

19.11.2 Systemic lupus erythematosus and related d

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19.11.2 Systemic lupus erythematosus and related disorders 4499 Physicians treating patients with autoimmune rheumatic diseases need to be constantly aware of the possibility of organ involvement, prompt diagnosis and treatment being necessary to prevent irreversible end organ damage. The immunosuppressive therapy used will be similar, regardless of the particular diagnosis. Precise identification of an autoimmune rheumatic disease is reliant upon clinical and laboratory features, of which the presence of antinuclear antibody (and its pattern of staining), antibodies to extractable nuclear antigens, disease-specific antibodies, or antineutrophil cytoplasmic antibody are crucial. There are many instances where the disease may not be precisely labelled, and up to 20% of patients have features of several autoimmune rheumatic diseases, most commonly systemic lupus erythematosus/scleroderma and systemic lupus erythematosus/rheumatoid arthritis, or those who would be considered to have an undifferentiated autoimmune rheumatic disease. In the case of these latter diseases, treatment is guided according to disease features and the pattern of organ/system involvement. FURTHER READING Aletaha D, et al. (2010). 2010 rheumatoid arthritis classification criteria: an American College of Rheumatology/European League Against Rheumatism collaborative initiative. *Ann Rheum Dis*, 69, 1580–8. Goldblatt, F, O'Neill, S (2013). Clinical aspects of autoimmune rheumatic disease. *Lancet*, 382, 797–808. Jennette J, et al. (2013). 2012 Revised International Chapel Hill consensus

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19.11.2 Systemic lupus erythematosus and related disorders

Anisur Rahman and David A. Isenberg

ESSENTIALS Systemic lupus erythematosus is an autoimmune rheumatic disorder that can present with symptoms in almost any organ or system of the body. It is 10 times commoner in women than men, and commoner in Afro-Caribbeans than in other ethnic groups. Aetiology is multifactorial, incorporating genetic, hormonal, and environmental elements. No single abnormality of the immune system can be considered responsible, pathogenesis depending on the interplay of several different factors, including autoantibodies, T lymphocytes, cytokines, the complement system, and apoptosis. Clinical features Common symptoms are constitutional (fatigue, anorexia), musculoskeletal (arthralgia/arthritis, myalgia), dermatological (alopecia, butterfly rash, vasculitic skin lesions, purpura), cardiopulmonary (breathlessness, pleurisy), and neurological (migraine, seizures, depression, psychosis). Examination may show evidence of weight loss, low-grade fever, lymphadenopathy, arthritis (but rarely synovitis or deformity), skin rash, oral ulcers, dry eyes/mouth, pleural rub, and peripheral neuropathy (usually sensory). Investigation and diagnosis Investigation commonly reveals abnormalities in the following systems: (1) renal—proteinuria, microscopic haematuria, impaired glomerular filtration rate; (2) haematological—anaemia, leucopenia, lymphopenia, thrombocytopenia; and (3) cardiopulmonary—pulmonary function abnormalities. The diagnosis of systemic lupus erythematosus is often made on the basis of published classification criteria, but in essence consists of a combination of clinical features, serological criteria, and immunological abnormalities. Prognosis and management Systemic lupus erythematosus can kill (mortality c.10% at 10 years from diagnosis), but it may run a fairly indolent course in which an initial flare is followed by many years of low-grade activity. General treatment measures include (1) rest—as appropriate; (2) avoidance of overexposure to sunlight; (3) attention to modifiable cardiovascular risk factors—women with lupus between 35 and 45 years have a 50× increased risk of coronary disease; and (4) prophylaxis/treatment of osteoporosis—usually induced by steroid therapy. Mild disease—patients whose disease activity is confined to arthralgia, tiredness, and/or mild rash can often be treated symptomatically (e.g. with simple analgesics and/or nonsteroidal anti-inflammatory agents, often with hydroxychloroquine added). Treatment of flares of disease—corticosteroids and immunosuppressant agents are used. A mild flare of arthralgia, myalgia, and general fatigue may be alleviated by a single intramuscular dose of corticosteroid. More severe flares of arthritis, pleuritis, or pericarditis require oral prednisolone (20–40 mg daily). Renal flares require the most aggressive treatment, generally involving both corticosteroids (high-dose oral and/or intravenous pulse) and cyclophosphamide/mycophenolate mofetil. Biological therapies are increasingly being used, with belimumab and rituximab most commonly prescribed. Uncontrolled studies have suggested that it may become possible to use biologics in early disease to avoid using corticosteroids. Antiphospholipid antibody syndrome—immunosuppression is rarely useful; lifelong anticoagulation is advised for those who have suffered recurrent thromboses or cerebral infarcts. Pregnancy—systemic lupus erythematosus may be exacerbated during the pregnancy. Babies born to mothers with lupus who have anti-Ro and/or anti La antibodies may suffer neonatal lupus, incorporating a transient rash and (less commonly) permanent heart block.

section 19 Rheumatological disorders 4500 Introduction Systemic lupus erythematosus (SLE) is an autoimmune rheumatic disorder that can present with symptoms in almost any organ or system of the body. Classification criteria should be used to make the diagnosis. These are shown in Tables 19.11.2.1 and 19.11.2.2 and demonstrate the wide variety of clinical and serological features that are associated with this condition. There are two alternative sets of criteria. Those published by the American College of Rheumatology (ACR) in 1997 (Table 19.11.2.1) are most widely used in scientific papers and state that at least four of 11 criteria must be fulfilled. The newer criteria published by the Systemic Lupus International Collaborative Clinics (SLICC) group in 2012 (Table 19.11.2.2) stress that at least one clinical and one serological criterion should be fulfilled, and that biopsy-proven lupus nephritis in the presence of antinuclear antibodies (ANA) or anti-dsDNA antibodies is sufficient to diagnose systemic lupus erythematosus. The Systemic Lupus International Collaborating Clinics criteria are more sensitive, but less specific, for systemic lupus erythematosus than the older criteria. It is important not to be too dogmatic in searching for 'pathognomonic' features of the disease, e.g. although the characteristic butterfly rash over the face is perhaps the best-known sign of systemic lupus erythematosus, many patients will never develop such a rash.

Historical perspective Although the term 'lupus' has been used for several hundred years, its meaning was vague until Cazenave and Clausit coined the term 'lupus erythematosus' in 1852, confining the condition to a skin rash affecting the face. The photosensitive nature of the rash (noted by Hutchinson in 1879) and the accompanying internal organ involvement (Kaposi in 1872) helped to frame the current usage of the term 'systemic lupus erythematosus' to define a multisystem disorder rather than a purely cutaneous condition. The development of the LE cell test (Hargreaves in 1948) and more importantly (and more specifically) the identification of anti-double-stranded (ds) DNA antibodies by four different laboratories (in 1957) facilitated the classification criteria by which systemic lupus erythematosus is now widely recognized.

Aetiology and pathology The aetiology is multifactorial, incorporating genetic, hormonal, and environmental elements. The best-established genetic link is with the presence of null alleles of genes encoding early components of the complement cascade (C1q, C2, and C4). Over 90% of patients homozygous for C1q deficiency and 75% of those with C4 deficiency develop a lupus-like disease (similar clinical features but a relative paucity of antibodies). Major histocompatibility complex (MHC) genes, particularly HLA A1, B8, and DR3, have also been associated with the presence of lupus in family studies, although part of this association may be due to linkage disequilibrium with the C4 and C2.

Table 19.11.2.1 Criteria of the American College of Rheumatology for the classification of systemic lupus erythematosus

- 1 Malar rash
- 2 Discoid rash
- 3 Photosensitivity
- 4 Oral ulcers
- 5 Arthritis
- 6 Serositis (a) Pleuritis or (b) Pericarditis
- 7 Renal disorder (a) Proteinuria >0.5 g/24 h or $3+$, persistently or (b) Cellular casts
- 8 Neurological disorder (a) Seizures or (b) Psychosis (having excluded other causes, e.g. drugs)
- 9 Haematological disorder (a) Haemolytic anaemia or (b) Leucopenia or $<4.0 \times 10^9$ /litre on two or more occasions (c) Lymphopenia or $<1.5 \times 10^9$ /litre on two or more occasions (d) Thrombocytopenia $<100 \times 10^9$ /litre
- 10 Immunological disorders (a) Raised antinative DNA antibody binding or (b) Anti-Sm antibody or (c) Positive finding of antiphospholipid antibodies
- 11 Antinuclear antibody in raised titre (in the absence of drugs known to be associated with drug-induced lupus)

a '... a person shall be said to have SLE if four or more of the 11 criteria are present, serially or simultaneously, during any interval of observation.' Tan EM et al. (1982). The 1982 revised criteria for the classification of systemic lupus erythematosus. *Arthritis and Rheumatism* 25, 1271-7.

