Overview of the management of systemic lupus erythematosus

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- Systemic lupus erythematosus (SLE) is a heterogeneous autoimmune disease with a broad clinical presentation
- When assessing a patient with SLE it is important to differentiate active disease from irreversible organ damage, adverse effects of treatment and other co-morbid conditions
- Patients with SLE have increased co-morbidities including osteoporosis, cardiovascular disease, infection risk and depression, which need to be identified and managed appropriately
- Corticosteroids and immunosuppressant therapies are the treatments of choice for active disease, but newer biological therapies may offer improved disease control and fewer adverse effects

Introduction

Systemic lupus erythematosus (SLE) is a systemic inflammatory autoimmune disease predominantly affecting women. The prevalence of lupus is estimated at 12.5–78.5 cases per 100,000 population in Europe and the USA with a female:male ratio of around 9:1. In the UK SLE is approximately 2.5 times more common in South Asian and 5–6 times more common in Afro-Caribbean individuals. Due to the rarity of SLE it is difficult to accurately determine the incidence, but it has been estimated to be between 2.0 and 7.6 cases per 100,000 population/year. The aetiology and immunopathogenesis of SLE have been extensively reviewed elsewhere. This review will focus on advances in the management of SLE in terms of both the disease itself and its associated co-morbidities.

Clinical features of SLE

SLE is one of a small number of truly multisystem disorders. The heterogeneous nature of the disease can result in delayed diagnosis and cause considerable difficulty in the design of robust clinical trials. There is no diagnostic test specific for SLE and as such the diagnosis remains a clinical one, relying on a combination of clinical and laboratory features. The 1992 Revised American College of Rheumatology (ACR) Classification Criteria, while developed to aid trial design, offer a useful aide-mémoire to the rheumatologist of some of the more common features of SLE (Table 1). Newer criteria have only recently been published but are likely to be more widely used in the future (Table 2).
### TABLE 1. 1997 Updated American College of Rheumatology criteria for classification of systemic lupus erythematosus.


<table>
<thead>
<tr>
<th>Criteria</th>
<th>Brief definition notes</th>
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<tbody>
<tr>
<td>1 Malar rash</td>
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<tr>
<td>2 Discoid rash</td>
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<tr>
<td>3 Photosensitivity</td>
<td>Patient history or physician observation</td>
</tr>
<tr>
<td>4 Oral ulcers</td>
<td>Oral or nasopharyngeal</td>
</tr>
<tr>
<td>5 Non-erosive arthritis</td>
<td>Tenderness, swelling or effusion in ≥2 peripheral joints</td>
</tr>
<tr>
<td>6 Pleurisy or pericarditis</td>
<td>Pleurisy: convincing history of pleuritic pain, pleural rub, or effusion or pericarditis: ECG evidence, rub, or effusion</td>
</tr>
<tr>
<td>7 Renal</td>
<td>Persistent proteinuria (&gt;0.5 g/day or &gt;3+ by dipstick) or cellular casts on microscopy (red, granular, tubular or mixed)</td>
</tr>
<tr>
<td>8 Neurological</td>
<td>Seizures or psychosis in the absence of drugs or metabolic derangements</td>
</tr>
<tr>
<td>9 Haematological</td>
<td>At least 1 of: Haemolytic anaemia with reticulocytosis Leucopenia (&lt;4000/mm³) on ≥2 occasions Lymphopenia (&lt;1500/mm³) on ≥2 occasions Thrombocytopenia (&lt;100,000/mm³) without drug cause</td>
</tr>
<tr>
<td>10 Immunological</td>
<td>At least 1 of: Anti-DNA antibody Anti-Smith antibody Positive antiphospholipid antibodies identified by: abnormal serum level of IgM or IgG anticardiolipin antibodies positive lupus anticoagulant</td>
</tr>
<tr>
<td>11 Positive ANA</td>
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</table>

At least 4 criteria are needed for the classification of SLE.

