20 Systemic Lupus Erythematosus: Pathogenesis and Clinical Features

George Bertsias, Ricard Cervera, Dimitrios T Boumpas

A previous version was coauthored by Ricard Cervera, Gerard Espinosa and David D'Cruz

Learning objectives:

- Use the epidemiology and natural history of systemic lupus erythematosus (SLE) to inform diagnostic and therapeutic decisions
- Describe and explain the key events in the pathogenesis of SLE and critically analyse the contribution of genetics, epigenetics, hormonal, and environmental factors to the immune aberrancies found in the disease
- Explain the key symptoms and signs of the diseases and the tissue damage associated with SLE
- State the classification criteria of lupus and their limitations when used for diagnostic purposes
- Describe and explain the clinical manifestations of SLE in the musculoskeletal, dermatological, renal, respiratory, cardiovascular, central nervous, gastrointestinal, and haematological systems
- Evaluate the challenges in the diagnosis and differential diagnosis of lupus and the pitfalls in the tests used to diagnose and monitor lupus activity
- Identify important aspects of the disease such as women's health issues (ie, contraception and pregnancy) and critical illness
- Outline the patterns of SLE expression in specific subsets of patients depending on age, gender, ethnicity, and social class
- Classify and assess patients according to the severity of system involvement and use appropriate clinical criteria to stratify patients in terms of the risk of morbidity and mortality

1 Introduction

Systemic lupus erythematosus (SLE) is the prototypic multisystem autoimmune disorder with a broad spectrum of clinical presentations encompassing almost all organs and tissues. The extreme heterogeneity of the disease has led some investigators to propose that SLE represents a syndrome rather than a single disease.

2 Major milestones in the history of lupus

The term 'lupus' (Latin for 'wolf') was first used during the Middle Ages to describe erosive skin lesions evocative of a 'wolf's bite'. In 1846 the Viennese physician Ferdinand von Hebra (1816–1880) introduced the butterfly metaphor to describe the malar rash. He also used the term 'lupus erythematosus' and published the first illustrations in his *Atlas of Skin Diseases* in 1856. Lupus was first recognised as a systemic disease with visceral manifestations by Moriz Kaposi (1837–1902). The systemic form was further established by Osler in Baltimore and Jadassohn in Vienna. Other important milestones include the description of the false positive test for syphilis in SLE by Reinhart and Hauck from Germany (1909); the description of the endocarditis lesions in SLE by Libman and Sacks in New York (1923); the description of the glomerular changes by Baehr (1935), and the use of the term

'diffuse connective tissue disease' by Klemperer, Pollack and Baehr (1941). The beginning of the modern era in SLE was the discovery of the 'LE' cell by Hargraves, Richmond and Morton at the Mayo Clinic in 1948.

3 Epidemiology

Prevalence rates in lupus are estimated to be as high as 51 per 100 000 people in the USA. The incidence of lupus has nearly tripled in the last 40 years, mainly due to improved diagnosis of mild disease. Estimated incidence rates in North America, South America, and Europe range from 2 to 8 per 100 000 per year. Women are affected nine times more frequently than men and African American and Latin American mestizos are affected much more frequently than Caucasians, and have higher disease morbidity. The disease appears to be more common in urban than rural areas. Sixty-five per cent of patients with SLE have disease onset between the ages of 16 and 55 years, 20% present before age 16, and 15% after the age of 55. Men with lupus tend to have less photosensitivity, more serositis, an older age at diagnosis, and a higher 1 year mortality compared to women. SLE tends to be milder in the elderly with lower incidence of malar rash, photosensitivity, purpura, alopecia, Raynaud's phenomenon, renal and central nervous system involvement, but greater prevalence of serositis, pulmonary involvement, sicca symptoms, and musculoskeletal manifestations.

4 Natural history and course

SLE is a chronic disease of variable severity with a waxing and waning course, with significant morbidity that can be fatal—if not treated early—in some patients (figure 1). The disease starts with a preclinical phase characterised by autoantibodies common to other systemic autoimmune diseases and proceeds with a more disease-specific clinically overt autoimmune phase (Bertsias *et al* 2010a). During its course periods of flares intercept periods of remission culminating in disease- and therapy-related damage, such as alopecia, fixed erythema, cognitive dysfunction, valvular heart disease, avascular necrosis, tendon rupture, Jaccoud's arthropathy, and osteoporosis. Early damage is mostly related to disease whereas late damage—namely infections, atherosclerosis, and malignancies—is usually related to complications of longstanding disease and immunosuppressive therapy.

5 Aetiology and pathogenesis

The aetiology of SLE includes both genetic and environmental components with female sex strongly influencing pathogenesis. These factors lead to an irreversible break in immunological tolerance manifested by immune responses against endogenous nuclear antigens.

5.1 Genetic factors

Siblings of SLE patients are approximately 30 times more likely to develop SLE compared with individuals without an affected sibling. The rate of gene discovery in SLE has increased during the past few years thanks to large genome-wide association studies (GWAS) using hundreds of thousands of single nucleotide polymorphism (SNP) markers (figure 2).

GWAS in lupus have confirmed the importance of genes associated with immune response and inflammation

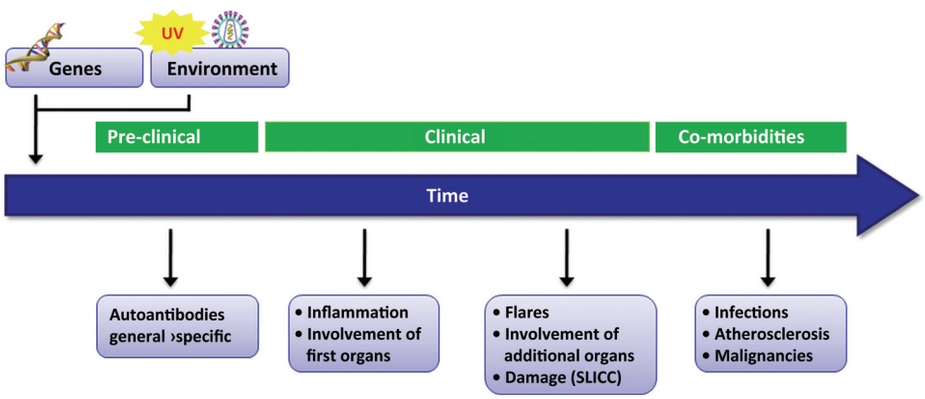

Figure 1 Natural history of systemic lupus erythematosus. SLICC, Systemic Lupus International Collaborating Clinics/American College of Rheumatology damage index. Reprinted with permission from Bertsias GK, Salmon JE, Boumpas DT. Therapeutic opportunities in systemic lupus erythematosus: state of the art and prospects for the new decade. *Ann Rheum Dis* 2010;**69**:1603–11.

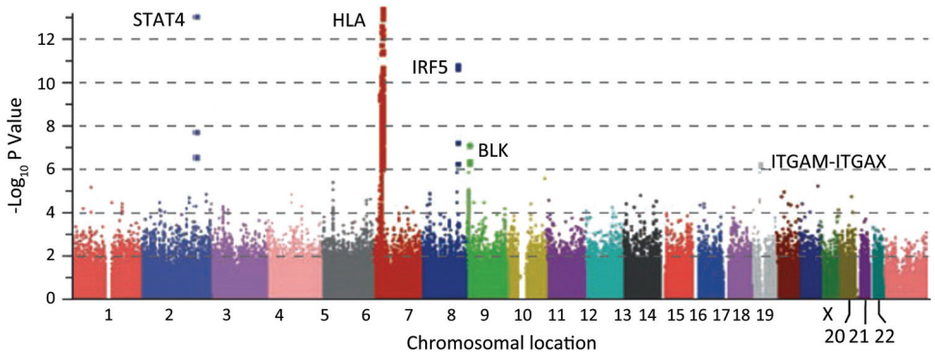

Figure 2 Manhattan plot of a genome-wide association study (GWAS) in systemic lupus erythematosus (SLE) involving 1311 cases and 3340 controls of European ancestry. Each dot in this figure (known as a Manhattan plot) corresponds to a genetic marker that, in this particular study, included ~550 000 single nucleotide polymorphisms (SNPs). Dots are colour coded and arranged along the x-axis according to position with each colour representing a different chromosome. The y-axis represents the significance level (–log P value) for the association of each SNP with SLE (ie, comparison between SLE cases and controls). Because of the multiple testing the level of significance for definitive genetic associations is quite high in the range of approximately 5×10^{-8} while results between –log P values of approximately 5–7 are considered as associations of borderline significance. Reprinted with permission from Criswell LA. Genome-wide association studies of SLE. What do these studies tell us about disease mechanisms in lupus? *The Rheumatologist* 2011.

(*HLA-DR*, *PTPN22*, *STAT4*, *IRF5*, *BLK*, *OX40L*, *FCGR2A*, *BANK1*, *SPP1*, *IRAK1*, *TNFAIP3*, *C2*, *C4*, *CIq*, *PXK*), DNA repairs (*TREX1*), adherence of inflammatory cells to the endothelium (*ITGAM*), and tissue response to injury (*KLK1*, *KLK3*). These findings highlight the importance of Toll-like receptor (TLR) and type 1 interferon (IFN) signalling pathways. Some of the genetic loci may explain not only the susceptibility to disease but also its severity. For instance, STAT4, a genetic risk factor for rheumatoid arthritis and SLE, is associated with severe SLE. One of the key components of these pathways is TNFAIP3, which has been implicated in at least six autoimmune disorders, including SLE.

5.2 Epigenetic effects

The risk for SLE may be influenced by epigenetic effects such as DNA methylation and post-translational modifications of histones, which can be either inherited or environmentally modified. Epigenetics refers to inherited changes in gene expression caused by mechanisms other than DNA base sequence changes. The most well understood type of epigenetic factor is DNA methylation, which plays a role in a variety of human processes, such as X chromosome inactivation and certain cancers. Previous research has also implicated the importance of DNA methylation in SLE. Differences in the methylation status of genes may explain, at least in part, the discordance observed in some identical twins that are discordant for SLE. Epigenetic mechanisms may represent the missing link between genetic and environmental risk factors.

5.3 Environmental factors

Candidate environmental triggers of SLE include ultraviolet light, demethylating drugs, and infectious or endogenous viruses or viral-like elements. Sunlight is the most obvious environmental factor that may exacerbate SLE. Epstein–Barr virus (EBV) has been identified as a possible factor in the development of lupus. EBV may reside in and interact with B cells and promotes interferon α (IFNα) production by plasmacytoid dendritic cells (pDCs), suggesting that elevated IFNα in lupus may be—at least in part—due to aberrantly controlled chronic viral infection.

It is well established that certain drugs induce autoantibodies in a significant number of patients, most of whom do not develop signs of an autoantibody associated disease. Over 100 drugs have been reported to cause drug-induced lupus (DIL), including a number of the newer biologics and antiviral agents. Although the pathogenesis of DIL is not well understood, a genetic predisposition may play a role in the case of certain drugs, particularly those agents that are metabolised by acetylation such as procainamide and hydralazine, with disease more likely to develop in patients who are slow acetylators. These drugs may alter gene expression in $CD4^+$ T cells by inhibiting DNA methylation and induce over-expression of LFA-1 antigen, thus promoting autoreactivity.

5.4 Hormonal factors

In murine models, addition of oestrogen or prolactin can lead to an autoimmune phenotype with an increase in

mature high-affinity autoreactive B cells. Oral contraceptive use in the Nurses' Health Study was associated with a slightly increased risk of developing SLE (relative risk 1.9 compared to never users). This poses important questions pertaining to the use of oestrogens for oral contraception or as hormone replacement therapy in postmenopausal women. While it is clear that hormones can influence autoimmune development in murine models, the use of oral contraceptives does not increase disease flares in women with stable disease (Sanchez-Guerrero *et al* 2005). Pregnancy may cause in some cases a lupus flare, but this is not due to an increase in oestradiol or progesterone; in fact, the levels of these hormones are lower in the second and third trimester for SLE patients in comparison with healthy pregnant women.

6 Pathogenesis and pathophysiology

Immune responses against endogenous nuclear antigens are characteristic of SLE. Autoantigens released by apoptotic cells are presented by dendritic cells to T cells leading to their activation. Activated T cells in turn help B cells to produce antibodies to these self-constituents by secreting cytokines such as interleukin 10 (IL10) and IL23 and by cell surface molecules such as CD40L and CTLA-4. In addition to this antigen-driven T cell-dependent production of autoantibodies, recent data support T cell-independent mechanisms of B cell stimulation via combined B cell antigen receptor (BCR) and TLR signalling. The pathogenesis of SLE involves a multitude of cells and molecules that participate in apoptosis, innate and adaptive immune responses (table 1).

6.1 Pathogenesis: key events

Increased amounts of apoptosis-related endogenous nucleic acids stimulate the production of IFNα and promote autoimmunity by breaking self-tolerance through activation of antigen-presenting cells (figure 3). Once initiated, immune reactants such as immune complexes amplify and sustain the inflammatory response.

