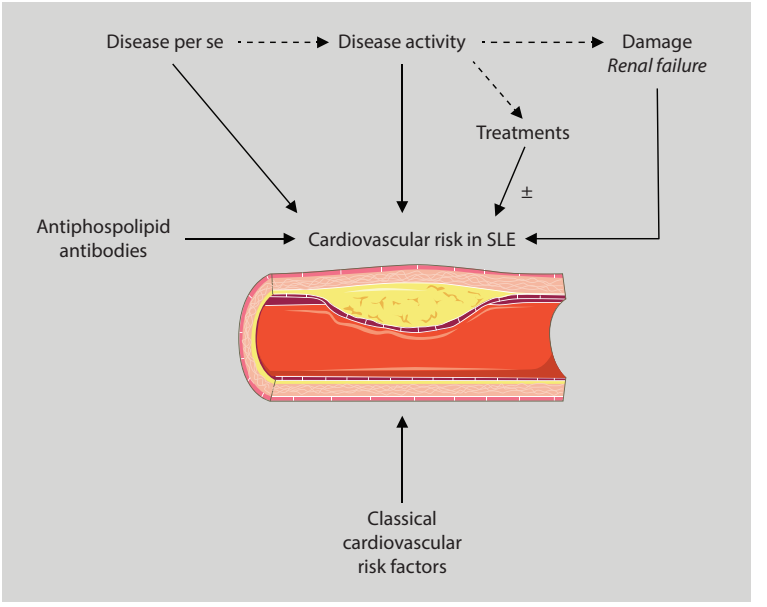

Figure 7.1 Determinants of cardiovascular risk in systemic lupus erythematosus. Elements of this illustration were provided by Servier Medical Art by Servier (http://smart.servier.com/), licensed under a Creative Commons Attribution 3.0 Unported Licence.

7.5.1 Subclinical atherosclerosis

Several studies have assessed the prevalence of preclinical markers of atherosclerosis in SLE, such as by measuring the carotid intima-media thickness, or the frequency of carotid plaques or coronary calcifications (coronary calcium score). Most [82-84] but not all of these studies [85], report increased parameters of preclinical atherosclerosis in SLE patients compared to controls. However, the follow-up duration is usually limited in this study, and the association between pre-clinical parameters and the actual risk of cardiovascular events is debated in SLE.

7.5.2 Risk of cardiovascular events

Several case-control studies have shown that the relative risk of CVE is higher in SLE patients compared with matched controls. The absolute risk of coronary event at 10 years is generally estimated to be 10–15%, and that of ischemic stroke of 5–10% [86,87].

7.5.3 Traditional cardiovascular risk factors and cardiovascular events

Traditional cardiovascular risk factors such as age, hypertension, hypercholesterolemia, smoking, and diabetes alone cannot explain the high incidence of CVE in SLE [87,88], but independently contribute to their occurrence [89].

7.5.4 Disease activity and cardiovascular events

Data regarding the possible association between CVE and disease activity in SLE are difficult to interpret, as there are many alternative definitions of disease activity and available evidence are conflicting. An association between CVE and the SLE Disease Activity Index (SLEDAI) score has been reported in some [89] but not all [82] studies. Also, the association between carotid plaques [84], carotid intima-media thickness [90], coronary calcium score [90], and disease activity has not been observed in all studies. It is therefore difficult to formally decide whether disease activity per se contributes to the development of cardiovascular complications in SLE.

7.5.5 Complications of the disease and cardiovascular events

While the American College of Rheumatology (ACR)/ Systemic Lupus Collaborating Clinics (SLICC) damage index has not been associated with preclinical markers of CVE in SLE [82], several [91] but not all [90] studies have reported an association between kidney disease and increased clinical or preclinical cardiovascular complications in SLE.

7.5.6 Corticosteroids and cardiovascular events

SLE treatment may influence the occurrence of cardiovascular complications, since corticosteroids promote hypertension, weight gain, diabetes, and induce dyslipidemia. However, the association between use of corticosteroids and CVE has been found inconstant, being reported in some [88,89,91] but not all studies [82,84]. A potential explanation for this apparent paradox could be that the benefit of better disease activity control may, in some cases, outweigh the pro-atherogenic risk of the treatment.

7.5.7 Strategies for assessment of cardiovascular risk in systemic lupus erythematosus patients

Cardiovascular risk prevention strategies in the general population are currently based on estimates of individual cardiovascular risk, using algorithms such as the Framingham score or European index Systematic COronary Risk Evaluation (SCORE) . These tools are validated in the general population but are not suitable for estimating individual cardiovascular risk in SLE patients because they strongly underestimate the actual risk [92]. Considering SLE as an additional CVRF [92], using an adjustment factor to correct estimates obtained for the general population [93] or using specific cardiovascular risk scores [89] are popular available options, but none of these method has been formally validated.

7.5.8 Prevention of cardiovascular events in systemic lupus erythematosus patients

Based on data from the general population, treatment of modifiable classical cardiovascular risk factors, such as definitive smoking cessation, is generally recommended in SLE. However, the benefit of such interventions has not been formally assessed in SLE, except for the use of antihypertensive treatments that have been shown to decrease the risk of CVE [94]. The use of statins for primary prevention of CVE has proven beneficial in the general population, but all randomized controlled trials performed in SLE have failed to reach their primary endpoint [95–97]. Therefore the use of statins in all SLE patients for the primary prevention cannot be recommended. The use of low-dose aspirin for the primary prevention of CVE in SLE patients carrying a persistent aCL or lupus anticoagulant is advocated by current recommendations [98], and has been further supported by two recent meta-analyses [99,100]. Finally, observational data suggest that hydroxychloroquine may be protective against the risk of CVE in SLE [101]. Table 7.7 shows the key messages on cardiovascular risk in SLE.