It is interesting to note that, in addition to differences in disease prevalence, marked ethnic variation in organ involvement has also been reported; for example, when compared to Caucasian lupus patients Afro-Caribbean patients have an increased risk of renal disease while antiphospholipid syndrome (APS) is less common.

A wide spectrum of autoantibodies can be found in patients with SLE and are often associated with specific clinical features. Antinuclear antibodies (ANA) are found in 98% of SLE patients but are non-specific. The presence of anti-double-stranded DNA (dsDNA) is highly specific for SLE but they are only present in around 70% of cases. Other autoantibodies reported in patients with SLE include anti-Smith, anti-ribosomal P and anti-proliferating cell nuclear antigen (PCNA). Of all these antibodies, it is only dsDNA that has been shown to be pathogenic (for lupus nephritis) – the others appear to be biomarkers for the presence of an autoimmune state.

**Mortality in SLE**

There has been a significant reduction in mortality among lupus patients over the last 50–60 years; the 5-year survival is now estimated at around 95%. This does of course still mean there is an unacceptably high mortality in this condition affecting younger women. In the largest observational study to date (of c.9500 lupus patients) increased mortality was seen in female patients, particularly within the first year following diagnosis. This early peak in mortality, which is commonly due to lupus disease activity and infection, is followed by a second later peak chiefly due to cardiovascular disease (CVD).

<table>
<thead>
<tr>
<th>Clinical criteria</th>
<th>Brief definition notes</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Acute cutaneous lupus</strong></td>
<td>Lupus malar rash (do not count if malar discoid), bullous lupus, toxic epidermal necrolysis variant of SLE, maculopapular lupus rash, photosensitive lupus rash or subacute cutaneous lupus (nonindurated psoriaform and/or annular polycyclic lesions that resolve without scarring, although occasionally with postinflammatory dyspigmentation or telangiectasias)</td>
</tr>
<tr>
<td><strong>Chronic cutaneous lupus</strong></td>
<td>Classical discoid rash [localised – above the neck; generalised – above and below the neck], hypertrophic ( verrucous) lupus, lupus panniculitis (profundus), mucosal lupus, lupus erythematosus tumidus, chilblains lupus, discoid lupus/lichen planus overlap</td>
</tr>
<tr>
<td><strong>Oral ulcers</strong></td>
<td>Palate [buccal, tongue] or nasal ulcers (in the absence of other causes)</td>
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<tr>
<td><strong>Nonscarring alopecia</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Synovitis</strong></td>
<td>≥2 joints, characterised by swelling or effusion or tenderness in ≥2 joints and ≥30 minutes of morning stiffness</td>
</tr>
<tr>
<td><strong>Serositis</strong></td>
<td>Typical pleurisy for &gt;1 day, or pleural effusions, or pleural rub or typical pericardial pain for &gt;1 day, or pericardial effusion, or pericardial rub, or pericarditis by ECG</td>
</tr>
<tr>
<td><strong>Renal</strong></td>
<td>Urine protein:creatinine ratio (or 24-hr urine protein) representing 500 mg protein/24 hr or red blood cell casts</td>
</tr>
<tr>
<td><strong>Neurological</strong></td>
<td>Seizures, psychosis, mononeuritis multiplex, myelitis, peripheral or cranial neuropathy, acute confusional state (in the absence of other causes)</td>
</tr>
<tr>
<td><strong>Haemolytic anaemia</strong></td>
<td></td>
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<tr>
<td><strong>Leucopenia</strong></td>
<td>Leucopenia (&lt;4000/mm³ at least once) or lymphopenia (&lt;1000/mm³ at least once)</td>
</tr>
<tr>
<td><strong>Thrombocytopenia</strong></td>
<td>Platelet (&lt;100,000/mm³) at least once</td>
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<tr>
<td><strong>Immunological criteria</strong></td>
<td></td>
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<tr>
<td><strong>ANA</strong></td>
<td>Above reference range</td>
</tr>
<tr>
<td><strong>Anti-dsDNA</strong></td>
<td>≥x2 above if ELISA</td>
</tr>
<tr>
<td><strong>Anti-Smith</strong></td>
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<tr>
<td><strong>Antiphospholipid</strong></td>
<td>Lupus anticoagulant, false-positive RPR, medium- or high-titre antcardiolipin (IgA, IgG or IgM), anti-β₂-glycoprotein I (IgA, IgG or IgM)</td>
</tr>
<tr>
<td><strong>Low complement</strong></td>
<td>Low C3, C4 or CH50</td>
</tr>
<tr>
<td><strong>Positive direct Coombs’ test</strong></td>
<td>In the absence of haemolytic anaemia</td>
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</table>