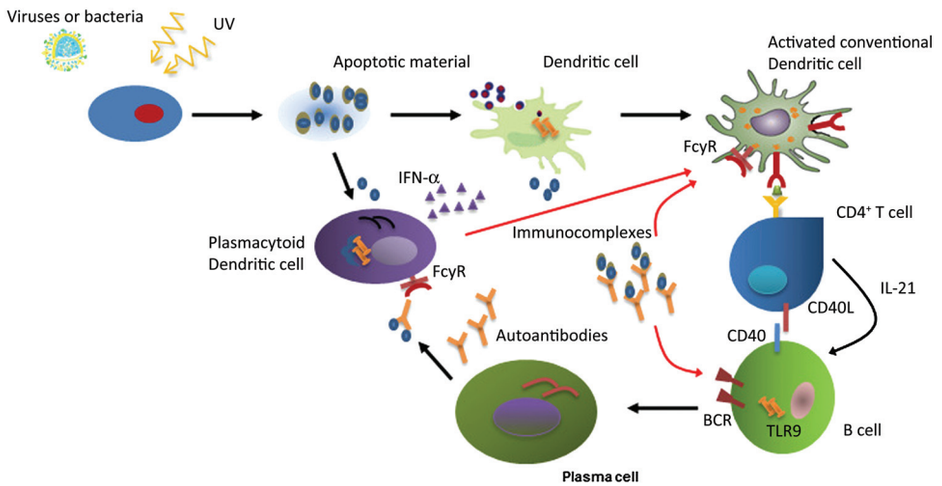

Figure 3 In systemic lupus erythematosus all pathways lead to endogenous nucleic acids-mediated production of interferon α (IFNα). Increased production of autoantigens during apoptosis (UV-related and/or spontaneous), decreased disposal, deregulated handling and presentation are all important for the initiation of the autoimmune response. Nucleosomes containing endogenous danger ligands that can bind to pathogen-associated molecular pattern receptors are incorporated in apoptotic blebs that promote the activation of DCs and B cells and the production of IFN and autoaantibodies, respectively. Cell surface receptors such as the BCR and FcRIIa facilitate the endocytosis of nucleic acid containing material or immune complexes and the binding to endosomal receptors of the innate immunity such as TLRs. At the early stages of disease, when autoantibodies and immune complexes may not have been formed, antimicrobial peptides released by damaged tissues such as LL37 and neutrophil extracellular traps, may bind with nucleic acids inhibiting their degradation and thus facilitating their endocytosis and stimulation of TLR-7/9 in plasmacytoid DCs. Increased amounts of apoptosis-related endogenous nucleic acids stimulate the production of IFN and promote autoimmunity by breaking self-tolerance through activation and promotion of maturation of conventional (myeloid) DCs. Immature DCs promote tolerance while activated mature DCs promote autoreactivity. Production of autoantibodies by B cells in lupus is driven by the availability of endogenous antigens and is largely dependent upon T cell help, mediated by cell surface interactions (CD40L/CD40) and cytokines (IL21). Chromatin-containing immune complexes vigorously stimulate B cells due to combined BCR/TLR crosslinking. DC, dendritic cell, BCR, B cell receptor, FcR, Fc receptor, UV, ultraviolet; TLR, toll-like receptor. Reprinted with permission from Bertsias GK, Salmon JE, Boumpas DT. Therapeutic opportunities in systemic lupus erythematosus: state of the art and prospects for the new decade. *Ann Rheum Dis* 2010;**69**:1603–11.

- **Apoptosis:** a source of autoantigens and molecules with adjuvant/cytokine (interferon α (IFNα)) inducer activity. Apoptotic cell blebs are rich in lupus autoantigens. Increased spontaneous apoptosis, increased rates of ultraviolet-induced apoptosis in skin cells, or impaired clearance of apoptotic peripheral blood cells have been found in some lupus patients.
- **Nucleic acids (DNA and RNA):** a unique target in lupus linked to apoptosis. Their recognition in healthy individuals is prohibited by a variety of barriers which are circumvented in lupus whereby alarmins released by from stressed tissues (HMGB1), antimicrobial peptides, neutrophil extracellular traps (NETs), and immune complexes facilitate their recognition and transfer to endosomal sensors (see below TLRs, NLRs).

Innate immunity

- **Toll-like receptors (TLRs):** conserved innate immune system receptors strategically located on cell membranes, cytosol and in endosomal compartments where they survey the extracellular and intracellular space. TLRs recognising nucleic acids (TLRs-3,-7,-8 and -9) are endosomal. Autoreactive B or T lymphocytes peacefully coexisting with tissues expressing the relevant antigens may become pathogenic after engagement of TLRs. TLRs also activate APCs (dendritic, MO, B cells) enhancing autoantigen presentation. B cells from active lupus patients have increased TLR9 expression. Compared to other antigens, chromatin containing immune complexes are 100-fold more efficacious in stimulating lupus B cells because of the presence of nucleic acids and the resultant combined BCR and TLR stimulation.
- **Dendritic cells:** Two types: plasmacytoid dendritic cells (pDCs) and myeloid (CD11c+) DC (mDCs).
- **pDCs:** represent genuine 'IFNα' factories. In lupus, exogenous factors/antigens (ie, viruses) or autoantigens recognised by the innate immune system receptors activate DCs and produce IFNα. **mDCs:** involved in antigen presentation with immature conventional mDCs promoting tolerance while mature autoreactivity. In lupus, several factors (IFNα, immune complexes, TLRs) promote mDC maturation and thus autoreactivity.
- **Interferon α:** a pluripotent cytokine produced mainly by pDCs via both TLR-dependent and TLR-independent mechanisms with potent biologic effects on DCs, B and T cells, endothelial cells, neuronal cells, renal resident cells, and other tissues. Several lupus-related genes encode proteins that mediate or regulate TLR signals and are associated with increased plasma IFNα among patients with specific autoantibodies which may deliver stimulatory nucleic acids to TLR7 or TLR9 in their intracellular compartments. Activation of the IFN pathway has been associated with the presence of autoantibodies specific for RNA-associated proteins. RNA-mediated activation of TLR is an important mechanism contributing to production of IFNα and other proinflammatory cytokines. Activation of the IFN pathway is associated with renal disease and many measures of disease activity.
- **Complement:** Activation of complement shapes the immune inflammatory response and facilitates clearance of apoptotic material.
- **Neutrophils:** In lupus a distinct subset of proinflammatory neutrophils (low density granulocytes) induces vascular damage and produces IFNα. Pathogenic variants of ITAM increase the binding to ICAM and the adhesion leucocytes to activated endothelial cells.
- **Endothelial cells:** In lupus, impaired DNA degradation as a result of a defect in repair endonucleases (TREX1) increases the accumulation of ssDNA derived from endogenous retro-elements in endothelial cells and may activate production of IFNα by them. IFNα in turn propagates endothelial damage and impairs its repair.

Adaptive immunity

- **T and B cells:** Interactions between co-stimulatory ligands and receptors on T and B cells, including CD80 and CD86 with CD28, inducible costimulator (ICOS) ligand with ICOS, and CD40 ligand with CD40, contribute to B cell differentiation to antibody producing plasma cells. Autoantibodies also facilitate the delivery of stimulatory nucleic acids to TLRs. Cytokines and chemokines produced by T and B cells also shape the immune response and promote tissue damage.
- **B lymphocyte stimulator (Blys):** The soluble TNF family member BlyS is a B cell survival and differentiation. Blys is increased in serum of many lupus patients; inhibition of Blys prevents lupus flares.
- **Immune complexes:** In healthy individuals, immune complexes are cleared by FcR and complement receptors. In lupus, genetic variations in FcR genes and the C3bi receptor gene (*ITGAM*) may impair the clearing of immune complexes which then deposit and cause tissue injury at sites such as the skin and kidney.

Table 1 Key pathogenic processes, cells and molecules in systemic lupus erythematosus

6.2 Disease mechanisms and tissue damage

Immune complexes and complement activation pathways mediate effector function and tissue injury. In healthy individuals, immune complexes are cleared by Fc and complement receptors; failure to clear immune complexes results in tissue deposition and tissue injury at sites. Tissue damage is mediated by recruitment of inflammatory cells, reactive oxygen intermediates, production of inflammatory cytokines, and modulation of the coagulation cascade.

Autoantibody-mediated tissue injury has been implicated in neuropsychiatric SLE (NPSLE), where antibodies reacting with both DNA and glutamate receptors on neuronal cells can mediate excitotoxic neuronal cell death or dysfunction.

Locally produced cytokines, such as IFNα and tumour necrosis factor (TNF), contribute to affected tissue injury and inflammation. These mediators, together with the cells producing them (macrophages, leucocytes, dendritic cells and lymphocytes), are the subject of investigation as potential therapeutic targets in lupus. Recent studies have also highlighted the role of locally expressed factors for the protection of tissues under immune attack. For example, defects in kallikreins may jeopardise the ability of lupus kidneys to protect themselves from injury, PD-1-ligand down-regulates the activity of the infiltrating lymphocytes, and impaired regulation of complement amplifies vascular injury.

Vascular damage in SLE has received increased attention in view of its relationship with accelerated atherosclerosis. Homocysteine and proinflammatory cytokines, such as IFNα, impair endothelial function and decrease the availability of endothelial precursor cells to repair endothelial injury. Pro-inflammatory high density lipoproteins (HDL) and a dysfunction of HDL mediated by antibodies have also been implicated in defective repair of endothelium. Moreover, pathogenic variants of ITAM (immuno-tyrosine activation motif) alter its binding to ICAM-1 (intercellular adhesion molecule 1) and may increase the adherence of leucocytes to activated endothelial cells. Impaired DNA degradation as a result of mutations of the 3' repair exonuclease 1 (TREX1), and increased accumulation of single stranded DNA derived from endogenous retro-elements in endothelial cells, may activate the IFN-stimulatory DNA response and direct immune-mediated injury to the vasculature.

7 Classification criteria

Criteria for SLE classification were developed in 1971, revised in 1982, and revised again in 1997 (table 2) (Hochberg 1997). These criteria distinguish patients with the disease in question from those without the disease. The American College of Rheumatology (ACR) classification criteria were developed for clinical studies of lupus to ensure that cases reported in the literature do in fact have the disease. In addition to the wide variety of manifestations, SLE runs an unpredictable course. The dynamic nature of the disease often makes its diagnosis challenging.

Although the ACR classification criteria may also be used as a diagnostic aid, there are several caveats in their use for diagnostic purposes. These criteria were developed and validated for the classification of patients with a longstanding established disease and may exclude patients with early disease or disease limited to a few organs. Thus, in spite of their excellent sensitivity (>85%) and specificity (>95%) for patients with established disease, their sensitivity for patients early in the disease may be significantly lower. Some systems are overrepresented; the mucocutaneous manifestations, for example, are represented with four criteria (photosensitivity, malar rash, discoid lesions, and oral ulcers). All features included in the classification criteria are contributing equally without any weight based upon sensitivity and specificity for each individual criterion. Thus, studies have shown and experience supports that criteria such as objective evidence of renal disease (significant proteinuria, active urine sediment or renal biopsy with evidence of lupus nephritis), discoid rash, and cytopenias are more useful in establishing the diagnosis of lupus than the other criteria. Because SLE is a disease whose course is typified by periodic involvement of one organ system after another, it is apparent that patients must have the disease for years before they fulfil the classification criteria. Among patients referred for lupus to tertiary care centres, two thirds of patients fulfil ACR criteria, approximately 10% have clinical lupus but do not fulfil criteria, and 25% have fibromyalgia-like symptoms and positive antinuclear antibody (ANA) but never develop lupus.

8 Activity indices

Assessing disease activity in SLE is crucial to the physician as it forms the basis for treatment decisions. Disease activity needs to be distinguished from damage as this has important implications for the long term prognosis and the appropriate treatment. Several validated global and organ-specific activity indices are widely used in the evaluation of SLE patients (Urowitz and Gladman 1998). These include the European Consensus Lupus Activity Measure (ECLAM), the British Isles Lupus Assessment Group Scale (BILAG), the Lupus Activity Index (LAI), the National Institutes of Health SLE Index Score (SIS), the Systemic Lupus Activity Measure (SLAM), and the SLE

Criteria	Definition
Malar rash	Fixed erythema, flat or raised, over the malar eminences, tending to spare the nasolabial folds
Discoid rash	Erythematous raised patches with adherent keratotic scaling and follicular plugging; atrophic scarring occurs in older lesions
Photosensitivity	Skin rash as a result of unusual reaction to sunlight, by patient history or physician observation
Oral ulcers	Oral or nasopharyngeal ulceration, usually painless, observed by a physician
Arthritis	Non-erosive arthritis involving two or more peripheral joints, characterised by tenderness, swelling or effusion
Serositis	a. Pleuritis: convincing history of pleuritic pain or rub heard by a physician or evidence of pleural effusion or b. Pericarditis: documented by ECG or rub or evidence of pericardial effusion
Renal disorder	a. Persistent proteinuria >0.5 g per day or >3+ if quantitation is not performed or b. Cellular casts: may be red cell, haemoglobin, granular tubular, or mixed
Neurological disorder	a. Seizures: in the absence of offending drugs or known metabolic derangements (eg, uraemia, acidosis, or electrolyte imbalance) or b. Psychosis: in the absence of offending drugs or known metabolic derangements (eg, uraemia, acidosis, or electrolyte imbalance)
Haematologic disorder	a. Haemolytic anaemia with reticulocytosis, or b. Leucopenia: <4000/mm^3, or c. Lymphopenia: <1500/mm^3, or d. Thrombocytopenia: <100 000/mm^3 in the absence of offending drugs
Immunologic disorder	a. Anti-DNA: antibody to native DNA in abnormal titre, or b. Anti-Sm: presence of antibody to Sm nuclear antigen, or c. Positive finding of antiphospholipid antibodies based on: (1) an abnormal serum concentration of IgG or IgM anticardiolipin antibodies, (2) a positive test result for lupus anticoagulant using a standard method, or (3) a false positive serologic test for syphilis known to be positive for at least 6 months and confirmed by *Treponema pallidum* immobilisation or fluorescent treponemal antibody absorption test
Antinuclear antibody	An abnormal titre of antinuclear antibody by immunofluorescence or an equivalent assay at any point in time and in the absence of drugs known to be associated with 'drug-induced lupus' syndrome

Adapted from Hochberg 1997.

Table 2 The American College of Rheumatology revised classification criteria for systemic lupus erythematosus

Disease Activity Index (SLEDAI). These indices have been developed in the context of long term observational studies and have been shown to be strong predictors of damage and mortality, and reflect change in disease activity. Moreover, they have been validated against each other. We recommend the use of at least one of these indices for monitoring of disease activity. In our experience the ECLAM and the SLEDAI (table 3) are more convenient for use in daily practice. Computerised clinical charts that compute several disease activity indices simultaneously have been developed.

Existing disease activity indices have important limitations when used in the context of clinical trials. For clinical trials, composite end points and responder indices may be more useful, especially for studies in general lupus, as compared to studies for lupus affecting single organs (eg, nephritis). To this end, using composite index (SLE responder index, SRI) investigators in the Belimumab trial were able to show efficacy. The SRI includes improvement in SLEDAI by at least 4 without worsening in BILAG and PGA. The SRI could be adjusted to look for larger treatment effects (for instance, more than 7 or 12 points difference in SLEDAI) similar to what is being used in rheumatoid arthritis (ACR 20, and 50, or EULAR moderate and good response).

