



The 2026 British Society for Rheumatology guideline for the management of children, young people and adults with systemic lupus erythematosus

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§See [Supplementary Material S1](#) available at *Rheumatology* online for a list of the British Society for Rheumatology Guidelines Steering Group.



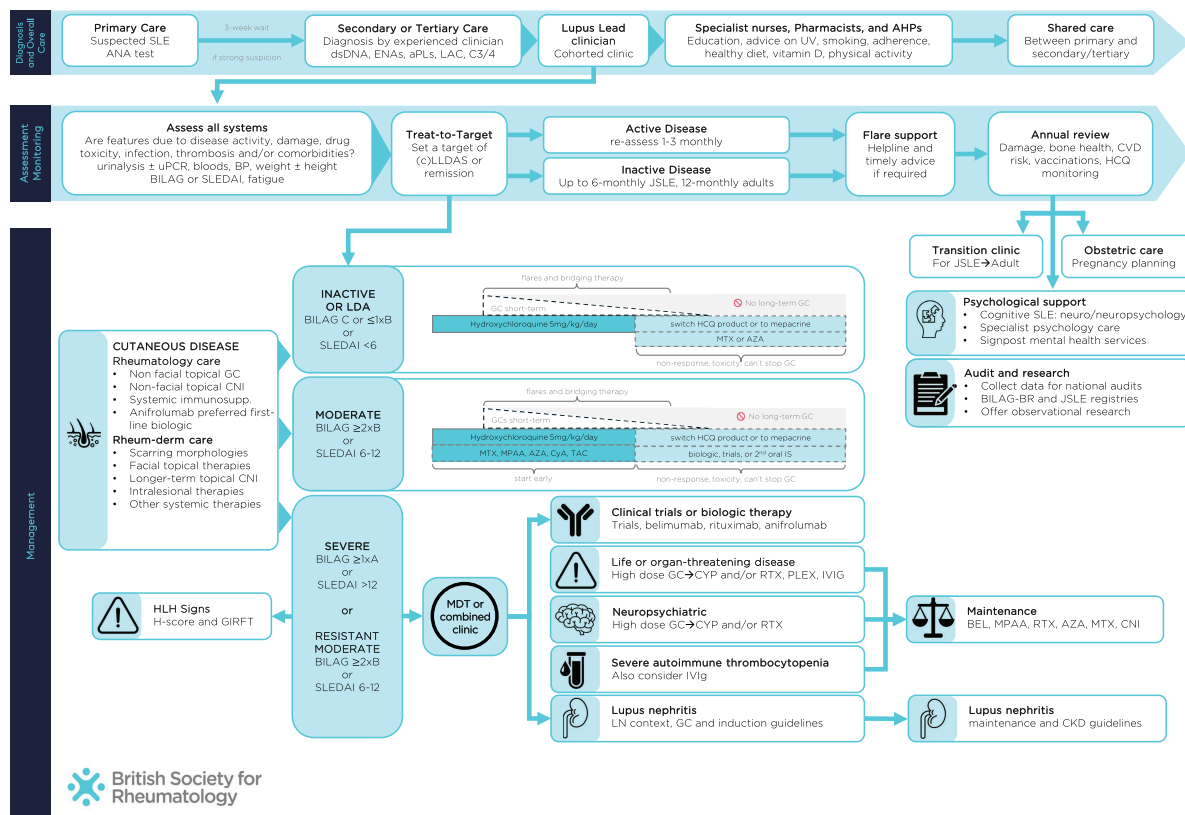
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Abstract

Systemic lupus erythematosus (SLE) is a lifelong autoimmune condition with multi-system involvement that is associated with morbidity, mortality, and poor quality of life. The key aim of management should be to empower individuals with SLE to manage their condition, suppressing systemic disease activity, and preventing organ damage. This guideline builds on and expands the recommendations developed for the first guideline published in 2017 for adults living with SLE. This comprehensive life-course guideline was developed according to the British Society for Rheumatology Guidelines Protocol by a Guideline Working Group (GWG) comprising healthcare professionals with expertise in paediatric and adult SLE, and people with lived experience. The GWG reviewed published guidelines, undertook a systematic literature review and utilised expertise from specialist lupus centres across the UK and patient representatives to formulate a list of 102 recommendations with corresponding strength of recommendations and agreement scores. These recommendations encompass advances in the assessment, diagnosis, monitoring, general approaches to management, non-pharmacological and pharmacological management of SLE, organ-specific treatment including lupus nephritis and cutaneous lupus erythematosus, as well as the delivery of care in the context of the UK healthcare system. Furthermore, we have provided research and audit recommendations to support equitable access to care and improve health outcomes in SLE.

Graphical abstract



Keywords biological DMARD, guideline, lupus nephritis, management, systemic lupus erythematosus

Introduction

Background

Systemic lupus erythematosus (SLE) is a complex, life-long autoimmune disease that causes inflammation and subsequent damage to multiple organs. Combinations of genetic, environmental, immunological and hormonal factors are thought to play a key role in the pathogenesis of SLE. It can present at any age with 15–20% of people developing SLE in childhood. In adults, females are nine times more likely to be affected than males with a peak incidence in the reproductive years [1]. This sex difference is less pronounced in childhood (before puberty) [2]. Around one in 1000 adults in the UK have SLE [3]. The prevalence and severity of SLE varies according to ancestry and age. Globally, SLE is most common in South Asians, East Asians and other non-White groups, compared with White individuals. People of Black African ancestry, East Asian, South Asian and Hispanic have more severe disease and damage accumulation [4]. In the UK, SLE is most frequently observed in people of Black African and South Asian ancestry, thus prevalence across regions of the UK varies in line with these demographics [3, 5]. Similar to the global picture, in the UK, these ancestral groups are associated with more severe lupus and have poorer outcomes compared with people of European ancestry [6]. Juvenile-onset SLE (JSLE) has a more aggressive presentation and disease course compared with adult-onset SLE [7]. For example, higher numbers of children have renal and neurological complications [8] and 20% of children accrue organ damage within 1 year of diagnosis [9].

Once SLE is diagnosed, problems are lifelong, typically characterised by periods of relapse and remission following treatment with immunosuppressants. Mortality is high in SLE; there is an 18-fold increase in standardised mortality rate in JSLE and a 3-fold increase in adult-onset SLE compared with the general population, particularly if lupus nephritis (LN) develops [7, 10–12]. Although death may occur due to disease activity in SLE, the top three causes of mortality are long-term complications such as infection, cancer and cardiovascular disease [13]. While survival has improved markedly over the last 40 years in the UK [14], adults with SLE still die on average 25 years earlier than expected [15], with mortality rates of up to 10% within 10 years of JSLE diagnosis [16]. Direct and indirect healthcare costs also increase over time, particularly for those with moderate-to-severe SLE [17, 18]. Furthermore, SLE negatively impacts on school attendance and performance [19], work productivity, career choices [20] and significantly impairs quality of life similarly to other chronic diseases such as congestive cardiac failure but at a younger age [21]. Thus, early diagnosis, empowering individuals to manage their condition, instituting appropriate immunosuppression swiftly and limiting toxicity from treatment are key to mitigating organ damage and mortality from SLE, and improving quality of life.

Rationale for guideline development

The rationale behind the update of the first British Society for Rheumatology (BSR) guideline in 2017 for the management of adult SLE [22] is described in the Guideline Scope [23]. In summary, since the last literature search underpinning that guideline, there have been rapid advances in the diagnosis, assessment and treatment of SLE. For example, the only licensed biologic therapy in 2017 was belimumab (B-cell activating factor inhibitor), while rituximab (anti-CD20

monoclonal antibody) was commissioned through the NHS England (NHSE) Clinical Commissioning Policy. Since that guideline, new therapies have been licensed for adult SLE such as belimumab in the context of LN, voclosporin (a calcineurin inhibitor) in LN, anifrolumab (a type I interferon receptor monoclonal antibody) in non-renal SLE and obinutuzumab (a type 2 anti-CD20 monoclonal antibody) in LN. Obinutuzumab also has recently met its primary end point in a Phase III randomised controlled trial (RCT) in non-renal SLE [24], and licensing for this indication is expected to follow soon. At the time of this BSR guideline, of the new licensed therapies above, only voclosporin [25] and obinutuzumab [26] (both in LN) are approved by National Institute for Health and Care Excellence (NICE). Each of these therapies comes with nuances regarding those who are most likely to benefit. Therefore, guidance is needed on how these new therapies fit within UK practice that already includes many off-label therapies.

Care of SLE is complex, involving many specialties and we considered that there were some areas where more detailed guidelines would improve care. This guideline builds on and widens the scope from the 2017 BSR SLE guideline by incorporating recommendations on the non-pharmacological approaches, the management of cutaneous lupus erythematosus (CLE) and delivery of care to harmonise the approach within the UK system and define auditable standards. Perhaps the most significant developments in evidence are for LN. Since the 2017 BSR SLE guideline, the historic standard of care, mycophenolate (MMF) with glucocorticoids (GC) is now known to be inferior to several subsequently described therapies and combinations of therapy for remission induction of LN [27–29]. Finally, there has previously been no national guidance on how to manage JSLE. To promote equity in care and represent the needs of children and young people in whom evidence from adults may have relevance, our SLE guideline is the first to adopt a whole life-course approach.

Objectives of the guideline

The objective of this life-course guideline is to produce comprehensive, patient-focused, evidence-based and expert consensus recommendations for the management of people with SLE that cover the diagnosis, assessment, monitoring, non-pharmacological and pharmacological management, and the delivery of care in the UK, across all four nations.

Target audience

Our target audience includes paediatric, adolescent and adult rheumatologists, dermatologists, nephrologists, immunologists, neurologists, respiratory physicians, obstetricians, GPs and other clinicians involved in the management of people with SLE, specialist nurses, pharmacists and allied healthcare professionals (AHPs) involved in their care, policymakers, as well as people with SLE and their carers.

Areas the guideline does not cover

- Neonatal lupus and those with lupus-like syndromes (e.g. monogenic interferonopathies).
- Detailed management of contraception and reproductive health. Instead, we refer to other national and international relevant guidelines.

- Safety use of drugs during pregnancy and breastfeeding. Instead, we refer to the relevant BSR guideline [30].
- Specific management of all complications/comorbidities associated with SLE and its treatment, including cardiovascular risk, osteoporosis, infection and cancer risk. These should be managed as for other patients with similar risk factors according to national and international guidelines.
- Management of thrombosis will be limited to secondary antiphospholipid syndrome (APS) in people with SLE.

Stakeholder involvement

This guideline was produced by a multidisciplinary guideline working group (GWG), co-chaired by Associate Professor Md Yuzaiful Md Yusof and Professor Edward M Vital (both are adult consultant rheumatologists), and included representation from Lupus UK (Miss Debbie Kinsey; Mr Paul Howard left the GWG following publication of Guideline Scope), experts by experience members (Miss Naomi Maxwell and Miss Dalila Tremarias; Miss Jenny Ainsworth and Miss Morgan Bown left the GWG following publication of Guideline Scope), paediatric consultant rheumatologists (Dr Eve MD Smith—Lead, Dr Kate Armon, Professor Michael W Beresford, Dr Elena Moraitis and Dr Clarissa Pilkington), an adolescent consultant rheumatologist (Dr Natasha Jordan), adult consultant rheumatologists (Professor Christopher J Edwards, Dr Bridget Griffiths, Professor Caroline Gordon, Professor David Isenberg, Dr Arvind Kaul, Dr Peter Lanyon, Dr Sarah Skeoch, Dr Chris Wincup and Dr Asad Zoma), an embedded BSR Guidelines Steering Group (GSG) member and an adult consultant rheumatologist (Dr Zoe McLaren), a GP (Professor Christian Mallen), adult consultant nephrologists (Professor Liz Lightstone and Dr Ruth J Pepper), a paediatric consultant nephrologist (Professor Stephen D Marks), a dermatologist (Dr Philip M Laws), two resident doctors in paediatric and adult rheumatology, respectively (Dr Hanna Lythgoe and Dr Antonios Psarras), rheumatology specialist nurses in adult and paediatric rheumatology, respectively (Miss Rebecca Gilman and Miss Heather Rostron), pharmacists in adult and paediatric rheumatology (Miss Kalveer Flora and Miss Clare Nash), a physiotherapist (Miss Jade Skeates) and a podiatrist (Dr Lindsey Cherry). The systematic literature review was led by three researchers with evidence synthesis expertise (Miss Nadia Corp, Mr Lambert Felix and Professor Danielle A van der Windt).

Methods

Rigour of development

This guideline was developed in line with the BSR Guidelines Protocol (version 5.4, November 2023) using Grading of Recommendations, Assessment, Development and Evaluation (GRADE) [31] and Appraisal of Guidelines for Research and Evaluation II (AGREE II) [32] methodologies. Following a virtual meeting, the scope of the guideline was agreed to address 13 key questions and was then published [23]. The full guideline was then developed over a series of seven virtual meetings of the full GWG, three rounds of Delphi, and the final draft submitted to the BSR GSG for stakeholder and internal review and feedback.

Systematic literature review

Searches

The literature searches were informed by the Guideline Scope [23]. To identify relevant RCTs, an information specialist (N.C.) performed searches across seven databases (MEDLINE, EMBASE, AMED, EMCARE [all OVID]; CINHALPlus, PsycINFO [both EBSCO]; and Cochrane CENTRAL) on 7 November 2023. The start date of searches was from inception for JSLE, as well as interventions that were not covered by previous related guidelines (treat-to-target, dietary advice, fatigue management strategies, promotion of bone health). Given this was an update, date limits were imposed for adult studies as follows:

- Non-renal SLE: 2015 onwards (update from 2017 BSR SLE guideline [22], search date: June 2015).
- LN: 2018 onwards [update from 2019 European Alliance of Associations for Rheumatology (EULAR)-European Renal Association (ERA)-European Dialysis and Transplant Association (EDTA) Renal Recommendations [33], search date: December 2018].
- Cutaneous lupus erythematosus: 2020 onwards [update from 2021 British Association of Dermatologists (BAD) Guidelines for management of cutaneous lupus erythematosus [34], search date: Dec 2020].
- Non-pharmacological approaches to SLE: 2021 onwards [update from 2023 EULAR recommendation [35] (search date: June 2021)] for sun protection, smoking cessation, exercise including physiotherapy, self-management, patient education, multidisciplinary interventions and psychological support.