Table 19.11.2.2 The Systemic Lupus International Collaborative Clinics Criteria for the classification of systemic lupus erythematosus

Clinical criteria

Immunologic criteria

Acute cutaneous lupus

ANA

Chronic

cutaneous lupus Anti-dsDNA Oral or nasal ulcers Anti-Sm Non-scarring alopecia Antiphospholipid antibodies (lupus anticoagulant and/or anticardiolipin and/or anti- β -2-GPI) Arthritis Low complement (C3, C4, or CH50) Serositis Direct Coombs test in the absence of haemolytic anaemia Renal involvement—measurement of urine protein representing 500 mg/ day or red cell casts in urine Neurologic Haemolytic anaemia Leucopenia $<4000 /\text{mm}^3$ or lymphopenia $<1000 /\text{mm}^3$ Thrombocytopaenia $<100\,000 /\text{mm}^3$

A person will be said to have systemic lupus erythematosus if four or more criteria are present, but this must include at least one clinical criterion and one immunologic criterion. All four need not be present concurrently. There is an exception in the case of renal disease, where systemic lupus erythematosus can be diagnosed if there is biopsy-proven lupus nephritis with positive ANA or anti-dsDNA (i.e. only two criteria need be fulfilled). Petri M et al. (2012) Derivation and validation of Systemic Lupus International Collaborative Clinics classification criteria for systemic lupus erythematosus. *Arthritis and Rheumatism* 64, 2677–86.

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4501 genes also present in that region of chromosome 6. Genome-wide association studies have identified other lupus-associated genes, which can be classified into three groups; those associated with the innate immune response, those associated with lymphocyte activation, and those associated with clearance of immune complexes. Hormones are likely to play a role in pathogenesis because systemic lupus erythematosus is far more common in women than in men. However, attempts to treat the condition with hormonal agents have been largely disappointing. Viruses may be important in triggering the autoimmune dysfunction that leads to the production of pathogenic autoantibodies in systemic lupus erythematosus. Reactivation of BK polyomavirus infection, in particular, has been associated with the presence of antibodies to dsDNA in Norwegian studies, but not confirmed in other populations. Exposure to ultra-violet light can precipitate a flare of lupus, usually (but not always) in the skin. This accounts for the phenomenon of photosensitivity seen in many patients. Certain drugs induce a form of systemic lupus erythematosus that is generally characterized by the presence of antihistone rather than anti-dsDNA antibodies, a milder course of disease, and total remission when the causative drug is withdrawn. The most common drugs involved are isoniazid, procainamide, hydralazine, minocycline, penicillamine, tumour necrosis factor blocking agents and anticonvulsants (see Chapter 19.12). Abnormalities of the immune system

No single abnormality of the immune system can be considered to be the sole cause of systemic lupus erythematosus. The pathogenesis of the disease depends on the interplay of several different factors, the relative importance of which may differ from one patient to another. These include autoantibodies, T lymphocytes, cytokines, the complement system, and apoptosis. Research to unravel this complex system of inter-related factors has been carried out by studying properties of cells and tissue components derived from patients with systemic lupus erythematosus and by studying mouse models of the condition. B lymphocytes and autoantibodies

Autoantibodies are those that bind to antigens present within the tissues of the body itself. A wide variety of different autoantibodies has been described in systemic lupus erythematosus. Those most frequently reported are listed in Table 19.11.2.3. Anti-dsDNA antibodies have been cited widely as possible causative agents in systemic lupus erythematosus, particularly in lupus glomerulonephritis. Raised titres of anti-dsDNA antibodies are found in 50 to 70% of patients with systemic lupus erythematosus, but hardly ever in healthy people or those with other diseases. Levels of these antibodies often rise and fall with disease activity, and deposits of anti-dsDNA antibodies occur in the glomeruli of patients with lupus nephritis. In experimental murine models of systemic lupus erythematosus, monoclonal anti-dsDNA antibodies can be shown to deposit in the

glomeruli and to be associated with proteinuria. The titre of anti-dsDNA antibodies present in the bloodstream of patients with systemic lupus erythematosus can be a useful indicator of disease activity. It is increasingly clear, however, that not all anti-dsDNA antibodies are equally likely to be associated with tissue damage. Antibodies of the IgG isotype, which show specific high-affinity binding to dsDNA, generally show the closest association

Antibodies	Antigen/epitope	Approximate prevalence (%)
Intracellular DNA	dsDNA, (ssDNA)	50–70
Histone	H1, 2A, 2B, 3, 4	30–80
Sm	B/B', D, E, F, G	30 (Afro-Caribbean), c.10 (Caucasian)
U1RNP	A, C, 70 kDa ribonucleoprotein	20–35
rRNP	Three subunits: 38, 19, 17 kDa	5–15
Ro/SS-A	60, 52 kDa protein bound to cytoplasmic RNA (hY1–hY5)	25–35
La/SS-B	48 kDa protein bound to variety of RNA, U1RNA, hY RNA	10–15
Heat shock protein (hsp)	hsp 90	30
hnRNP A2	protein (also known as RA-33)	30
Cell membrane	Cardiolipin Phospholipids	20–40
Neuronal antigen	Expressed on neuronal cell lines grown in vitro	70–90 (+CNS), c.10 (–CNS)
Lymphocyte HLA component	c.75 (IgM), c.45 (IgG)	
Red cell Non-Rh related		<10
Platelet		<10
Extracellular		
Rheumatoid factor	Fc region of IgG	c.25
C1q	Complement component	20–45

section 19 Rheumatological disorders 4502 with disease activity in patients and the greatest ability to cause renal damage in experimental models. More recent work has suggested that a subpopulation of B lymphocytes, called regulatory B cells and characterized by the production of IL-10, may play a suppressive role in autoimmunity, and that dysfunction of these cells may also contribute to development of systemic lupus erythematosus. Why are autoantibodies produced in patients with systemic lupus erythematosus? Studies of monoclonal anti-dsDNA antibodies derived from patients or mice indicate that those that show the isotype and binding properties described here often show sequence characteristics suggestive of antigen-driven somatic mutation. This is the process whereby mutations accumulate in the expressed immunoglobulin gene sequences of a B lymphocyte under the influence of a particular antigen. The mutations are accumulated nonrandomly, such that the end-result is an increase in specificity and affinity of binding. This process is dependent on help from T lymphocytes and on the presence of an appropriate antigen. Naked mammalian DNA is, however, a poor immunogen in experimental animals, and the concentration of free DNA in the bloodstream is low even in patients with systemic lupus erythematosus. It is therefore believed that the antigen that stimulates production of high-affinity anti-dsDNA antibodies is probably a complex of DNA and protein. Cell fragments (blebs) derived from apoptosis are the most important source of antigens involved in stimulating both T cells and B cells in systemic lupus erythematosus. Nucleosomes in these blebs can stimulate production of antinucleosome and anti-dsDNA antibodies, whereas other antigens such as Ro and anionic phospholipids can trigger production of some of the other antibodies seen in Table 19.11.2.3. Studies on stored blood samples (taken routinely as part of military protocol) from healthy American soldiers who subsequently developed systemic lupus erythematosus show that the production of autoantibodies can pre-date the onset of the disease by up to 10 years. How do autoantibodies exert their pathogenic effects in tissues? Deposition of IgG and complement in inflamed tissues such as kidney and skin is a consistent feature of active systemic lupus erythematosus. The pathogenic potential of autoantibodies in systemic lupus erythematosus (particularly IgG anti-dsDNA) may therefore rest on their ability to deposit in these tissues and to activate complement. Much of the work designed to find out why autoantibodies are deposited in target tissues has concentrated on lupus nephritis. Originally, it was felt that DNA-anti-DNA immune complexes would form in the bloodstream and accumulate in glomeruli as the blood was

