Management of systemic lupus erythematosus in adults

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Earlier this year, the British Society for Rheumatology (BSR) published the first UK guideline on the management of systemic lupus erythematosus (SLE) in adults. This article summarises its recommendations on diagnosis, monitoring and treatment.

Systemic lupus erythematosus (SLE) is a challenging disorder for clinicians and those affected. It is rare: the age-standardised prevalence in the UK is 8.3/100,000 for women and 1.4/100,000 for men, but among people of African Caribbean descent the figure is 31.4/100,000. It is a multisystem autoimmune disease that can occur at any age and, though it is most frequent among women of reproductive age, the mean age at diagnosis is 49 years.

SLE is characterised by relapses and remissions. Flares cause considerable morbidity and organ damage accumulates, increasing the risk of premature death due to infection or cardiovascular disease. One-third of people with SLE develop nephritis, further reducing the mean age at death from 54 to 40 years, with an average of only seven to eight years between the onset of nephritis and death.

The first UK guideline on SLE management
The British Society for Rheumatology (BSR) has published a guideline on the management of SLE in adults because “Despite some improvement in survival data over the last 40 years, lupus patients still die on average 25 years earlier than the mean for women and men in the UK. The disease can present with slowly or rapidly progressive active disease at any age and can be associated with the rapid accumulation of damage if not promptly diagnosed, appropriately treated and regularly monitored.” This is the first UK guideline on the overall management of SLE, updating the 2008 guidance published by the European League Against Rheumatism (EULAR).

The aim of the guideline is to “produce recommendations for the management of adult lupus patients in the UK that cover the diagnosis, assessment and monitoring of lupus and the treat-
ment of mild, moderate and severe active lupus disease”. It is a mammoth task to provide succinct advice about such a complex disorder – and the 400 references culled from a literature search up to June 2015 that are cited in support of the recommendations is testament to the work that has gone into the document (there is an executive summary for quick reference).

But even this has only been possible by limiting the guideline’s scope. The management of renal disease is covered by other guidance. The BSR does not include isolated cutaneous lupus, it directs the reader elsewhere for advice on management during pregnancy, and does not address complications such as chronic fatigue, osteoporosis, infection and the risk of cardiovascular disease and cancer because their management is not unique to lupus patients.

People with SLE, of whom 80% report fatigue and 50% report severe fatigue, might not endorse such a separation. The guideline’s focus is made clear in a table listing the incidence of SLE manifestations in published reports: though superficially exhaustive, it does not mention fatigue. An otherwise positive commentary published alongside the guideline notes that only the role of the specialist is defined and “active patient involvement, shared decision-making and patient empowerment are excluded in the BSR management recommendations, as unfortunately is patient education”. This is not the NICE style of guideline with which we’ve become familiar.

The guideline has six sections covering recommendations for clinical and serological features prompting diagnosis; patient assessment; monitoring; and the management of mild, moderate and severe SLE. Each section includes a detailed description of the evidence base underpinning the recommendations.

### Diagnosis

Diagnosis requires a combination of clinical features and the presence of at least one relevant immunological abnormality. SLE is clinically heterogeneous and should be considered in the differential diagnosis of many acute and subacute presentations; delays in diagnosis are common. The guideline’s table of SLE manifestations illustrates the wide variety of signs and symptoms, but the causes of major morbidity are renal and neurological complications, and one- to two-thirds of patients have gastrointestinal and hepatic features that are often unrecognised as being due to SLE.

In acute SLE, inflammation is triggered by the formation of immune complexes involving autoantibodies and complement consumption and, in some people, thrombosis due to antiphospholipid antibodies. For patients with a strong clinical likelihood of SLE, the presence of anti-double stranded DNA antibodies, low complement C3 and C4, and anti-Smith antibodies is highly predictive of a diagnosis. The presence of antiphospholipid antibodies predicts an increased risk of thrombosis and adverse pregnancy outcomes. Levels of other autoantibodies may be raised but they are not specific for lupus.

The guideline adopts a classification system for SLE that requires the presence of four clinical and immunological criteria, including at least one of each (see Table 1). Alternatively, the diagnosis can be made if biopsy-proven nephritis compatible with SLE is present with antinuclear antibodies or anti-double stranded DNA antibodies. However, SLE may also be diagnosed in people who do not meet these criteria but have appropriate serology.