The search utilised both subject headings and text word searching and combined terms for systemic lupus erythematosus AND randomised controlled studies using validated search filters, AND either (i) a date limit or (ii) terms for paediatrics, fatigue management, bone health, dietary advice or treat to target; this enabled a single search to be carried out in each database to cover all guideline research questions concerning treatment interventions. No language restrictions were applied. Published conference abstracts of unpublished RCTs reporting main results from 2021 onwards only were also searched. We also included a key paper informing our guideline (obinutuzumab in LN) which was published after the 7 November 2023 search but before the Delphi survey.

The search results were downloaded into Endnote™ 20 (Clarivate Analytics, available at www.endnote.com) for deduplication, and the resulting unique records imported into Rayyan [36] (available at www.rayyan.ai) for title screening, and then Covidence systematic review software (Veritas Health Innovation, available at www.covidence.org) for abstract and then full text screening. Please see [Supplementary Material S2 and S3](#), available at *Rheumatology* online, for all database searches and search results.

Selection criteria

Full eligibility and selection criteria are described below and in [Supplementary Material S4 and S5](#), available at *Rheumatology* online.

Population

Studies within primary (including community), secondary or tertiary care settings were included if they concerned adults,

children or young people with SLE including LN, CLE with/without SLE, inactive to low disease or moderate-to-severe activity SLE, neuropsychiatric SLE, concurrent anti-phospholipid syndrome or pulmonary arterial hypertension. Other inflammatory arthritis, forms of nephritis and skin conditions were excluded.

Intervention/exposures

Studies of pharmacological and non-pharmacological interventions were eligible. This included any pharmaceutical drug or combination (excluding non-steroidal anti-inflammatory drugs, NSAIDs) and encompassed treat-to-target, induction and maintenance therapies for LN, vaccination (where effect on SLE treatment or outcomes reported) and treatment of women with SLE during pregnancy (if interventions specific to SLE were to prevent lupus complications). Specific non-pharmacological interventions were considered, namely sun protection, dietary advice (including supplements), smoking cessation, exercise and physiotherapy to increase physical activity, fatigue management strategies, management of comorbidities of interest (cardiovascular, infection and bone health) where their effect on SLE-related outcomes were reported, psychological support, multidisciplinary care/team, patient education and self-management. Studies were included that involved any comparator (i.e. active, sham or placebo). Studies were excluded if they focused on surgical or nursing/service level interventions, other non-pharmacological interventions including complementary and alternative therapies.

Study design

For questions related to the efficacy and safety of an intervention, we included RCTs of any design, secondary, post-hoc and sub-group analyses of individual RCTs, pooled analyses for safety outcomes only and where individual study data provided, and extension studies (i) where original allocation/blinding maintained or (ii) if allocation/blinding changes, then safety outcomes only for longest follow-up timepoint. Other study types including secondary evidence, pilot RCTs, Phase I clinical studies, RCT extension studies where the main results were reported in the previous guideline(s), quantitative primary studies that were not RCTs (i.e. non-randomised controlled studies, before-after studies, cohort studies, case series and case studies), qualitative studies, editorials, commentaries, trial protocols, letters, trials registry records and study protocols were excluded. For questions not related to intervention options, more specific, focused evidence searches were conducted. Please see [Supplementary Material S3](#), available at *Rheumatology* online.

Outcomes

Disease activity measures or responder criteria, disease impact (i.e. patient-reported outcomes), disease progression and incidence of adverse events were included. Pharmacokinetic, pharmacodynamic and economic/cost utility outcomes were excluded.

Other criteria

Studies published the same year as, or before, the respective related guidelines' search end-date were checked against the guidelines contents before being included or excluded. Full papers in any language other than English without an English translation were excluded.

Screening

Titles were single screened against eligibility criteria. Abstracts and then full texts were independently screened by two reviewers (N.C., H.L., M.Y.M.Y., A.P. and E.M.D.S.). Any disagreement was resolved by a third reviewer (D.A.vd.W.).

Data extraction and risk of bias assessment

A standardised data extraction form was developed, piloted and used to collect data for analysis using the PICO format. We collected data on the aspects below:

- Trial ID, first author and year of publication, country, type and phase of trial.
- Population characteristics including diagnosis and clinical presentation, sample size, mean age, sex, ethnicity and disease duration.
- Characteristics of interventions: treatment type, characteristics of delivery, type of control, co-prescriptions (offered to all participants as part of the intervention).
- Outcome measures and timepoints, with summary effect estimates where reported

Concurrent to data extraction, risk of bias was assessed using the Cochrane Risk of Bias v1 for RCTs [37]. Data extraction and risk of bias assessment was undertaken by one reviewer (H.L., B.G., M.Y.M.Y., A.P., C.N., J.S., S.S., E.M.D.S., L.F. and C.W.) and independently checked by a second reviewer (N.C.) for correctness and consistency. Any disagreement was resolved by consulting a third reviewer (D.A.vd.W.) if necessary.

Formulating and grading recommendations

The GWG members were allocated into six main groups: (i) Non-Therapy Aspects of SLE; (ii) Non-Pharmacological Approach; (iii) Non-Renal SLE; (iv) Cutaneous Lupus Erythematosus; (v) Lupus Nephritis; and (vi) Delivery of Care to derive and grade draft recommendations based on the evidence tables provided from the data extraction process and a review of other related documents.

Evidence tables were prepared following the data extraction process, which included a summary of study characteristics, risk of bias, and study results categorised by specific type of intervention, adults or children/young people, and specific outcomes where appropriate. An approach informed by GRADE [31] was used to summarise certainty in the evidence for each outcome across studies, separately for each treatment type and for each efficacy or safety outcome. As this was an update of an existing guideline for adult SLE, certainty in the evidence was graded from the update searches only, while from the inception date for JSLE. Certainty in the evidence was graded as high, moderate, low or very low. High certainty was based on multiple RCTs with consistent findings, adequate precision and low risk of bias. Evidence was downgraded if supported by one RCT only and if there were concerns regarding (i) study limitations (e.g. at least 50% of RCTs had high risk of bias, or all were assessed as unclear); (ii) inconsistency of findings or clinical heterogeneity; (iii) indirectness (irrelevant outcomes or delivery of intervention); or (iv) precision (insufficient sample size or poor reporting of effect estimates). Downgrading for indirectness did not occur as eligibility criteria ensured relevance of evidence for the guideline questions. [Supplementary Material S6](#), available at *Rheumatology*

online summarises the approach used to grade the certainty of the evidence. Evidence tables for key RCTs that informed our guideline is provided in [Supplementary Material S7–S34](#), available at *Rheumatology* online. Extracted data for the remaining RCTs are available in Excel format and can be shared upon justifiable request to the corresponding author. Since the field of therapeutics in SLE is experiencing a rapid advance, we also provide a ‘Horizon Scanning’ section in the evidence tables to bring the readers’ attention to some emerging and promising therapies in lupus.

In addition to the evidence tables and the guidelines cited in the ‘Search’ section above, the GWG members also reviewed other relevant documents including the 2023 update of the EULAR recommendations for the management of SLE [38], the 2024 Kidney Disease Improving Global Outcomes (KDIGO) for LN [39], the Single Hub and Access point for paediatric Rheumatology in Europe (SHARE) initiative for JSLE [40–42], the 2024 International Consensus on physical activity and exercise [43], the 2023 EULAR recommendations for the management of fatigue [44], the 2020 Royal College of Ophthalmologists guidance for hydroxychloroquine and chloroquine retinopathy [45, 46], Getting It Right First Time (GIRFT) guidance on Haemophagocytic Lymphohistiocytosis (HLH) H-score [47] and the 2021 GIRFT Programme National Rheumatology Specialty Report [48], and National Institute for Health and Care Excellence (NICE) Technology Appraisals and National Health Service England (NHSE) Clinical Commissioning Policies for SLE [25, 49, 50].

In line with the BSR protocol, the GWG members then graded level of the evidence (LoE) of each proposed recommendation into A (high), B (moderate), C (low) or D (very low). High quality (e.g. well-performed RCTs or other overwhelming evidence such as well-executed observational studies with very large effects) suggests that further research is very unlikely to change the confidence in the effect estimate. Moderate (e.g. RCTs with important limitations, or from other study designs with special strength), low (e.g. observational studies or from controlled trials with very serious limitations) or very low (e.g. non-systematic observations, biologic reasoning or observational studies with serious limitations quality) suggest that further research is likely or very likely to have an important impact on the confidence in the intervention effect estimate and may change the conclusion.

Strength of recommendation

The strength of recommendation (SoR) for each recommendation was graded as either strong = 1 or weak = 2. A strong recommendation in favour of an intervention was made when the benefits clearly outweighed the risks, or vice versa (recommendation against), for nearly all people with SLE, or weak when risks and benefits were more closely balanced or where there was more uncertainty. A draft document containing proposed voting statements from each subgroup was then circulated to the full GWG for review and revision prior to voting.

Strength of agreement

During the Delphi survey, the recommendations in the final document were completed by 32/34 GWG members with full voting rights and subjected to a vote relating to strength of agreement (SoA) on a scale of 1 [no agreement] to 100% [complete agreement] using the Qualtrics online survey platform (Qualtrics, Provo, UT, USA). Mean values were then calculated to generate a SoA score.

The GWG members also agreed for the range to be included in the full guidance to reflect the variability in agreement. Six members abstained from rating the recommendations pertaining to pharmacological interventions as they felt that they did not have sufficient clinical knowledge. While they did not disagree with the respective recommendations, they did not wish to score for each of these and did not contribute to the final SoA score for those recommendations. After Round 1 Delphi, nine draft statements were removed due to duplication and/or being no longer required. The wording of each of the 102 recommendations was revised until all GWG members were satisfied that they would score at least 80%. We interpreted the term ‘should’ in our voting statements in line with GMC Good Medical Practice, which says that in contrast to ‘You must’, ‘You should’ is used for duties or principles that either may not apply to you or to the situation you are currently in, or you may not be able to comply with because of factors outside your control [51].

After completion of Round 3 Delphi (April 2025) and during preparation of the full BSR guideline manuscript, three key guidelines were fully published: (i) the 2024 American College of Rheumatology (ACR) guideline for the screening, treatment and management of LN [52]; (ii) the 2025 EULAR recommendations for the management of SLE with kidney involvement [53]; and (iii) the 2025 ACR guideline for the treatment of non-renal SLE [54]. The BSR GWG reviewed these and agreed that our recommendations were already aligned with the latest guidelines above where relevant, but more granular and up to date in some respects. Therefore, we did not have to revise our recommendations but discussed these guidelines in the narrative. Importantly, our recommendations are tailored for the care of people with SLE within UK system.

The Guideline

For each question addressed by the literature review, we provide the recommendations followed by the SoR (1 or 2), LoE (A, B, C or D) and mean (range) of SoA score across the GWG in percentage. We also provide the rationale supporting the recommendations. The full list of recommendations is provided in [Table 1](#).

Diagnosis: what clinical and serological features should prompt consideration of a diagnosis of SLE in primary or secondary care?

Recommendation 1 People suspected to have SLE should be referred to secondary or tertiary care for diagnosis. Those with a strong suspicion of a new diagnosis of SLE should be prioritised as a 3-week wait target (SoR 1 and LoE C) [SoA (range) 96.4% (83–100)].

Importance of timely referral to secondary or tertiary care for diagnosis

SLE is heterogeneous in terms of pathophysiology and clinical features. Early symptoms may be non-specific, and several other

Table 1 BSR guideline for the management and treatment of children, young people and adults with SLE.