Key messages on cardiovascular risk

General comments:

- Systemic lupus erythematosus (SLE) patients have an early and increased risk of cardiovascular events (CVE)
- All causes of mortality, but CVE, have decreased in SLE during the last decades [81]
- In SLE, CVE result from classic cardiovascular risk factors, the disease per se, its treatments, and in some cases, presence of antiphospholipid antibodies
- Many studies show conflicting results, and results obtained in a given population may not be generalizable to another

Subclinical atherosclerosis:

- Preclinical markers of atherosclerosis such as the carotid intima-media thickness, carotid plaques or coronary calcifications (coronary calcium score) are generally increased in SLE

Risk of cardiovascular events:

- The absolute risk of coronary event at 10 years is generally estimated to be of 10 to 15%, and that of ischemic stroke of 5 to 10%

Risk factors and CVE:

- Traditional cardiovascular risk factors such as age, hypertension, hypercholesterolemia, smoking, and diabetes cannot alone explain this high incidence of CVE in SLE, but independently contribute to their occurrence
- Data regarding the possible association between CVE and disease activity in SLE are difficult to interpret, as there are many alternative definitions of disease activity and available evidence are conflicting
- Several studies have reported an association between kidney disease and increased clinical or preclinical cardiovascular complications in SLE
- The link between corticosteroids and CVE is inconstant. In some cases, the benefit of a better disease activity control may overweight the pro-atherogenic risk of the treatment

Strategies for assessment of cardiovascular risk:

- Cardiovascular risk prevention strategies in the general population are currently based on estimates of individual cardiovascular risk, using algorithms such as the Framingham score or European index SCORE
- These tools are not suitable for estimating individual cardiovascular risk in SLE patients
- Considering SLE as an additional CVRF, using an adjustment factor to correct estimates obtained for the general population or specific cardiovascular risk scores are available options, but none of is formally validated

Prevention of CVE:

- Treatment of modifiable classical cardiovascular risk factors is generally recommended in SLE, but the benefit of these interventions has generally not been formally assessed
- The randomized controlled trials of statins for primary prevention of CVE in SLE have largely failed to reach their primary endpoint
- The use of low-dose aspirin for the primary prevention of CVE in SLE patients carrying a persistent aCL or lupus anticoagulant is advocated by current recommendations, unless contra-indicated
- Observational data suggest that hydroxychloroquine may be protective against the risk of CVE in SLE

Table 7.7 Key messages on cardiovascular risk.

7.6 Infections and vaccines

Infections are among the most common complications of SLE, and remain one of the first causes of morbidity [102] and mortality [103,104] during the course of the disease.

7.6.1 Rate and types of infections

In the Euro-Lupus cohort, 27% of patients have presented infections during the first 5 years of follow-up [105]. In the US Medicaid database [106], the total infection incidence rate was of 10.8 per 100 person-years in the SLE cohort and as high as 23.9 in those with lupus nephritis.

The most common types of infections in SLE are community-acquired pneumonia, urinary tract infections, and skin and soft-tissue infections. Bacterial infections are mostly caused by *Streptococcus pneumoniae* [107], *Escherichia coli,* and *Staphylococcus aureus* [108], but virtually all infectious agents reported in the general population can be responsible for infections in SLE. SLE patients are, however, at increased risk for developing infections due to encapsulated bacteria and salmonella [109]. The risk of tuberculosis seems to be increased compared with the general population, but is difficult to assess as it varies strongly according to the area studied (110, 111). Herpes zoster is the most common type of viral infection in SLE [112]. Other common viral infections in SLE patients include parvovirus B19 [113], Epstein-Barr virus (EBV) (114) and cytomegalovirus (CMV) [115], and a controversy remains as to whether these infections could act as risk factors for the disease (see Chapter 1). Opportunistic and invasive fungal infections such as pneumocystosis, candidiasis, aspergillosis, cryptococcosis, disseminated histoplasmosis, and paracoccidioidomycosis are uncommon in SLE but highly lethal [108].

7.6.2 Risk factors for infections

Main risk factors for infections in SLE are the use of corticosteroids [106] or immunosuppressive agents [106,116,117], complement deficiencies, visceral involvements such as kidney disease [106], functional hyposplenia or asplenia, and possibly disease activity [118] or lupus per se (Figure 7.2). Conversely, cytopenia due to SLE activity are not generally considered to be major risk factors for infections [119]. Interestingly,

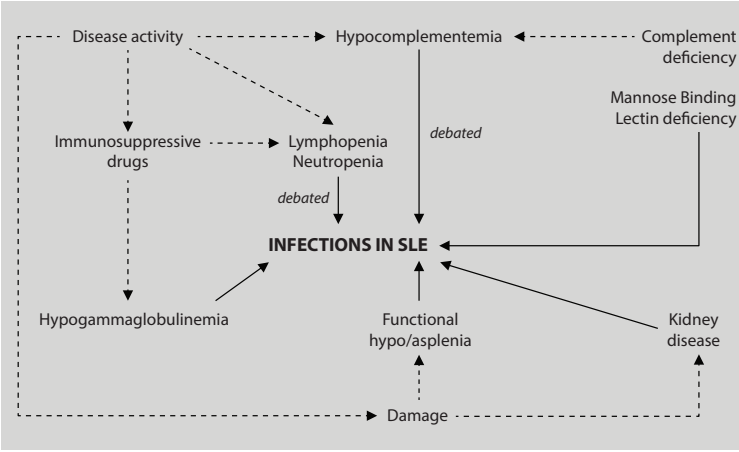

Figure 7.2 Pathogenesis of infections in systemic lupus erythematosus.

a few studies [106,117] have suggested that hydroxychloroquine use is associated with a decrease in the risk of infection in SLE. Treatment with cyclophosphamide has been associated with Herpes zoster infections [120] and high-dose corticosteroids with invasive fungal infections [121].