**Classify a patient as having SLE if:**
- the patient satisfies 4 of the criteria listed in the table including at least 1 clinical criterion and 1 immunological criterion, OR
- the patient has biopsy-proven nephritis compatible with SLE and with ANA or anti-dsDNA antibodies.

**Note:** criteria are cumulative and need not be present concurrently.

ANA antinuclear antibodies; dsDNA double-stranded deoxyribonucleic acid; ECG electrocardiogram; ELISA enzyme-linked immunosorbent assay; Ig immunoglobulin; RPR rapid plasma reagin; SLE systemic lupus erythematosus
**Identification of ‘high-risk’ patients**

No universal prognostic factor has been identified, but some clinical features of SLE are associated with a worse prognosis. In a study by Lopez et al of 350 lupus patients, older age, higher disease activity and pre-existing organ damage were all independently associated with premature death. In addition, renal disease (identified either at biopsy or by measurement of serum creatinine) and thrombocytopenia are associated with increased mortality. Perhaps most importantly, it is increased lupus disease activity overall that should alert the rheumatologist to the fact that the patient is at risk of a poor outcome.

**Morbidity in SLE**

The clinical course in SLE can vary markedly from relatively mild symptoms through to life-threatening multi-organ disease. A thorough assessment of lupus patients is important to clearly identify active disease and the presence of organ involvement. Disease activity scoring systems have been developed primarily for use in research studies in order to try to capture activity in this heterogeneous disease (reviewed in Griffiths et al). Although developed for use in research studies, these scoring systems offer a useful framework for the treating physician.

Global scoring systems such as the Systemic Lupus Erythematosus Disease Activity Index (SLEDAI) provide a single total activity score, with serious manifestations (e.g. neurological disease) weighted more heavily. Recent updates to SLEDAI include SELENA-SLEDAI (Safety of Estrogens in Lupus Erythematosus: National Assessment-SLEDAI) and SLEDAI-2K, both of which aim to capture ongoing rather than just new or recurrent activity.

The British Isles Lupus Assessment Group (BILAG) index offers a more comprehensive approach to the assessment of lupus disease activity. Rather than generating a global activity score, the BILAG-2004 index classifies activity, over a 4-week period, according to 9 different organ systems. Furthermore, rather than using an arbitrary definition of disease activity the benchmark is set against whether or not the signs or symptoms would prompt an escalation of therapy. It is important when using indices such as BILAG that only features due to SLE activity per se (and not damage or other conditions) are recorded.

Against a background of a cluster of negative randomised trials (see below) new scoring systems to capture therapeutic response in SLE are being developed. These response indices, analogous to an ACR or European League Against Rheumatism (EULAR) response in rheumatoid arthritis, aim to quantify changes in disease activity in clinical trials. The SLE Responder Index (SRI) comprises a reduction in SELENA-SLEDAI score of ≥4 points, no new BILAG ‘A’ or more than 1 new ‘B’ score, and no significant worsening in Physician’s Global Assessment (PGA) score. This composite scoring system has thus far only been used in the clinical trials of belimumab. The development of sensitive and reproducible scoring systems will be essential for the conduct of more robust clinical trials.