Statements and strength of recommendation	Strength of agreement, mean (range) %
Diagnosis: what clinical and serological features should prompt consideration of a diagnosis of SLE in primary or secondary care?	
1. People suspected to have SLE should be referred to secondary or tertiary care for diagnosis. Those with a strong suspicion of a new diagnosis of SLE should be prioritised as a 3-week wait target (1C).	96.4 (83–100)
2. SLE should be diagnosed by clinicians experienced in its management and requires a combination of clinical, laboratory and immunological features attributable to SLE (2B).	98.3 (81–100)
3. Current classification criteria (SLICC 2012 or EULAR/ACR 2019) may be used as a guide but not as diagnostic criteria (2C).	97.7 (82–100)
4. Antinuclear antibody (ANA) test should only be performed where there is reasonable clinical suspicion of SLE or related diseases. ANAs are present in 95–99% of people with SLE, so a negative test makes SLE unlikely (results can fluctuate so a negative test does not rule out SLE where there have been past positives) (2B).	95.2 (80–100)
5. ANA test should be supplemented by tests for anti-dsDNA antibodies, extractable nuclear antigen antibodies and C3/C4 complement levels since the presence of anti-dsDNA antibodies (2B), low complement levels (2C) and/or anti-Smith (Sm) antibody (2C) is highly supportive of SLE diagnosis in people with relevant clinical symptoms.	97.4 (80–100)
6. In children and young people with symptoms suggestive of SLE but negative ANA, monogenic lupus and complement deficiencies should be considered (2C).	98.7 (91–100)
7. Antiphospholipid antibodies (aPLs) and lupus anticoagulant (LAC) should be tested in all people with SLE at diagnosis (2B). A positive test requires confirmation on two occasions at least 12 weeks apart (2B).	98.0 (81–100)
Assessment: what is the best way to assess people with SLE?	
8. Clinical manifestations in people with SLE should be assessed to determine whether they are due to disease activity, damage, drug toxicity, infection, thrombosis or the presence of comorbidities (2B).	98.1 (80–100)
9. People with SLE should be assessed for manifestations in all systems and relevant clinical examination and investigations performed (2C).	98.9 (90–100)
10. The use of a validated disease activity tool such as BILAG-2004 and SLEDAI-2K is recommended (2B).	97.0 (80–100)
11. Validated instruments should be used to categorise disease activity as absent, mild, moderate and severe, with the occurrence of flares (2C).	96.5 (84–100)
12. Urinalysis and blood pressure should be performed at every visit (2C).	97.2 (80–100)
13. In people with SLE with unexplained fever, especially when associated with falling blood counts and high ferritin, evolving HLH/MAS should be considered together with other differentials such as infection or flare. Investigate as per the GIRFT guidance, including calculation of the H-score (2C).	97.1 (80–100)
14. Cognitive impairment affecting daily activities, decisions (and schooling in JSLE), should be assessed in collaboration with a neurologist, neuropsychologist or other experienced professionals (2C).	96.0 (84–100)
Monitoring: what is the best way to monitor people with SLE?	
15. Those with active disease should be reviewed at least every 1–3 months (2C), with blood pressure (1A), urinalysis (1A) and renal function including proteinuria estimation (1A), anti-dsDNA antibodies (2B), complement levels (2C), inflammatory markers (2C), full blood count (2C) and liver function tests (2D) forming part of the assessment, and further tests as necessary (2D).	95.0 (80–100)

(continued)

Table 1 (continued)

Statements and strength of recommendation	Strength of agreement, mean (range) %
16. Body weight should be checked at each visit, and for children and young people with SLE, height should also be checked at each visit to monitor linear growth (2C).	97.0 (86–100)
17. People with SLE with stable low disease activity or in remission can be monitored less frequently. The interval will vary according to age, initial severity, duration of remission and therapy changes, but should be no longer than 12-monthly (adults) or 6-monthly (children) (2D).	97.4 (80–100)
18. People with SLE should have a systematic assessment of disease damage every 12–24 months. The SLICC/ACR damage index may be used (2C).	96.8 (82–100)
19. Immunosuppressive therapy and biologics may lead to toxicities. Close monitoring of drugs by regular laboratory tests and clinical assessment should be performed in accordance with drug monitoring guidelines (2D).	99.1 (90–100)
20. The presence of aPLs is linked to thrombotic events, organ damage and adverse pregnancy outcomes (2B). If previously negative, aPLs should be re-evaluated before pregnancy, major surgery or following a new severe manifestation or vascular event (2D).	96.7 (80–100)
21. Anti-Ro/SSA and anti-La/SSB antibodies are associated with neonatal lupus (including congenital heart block) and should be re-assessed prior to pregnancy, and pre-pregnancy counselling provided (1A).	98.5 (81–100)
Treatment target: what is the role of a treatment target in the management of SLE?	
22. Early diagnosis, regular screening for organ or system involvement, prompt initiation of treatment and regular assessment of adherence is recommended in the management of SLE (2C).	98.8 (80–100)
23. The primary treatment goal should be to achieve remission, or if remission is not possible, Lupus Low Disease Activity State (or cLLDAS in childhood-onset SLE), following a treat-to-target (T2T) approach (2C).	97.4 (80–100)
Non-pharmacological approach: what non-pharmacological interventions are supported by evidence and/or expert consensus to inform a BSR guideline?	
24. People with SLE and their parents/carers should be offered age, culture and language-appropriate education and self-management support as part of routine care (1C).	96.9 (80–100)
25. Clinicians should promote and monitor adherence. For example: discuss the importance of adherence on disease control and long-term outcomes, monitor prescriptions and drug levels, practice shared decision-making on treatment and route of administration (1D).	98.0 (87–100)
26. People with SLE should be advised at diagnosis and more frequently as necessary to use high sun protection factor (SPF), broad-spectrum UV-A and UV-B sunscreen (1B) and to consider safe sun exposure strategies such as reduced sun exposure and the use of protective clothing (1D).	96.9 (84–100)
27. In people with SLE, smoking habits should be assessed, and people guided to cessation strategies (1C).	98.2 (83–100)
28. Physical activity should be encouraged as appropriate to disease status in adults (1B) and children (1C) with SLE. This will include tailored advice for some patients.	97.0 (80–100)
29. A healthy, balanced diet, as recommended for people without SLE, should be recommended for people with SLE. More specific advice may be required for those with LN (1D).	96.8 (80–100)
30. Clinicians should recommend that people with SLE take a daily vitamin D supplement throughout the year, particularly in autumn and winter (1B). Where deemed appropriate, vitamin D levels should be tested and additional supplementation recommended if below the normal range (1C).	96.6 (80–100)

(continued)

Table 1 (continued)

Statements and strength of recommendation	Strength of agreement, mean (range) %
31. People with SLE are at increased risk of cardiovascular comorbidities, therefore assessment and management of modifiable risk factors (e.g. hypertension, dyslipidaemia, diabetes, high BMI and smoking) should take place at baseline and at least annually, using appropriate risk assessment tool where applicable (1B).	96.6 (83–100)
32. The importance of receiving eligible vaccinations should be emphasised at least annually. Additionally, when boosters or new vaccinations are recommended, this guidance should be reinforced (1C).	98.4 (87–100)
33. Annual assessment and management of bone health should be performed including diet, exercise, lifestyle factors and medications. Vitamin D status and bone density should be assessed where indicated (2C).	97.6 (87–100)
34. Health professionals should incorporate assessment of fatigue severity, impact and coping strategies alongside disease activity assessment during clinical consultations (1D).	95.4 (80–100)
35. Psychological support should be available to people with SLE, whenever possible as part of the multidisciplinary team (MDT) (1C).	96.7 (83–100)
36. Specialist psychology care should be available for specific problems associated with SLE in adults (1A) and children (1C).	96.3 (80–100)
37. All healthcare professionals assessing people with SLE should know how to signpost towards and/or refer to mental health services where there is an identified need for support (1D).	97.8 (83–100)
Antimalarials in SLE: general recommendations and what is the best evidence for monitoring therapies?	
38. Hydroxychloroquine (HCQ) is recommended for all people with SLE unless contraindicated (1A), at long-term target dose of 5 mg/kg/day (based on actual body weight, usual maximum 400 mg/day) (2C). Dose can be individualised based on risk of flare (2B), risk of retinal toxicity (2C) and other adverse events (2D). Dose reduction of 50% may be needed if eGFR < 30 mL/min/1.73 m ² (2C).	99.1 (91–100)
39. If people with SLE suffer persistent non-serious adverse effects with HCQ, consider switching to a HCQ product made by a different manufacturer as excipients may differ (2C).	97.6 (81–100)
40. We recommend following the Royal College of Ophthalmologists (RCOphth) guidelines for HCQ with ocular toxicity monitoring at 5 years, then annually thereafter (1B for adults, 2D for JSLE). For higher risk patients including those on HCQ dose of >5 mg/kg/day based on actual body weight, on tamoxifen, those with renal impairment, and those who have taken chloroquine for greater than one year, annual screening is recommended (2B).	98.1 (90–100)
41. Pathways should be established locally to facilitate ocular toxicity monitoring in accordance with the RCOphth Guidelines (2D).	97.9 (83–100)
42. The date of commencement of HCQ and dosing should be recorded in the medical records in a way that is easily retrievable (2D).	95.4 (80–100)
43. When using a standard HCQ dose, baseline or monitoring ECGs are not required unless there are specific drug-drug interactions, especially with other therapies causing long-QT (2C).	97.0 (80–100)
Non-renal SLE: what is the best evidence for the management of inactive or low disease activity SLE?	
44. Other treatments to be considered for the management of mild non-organ threatening disease that is refractory to HCQ include methotrexate (1B), mepacrine (2C) and azathioprine (2C) (azathioprine especially for those who may become pregnant) (2C).	97.4 (90–100)
45. Glucocorticoids (GC) including topical preparations, intra-articular or intra-muscular injections or intravenous methylprednisolone may be used depending on the type and severity of organ involvement, as a bridging therapy to settle a flare and/or while HCQ or a new or increased dose of an immunosuppressant takes effect (2C).	97.5 (85–100)

(continued)

Table 1 (continued)

Statements and strength of recommendation	Strength of agreement, mean (range) %
46. Long-term maintenance treatment with oral GC is not routinely recommended to treat disease activity. If used, target dose should be as low as possible aiming for ≤ 5 mg/day prednisolone (or equivalent) in adults (0.1 mg/kg/day, up to 5 mg/day in children) (1B).	97.4 (86–100)
Non-renal SLE: what is the best evidence for the management of moderate-to-severely active SLE?	
47. In people with SLE with moderate disease activity but no evidence of organ or life-threatening disease, immunosuppression such as methotrexate (1B), mycophenolate (2B), azathioprine (2C) or ciclosporin/tacrolimus (2C), in addition to HCQ, should be started early.	98.8 (92–100)
48. In people with SLE with moderate-to-severe non-renal disease or the inability to withdraw GC despite the use of at least one immunosuppressant, discuss biological therapy and consider clinical trials with a specialised centre MDT (follow local processes for urgent cases) (2C).	98.2 (86–100)
49. Belimumab is recommended as add-on treatment in autoantibody-positive people with SLE aged five or over with high disease activity [i.e. defined as at least 1 serological biomarker (positive anti-dsDNA or low complement) and a SLEDAI score of ≥ 10] despite standard treatment (1A).	96.9 (80–100)
50. Depending on specific patient presentation and situation, rituximab (2B) or anifrolumab (1A) may be more appropriate than belimumab or clinical trials in non-renal SLE.	97.1 (80–100)
51. Intravenous immunoglobulin could be considered for severe autoimmune thrombocytopaenia attributed to SLE (1B).	98.3 (87–100)
52. In people with SLE with active and non-thrombotic neuropsychiatric disease attributed to SLE, GC and intravenous cyclophosphamide (2C), rituximab (2C) or combination of cyclophosphamide and rituximab (2C) should be considered.	97.6 (80–100)
53. For remission induction of people with SLE with organ-threatening or life-threatening non-renal disease attributed to disease activity, high-dose GC with intravenous cyclophosphamide (2C), rituximab (2C) or combination of cyclophosphamide and rituximab (2C) should be considered. Plasma exchange and intravenous immunoglobulin could be considered (2D).	97.0 (81–100)
54. Following remission induction for organ-threatening or life-threatening non-renal disease attributed to SLE, maintenance therapy with belimumab (1A), anifrolumab (1A), mycophenolate (1B), rituximab (2C), azathioprine (2C), methotrexate (2C) or ciclosporin/tacrolimus (2C) should be considered.	98.3 (87–100)
Organ-specific approach: what is the best evidence for management of cutaneous lupus erythematosus?	
55. In people with SLE with cutaneous manifestations, consider drug-induced lupus as a cause (2C).	97.4 (80–100)
56. Scarring and/or refractory cutaneous involvement in SLE should be managed in a timely manner in conjunction with dermatologists (1D).	98.3 (80–100)
57. Offer very potent/potent topical GC as a first-line therapy in cutaneous involvement (non-facial) attributed to SLE, for up to 4 weeks (1B).	95.9 (80–100)
58. Consider topical GC on the face with appropriate dermatology guidance (2C).	94.0 (80–100)
59. Offer topical calcineurin inhibitors in cutaneous involvement (non-facial) attributed to SLE for up to 4 weeks and longer if agreed with dermatologists (1B).	96.8 (80–100)
60. Offer very potent/potent topical GC and/or calcineurin inhibitors as an adjuvant to systemic therapy when there is widespread cutaneous involvement in SLE (1B).	96.2 (80–100)

(continued)

Table 1 (continued)

Statements and strength of recommendation	Strength of agreement, mean (range) %
61. Consider concomitant short-term systemic GC alongside other systemic and topical therapies, especially in people with SLE at high risk of scarring with appropriate guidance by dermatologists (2D).	94.9 (80–100)
62. In refractory cutaneous SLE, optimise hydroxychloroquine by adding mepacrine (2B) and refer to dermatology to consider other therapeutic options; for example, intralesional GC (2D), retinoids (2C), dapsone (2C), clofazimine (2C), thalidomide (2C), lenalidomide (2C) or ciclosporin (2C).	95.2 (81–100)
63. For refractory cutaneous involvement in SLE, the best evidence is for anifrolumab and this should be used as first-line biologic if available (1B). If not available, other biologics can be considered as per management of non-renal SLE (2B).	97.0 (80–100)
Organ-specific approach: what is the best evidence for general management of lupus nephritis?	
64. All people with lupus nephritis should be managed in combined services with rheumatology and renal expertise for use of adjunctive therapies in addition to immunosuppression, and to ensure optimal management of acute kidney injury and CKD. Consult the KDIGO, EULAR, ACR and SHARE guidelines as appropriate (2D).	97.8 (80–100)
65. A timely kidney biopsy should be included in the initial diagnosis of lupus nephritis (2B).	98.5 (81–100)
66. For detailed guidance on monitoring for proteinuria, the role of biopsy and other diagnostic tests in adults and children, consult the KDIGO, EULAR, ACR and SHARE guidelines, respectively (2B).	98.1 (80–100)
67. Before deciding treatment, identify important prognostic factors including first episode of nephritis or a relapse, prior therapy failures, patient understanding and potential adherence concerns, histological LN class, baseline kidney function and degree of chronicity on the biopsy, presence of crescents or tubulointerstitial lesions, renal function, level of proteinuria, non-renal SLE features, relevant renal and non-renal co-morbidities, and GC toxicity (prior or future risk) (2B).	98.0 (80–100)
Organ-specific approach: what is the best evidence for active lupus nephritis induction treatment?	
68. For adults with LN requiring induction therapy, start GC therapy with 250–500 mg intravenous methylprednisolone/day for 1–3 days. For children and young people with LN, 10–30 mg/kg/day up to 500 mg total for 1–3 days (2B). Higher doses, up to 1000 mg/day, may be used for adults, children or young people under expert guidance (e.g. severe renal failure or multi-organ involvement).	98.2 (90–100)
69. Following IV methylprednisolone, adults with LN should be treated with one of the KDIGO GC regimens with the taper planned from the outset (2B).	96.3 (80–100)
70. In adults with LN without severe histology or high-risk features, and while treatment response remains acceptable, the KDIGO GC reduced-dose regimen is preferable and is especially suitable with combination immunosuppressants and/or those with high risk of GC toxicity (2B).	96.6 (81–100)
71. In adults with LN with severe histology, severe extra renal disease, not able to take combination immunosuppressants or poor initial response, the KDIGO moderate (or rarely high dose) GC regimen may be preferable (2B).	95.3 (80–100)
72. For children and young people with SLE, a similar principle should be followed for oral GC prescription in LN induction therapy (prescribing proportionate to patient characteristics and planning GC taper in advance) using weight-based dosing as appropriate (2B).	96.6 (80–100)
73. Planned GC tapering should be supervised by a physician and adjusted as appropriate to response (2B).	98.7 (90–100)