7.6.3 Diagnostic strategy

A common caveat in SLE is to distinguish between a lupus flare and an acute infection. Both clinical and serological parameters may be useful to distinguish between both conditions. CRP levels are generally normal in SLE patients (Table 7.8) and do not reflect disease activity, except in case of serositis [122] or hemophagocytic syndrome [123]. Consumption of C3 and C4 is seen in some patient with active SLE (particularly those with active proliferative lupus nephritis and hematological manifestations).

Clinical setting	CRP values, median (range)
Mild inflammation or viral infection	10–50 mg/L
Major inflammation or bacterial infection	50–400 mg/L
SLE flares without serositis*	16 mg/L (1–53mg/L)
SLE patients with active serositis*	76mg/L (2–375mg/L)
SLE patients with infection*	60mg/L (1–400mg/L)

Table 7.8 Typical C-reactive protein values observed in systemic lupus erythematosus patients. CRP, C-reactive protein. Adapted from © The Journal of Rheumatology Publishing Company Limited, 1990. All rights reserved. ter Borg et al [126].

However, because C3 and C4 are acute phase proteins, their levels may be normal during inflammatory processes, despite ongoing complement consumption. Also, high levels of anti-dsDNA antibodies are suggestive of ongoing disease activity in SLE. Recently, an algorithm based on a combination of fever duration, CRP and anti-dsDNA levels, has been shown effective to differentiate infections from disease flares [124], but its use is still limited in clinical practice. Also, procalcitonin (PCT) can be used in the early differentiation between bacterial infection and flare in febrile SLE patients, as raised levels are strongly suggestive of a bacterial infection, in the absence of hemophagocytic syndrome [123].

7.6.4 Infectious agents and vaccines

Among the available strategies to reduce the risk of infection, vaccination can be considered one the most reliable option, despite a sub-optimal immunogenicity and theoretical risk of flare that has never been formally demonstrated [125]. SLE patients are at increased risk and severity of *S. pneumoniae* infections [107], and those are reported to account for 5–20% of all bacterial infections in SLE [107,125]. Importantly, the risk of S. pneumoniae infection has been shown to be irrespective of the use of immunosuppressive agents [107], which suggests that all SLE patients should be vaccinated against *S. pneumoniae*. Two vaccines against *S. pneumoniae* are currently available on the market, a 23-valent polysaccharide vaccine and a 13-valent pneumococcal conjugate vaccine. While both vaccines have been shown to be effective and well-tolerated in SLE patients, the optimal vaccination strategy still remains to be identified. Data regarding the use of conjugate vaccine against *Haemophilus influenzae* in SLE patients are very limited [127] while vaccines against *Neisseria meningitidis* have not been formally assessed. Influenza vaccine is well-tolerated in SLE patients, but its immunogenicity may be decreased due to the use of immunosuppressive agents and concurrent lymphopenia [128]. Vaccination against tetanus and diphtheria appears to be safe and effective in SLE patients [129] and are generally combined with an inactivated vaccines against poliomyelitis.

Combination vaccines are licensed to prevent measles, rubella, mumps (and also varicella, in some), and a vaccine for *Herpes zoster* is now

available [130]. As a reminder, live attenuated vaccines are contraindicated in patients receiving more than 10 mg/day of prednisone-equivalent or any immunosuppressive or biological agents.

Influenza vaccination is generally recommended in SLE patients, especially those treated with corticosteroids or immunosuppressive agents. However, current immunization schemes may be insufficient to reach proper immunization [131], as the use of immunosuppressive agents and lymphopenia have been independently associated with poorer vaccine response [128].

Currently, there are no data available to confirm the safety and efficacy of hepatitis A vaccine in SLE patients. Data regarding the risk of SLE onset or SLE flare following hepatitis B vaccine are highly controversial, but vaccination is generally able to induce protective antibody titers in SLE patients [132].

Finally, more than 100 types of human papilloma virus (HPV) have been described, and some of these have been associated with cervical cancer in SLE women [133] as well as with anogenital and oral cancers in both men and women. A bivalent and a quadrivalent vaccine against HPV have been licensed. Preliminary data suggest that these vaccines are generally safe and effective in SLE patients [134–136], but some studies have shown that there may be an association between the vaccination against HPV and subsequent risk for SLE in some patients [137].

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Chapter 8

Disease activity, outcomes, prognosis, and perspectives

8.1 Disease activity

The concept of disease activity in systemic lupus erythematosus (SLE) is fairly intuitive and most clinicians are used to thinking of their patient's condition as representing, at any given point in time, a high, moderate, or low disease activity, or even a remission: the complete absence of disease activity. However, behind these deceptively simple statements hides a complex multi-dimensional reality, where the specific clinical manifestations attributed to SLE, the subjective experiences of the patient, and treatments all interact (Figure 8.1). Considerable efforts have been made over the past several decades to arrive at standardized and quantitative measures of disease activity both for some of the individual SLE manifestations and for the overall disease.