**Clinical assessment of the lupus patient**

In the assessment of symptomatic patients consideration should be given as to whether the clinical features are due to:
- Lupus disease activity (i.e. a lupus flare)
- Other lupus-related pathology, e.g. thrombosis or vasospasm
- Irreversible organ damage
- Non-lupus causes, e.g. infection, atherosclerosis, other autoimmune diseases or drug-related adverse events.

It is important to remember that other diseases (e.g. infection) can co-exist in the SLE patient and can be worsened by a lupus flare, resulting in ‘dual-pathology’. An accurate diagnosis therefore relies on interpretation of symptoms against a background of probability. For example, haematuria and proteinuria are more likely to be due to a urinary tract infection rather than lupus nephritis. Indeed, concomitant infections are one of many co-morbidities common in SLE and are discussed in detail below. The Systemic Lupus International Collaborating Clinics Damage Index (SLICC-DI) allows damage to be recorded and quantified as a score between 0 and 46. Unlike the measures of disease activity all damage is scored from the time of diagnosis of SLE onwards, regardless of whether or not it can be attributed to lupus.

**Can a lupus flare be predicted?**

SLE often follows a relapsing and remitting pattern of disease. The ability to identify those patients in whom a flare is likely allows either a proactive increase in therapy or instigation of more stringent monitoring. No single predictive marker for lupus flare has yet been identified. Perhaps the most recognised link is that between raised dsDNA titre and/or low serum complement (C3, C4 and C1q) and the development or flare of lupus nephritis. An increase in dsDNA titre, or the development of blood dyscrasias (anaemia, lymphocytopenia or thrombocytopenia) can also predict flare in lupus cohorts and has been reviewed by Bertsias et al. A combination of clinical (disease activity) and laboratory features (full blood
count, serum complement) is therefore recommended for monitoring SLE patients, as reflected for example in the 2010 EULAR guidelines for the monitoring of lupus patients both in clinical practice and in observational studies.\textsuperscript{31}

**Management of lupus: no major organ involvement**

The general principle of management of SLE is analogous to that of other inflammatory disorders: suppression of inflammation in an attempt to prevent organ damage. The intensity of therapy is therefore dictated by the severity and site of organ involvement, and the overall prognosis for specific organ involvement. The management of SLE is summarised in Figure 1.

Non-organ-specific symptoms in SLE are common and include marked fatigue, arthralgia, myalgia, fever, weight-loss and mood changes (often low mood and depression). These can be severe enough to significantly impair a patient’s quality of life.\textsuperscript{32} Management of these symptoms, particularly fatigue, is often challenging as the causes are multifactorial and no specific therapies exist. These symptoms will to some extent be improved by increasing overall control of the disease. Fatigue and chronic pain are therefore common in SLE, although there is evidence that the prevalence of fibromyalgia itself is lower than would be expected.\textsuperscript{33}

In mild–moderate lupus, musculoskeletal and mucocutaneous features are likely to dominate the clinical picture. Common manifestations include mucosal ulceration (typically oral and nasal), scarring alopecia, non-erusive arthropathy (Jaccoud’s arthropathy) and skin rashes (malar rash, discoid lesions and other photosensitive rashes). Oral corticosteroids at low–moderate doses and antimalarial therapy are the mainstay of management of mild–moderate disease, using the lowest dose of steroids to adequately control the symptoms. Higher-dose steroids and steroid-sparing agents are used when this approach is insufficient to control the disease. In addition, steroid and antimalarial agents can be important adjuvant therapy to reduce the risk of flare in patients with more severe disease.