(continued)

Table 1 (continued)

Statements and strength of recommendation	Strength of agreement, mean (range) %
74. People with SLE with new or relapsing class III or IV LN (with or without class V) should be offered combination immunosuppressant regimen including GC, HCQ and one of these combinations of immunosuppressants: • mycophenolic acid analogues (MPAA) and obinutuzumab (1A, 2D for JSLE); • MPAA and calcineurin inhibitors (CNI) (voclosporin 1A for adults, 2D for JSLE, tacrolimus 1B for adults, 2C for JSLE); • MPAA and belimumab (1A for adults, 2C for JSLE).	95.6 (82–100)
75. If the regimens in #74 are not suitable or available as remission induction for LN, then alternative immunosuppressant options with substantial evidence but lower efficacy are as follows: • EuroLupus dose cyclophosphamide combined with belimumab (1A); • MPAA combined with rituximab (2B); • MPAA alone (1A); • EuroLupus dose cyclophosphamide alone (2B).	95.5 (80–100)
76. People with SLE with new or relapsing pure class V LN with proteinuria >100 mg/mmol should receive a combination immunosuppression regimen consisting of oral GC using the reduced-dose KDIGO regimen and MPAA and calcineurin inhibitor (1A). If not appropriate or tolerated, consider alternative therapies including oral GC + MPAA + anti-CD20 therapies (2B), oral GC + MPAA + belimumab (2C) or oral GC + EuroLupus dose cyclophosphamide + belimumab (2C).	96.1 (83–100)
77. In cases of exceptionally severe or life- or organ-threatening LN, initial therapy should be discussed with a specialist centre as the National Institute for Health (NIH) regimen of IV cyclophosphamide (2B), with or without anti-CD20 agents (2C), may be more appropriate than standard LN induction therapy initially. In such cases, the number of cyclophosphamide infusions should be limited and therapy switched to options with lower toxicity once disease activity improves.	93.8 (80–100)
78. Therapy should be reconsidered early if people with LN are not meeting these treatment targets (2C): • at 3 months, 25% reduction in urinary protein to creatinine ratio (uPCR); • at 6 months, 50% reduction in uPCR; • at 12 months, uPCR <70 mg/mmol; with preserved or improving kidney function. In those with class V LN, slower reduction of proteinuria is acceptable as long as improving.	95.6 (80–100)
79. In people with LN with a partial response to the induction regimen treatment but not meeting treatment targets, expert opinion, or more specialist advice, should be used to decide on repeat biopsy and whether further induction regimen required or a change of maintenance therapy (2B).	98.4 (85–100)
80. In people refractory to the initial treatment for LN, reasons for suboptimal response should be fully re-assessed including checking adherence, optimising doses of immunosuppressants and checking drug levels, and considering a repeat renal biopsy. Expert opinion, or more specialist advice, must be used to decide therapy (2B).	98.7 (90–100)
81. Treatment options for refractory LN include clinical trials (2B), switching to one of the other induction immunosuppressant combinations in #74 (2B) and/or restarting induction GC (2B).	96.6 (88–100)
Organ-specific approach: what is the best evidence for lupus nephritis maintenance treatment?	
82. Maintenance therapy should be continued for at least 3 years (1A). Longer durations may be advantageous in many people with LN and the decision should be individualised based on quality of response, prior relapses, risk associated with relapse, tolerability, biomarkers, extra-renal disease activity and patient preference (2C).	97.5 (87–100)
83. In people with LN meeting the 12-month treatment targets after induction therapy using regimens in #74, the following treatment maintenance should be continued for at least 3 years: • MPAA + obinutuzumab (1B); • MPAA + belimumab (1A); • MPAA + CNI (1A).	96.2 (85–100)

(continued)

Table 1 (continued)

Statements and strength of recommendation	Strength of agreement, mean (range) %
84. In people with LN who received a different induction option to regimens in #74, combination therapies in #83 could be added for maintenance if appropriate (2B).	95.2 (80–100)
85. If rituximab and MPAA were used for induction with good response, then this combination could be continued for maintenance, individualising retreatment interval (2C).	97.8 (90–100)
86. If combination therapy cannot be used, then MPAA should be used for maintenance therapy (1A).	97.3 (87–100)
87. If MPAA cannot be taken or pregnancy is planned, then azathioprine (or combination of azathioprine and tacrolimus) can be used for maintenance with closer monitoring for LN flare (1A).	98.3 (84–100)
88. Following the GC induction regimen for LN, full withdrawal of GC should be attempted; use of GC is not recommended for long-term control of disease activity after either full or partial response (2B).	97.4 (82–100)
89. During maintenance therapy, people with LN should continue to be managed by renal services, combined with rheumatology if necessary, to ensure appropriate chronic kidney disease (CKD) management using adjunctive therapies (2B).	97.0 (83–100)
Delivery of care: how should care be delivered to optimise management of people with SLE?	
90. Where there is complex multisystem disease, people with SLE should be co-managed with relevant specialties in joint clinics or if not, at least with regular multispecialty/multiprofessional MDT meetings that enable rapid communication (1D).	99.8 (95–100)
91. Every healthcare organisation treating SLE should be part of a regional specialised network/regional MDT meetings so that people with SLE can receive access to additional specialised care and advice, combined with ongoing local hospital care, regardless of geography (1C). Such services are still in development for JSLE but should be used when available.	98.1 (82–100)
92. All people with SLE with severe, complex or refractory disease including those with lupus nephritis, especially those being considered for biologic drugs must be discussed with and/or managed by a specialist lupus centre (1D).	98.4 (84–100)
93. Shared care within secondary care and between primary and secondary/tertiary care should be funded, supported and standardised (1D).	99.6 (95–100)
94. A coordinated transition plan including paediatric and adult specialists should be put in place to manage this high-risk period of SLE in a young person's journey (1C).	97.9 (80–100)
95. People with SLE should be seen in dedicated/cohorted clinics with specific clinic templates adjusted for complexity to allow adequate time for a full multisystem holistic assessment (1C).	98.6 (82–100)
96. Services should consider and develop ways to address potential health inequalities particularly those faced by minoritised and underserved groups and from low socioeconomic backgrounds to ensure equitable access to optimal management (1D).	97.4 (82–100)
97. Where there are communication barriers including where interpreters are required, longer clinic appointment times are recommended (1D).	96.7 (80–100)
98. Each healthcare organisation should have a lead clinician for the delivery of service for people with SLE, with recognition in job plan for this activity (1D).	96.8 (80–100)
99. Every individual with SLE should have access to a specialist nurse with understanding and expertise in management of lupus with dedicated time within their job plan, including access to a telephone and/or email advice line (1C).	97.7 (82–100)

(continued)

Table 1 (continued)

Statements and strength of recommendation	Strength of agreement, mean (range) %
100. People with SLE with disease flares or possible drug-related side effects should be able to receive timely advice (ideally within 1–2 working days) of contacting their hospital service (1C).	98.4 (86–100)
101. All people with SLE should be given the opportunity of taking part in observational research studies, and if treated with biologic drugs, with their consent should be registered with the National Biologics Register (BILAG BR) and/or UK Juvenile-onset SLE (JSLE) Cohort Study and Repository (1D).	98.8 (80–100)
102. All departments should collect the required data for national audits and registries. Healthcare organisations should ensure that there is appropriate administrative support for audit participation. Clinical and operational teams should review their audit data and take any required action (1D).	97.3 (80–100)

medical conditions can mimic SLE. Moreover, the cardinal features are usually not present during the initial assessment and may accumulate over time. This makes the diagnosis challenging. Indeed, a survey by Lupus UK reported that mean time from developing initial symptoms to reaching a diagnosis of SLE was 6.4 years and that 47% of respondents were originally misdiagnosed [55]. A delay in SLE diagnosis can lead to increased disease activity, organ damage and significantly impair quality of life and long-term health outcomes [56].

Studies have shown that the rates of GP consultations and healthcare resources utilised in the community by people with an ultimate diagnosis of SLE increased exponentially in the years leading to diagnosis [17, 57]. Thus, when SLE is suspected by GPs, it is pertinent for these people to receive a timely referral to specialists in secondary or tertiary care. Detailed signs and symptoms should be explicitly stated in the referral to enable effective triage for individuals deemed to be of high risk of SLE, balancing routine and urgent appointments as appropriate. Currently, there is no published national standard for referral in SLE. Since delayed diagnosis has a profound impact on increased morbidity and mortality [58, 59], the GWG members recommend that people with a strong suspicion of a new diagnosis of SLE should be prioritised as a 3-week wait target, in line with the NICE quality standard of referral for suspected Early Inflammatory Arthritis [60]. It is important to note that ‘strong suspicion’ is uncommon among ANA positive referrals, and only a minority would need to be prioritised in this way.

Recommendation 2	SLE should be diagnosed by clinicians experienced in its management and requires a combination of clinical, laboratory and immunological features attributable to SLE (2B) [98.3% (81–100)].
Recommendation 3	Current classification criteria (SLICC 2012 or EULAR/ACR 2019) may be used as a guide but not as diagnostic criteria (2C) [97.7% (82–100)].

Classification criteria for SLE

In the last BSR guideline, the 2012 Systemic Lupus International Collaborating Clinics (SLICC) criteria were widely used for the inclusion of people with SLE in clinical trials and in the NHS England clinical commissioning policy for rituximab [49]. In

short, the SLICC criteria require (i) fulfilment of at least four criteria, with at least one clinical criterion AND one immunologic criterion [either anti-nuclear antibody (ANA), anti-dsDNA, anti-Sm or antiphospholipid antibody positive, low complement level, positive Direct Coombs test in the absence of haemolytic anaemia] OR (ii) LN as the sole clinical criterion in the presence of ANA or anti-dsDNA antibodies [61].

Since that guideline, the revised 2019 EULAR-American College of Rheumatology (ACR) classification criteria were published. There are two main differences to the SLICC criteria: (i) ANA-positive ($\geq 1:80$ titre) as an entry criterion and (ii) each criterion is assigned a weight of 2–10, where only the highest item of each domain is counted. Only the highest-weighted criterion score within a single domain should be used. People can be classified as having SLE if fulfilling a score of 10 or more, including at least one clinical criterion [62]. For both sets of criteria, features do not have to be present simultaneously and SLE must be the most likely explanation for each criterion.

Performances of both criteria have been studied extensively. A systematic literature review (SLR) and meta-analysis of 29 studies reported that the pooled diagnostic odds ratio ranked highest for the 2019 EULAR-ACR criteria in adult-onset SLE (131.570, 95% CI 61.50–281.47) while the 2012 SLICC criteria were ranked highest in JSLE (191.07, 95% CI 76.06–480.01) [63]. It is worth noting that while often used interchangeably, classification criteria are primarily for grouping patients for research, while diagnostic criteria are used to identify and diagnose people with SLE in clinical practice. Classification criteria are often stricter than diagnostic criteria and have high specificity (i.e. they have a low rate of false positives). Consequently, some common features that are less specific for SLE (Raynaud’s, anti-Ro and anti-RNP antibodies) and some uncommon features (e.g. lupus hepatitis, lupus enteritis, myocarditis and various forms of ophthalmic lupus) are omitted in the classification criteria [64]. All features in the SLE classification criteria have other possible causes and determining attribution to SLE requires a high degree of expertise and experience, and sometimes other investigations. For this reason, as well as since there are no definitive diagnostic criteria, SLE can only be assessed and diagnosed by clinicians experienced in its management and requires a combination of clinical, laboratory and immunological features attributable to lupus. Although not diagnostic, classification criteria may still be helpful when considering the diagnosis.

However, in early phases of SLE, features gradually accumulate over time and diagnosis should not be delayed waiting for criteria to be fully fulfilled; many individuals not yet fulfilling criteria have objective inflammation requiring treatment [62, 65].

Recommendation 4	Antinuclear antibody (ANA) test should only be performed where there is reasonable clinical suspicion of SLE or related diseases. ANAs are present in 95–99% of people with SLE, so a negative test makes SLE unlikely (results can fluctuate so a negative test does not rule out SLE where there have been past positives) (2B) [95.2% (80–100)].
Recommendation 5	ANA test should be supplemented by tests for anti-dsDNA antibodies, extractable nuclear antigen antibodies and C3/C4 complement levels, since the presence of anti-dsDNA antibodies (2B), low complement levels (2C) and/or anti-Smith (Sm) antibody (2C) is highly supportive of SLE diagnosis in people with relevant clinical symptoms [97.4% (80–100)].
Recommendation 6	In children and young people with symptoms suggestive of SLE but negative ANA, monogenic lupus and complement deficiencies should be considered (2C) [98.7% (91–100)].
Recommendation 7	Antiphospholipid antibodies (aPLs) and lupus anticoagulant (LAC) should be tested in all people with SLE at diagnosis (2B). A positive test requires confirmation on two occasions at least 12 weeks apart (2B) [98.0% (81–100)].