8.1.1 Disease activity in individual organ systems

For some of the organ manifestations of SLE well-established measures exist to assess and document the activity in that organ; for others, the measures that are used remain somewhat unproven; and for some SLE manifestations there are no systems other than the use of common clinical skills.

For lupus nephritis, assessment of activity builds on the same analyses that are used generally in medicine and nephrology: measurements of renal function, proteinuria, and the presence in the urinary sediment of casts, erythrocytes, or leucocytes. All of these can readily be quantified,

L. Arnaud and R. van Vollenhoven, *Advanced Handbook of Systemic Lupus Erythematosus*, https://doi.org/10.1007/978-3-319-43035-5_8

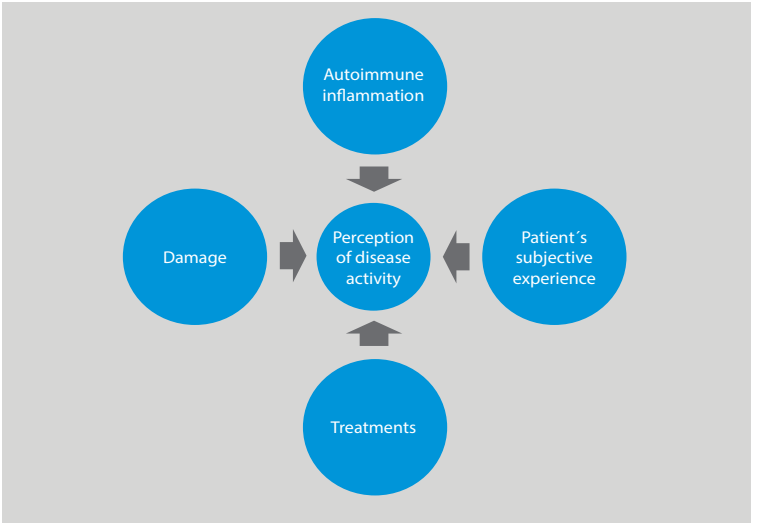

Figure 8.1 'Disease activity' may appear to be a simple concept but its perception is influenced by factors other than the actual autoimmune inflammation of systemic lupus erythematosus.

but it is less clear how a distinction can be made between those findings that are truly indicative of disease activity (ie, inflammation) and those that are due to damage in the glomeruli or the interstitium. Clinical trials in lupus nephritis have used ad hoc definitions of disease activity (as inclusion criteria, and to assess response) based on various combinations of these measures. A data-driven scoring system for lupus nephritis activity was published by Petri et al [1] but has not been used extensively (Table 8.1). However, it is simple and applicable to daily clinical care, and further studies of this system would be useful.

Proteinuria 0.5–1 gm/day	3 points
Proteinuria >1–3 gm/day	5 points
Proteinuria > 3 gm/day	11 points
Urine red blood cell count >10/high-power field	3 points
Urine white blood cell count >10/high-power field	1 point

Table 8.1 The systemic lupus international collaborating clinics (SLICC) renal disease activity score. The renal activity score is computed by adding up the points for proteinuria (3 levels), erythrocyturia, and leukocyturia. Adapted from © John Wiley & Sons, Inc, 2008. All rights reserved. Petri et al [1].

Needless to say, the gold standard for assessing lupus nephritis remains the kidney biopsy. The World Health Organization (WHO) system includes both histological grading in six types and further subtypes as well as the assessment of activity on a 0–24 point scale and of chronicity on a 0–12 point scale (Table 8.2) [2]. Some studies suggest that follow-up biopsies in patients with lupus nephritis are valuable [3,4] but the main limitation to doing renal biopsies remains the invasiveness and risks of the procedure.

For cutaneous lupus a validated scoring system exists, the cutaneous lupus activity and severity index (CLASI) [5]. It has been used in several trials, most notably a recently published trial with sifalimumab, where it achieved the highest differentiation between active drug and placebo of all tested outcomes; however, a very high placebo rate was also seen [6]. Another instrument for assessing cutaneous lupus, the revised (R)-CLASI, has also been published and validated and is being used in an ongoing trial [7].

SLE-related arthritis is common and one might expect that it would be easy to develop a simple system for quantifying the activity in this organ system. Remarkably, that appears not to have been the case. Joint counts where swollen and tender joints are counted or scored, such as in the assessment of rheumatoid arthritis (RA), have been included in

Active and chronic glomerular lesions
Active lesions: • Endocapillary hypercellularity with or without leukocyte infiltration and with substantial luminal reduction • Karyorrhexis • Fibrinoid necrosis • Rupture of glomerular basement membrane • Crescents, cellular or fibrocellular • Subendothelial deposits identifiable by light microscopy (wireloops) • Intraluminal immune aggregates (hyaline thrombi)
Chronic lesions: • Glomerular sclerosis (segmental, global) • Fibrous adhesions • Fibrous crescents

Table 8.2 The lupus nephritis activity and chronicity indices. For scoring lupus nephritis activity, each item on the list is score semi-quantitatively from 0 to 3, and the totals added up. The score for crescents is counted twice, so the maximum total is 24. Chronicity is scored similarly but based on different items. Adapted from © The American Society of Nephrology, 2004. All rights reserved. Weening et al [2].

some recent SLE clinical trials but with disappointing results. It has been suggested to forgo the distinction between swelling and tenderness and simply score the 'involved' joints in SLE – this approach will have to be studied more.