**UV protection**

Exposure to sunlight is a recognised precipitant of a lupus flare. Patients often have photosensitive rashes, or may experience a worsening of systemic symptoms in response to ultraviolet (UV) radiation. Lupus patients should be advised to avoid sitting in direct sunlight and to use physical protection from the sun (e.g. long sleeves, hats and sun-protective clothing) where appropriate. Diffusers on low-energy light bulbs and fluorescent light sources may also be of help. High-factor sunblock (ideally sun protection factor (SPF) ≥50) is also recommended and should be applied regularly. Sunlight avoidance may, however, partly contribute to the increased prevalence of vitamin D deficiency in patients with SLE.\textsuperscript{34} Although the clinical relevance of low vitamin D in SLE with regard to immunological function is currently under investigation, vitamin D deficiency is of course an established risk factor for poor bone health, including the development of osteomalacia and osteoporosis (the latter is discussed below).

\begin{figure}
\centering
\begin{tabular}{|c|c|}
\hline
**Establish diagnosis** & **No major organ involvement** \\
\hline
**Determine likely prognosis** & **· Antimalarials** \\
\hline
**Assess severity and organ involvement** & **· Low-dose steroids** \\
\hline
& **· Azathioprine/methotrexate** \\
\hline
\end{tabular}
\end{figure}
**Antimalarial therapy**

Hydroxychloroquine (HCQ) (up to 6.5 mg/kg daily) has been shown to be very effective in the management of mucocutaneous disease, serositis and fatigue.\(^{35,36}\) It should be noted that prolonged use of chloroquine phosphate (but to a lesser extent HCQ) can lead to the development of retinopathy.\(^{37}\) In 2009 the Royal College of Ophthalmologists issued good practice guidelines for the use of antimalarial therapy by rheumatologists and dermatologists.\(^{38}\) In the absence of pre-existing retinal disease routine ophthalmological review is not recommended. In more refractory cases, or if ocular toxicity is a concern, mepacrine has also been used with good effect, although it can result in a dose-dependent yellow discoloration of the skin. HCQ and mepacrine can also be efficacious in combination. The therapeutic options for treatment of cutaneous lupus have been extensively reviewed by Kuhn et al.\(^{39}\) Importantly, HCQ use has also been associated with a reduction in overall mortality in lupus patients.\(^{40}\)

**Corticosteroids**

Systemic corticosteroids remain a keystone in the management of SLE, particularly when a rapid response is desirable. The response of moderately active lupus to steroid therapy is such that if effectiveness alone were the only consideration then other agents would rarely be needed. Low doses (e.g. 5–10 mg daily) are often sufficient for mild disease, but can be increased to 0.5 mg/kg where the disease is moderately active. Corticosteroid therapy is, however, associated with significant unwanted effects and hence long-term high or moderate doses are undesirable.\(^{41}\) The therapeutic aim should therefore be to maximise benefit while minimising steroid-related harms. Steroid-sparing therapies such as azathioprine (AZA) can therefore be used in order to reduce the cumulative exposure to steroids. EULAR guidelines for the management of steroid therapy in rheumatic diseases were published in 2007 and cover issues such as risk stratification, monitoring and management of complications of glucocorticoids.\(^{42}\)

**Immunosuppressant agents**

Azathioprine (AZA) (1–3 mg/kg) is the most commonly used steroid-sparing agent for the management of patients with SLE.\(^{43}\) The effective metabolism of AZA is dependent on normal thiopurine methyltransferase (TPMT) activity. Patients should therefore be screened for a homozygous deficiency of TPMT (present in 1 in 300 of the population) which results in an extremely high risk of bone marrow suppression.\(^{44}\) In homozygous-deficient patients AZA should be avoided. Patients with heterozygous deficiency should have their ‘target’ AZA dose adjusted downwards by approximately 50% and any further dose adjustments should be carefully monitored. In patients with inflammatory arthritis methotrexate (MTX) is often beneficial in controlling synovitis and may also reduce cutaneous disease.\(^{45}\) The effect of MTX on disease activity appears to be rather modest, but there is clinical trial evidence that MTX can allow more rapid and greater steroid withdrawal.\(^{46}\) Sulfasalazine is usually avoided in SLE due to its association with drug-induced lupus. The evidence for this association is, however, limited to case reports and has not been clearly demonstrated in larger cohorts.\(^{47}\)