filtered there. However, it has not been possible to demonstrate large quantities of such complexes in the blood of patients with systemic lupus erythematosus, although their clearance may well be abnormal due to complement deficiency. The key determinant is the presence in the tissue of an antigen to which specific autoantibodies can bind. Anti-dsDNA antibodies may be targeted to the kidney due to cross-reaction with cell surface proteins there, or may deposit due to an interaction with histones and heparan sulphate. According to this latter model, anti-dsDNA antibodies bind to DNA in nucleosomes, and the positively charged histones in these nucleosomes bind to negatively charged heparan sulphate in the renal basement membrane. Electron microscope studies have indeed demonstrated the presence of nucleosome deposits that colocalize with deposited IgG in renal biopsies from patients with lupus nephritis. Anti-Ro antibodies can deposit in the fetal heart of anti-Ro positive pregnant women with systemic lupus erythematosus, yet not in the mother's heart. This is believed to be because Ro is expressed on the surface of cardiomyocytes during development of the fetal heart, but not in adults. Antiphospholipid antibodies Antiphospholipid (APL) antibodies may be present in healthy people or in those with infectious diseases such as syphilis, in which case they have no adverse effects. They are found in 30-40% of patients with systemic lupus erythematosus. In some, but not all of these patients, the APL antibodies may cause arterial or venous thromboses or miscarriages; this is known as the antiphospholipid syndrome (APS). APS occurring in the absence of systemic lupus erythematosus or any other autoimmune rheumatic disease is called primary APS. Although it was previously thought that APL antibodies exerted their effects almost wholly through promotion of thrombus formation, it is now clear that they may have many other direct effects on platelets, monocytes, endothelial cells, and the trophoblast. The mechanism by which thrombosis is altered is not fully understood, but it has become clear that APL antibodies found in APS often bind to protein antigens associated with phospholipids rather than the phospholipids themselves. The most important of these proteins is β 2-glycoprotein I, and a direct test for anti- β 2-glycoprotein I is one of the three diagnostic tests for APS. T lymphocytes As the process of antigen-driven selection of mutations in B lymphocytes is dependent on help from helper T lymphocytes, it would be reasonable to suppose that antigen-specific T cells might also contribute to the pathogenesis of the disease. The isolation of T-cell clones reactive with DNA and/or DNA-binding proteins such as histones has been demonstrated from both patients with systemic lupus erythematosus and murine models of the disease. The clones frequently show specificity for histone epitopes that are cryptic (i.e. not exposed) in normal chromatin. These results reinforce the idea that the antigenic stimulus for production of both pathogenic T cells and autoantibodies in systemic lupus erythematosus may be a DNA/ histone complex rather than DNA alone. Patients with systemic lupus erythematosus have decreased levels of the subset of T cells carrying the CD4 and CD45 surface markers. This population may be involved in stimulation of suppressor T lymphocytes such that suppression in these patients is insufficient to prevent the production and survival of autoreactive B-lymphocyte and helper T-lymphocyte clones. Invariant natural killer T cells (iNKT cells) are a small population of specialized immunomodulatory T cells that are stimulated specifically by lipids and which appear to be dysfunctional in some patients with systemic lupus erythematosus. Apoptosis and complement The links between apoptosis, complement, and lupus are complicated. Murphy Roths Large (MRL) *lpr/lpr* mice are deficient in

19.11.2 Systemic lupus erythematosus and related disorders 4503 apoptosis because they lack the Fas protein that plays a major role in promoting this process. These mice develop a disease very similar to systemic lupus erythematosus, with death resulting from glomerulonephritis. One

possible reason for this might be the failure of the immune system to delete by apoptosis autoreactive clones of T or B lymphocytes, which are then able to cause autoimmune disease. By contrast, humans with the equivalent genetic lesion to MRL lpr/lpr mice do not develop systemic lupus erythematosus, and other strains of mice show an accumulation of apoptotic debris within nephritic kidneys, which resemble those of systemic lupus erythematosus. A simple deficiency in apoptosis is therefore unlikely to be the underlying mechanism in systemic lupus erythematosus. Apoptosis leads to the production of surface blebs of cellular material. These blebs include several antigens to which autoantibodies develop in systemic lupus erythematosus, notably DNA and associated nuclear proteins and negatively charged phospholipids. A deficiency in the clearance of products of apoptosis has been demonstrated in patients with systemic lupus erythematosus which might allow the production of a wide spectrum of autoantibodies. Removal of immune complexes containing such potentially antigenic material may be compromised in patients with systemic lupus erythematosus. Monocytes derived from such patients show reduced phagocytosis of cell debris in vitro. This process may be complement dependent, as people with homozygous C2 deficiency process immune complexes very differently from normal controls. Administration of fresh frozen plasma to such (rare) patients as a source of complement is successful in ameliorating symptoms and in normalizing (albeit transiently) their processing of immune complexes. C1q knockout mice develop a form of glomerulonephritis similar to that seen in systemic lupus erythematosus, and their kidneys are characterized by accumulations of apoptotic debris. In fact knockout mice deficient in both the classic and alternative pathways of complement develop this form of glomerulonephritis, showing that in this model the protective effects of complement outweigh its role as an effector of inflammation. Similarly, as noted earlier, humans homozygous for C1q deficiency develop a form of systemic lupus erythematosus with the frequent occurrence of nephritis.

Cytokines enhance the ability of cells to interact and are therefore critically important in abnormalities in both T- and B-cell functions seen in patients with lupus. Table 19.11.2.4 summarizes the major differences between the different subsets of T-helper (Th) cells in terms of their cytokine profiles and functions. The balance between cytokines from Th1 and Th2 cells is essential in determining the outcome of the immune response. Lupus might be expected to be a disease in which Th2 cells predominate, resulting in excessive help for B cells and overproduction of antibodies. In support of this notion, increased levels of interleukin 10 (IL-10) have been found in patients with lupus. This cytokine promotes secretion of antibodies by B lymphocytes, but suppresses Th1 cells and thus impairs cell-mediated immunity, a characteristic feature of the disease. Both macrophage and natural killer cell-mediated cytotoxicity are frequently impaired in patients with lupus. Interferon- γ -induced enhancement of both types of cytotoxicity is also impaired, despite normal levels of interferon- γ production by lupus Th1 cells. Accessory cells in lupus seem to produce insufficient amounts of IL-1 to provide the necessary activation signals for T cells. Both CD4⁺ and CD8⁺ T cells have been described as producing either normal or decreased amounts of IL-2 in response to exogenous antigens. Such a reduction is likely to have a profound effect on T-cell responses. Interferon- α is increasingly recognized as playing a major role in the development of systemic lupus erythematosus. Levels of this cytokine are raised in patients with systemic lupus erythematosus, genetic studies show that interferon-related genes are risk factors for systemic lupus erythematosus, and gene expression studies show that such genes are activated in patients with the disease.

Lupus in Table 19.11.2.4 (a) Subsets of CD4⁺ T cells; (b) Cytokine profiles in patients with active systemic lupus erythematosus

Function	Cytokines
(a) Subsets of CD4 ⁺ T cells	T-helper 1 cell
Cell-mediated immunity	IFN- γ , IL-10 (humans only), IL-12, TNF α
T-helper 2 cell	B-cell help
	IL-4, IL-10
(b) Cytokine profiles in patients with active systemic	

lupus erythematosus Cytokine Serum levels Spontaneous Stimulation in vitro IFN- γ $\uparrow$ Low $\downarrow$ TNF α $\uparrow$ (or normal) $\downarrow$ (DR2, DQw1; $\uparrow$ nephritis), $\uparrow$ (DR3, 4; $\downarrow$ nephritis) $\downarrow$ IL-1 n.d. $\uparrow$ PBM production $\downarrow$ Monocyte production IL-2 $\uparrow$ Low $\downarrow$ IL-4 n.d. Low Low IL-6 $\uparrow$ $\uparrow$ – IL-10 $\uparrow$ (or normal) $\uparrow$ (or normal) Normal IFN- γ , interferon- γ ; n.d., not detected; PBM, peripheral blood mononuclear cell; TNF α , tumour necrosis factor- α . a Serum levels of cytokines are difficult to interpret since these may be affected by soluble cytokine receptors which are shed from cells. Among the known shed receptors are those for IL-1, IL-2, IL-6, TNF α , and IFN- γ . Soluble TNF α R and IL-2R levels are increased in systemic lupus and correlate with disease activity and lupus nephritis.