Descriptor	Definition	Score
Seizure	Recent onset. Exclude metabolic, infectious or drug-related causes	8
Psychosis	Altered ability to function in normal activity due to severe disturbance in the perception of reality. Includes hallucinations; incoherence; marked loose associations; impoverished thought content; marked illogical thinking; bizarre disorganised or catatonic behaviour. Exclude the presence of uraemia and offending drugs	8
Organic brain syndrome	Altered mental function with impaired orientation or impaired memory or other intellectual function, with rapid onset and fluctuating clinical features. Includes a clouding of consciousness with a reduced capacity to focus and an inability to sustain attention on environment and at least two of the following: perceptual disturbance, incoherent speech, insomnia or daytime drowsiness, increased or decreased psychomotor activity. Exclude metabolic infectious and drug-related causes	8
Visual	Retinal changes from systemic lupus erythematosus cytoid bodies, retinal haemorrhages, serous exudate or haemorrhage in the choroid, optic neuritis (not due to hypertension, drugs or infection)	8
Cranial nerve	New onset of a sensory or motor neuropathy involving a cranial nerve	8
Lupus headache	Severe, persistent headache; may be migrainous	8
Cerebrovascular	New syndrome. Exclude arteriosclerosis	8
Vasculitis	Ulceration, gangrene, tender finger nodules, periungal infarction, splinter haemorrhages. Vasculitis confirmed by biopsy or angiogram	8
Arthritis	More than two joints with pain and signs of inflammation	4
Myositis	Proximal muscle aching or weakness associated with elevated creatine phosphokinase/aldolase levels, electromyographic changes, or a biopsy showing myositis	4
Casts	Heme, granular or erythrocyte	4
Haematuria	More than 5 erythrocytes per high power field. Exclude other causes	4
Proteinuria	More than 0.5 g of urinary protein excreted per 24 h. New onset or recent increase of more than 0.5 g per 24 h	4
Pyuria	More than 5 leucocytes per high power field. Exclude infection	4
New malar rash	New onset or recurrence of an inflammatory type of rash	4
Alopecia	New or recurrent. A patch of abnormal, diffuse hair loss	4
Mucous membrane	New onset or recurrence of oral or nasal ulceration	4
Pleurisy	Pleuritic chest pain with pleural rub or effusion, or pleural thickening	4
Pericarditis	Pericardial pain with at least one of rub or effusion. Confirmation by ECG or echocardiography	4
Low complement	A decrease in CH50, C3 or C4 levels (to less than the lower limit of the laboratory determined normal range)	2
Increased DNA binding	More than 25% binding by Farr assay (to more than the upper limit of the laboratory determined normal range, eg, 25%)	2
Fever	More than 38°C after the exclusion of infection	1
Thrombocytopenia	Fewer than 100 000 platelets	1
Leucopenia	Leucocyte count <3000/mm^3 (not due to drugs)	1

Table 3 The Systemic Lupus Erythematosus Disease Activity Index (SLEDAI)

Item	Score
Ocular (either eye by clinical assessment)	
Any cataract ever	0, 1
Retinal change or optic atrophy	0, 1
Neuropsychiatric	
Cognitive impairment (eg, memory deficit, difficulty with calculation, poor concentration, difficulty in spoken or written language, impaired performance level) **or** major psychosis	0, 1
Seizures requiring therapy for 6 months	0, 1
Cerebrovascular accident ever (score 2 if >1)	0, 1, 2
Cranial or peripheral neuropathy (excluding optic)	0, 1
Transverse myelitis	0, 1
Renal	
Estimated or measured glomerular filtration rate <50%	0, 1
Proteinuria >3.5 g/24 h	0, 1
or end-stage renal disease (regardless of dialysis or transplantation)	**or** 3
Pulmonary	
Pulmonary hypertension (right ventricular prominence, or loud P2)	0, 1
Pulmonary fibrosis (physical and radiographical)	0, 1
Shrinking lung (radiograph)	0, 1
Pleural fibrosis (radiograph)	0, 1
Pulmonary infarction (radiograph)	0, 1
Cardiovascular	
Angina **or** coronary artery bypass	0, 1
Myocardial infarction ever (score 2 if >1)	0, 1, 2
Cardiomyopathy (ventricular dysfunction)	0, 1
Valvular disease (diastolic murmur, or systolic murmur >3/6)	0, 1
Pericarditis for 6 months **or** pericardiectomy	0, 1

Item	Score
Peripheral vascular	
Claudication for 6 months	0, 1
Minor tissue loss (pulp space)	0, 1
Significant tissue loss ever (eg, loss of digit or limb) (score 2 if >1 site)	0, 1, 2
Venous thrombosis with swelling, ulceration **or** venous stasis	0, 1
Gastrointestinal	
Infarction or resection of bowel below duodenum, spleen, liver or gallbladder ever, for any cause (score 2 if >1 site)	0, 1, 2
Mesenteric insufficiency	0, 1
Chronic peritonitis	0, 1
Stricture **or** upper gastrointestinal tract surgery ever	0, 1
Chronic pancreatitis	0, 1
Musculoskeletal	
Muscle atrophy or weakness	0, 1
Deforming or erosive arthritis (including reversible deformities, excluding avascular necrosis)	0, 1
Osteoporosis with fracture or vertebral collapse (excluding avascular necrosis)	0, 1
Avascular necrosis (score 2 if >1)	0, 1, 2
Osteomyelitis	0, 1
Tendon rupture	0, 1
Skin	
Scarring chronic alopecia	0, 1
Extensive scarring of panniculum other than scalp and pulp space	0, 1
Skin ulceration (excluding thrombosis for >6 months)	0, 1
Premature gonadal failure	0, 1
Diabetes (regardless of treatment)	0, 1
Malignancy (exclude dysplasia) (score 2 if >1 site)	0, 1

Table 4 The Systemic Lupus International Collaborating Clinics/American College of Rheumatology (SLICC/ACR) Damage Index for systemic lupus erythematosus

9 Chronicity and damage index

The Systemic Lupus International Collaborating Clinics/American College of Rheumatology (SLICC/ACR) damage index is a validated instrument specifically designed to ascertain damage in SLE (Gladman *et al* 1996). Damage in SLE may be due to the disease itself or to drug therapy. The index records damage in 12 organs or systems (table 4). There is no index to measure harms caused by drugs in lupus at present. The change must have been present for at least 6 months and is ascertained clinically or by simple investigations. Studies have shown that the early acquisition of damage is a sign of a poor prognosis.

LE specific skin lesions	LE non-specific skin lesions
Acute cutaneous LE Localised	Cutaneous vascular disease Vasculitis
Generalised Subacute cutaneous LE	Leucocytoclastic Palpable purpura Urticarial vasculitis
Annular Papulosquamous (psoriasiform)	Polyarteritis nodosa-like Papulonodular mucinosis Dego's disease-like
Chronic cutaneous LE 'Classical' LE (DLE) Localised	Atrophy blanche-like Livedo reticularis Thrombophlebitis
Generalised Hypertrophic (verrucous) DLE Lupus panniculitis (profundus)	Raynaud's phenomenon Erythromelalgia LE non-specific bullous lesions
Mucosal LE Lupus tumidus Chilblains lupus	Epidermolysis bullosa acquisita Dermatitis herpetiformis-like bullous LE Pemphigus erythematosus
	Porphyria cutanea tarda Urticaria Vasculopathy
	Anetoderma/cutis laxa Acanthosis nigricans (type B insulin resistance) Periungal telangiectasia
	Erythema multiforme Leg ulcers Lichen planus
	Alopecia (non-scarring) 'Lupus hair' Telogen effluvium
	Alopecia areata Sclerodactyly Rheumatoid nodules
	Calcinosis cutis

Table 5 Classification of lupus erythematosus (LE) associated skin lesions

10 Clinical features

10.1 Mucocutaneous features

Mucocutaneous involvement is almost universal in SLE with both lupus-specific and non-specific lesions (table 5). Lupus-specific lesions can be further classified as acute, subacute, and chronic lesions.

Acute rashes-malar rash. The classic lupus 'butterfly' rash presents acutely as an erythematous, elevated lesion, pruritic or painful, in a malar distribution, commonly precipitated by exposure to sunlight (figure 4). The rash may last from days to weeks and is commonly accompanied by other inflammatory manifestations of the disease. The acute butterfly rash should be differentiated from other causes of facial erythema such as rosacea, seborrhoeic, atopic, and contact dermatitis, and glucocorticoid-induced dermal atrophy and flushing. Other acute cutaneous lesions include generalised erythema and bullous lesions. The rash of acute cutaneous lupus erythematosus can be transient and heal without scarring, although persistently active rashes may result in permanent telangiectasias.

Subacute rashes. Subacute cutaneous lupus erythematosus (SCLE) is not uniformly associated with SLE. Approximately 50% of affected patients have SLE and about 10% of patients with SLE have this type of skin

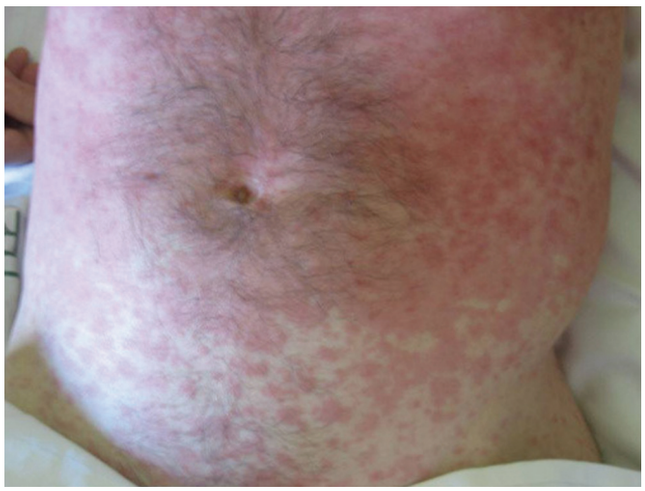

Figure 4 Acute cutaneous lupus erythematosus. These lesions are abrupt in onset, frequently appear after exposure to the sun, and are characterised by erythema and oedema.

lesion. Patients with SCLE may present with annular or psoriasiform skin lesions, and this is strongly associated with anti-Ro (SS-A) and anti-La (SS-B) antibodies. Patients with SCLE have a high incidence of photosensitivity and in rare instances can present with erythema multiforme-like lesions (Rowell's syndrome). SCLE lesions begin as small, erythematous, slightly scaly papules that evolve into either a psoriasiform (papulosquamous) or annular form. The latter often coalesce to form polycyclic or figurative patterns (figure 5). The lesions typically have erythematous, and sometimes crusted, margins. Commonly affected areas are the shoulders, forearms, neck, and upper torso. The face is usually spared.

Chronic rashes. Discoid lupus erythematosus (DLE) lesions develop in up to 25% of SLE patients. Patients with DLE have approximately a 5–10% risk of developing SLE which tends to be mild. Risk is even higher with numerous and widespread skin lesions. Discoid lesions are characterised by discrete, erythematous, slightly infiltrated plaques covered by a well-formed adherent scale that extends into dilated hair follicles (follicular plugging) (figure 6). They are often seen on the face, neck, and scalp, but also occur on the ears, and infrequently on the upper torso. They slowly expand with active inflammation at the periphery, and then heal, leaving depressed central scars, atrophy, telangiectasias, and dyspigmentation (hyper- or hypopigmentation). The differential diagnosis includes hypertrophic lichen planus, eczema, and actinic keratosis; some early and scaly discoid lesions must also be differentiated from psoriasis.

Other rashes (figure 7). Lupus profundus presents as a firm nodular lesion with or without an overlying cutaneous lesion. The nodules are often painful and consist of perivascular infiltrates of mononuclear cells plus panniculitis, manifested as hyaline fat necrosis with mononuclear cell infiltration and lymphocytic vasculitis. They usually appear on the scalp, face, arms, chest, back, thighs, and buttocks; ulcerations are uncommon and they usually resolve leaving a depressed area. Lupus tumidus, a rare variant, is characterised by photodistributed lesions with chronic pink indurated plaques or broad lesions that are slow to heal.

Alopecia. Alopecia—defined as exaggerated hair loss—occurs in most SLE patients. It may involve the scalp, eyebrows, eyelashes, beard, and body hair. Scarring alopecia is a complication of discoid lupus that typically affects the scalp. 'Lupus hair' is characterised by thin hair that easily fractures. It usually occurs along the frontal hairline, is associated with disease activity, and grows back normally as the disease subsides.

Photosensitivity. Photosensitivity is defined as the development of a rash after exposure to ultraviolet (UV) B radiation coming from sunlight or fluorescent lights. It occurs in 60–100% of SLE patients. Some patients are also sensitive to UVA radiation (emitted from photocopiers or some light bulbs), and may even be sensitive to the visible light spectrum. Not all photosensitive individuals have lupus, nor are the two disorders causally linked in all SLE patients.

Pathology and the 'lupus band test'. Biopsy specimens of skin lesions from patients with DLE and SLE contain the membrane attack complex (C5b through C9) as well as immune complexes at the dermal–epidermal junction. The search for immunoreactant deposition in non-lesional skin of lupus patients has been referred to as the 'lupus band test' (LBT). The diagnostic and prognostic significance of the non-lesional LBT is controversial.

Differential diagnosis. Several dermatologic entities can mimic LE-specific lesions and should be considered in patients with atypical features and/or refractoriness to standard therapy. Acne rosacea can result in a red face and is often confused with acute cutaneous LE. Photosensitive psoriasis can simulate papulosquamous SCLE, while occasionally erythema multiforme may be confused with annular SCLE. Other common dermatoses may co-exist in SLE patients such as contact dermatitis, eczema, and seborrhoeic dermatitis.

Mucous membranes. Involvement of the mucous membranes occur in 25–45% of SLE patients. The most common manifestations include irregularly shaped raised

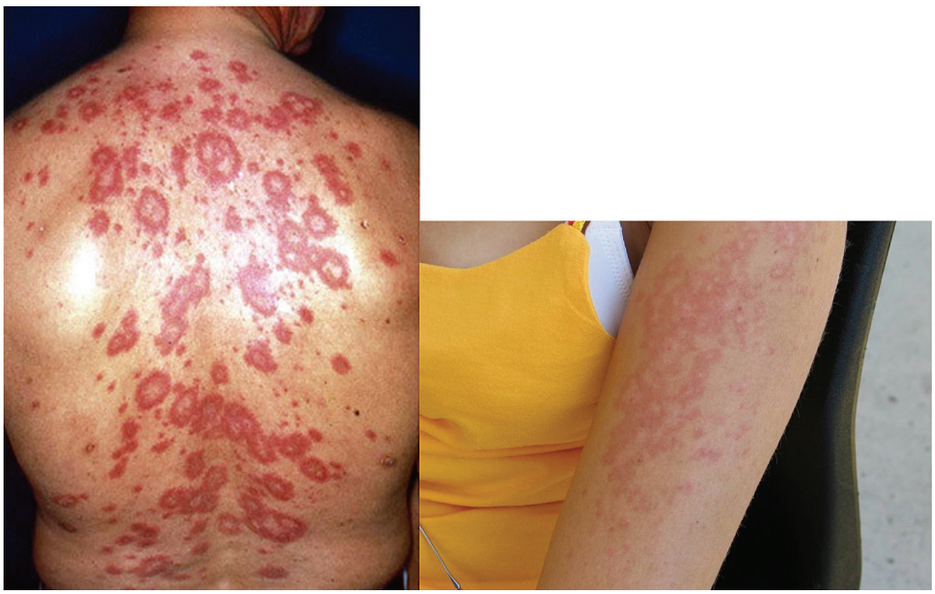

Figure 5 Subacute cutaneous lupus lesions. Typical features include symmetric, widespread, superficial, and non-scarring lesions. Involvement of the neck, shoulders, upper chest, upper back, and extensor surface of the hand is common. These lesions begin as small photosensitive, erythematous, scaly papules or plaques that evolve into a papulosquamous (psoriasiform) or annular polycyclic form as in this patient. Subacute cutaneous lupus erythematosus has been associated with the presence of anti-Ro/SS-A antibodies, genetic deficiencies of complement C2 and C4, and certain medications, such as hydrochlorothiazide.