ANA and beyond

The immunologic hallmark of SLE is the presence of antinuclear antibodies (ANAs), which are antibodies that target components within the cell nucleus. ANAs are present in 95–99% of people with SLE at some point during the course of the disease [66, 67], so a negative test makes SLE unlikely. Results can also fluctuate, can become negative following treatment and can vary with assays [68, 69], so a negative test does not rule out SLE where there have been past positives. However, in adults, it is less likely that ANA would be negative at the time of active untreated disease when the diagnosis is first being made. ANA has low specificity; ~5–10% of healthy adults have a positive ANA test [70, 71], far exceeding the prevalence of SLE. As well as being present in those with no clinical feature of SLE, ANA can occur in a variety of conditions including other autoimmune connective tissue diseases (e.g. Sjögren's disease, inflammatory myopathies, mixed connective tissue disease and systemic sclerosis), non-rheumatic autoimmune diseases (e.g. autoimmune hepatitis and autoimmune thyroid disease), viral infections (infectious mononucleosis [72] and COVID-19 [73]) and malignancy [65]. An SLR and meta-regression analysis showed that ANA titre of 1:80

was found to represent sufficient sensitivity and reasonable specificity to be used as an entry criterion in the 2019 EULAR-ACR classification criteria [67]. Therefore, ANA is only useful as a screening test where there is clinical suspicion of SLE or other autoimmune connective tissue diseases. ANA should not be tested in the absence of clinical indicators.

People with JSLE with pre-pubertal onset of disease may be ANA-negative at diagnosis. The UK JSLE Cohort Study reported 86% of people to be ANA-positive during pre-pubertal years (<7 years) compared with 96% post-pubertally (>13 years) [2]. This could be attributed to the higher frequency of monogenic lupus-like diseases and increased number of risk alleles among people with JSLE compared with adult-onset SLE, affecting a range of genes implicated in the innate immune system or non-immune genes [2, 74]. Thus, in children and young people with symptoms suggestive of SLE but negative ANA, monogenic lupus (e.g. Aicardi-Goutières syndrome, chronic atypical neutrophilic dermatosis with lipodystrophy and elevated temperature, familial chilblain lupus, STING-associated vasculopathy with onset in infancy, spondyloenchondrodysplasia and many more) and complement deficiencies should be considered.

In people with suspected SLE, ANA should be supplemented by tests with higher specificity for SLE including anti-dsDNA antibodies, anti-Smith (Sm) antibody as a part of extractable nuclear antigen antibodies (ENAs) and complement C3 and C4 levels. Key ENAs include Sm, Ro (SSA), La (SSB), RNP, Scl-70 and Jo-1. Anti-Ro (SSA) and anti-La (SSB) are less specific for SLE but can be associated with features such as photosensitivity and subacute cutaneous lupus [75]. Moreover, anti-Ro and anti-La antibodies are associated with neonatal lupus syndrome including congenital heart block (CHB) in children born to mothers with these antibodies [76]. Anti-RNP antibodies are found in 25–30% people with SLE [77, 78] and may represent overlap conditions such as mixed connective tissue disease (MCTD). The majority of healthcare organisations use enzyme-linked immunosorbent assay (ELISA) or multiplex immunoassays for ANA testing over the gold standard indirect immunofluorescence assay (IFA). ELISA typically measures a single analyte per assay while the multiplex assays utilise beads coated with different antigens and have the advantages in detecting multiple autoantibodies in a single test, thus saving time and resources. It is important to note that these assays can yield false-positive results up to 7%, particularly when low titres are detected [79]. Low-level detection of ANAs and ENAs are often supplemented by ANA testing on IFA to improve sensitivity. Indeed, a criterion for a positive anti-dsDNA antibody in the 2012 SLICC requires a level of twice the laboratory reference range when tested using ELISA.

All people with SLE should ideally be tested for both antiphospholipid antibodies (aPLs) (i.e. IgM or IgG for anti-cardiolipin antibodies and anti-beta-2 glycoprotein 1 antibodies) and lupus anticoagulant (LAC) because their presence preludes to a group at increased risk of arterial/venous thrombotic events and adverse pregnancy outcomes [80, 81]. A positive test for either of the two aPLs or LAC requires confirmation on two occasions at least 12 weeks apart. To refer to the 2023 ACR/EULAR antiphospholipid syndrome classification criteria for more details [81]. Treatment with anticoagulation should not be delayed while waiting for confirmation of antibody persistence (which requires testing 12 weeks apart) if the clinical suspicion of APS is high [80, 82]. For people with suspected APS who are already

Table 2 Definitions, descriptions and examples of clinical disease activity and flare of SLE.

Description	Absent	Mild activity/Flare	Moderate activity/Flare	Severe activity/Flare
Definition	Clinical remission, with or without therapy. May be serologically or immunologically active but with no intention by the clinicians to treat with immunosuppressive therapy.	Active but clinically stable disease with no life-threatening organ involvement. Not likely to cause significant scarring or damage. Change in immunosuppressive or other treatment likely to be beneficial.	More serious features, which if left untreated would cause significant chronic scarring or damage. Immunosuppressive therapy required.	Organ- or life-threatening features. Reflects the most serious form of systemic disease that requires potent immunosuppression.
Assessments using validated tools	• BILAG D or E score OR a single BILAG C score • Clinical SLEDAI-2K = 0	• BILAG C scores OR a single BILAG B score • SLEDAI-2K <6	• BILAG B scores in two or more domains • SLEDAI-2K between 6 and 12	• BILAG A score in at least one domain • SLEDAI-2K >12
Examples of features attributed to SLE	No symptoms and signs. There may be one mild feature in isolation that is not considered to warrant treatment especially if attribution or impact are unclear (e.g. myalgia, fatigue, lymphocytes $<1.0 \times 10^9/L$).	Malar rash, diffuse alopecia, mouth ulcers, platelets $50-149 \times 10^9/L$	Fever, rash up to 18% body surface area, cutaneous vasculitis, alopecia with scalp inflammation, arthritis, pleurisy, pericarditis, hepatitis, platelets $25-49 \times 10^9/L$.	Lupus nephritis, rash involving >18% body surface area, myositis, severe pleurisy and/or pericarditis with effusion, ascites, enteritis, myelopathy, psychosis, platelets $<25 \times 10^9/L$.

anticoagulants and require confirmatory tests for aPLs, to refer to [Table 3](#) of the 2024 British Society for Haematology Guidelines on the investigation and management of antiphospholipid syndrome [82] and liaise with haematologists.

Summary

When considering people with suspected SLE, a review of relevant clinical features, as well as serological and immunological parameters (ANA, anti-dsDNA, ENA, complement levels and aPL) is required. Prompt referral to specialists in secondary or tertiary care is required and first specialist assessment prioritised. The diagnosis should not be made without evidence of at least one autoantibody or low complement levels. The 2012 SLICC and the 2019 EULAR-ACR classification criteria are not diagnostic criteria but may be helpful when considering the diagnosis. In children and young people with symptoms suggestive of SLE but with a negative ANA, consider monogenic diseases and complement deficiencies.

Assessment: what is the best way to assess people with SLE?

Recommendation 8 Clinical manifestations in people with SLE should be assessed to determine whether they are due to disease activity, damage, drug toxicity, infection, thrombosis or the presence of comorbidities (2B) [98.1% (80–100)].

Recommendation 9 People with SLE should be assessed for manifestations in all systems and relevant clinical examination and investigations performed (2C) [98.9% (90–100)].

Clinical assessment

Owing to the diversity of clinical and laboratory manifestations of SLE, a systematic approach should be taken during clinical assessment. People with SLE should be assessed for manifestations in all systems including a detailed history, as well as relevant clinical examination and investigations. Urinalysis and blood pressure should be performed at every visit in which the SLE overall clinical status is being assessed. These tests should not be neglected if the visit is conducted through remote/virtual review. All manifestations should be assessed to determine whether they are due to disease activity, organ damage, drug toxicity, infection, thrombosis or the presence of comorbidities. Urinalysis and blood pressure must not be forgotten as they may be the only features indicating lupus nephritis, including in people with no active symptoms.

It is important to standardise clinical assessment since a multicentre audit of the 2017 BSR SLE guideline reported marked divergence in practice between centres. Compliance with the BSR standards were met for blood pressure and estimated glomerular filtration rate (eGFR) measurement and were within 10% of the BSR standards pertaining to appropriate urine protein quantification, enrolment in British Isles Lupus Assessment Group (BILAG) Biologics Register (BILAG-BR) for people with SLE on

rituximab and concurrent prednisolone dose of ≤ 7.5 mg daily if people had inactive SLE. However, compliance fell below the BSR standards in several aspects including assessment of disease activity using the BILAG-2004 disease activity index or SLE Disease Activity Index version 2000 (SLEDAI-2K), documentation of monitoring for hydroxychloroquine retinopathy, enrolment of people on belimumab in BILAG-BR, and documentation within the last 12 months of lipid profile, vaccination advice, ultra violet (UV) protection, smoking status and pregnancy counselling [86].

Recommendation 10	The use of a validated disease activity tool such as BILAG-2004 and SLEDAI-2K is recommended (2B) [97.0% (80–100)].
Recommendation 11	Validated instruments should be used to categorise disease activity as absent, mild, moderate and severe, with the occurrence of flares (2C) [96.5% (84–100)].
Recommendation 12	Urinalysis and blood pressure should be performed at every visit (2C) [97.2% (80–100)].

Disease activity and validated clinical tools

Use of disease activity instruments helps systematic assessment, ensures that items such as urinalysis are not forgotten, allows comparison of clinical impressions between multiple clinicians over the disease course, allows communication with multidisciplinary team (MDT) and compliance with commissioning criteria for some therapies.

The two recommended validated clinical tools to capture disease activity in clinic are BILAG-2004 index and SLEDAI-2K. This is also recommended by the EULAR [38] and the ACR [54] guidelines. Although we recommend using these instruments, they should not be regarded as the totality of the lupus assessment for clinical decisions. Doctors will also need to comment on their overall clinical impression and how they have attributed disease activity.

BILAG-2004 index measures disease activity in nine domains or organ systems affected by SLE based on clinical assessments and laboratory results over the past 4 weeks [87]. Each of the 97 items is scored as 0=not present, 1=improving, 2=same, 3=worse or 4=new, and graded separately from A, highly active and likely to necessitate escalation in therapy, to E, no current or previous disease activity. Modifications have been made to the index for use in pregnancy (BILAG-2004-P) to take into account the relevant pathophysiological changes of pregnancy [88]. The main strengths of this tool are that it focuses on individual bodily systems rather than a global or overall score, captures both common and rare features, allows all manifestations to be scored as mild, moderate or severe as appropriate, rather than the fixed weightings of the SLEDAI, and it captures change over time including partial improvements, worsening and exacerbations of existing disease features. In its original form, disadvantages included a high administrative burden and greater training requirement. To improve these limitations, Easy-BILAG was developed. This tool provides the same output data as the original BILAG-2004, but scores it with a 2-page document, of which the second page is only required if rare features are present, with embedded glossary and colour-coding to assist domain scoring. The use of Easy-BILAG resulted in improved accuracy and faster

completion time compared with the standard method of scoring BILAG-2004 with users rating it as highly feasible to use within routine clinical practice [89]. The BILAG group therefore recommend that Easy-BILAG should be used for scoring the BILAG-2004 index.

In SLEDAI-2K, a selection of 24 disease activity items is rated as either absent or present within the last 30 days. Both clinical and laboratory variables are weighted by the type of manifestation but not by severity [90]. For example, arthritis of any severity scores 4 points and rash of any severity scores 2 points. The maximum points available are 105 although scores over 20 are uncommon. The advantages of SLEDAI-2K include its low administrative burden and practicality. The disadvantages include its inability to capture improving or worsening of symptoms, that it does not take account of the severity within an organ system, and some items that are clinically important and potentially life-threatening, such as haemolytic anaemia and ascites, are not included as descriptors or score very low (e.g. thrombocytopenia irrespective of severity). Although ticking items from a list seems conceptually simple, this simplicity may be deceptive. A high degree of experience and expertise is required since items should only be scored if attributed to SLE. Inexperienced users tend to over-score SLE mimics such as rosacea or osteoarthritis. In contrast, the greater detail of Easy-BILAG guards against such errors.

For the purposes of medical record keeping and planning appropriate treatment, disease activity should be categorised as absent, mild, moderate and severe using the validated tools above and remission criteria [87, 90, 91]. Similarly, worsening of disease or termed ‘flare’ should be categorised into mild, moderate and severe [92, 93]. Definitions of these categories and examples are adapted from the last BSR guideline [22] and described in Table 2 as guidance.

Recommendation 13	In people with SLE with unexplained fever, especially when associated with falling blood counts and high ferritin, evolving HLH/MAS should be considered together with other differentials such as infection or flare. Investigate as per the GIRFT guidance, including calculation of the H-score (2C) [97.1% (80–100)].
Recommendation 14	Cognitive impairment affecting daily activities, decisions (and schooling in JSLE) should be assessed in collaboration with a neurologist, neuropsychologist or other experienced professionals (2C) [96.0% (84–100)].

Complications of SLE

The GWG highlighted two aspects of SLE that may not be easily detected using the above assessments for which specific consideration is important. Hemophagocytic lymphohistiocytosis (HLH) or macrophage activation syndrome (MAS) is a rare but severe, potentially life-threatening hyperinflammatory condition which can occur in people with SLE. HLH/MAS is characterised by high fever, organ involvement (neurological symptoms, hepatomegaly, splenomegaly), pancytopenia, coagulopathy,

elevation of liver enzymes, ferritin and triglycerides. Data in England has shown a crude one-year mortality rate of 50% [94], hence prompt recognition and aggressive treatment are required to improve survival rates. Even when HLH is triggered by underlying SLE, it usually needs a separate treatment strategy as recommended for HLH of any underlying cause. These treatments are distinct from those used to treat other features of SLE (notably the use of anakinra and etoposide). Diagnostic features such as fevers and cytopenias can also occur in SLE without HLH, and it is important that these pathologies are differentiated. The GWG members therefore recommended for people with SLE suspected to have HLH/MAS, to investigate as per the Getting It Right First Time (GIRFT) guidance, including calculation of the H-score [47]. In children and young people, MAS diagnostic models derived based on data from paediatric case series have suggested lower ferritin cut-offs (500–1000 µg/l) compared with the levels used in H-score calculation [95, 96], and trend in ferritin and blood counts should be carefully assessed.