section 19 Rheumatological disorders 4504 the NZB/NZW mouse model of lupus can be accelerated by the presence of interferon- α . Cytokines such as interferon- α and IL-10 are increasingly being considered as possible targets for future therapeutic agents in lupus. There is some evidence that TNF α may play a protective, rather than pathogenic role in systemic lupus erythematosus, partially from murine models, and partly from the observation that some patients treated with anti-TNF α agents for other diseases develop anti-dsDNA antibodies. Histopathology The two tissues most often subjected to biopsy in systemic lupus erythematosus are the skin and kidneys. Skin biopsies are chiefly carried out to facilitate the diagnosis of an atypical rash. If systemic lupus erythematosus is suspected, it is important to take a sample of apparently normal skin as well as skin from the rash. Both should show deposition of IgG and complement at the dermo-epidermal junction (Fig. 19.11.2.1). Renal biopsy may be performed to establish the diagnosis of systemic lupus erythematosus when this is not certain, e.g. in a patient with a poorly characterized multisystem disease with renal involvement. In a patient with known systemic lupus erythematosus it may be employed to help determine prognosis and decide on treatment when renal function is deteriorating, e.g. with the development of nephrotic syndrome and/or declining glomerular filtration rate (GFR). The glomerular pathology can be graded on a scale of I to VI according to the International Society of Nephrology/Renal Pathology Society criteria, and scores for activity and chronicity can be used to determine appropriate treatment and the risk of a progressive decline in renal function. The subject of renal pathology in systemic lupus erythematosus is considered further in Chapter 21.10.3. Epidemiology The incidence of systemic lupus erythematosus in the United Kingdom is about five cases/100 000 people per year and the prevalence is 1 in 1000. It occurs about 10 times more frequently in women than in men, and is more common in Black ethnic groups. A study published in 2014 using the United Kingdom Clinical Practice Research Datalink gave the prevalence of systemic lupus erythematosus as 518 per 100 000 in people of Black Caribbean ethnicity, 180 per 100 000 in those of Black African ethnicity, and 135 per 100 000 in white people. The figures for different Asian groups ranged from 143 to 193 per 100 000. These gender and racial differences are broadly consistent with those reported from studies in the United States of America and the Caribbean, although the reported prevalence of systemic lupus erythematosus in Africa is much lower. Clinical features Systemic lupus erythematosus is a chronic condition punctuated by flares of acute activity. The overall severity of the disease in a particular patient depends on the nature and frequency of these flares and the long-term permanent damage that they cause. The diverse clinical features of systemic lupus erythematosus mean that the disease may present to any of a number of different specialists, including rheumatologists, dermatologists, nephrologists, and general physicians. It is important to be aware of systemic lupus erythematosus as a possible diagnosis in any patient, especially a woman aged between 15 and 50, in whom several different organs are inflamed either

simultaneously or sequentially. The frequency of occurrence of symptoms in various organs is shown in Table 19.11.2.5. Table 19.11.2.5 Cumulative prevalence of clinical features in patients with systemic lupus erythematosus

Clinical feature	Approximate cumulative prevalence (%)
Musculoskeletal	
Arthralgia/arthritis	90
Tenosynovitis	20
Myalgia	50
Myositis	5
Cardiopulmonary	
Shortness of breath	40
Pleurisy	35
Pleural effusion	25
Lupus pneumonitis	5
Interstitial fibrosis	5
Pulmonary function abnormalities	85
Cardiomegaly	20
Pericarditis	15
Cardiomyopathy	10
Myocardial infarction	5

Fig. 19.11.2.1 Immunofluorescence microscopy showing deposition of IgG at the dermoepidermal junction in the skin of a patient with systemic lupus erythematosus (sometimes called the lupus band test). (continued)

19.11.2 Systemic lupus erythematosus and related disorders 4505 According to the classification criteria published by the American College of Rheumatology (see Table 19.11.2.1), systemic lupus erythematosus may be diagnosed where a patient meets at least 4 of the 11 criteria specified (though not necessarily at a single time). In everyday practice, however, these requirements may be too stringent, and systemic lupus erythematosus is often suspected on the basis of typical clinical findings in one organ or tissue combined with the presence of appropriate autoantibodies. The Systemic Lupus International Collaborating Clinics criteria (see Table 19.11.2.2) recognize this specifically in the case of nephritis.

Constitutional symptoms Patients with systemic lupus erythematosus find fatigue to be the most troublesome feature of the disease, excessive tiredness being both very common and difficult to treat. Hypothyroidism coexists in 5–10% of patients with systemic lupus erythematosus and so thyroid function tests should be performed in the fatigued patient. Fibromyalgia may coexist with systemic lupus erythematosus, in which case treating the patient with corticosteroids or immunosuppressants may not improve their fatigue. Weight loss and low-grade fever may both be indicative of disease activity. Lymphadenopathy is also recognized. The nodes may be markedly enlarged but show no diagnostic features on biopsy, which may nevertheless be necessary to exclude other conditions such as lymphoma.

Musculoskeletal involvement Arthralgia/arthritis is the most common symptom in systemic lupus erythematosus, occurring in 90% of patients. This may be severe but is rarely associated with frank synovitis. Effusions may occur but the fluid shows no diagnostic features. Erosive arthritis is uncommon, but up to 5% of patients may have an overlap syndrome with features of rheumatoid arthritis as well as systemic lupus erythematosus. These patients tend to have both serum rheumatoid factor and erosions. When progressive deformity of the hands does occur in systemic lupus erythematosus, it is usually due to an aggressive tenosynovitis and tendon dysfunction rather than to joint damage. This leads to reversible subluxation of the joints, often known as Jaccoud's arthropathy (Fig. 19.11.2.2). Development of hip pain in patients who have been treated with corticosteroids should raise the suspicion of avascular necrosis of the femoral head, which may be diagnosed on a plain radiograph or, in earlier stages, by MRI. Corticosteroids also promote osteoporosis, which can be diagnosed in the presymptomatic phase by bone density scanning, but may present with the acute pain of a vertebral fracture.

Clinical feature

Clinical feature	Approximate cumulative prevalence (%)
Gastrointestinal	
Anorexia	40
Nausea	15
Vomiting	<10
Diarrhoea	<10
Ascites	<10
Abdominal pain	30
Hepatomegaly	25
Splenomegaly	10
Renal	
Haematuria	10
Proteinuria	60
Casts	30
Serum albumin	<35 g/litre
Serum creatinine	>125 µmol/litre
Reduced 24-h creatinine clearance	35
Cerebral	
Depression	15
Psychosis	<5
Seizures	20
Hemiplegia	10
Cranial nerve lesions	10
Cerebellar signs	5
Meningitis	1
Migraine	40
Haematological	
Anaemia (iron deficiency)	30
Anaemia (of chronic disease)	75
Autoimmune haemolytic anaemia	15
Leucopenia	40
Lymphopenia	80
Thrombocytopenia	25
Circulating anticoagulants	15

Dermatological Butterfly rash 40 Erythematous maculopapular eruption 35 Discoid lupus 20 Relapsing nodular nonsuppurative panniculitis <5 Vasculitic skin lesions 40 Livedo reticularis 20 Purpuric lesions 40 Alopecia 20–50 Table 19.11.2.5 Continued Fig. 19.11.2.2 Deforming Jaccoud's arthropathy.

section 19 Rheumatological disorders 4506 Myalgia is common and a true myositis may occur in 5% of cases. Corticosteroid-induced proximal myopathy may also be a problem where these drugs have been used for long periods. Cutaneous and mucosal involvement Photosensitivity is very common, particularly in white female patients. Patients should be advised to avoid strong sunlight and to wear protective clothing and/or a high-factor sunblock. The butterfly rash over the malar area of the face occurs in up to one-third of patients (Fig. 19.11.2.3). A number of other forms of cutaneous involvement can occur, although these are less specific for systemic lupus erythematosus. These include maculopapular rash, discoid lesions, alopecia, panniculitis, and nailfold infarcts. Scarring alopecia may be particularly distressing and difficult to treat (Fig. 19.11.2.4). A variant of systemic lupus erythematosus in which cutaneous manifestations dominate is known as subacute cutaneous lupus. This condition is often associated with anti-Ro antibodies and may be exacerbated by smoking cigarettes. APL antibodies are associated with a nonraised lattice-like rash concentrated particularly over the thighs and arms: livedo reticularis (Fig. 19.11.2.5). Recurrent crops of oral ulcers are common enough to be recognized as one of the diagnostic criteria for systemic lupus erythematosus. About 15% of patients develop secondary Sjögren's syndrome; in this condition the dry eyes and mouth may respond to artificial tears and saliva. Renal involvement Glomerulonephritis is the most serious and potentially lethal manifestation of systemic lupus erythematosus. Its presence may be detected by the finding of haematuria and/or proteinuria on routine stick testing of the urine. It may present as the nephrotic syndrome or, less commonly, as a florid nephritis with haematuria, proteinuria, hypertension, and acute renal failure with red cell casts in the urine. The diagnosis and management of glomerulonephritis in systemic lupus erythematosus are more fully discussed in Chapter 21.10.3. It is important to be aware of the possibility of glomerulonephritis in any patient with systemic lupus erythematosus (Fig. 19.11.2.6). Measurement of blood pressure and analysis of urine should be carried out at each consultation. Early diagnosis and treatment are Fig. 19.11.2.3 Malar 'butterfly' rash. Fig. 19.11.2.4 Severe scarring alopecia. Fig. 19.11.2.5 Livedo reticularis.