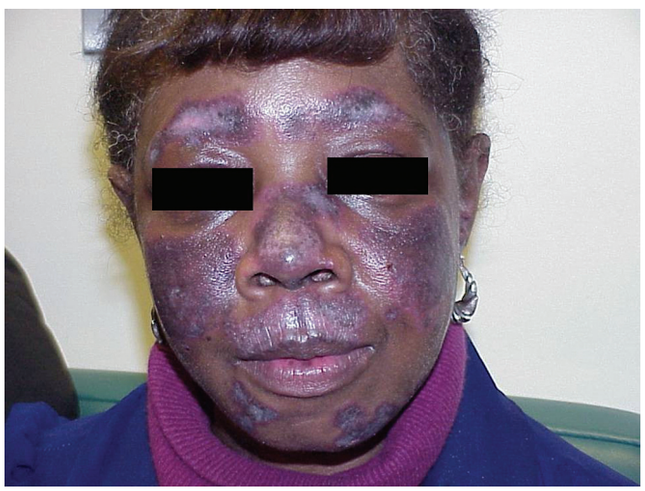

Figure 6 Facial discoid lupus rash with a malar distribution. Note the erythema (indicating disease activity), keratin plugged follicles, and dermal atrophy. The characteristic pattern of hyperpigmentation at the active border and hypopigmentation at the inactive centre is especially evident in black patients. Discoid lesions are usually found on the face, scalp, ears or neck. Patient consent: obtained.

white plaques, areas of erythema, silvery white scarred lesions, and ulcers with surrounding erythema on the soft or hard palate or buccal mucosa. These lesions should be distinguished clinically from those of lichen planus, candidiasis, aphthous stomatitis, intraoral herpes, Adamantiades-Behçet's disease, bite marks, leukoplakia, and malignancy. Oral ulcers in SLE are usually painless and there is not always temporal association with systemic disease activity. Oral lesions may be the first signs of lupus. Typical discoid lesions with erythema atrophy and depigmentation can occur on the lips. Nasal ulcers have been noted in patients with SLE. Involvement of the upper airway mucosa can also occur and cause hoarseness.

10.2 Musculoskeletal features

The musculoskeletal system is affected in 53–95% of SLE patients.

Arthritis/arthropathy. Joint involvement is classically described as non-erosive, non-deforming arthralgias/arthritis in a distribution similar to that of rheumatoid arthritis, primarily affecting the small joints of the hands, wrists, and knees (figure 8). Arthritis may be the presenting symptom or accompany other lupus manifestations during a flare. The patient's symptoms (pain and stiffness) are usually out of proportion to the degree of synovitis present on physical examination, and synovitis may be transient (resolving within a few days in some patients), migratory, and reversible. At the other extreme are a few patients with an impressive synovitis indistinguishable from rheumatoid arthritis for which the term '*rhupus*' has been used. Tenosynovitis is an early manifestation of SLE and tendon rupture syndromes have been reported in a number of different sites in the body including the patellar tendons, the Achilles tendon, the long head of the biceps, the triceps, and the extensor tendons of the hands. Subcutaneous nodules along the flexor tendons of the hand can be found in SLE. Chest pain or discomfort secondary to costochondritis has been reported and other conditions such as angina pectoris,

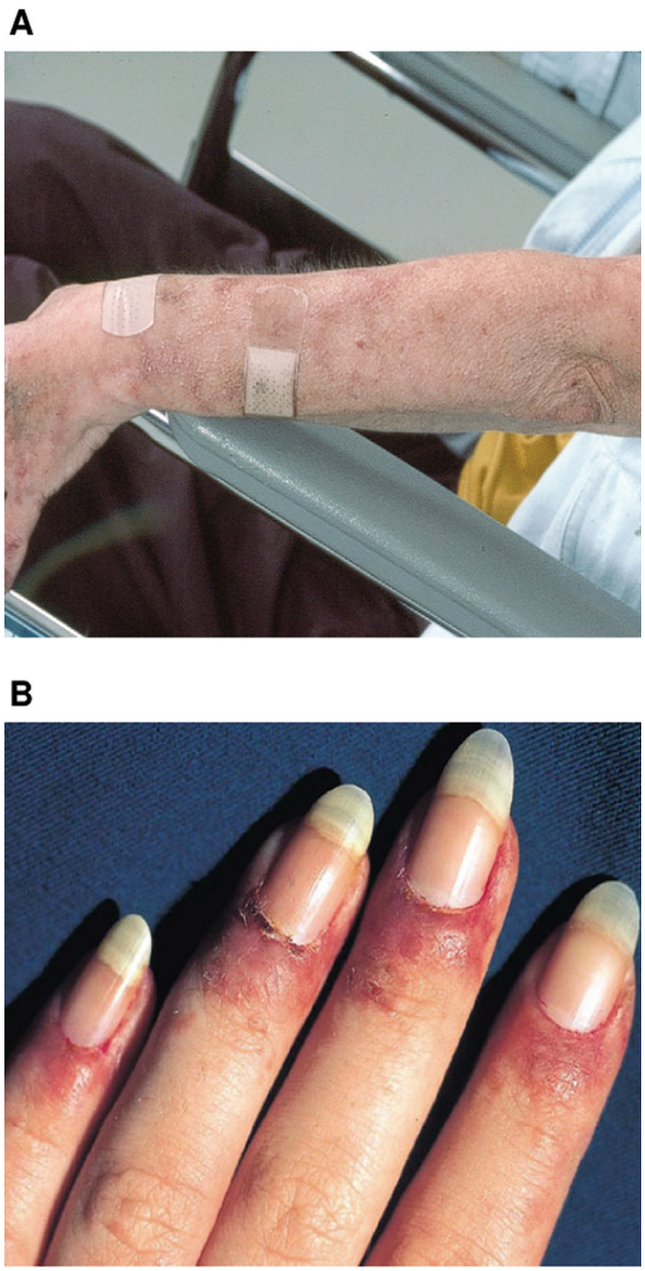

Figure 7 (A) Livedo reticularis and (B) periungal erythema with nailfold vasculitis.

pericarditis, and oesophageal spasm must be ruled out. Relapsing polychondritis can also occur and it usually responds to low-dose corticosteroid treatment.

Myositis. Generalised myalgia and muscle tenderness are common during disease exacerbations. Inflammatory myositis involving the proximal muscles has been reported in 5–11% of cases and may develop at any time during the course of the disease. A low serum creatine phosphokinase (CPK) value can be found in patients with connective tissue disease including SLE; thus a normal

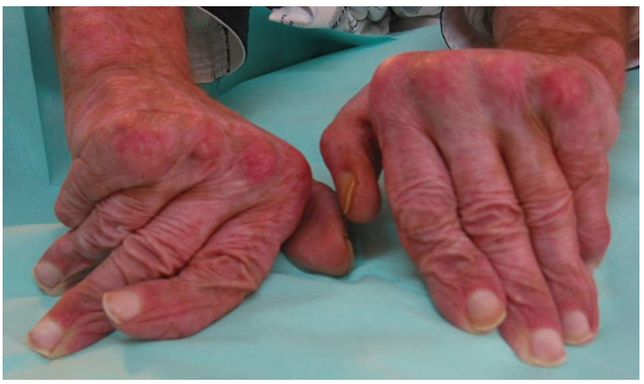

Figure 8 Jacoud-type arthropathy. Deformities in the hands such as ulnar drift at the metacarpophalangeal joints, swan neck and boutonniere deformities, and hyperextension at the interphalangeal joint of the thumb closely resemble those seen in rheumatoid arthritis. The absence of erosions on radiographs and their reducibility distinguish this condition from the deforming arthritis of rheumatoid arthritis. Courtesy of Dr D Vassilopoulos.

CPK value in the presence of symptoms and signs of myositis should not dissuade the physician from its diagnosis. The skin lesions of dermatomyositis can also appear in patients with SLE.

Avascular bone necrosis. Avascular necrosis (AVN) of bone is a major cause of morbidity and disability in SLE. Symptomatic AVN occurs in 5–12%. Higher prevalence has been reported when magnetic resonance imaging (MRI) is used for its detection. Acute joint pain presenting late in the course of SLE and localised to a very few areas, especially shoulders, hips, and knees, may indicate AVN. Factors that can induce bone ischaemia and necrosis include Raynaud's phenomenon, vasculitis, fat emboli, corticosteroids, and the antiphospholipid syndrome. Osteonecrosis often develops shortly after the onset of high-dose corticosteroid therapy.

10.3 Renal features (see also in-depth discussion)

Renal involvement occurs in 40–70% of all SLE patients and is a major cause of morbidity and hospital admissions. Immune complex formation/deposition in the kidney results in intra-glomerular inflammation with recruitment of leucocytes and activation and proliferation of resident renal cells (figure 9). Proteinuria of various levels is the dominant feature of lupus nephritis (LN) and is usually accompanied by glomerular haematuria. Urinalysis is the most important and effective method to detect and monitor disease renal activity. To assure its quality, several steps

have to be taken. These include expeditious examination of a fresh, early morning, midstream, clean catch, non-refrigerated urine specimen; and flagging of specimens from patients at substantial risk of developing LN to ensure careful examination at central laboratories. Haematuria (usually microscopic, rarely macroscopic) indicates inflammatory glomerular or tubulointerstitial disease. Erythrocytes are fragmented or misshaped (dysmorphic). Granular and fatty casts reflect proteinuric states while red blood cell, white blood cell, and mixed cellular casts reflect nephritic states. Broad and waxy casts reflect chronic renal failure. In severe proliferative disease, urine sediment containing the full range of cells and casts can be found ('telescopic urine sediment') as a result of severe glomerular and tubular ongoing disease superimposed on chronic renal damage. Renal biopsy rarely helps the diagnosis of lupus, but is the best way of documenting the renal pathology (figure 10). In the absence of renal abnormalities, renal biopsy has nothing to offer and should not be performed.

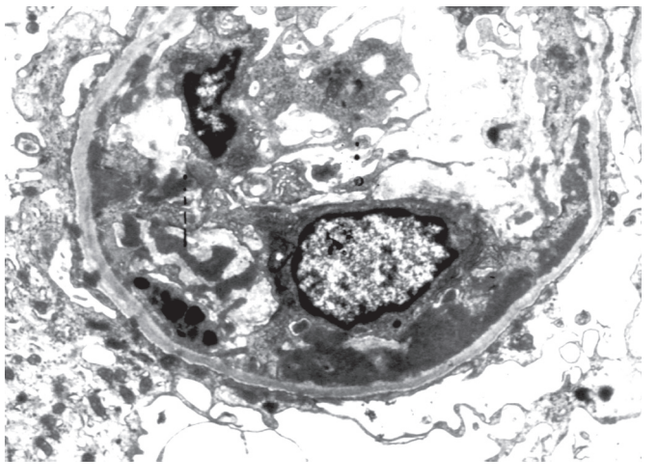

Figure 9 Electron microscopy demonstrating subendothelial deposition of electron dense immune complexes in a patient with proliferative lupus nephritis. Electron microscopy helps to define distribution (ie, subendothelial, epithelial, membranous deposits) of immune complexes and may be useful in the recognition of early proliferative changes when the light microscopy findings may be more subtle. In such cases the presence of subendothelial deposits—even if scarce—along with other features of proliferative nephritis (nephritic sediment, low C3, anti-DNA antibodies) are strongly suggestive of the diagnosis of proliferative lupus nephritis.

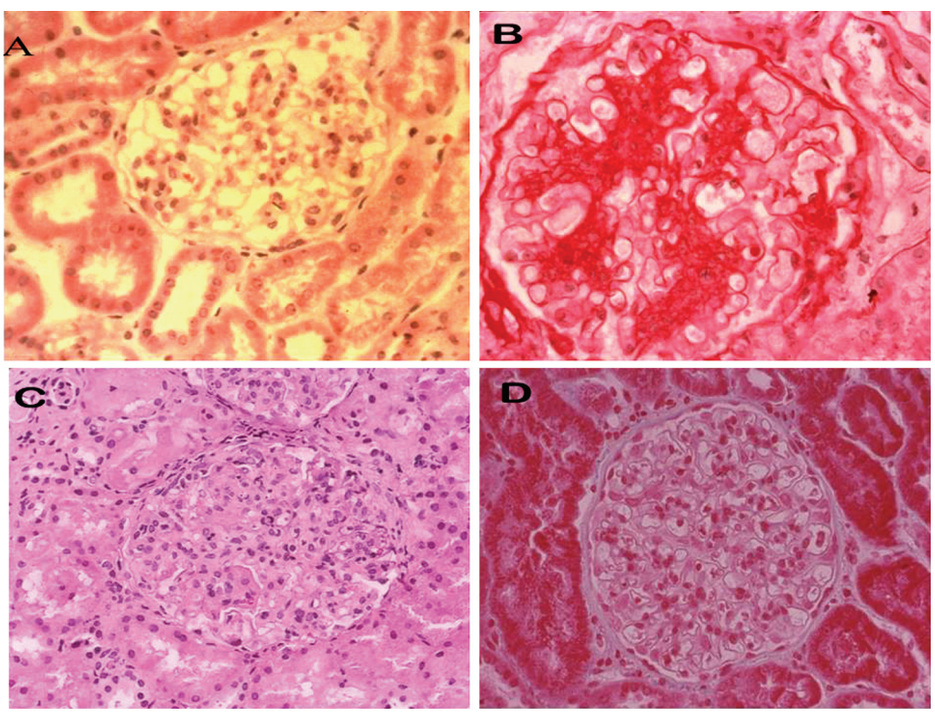

Figure 10 WHO types of lupus nephritis. (A) Normal glomerulus (class I). (B) Mesangial disease (type II). Note mesangial hypercellularity and expansion of the mesangial matrix which, however, does not compromise the capillary loops. (C) Proliferative nephritis. Dramatic diseases in mesangial and endocapillary cellularity produce a lobular appearance of the glomerular tufts and compromise the patency of most capillary loops. When less than 50% of glomeruli are involved, nephritis is denoted as focal (type III). When more than 50% glomeruli are involved, it is denoted as diffuse (type IV). (D) Membranous nephropathy (type V). In membranous lupus nephropathy the capillary walls of the glomerular tuft are prominent and widely patent, resembling 'stiff' structures with decreased compliance.