8.1.2 Instruments for measuring the overall activity of SLE

Besides assessing the activity of a specific organ system in SLE, it has been deemed useful to assess the overall activity of the disease in a systematic manner. Several methods for this have been developed over the past several decades. Some have clearly fallen by the wayside while others are in widespread use in clinical research and clinical trials, and to an increasing extent also in the regular care of patients with SLE.

8.1.2.1 Systemic lupus erythematosus disease activity index

The systemic lupus erythematosus disease activity index (SLEDAI) was initially developed by a group of Canadian SLE experts and based on patient cases and consensus finding [8]. In the year 2000 the same group made a number of data-driven modifications that led to the SLEDAI-2K [9]. Around the same time another group of investigators, the Safety of Estrogens in Lupus Erythematosus National Assessment (SELENA) group, published a different modification of the SLEDAI, the SELENA-SLEDAI [10]. Fortunately, the three versions have remained quite similar in many ways.

The SLEDAI and its modifications consist of a list of 24 SLE manifestations that are each scored as present or absent (Figure 8.2). If present, each contributes a fixed number of points to the final score, which in theory can range from 0 to 105. In practicality, values of 20 or higher are rarely seen and I am personally not aware of any patient having scored more than 34.

The SLEDAI and its modifications have some clear strengths. The instrument is relatively easy to score, and once scored, the final value is a simple addition. It therefore lends itself to use in practice, registries, and trials. Definitions are given for each manifestation. The modifications that led to SLEDAI-2K and SELENA-SLEDAI both aimed to focus on active manifestations rather than fixed damage. There is now a large body of

SLEDAI: DATA COLLECTION SHEET

Chart no.:_____ **Date of visit:** _____

M.D:_____ **Patient's name:** _____

(Enter weight in SLEDAI Score column if descriptor present at the time of the visit or in the preceeding 10 days)

Weight	SLEDAI score	Descriptor	Definition
8	_____	Seizure	Recent onset. Exclude metabolic, infectious, or drug causes.
8	_____	Psychosis	Altered ability to function in normal activity due to severe disturbance in the perception of reality. Include hallucinations, incoherence, marked loose associations, impoverished thought content, marked illogical thinking, bizarre, disorganized, or catatonic behavior. Exclude uremia and drug causes.
8	_____	Organic brain syndrome	Altered mental function with impaired orientation, memory, or other intellectual function, with rapid onset and fluctuating clinical feautures. Include clouding of consciousness with reduced capacity to focus, and inability to sustain attention to environment, plus at least 2 of the following: perceptual disturbance, incoherent speech, insomnia or daytime drowsiness, or increased or decreased psychomotor activity. Exclude metabolic, infectious, or drug causes.
8	_____	Visual disturbance	Retinal changes of SLE. Include cytoid bodies, retinal hemorrhages, serous exudate or hemorrhages in the choroid, or optic neuritis. Exclude hypertension, infection, or drug causes.
8	_____	Cranial nerve disorder	New onset of sensory or motor neuropathy involving cranial nerves.
8	_____	Lupus headache	Severe, persistent headache; may be migrainous, but must be nonresponsive to narcotic analgesia.
8	_____	CVA	New onset of cerebrovascular accident(s). Exclude arteriosclerosis.
8	_____	Vasculitis	Ulceration, gangrene, tender finger nodules, periungual infarction, splinter hemorrhages, or biopsy or anglogram proof of vasculitis.
4	_____	Arthritis	More than 2 joints with pain and signs of inflammation (ie, tenderness, swelling, or effusion).
4	_____	Myositis	Proximal muscle aching/weakness, associated with elevated creatine phosphokinase/aldolase or electromyogram changes or a biopsy showing myositis.
4	_____	Urinary casts	Heme-granular or red blood cell casts.
4	_____	Hematuria	>5 red blood cells/high power field. Exclude stone, infection, or other cause.
4	_____	Proteinuria	>0.5 gm/24 hours. New onset or recent increase of more than 0.5 gm/24 hours.
4	_____	Pyuria	>5 white blood cells/high power field. Exclude infection.
2	_____	New rash	New onset or recurrence of inflammatory type rash.
2	_____	Alopecia	New onset or recurrence of abnormal, patchy or diffuse loss of hair.

Figure 8.2 The systemic lupus erythematosus disease activity index (SLEDAI; continues overleaf). Reproduced with permission from © John Wiley & Sons, Inc, 2005. All rights reserved. Bombadier [8].

2	_____	Mucosal ulcers	New onset or recurrence of oral or nasal ulcerations.
2	_____	Pleurisy	Pleuritic chest pain with pleural rub or effusion, or pleural thickening.
2	_____	Pericarditis	Pericardial pain with at least 1 of the following: rub, effusion, or electrocardiogram or echocardiogram confirmation.
2	_____	Low complement	Decrease in CH50, C3, or C4 below the lower limit of normal for testing laboratory.
2	_____	Increased DNA binding	>25% binding by Farr assay or above normal range for testing laboratory.
1	_____	Fever	>38°C. Exclude infectious cause.
1	_____	Thrombo-cytopenia	<100.000 platelets/mm^3.
1	_____	Leukopenia	< 3,000 white blood cells/mm^3. Exclude drug causes.
TOTAL SLEDAI SCORE	_____		

Figure 8.2 The systemic lupus erythematosus disease activity index (SLEDAI; continued). Reproduced with permission from © John Wiley & Sons, Inc, 2005. All rights reserved. Bombadier [8].

literature where the SLEDAI and its modifications have been used and analyzed. Its metric properties (for example, sensitivity to change) and its validity (such as construct validity) have been established.