19.11.2 Systemic lupus erythematosus and related disorders 4507 invaluable in avoiding deterioration of renal function to the extent that dialysis or renal transplantation become necessary. Patients with APS may develop a different type of renal lesion characterized by thrombi in small renal vessels rather than by glomerulonephritis. These patients develop hypertension and impairment of renal excretory function, detected as a fall in estimated GFR (eGFR), rather than proteinuria, and are best managed by anticoagulation rather than immunosuppression. Respiratory involvement The most common form of respiratory involvement in systemic lupus erythematosus is pleuritis, manifesting either as pleuritic chest pain or as breathlessness caused by pleural effusion. The lung parenchyma is more rarely involved, but fibrosis can occur. A patient with systemic lupus erythematosus may present with shortness of breath or chest pain for several reasons. Pulmonary emboli must be suspected in those with APL antibodies. Infections are common in immunosuppressed patients and rib fractures may occur, particularly in those rendered osteoporotic by treatment with corticosteroids. The shrinking lung syndrome is characterized by reduced lung volumes and poor respiratory reserve in the face of a normal appearance of the lung

parenchyma on computed tomography (CT). It is believed to arise from basal atelectasis in association with diaphragmatic dysfunction.

Cardiovascular involvement

The most common cardiac manifestation of systemic lupus erythematosus is pericarditis, which occurs in about 15% of patients. This generally presents with chest pain or an asymptomatic friction rub. Pericardial effusions may occur, but are rarely large enough to cause haemodynamic compromise. Myocarditis and endocarditis are less common, though post-mortem and echocardiographic studies suggest that both may occur without symptoms in a significant proportion of patients with systemic lupus erythematosus, e.g. the classic endocarditis described by Libman and Sacks is characterized by small vegetations that often do not cause murmurs or cardiac compromise, but which have been identified in up to 50% of patients with systemic lupus erythematosus post-mortem. It is increasingly recognized that atherosclerosis and its sequelae in the cerebral and cardiac circulations are more common in patients with systemic lupus erythematosus than in the general population. Overall, patients with systemic lupus erythematosus have 5–10-fold greater risk of developing cardiovascular disease than healthy people of the same age or sex. The cause of this increased risk is complex, but includes both generic factors such as smoking and hypertension, and disease-associated factors such as autoantibodies and use of corticosteroids.

Raynaud's phenomenon

Raynaud's phenomenon occurs in about a third of patients with systemic lupus erythematosus, although it is not usually as severe as that seen in systemic sclerosis. Vasculitis presents with a skin rash or ulcers that may be very difficult to heal, but rarely affects the internal organs.

Gastrointestinal involvement

Similar to pleuritis, peritonitis may occur in patients with systemic lupus erythematosus and must be considered in the event of abdominal pain, while remembering that patients with lupus are not protected from more common causes of this condition, e.g. appendicitis. Lupus mesenteric vasculitis is a rare but severe manifestation that presents with an acute abdomen. Involvement of the liver and pancreas is recognized but uncommon. The term 'lupoid hepatitis' was previously used for a form of autoimmune hepatitis characterized by the presence of autoantibodies, but these patients do not generally have any form of systemic lupus erythematosus and the term is misleading. Minor enlargements of the liver and/or spleen occur in 10 to 25% of cases, but these are usually asymptomatic and require no treatment.

Neuropsychiatric involvement

Systemic lupus erythematosus can affect the nervous system in many ways, so that the true incidence of neuropsychiatric involvement is difficult to quantify. Symptoms such as poor memory, change of personality, and depression or anxiety occur in many patients. It is difficult, however, to be sure whether these are caused by cerebral systemic lupus erythematosus or represent a reaction to the diagnosis and treatment of the disease. More florid presentations such as psychotic episodes and convulsions are well recognized but rare. By contrast to the milder symptoms noted here, these manifestations generally call for immunosuppression. In a large multinational study of over 1000 patients with systemic lupus erythematosus, 40% suffered from neuropsychiatric symptoms at some time during a two-year follow-up period, but in most cases these were mild, not due to active lupus, and did not require treatment with immunosuppression. Migraine occurs in up to 40% of patients with systemic lupus erythematosus, particularly in the presence of APL antibodies. Peripheral neuropathy can occur, and is usually sensory rather than motor. Cranial nerve palsies are less common, as is transverse myelitis (another feature linked to APL antibodies). Ocular involvement can include episcleritis, conjunctivitis, and the presence of cytoid bodies (white patches on the retina). Patients treated with high-dose steroids may develop cataracts.

Haematological involvement

A normochromic normocytic anaemia is frequently seen in systemic lupus erythematosus, particularly during periods of high disease

Fig. 19.11.2.6 Immunofluorescence microscopy showing deposition of IgG in

the glomerulus of a patient with lupus nephritis.

section 19 Rheumatological disorders 4508 activity. Microcytic iron-deficiency anaemia may result from blood loss from gastritis and ulcers in patients treated with nonsteroidal anti-inflammatory drugs. Anaemia may also result from chronic renal failure in lupus nephritis. A positive Coombs' test, signifying the presence of antibodies to red blood cells, is present in up to 20% of patients with systemic lupus erythematosus but does not always indicate haemolytic anaemia. The presence of lymphopenia (less than $1.5 \times 10^9/l$) is common, occurring in up to 80% of patients. Neutropenia may occur secondary to the use of cytotoxic drugs such as azathioprine or cyclophosphamide. Three different types of thrombocytopenia occur in systemic lupus erythematosus. The mildest form (often seen in patients with APL) is characterized by stable platelet levels of between 50 and $100 \times 10^9/l$, is rarely symptomatic, and usually requires no treatment. Other patients develop an acute autoimmune thrombocytopenia with levels dropping rapidly below $25 \times 10^9/l$, but usually rising when treated with oral steroids. A third group of patients present with thrombocytopenia alone, are treated with steroids, intravenous immunoglobulins, rituximab, or (very rarely these days) splenectomy, and some years later develop full-blown systemic lupus erythematosus. Thrombocytopenia is also a common feature of the APS. Other complicating disorders About 30% of lupus patients have another autoimmune condition, including Sjögren's syndrome (the most common, affecting some 15 to 20% of patients with lupus), APS (10 to 15%), autoimmune thyroid disease (hyper- or hypothyroidism, 5 to 10%), and (less frequently) rheumatoid arthritis, myasthenia gravis, coeliac disease, diabetes, and pernicious anaemia. Differential diagnosis Systemic lupus erythematosus is truly a chameleon of a disease. Its protean clinical manifestations mean that, theoretically, it could enter the differential diagnosis of virtually any unexplained symptom/feature. It is very important to remember, however, that most people with symptoms such as fatigue, joint pain, and rash do not have lupus, even though an internet search may have raised a patient's anxiety about that diagnosis. Among its general features, fever, weight loss, anorexia, and lymphadenopathy may easily be confused with a lymphoproliferative cancer, hence biopsy of a swollen lymph gland may often be required to be sure of the underlying problem. Polyarthralgia or polyarthritis in a young woman could be due to rheumatoid arthritis or lupus. As both rheumatoid factor and antinuclear antibodies can be found in either condition, there is obvious room for confusion, but anti-CCP antibodies (rheumatoid) and anti-dsDNA antibodies (lupus) are more specific tests that can usually resolve the matter. About 15% of patients presenting with 'idiopathic' thrombocytopenic purpura will eventually develop lupus. Unfortunately there are usually no clues at the onset to distinguish this 15% and very long-term follow-up may be needed. Antibodies to Ro, La, Sm, RNP (ribonucleoprotein), and dsDNA may be detectable in the serum of patients who will develop lupus up to 10 years before the disease becomes clinically manifest, and rarely these antibodies are found in the healthy relatives of patients. Occasionally lupus may present with isolated central nervous system (CNS) disease including convulsions, schizophrenic-like conditions, and neuropathies. As with many other clinical features, the most important consideration is to try to include systemic lupus in the differential diagnosis. The serological tests for it are widely available and will help to establish, quickly, the correct diagnosis. Clinical investigation Autoantibodies The most commonly requested test to screen for systemic lupus erythematosus is the antinuclear antibody assay. A positive antinuclear antibody test simply indicates that the patient's blood contains antibodies that will bind to the nuclei of a sample of cells used in the test. The test is a sensitive one because over 95% of patients with systemic lupus erythematosus are antinuclear antibody positive. Although a small group