### Assessment

The diversity and complexity of SLE means a systematic approach to assessment is essential but categorising SLE disease activity has, in the past, seemed a convoluted process. To make planning treatment more straightforward, this guideline greatly simplifies the issue by defining categories for mild, moderate and severe SLE (see Table 2), but also correlates these with the more traditional assessment instrument scores.

The guideline stresses the importance of taking a detailed history and carrying out a full physical examination, then carrying out the appropriate laboratory investigations. Treatment for a flare, categorised by activity level, directs the reader elsewhere for advice.

### Monitoring

People with active SLE should be reviewed every month initially then every

<table>
<thead>
<tr>
<th>Activity</th>
<th>Definition</th>
<th>Typical SLE manifestations</th>
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<tbody>
<tr>
<td>Mild</td>
<td>Clinically stable disease with no life-threatening organ involvement and that is not likely to cause significant scarring or damage</td>
<td>Fatigue, malar rash, diffuse alopecia, mouth ulcers, arthralgia, myalgia, platelets 50–149 x 10⁹/L</td>
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<tr>
<td>Moderate</td>
<td>More serious manifestations, which if left untreated would cause significant chronic scarring</td>
<td>Fever, lupus-related rash up to 2/9 body surface area, cutaneous vasculitis, alopecia with scalp inflammation, arthritis, pleurisy, pericarditis, hepatitis, platelets 25–49 x 10⁹/L</td>
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<tr>
<td>Severe</td>
<td>Organ or life threatening and reflects the most serious form of systemic disease that requires potent immunosuppression</td>
<td>Rash involving &gt;2/9 body surface area, myositis, severe pleurisy and/or pericarditis with effusion, ascites, enteritis, myelopathy, psychosis, acute confusion, optic neuritis, platelets &lt;25 x 10⁹/L</td>
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Table 2. Definitions of mild, moderate and severe systemic lupus erythematosus (SLE) activity¹
three months; those who are in remission or have stable low activity disease should be seen every 6–12 months. Monitoring should cover SLE manifestations, risks associated with pregnancy, drug toxicity (e.g., due to immunosuppressants) and co-morbidities such as atherosclerotic disease, osteoporosis, avascular necrosis, malignancy and infection. There is always a risk of flare contributing to cumulative damage and patients should be advised to report new or significant worsening of clinical manifestations.

For all patients, monitoring should be more frequent if there is renal involvement or if treatment is being withdrawn or stopped, even during remission. The guideline provides detailed advice on interpreting laboratory tests and on the value of monitoring autoantibody levels for disease activity, predicting flares and adjusting treatment.

Managing mild SLE
Treatment of mild SLE relieves patients of troubling symptoms and may prevent progression to more severe forms. There are five options: corticosteroids, hydroxychloroquine (or the less well-tolerated chloroquine), methotrexate, NSAIDs and sunscreens.

Topical steroids are recommended for skin manifestations and, via intra-articular or intramuscular injections, for arthritis. When local treatment is not possible or ineffective, a short course of oral prednisolone can induce remission and may also be offered to women who are trying to conceive, are pregnant or are breast-feeding. Doses should be the lowest possible due to adverse effects and the risk of contributing to chronic damage.

Hydroxychloroquine, one of the few drugs licensed specifically for SLE (the others are steroids and belimumab), has anti-inflammatory and anti-thrombotic activity. It is the most frequently prescribed drug for SLE and it should be given to all patients with mild lupus to prevent flares and the development of damage, and to improve survival. It can improve skin and joint symptoms, myalgia, fever, fatigue and pleurisy and reduces the development of renal disease; it is also steroid-sparing. Patients taking hydroxychloroquine should have normal renal and liver function. Although treatment is usually well tolerated, the risk of retinopathy increases with duration of use and cumulative dose. In practice, the average duration of treatment is about six years and retinal damage, though unpredictable, is unlikely within seven years. Optician eye tests should be carried out at baseline and annually, with more detailed ophthalmological examinations after five years.

Methotrexate is not licensed for the treatment of SLE but is used to control inflammatory arthritis and rash. It may be co-prescribed with hydroxychloroquine to minimise steroid use. Caution is needed in patients with nephritis, who are at increased risk of toxicity, and it is teratogenic.