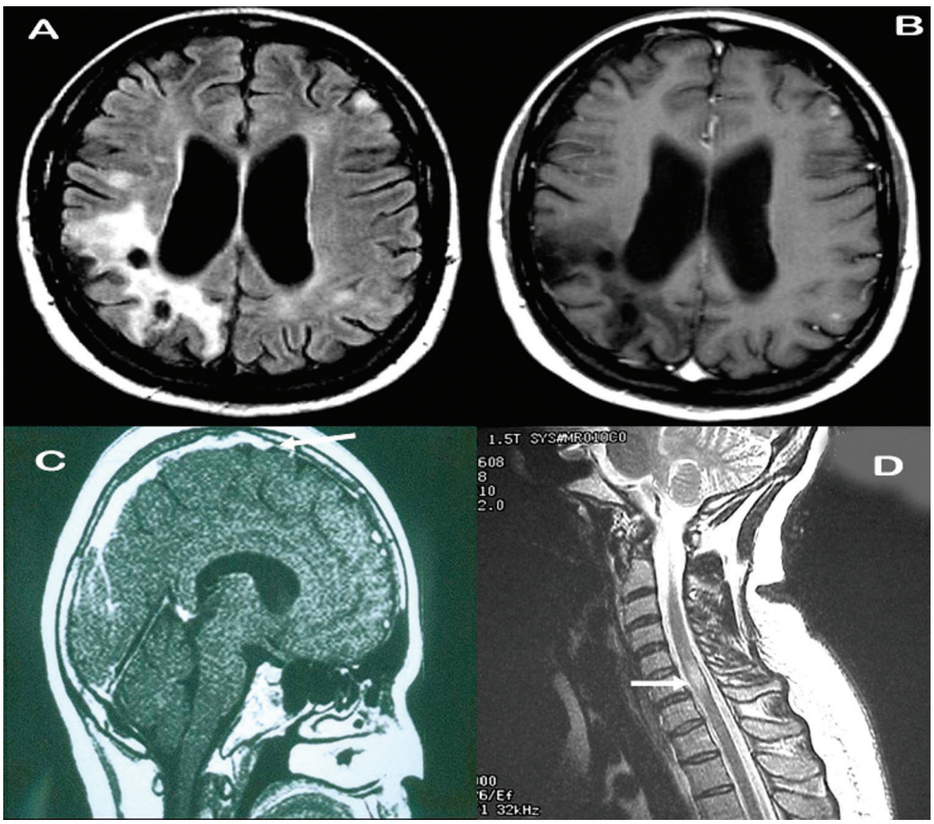

Figure 11 Severe neuropsychiatric lupus. MRIs showing cerebrovascular disease (A and B); thrombosis in the sagittal sinus in a patient with antiphospholipid antibodies (C); and acute transverse myelitis (D).

10.4 Nervous system features (see also in-depth discussion)

SLE affects both the central nervous system (CNS) and the peripheral nervous system (PNS) (figure 11). Nervous system involvement in SLE remains one of the major causes of morbidity and mortality; it is the least understood manifestation of the disease, and remains a complex diagnostic entity as a result of its multiple clinical presentations. The ACR described case definitions and classification criteria for 19 CNS and PNS syndromes observed in patients with SLE, which collectively are referred to as neuropsychiatric SLE (NPSLE) syndromes (table 6). The EULAR task force on SLE has critically reviewed the literature on NPSLE in an effort to provide an evidence and expert-based response to common clinical questions encountered in the disease (Bertsias *et al* 2010b).

10.4.1 An overview of specific NPSLE manifestations.

The association between SLE and headache is controversial. Studies have shown that headaches are common (>20–40%), but usually are not related to lupus. However, in rare cases headaches may herald severe pathology and need to be investigated in the presence of 'red-flag' symptoms or signs (unusual intensity not subsiding to analgesics, fever, confusion, meningeal or focal neurologic signs), with imaging and lumbar puncture. Cognitive dysfunction has been reported in up to 20–30% of SLE patients, but it is usually mild. Psychosis is reported in up to 3.5% and is characterised by either the presence of delusions or hallucinations. The latter are most frequently auditory. Generalised and focal seizures are reported in 7–10% of patients and may occur either in the setting of active generalised multisystem lupus or as isolated neurologic events. Seizures are also associated with the presence of antiphospholipid antibodies. Demyelination, transverse myelopathy, and chorea are rare manifestations occurring in <1% of patients. Clinical and neuroimaging evidence of demyelination may be indistinguishable from multiple sclerosis. Myelitis may present either with grey matter signs (upper motor neuron signs, spasticity, hyperreflexia) or white matter signs (lower motor neuron syndrome with flaccid paralysis and decreased reflexes). The latter associates with neuromyelitis optica (NMO) and

Central nervous system
Aseptic meningitis
Cerebrovascular disease Demyelinating syndrome Headache (including migraine and benign intracranial hypertension)
Movement disorder (chorea) Myelopathy Seizure disorder
Acute confusional state Anxiety disorder Cognitive dysfunction
Mood disorder Psychosis
Peripheral nervous system
Acute inflammatory demyelinating polyradiculoneuropathy (Guillain-Barré syndrome) Autonomic disorder
Mononeuropathy, single/multiplex Myasthenia gravis Neuropathy, cranial
Plexopathy Polyneuropathy

Adapted from the American College of Rheumatology nomenclature and case definitions for neuropsychiatric lupus syndromes.

Table 6 Neuropsychiatric syndromes in systemic lupus erythematosus

the presence of antibodies to aquaporin. Peripheral sensorimotor neuropathy has been reported in up to 1% of SLE patients and may occur independently of other disease characteristics.

10.5 Cardiovascular features

Pericarditis may occur in approximately 25% of SLE patients. Pericardial effusions may be asymptomatic and are usually mild to moderate. Tamponade is rare. Myocardial involvement is rare and typically occurs in the presence of generalised lupus activity. The patient may present with fever, dyspnoea, tachycardia, and congestive heart failure. Clinical features of left ventricular dysfunction, non-specific ST-T wave changes, segmental wall motion abnormalities, and decreased ejection fraction are found in >80% of patients. MRI has been used to detect both clinical and subclinical myocardial involvement in SLE.

SLE patients have substantially increased morbidity and mortality from cardiovascular disease (CVD). This includes accelerated, premature atherosclerosis and valvular heart disease. Studies have also demonstrated an increased risk for myocardial infarction or stroke compared to the healthy population, and this risk cannot be fully explained by the traditional CVD risk factors. Valvular heart disease is common in SLE and has been linked to the presence of antiphospholipid antibodies. The most common abnormality is diffuse thickening of the mitral and aortic valves followed by vegetations, valvular regurgitation, and stenosis in decreasing order of frequency. The combined incidence of stroke, peripheral embolism, heart failure, infective endocarditis, and the need for valve replacement is approximately threefold higher in those patients with valvular disease compared to those without it. Pathologic studies have shown active and healed valvulitis, as well as active Libman-Sacks vegetations with acute thrombus, healed vegetations with or without hyalinised thrombus, or both active and healed vegetations, in the same or different valves.

10.6 Pleura and lungs

The most common pleuropulmonary manifestation of SLE is pleuritis (table 7). Pleuritic pain is present in 45–60% of patients and may occur with or without a pleural effusion, with clinically apparent pleural effusions reported in up to 50%. Effusions are usually bilateral and equally distributed between the left and right hemithoraces. The effusion is invariably exudative with higher glucose and lower lactate dehydrogenase levels than those found in rheumatoid arthritis.

Clinically significant interstitial lung disease (ILD) complicates SLE in 3–13% of patients, but is rarely severe. Acute lupus pneumonitis presenting as cough, dyspnoea, pleuritic pain, hypoxaemia, and fever occurs in 1–4%. Chest radiographs reveal unilateral or bilateral infiltrates. Pulmonary haemorrhage is a rare but potentially catastrophic complication of SLE. Clinical features are non-specific but diffuse alveolar infiltrates, hypoxaemia, dyspnoea, and anaemia are characteristic. Alveolar haemorrhage usually occurs in patients with a known history of SLE, high titres of anti-DNA antibodies, and active extrapulmonary disease. Fibreoptic bronchoscopy with bronchoalveolar lavage (BAL) and transbronchial lung biopsies are usually needed to substantiate the diagnosis.

The 'shrinking lung syndrome' is characterised by progressive dyspnoea and small lung volumes on chest radiographs, and is thought to be secondary to

Pleuropulmonary manifestation	Frequency
Pleuritic chest pain or pleurisy	Common, with or without effusion or friction rub
Pleural effusion	Exudate; unilateral or bilateral
Acute pneumonitis	Not common; presentation includes: fever, non-productive cough, infiltrates, hypoxia; high mortality rates
Interstitial lung disease	Insidious onset of dyspnoea on exertion, non-productive cough, pleuritic chest pain
Bronchiolitis obliterans with organising pneumonia	Can be difficult to diagnose; requires biopsy; responds to corticosteroids
Pulmonary capillaritis or diffuse alveolar haemorrhage	Rare, associated with antiphospholipid antibodies; poor prognosis
Shrinking lung syndrome	Occurs in patients with longstanding SLE; possible cause: diaphragmatic weakness
Pulmonary embolism or infarction	Common in patients with antiphospholipid antibodies
Pulmonary hypertension	Insidious onset of dyspnoea on exertion, chronic fatigue, weakness, palpitations, oedema
Lymphadenopathy	Massive mediastinal lymphadenopathy uncommon in patients with SLE alone. Cervical and auxiliary common, correlates with disease activity
Infection	Typical and atypical pathogens. Due to immune dysfunction and immunosuppressive medications
Malignant tumour	Lung cancer; lymphoma more common

Table 7 Pleuropulmonary manifestations of systemic lupus erythematosus (SLE)

diaphragmatic dysfunction. It can be difficult to differentiate from respiratory muscle weakness, primary parenchymal disease or pleural causes of low lung volumes without the use of invasive studies. Pulmonary hypertension (PH) is a rare but potentially life-threatening complication. Dyspnoea is the most common presenting symptom while up to 58% of patients have Raynaud's phenomenon.

10.7 Lymphadenopathy and splenomegaly

Lymphadenopathy occurs in approximately 40% of patients, usually at the onset of disease or during disease flares. Lymph nodes are typically soft, non-tender, discrete, and usually detected in the cervical, axillary, and inguinal area. Clinically significant lymphadenopathy that raises diagnostic issues is less common. Patients with lymphadenopathy are more likely to have constitutional symptoms. A lymph node biopsy may be warranted when the degree of lymphadenopathy is out of proportion to the activity of the lupus. Splenomegaly occurs in 10–45% of patients, particularly during active disease, and is not necessarily associated with cytopenias. Splenic atrophy and functional hyposplenism have also been reported in SLE and may predispose to severe septic complications.

10.8 Haematologic features

Haematologic abnormalities are common and can be the presenting symptom or sign in SLE. Major clinical manifestations include anaemia, leucopenia, thrombocytopenia, and the antiphospholipid syndrome.

Anaemia. Anaemia in SLE is common and correlates with disease activity. Its pathogenesis includes anaemia of chronic disease, haemolysis (autoimmune or microangiopathic), blood loss, renal insufficiency, medications, infection, hypersplenism, myelodysplasia, myelofibrosis, and aplastic anaemia. A frequent cause is suppressed erythropoiesis from chronic inflammation. Overt autoimmune haemolytic anaemia has been reported in up to 10% of patients; of note, SLE patients may have a positive Coombs test without overt haemolysis. Blood loss, either from the gastrointestinal (GI) tract, usually secondary to medications (non-steroidal anti-inflammatory drugs (NSAIDs)), or due to excessive menstrual bleeding, may cause an iron deficiency anaemia. A rare cause of iron deficiency anaemia in SLE may be low grade pulmonary haemorrhage without signs of haemoptysis.

A microangiopathic haemolytic anaemia with or without the other features (fever, thrombocytopenia, kidney involvement, neurologic symptoms) of thrombotic

thrombocytopenic purpura (TTP) has been described in SLE. The presence of schistocytes in the peripheral blood smear and increased lactate dehydrogenase (LDH) levels are the hallmarks of this disorder. When this occurs in the setting of generalised lupus activity, we prefer to call it TTP-like syndrome and use immunosuppressive therapy. In the absence of generalised lupus activity we view it as a bona fide TTP. A similar syndrome can also occur in the presence of antiphospholipid antibodies. Red cell aplasia due to antibodies against erythrocyte progenitors has been rarely reported in SLE patients.

Leucopenia. Leucopenia is common in SLE; it can be the presenting symptom and is usually associated with disease activity. A white blood cell count <4500/mm^3 has been reported in up to 30–40% of cases, especially in the presence of active disease. Severe leucopenia (neutrophil count <500/mm^3) is rare. Lymphocytopenia (lymphocyte count <1500/mm^3) occurs in approximately 20% of SLE patients.

Thrombocytopenia. Mild thrombocytopenia (platelet counts 100 000–150 000/mm^3) has been reported in 25–50% of patients; counts <50 000/mm^3 occur in only 10%. The most common cause of thrombocytopenia in SLE is immune-mediated platelet destruction, but increased platelet consumption may also occur due to microangiopathic haemolytic anaemia or hypersplenism. Impaired platelet production secondary to medications is another contributing factor. *Idiopathic thrombocytopenic purpura* (*ITP*) may be the first sign of SLE, followed by other symptoms as long as many years later. In such cases, presence of high-titre ANAs or *extractable nuclear antigens* (ENAs) raise the possibility of underlying SLE. Table 8 depicts our approach to thrombocytopenia in lupus.

10.9 Liver and GI tract features

GI tract. GI manifestations are reported in 25–40% of patients with SLE, and represent either lupus GI involvement or effects of medications. Dyspepsia has been reported in 11–50%, and peptic ulcers (usually gastric) in 4–21%.