of patients do seem to have persistently antinuclear antibody-negative systemic lupus erythematosus, the absence of antinuclear antibody in a patient with suspected lupus raises serious doubt about the diagnosis. The specificity of the antinuclear antibody test for systemic lupus erythematosus is not high. The titre of antibody represents the highest dilution of the patient's serum at which the test is still positive. Low-titre antinuclear antibody (1 in 10) is of little significance and may occur in healthy people. Higher titres (1 in 160 or more) are more worrying and are found in most patients with systemic lupus erythematosus and in some patients with other autoimmune conditions including rheumatoid arthritis, systemic sclerosis, and Sjögren's syndrome. However, some people with high-titre antinuclear antibody may be followed in rheumatology clinics for years without developing a frank autoimmune disease. The finding of a positive antinuclear antibody in a patient with symptoms suggestive of systemic lupus erythematosus should lead to a series of other autoantibody tests. These are listed in Table 19.11.2.3 together with the identity of the target antigen and the approximate prevalence of the antibodies. Anti-dsDNA antibody levels are particularly useful. This test is virtually specific for systemic lupus erythematosus (as is the anti-Sm antibody), especially if the immunoglobulins are of the IgG isotype. The anti-dsDNA result is usually quantified and this value is often a measure of the activity of the disease, but there is a group of patients who have persistently high anti-dsDNA antibody levels but no clinically active disease (serologically active, clinically quiescent). Long-term follow-up suggests that many but not all of these patients will eventually flare. In one study, trial patients were treated with high-dose corticosteroids on the basis of anti-dsDNA levels alone. In comparison with a control group treated only when symptoms or signs also suggested disease activity, the trial group had less disease activity overall and fewer flares. However, frequent large doses of corticosteroids resulted in significant side effects and several participants dropped out of this arm of the trial. Anti-dsDNA should be used only as an adjunct to the clinical impression of disease activity when deciding on a treatment regimen. Anti-Ro and anti-La antibodies are linked to concurrent Sjögren's syndrome. Mothers who have these antibodies have a higher incidence of neonatal lupus and should be advised about this before

19.11.2 Systemic lupus erythematosus and related disorders 4509 embarking on a pregnancy. Anti-Ro antibodies are also associated with photosensitivity. There are no good antibody markers for the presence of disease of the CNS. Antibodies to ribosomal protein P were previously thought to have some value in the diagnosis of CNS lupus, but this has not been borne out by later results and the test is not available routinely in most laboratories. More recently, murine and clinical studies have suggested that antibodies to the N-Methyl-D-aspartate receptor (anti-NMDAR) may act on certain cerebral tissues (e.g. the amygdala) to cause clinical features of CNS lupus, but this test is not used routinely in clinical practice. APL antibodies can be recognized by one of three assays. The enzyme-linked immunosorbent assay (ELISA) for binding to cardiolipin distinguishes IgM and IgG isotypes, as does a second ELISA for anti- β 2-glycoprotein 1 antibodies. This is helpful because the level of IgG APL antibodies is a better predictor of clinical sequelae than that of IgM. APL antibodies can also be diagnosed by testing the clotting properties of the blood in vitro in the Russell's viper venom test. An abnormal result in this assay is reported as showing the presence of a lupus anticoagulant. The ELISAs and lupus anticoagulant test do not always give the same result. Patients may be positive in one but not in the others. Patients positive in all three tests have the highest risk of thrombosis. Coombs' test and assays for antithyroid antibodies are often requested in patients with systemic lupus erythematosus, particularly those with coexisting anaemia or hypothyroidism. Measures of disease activity and end-organ damage Blood and urine tests The

most reliable measures of highly active disease are depletion of complement and high anti-dsDNA levels. The erythrocyte sedimentation rate (ESR) also tends to be increased in active disease, unlike the level of C-reactive protein (CRP). The combination of high ESR and normal CRP in a patient with a multisystem disorder should raise the suspicion of systemic lupus erythematosus, leading to appropriate autoantibody tests as described here. The CRP may, however, be raised in the presence of infection, serositis, or arthritis. Complement components C3 and C4 are the most commonly measured, and both tend to fall in active systemic lupus erythematosus. A persistently very low level of either C3 or C4 (or a high level of their degradation products C3d or C4d), regardless of immunosuppressive therapy, may signify the presence of a homozygous complement deficiency disorder. Although such disorders are very rare, it is important to diagnose them because they respond better to infusions of fresh frozen plasma than to immunosuppression. It is important to measure creatinine and electrolyte values regularly and to check the urine for proteinuria and/or haematuria. These measures ensure that renal involvement is diagnosed early. It must be remembered that substantial deterioration in renal function may occur before serum creatinine rises beyond the normal range, an issue emphasized by the now routine reporting of eGFR. If the patient can reliably perform a 24-h urinary collection, then creatinine clearance can provide a more precise estimate of GFR, but this, or radio-isotopic methods of measuring GFR, are rarely required in routine clinical practice. Persistent proteinuria on dipstick testing should be quantified by measuring the albumin/protein:creatinine ratio in a spot urinary sample (or with a 24-h urinary collection). Liver function tests are abnormal in fewer than 10% of patient with systemic lupus erythematosus, but a baseline value should be measured, particularly in cases where potentially hepatotoxic drugs such as azathioprine may be used. Thyroid function abnormalities, particularly hypothyroidism, are well recognized to coexist with systemic lupus erythematosus. A full blood count should be measured regularly. Falling haemoglobin, white cell count, and platelet counts may all occur (see previous section, 'Haematological involvement'). Anaemia in the presence of a positive Coombs' test may indicate haemolysis, which can be confirmed by requesting a blood film and serum haptoglobins. Infections occur commonly in patients with systemic lupus erythematosus, particularly in those on high-dose immunosuppressants. Infection may not always be accompanied by high fever or leucocytosis, although CRP is usually raised. It is wise to carry out blood and urine cultures whenever even mild pyrexia is accompanied by a deterioration in health. Imaging Plain radiographs are rarely useful in systemic lupus erythematosus. There is no characteristic appearance in the joints, and chest radiographs are unlikely to show abnormalities except in the presence of infection or effusion. Requests for more specialized imaging studies should be directed by the clinical findings, e.g. the presence of dyspnoea and abnormal respiratory function tests often necessitates a high resolution CT scan of the thorax, which is the investigation of choice for diagnosis of pulmonary fibrosis. Echocardiography is useful if pericardial effusion, myocarditis, or endocarditis are suspected clinically. Bone density scanning is becoming increasingly important, since patients with systemic lupus erythematosus are often at risk of osteoporosis due to the use of corticosteroids and reduced capacity for physical exercise during young adult life.

Criteria for diagnosis Although strictly speaking classification and diagnostic criteria are not synonymous, the classification criteria discussed earlier, and shown in Tables 19.11.2.1 and 19.11.2.2, are widely used for diagnostic purposes.