Cognitive dysfunction in SLE is an important complication to be assessed as it can affect daily activities, decisions and schooling in JSLE. It can also impact on the ability of people with SLE to understand and follow management plans for all their lupus features, which are often complex, further exacerbating overall impact of disease. Various domains can be affected including memory (learning and recall), attention (complex and simple), executive skills, visual-spatial processing, language, reasoning/problem-solving and psychomotor speed. An SLR and meta-analysis reported a pooled prevalence of cognitive dysfunction of 38% (95%; CI: 33–43%) in SLE. The relative risk for cognitive dysfunction in SLE was greater compared with rheumatoid arthritis and healthy individuals, 1.80 and 2.80, respectively [97]. Despite their impact, these features often appear subtle during routine consultations and may be easily missed without specific questioning. There is a lack of standardised and sensitive neuropsychological tests and validated diagnostic biomarkers for cognitive dysfunction in SLE, so this is best assessed in collaboration with a neurologist, neuropsychologist or other experienced professionals.

Summary

People with SLE should be assessed for manifestations in all systems and it should be ascertained whether they are due to disease activity, organ damage, drug toxicity, infection, thrombosis or the presence of comorbidities. Validated clinical tools such as BILAG-2004 disease activity index and/or SLEDAI-2K should be used to capture disease activity where items are scored if they are attributed to SLE. Prompt recognition is needed when assessing people with SLE with suspected HLH/MAS and cognitive dysfunction.

Monitoring: what is the best way to monitor people with SLE?

Recommendation 15 Those with active disease should be reviewed at least every 1–3 months (2C), with blood pressure (1A),

(continued)

urinalysis (1A) and renal function including proteinuria estimation (1A), anti-dsDNA antibodies (2B), complement levels (2C), inflammatory markers (2C), full blood count (2C) and liver function tests (2D) forming part of the assessment, and further tests as necessary (2D) [95.0% (80–100)].

Recommendation 16 Body weight should be checked at each visit, and for children and young people with SLE, height should also be checked at each visit to monitor linear growth (2C) [97.0% (86–100)].

Recommendation 17 People with SLE with stable low disease activity or in remission can be monitored less frequently. The interval will vary according to age, initial severity, duration of remission and therapy changes, but should be no longer than 12-monthly (adults) or 6-monthly (children) (2D) [97.4% (80–100)].

Recommendation 18 People with SLE should have a systematic assessment of disease damage every 12–24 months. The SLICC/ACR damage index may be used (2C) [96.8% (82–100)].

Recommendation 19 Immunosuppressive therapy and biologics may lead to toxicities. Close monitoring of drugs by regular laboratory tests and clinical assessment should be performed in accordance with drug monitoring guidelines (2D) [99.1% (90–100)].

Recommendation 20 The presence of aPLs is linked to thrombotic events, organ damage and adverse pregnancy outcomes (2B). If previously negative, aPLs should be re-evaluated before pregnancy, major surgery or following a new severe manifestation or vascular event (2D) [96.7% (80–100)].

Recommendation 21 Anti-Ro/SSA and anti-La/SSB antibodies are associated with neonatal lupus (including congenital heart block) and should be re-assessed prior to pregnancy, and pre-pregnancy counselling provided (1A) [98.5% (81–100)].

Frequency and type of clinic visits

There is no RCT comparing the effectiveness of the different monitoring strategies in terms of frequency of clinical visits and details of assessments performed. Our recommendations are informed by data from cohort studies, previous guidelines and expert opinion [22, 98–102].

For most people with SLE with active clinical disease, clinic visits should be approximately every month initially, gradually reducing to about 3-monthly reviews as the disease activity becomes more controlled. People with SLE should be advised to

report to clinicians through a dedicated telephone and/or email advice line if they develop any new or significant worsening of clinical features. Clinical review (i.e. preferably by the same clinician or clinical team since multiple doctors in charge may be associated with increased damage accrual [103]) then should become more frequent if the disease becomes more active, especially if there is renal involvement.

For those with mild features, including those who are clinically quiescent but immunologically active (e.g. anti-dsDNA positive and/or low complement levels), 3–4 monthly visits appears to be adequate [104]. For people with SLE with inactive disease, without previous renal involvement or organ damage, review may be less frequent [e.g. should be no longer than 12-monthly (adults) or 6-monthly (children) providing treatment is stable and suitable drug monitoring is in place] [100]. This interval can also be decided according to age, initial severity, duration of remission and therapy changes.

When people with SLE are in remission and the immunosuppressant is subsequently being tapered or withdrawn, a safety net for people with SLE to alert the clinicians in the event of a flare should be provided. Flares of SLE are not uncommon after immunosuppressant discontinuation, thus close monitoring is required [99, 105].

During the peak of the COVID-19 pandemic, telemedicine was adopted by several health services to minimise the risk of people with SLE from SARS-CoV-2 exposure. A single centre pragmatic RCT randomised people with LN in a 1:1 ratio to either follow-up via videoconferencing or conventional in-person outpatient care. At one year, there was no difference in the primary outcome between the two groups (i.e. the proportion of participants in low disease activity or remission). However, significantly more participants in the telemedicine group required a switch of follow-up mode and a higher proportion of them were hospitalised during the study period [106]. Telemedicine may have a role to monitor people with SLE with stable low disease activity or remission but should be supplemented by clinical observation and laboratory tests. Until more evidence is available on this matter, as well as the effectiveness and safety of self-reported patient-reported outcome measures and patient-initiated follow-up programme, in-person assessment is recommended.

Monitoring for clinical observation and laboratory tests

During the clinical assessment, we recommend monitoring for clinical observations including blood pressure measurement, actual body weight, height for people with JSLE to monitor linear growth, and urinalysis. These are important to detect disease activity or complications of SLE that are otherwise clinically silent. Good record-keeping of actual body weight will facilitate assessment of BILAG-2004 and determine treatment doses for people with SLE. From the laboratory perspective, if urine dipstick shows $\geq 1+$ protein (as opposed to negative or trace only), then urine protein quantification [spot urine protein-to-creatinine ratio (uPCR) or spot urine albumin-creatinine ratio (uACR)] should be requested. For other dipstick abnormalities, screening for infection and urine protein quantification should be performed. Routine serological assessments including full blood count, liver function tests and inflammatory markers may be requested as a part of clinical assessment and in accordance with drug

monitoring guidelines [30]. C-reactive protein (CRP) is usually within the normal range even in active SLE, or slightly elevated in the presence of serositis, arthritis or myositis [107, 108]. This therefore cannot be relied upon to confirm inactive disease. A significantly raised CRP in a patient with SLE is more likely to suggest an infection. Therefore, people with SLE and a significantly raised CRP should be thoroughly assessed for infection. This contrasts with ESR which is more frequently elevated in SLE, but a raised ESR does not discriminate between active SLE and infection [109].

Serial measurements of anti-dsDNA antibodies and C3 and C4 levels are useful because rising, high anti-dsDNA antibodies and falling, low complement levels are associated with an impending flare [110, 111] particularly in people with LN [33]. Testing for these markers should also form a part of assessment of treatment response to belimumab [50] and rituximab [49] and may help guide the retreatment decision for the latter.

If negative at baseline or at previous assessment, aPLs should be re-evaluated before pregnancy, major surgery or following a new severe manifestation or vascular event since aPLs is associated with thrombotic events, organ damage and adverse pregnancy outcomes [80]. Positive aPLs should be repeated after 12 weeks to confirm positivity although LAC cannot be evaluated if anticoagulation has been started, as this interferes with the assay [82].

Pre-pregnancy counselling pertaining to the risk of anti-Ro/SSA and/or anti-La/SSB antibodies and neonatal lupus syndrome is important. In women planning pregnancy or in early pregnancy, anti-Ro/SSA and anti-La/SSB antibodies should be measured since they may be transferred across the placenta and are associated with congenital heart block (CHB) in ~ 2 –3% of babies born to mothers with SLE and anti-Ro/SSA and anti-La/SSB antibodies [112, 113]. For pregnant women with anti-Ro/SSA and/or anti-La/SSB antibodies, it is advised to liaise with obstetricians early. Fetal heart rate monitoring should be instituted from week 16 of pregnancy and continue through week 26 in women with either of these antibodies as CHB rarely occurs after 26 weeks [114]. Rates of CHB are significantly higher ($\sim 18\%$) in subsequent pregnancies following an index CHB case [115]. Prospective studies of infants born to women with anti-Ro/SSA and/or anti-La/SSB antibodies show that $\sim 10\%$ develop neonatal lupus rash, 20% transient cytopenia and 30% mild transient transaminitis [116, 117]. These complications are short-lived and often resolve spontaneously as the child's maternal antibodies disappear, and with no increased risk of developing SLE in later life.

Monitoring for drug toxicities and damage

Monitoring for an immunosuppressant should be as for these drugs in other rheumatic diseases. As per BSR 2025 conventional DMARDs guideline, monitoring for drug toxicities should be a collaborative effort between primary care and specialist rheumatology providers. A shared care protocol should be agreed upon (including in the paediatric age group when shared care exists), delineating the responsibilities of each party [30, 118]. However, personalised guidance may need to be communicated to GPs for some patients pertaining to the anticipated cytopenia, abnormal renal or liver function parameter related to SLE activity. For example, there may be neutropenia due to Black African ancestry or SLE disease activity that pre-dates initiation

of immunosuppressants and therefore should not trigger stopping therapy during monitoring. In these cases, it may be useful to set a different acceptable range of readings or offer specialist review of abnormal results.

Accrual of organ damage in people with SLE is associated with poorer health outcomes, including decreased physical functioning, reduced health-related quality of life and increased mortality [119–121]. Accrual of damage may prompt a review of long-term immunosuppressive strategy, risk factors or other interventions or referrals to manage damage. People with SLE should have a systematic assessment of organ damage every 12–24 months. Consider using the SLICC/ACR Damage Index (SDI), which is currently the only validated instrument for assessing damage [122].

Summary

Following initial assessment, people with SLE should be monitored for changes in disease activity, accrual of organ damage, drug toxicities, pregnancy adverse outcomes, thrombosis and development of comorbidities, since these aspects influence long-term outcomes. Monitoring strategies can be individualised according to disease status.

Treatment target: what is the role of a treatment target in the management of SLE?

Recommendation 22 Early diagnosis, regular screening for organ or system involvement, prompt initiation of treatment and regular assessment of adherence is recommended in the management of SLE (2C) [98.8% (80–100)].

Recommendation 23 The primary treatment goal should be to achieve remission, or if remission is not possible, Lupus Low Disease Activity State (or cLLDAS in JSLE), following a treat-to-target (T2T) approach (2C) [97.4% (80–100)].

Rationale

Treat-to-target (T2T) has been recommended by EULAR and the Paediatric Rheumatology European Society (PReS) for both JSLE and adult onset SLE [38, 123, 124]. EULAR recommend that the primary treatment goal should be to achieve the 2021 DORIS remission, or if remission is not possible, the Lupus Low Disease Activity State (or cLLDAS in JSLE). Efforts to develop a paediatric-specific framework for T2T are more recent than in adult-onset SLE, commencing in 2021, with the formation of the International cSLE T2T Task Force. This multidisciplinary group is led from the UK, with representation from the major paediatric rheumatology organisations (PReS, CARRA in North America), nephrology and adult rheumatology. They have developed consensus-based principles and points-to-consider for T2T in cSLE [124] and paediatric-specific targets which align closely with adult targets, including minor changes to better suit paediatric populations [123, 125].

DORIS remission requires the following criteria: (i) clinical cSLEDAI-2K=0; (ii) Physician's Global Assessment (PGA) ≤ 0.5 point; (iii) prednisolone-equivalent dosage ≤ 5 mg/day [for children, this is entitled Clinical Remission on GC (cCR) rather than DORIS remission [125] and the GC limit is 0.1 mg/kg/day, maximum of 5 mg]; AND (iv) stable therapy with antimalarials, immunosuppressives and biologics [91, 125]. In children, maintenance treatment is considered stable if changes are not due to disease activity, but made due to side effects, adherence, changes in weight and/or when building up to target dose [125]. Due to the significant impact of GC on growth, development and damage accrual in children with SLE, an additional remission target requiring GC withdrawal was considered essential by the International T2T Task Force, entitled Clinical Remission off GC (cCR-0); this includes the same criteria as cCR but mandated complete GC withdrawal [125].

LLDAS requires the following criteria: (i) SLEDAI-2K ≤ 4 points (with no activity in major organ systems); (ii) no new features of lupus disease activity compared with the previous assessment; (iii) PGA ≤ 1 point; (iv) prednisolone-equivalent dosage ≤ 7.5 mg/day (for children, the GC limit is 0.15 mg/kg/day, maximum of 7.5 mg); AND (v) stable therapy with immunosuppressant [123, 126, 127]. In children and young people, this is entitled cLLDAS rather than LLDAS, with the same stipulation regarding how to define stable immunosuppression as outlined above for remission [123]. The paediatric target definitions explicitly accommodate paediatric-specific treatment adjustments related to growth and side effects, while remaining consistent with adult-onset SLE definitions to foster life-course clinical approaches and research. Validation of these targets using data from the UK JSLE Cohort Study data has confirmed that these targets accurately reflect disease control in younger, lighter individuals, with attainment linked to reduced severe flares and damage risk, and comparable performance to adult targets [128]. Crucially, target attainment has been shown to be associated with improved health-related quality of life (HRQOL) of children with SLE in UK JSLE Cohort [129].