NSAIDs are useful in the short term to treat inflammatory arthralgia, myalgia, chest pain and fever when paracetamol is not sufficient. Patients with nephritis are at increased risk of renal toxicity and SLE generally is associated with greater susceptibility to allergic reactions, aseptic meningitis, cutaneous reactions and hepatotoxicity.

People with SLE have an abnormal reaction to UV light, and both UVA and UVB can induce cutaneous lupus. Patients should be informed about sources of UV radiation and advised to cover up in the sun. High-factor sunscreens (five stars for UVA protection; SPF factor 30–50 for UVB) can be prescribed on the NHS.

Managing moderate SLE
Immunosuppressants should be prescribed in addition to hydroxychloroquine to reduce disease activity, prevent the risk of flares, reduce the risk of damage accumulation and to minimise exposure to steroids. Options include leflunomide and, in patients with non-renal disease, methotrexate, azathioprine, mycophenolate mofetil, ciclosporin and tacrolimus. Steroids remain an option. The dose and choice of drug should be altered if the response to treatment is weaker than anticipated within the expected time frame.

If SLE is refractory to these drugs, rituximab or belimumab (which target B cells by different mechanisms) are further options but should only be prescribed at specialist centres. NHS England has a commissioning policy for rituximab for this indication. NICE has recommended belimumab as add-on therapy for patients with SLE towards the more severe end of moderate activity. Patients prescribed either drug must be enrolled in the British Isles Lupus Assessment Group Biologics Register.

Managing severe SLE
Other aetiologies, such as infection, should be excluded in patients presenting with severe SLE, including renal and neuropsychiatric manifestations. The evidence base is strongest for the management of nephritis, less so for neuropsychiatric disease and weakest for other organ-specific manifestations. The underlying aetiology may be inflammatory, thrombotic or both and this determines the choice of treatment with an immunosuppressant and/or anticoagulant. Regimens for immunosuppression include a high-dose steroid, usually with a second immunosuppressant, to induce remission; and mycophenolate mofetil or ciclosporin for lupus nephritis and refractory, severe non-renal disease. If such strategies are ineffective or not tolerated, rituximab or belimumab are further options.

Patients with refractory cytopenias, thrombotic thrombocytopenic purpura, rapidly deteriorating acute confusional state or the catastrophic variant of antiphospholipid syndrome may be considered for treatment with IV immunoglobulin G and plasmapheresis.

The guideline in practice
The authors repeat that the diagnosis and assessment of SLE “can be difficult due to multisystem involvement and variable laboratory and serological test results”. They acknowledge that relatively few of the developments in management emerging in the past 10 years come from high-quality randomised controlled trials (and given the rarity of SLE that is not surprising) but they believe the new guideline “will increase knowledge and raise the standard of care for patients with lupus”. They foresee no barriers to imple-
mentation other than funding limitations for rituximab and belimumab. A form to facilitate audit of the guideline is available from the BSR (www.rheumatology.org.uk).

People with suspected or known SLE should be referred to a clinician experienced in SLE care and managed by a multidisciplinary team that includes nurse specialists and physiotherapists. The team should be able to call on a wide range of specialties within a collaborative clinical network that involves regional specialist centres, local hospitals and GPs.

The aim of drug treatment is to reduce disease activity to a low level (which is not defined) or remission to reduce cumulative damage from the disease, and to minimise the use of steroids. If drug treatment is not working as expected, the possibility of non-adherence should be considered.

The guideline recommends patients are given personalised advice, written information and education about SLE and its treatment. Measures such as sun avoidance, adequate vitamin D intake, lifestyle change (weight control, exercise, not smoking), reducing atherosclerotic risk factors, cancer screening, contraception and pregnancy planning are heavily dependent on personal motivation, so the patient’s role (and the professional’s role in fostering it) might usefully have received greater prominence.

Summary
The first UK guideline on the management of SLE provides a comprehensive, evidence-based structure for a disorder that crosses the boundaries of many specialties and presents diagnostic and therapeutic challenges. Though the details are of interest primarily to specialists, everyone involved in providing or commissioning services for people with SLE will benefit from a greater understanding of the need for careful and thorough investigation, and the limitations and potential benefits of treatment. While implementing this advice, clinicians need to remember the many relevant guidelines that contribute to overall management but fall outside the immediate remit of rheumatology.

References

Declaration of interests
None to declare.
Steve Chaplin is a medical writer specialising in therapeutics