Abdominal pain. Abdominal pain accompanied by nausea and vomiting occurs in up to 30% of SLE patients. Special consideration should be given in conditions such as peritonitis, mesenteric vasculitis with intestinal infarction, pancreatitis, and inflammatory bowel disease. Risk factors for the development of mesenteric vasculitis include peripheral vasculitis and CNS lupus. The clinical presentation is usually with insidious symptoms that may be intermittent for months before the development of an acute abdomen with nausea, vomiting, diarrhoea, GI bleeding, and fever. Patients with acute presentation may also have mesenteric thrombosis and infarction, often in association with antiphospholipid antibodies. The diagnosis of mesenteric vasculitis may be difficult to establish. Plain radiographic studies may reveal segmental bowel dilatation, air-fluid levels, 'thumb-printing' or narrowing of the lumen, and pseudo-obstruction. Abdominal computed tomography (CT) scan findings compatible with mesenteric vasculitis include prominence of mesenteric vessels with a comb-like appearance supplying dilated bowel loops, small bowel thickening and ascites. Vasculitis generally involves small arteries, which can lead to a negative arteriogram. Pancreatitis due to lupus may result from vasculitis or thrombosis and occurs in as many as 2–8% of patients. Elevated levels of serum amylase have been described in patients with SLE without

Lupus related? ● Rule out drug effects. Ask for over-the-counter drugs such as quinine for leg cramps, vitamins, supplements or herbal medicines ● Discontinue all but absolutely essential drugs ● Discontinue agents that may interfere with platelet function (aspirin, non-steroidal anti-inflammatory drugs)
Confirm autoimmune aetiology by examining peripheral smear. Rule out platelet clumping that can cause false thrombocytopenia and abnormalities of the white or the red blood cells ● Consider bone marrow examination especially in older patients to rule out occult myelodysplasia ● Tests for antiplatelet antibodies are not helpful ● Rule out thrombotic thrombocytopenic purpura or antiphospholipid-related microangiopathic haemolytic anaemia (anaemia with pronounced reticulocytosis and fragmented erythrocytes in the peripheral smear; antiphospholipid antibodies or syndrome)
Look for evidence of lupus activity in other organs (especially major organs) ● Determine severity: severe: platelets <20×10^3/μl; moderate-to-severe: platelets 20–50×10^3/μl ● Treatment goal is not a normal platelet count but a safe platelet count (30–50×10^3/μl)

Table 8 An approach to thrombocytopenia in systemic lupus erythematosus

pancreatitis and thus should be interpreted in light of the overall clinical examination.

Liver disease. Hepatic disease may be more common in SLE than initially thought. However, clinically significant hepatic disease is generally unusual. The incidence of hepatomegaly is 12–25%. Excessive fatty infiltration (steatosis) is a common finding and may occur as part of the disease process or may be secondary to corticosteroid treatment. Liver chemistries (aspartate aminotransferase (AST), alanine aminotransferase (ALT), LDH, alkaline phosphatase) may be abnormal in patients with active disease or those receiving NSAIDs. The term 'lupoid hepatitis' was formerly used to describe autoimmune hepatitis because of clinical and serologic similarities to SLE. Autoantibodies may help to distinguish between autoimmune hepatitis and liver disease associated with lupus. ANAs can be seen in both disorders, but anti-smooth muscle and anti-mitochondrial antibodies are not common in SLE (<30%) and usually when found are in low titres. In lupus-associated hepatitis histology rarely shows the periportal (interface) hepatitis with piecemeal necrosis characteristic of autoimmune hepatitis, and liver-associated chemistries tend to be lower in lupus with only mild (usually up to three to four times normal) elevation. The absence of these antibodies and the presence of anti-ribosomal P protein antibodies could be suggestive of lupus hepatitis.

Ascites is uncommon in SLE and, when detected, infectious causes and/or perforation must be excluded by paracentesis. Congestive heart failure and hypoalbuminaemia secondary to nephrotic syndrome or protein-losing enteropathy represent other possible causes of ascites in patients with lupus. Protein-losing enteropathy has been described in some patients with SLE and can be the first manifestation of the disease. It usually occurs in young women and is characterised by the onset of profound oedema and hypoalbuminaemia.

10.10 Ophthalmic features

Up to 8% of SLE patients develop inflammation of the retinal artery during the course of their disease. An equal number of patients have infarction of the retinal vasculature secondary to antiphospholipid antibodies. Both conditions can lead to the presence of 'cotton wool' spots in the retina visible on ophthalmoscopy or fluorescein angiography (where perivascular exudates and patches of dye leakage along the vessels are seen). Cotton wool spots result from focal ischaemia and are not pathognomonic for lupus. Retinal vasculitis is usually associated with generalised active systemic disease and presents early in the disease process. Corneal and conjunctiva involvement is usually part of Sjögren's syndrome associated with SLE; uveitis and scleritis are extremely rare manifestations in SLE, seen in <1% of patients. Optic neuritis is rare and may be associated with transverse myelitis.

11 Diagnosis

11.1 Serologic tests

Antinuclear antibodies. The ANA assay is an ideal screening test because of its sensitivity (95% when using human cultured cells as the substrate) and simplicity. The entity of 'ANA-negative lupus' described in previous years is usually associated with the presence of other cytoplasmic autoantibodies such as anti-Ro (SS-A) and anti-ribosomal P protein. The specificity of ANAs for SLE is low, since they are found in many other conditions such as scleroderma, polymyositis, dermatomyositis, rheumatoid arthritis, autoimmune thyroiditis, autoimmune hepatitis, infections, neoplasms, and in association with many drugs. Also, some healthy individuals test positive for ANAs. The formation of ANAs is age-dependent; it is estimated that 10–35% of individuals older than 65 years have ANAs. However, the titres are generally lower (<1:40) than those in systemic autoimmune diseases. In contrast to the low positive predictive value of ANA testing, a patient with a negative test has less than a 3% chance of having SLE; thus, a negative ANA test is useful for excluding the diagnosis of SLE. However, in the presence of typical features of lupus, a negative ANA test does not exclude the diagnosis. This is especially true for laboratories that employ enzyme immunoassays or other automated assays which display marked inter-manufacturer variation in performance. In such cases, reported sensitivity against positive immunofluorescence ANA with titre at 1:160 ranges from 70–98%.

Antibodies to extractable nuclear antigens (ENAs). The nucleosome—a complex of DNA and histones—was the first identified lupus autoantigen. Autoantibodies to single stranded DNA (ssDNA) and individual histones are common in SLE as well as in drug-induced lupus. Antibodies to double stranded (ds) DNA are found in up to 70% of SLE patients at some point during the course of

their disease, and are 95% specific for SLE, making them a valuable disease marker. Anti-Sm (Smith) antibodies are detected in 10–30% and their presence is pathognomonic for SLE. Anti-nRNP antibodies are associated with anti-Sm but are not disease specific. Anti-ribosomal antibodies are specific for SLE but less sensitive than anti-dsDNA or anti-Sm antibodies.

11.2 Prognostic markers and the role of autoantibodies

Analysis of large cohorts has defined clusters of autoantibodies associated with distinct SLE features. Serum anti-dsDNA titres have been correlated with LN, progression to end-stage renal disease, and increased disease severity, damage or poor survival. Antiphospholipid antibodies are strongly associated with features of the antiphospholipid syndrome (APS) (arterial/venous thrombosis, fetal loss, thrombocytopenia), CNS involvement (especially cerebrovascular disease), severe LN, damage accrual, and death. Anti-Ro (SS-A) and anti-La (SS-B) antibodies have been associated with neonatal lupus, and congenital heart block in the children of seropositive mothers. Antibodies to other extractable nuclear antigens (anti-Ro/La/Sm/RNP) have been associated with mucocutaneous involvement and less severe nephropathy in most studies.

11.3 Diagnosis: typical and atypical presentations

The diagnosis of lupus requires integration of patient's symptoms, physical examination findings, and the results of diagnostic tests. Table 9 shows the frequency of various manifestations both at disease onset and at anytime during the disease course. Presence of one or more of these features or the involvement of at least two different organs in young women should always raise the possibility of lupus. However, many of these features are not unique to lupus but could be seen in other infectious, metabolic, malignant, and other systemic rheumatic diseases.

11.3.1 Pitfalls and challenges in diagnosis

Undifferentiated connective tissue disease. The recognition that systemic rheumatic diseases have several common features which makes a specific diagnosis difficult has led to the concept of the undifferentiated connective tissue syndromes. These patients account for 10–20% of patients referred to tertiary care centres. Among patients presenting with symptoms suggestive of a connective tissue disease, only a small fraction (10–15%) fulfil classification criteria for SLE after 5 years follow-up. Prognostic factors for SLE are young age, alopecia, serositis, discoid lupus, positive Coombs test, and positive anti-Sm and anti-DNA antibodies. Latent or incomplete lupus describes patients who present with a constellation of symptoms suggestive of SLE, but do not qualify by clinical intuition or classification criteria as having classical SLE. These patients usually present with one or two of the ACR criteria and other features not included in the classification criteria. Most of these patients do not develop SLE or when they do it is usually mild and rarely involves major organs.

Case series suggest that SLE may occasionally present with high fever and lymphadenopathy simulating lymphoid or haematological malignancy, neurological events (chorea, cerebrovascular accident, myelitis),

Manifestations	Onset	Anytime
Arthralgia	77%	85%
Constitutional	53%	77%
Skin	53%	78%
Arthritis	44%	63%
Renal	38%	74%
Raynaud's	33%	60%
Central nervous system	24%	54%
Vasculitis	23%	56%
Mucous membranes	21%	52%
Gastrointestinal	18%	45%
Lymphadenopathy	16%	32%
Pleurisy	16%	30%
Pericarditis	13%	23%
Lung	7%	14%
Nephrotic syndrome	5%	11%
Azotaemia	3%	8%
Myositis	3%	3%
Thrombophlebitis	2%	6%
Myocarditis	1%	3%
Pancreatitis	1%	2%

Table 9 Frequency of various manifestations of systemic lupus erythematosus at disease onset and at any time during the disease

unusual skin rashes (chronic urticarial, paniculitis), abdominal vasculitis, pneumonitis/pulmonary haemorrhage, pulmonary hypertension, isolated serositis, myocarditis, aplastic anaemia or isolated cytopenias. A careful history for manifestations of lupus in the past and a careful examination together with serology may help recognise the disease.

11.4 Differential diagnosis

Differential diagnosis from other polyarticular diseases affecting young women, such as rheumatoid arthritis or Still's disease, may not be easy at the initial stages. Other diseases to be considered include undifferentiated connective tissue disease, primary Sjögren's syndrome, primary antiphospholipid syndrome, fibromyalgia with positive ANA, idiopathic thrombocytopenic purpura, drug induced lupus, and autoimmune thyroid disease. Patients presenting with fever or splenomegaly/lymphadenopathy must be differentiated from infectious diseases or lymphoma. In febrile patients with known SLE, leucocytosis, neutrophilia, shaking chills, and normal levels of anti-DNA antibodies favour infection. Lupus may present with localised or generalised lymphadenopathy or splenomegaly, but the size of lymph nodes is rarely >2 cm while splenomegaly is mild-to-moderate. Patients with known or suspected SLE with prominent lymphadenopathy, massive splenomegaly or expansion of a monoclonal $CD19^+$/$CD22^+$ B cell population should raise the suspicion of non-Hodgkin lymphoma. In patients presenting with neurological symptoms, infections, cerebrovascular accidents or immune mediated neurologic diseases such as multiple sclerosis or Guillain-Barré disease must be considered. Finally, in patients presenting with pulmonary–renal syndrome, the disease must be differentiated from Goodpasture's syndrome, or antineutrophil cytoplasmic antibody (ANCA) associated vasculitis. The differential diagnosis of glomerulonephritis includes post-infectious glomerulonephritis (streptococcal, staphylococcal, subacute bacterial endocarditis, or hepatitis C virus), membranoproliferative glomerulonephritis, or renal vasculitis (ANCA or anti-GBM associated).

12 SLE and pregnancy

Mothers. There is no significant difference in fertility between patients with SLE and unaffected individuals. Pregnancy may increase lupus activity but flares are usually mild. Pregnancy outcome is optimal when the disease is in clinical remission for 6–12 months and the patient's renal function is stable and normal or near-normal. Patients with LN and antiphospholipid antibodies are at risk of developing pre-eclampsia and should be monitored closely. Proteinuria may increase during pregnancy in women with underlying kidney disease. Differentiation of pre-eclampsia from lupus renal activity is not difficult in most cases. Very low serum complement, active urine sediment, and evidence of generalised lupus activity favour the latter. Other features such as hypertension, thrombocytopenia, rise in serum uric acid levels, and proteinuria may be observed in both conditions. Low grade activation of the classic complement pathway may be attributable to pregnancy alone. Ovarian induction and fertilisation can be successful in SLE patients, but rates of fetal and maternal complication may be higher.

Fetus. SLE may affect the fetus in several ways, especially if the mother has a history of LN, antiphospholipid, anti-Ro and/or anti-La antibodies. These conditions are associated with increased risk of miscarriage, stillbirth, premature delivery, intrauterine growth restriction, and fetal heart block. Neonatal lupus is a passively transferred autoimmune disease that occurs in some babies born to mothers with anti-SS-A/Ro and/or anti-SS-B/La antibodies. The most serious complication in the neonate is complete heart block, which occurs in up to 2% of such pregnancies. Isolated skin rash occurs in a similar percentage. Once a woman has given birth to an infant with congenital heart block, the recurrence rate is about 15%.

Table 10 summarises the key points relevant to the management of pregnancy in SLE patients.

13 Lupus in childhood and adolescence

Approximately 15–20% of all SLE cases are diagnosed in childhood. Paediatric SLE may differ from adult SLE, in disease expression, physiologic, developmental and psychosocial issues. Because of paucity of data in paediatric SLE, little is known about its epidemiology, long term outcome, and optimal management. In general, the same principles are applied in the management of paediatric lupus; however, the special needs of this population also have to be taken into consideration.

• Planning of pregnancy
– Ensure that lupus is inactive for at least 6 months. Reassure patient (small risk for major flare)
– Discourage pregnancy if creatinine is >2 mg/dl
• Check for antiphospholipid antibodies and other antibodies that may be of relevance during pregnancy (eg, anti-SSA, anti-SSB)
• Check baseline labs including serology, and serum chemistry including creatinine, albumin, uric acid, anti-dsDNA, C3, C4
• Be aware of the small risk for congenital heart block (CHB), especially in women with both anti-SSA and anti-SSB antibodies or with a prior episode of CHB. In such cases, may monitor for CHB between 16 and 24 weeks of gestation
• Monitor closely blood pressure and proteinuria. Should this develop, differentiate between active nephritis and pre-eclampsia. The presence of generalised lupus activity and active urine sediment and significantly low serum complement favours lupus nephritis

Table 10 An approach to the management of pregnancy in systemic lupus erythematosus

14 Drug-induced lupus

A variety of drugs have been identified as being definite, probable or possible causes of lupus (table 11). DIL should be suspected in patients with no diagnosis or history of SLE, who develop a positive ANA and at least one clinical feature of lupus after an appropriate duration of drug exposure, and whose symptoms resolve after discontinuation of the drug. DIL is probably under-reported since most cases are mild and self-limiting once the offending drug is discontinued. Clinical features include fever, myalgias, rash, arthritis, and serositis. Haematological abnormalities, kidney disease, and CNS lupus are uncommon. Antihistone antibodies are present in more than 95% of cases, whereas hypocomplementaemia and anti-DNA antibodies are rare, with the probable exception of disease associated with use of IFNα and anti-TNF therapies.