For BILAG, disease activity with no domain scoring higher than C can be considered to be low disease activity, and all domains scoring D or E can be considered remission. Combining these scores with the GC doses for LLDAS and DORIS seems reasonable while formal definition of these BILAG-based low-disease activity state or remission endpoints for trials is in progress.

Integration of biomarkers alongside the T2T approach is also gaining interest, with two studies from the UK and Netherlands demonstrating the association between serum interferon alpha levels and T2T states [130, 131]. Next steps include prospective multicentre studies to assess the feasibility and impact of T2T implementation in routine clinical practice, and to evaluate its effect on key longer-term outcomes. These studies will be critical to establishing T2T as a standard of care in JSLE and ensuring its scalability across diverse healthcare settings.

A UK multicentre audit of the 2017 BSR SLE guideline showed that almost 30% of people with SLE had active disease despite current therapies, while in those with inactive disease, oral prednisolone dose was not tapered [86]. Although RCTs on T2T are ongoing in SLE, we considered that there are sufficient observational evidence and expert agreement for the GWG to recommend this approach in our guideline. Practical implementation has begun in the UK, notably in a prospective study in a large

tertiary centre involving 162 adolescents and young adults with SLE [132], demonstrating that T2T implementation over a 12-month period was associated with significant improvements in target attainment and that achievement of cLLDAS for >3 months was associated with significant reduced damage accrual at 12 months. A paediatric specific T2T feasibility study is ongoing in the northwest of England.

Maintaining DORIS remission, LLDAS and paediatric specific targets (cLLDAS, cCR, cCR-0) is associated with lower rates of subsequent flare, organ damage accrual and mortality, better HRQoL and reduced healthcare costs [127, 128, 133–143].

Summary

Adjusting treatment in order to achieve a target of low disease activity or remission is associated with GC sparing and better long-term outcomes in SLE; systematic assessment is recommended to ensure this occurs.

Non-pharmacological approach: what non-pharmacological interventions are supported by evidence and/or expert consensus to inform a BSR guideline?

Rationale

The recommendations for a non-pharmacological approach in this BSR guideline build on the 2017 BSR SLE guideline [22] and draw from the 2023 EULAR recommendations for the non-pharmacological management of SLE and systemic sclerosis [35]. We also performed a further search from their respective last search dates to update evidence and inform our recommendations. Additionally, we referred to the 2022 EULAR recommendations for cardiovascular risk management in rheumatic and musculoskeletal diseases (RMDs), including SLE and APS [144], the 2024 International Consensus on physical activity and exercise [43] and the 2023 EULAR recommendations for fatigue management [44]. Healthcare professionals in SLE include doctors, nurses, pharmacists and AHPs (physiotherapists, occupational therapists, podiatrists, clinical psychologists, nutritionists and others). To refer to NICE and EULAR guidelines in inflammatory arthritis [145, 146] and RMDs [147] for the roles of AHPs.

Recommendation 24 People with SLE and their parents/carers should be offered age, culture and language-appropriate education and self-management support as part of routine care (1C) [96.9% (80–100)].

Recommendation 25 Clinicians should promote and monitor adherence. For example: discuss the importance of adherence on disease control and long-term outcomes, monitor prescriptions and drug levels, practice shared decision-making on treatment and route of administration (1D) [98.0% (87–100)].

General principle: education and adherence

Education

The 2023 EULAR recommendations for the non-pharmacological management recommend people with SLE should be offered patient education and self-management support. Since their last search, a large RCT ($n=560$ participants) in Canada used Patient Activated Measure (PAM) score, a validated tool to assess a person's knowledge, skills and confidence in managing their health and well-being as the primary end point. The study showed no significant difference in PAM scores between people with SLE who received either immediate access to the MyLupusGuide site (i.e. a web-based education programme) or delayed access starting on month 3. However, the study did show improvement in self-efficacy before and after accessing the MyLupusGuide site, which supported the benefit of the patient education and self-management programme [148]. Another small RCT ($n=30$ participants) did not demonstrate additional benefit from the implementation of weekly phone education session for 12 weeks about SLE with a patient navigator compared with standard of care [149]. After reviewing the available evidence, the BSR GWG agree that people with SLE and their parents/carers should be offered education and self-management support, as well as emphasising the need for these resources to be age, culture and language-appropriate consistent with the groups of people most affected by SLE.

Adherence

Adherence to self-management, well-being, psychological and pharmacological interventions is a key aspect to the management of SLE. Indeed, non-adherence to treatment is considered a major cause of treatment failure, increasing the risk of disease flares, worsening outcomes and requiring more intensive treatment escalations including GC [150–152]. Adherence can be particularly problematic during transition from JSLE to adulthood [153, 154]. It is vital to explore the reasons behind non-adherence. Studies have shown that this is multifactorial including patient-related reasons (forgetfulness, low self-efficacy or beliefs about medication), healthcare-related factors (poor communication between patients and physicians, complex instructions, lack of education about treatments) and disease-specific challenges (complex treatment regimens, higher disease activity score, cognitive dysfunction and memory loss due to SLE) [150, 154–157].

Monitoring drug levels (e.g. hydroxychloroquine, ciclosporin, tacrolimus and mycophenolate), may be a strategy to monitor adherence. Despite advancement in this field since the last BSR guideline, particularly for hydroxychloroquine with an SLR and meta-analysis to support monitoring of drug level, hydroxychloroquine level measurement is not widely available [158]. A good relationship between physicians, specialist nurses, pharmacists and people with SLE remains key to reduce the risk of non-adherence. Indeed, a prospective study which evaluated clinician-led adherence intervention through effective communication and reviewing together real-time pharmacy refill data showed that patient-physician discussions on non-adherence which took an average of 3.8 min per consultation resulted in 44% of participants with $\geq 20\%$ increase in 90-day refill

prescription following this intervention [159]. If non-adherence is known, more frequent appointments and close monitoring may be needed to promptly identify flares. Furthermore, in a pragmatic open-label randomised controlled trial in people with LN, intervention by pharmacists (Dader method) appeared to improve drug adherence compared with control group (usual care); 27% effectiveness (95% CI -6% to 50%) in the intention to treat analysis and 31% (95% CI 0% to 52%) in per protocol analysis, considering all drugs [160].

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- Recommendation 26 People with SLE should be advised at diagnosis and more frequently as necessary to use High Sun Protection Factor (SPF), broad-spectrum UV-A and UV-B sunscreen (1B) and to consider safe sun exposure strategies such as reduced sun exposure and the use of protective clothing (1D) [96.9% (84–100)].
- Recommendation 27 In people with SLE, smoking habits should be assessed, and people guided to cessation strategies (1C) [98.2% (83–100)].
- Recommendation 28 Physical activity should be encouraged as appropriate to disease status in adults (1B) and children (1C) with SLE. This will include tailored advice for some patients [97.0% (80–100)].
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Lifestyle measures

Sun protection

Pertaining to exposure to ultraviolet A (UV-A) and ultraviolet B (UV-B), there is no new high-quality study since the last search of the previous BSR guideline [22] and the 2023 EULAR recommendations for the non-pharmacological management [35]. The BSR GWG's recommendation remains unchanged that people with SLE should be advised and reminded to use high sun protection factor (SPF), broad-spectrum UV-A and UV-B sunscreen and to consider safe sun exposure strategies such as reduced sun exposure and the use of protective clothing (e.g. physical barriers such as hats, sunglasses, long-sleeved shirts, trousers, leggings and dresses). It is important to note that when choosing a sunscreen, UV-B protection is indicated by the SPF while UV-A protection is indicated by the UV-A logo or the UV-A star system (i.e. one to five stars). SPF and UV-A protection are often linked, so a higher SPF sunscreen will have more UV-A protection as per document produced by the British Association of Dermatologists (BAD) [161]. The BSR GWG discussed whether to specifically recommend the minimum SPF for people with SLE. Due to the lack of high-quality evidence, we adopted the recommendation by the BAD (i.e. high SPF as defined by at least 30 and with a UV-A logo or UV-A with 4-star or 5-star protection). The sunscreen should be reapplied at least every two hours, regardless of its SPF [161].

The use of high SPF, broad-spectrum UV-A and UV-B sunscreen is fundamental in the management and prevention of UV-induced skin lesions [22, 34, 162]. Additionally, it can also prevent systemic flares as supported by low quality studies from

the 2023 EULAR recommendations for the non-pharmacological management [35]. Detecting photosensitivity may be limited by a potential lag period of several weeks between sun exposure and skin lesions [163]. A qualitative study identified additional barriers to adequate photoprotection including unclear advice from clinicians, cost, tolerability, time constraints and conforming to social norms [164]. Thus, people with SLE should be advised at diagnosis and more frequently as necessary pertaining the use of high SPF, broad-spectrum UV-A and UV-B sunscreen.

Smoking

There is no new high-quality study since the last search of the previous BSR guideline [20]. The 2022 EULAR recommendations for management of cardiovascular risk recommend that people with SLE and/or APS to be thoroughly assessed for traditional cardiovascular factors including smoking and disease-related risk factors to guide risk factor modification [144]. Beyond increasing cardiovascular risk, an SLR and meta-analysis of cohort studies showed that smoking may also reduce the efficacy of hydroxychloroquine and belimumab [165]. The BSR GWG are in agreement with the statement by EULAR [144]. Smoking habits should be assessed and reviewed, and people with SLE guided to cessation strategies. The latter could be done by liaising with GPs and healthcare professionals in the community or signposting people to local stop-smoking support, if available, as per 2025 NICE guideline of smoking cessation for the general public [166]. We found no current substantive evidence about vaping in SLE.

Physical activity

Three main types of exercise are relevant: (i) aerobic which refers to the type of repetitive, structured physical activity, and requires the body's metabolic system to use oxygen to produce energy (e.g. walking, jogging, cycling and dancing); (ii) resistance which builds strength, anaerobic endurance and size of skeletal muscles (e.g. using resistance bands, hand weights and machines), or achieved via functional means such as stair climbing and rising from a chair to induce muscular contraction; and (iii) balance and flexibility which is aimed to help patients stay steady, prevent falls, and improve range of movement of specific joints (e.g. yoga, tai chi or stretching) [167]. The World Health Organisation (WHO) recommend (i) all adults living with chronic conditions irrespective of diagnoses should undertake regular physical activity; (ii) should do at least 150–300 min of moderate-intensity aerobic physical activity or at least 75–150 min of vigorous-intensity aerobic physical activity or an equivalent combination of moderate and vigorous-intensity activity throughout the week for substantial health benefits; and (c) should do muscle strengthening activities at moderate or greater intensity that involve all major muscle groups on two or more days a week [168]. Although these are strong recommendations and with moderate certainty, the data to support this are from chronic diseases such as hypertension, cancer, diabetes and HIV.

From the perspective of SLE, the 2023 EULAR recommendations for the non-pharmacological treatment recommend that (i) physical exercise should be considered for people with SLE; and (ii) aerobic exercise should be considered for increasing aerobic capacity, reducing fatigue and depressive symptoms [35]. These were based on evidence from two SLRs and their meta-analyses of RCTs and quasi experimental studies [169, 170]. In making our recommendation, the BSR GWG also considered the Cochrane review of exercise

as adjunctive therapy for adults with SLE with a search date up until 30 March 2021. This review included RCTs only and 13 studies were included with 540 participants. Some RCTs (especially the most recent ones) were not included in the two SLRs above, as well as another SLR and meta-analysis of RCTs published in 2021 [171]. The results from the Cochrane review of RCTs differed in that the benefits of exercise on fatigue, functional capacity, disease activity and pain, compared with placebo, usual care or advice and relaxation therapy were unclear due to low- to very low-certainty evidence. Similarly, there was uncertainty regarding potential harms from the structured exercise intervention due to small numbers of studies reporting adverse events (although in those that did, no serious adverse events were reported) [172]. It is important to note that these RCTs used various different endpoints, participants mostly had minimal disease activity (i.e. SLEDAI-2K <4 points), had shorter study duration or follow-up and did not assess the impact of physical activity on cardiovascular risk outcomes.

Exercise also has wider benefits in JSLE as evidenced by an SLR of non-pharmacological intervention [173]. In one RCT of 19 participants, people with JSLE who received 12 weeks of twice weekly supervised aerobic exercise showed a statistically significant increase in exercise tolerance and heart rate recovery, as well as an improved cardiorespiratory capacity compared with non-trained people with JSLE [174].

The 2024 International Consensus on physical activity and exercise in SLE outlines specific recommendations for exercise in SLE including the need for a medical evaluation before starting exercise to identify potential contraindications and the recommended regimen for those with inactive, mild disease activity or during articular flares [43]. The BSR GWG concurred that disease activity status is key in recommending the type, intensity and frequency of exercise. Therefore, after considering the current available evidence and recognising the wider benefits of exercise, physical activity should be encouraged in people with SLE as appropriate to disease status including tailored advice for some individuals.

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- Recommendation 29 A healthy, balanced diet, as recommended for people without SLE, should be recommended for people with SLE. More specific advice may be required for those with LN (1D) [96.8% (80–100)].
- Recommendation 30 Clinicians should recommend that people with SLE take a daily vitamin D supplement throughout the year, particularly in autumn and winter (1B). Where deemed appropriate, vitamin D levels should be tested and additional supplementation recommended if below the normal range (1C) [96.6% (80–100)].
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Dietary measures and supplementation

Dietary measures

Diet is an area of interest for people with SLE and their family and caregivers. This aspect was not included in the last 2017 BSR SLE guideline scope [20]. In the 2023 EULAR recommendations of non-pharmacological treatment of SLE, this is included in the research agenda due to limited current evidence [35].