Treatment Systemic lupus erythematosus is a disease that still has the potential to kill. In many cases, however, the condition runs a fairly indolent course in which an initial flare is followed by many years of low-grade activity. General measures of value in the treatment of systemic lupus erythematosus are shown in Table 19.11.2.6. In the pharmacological management of a

patient with systemic lupus erythematosus, the clinician will typically seek to answer four 'classic' questions: 1 Can the patient be managed without immunosuppression? 2 If immunosuppression is needed, how should it best be started?

section 19 Rheumatological disorders 4510 3 If immunosuppression is being used, is the current level of immunosuppression inadequate or excessive? How should it be increased or reduced? 4 Does the patient have any side effects from the drugs? A fifth is increasingly being posed: would any of the new biologic treatments be of value? Is immunosuppression required? Patients whose disease activity is confined to arthralgia, tiredness, and/or mild rash do not usually have greatly raised ESR or anti-dsDNA antibodies or reduced complement. These patients can often be treated symptomatically, e.g. with agents such as paracetamol and diclofenac to control joint pain. The antimalarial agent hydroxychloroquine at a starting dose of 400 mg/day is often useful for these problems. This drug carries a very low risk of retinal toxicity but it is advisable for patients to be monitored by an optician or ophthalmologist annually after taking hydroxychloroquine continuously for five years or more. Regular blood tests are not required to monitor the effects of hydroxychloroquine. Long-term studies consistently show better outcomes in patients on hydroxychloroquine in terms of disease-associated damage and cardiovascular risk factors. On balance, therefore, many rheumatologists advise patients with systemic lupus erythematosus to stay on this drug even when in remission. Immunosuppression is rarely useful where the main symptoms in a patient with systemic lupus erythematosus are those of the APS. Aspirin at a dose of 150 to 300 mg daily is recommended for those with mild symptoms of the disease or who have other risk factors for thrombosis. Patients who have had recurrent thromboses or cerebral infarcts and who have persistently positive serum APL antibodies should usually be treated with lifelong anticoagulation. This is a major commitment for a young patient and raises particular problems in pregnancy (discussed in 'Systemic lupus erythematosus in pregnancy' later in this chapter). Some patients require a low maintenance dose of oral steroids to control their symptoms even though laboratory indices do not indicate high activity of disease. A dose of prednisolone of 5–7.5 mg daily is typically used in such cases. Topical steroids may be useful where lupus activity is confined to the skin. Judging the dose of immunosuppression Corticosteroids and cytotoxic agents are used to treat flares of disease. A mild flare of arthralgia, myalgia, and general fatigue may be alleviated by a single intramuscular dose of a corticosteroid preparation such as prednisolone acetate (usually 50 to 125 mg) or methylprednisolone (80–120 mg). More severe flares of arthritis, pleuritis, or pericarditis require oral prednisolone at a dose of 20 to 40 mg daily. This usually leads to a rapid improvement in symptoms, and the dose of prednisolone can then be reduced by 5 mg every 1 to 2 weeks until it reaches 5 mg/day. It may not be possible to withdraw the drug completely for several months. Alternatively, a shorter course of corticosteroids can be given intravenously. A typical course would consist of 500 to 750 mg methylprednisolone given over 3 to 4 h on each of three successive days. This requires admission to hospital, making it less convenient than oral therapy, and it is generally reserved for those patients who are not responding to oral prednisolone or cannot tolerate that drug in high doses. Autoimmune haemolytic anaemia requires higher doses (60–80 mg/day) of oral prednisolone, with the dose reduced in 5- to 10-mg increments according to the clinical response. Azathioprine may be required as a steroid-sparing agent and is used at a dose of 2.5 to 3 mg/kg per day. Renal flares of systemic lupus erythematosus require the most aggressive treatment, generally involving both corticosteroids and immunosuppressants. Several regimens have been used, with debate continuing as to which is best. An 'older' regimen of high-dose oral prednisolone and 750 mg intravenous cyclophosphamide monthly for six months, then

three-monthly for two years, has fallen into disrepute. Although reasonably effective, its side effects (especially infection and infertility) have led to the use of alternative regimens, including lower doses of intravenous cyclophosphamide (around 500 mg) every two weeks for six doses, and the use of oral mycophenolate mofetil (generally 2–3 g/day) instead of cyclophosphamide. Trial data suggest that mycophenolate is as effective as cyclophosphamide and has fewer serious side effects. In renal systemic lupus erythematosus it is critically important to control the patient's blood pressure. Angiotensin converting enzyme (ACE) inhibitors, α -adrenergic antagonists such as doxazosin, and calcium channel blockers such as nifedipine are the agents most commonly used. The treatment of CNS lupus varies depending on the manifestation of cerebral dysfunction. Mild cases may respond to relatively small doses of oral steroids (up to 30 mg/day). More florid manifestations such as convulsions or major psychosis require treatment with appropriate anticonvulsants or antipsychotic drugs, higher-dose oral steroids (60–80 mg/day), and sometimes azathioprine or intravenous pulses of cyclophosphamide in similar doses to those used in renal systemic lupus erythematosus. Does the patient have drug side effects? The side effects of corticosteroids are well known. The most common early problems are weight gain, hirsutism, easy bruising, and insomnia. It is difficult to prevent them, except by using the lowest dose of steroid that is effective and reducing it as rapidly as possible while maintaining control of the disease. Longer-term sequelae of corticosteroid use include increased susceptibility to infection, osteoporosis, avascular necrosis, and

Table 19.11.2.6 Treatment of lupus—general measures

- 1 Rest as appropriate; try to avoid stress
- 2 Avoid overexposure to heat and sunlight. Use sun protection factor 15+ (30+ in United States) if in a sunny country; avoid exposing an arm on an open car window
- 3 Try to adhere to a low-fat diet and consider adding fish oil derivatives
- 4 'Live' vaccines should not be given to patients on >10 mg prednisolone per day and/or immunosuppressants. Apart from that, vaccination for foreign travel, and so on is not contraindicated, though the precise nature of the immune response differs from that in healthy individuals
- 5 Medium- or high-oestrogen contraceptive pills should be avoided—progesterone only or the lowest possible oestrogen pill (or other methods of contraception) are advised
- 6 The use of hormone replacement in the menopause remains controversial. Many patients do tolerate it without flaring, but not all
- 7 Avoid smoking tobacco in order to improve skin disease and reduce risk of cardiovascular disease and osteoporosis

19.11.2 Systemic lupus erythematosus and related disorders

4511 diabetes mellitus. The most rapid loss of bone in steroid-induced osteoporosis occurs within the first year of treatment, although doses of 7.5 mg/day or less of prednisolone are thought to have little effect on bone. At higher doses, it may be advisable to carry out a bone density scan and to give either calcium and vitamin D tablets or a bisphosphonate (either etidronate or alendronate is commonly used) as prophylaxis. Cyclophosphamide causes alopecia, nausea, bladder toxicity, and gonadal dysfunction that may lead to infertility. The problem of infertility becomes more likely with increasing age, women over 30 given cyclophosphamide being at particular risk. Again, the best way to prevent such problems is to use as small a cumulative dose of the drug as is feasible. Bone marrow suppression may occur. During a programme of cyclophosphamide pulses the white blood cell count falls to a nadir 10 days after each pulse and should be measured at that time to decide whether the next pulse can be given safely. Nausea and vomiting during pulses may be so severe that antiemetics such as metoclopramide or granisetron are necessary. Azathioprine also causes bone marrow suppression and can cause abnormalities of liver enzymes, which resolve once the drug is withdrawn. Mycophenolate is contraindicated in pregnancy so that starting this agent may