15 Emergencies and critical illness

Emergency room (ER) visits. SLE patients may visit the ER for complications related to lupus itself or its treatment, or for unrelated reasons. Critical questions confronting the clinician are: (1) whether the event is related to lupus; and (2) whether in the presence of lupus the management should differ. In general, lupus-related emergencies frequently occur when disease is active. For example, approximately 60% of primary NPSLE events occur in the presence of generalised lupus activity. Common symptoms bringing lupus patients to the ER are fever, shortness of breath, and chest pain. Poor compliance, low education level, severity of the underlying disease, and higher damage scores are risk factors for hospitalisation.

Lupus in the intensive care unit (ICU). Life-threatening illness can develop in patients with lupus from any of the following causes: (1) exacerbation of pre-existing manifestations of SLE; (2) development of new life-threatening manifestations of SLE; (3) infections resulting from immunosuppression; (4) adverse effects of drugs used to treat SLE; (5) malignancy resulting from prolonged use of cytotoxic drugs, and (6) acute serious illnesses that are unrelated to SLE, but whose manifestations are altered or exaggerated by it. Infection is the most common form of pulmonary involvement in patients with SLE.

Infections in SLE patients can be confused with disease exacerbation, and empiric therapy with broad spectrum antibiotics is warranted until infection is ruled out. In the case of the lungs, a diagnosis of acute lupus pneumonitis can be made after rigorously excluding infections in patients presenting with features resembling infectious pneumonia. A high index of suspicion should be maintained for the young female patient presenting with unexplained pulmonary infiltrates. Alveolar haemorrhage is also a serious but rare complication of lupus with high morbidity and mortality. Respiratory failure may occur, and more than half of affected patients in most series required mechanical ventilation. Patients with alveolar haemorrhage usually have lupus nephritis as a pre-existing condition.Vascular events (myocardial or cerebrovascular) due to premature accelerated atherosclerosis are increasingly recognised among SLE patients. Although patients are often concerned about vasculitis, the majority of coronary occlusive disease in SLE results from atherosclerosis or thrombosis. Cases of left ventricular free wall rupture, acute mitral regurgitation following rupture of chordae tendinae, and aortic dissection have been described. Cerebrovascular accidents presenting acutely with hemiplegia, aphasia,

Agent	Risk
Antiarrhythmics	
Procainamide	High
Quinidine	Moderate
Disopyramide	Very low
Propafenone	Very low
Antihypertensives	
Hydralazine	High
Methyldopa	Low
Captopril	Low
Enalapril	Low
Acebutolol	Low
Labetalol	Very low
Pindolol	Very low
Clonidine	Very low
Minoxidil	Very low
Prazosin	Very low
Antipsychotics	
Chlorpromazine	Low
Perphenazine	Very low
Phenelzine	Very low
Lithium carbonate	Very low
Anticonvulsants	
Carbamazepine	Low
Phenytoin	Very low
Trimethadione	Very low
Primidone	Very low
Ethosuximide	Very low
Antibiotics	
Isoniazid	Low
Minocycline	Very low
Nitrofurantoin	Very low
Anti-inflammatories	
D-Penicillamine	Low
Sulfasalazine	Low
Phenylbutazone	Very low
Zafirlukast	Very low
Mesalamine	Low
Diuretics	
Chlorthalidone	Very low
Hydrochlorothiazide	Very low
Antihyperlipidaemics	
Lovastatin	Very low
Simvastatin	Very low
Miscellaneous	
Propylthiouracil	Low
Levodopa	Very low
Aminoglutethimide	Very low
Timolol eye drops	Very low
Biologic agents	
TNFα blockers	High
Interferon α	Low

Table 11 Drugs reported to induce lupus-like disease and associated autoantibodies

cerebral dysfunction, cortical blindness or other deficits of cerebral function can be caused by intracranial haemorrhage from ruptured aneurysms, thrombotic strokes from vasculitis or vasculopathy secondary to antiphospholipid antibodies, or embolic strokes from cardiac emboli. Spinal cord myelopathy is a devastating manifestation of SLE. Patients present with weakness or paralysis, bilateral sensory deficits, and impaired sphincter control. Symptoms usually evolve in a matter of hours or days. MRI of the spinal cord may show characteristic abnormalities of cord oedema if obtained early. Because of the poor prognosis early diagnosis and aggressive therapy are important.

Acute abdomen in SLE patients may be secondary to mesenteric arterial thrombosis, ischaemic bowel, ruptured hepatic aneurysms, cholecystitis, perforated rectal ulcer, appendix, caecum or colon, and pancreatitis. Active SLE presenting with acute abdomen and a high SLEDAI score are more likely to have active intra-abdominal vasculitis than patients with active lupus but low SLEDAI scores, and should be promptly referred for abdominal CT with contrast. In view of the high mortality in this subgroup, patients with a high index of suspicion should undergo early laparotomy.

16 Recommended assessment and monitoring and referral guidelines

Due to its low prevalence, most general internists and primary care physicians will not have experience in the

management of moderate to severe disease. However, their role in the early diagnosis, monitoring of patients with mild, stable diseases, and the referral for patients with unstable or moderate to severe disease is essential. Guidelines for the initial assessment and frequency of monitoring for general use are shown in table 12.

17 Prognosis, morbidity and comorbidities, and mortality

17.1 Prognosis

Although current treatment of lupus has improved survival dramatically, prolonged and complete remission—defined as 5 years without clinical and laboratory evidence of active disease and on no treatment—has remained elusive for most patients. The incidence of flare is estimated to 0.65 per patient-year of follow-up. Moreover, a significant number of patients (10–20% in tertiary referral centres) do not respond adequately to immunosuppressive therapies.

17.2 Morbidity, comorbidities, and mortality

In lupus, treatment-related morbidity may not be easily separable from disease-related morbidity. The incidence of hospital admissions for patients with lupus is 0.69 admissions per patient-year. Infections, coronary artery disease, and orthopaedic management of osteonecrosis were prominent reasons for hospitalisation. A bimodal mortality pattern was first described in 1974 showing that early mortality in SLE is associated with lupus activity and infection, whereas late mortality is associated with atherosclerotic complications.

Infections. Infections account for 20–55% of all deaths in SLE patients. Susceptibility to infections may be due to underlying immune dysregulation and therapeutic factors, particularly high-dose glucocorticoids (GC) and immunosuppressive drugs. A broad spectrum of infections have been reported in SLE, including bacterial, mycobacterial, viral, fungal,

History: review of systems Joint pain/swelling, Raynaud's phenomenon Photosensitivity, rash, hair loss, Shortness of breath, pleuritic chest pain General symptoms (depression, fatigue, fever, weight change)
Physical examination Rashes (acute, subacute, chronic, non-specific, others), alopecia, oral or nasal ulcers Lymphadenopathy, splenomegaly, pericardial or pleural effusions Fundoscopic examination, oedema Other features as suggested by history/symptoms
Imaging: laboratory Haematology* Chemistry* PT/PTT, antiphospholipid antibodies Urinalysis* Serology (ANA, ENA including anti-dsDNA†, complement†) Chest x-ray ECG Other tests as suggested by history/symptoms
Disease activity index (at each visit or at major changes in therapy)
Side effects of therapy
Damage index (SLICC) (every 1-2 years)

*Every 3–6 months, if stable.
†Every 3–6 months in patients with active renal disease.
ANA, antinuclear antibody; ENA, extractable nuclear antigen; ECG, electrocardiogram; PT, prothrombin time; PTT, partial thromboplastin time; SLICC, Systemic Lupus International Collaborating Clinics.

Table 12 Recommended initial assessment and monitoring of systemic lupus erythematosus

and parasitic infections, with the respiratory, urinary tract, and CNS the most commonly involved sites. Risk factors for infections include increased clinical and/or serological lupus activity at baseline, major organ involvement (especially renal and lung involvement), lymphopenia, persistent neutropenia (<1000/mm^3), hypoalbuminaemia (especially for severe CNS infections), high dose of GC (each increase of 10 mg/day prednisone is associated with an 11-fold increased risk for serious infection), and prior (within the last 6 months) use of cytotoxic drugs (especially, azathioprine, and cyclophosphamide). The evaluation of a lupus patient who receives immunosuppressive therapy and presents with symptoms or signs suggestive of infection possesses diagnostic and therapeutic challenges. Findings that favour the diagnosis of infection include the presence of shaking chills, leucocytosis and/or neutrophilia (especially in the absence of steroid therapy), increased numbers of band forms or metamyelocytes on peripheral blood smear, and concomitant immunosuppressive therapy. The diagnosis of SLE fever is favoured by the presence of leucopenia (not explained by cytotoxic therapy), normal or only slightly increased C reactive protein, low C3/C4, and elevated anti-DNA antibodies. Pending microbiology results, adequate antimicrobial therapy (including broad spectrum antibiotics in suspected nosocomial infection) is recommended to reduce adverse outcomes.

Atherosclerosis. SLE patients have 2.3–7.5 increased risk for developing coronary heart disease compared to age-matched controls, after adjusting for traditional CVD risk factors. Traditional CVD risk factors are reinforced by disease-related risk factors, such as circulating prothrombotic antiphospholipid antibodies, antibodies against HDL cholesterol interfering with its function, a typical lupus pattern of dyslipidaemia (low HDL cholesterol, high triglycerides, normal or slightly elevated low density lipoprotein (LDL) cholesterol (LDL-C), and abnormal serum homocysteine levels) and the proatherogenic effect of systemic inflammation. Aggressive treatment of dyslipidaemia (target LDL-C <100 mg/dl (<2.6 mmol/l) and triglycerides <150 mg/dl (<1.7 mmol/l)) is recommended for patients with multiple risk factors, especially those with moderate or severe lupus particularly in the presence of carotid thickening by ultrasound imaging techniques.

Osteoporosis. Uncontrolled disease activity, premature menopause, relative vitamin D deficiency due to avoidance of sun exposure, and the use of systematic GC all contribute to reduced bone mineral density in SLE. Vertebral compression fractures are common, especially as the age of patients increases.

Malignancies. Haematological malignancies (particularly non-Hodgkin's lymphoma (NHL)), and cervical and lung cancer occur more commonly in SLE compared to the general population. Immunosuppressive therapy and intrinsic SLE-related mechanisms may account for this risk. NHL is associated with SLE (standardised incidence ratio (SIR) 3.6), with the most commonly identified histologic subtype being diffuse large B cell lymphoma, which usually runs an aggressive course. Hodgkin's lymphoma (HL) is also more frequent in SLE (SIR 3.2). The risk for haematological malignancies may increase after exposure to immunosuppressive medications, particularly after a period of 5 years following cessation of therapy. Since SLE and lymphomas share clinical manifestations (fever, lymphadenopathy, splenomegaly, cytopenias, monoclonal expansion of B cells), a high index of suspicion is necessary for early detection of the latter. In such cases, an aggressive investigation is warranted with appropriate imaging studies and, potentially, lymph node biopsy. Cervical dysplasia is increased in women with lupus as a result of impaired clearance of human papilloma virus (HPV) due to exposure to cytotoxic agents, particularly cyclophosphamide (increase by 1 g of intravenous cyclophosphamide exposure corresponding to 13% increased risk of cervical carcinoma). Therefore, SLE should be regarded as a risk factor for cervical malignancy and high-risk HPV infection. We would recommend cervical cytology for cancer screening once (EULAR) or twice (United States Preventive Services Task Force) in the first year and then annually, adding HPV testing to the first year obtained cervical smears and then modifying subsequent screening based on these results (cervical cytology screening every 6 months for women with detectable HPV DNA and annually for others). Although the efficacy of HPV vaccine has not been investigated in patients with autoimmune diseases, the EULAR guidelines concluded that HPV vaccination should be considered for women with SLE until the age of 25 years, similar to the general population.

General management
Prognosis In patients with SLE, new clinical signs (rashes **(B)**, arthritis **(B)**, serositis **(B)**, neurological manifestations -seizures/psychosis **(B)**), routine laboratory (complete blood count (CBC) **(B)**, serum creatinine **(B)**, proteinuria **(B)** and urinary sediment **(B)**), and immunological tests (serum C3 **(B)**, anti-dsDNA **(B)**, anti-Ro/SSA **(B)**, anti-La/SSB **(C)**, anti-phospholipid **(B)**, anti-RNP **(B)**), may provide prognostic information for the outcome in general and involvement of major organs, and thus should be considered in the evaluation of these patients. Confirmation by imaging (brain MRI **(B)**), and pathology (renal biopsy **(B)**) may add prognostic information and should be considered in selected patients.
Monitoring New clinical manifestations such as number and type of skin lesions **(C)** or arthritis **(D)**, serositis **(D)**, and neurological manifestations (seizures/psychosis) **(D)**, laboratory tests (CBC) **(B)**, immunological tests (serum C3/C4 **(B)**, anti-C1q **(B)**, anti-dsDNA **(B)**), and validated global activity indices **(D)** have diagnostic ability for monitoring for lupus activity and flares, and may be used in the monitoring of lupus patients.
Comorbidities SLE patients are at increased risk for certain comorbidities, either due to the disease and/or its treatment. These comorbidities include infections (urinary track infections **(B)**, other infections **(C)**), atherosclerosis **(B)**, hypertension **(B)**, dyslipidaemias **(B)**, diabetes **(C)**, osteoporosis **(C)**, avascular necrosis **(C)**, malignancies (especially non-Hodgkin lymphoma) **(B)**. Minimisation of risk factors together with a high index of suspicion, prompt evaluation, and diligent follow-up of these patients is recommended.
Neuropsychiatric lupus
Diagnosis In SLE patients the diagnostic work-up (clinical **(A–C)**, laboratory **(B)**, neuropsychological **(C)**, and imaging tests **(B–C)**) of neuropsychiatric manifestations should be similar to that in the general population presenting with the same neuropsychiatric manifestations.
Pregnancy in lupus
Pregnancy affects mothers with SLE and their offspring in several ways. a) Mother. There is no significant difference in fertility in lupus patients **(C)**. Pregnancy may increase lupus disease activity but these flares are usually mild **(B)**. Patients with lupus nephritis and anti-phospholipid antibodies are more at risk of developing pre-eclampsia and should be monitored more closely **(B)**. b) Fetus. SLE may affect the fetus in several ways, especially if the mother has a history of lupus nephritis, anti-phospholipid, anti-Ro and/or anti-La antibodies. These conditions are associated with an increase of the risk of miscarriage **(B)**, stillbirth **(B)**, premature delivery **(B)**, intrauterine growth restriction **(C),** and fetal heart block **(B)**. Prednisolone **(D)**, azathioprine **(D)**, hydroxychloroquine **(A)**, and low dose aspirin **(D)** may be used in lupus pregnancies. At present evidence suggests that mycophenolate mofetil, cyclophosphamide and methotrexate must be avoided **(D)**.
Anti-phospholipid syndrome
In patients with SLE and anti-phospholipid antibodies, low-dose aspirin may be considered for primary prevention of thrombosis and pregnancy loss **(D)**. Other risk factors for thrombosis should also be assessed. Oestrogen-containing drugs increase the risk for thrombosis **(D)**. In non-pregnant patients with SLE and anti-phospholipid syndrome-associated thrombosis, long term anticoagulation with oral anticoagulants is effective for secondary prevention of thrombosis **(A)**. In pregnant patients with SLE and anti-phospholipid syndrome, combined unfractionated or low molecular weight heparin and aspirin reduce pregnancy loss and thrombosis and should be considered **(A)**.
Lupus nephritis
Monitoring Renal biopsy **(B)**, urine sediment analysis **(B)**, proteinuria **(B)**, and kidney function **(B)** may have independent predictive ability for clinical outcome in therapy of lupus nephritis but need to be interpreted in conjunction. Changes in immunological tests (anti-dsDNA, serum C3) **(B)** have only limited ability to predict the response to treatment and may be used only as supplemental information.