**Management of lupus: major organ involvement**

In patients with significant major organ involvement rapid resolution of inflammation is needed in order to prevent the development of irreversible damage. The therapeutic options include high-dose intravenous (IV) methylprednisolone, immunosuppressant therapies (including cyclophosphamide (CYC) and mycophenolate mofetil (MMF)) and biological therapies. It should however be noted that there is no clear evidence for any additional benefit of IV methylprednisolone over high-dose oral prednisolone.\(^{48}\) The treatment choice is dictated primarily by the site and extent of organ involvement, although other issues (e.g. gonadal function, CYC) need to be considered. Much of the evidence for the effectiveness of these therapies in SLE, particularly CYC, is derived from studies of lupus nephritis. However, CYC is also used widely for systemic features where rapid disease control is needed (e.g. vasculitis, transverse myelitis, pulmonary haemorrhage). Although a comprehensive review of the management of lupus nephritis is beyond the scope of this review an excellent summary was recently published by Houssiau.\(^{49}\)

**Mycophenolate mofetil**

MMF is the pro-drug of mycophenolic acid which targets lymphocyte activation and survival by inhibiting de novo purine synthesis. As with CYC, much of the evidence base for the use of MMF in lupus is in the context of renal disease. A meta-analysis of 4 randomised controlled trials (RCTs) shows that MMF is as effective as CYC for induction of remission and is associated with fewer adverse events (gonadal failure and alopecia).\(^{50}\) MMF is therefore increasingly being used in preference to CYC in lupus nephritis and other major organ disease. Also MMF was superior to AZA for maintenance therapy for nephritis in the ALMS (Aspreva Lupus Management Study) trial,\(^{51}\) but not in the MAINTAIN (Mycophenolate Mofetil Versus Azathioprine for Maintenance Therapy of Lupus Nephritis) trial.\(^{52}\) These two trials differed significantly in terms of size and the racial composition of the study group. Although the positive results from these studies has
led to the use of MMF for non-renal manifestations of lupus with much anecdotal success, there is relatively limited published data on its use.53

**Calcineurin inhibitors**

Ciclosporin A and tacrolimus have both made the transition from transplant medicine to management of lupus although they are less commonly used than the agents described above. Both ciclosporin and tacrolimus offer an adjunct therapy to MMF in systemic disease and a potential alternative for induction/maintenance therapy in lupus nephritis.54,55 Ciclosporin may be particularly attractive in lupus nephritis as it may be safer than MMF in pregnancy.56 Topical tacrolimus can also be particularly useful for the management of both subacute cutaneous lupus and discoid lupus.57

**Rituximab**

Abnormalities in B-cell activation in lupus prompted the off-licence use of B-cell-depleting therapies, most notably rituximab (RTX). RTX is a chimeric monoclonal antibody directed against CD20 which is expressed on the surface of B-cells. Treatment results in a rapid and prolonged depletion of B-cells. A recent meta-analysis of all the available open-label studies suggests that B-cell depletion occurs in around 95% of patients, with an associated improvement in disease activity.58 It was disappointing, therefore, that two RCTs failed to show any benefit. The EXPLORER (Exploratory Phase II/III SLE Evaluation of Rituximab) and the LUNAR (Lupus Nephritis Assessment with Rituximab) trials both showed no improvement with RTX when compared to the placebo arm.59,60 In both of these studies RTX was used as an adjunct to existing therapy (high doses of corticosteroids or MMF) which likely blunted any true benefit of RTX. Despite these trials RTX remains an attractive option to treat patients who have failed conventional immunosuppression, and in the UK an open-label prospective register is being established to assess safety and patterns of use of this and other biologic agents in SLE (http://www.bilagbr.org).