be inadvisable in young women aiming to conceive in the next few years. Biologic therapies We are entering an exciting era in which improved understanding of the causes of lupus is leading to newer therapeutic approaches. In particular, drugs targeting B lymphocytes have been studied in several trials. B-cell depletion achieved by the anti-CD20 chimaeric reagent rituximab (1 g given on two occasions two weeks apart, or in more severe cases using this with intravenous cyclophosphamide 750 mg twice and intravenous methylprednisolone 125–250 mg twice) gave very promising results in open studies, but formal phase 3 clinical trials showed no benefit of adding rituximab to standard-of-care therapy. However, those trials had several design limitations and rituximab is still widely used, especially in renal and haematological disease. The use of fully humanized anti-CD20 monoclonal antibodies is also being explored. A monoclonal antibody (belimumab) directed against the B-cell activating factor BLYS does not deplete B cells but modulates their activity. This drug was more effective compared to standard-of-care treatment in large clinical trials in systemic lupus erythematosus affecting the joints and skin. It has been approved for use in systemic lupus erythematosus by regulatory agencies in Europe and the United States. Further studies are ongoing. However, another anti-BLYS monoclonal, tabalimumab, although partially successful in two major trials, is not being further developed. In contrast, atacept which blocks two B-cell activating factors BLYS and APRIL, performed well in a flare prevention study and in an active disease treatment study. Another anti-B-cell agent which blocks CD22 (epratuzumab) was successful in an early study but not in a phase III trial. Abatacept, which blocks the link between antigen presenting cells and T cells, seems to be of modest benefit only. Trials using two anti-interferon drugs (sifalimumab and anifrolumab) have produced encouraging early results. It is likely that the landscape of biologics for systemic lupus erythematosus will change considerably over the next 10–20 years. A recent open study of 50 patients described a new way of using rituximab in patients with systemic lupus erythematosus. Newly diagnosed patients with lupus nephritis were treated with rituximab followed by mycophenolate, and without oral corticosteroids. The aim was to control the disease rapidly to avoid the need for long-term corticosteroid therapy. Results were promising but a clinical trial (Rituxilup) of this combination was stopped because of slow recruitment and problems with obtaining the rituximab. Systemic lupus erythematosus in pregnancy Systemic lupus erythematosus itself does not usually reduce the ability to conceive, although as described the drugs used to treat it, notably cyclophosphamide, may induce infertility due to gonadal failure. There is an increased risk of spontaneous abortion, particularly in the presence of high-titre APL antibodies. Pregnant mothers with a high APL antibody level and a history of previous miscarriage should be treated with daily heparin and aspirin until the birth of the baby. As warfarin is potentially teratogenic, heparin may be used from the second trimester until parturition. Parents often ask whether their children are likely to inherit systemic lupus erythematosus. Inheritance of the adult form of the disease is very rare (approximately 1% of all cases), although a transient illness termed ‘neonatal lupus’ can occur. The characteristics of this condition are rash, hepatitis, anaemia, and thrombocytopenia, which usually resolve by 8 months after birth, and inflammation of the cardiac conducting tissues that may lead to heart block in the fetus. The cardiac problem may be diagnosed by ultrasound scans of the fetal heart between 16 and 24 weeks’ gestation. Treatment of the mother with 4 mg oral dexamethasone/day may prevent progression from incomplete to complete fetal heart block. If complete heart block occurs, the neonate may require a cardiac pacemaker. Interestingly, children born with neonatal lupus sometimes develop heart block later in life, with one reported case of this problem occurring at the age of 35. The presence of maternal anti-Ro and anti-La antibodies predicts a higher risk of neonatal lupus. Where both are

present the risk is approximately 2 to 5%. It is believed that the antibodies cross the placenta and bind to some component of the fetal cardiac tissue. Ro itself is expressed on the surface of cardiac myocytes at some point in fetal development and may be an important target for the anti-bodies. This may be why the fetal heart, but never the mother's heart, is affected by anti-Ro antibodies. Although overall the risk of a flare during pregnancy is probably no greater than at other times, systemic lupus erythematosus may be exacerbated during the pregnancy. Corticosteroids may be used in moderate doses without affecting the fetus, but higher doses (over 30 mg) given for long periods can potentially cause fetal adrenal suppression. If lupus activity is such that these doses are required, the risk to the fetus of not treating the disease adequately should outweigh any risk from the drug. Cyclophosphamide, mycophenolate, and methotrexate are contraindicated in pregnancy, although there have been many successful pregnancies in transplant recipients taking azathioprine without obvious increased risk of adverse effect. Hydroxychloroquine and low dose oral corticosteroids are safe. It may be difficult to distinguish pre-eclampsia from a flare of renal lupus. Both can cause hypertension and proteinuria, but in

section 19 Rheumatological disorders 4512 pre-eclampsia—unlike systemic lupus erythematosus—there are rarely urinary casts and levels of anti-dsDNA antibodies and complement are normal. For further discussion of autoimmune rheumatic disorders in pregnancy see Chapter 14.14. Occupational and psychological aspects of systemic lupus erythematosus Systemic lupus erythematosus typically presents in young people, especially women. The onset of a chronic, essentially incurable condition at a time of life when the patient is otherwise healthy and has many plans and responsibilities is an unexpected and unwelcome burden. Many concerns arise; in particular the outlook for fertility and the ability to care for children are substantial worries. In those cases where the use of high-dose corticosteroids and immunosuppressive agents is essential, detailed explanations of the benefits and risks of these treatments in both the short and the long term are necessary. Although a 10-year survival rate of 90% may appear reassuring, it is probably less so to a 25 year old who recognizes a 10% chance of dying by the age of 35. In making the diagnosis of systemic lupus erythematosus, therefore, the doctor must consider the effect of this condition on the overall life of the patient as well as his or her individual organs. A sympathetic understanding of the anxieties associated with the diagnosis is vital. Prognosis Mortality from systemic lupus erythematosus has fallen significantly over the last half century. Whereas systemic lupus erythematosus was reported to have a 50% 5-year survival rate in the 1950s, 10-year survival rates rose to between 80 and 90% by the 1970s. Since then, survival rates have improved a little, but deaths from renal failure have become less common, while those from infection and cardiovascular disease have increased. Infection is generally associated with immunosuppressive therapy, highlighting the need for better and more accurately targeted methods of treating the underlying immunological abnormalities in this disease. Morbidity from systemic lupus can be considerable. From the less serious, but troubling, severe fatigue to the necessity for renal dialysis, many aspects of lupus result in it having a big effect on quality of life. Analyses using the medical outcome survey, short form 36 (SF-36) quality-of-life index have shown that patients with lupus have impaired scores in every aspect of this index. A damage index for lupus, derived by the Systemic Lupus International Collaborating Clinics group, has shown that within 10 years about two-thirds of patients have acquired permanent problems. Furthermore, early acquisition of damage—within 1 year of diagnosis—substantially increases the risk of mortality (fourfold) within 10 years. Controversial areas and future prospects We do not yet have a cure for systemic lupus erythematosus, or even a method of controlling the disease without the risk of significant side effects. The main sources of controversy concern attempts to develop new forms

of treatment and to establish indices of disease activity that can be used to measure the effects of these treatments. Plasma exchange and intravenous immunoglobulin therapy have been tried in systemic lupus erythematosus, particularly in renal crises. Overall, the results do not suggest that either form of treatment should be used routinely. There are now many different murine models of systemic lupus erythematosus. These differ in their clinical and serological characteristics and each represents at best a partial approximation to the human disease. This is important, because it is now possible to administer agents such as monoclonal anticytokine antibodies to these mice and to assess the effect on the disease process, but how far such studies can be used to predict which of these agents might be effective in humans remains unknown. If new drugs or monoclonal antibodies are to be used in human systemic lupus erythematosus, it is necessary, given that mortality is now (thankfully) an uncommon end-point, to have recognized tools by which to judge the response to treatment. A combination of a disease activity index, a damage index, a patient health perception index, a record of toxicity, and cost is required. Several global score disease activity indices; for example, the Systemic Lupus Erythematosus Disease Activity Index (SLEDAI) and the European Community lupus activity measure (ECLAM) have been developed and provide a 'rough and ready' guide to overall activity. A more sophisticated approach based on the 'physician's intention to treat principle' has been derived by the British Isles Lupus Activity Group, providing an 'at a glance' review of activity in eight different organs or systems. A single damage index (the SLICC/ACR damage index) has been developed, which records a wide variety of potential permanent (present for at least six months) changes (e.g. avascular necrosis, myocardial infarction) that can occur in patients with lupus as part of the development of the disease. The medical outcome survey SF-36 provides a useful health perception index for patients with lupus. Although not designed specifically for this condition, it has been widely used in several ongoing drug trials, but it is likely that a more specific lupus quality-of-life index will be more widely used in future (three are being validated at present). It is likely that the treatment of systemic lupus erythematosus in 10 years' time will be different from that given now. Basic science research is starting to identify the various strands of immune dysfunction at the core of this disease. At the same time, drug development is providing agents that are capable of selectively targeting single cell types or cytokines within the immune system. At least some of these agents are likely to be relevant to the dysfunctional mechanisms in systemic lupus erythematosus. In addition, clinicians are becoming more aware that conditions such as atherosclerosis and osteoporosis are common in patients with systemic lupus erythematosus. By increasing efforts to detect and control these associated conditions, as well as seeking to attack the underlying autoimmune disease, it should be possible to improve the lives of patients with systemic lupus erythematosus, even if a cure for the disease remains a distant prospect. FURTHER READING Arbuckle MR, et al. (2003). Development of autoantibodies before the clinical onset of systemic lupus erythematosus. *N Engl J Med*, 349, 1526–33.

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