The limitations of the SLEDAI and its modifications are also clear. Because each item is scored as absent or present, an improvement in a disease manifestation is not recognized until the manifestation is completely gone. The weighting of the SLEDAI items is in some cases at odds with clinical perceptions (for example, thrombocytopenia, even when life-threatening, gives one point). The SLEDAI includes the item 'lupus headache', a still-controversial manifestation of SLE that, even if it does exist, is so hard to differentiate from other types of headache that the risk of incorrect and inconsistent attribution is large. In general, attribution remains the achilles heel for SLEDAI scoring (as it is for all other instruments): the clinician has to form a judgment of whether each manifestation is due to SLE or not, and in actual practice this remains a major challenge.

The SLEDAI (or its modifications) have been used in many clinical trials, cementing its position as one of the two preferred disease activity scoring instruments, and it has also been supported by the large regulatory organizations United States Food and Drug Administration (US FDA) and European Medicines Agency (EMA). Because of its relative simplicity, the SLEDAI is also used widely in registers and observational studies, and increasingly in clinical practice settings. For the future, it can be hoped that agreement can be reached on the best version of the SLEDAI to use.

8.1.2.2 British Isles Lupus Assessment Group

The British Isles Lupus Assessment Group (BILAG) scoring instrument, also generally referred to as 'the BILAG', was developed by a consortium of SLE experts on the British Isles based on patient cases in their own registries [11]. This scoring system was derived from the actions taken by clinicians in various real-life situations. It consists of a list of 86 SLE manifestations (symptoms, signs, laboratory values, or other investigations) grouped by organ system. The clinician is asked to score each item. If present, an item has to be specified further in reference to the same patient's condition one month earlier, as new, worsened, improved, or stable. Based on these entries, lettered scores are calculated for each of eight organ systems, according to complex algorithms that cannot easily be carried out by an individual clinician. The lettered scores range from A to E and were made to correspond with clinical actions. 'A' (alert), the highest level of activity, would normally be treated with high-dose glucocorticoids and/or immunosuppressives. 'B' (beware) would normally be treated with low- or moderate-dose glucocorticoids. 'C' (contentment), while representing active disease, would normally not require (immediate) therapeutic action. 'D' represents inactive disease in a previously involved organ system, and 'E' denotes the absence of disease activity in that organ system at any time during the patient's disease course.

It is possible to convert the eight-lettered scores to a single numerical score, but the latter has not been studied very well, and the BILAG group of investigators has not recommended that way of scoring. The BILAG score was modified and updated, by the BILAG group, in 2004

and since then the BILAG-2004 score has been used almost exclusively [12]; in comparing results from earlier and later publications this has to be considered, although in practicality the differences are not large.

The BILAG has considerable strengths. As a 'case report form' it encompasses almost any conceivable SLE manifestation, thus providing a very accurate record of the patient's disease. The comparison to the previous month allows it to detect changes in disease manifestations. The BILAG has been studied very intensively for many years and its metric properties and validity have been described in detail.

The disadvantages of the BILAG are also clear. Completion of the form's 86 items is time consuming, and the need to compare with a prior visit runs into many practical issues, including issues of actual recall, recall bias, intra- and inter-observer inconsistencies, and the fact that monthly physician visits are rarely feasible in usual health care. Scoring the BILAG is complex and mostly done at dedicated centers. As indicated earlier, the achilles heel of all scoring systems is attribution, and the BILAG cannot help determine if a given manifestation is due to SLE or not.

The BILAG has been used in most of the largest pharmaceutical trials, so that it has been established as one of the two preferred disease activity scoring instruments in drug development, which has also been supported by the US FDA and EMA. However, it is doubtful that this complicated instrument can be used by clinicians in practice other than in highly specialized, dedicated centers.

8.1.2.3 The SLE responder index

When phase III trials were designed for belimumab, the sponsor working together with experts and the FDA decided to use a wholly novel outcome: the SLE responder index (SRI), which was based on the SLEDAI, the BILAG, and the physician's global assessment by visual analog scale (VAS) [13,14]. The SRI was defined as a dichotomous measure of response whereby a patient would be declared a responder if (s)he had an improvement from baseline in the SLEDAI by at least 4 points, without having a worsening in the BILAG (which in turn was defined as having at least one new BILAG 'A' or at least 2 new BILAG 'B's), and also not having a worsening on the physician's VAS. The thinking behind this outcome was that the basic

improvement was determined using the SLEDAI, and that an improvement by at least 4 points was considered clinically relevant; but because the SLEDAI has 'holes' – manifestations of SLE that are not captured – it was felt to be necessary also to require that the other two measures did not register a worsening. In actual fact, subsequent analyses of the results obtained with the SRI have amply shown that they are driven to more than 90% by the results of the SLEDAI, so that the other two conditions have had little importance. But because the two phase III trials with belimumab were successful, the SRI has since been used in many other SLE clinical trials (in some, a slight modification of the SRI was used, whereby the responder had to have at least 5 points improvement on the SLEDAI; indicated as SRI-5). To date, few if any of those trials have been successful, and it can be asked if there is a good reason for continuing to use this compound of compounded measures. A clear disadvantage is the lack of easily understandable clinical 'meaning' of the SRI (however, a recent study examining this issue found that an SRI response was associated with many self-evident improvements).

8.1.3 Other disease activity instruments

In addition to the SLEDAI and the BILAG, several other systems for scoring global disease activity in SLE have been published. Some of these have been used quite extensively for some time, only to fall into disuse for practical rather than scientific reasons.