**Belimumab**

In 2011 belimumab (Benlysta) became the first drug for 50 years to be licensed for treatment of SLE. Belimumab is a fully-humanised monoclonal antibody which blocks the binding of the activating factor, B-lymphocyte stimulator (BlyS), to its receptor on the surface of B-cells. Two large RCTs (BLISS (Belimumab in Subjects with Systemic Lupus Erythematosus)-52 and BLISS-76) with over 1600 patients demonstrated that belimumab resulted in a modest but significant improvement in lupus disease activity when compared to adjustments of standard of care alone (as assessed using the SRI discussed above).25,26 These positive findings are encouraging, and the investigators recognised a subpopulation of patients who particularly responded to treatment (i.e. patients with increased dsDNA and low complement). Further studies are needed in order to identify those patients who are most likely to benefit, and to confirm the current safety data over a longer time period.

**Management of co-morbidities in patients with SLE**

The assessment and management of disease activity constitutes only part of the care of lupus patients. It is equally important to address co-morbid conditions which arise either from the lupus disease itself or as adverse effects of treatment. The 2010 EULAR guidelines for the monitoring of lupus focus on the identification of co-morbidities.31

**Osteoporosis**

Patients with SLE have an increased risk of osteoporosis compared to the general population. Risk factors for reduced bone mineral density (BMD) include age, low body weight, inflammatory markers (erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP)) and pre-existing organ damage.61 In addition, corticosteroid doses of >7.5 mg in particular are associated with a greater risk of osteoporosis.52 Management of bone health in these patients should follow established practice for osteoporosis in other patient groups: conservative measures (including smoking cessation and exercise), optimisation of vitamin D levels (which are frequently deficient), calcium supplementation, and use of bisphosphonates.63 It is also worth noting that the FRAX tool (http://www.shef.ac.uk/FRAX) which is commonly used to assess future risk of fracture is validated for patients between 40 and 90 years, and so caution should be exercised when using such a tool in younger female lupus patients.

**Infection**

Severe infection remains the primary cause of mortality in approximately 25% patients with SLE. Bacterial infections, particularly pneumonia, are the most common cause of hospitalisation due to infection.64 The risk of infection is increased by both disease-related factors (lung involvement, renal disease, lymphopenia, complement consumption and functional hyposplenism) and drug-related effects (cumulative steroid exposure and immunosuppressant use).64,65 The most frequently seen viral infection is herpes zoster, while S. pneumoniae, E. coli and S. aureus are the most common bacterial pathogens in this group. Hyposplenism secondary to excessive immune complex deposition results in an increased risk of infection with encapsulated organisms (e.g. S. pneumoniae, H. influenzae, S. typhi). Opportunistic infections
Cardiovascular disease

Patients with SLE have a significantly increased risk of cardiovascular disease, around 5–6 times higher, compared to healthy controls.68 This increased risk is at least in part due to an increased prevalence of traditional cardiovascular risk factors, including smoking, hypertension, type 2 diabetes and dyslipidaemia.69,70 Guidelines for the management of these risk factors were proposed by Wajed et al.71 These offer a pragmatic ‘target-based’ approach to cardiovascular risk factor management for the clinician. It should be noted, however, that the evidence for these risk-reduction strategies is derived from their benefit in the general population; more studies are needed to demonstrate that these are beneficial in SLE.

In addition, there are lupus-specific factors that predispose these patients to premature atherosclerosis, including disease activity, renal disease and corticosteroid use.72 It is proposed, therefore, that control of inflammation, while minimising steroid exposure, may also reduce cardiovascular mortality in lupus.

Mental health

SLE has been shown to have a greater negative impact on health-related quality of life than other chronic diseases.73 The reason for this is unclear, but may be due to the systemic nature of the condition. Clear neuropsychiatric involvement is common, with a cumulative incidence of 30–40%. In 2010 EULAR guidelines for the management of neuropsychiatric lupus were published, covering the broad spectrum of disease manifestations.74 Of the quality of life assessment tools available, the LupusQoL is the most extensively validated.75 Despite the availability of these measures, there is little known about how quality of life can be improved for lupus patients. Management should therefore focus on the specific manifestations (e.g. depression, anxiety, fatigue) following conventional approaches.