* The strength of each statement (A–D) is given in parentheses, in bold. **A:** evidence from randomised controlled trials (RCTs) or meta-analysis of RCTs without concerns for the validity; **B:** as in A but with concerns about the validity of the evidence, or evidence from meta-analysis of epidemiological studies or prospective controlled studies without concerns about the validity of the evidence; **C:** evidence from non-prospective controlled (retrospective cohort, case–control, or cross-sectional) or uncontrolled studies without concerns about the validity; **D:** based on evidence from meta-analysis from epidemiological studies, non-randomised controlled studies (prospective or non-prospective), or uncontrolled studies with major concerns about the validity of the evidence; or no data (expert opinion).

Adapted from Bertsias *G,* Ioannidis JP, Boletis J, *et al.* EULAR recommendations for the management of systemic lupus erythematosus. Report of a Task Force of the EULAR Standing Committee for International Clinical Studies Including Therapeutics. *Ann Rheum Dis* 2008;**67**:195–205.

Table 13 Summary of the EULAR statements and recommendations on the diagnosis and monitoring of systemic lupus erythematosus (SLE) based on evidence and expert opinion

18 Evidence-based recommendations for the management of SLE

The EULAR Task Force on SLE has developed recommendations covering the most important aspects in the management (Bertsias *et al* 2008). These recommendations—developed not only for the specialists but for all internists—were based on a combined research-based evidence approach and expert opinion consensus. The recommendations for the diagnosis and monitoring of SLE are shown in table 13.

19 Lupus in Europe: the Euro-Lupus Cohort

The Euro-Lupus Cohort is composed of 1000 patients with SLE that have been followed prospectively since 1991. These patients have been gathered by a European consortium of more than 40 investigators from seven European countries. The general clinical and serologic characteristics of this cohort at the beginning of the study are shown in tables 14 and 15 (Cervera *et al* 1993).

SLE manifestation	Prevalence (%)
Arthritis	84
Malar rash	58
Fever	52
Photosensitivity	45
Nephropathy	39
Serositis	36
Raynaud's phenomenon	34
Neurologic involvement	27
Oral ulcers	24
Thrombocytopenia	22
Sicca syndrome	16
Livedo reticularis	14
Thrombosis	14
Lymphadenopathy	12
Discoid lesions	10
Myositis	9
Haemolytic anaemia	8
Lung involvement	7
Subacute cutaneous lesions	6
Chorea	2

Table 14 Clinical manifestations in a series of 1000 European systemic lupus erythematosus (SLE) patients

In the Euro-Lupus Cohort, 76 out of the 1000 patients with SLE (8%) developed the disease before the age of 14 years. The female: male ratio (7:1) was lower than the general SLE population (10:1). In addition, the clinical and immunological patterns of SLE in childhood onset patients differed slightly from the disease in other SLE patients. Childhood onset patients were more likely to have severe organ involvement, especially nephropathy, at presentation. Other major manifestations, such as neurologic involvement, thrombocytopenia and haemolytic anaemia, were also common initial features in the childhood onset group. However, during the disease evolution, the pattern was quite similar in childhood onset and adult patients. Interestingly, the initial diagnosis in the childhood onset group was delayed, presumably because doctors are reluctant to diagnose SLE in childhood patients and because typical signs and symptoms are less common. This is reflected in a mean 5 year delay in establishing the diagnosis of SLE in the childhood onset group.

Although SLE has traditionally been considered a disease of young women, several reports have described SLE in older populations. In the Euro-Lupus Cohort, 90 patients (9%) developed the disease after the age of 50. Female predominance was not so pronounced in the older onset group (5:1). Of interest, the clinical expression of SLE in older patients differed in several aspects from the disease in young adults. The clinical picture in older-onset best resembles patients with drug-induced SLE, primary Sjögren's syndrome, or polymyalgia rheumatica. Thus, in the Euro-Lupus Cohort, typical SLE manifestations, such as malar rash,

Serological features	Prevalence (%)
Antinuclear antibodies	96
Anti-DNA antibodies	78
Anti-Ro (SSA) antibodies	25
Anti-LA (SSB) antibodies	19
Anti-RNP antibodies	13
Anti -Sm antibodies	10
Rheumatoid factor	18
IgG anticardiolipin antibodies	24
IgM anticardiolipin antibodies	13
Lupus anticoagulant	15

Table 15 Prevalence of serological features in a series of 1000 systemic lupus erythematosus patients

photosensitivity, arthritis or nephropathy, were less common than in the younger patients. In contrast, sicca syndrome was common.

In terms of the effect of gender in the clinical expression of lupus, 92 out of the 1000 (9%) patients with SLE were men. A higher prevalence of serositis was found in the male patients at presentation. In contrast, arthritis tended to occur less commonly in men, although the difference was not statistically significant. This atypical presentation is relevant because it can lead to a delay in diagnosis. During disease evolution, a lower prevalence of arthritis was found in the males. The prevalence of nephropathy, neurological involvement, thrombocytopenia, vasculitis, and serositis was similar in both groups. No significant immunological differences were found between men and women.

The frequencies of the main lupus manifestations during the initial 10 years of the prospective Euro-Lupus Cohort are slightly lower than those reported in several large series from the USA and Asia in the last decade. These lower frequencies of SLE clinical manifestations could be due to genetic or environmental differences between Europeans and Americans or Asians but could also reflect the effect of medical care during the study. Of interest, there was a lower frequency of most SLE manifestations during the last 5 years of this prospective study (1995–2000) (Cervera *et al* 2003), compared with the cumulative clinical manifestations during the initial 5 years of the study (1990–1995). For example, the frequency of active lupus nephropathy during the last 5 years was 6.8% compared to a cumulative prevalence of 22.2% during the initial 5 years of the study (table 16). The lower frequencies in the last 5 years probably reflect the effect of therapy and of medical care during the study, but may also reflect natural remissions which may occur with advancing age and the menopause.

Over the past 50 years, survival has improved dramatically in patients with SLE. In the Euro-Lupus Cohort, at 10 years from entry into the study survival was 92%. The slightly higher survival in this European cohort

SLE manifestations	1990–2000 (n=1000) No. (%)	1990–1995 (n=1000) No. (%)	1995–2000 (n=840)* No. (%)	p Value†
Malar rash	311 (31.1)	264 (26.4)	144 (17.1)	<0.001
Discoid lesions	78 (7.8)	54 (5.4)	50 (5.9)	
Subacute cutaneous lesions	67 (6.7)	46 (4.6)	21 (2.5)	0.023
Photosensitivity	229 (22.9)	187 (18.7)	112 (13.3)	0.002
Oral ulcers	125 (12.5)	89 (8.9)	61 (7.3)	
Arthritis	481 (48.1)	413 (41.3)	240 (28.6)	<0.001
Serositis	160 (16)	129 (12.9)	52 (6.2)	<0.001
Nephropathy	279 (27.9)	222 (22.2)	57 (6.8)	<0.001
Neurologic involvement	194 (19.4)	136 (13.6)	97 (11.5)	
Thrombocytopenia	134 (13.4)	95 (9.5)	76 (9.0)	
Haemolytic anaemia	48 (4.8)	33 (3.3)	24 (2.9)	
Fever	166 (16.6)	139 (13.9)	62 (7.4)	<0.001
Raynaud's phenomenon	163 (16.3)	132 (13.2)	74 (8.9)	0.003
Livedo reticularis	70 (7.0)	55 (5.5)	30 (3.6)	
Thrombosis	92 (9.2)	72 (7.2)	41 (4.9)	0.049
Myositis	43 (4.3)	40 (4)	11 (1.3)	<0.001

*Number of patients that continued in the study in 1995.
†All p values are a comparison between the frequencies in the 1990–1995 and in the 1995–2000 periods.

Table 16 Clinical manifestations related to systemic lupus erythematosus (SLE) in the Euro-Lupus Cohort during the 10 year prospective study (1990–2000)

when compared with the US series may be due to the predominance of Caucasian patients in the present cohort (97%). Thus, it is known that race influences outcome in SLE, and blacks and Hispanic Americans of mestizo or native Indian origin have a poorer outcome. The improved survival of patients with SLE has been associated with an alteration in the patterns of mortality. The Euro-Lupus Cohort showed a similar percentage of active SLE (27%), thromboses (27%), and infections (25%) as the main causes of death in the 10 year observational period. However, it is important to stress that when the causes of death during the initial 5 years were compared with those during the ensuing 5 years, active SLE and infections (29% each) appeared to be the most common causes during the initial 5 years, while thromboses (26%) became the most common cause of death during the last 5 years (table 17).

Causes of death	1990–2000 (total = 68) No. (%)	1990–1995 (total = 45) No. (%)	1995–2000 (total = 23) No. (%)
Active systemic lupus erythematosus (SLE)	18 (26.5)	13 (28.9)	5 (21.7)
Multisystem	5 (7.4)	4 (8.9)	1 (4.3)
Renal	6 (8.8)	4 (8.9)	2 (8.7)
Cardiopulmonary	3 (4.4)	3 (6.7)	0 (0)
Haematologic	1 (1.5)	1 (2.2)	0 (0)
Neurologic	3 (4.4)	1 (2.2)	2 (8.7)
Infections	17 (25)	13 (28.9)*	4 (17.4)‡
Bacterial sepsis	15 (22.1)	11 (24.4)	4 (17.4)
Pulmonary	6 (8.8)	4 (8.9)	2 (8.7)
Abdominal	5 (7.4)	4 (8.9)	1 (4.3)
Urinary	4 (5.9)	3 (6.7)	1 (4.3)
Fungal	1 (1.5)	1 (2.2)	0
Viral	1 (1.5)	1 (2.2)	0
Thromboses	18 (26.5)	12 (26.7)	6 (26.1)
Cerebral	8 (11.8)	5 (11.1)	3 (13)
Pulmonary	4 (5.9)	3 (6.7)	1 (4.3)
Coronary	5 (7.4)	3 (6.7)	2 (8.7)
Other	1 (1.5)	1 (2.2)	0 (0)
Malignancies	4 (5.9)	3 (6.7)	1 (4.3)
Breast	1 (1.5)	1 (2.2)	0 (0)
Lung	2 (2.9)	1 (2.2)	0 (0)
Lymphoma	1 (1.5)	1 (2.2)	0 (0)
Gastric bleeding	2 (2.9)	2 (4.4)†	0 (0)
Obstetric	1 (1.5)	1 (2.2)	0 (0)
Suicide	1 (1.5)	1 (2.2)	0 (0)
Surgical	1 (1.5)	1 (2.2)	0 (0)
Accident	1 (1.5)	0 (0)	1 (4.3)
Unknown	14 (20.6)	7 (15.6)	7 (30.4)

*In 6 patients, the cause of death was attributed to infection plus other factors (active SLE in 5 and thrombosis in 1). †In 2 patients the cause of death was attributed to gastric bleeding plus other factors (active SLE in 1 and infection in 1). ‡In 1 patient the cause of death was attributed to infection plus active SLE.

Table 17 Causes of death in the Euro-Lupus Cohort during the 10 year prospective study (1990–2000)

Summary points

- SLE is a multisystem autoimmune disorder with a broad spectrum of clinical presentations.
- There is a peak age of onset among women between the late teens and early 40s and a female to male ratio of 9:1.
- Ethnicity, age at onset, gender, and clinical and immunological features, especially antiphospholipid antibodies at onset, can all influence the prevalence and clinical disease evolution.
- The pathogenesis of SLE is complex and includes genetic, environmental, ethnic, and immunological factors.
- Criteria for classification of SLE as well as for describing central nervous system disorders and the pathologic description of lupus nephritis have been validated.
- Several systems have been validated for describing disease activity and the SLICC/ACR criteria are used to describe damage.
- Currently there are no diagnostic criteria for the disease. The ACR classification criteria may be used for diagnostic purposes but sensitivity—especially early in the disease—is low. To date, lupus remains a clinical diagnosis of exclusion.
- The antiphospholipid syndrome may co-exist with SLE and contribute to morbidity and mortality.
- There have been significant improvements in long term survival, but patients with SLE still have higher risks of premature mortality compared to the general population.
- Factors contributing to mortality include major organ involvement, especially nephropathy, thrombosis, accelerated atherosclerosis, and an increased risk of cancer.

20 Recommended textbooks

Wallace D, Hahn BHH, eds. *Dubois lupus erythematosus*, 7th edn. Lippincott Williams and Wilkins, 2007.

Lahita G, ed. *Systemic lupus erythematosus*, 5th edn. Amsterdam: Elsevier, 2011.

21 SLE: internet sites

http://www.lupus.org
http://www.lupusuk.com
http://www.mayoclinic.com/health/lupus/DS00115
http://www.lupus.org.uk
http://www.lupusresearchinstitute.org

22 Key references

(complete list of references available at http://www.eular.org/edu_textbook.cfm)

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