8.1.3.1 The European Consensus Lupus Assessment Measure

The European Consensus Lupus Assessment Measure (ECLAM) was derived from 704 patient cases in several European registries [15]. The most sensitive manifestations were selected for further use. The ECLAM consist of 15 items, each of which is scored as absent or present (some items have two levels of activity) and items that are present are given scores of 0.5, 1, or 2. Thus, it is an instrument that is both easy to record and easy to score. Its metric properties and validity were established and in direct comparison it performed equally well as SLEDAI and BILAG. Uniquely, it has been validated to be used retrospectively on previously collected cohort data [16]. Nonetheless, it has been used less than the

other instruments, and no major clinical trials have been done using the ECLAM as a primary outcome.

8.1.3.2 The Lupus Activity Index

The Lupus Activity Index (LAI) was developed at Johns Hopkins University and has been used almost exclusively in studies based on the Hopkins Lupus Cohort [17]. It consists of four visual analog scales (scaled 0–3), one each for four specific SLE manifestations; four other lupus manifestations are also scored. Thus, the instrument is very simple to use and has shown suitable measurement characteristics and validity.

8.1.3.3 The systemic lupus activity measure

The systemic lupus activity measure (SLAM) and its revision SLAM-R consists of 31 lupus features that are scored at up to three levels (mild, moderate, and severe) that are defined (semi-) quantitatively; the scores correspond to numerical values 1-2-3 and these are totaled [18]. The SLAM was used in clinical trials in the 1990s [19,20] and in many observational studies but has lately been used less. Its strengths include relative ease of completion and easy scoring. It includes highly subjective disease aspects (such as myalgias, fatigue), which can be considered a strength or a weakness depending upon one's perspective. An interesting modification of the SLAM, named the SLAQ, is completed entirely by the patient, and was shown to correspond reasonably well with the SLAM [21].

8.2 Lupus flares

The concept of SLE flares is intuitively understood by both patients and physicians, but defining it has turned out to be more complex than one would have imagined. The Lupus Foundation of America organized several international consensus-finding conferences in order to clarify the issue, and at the least, a verbal definition of flare was agreed upon: a flare is considered a measurable change in disease activity that would normally lead to at least the consideration of a change in therapy. Subsequent work has focused on achieving a workable flare instrument for use in

registries and trials, and possibly even in clinical care, and several such possibilities have been published.

A pragmatic approach to defining flare has been used in various settings including clinical trials. In these instances an increase in the SLEDAI by 4 or more, or the appearance of a new BILAG A or two new BILAG B's were considered to be a flare. For purposes of analyzing these trials it appears that these ad hoc definitions have performed rather well. The most widely used flare instrument is the SELENA flare index, also referred to as the SLEDAI flare index. The idea of this index is that the change in disease activity in the various organ systems can be predefined and scored as mild, moderate, or severe (in most versions the mild and moderate categories are taken together). Moreover, treatment decisions are also weighed in, and may in fact 'trump' the other definitions so that, for example, if the patient was given high-dose intravenous steroids it is inferred that the patient had a severe flare even if the specific definition of severe flare was not met. Despite years of development and use in various settings the ins and outs of the SELENA flare index remain incompletely defined at this time.

8.3 Response to treatment

Some work has also been done in defining a global SLE response index. An early attempt named the Response Index For Lupus Erythematosus (RIFLE) was used in some studies and appeared to perform reasonably well but has fallen into disuse. More recently it was proposed to add a feature to the SLEDAI that would enable the assessment of a response [22]. This feature, entitled S2K-50, allows the scoring of items that were present previously and are still present but that have improved by at least 50%. Normally for the SLEDAI they would receive the same score, but in this variation they are now given half the numerical value. The S2K50 has been used in a few studies. In the international registry for biologics in SLE (IRBIS) reporting the S2K50 by investigators was inconsistent.

8.4 Remission and low-disease activity

Intuitively, both the patient and the treating physician know what they want to achieve: the lowest possible level of disease activity. This apparent

simplicity is readily upset when it turns out that patients may find the relief of some symptoms more important than others, or when physicians may be hard-pressed to determine whether some symptoms or signs are related to active SLE. As a result, there are no generally agreed-upon definitions of 'low' disease activity or of the even more ambitious goal of remission, the absence of all disease activity. Fortunately, some progress is being made in these areas.

8.4.1 Low disease activity

A simple definition of low disease activity in SLE has been used in various studies, based on the SLEDAI (a SLEDAI score of less than 4) or the BILAG (only BILAG C categories or better). More recently, the Asia-Pacific Lupus Study Group derived, through an elaborate consensus-finding process, the lupus low disease activity state (LLDAS), which has since been tested in patient cohorts and has been found to perform very well, both in terms of its metric properties, its validity, and its ability to predict several important outcomes [23].

8.4.2 Remission

A recent review demonstrates that more than twenty ad hoc definitions of remission in SLE have been used in studies over the past decades. To end this confusion, an international task force was recently convened and has laid out a 'road map' for achieving a consensus definition of remission in SLE, the Definitions Of Remission In Lupus (DORIS) initiative [24]. The initial work of this group established the following structure for a definition of remission:

- the absence of disease activity by a validated measure (SLEDAI, BILAG, or ECLAM);
- a limitation on concomitant treatments; both remission 'on treatment' and remission 'off treatment' could be reported; and
- a further study of the duration of treatment.