Risk of thrombosis

In addition to traditional risk factors, patients with lupus have an increased risk of thromboembolic disease. Higher disease activity, lupus nephritis and hypertension may all contribute to this increased risk.76 APS is common in SLE, with clinical consequences in 10–15% of all patients.76 APS antibodies and lupus anticoagulant should be determined in all patients at baseline and following the emergence of any new risk factors for thrombosis.77 In non-pregnant patients with lupus and APS, long-term anticoagulation is required for secondary prevention of thrombosis. Assessment of thrombotic risk is also a key part of pregnancy assessment and management in SLE (see below).77,78

Premature gonadal failure

Early menopause is a common feature of SLE and other autoimmune diseases.79 Exposure to CYC may be a contributing factor in up to a half of cases.80 Distressing symptoms, including mood changes and severe flushing, are more difficult to treat in SLE due to concerns that hormone replacement therapy (HRT) may precipitate a disease flare.81 In patients with mild–moderate disease HRT increases the risk of mild–moderate flares and may also increase thrombotic risk. The effect on patients with more severe disease has not been studied. Alternative agents such as selective serotonin reuptake inhibitors (SSRIs), clonidine and topical oestrogens may be beneficial in symptom control.

Pregnancy

Many lupus patients are women of childbearing age, which has implications for the planning and monitoring of pregnancy, disease management during pregnancy and lactation, and risk of additional complications (e.g. thrombosis, pre-eclampsia, neonatal lupus/congenital heart block). Although a comprehensive review of immunosuppressant agents in pregnancy is beyond the scope of this article it should be remembered that only corticosteroids, HCQ and AZA are considered ‘safe’ to use in pregnancy. Other agents have potential effects on fertility (e.g. CYC) or teratogenesis (e.g. CYC, MTX, MMF) and the likely risk:benefit ratio of these treatments needs to be thoroughly discussed with the patient. The management of the pregnant lupus patient has recently been reviewed in detail by Baer et al.78

Summary and future research

Despite recent advances in the treatment of SLE, morbidity and mortality remain unacceptably high. The disease is poorly understood, leading to a paucity of proven targeted therapies. Furthermore, the significant disease heterogeneity can cloud the apparent benefits of new agents in clinical trials. More research is needed into the pathogenesis of SLE in order to identify new drug targets. Trials of
these new drugs will, however, only be successful if combined with more stringent and comprehensive disease outcome measures. It is highly likely that the disease that we understand as SLE comprises multiple related, but different, conditions. Identifying the exact clinical and pathological phenotype of these patients is essential in order to develop personalised treatment strategies. Until such a time, management of these patients is likely to remain as challenging as it is interesting.

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It is essential that GPs feel confident in their ability to treat common musculoskeletal conditions. However they often don’t fit neatly into the typical diagnosis, treatment and cure model.

Working with the Royal College of General Practitioners, Arthritis Research UK has funded and jointly developed a new training programme to improve GPs’ and GPSTs’ core skills in diagnosing and managing musculoskeletal conditions.

The **Core Skills in Musculoskeletal Care Project** has been developed by GPs for GPs and draws on the latest evidence and consensus thinking.

The training project consists of e-learning modules, face-to-face workshops focused on clinical skills, and an ‘impact toolkit’ which contains practical resources for GPs.

You can access the free e-learning modules at [www.elearning.rcgp.org.uk/msk](http://www.elearning.rcgp.org.uk/msk).

Go to [www.arthritisresearchuk.org/gpresources](http://www.arthritisresearchuk.org/gpresources) to download GP resources and self-management information for your patients.
Do you want to update your MSK core skills?

Arthritis Research UK and the Royal College of General Practitioners launch new core skills training for GPs and GPSTs

Please see overleaf for full details, including a link to the free e-learning modules.

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