8.5 Damage

Uncontrolled lupus activity may cause irreversible damage to the affected organs or tissues, and preventing such damage is one of the important

goals of lupus therapy. However, the therapies used to control SLE may also cause irreversible organ damage, underscoring the difficult choices clinicians are often faced with. In order to assess irreversible damage in patients with SLE a single scoring system was developed in the 1990s and has since stood the test of time: the systemic lupus international collaborating clinics (SLICC)/American College of Rheumatology (ACR) damage index (SDI) [25]. It consists of a list of 20 organs or organ systems and for each one or more specific kinds of damage that may be seen in the patient. A single point is given for each item that is present, with a few exceptions where two or three points are given. The SDI is the sum score.

The SDI has several major strengths, most importantly, it is rather intuitive and easy to use. Perhaps for this reason it has been very widely used in all types of SLE clinical studies, including all of the large randomized trials done in recent years. Regulatory authorities have declared that prevention of damage as measured by the SDI could be a primary outcome in a clinical trial, although to my knowledge this has never been tried. The SDI also has some unusual properties, such as the fact that because the items on the index are in principle irreversible the SDI is expected only to increase over time. Its distribution in SLE populations is highly skewed with the vast majority of individuals having scores of 0, 1, or 2. Importantly, even a score of 1 is associated with a considerably worse prognosis than 0 [26]. Weaknesses of the SDI include the fact that most items are weighted equally even though common sense tells us that a manifestation such as a cerebrovascular accident is more serious than a tendon rupture.

8.6 Patient-reported outcomes and quality of life

Patient-reported outcomes (PROs) are used in a broad range of clinical research and increasingly included in regular care. Some PROs are included in standardized outcome measures (for example, a patient-VAS is part of the SLAM and the LAI), and some key outcomes are almost exclusively assessed through a PRO (for example, physical function is often assessed by the health assessment questionnaire disability index [HAQ-DI]).

In addition, the concept of health-related quality of life (HR-QOL) is extremely important in chronic diseases such as SLE. From a patient's perspective, the goal of treatment must be not only to survive but to improve or at least stabilize HR-QOL ('to live, and to live well'). Measuring HR-QOL is a field of study in its own right. In the SLE literature, both generic and disease-specific instruments are used. Generic instruments such as the EQ5D and the SF36 have the advantage that comparison can be made with other diseases. Disease-specific instrument such as the Lupus-QOL may include some items that are particularly important for patients with this specific disease. Unfortunately, the proliferation of instruments has not helped the field; efforts are being made to consolidate these. Recently, PROs including measures of HR-QOL in lupus have been reviewed [27].

8.7 Prognosis

There is little doubt that over the past several decades, the prognosis for patients diagnosed with SLE has improved markedly. An often-cited study from the 1950s revealed a 10-year mortality of close to 50%, while more modern studies clearly show this not to be the case. However, one must bear in mind that the classification criteria for SLE did not exist in the 1950s and that the patient population in that study may well have represented the most severe group of patients, the 'tip of the iceberg'. Nevertheless, progress has clearly been made in some specific areas. For example, renal failure as a result of lupus nephritis was seen at only a minimal level in the 10-year follow-up of the Euro-Lupus study [28]. This may be attributable to the use of classic immunosuppressives including cyclophosphamide, in addition to glucocorticoids, in these patients. Many specialists who take care of patients with SLE also feel that the modern-day armamentarium of conventional and even biologic treatments allows them to provide better, more effective care for their patients than was the case 10, 20, or 30 years ago.

Nevertheless, in the case of SLE the glass is definitely also 'half empty'. There is still an early mortality due to SLE in patients who are struck by the most severe and devastating SLE manifestations, such as severe inflammatory disease in the central nervous system, the lungs,

the heart, or in widespread areas of the body. It has been singularly difficult to obtain solid epidemiological data on the frequency of this occurrence, but from personal experience I believe that somewhere between 5 and 10% of patients with SLE have a very severe, life-threatening presentation at onset, and a non-negligible minority of them cannot be helped despite all efforts. There is also a clear increase in late mortality, attributable in large part to an increase in cardiovascular disease. The cause is believed to be a complex interplay of the disease itself and the treatments used against it, most importantly glucocorticoids. In addition, there is late mortality due to infections and malignancies that can also be linked to the treatments.

In addition to the early and late mortality, there is the major issue of decreased HR-QOL. A patient survey in Sweden revealed that the average HR-QOL of patients with SLE was considerably lower than normal [29], and comparable to that seen in patients with advanced chronic obstructive pulmonary disease, stage III Hodgkin disease, or HIV infection. Clearly, behind that average statistic are many patients who do rather well, and others who suffer tremendously from the disease itself or from the consequences of chronic therapies. Additional negative contributors to health are also frequently present in patients with SLE, including depression, chronic non-inflammatory pain or fibromyalgia, and somatization. To some extent these poorly understood syndromes may be inevitable when individuals are struck by an uncommon, multifaceted, chronic disease that engender pain, impaired physical function, unpredictable flares, and the need for chronic medical treatments associated with risks and side-effects.

8.8 Perspectives

Thus, SLE remains a disease that despite our best effort can cause considerable suffering for the patient. Progress has been made, and many patients are leading relatively healthy and (hopefully) happy lives; but others are clearly in need of better therapies so as to control the manifestations of the disease, prevent flares, and avoid side effects due to longer-term treatments. Progress in defining new therapeutic targets in SLE has been slow but some encouraging developments have been noted in earlier chapters of

this book. At the present time, the best we can offer the patient with SLE is the committed and steadfast care by experienced specialists, often working in the much-needed multidisciplinary setting, and making optimal use of the therapeutic options that exist today; while holding out a reasoned hope to the patients that better treatments for SLE will be emerging tomorrow.

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