In our SLR, we found three RCTs of dietary intervention programme: (i) low glycaemic index (Low GI) diet vs calorie restricted (Low Cal) diet [175]; (ii) National Cholesterol Education Program Step 2 diet vs no dietary intervention [176]; and (iii) six steps with verbal and printed nutritional instruction vs no dietary intervention [177]. There was very low certainty that these dietary intervention programmes had a positive impact on measures of disease activity, fatigue or sleep in SLE.

We also found five RCTs evaluating the efficacy and safety of fish oil or omega-3 supplementation in non-renal SLE [178–182]. Overall, whilst 4/5 RCTs demonstrated improvement in at least one measure of disease activity, there was low certainty that either of these supplements would improve disease activity owing to the different outcome measures used, inconsistent effects and the absence of between-group comparisons or use of appropriate statistical comparison. For LN, in two RCTs [183, 184], there was also low certainty and inconsistency in findings that fish oil supplementation would improve renal parameters (complete renal response, proteinuria, eGFR or creatinine).

In the absence of high-quality evidence for specific dietary recommendation in SLE, the consensus from the BSR GWG is to recommend a healthy balanced diet as defined by WHO. This includes consuming at least 400 g of vegetables and fruit per day in adults and children above 10 years, and 250–350 g per day in younger children; obtaining the largest amount of energy from carbohydrates, mainly through legumes (e.g. lentils and beans) and wholegrain cereals; reducing total fats to <30% of total energy intake, shifting fat intake away from saturated and trans fat to unsaturated fats, and eliminating industrial trans fats from the diet; reducing free sugars to <10% (ideally 5%) of total energy intake; and limiting sodium intake to <2 g per day (equivalent to 5 g of salt) [185]. For people with LN, the 2024 KDIGO guideline also recommends avoiding a high sodium diet [39].

Vitamin D

We identified four RCTs including one study involving JSLE [186–189] that examined the impact of Vitamin D supplementation on disease activity or flare. There is low certainty evidence that vitamin D supplementation may reduce disease activity [SLEDAI and/or European Consensus Lupus Activity Measurement (ECLAM)] over placebo based on two RCTs [189]. The remaining two RCTs reported no difference in disease activity or flare vs placebo [186, 188]. One RCT reported improvement in fatigue with vitamin D supplementation over placebo [189] while another RCT reported no difference in HRQoL (i.e. LupusQoL) between the treatment groups [187]. Two RCTs reported numerically higher mild adverse events (e.g. grade 1 hypercalcaemia, gastrointestinal complaints and arthralgia) in the vitamin D supplementation group over placebo although the differences were not statistically significant. There was no difference in serious adverse events in both groups [186, 189].

The BSR GWG also reviewed the recommendation by the UK Government that everyone should consider taking a daily vitamin D supplement during the autumn and winter. For those who usually wear clothes that cover up most of their skin when outdoors which will include many people with SLE, the NHS recommend that people aged 4 years or older should be given a daily supplement containing 10 micrograms (400 IU) of vitamin D throughout the year [190]. Taking the evidence together, the

BSR GWG recommend that people with SLE take a daily vitamin D supplement throughout the year, particularly in autumn and winter.

In terms of assessment of vitamin D status, the last BSR GWG concurred with the last BSR guideline [22] and the 2023 EULAR recommendations for non-pharmacological approach [35] that vitamin D levels should be tested where deemed appropriate and additional supplementation recommended if below the normal range.

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- Recommendation 31 People with SLE are at increased risk of cardiovascular comorbidities, therefore assessment and management of modifiable risk factors (e.g. hypertension, dyslipidaemia, diabetes, high BMI and smoking) should take place at baseline and at least annually, using appropriate risk assessment tool where applicable (1B) [96.6% (83–100)].
- Recommendation 32 The importance of receiving eligible vaccinations should be emphasised at least annually. Additionally, when boosters or new vaccinations are recommended, this guidance should be reinforced (1C) [98.4% (87–100)].
- Recommendation 33 Annual assessment and management of bone health should be performed including diet, exercise, lifestyle factors and medications. Vitamin D status and bone density should be assessed where indicated (2C) [97.6% (87–100)].
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Cardiovascular comorbidities, vaccination and bone health

Cardiovascular comorbidities

People with SLE are two to three times more likely to develop cardiovascular diseases including atherosclerosis, myocardial infarction, stroke, peripheral vascular disease and heart failure compared with the general population based on an updated SLR and meta-analysis [191]. Moreover, for people with SLE who are pre-menopausal, the risk of developing cardiovascular disease is far greater compared with their healthy peers [192, 193]. Thus, thorough assessment and management of conventional cardiovascular risk factors, as well as disease-associated risk factors (e.g. disease activity, concurrent aPLs, a history of lupus nephritis, GC use and daily dosage and organ damage) are of paramount importance. Lower threshold for investigation of suspected cardiovascular disease in younger people with SLE who may lack traditional risk factors also should be considered.

Drawing from the last BSR guideline [22] and the 2022 EULAR recommendations of cardiovascular management in RMDs [144], the BSR GWG recommend that assessment and management of modifiable risk factors [e.g. hypertension, dyslipidaemia, diabetes mellitus, high body mass index (BMI) and smoking] should take place at baseline and at least annually, using appropriate risk assessment tools where applicable. This can be done in collaboration with GPs, other internal medicine

specialists including cardiologists and other healthcare providers. It is important to note that although a commonly used cardiovascular prediction tool such as QRISK3 incorporates a diagnosis of SLE and use of GC in the 10-year prediction of cardiovascular event [194], other disease-associated risk factors are not included. Hence, this may underestimate the risk in people with SLE. Thus, when assessing the modifiable risk factors, also consider disease-associated risk factors before deciding on appropriate cardiovascular management strategies for each individual. Several SLE-specific cardiovascular prediction tools are in development and validation stages that are beyond the scope of the current guideline. Furthermore, since obesity is associated with poor clinical outcomes and increased risk of cardiovascular disease [195, 196], data are needed to assess the effectiveness and safety of obesity intervention studies in SLE.

Vaccination

Infection is the leading cause of death in SLE based on an updated global meta-analysis study; standardised mortality ratio of 4.95; 95% CI, 4.25–5.64 compared with the general population [197]. Thus, infection programme strategies including appropriate and up-to-date vaccination and judicious use of immunosuppression including GC tapering or cessation is fundamental. The recommendation from this BSR guideline draws from the 2021 update of EULAR/Paediatric Rheumatology European Society (PRES) recommendations for vaccination of paediatric patients with autoimmune inflammatory rheumatic diseases [198], the 2019 update of EULAR recommendations for vaccination in adult patients with autoimmune inflammatory rheumatic diseases [199] and the 2022 EULAR recommendations for the management and vaccination of people with RMDs in the context of SARS-CoV-2 [200]. The BSR GWG recommend that the clinicians and healthcare professionals should emphasise to people with SLE the importance of receiving eligible vaccinations at least annually. Additionally, when boosters or new vaccinations are recommended, this guidance should be reinforced. Vaccines could include seasonal influenzae, pneumococcal, tetanus, respiratory syncytial virus (RSV), varicella zoster, herpes zoster, human papilloma virus (HPV), measles, mumps and rubella (MMR) and COVID-19. Clinicians and healthcare professionals should therefore refer to the UK Health Security Agency (UKHSA) Green Book, *Immunisation Against Infectious Disease* [201]. Chapters 6 and 7 of the Green Book offer guidance on vaccinating people at increased risk of vaccine-preventable diseases due to underlying chronic illnesses or immunosuppression [202, 203]. Guidance on the timing of vaccination in relation to immunosuppression can be found in the BSR guideline for the prescription and monitoring of conventional synthetic disease-modifying anti-rheumatic drugs [118].

Bone health

People with SLE are at risk of osteoporosis with a meta-analysis of case-control or cross-sectional studies reporting an odds ratio of 2.03 (95% CI 1.33–3.10) compared with the general population [204]. This increased risk could be due to the disease process (i.e. chronic inflammation) and the side effects of therapies, particularly GC. Our SLR did not yield high quality evidence to inform the assessment and management of bone health that is specific to SLE. Thus, our recommendations for assessment and management of bone health to be undertaken annually draw from the 2022 UK clinical guideline

for the prevention and treatment of osteoporosis in postmenopausal women, and men aged 50 years or older [205]. There is no UK-wide or EULAR guideline pertaining to the management of paediatric osteoporosis despite its negative impact on bone growth during a critical period for achieving peak bone mass [206, 207]. The BSR GWG recommend referring to the 2022 American College of Rheumatology (ACR) life-course guideline for the prevention and treatment of glucocorticoid-induced osteoporosis [208].

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- Recommendation 34 Health professionals should incorporate assessment of fatigue severity, impact and coping strategies alongside disease activity assessment during clinical consultations (1D) [95.4% (80–100)].
- Recommendation 35 Psychological support should be available to people with SLE, whenever possible as part of the multidisciplinary team (MDT) (1C) [96.7% (83–100)].
- Recommendation 36 Specialist psychology care should be available for specific problems associated with SLE in adults (1A) and children (1C) [96.3% (80–100)].
- Recommendation 37 All healthcare professionals assessing people with SLE should know how to signpost towards and/or refer to mental health services where there is an identified need for support (1D) [97.8% (83–100)].
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Fatigue and psychological support

Fatigue assessment and management

Fatigue is prevalent in about two-thirds of people with SLE and is two times more likely to be severe compared with moderate degree in terms of intensity [209]. It is recognised as one of the most challenging symptoms to manage, may impair key aspects of HRQoL and leads to employment disability [210–212].

The current BSR guideline recommendation draws from the last 2017 BSR SLE guideline [22] and the 2023 EULAR recommendations for management of fatigue in people with RMDs [44]. Regular assessment of fatigue severity, impact and coping strategies should be part of usual care provided by healthcare professionals. Although the majority of the studies identified in our SLR used FACIT-Fatigue, there was still variability in the tools used to assess fatigue severity and impact. To recommend specific tools in SLE for clinical practice or research is beyond the scope of this guideline but harmonisation of fatigue assessment in the future may help improve pooling of data and generalisability of results. Within the internationally agreed core and extended dataset for JSLE, the PROMIS Fatigue short form is recommended for use in clinical care and research [213].

The 2023 EULAR recommendations for management of fatigue in people with RMDs recommended that the presence or worsening of fatigue should trigger evaluation of inflammatory disease activity status and consideration of immunomodulatory treatment initiation or change, if clinically indicated [44]. Thus, assessment of fatigue should be undertaken alongside assessment of disease activity. The EULAR recommendation above was based on their SLR

and meta-analysis which included studies mostly concerning people with rheumatoid arthritis and spondyloarthritis [214]. Our SLR of RCT studies showed overall a lack of evidence/uncertainty for any particular pharmacological treatment or drug class for use specifically targeting fatigue in SLE. From the non-pharmacological approach perspective, our SLR showed low certainty evidence that exercise (in particular graded exercise therapy) may be effective for reducing fatigue in people with SLE [215, 216].

Psychological support and mental well-being

Living with SLE can have a marked effect on psychological well-being, including high rates of associated mental health issues such as depression, anxiety and cognitive dysfunction [217, 218]. Indeed, the 2023 EULAR recommendations for the non-pharmacological management of SLE recommended that psychosocial interventions should be considered to improve HRQoL, anxiety and depressive symptoms [35] based on SLRs and meta-analyses of RCTs [219, 220]. The psychological interventions were in the form of cognitive behavioural therapy (CBT), group therapy and psychoeducational programmes. Our SLR identified six more studies since the EULAR search including two studies in JSLE. There was low certainty evidence that psychological intervention may be effective in improving HRQoL, anxiety and depression in SLE.

Taking the evidence together, the BSR GWG recommend that psychological support should be available to people with SLE, whenever possible as part of the multidisciplinary team (MDT). Specialist psychology care should be available for specific problems associated with SLE including various challenges with the initial diagnosis, complications of SLE, impact on quality of life, transition of care from childhood to adult care, tolerability to therapies, adherence to therapies and associated mental health issues [221–225]. We recognise that psychology services vary across regions, but we feel that development of appropriate service should be an ambition. Acknowledging the increasing burden of mental health in people living with a chronic condition such as SLE, all healthcare professionals should know how to signpost towards and/or refer to mental health services where there is an identified need for support.

Summary

The recommendations on non-pharmacological approaches in the management of SLE will guide healthcare professionals and people with SLE towards a holistic and personalised management plan promoting their use alongside pharmacotherapy to improve the overall quality of care.

Antimalarials in SLE: general recommendations and what is the best evidence for monitoring therapies?

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- Recommendation 38 Hydroxychloroquine (HCQ) is recommended for all people with SLE unless contraindicated (1A), at long-term target dose of 5 mg/kg/day (based on
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(continued)

actual body weight, usual maximum 400 mg/day) (2C). Dose can be individualised based on risk of flare (2B), risk of retinal toxicity (2C) and other adverse events (2D). Dose reduction of 50% may be needed if eGFR < 30 mL/min/1.73 m² (2C) [99.1% (91–100)].

Recommendation 39 If people with SLE suffer persistent non-serious adverse effects with HCQ, consider switching to a HCQ product made by a different manufacturer as excipients may differ (2C) [97.6% (81–100)].

Recommendation 40 We recommend following the Royal College of Ophthalmologists (RCOphth) guidelines for HCQ with ocular toxicity monitoring at 5 years, then annually thereafter (1B for adults, 2D for JSLE). For higher risk patients including those on HCQ dose of >5 mg/kg/day based on actual body weight, on tamoxifen, those with renal impairment, and those who have taken chloroquine for greater than one year, annual screening is recommended (2B) [98.1% (90–100)].

Recommendation 41 Pathways should be established locally to facilitate ocular toxicity monitoring in accordance with the RCOphth Guidelines (2D) [97.9% (83–100)].

Recommendation 42 The date of commencement of HCQ and dosing should be recorded in the medical records in a way that is easily retrievable (2D) [95.4% (80–100)].

Recommendation 43 When using a standard HCQ dose, baseline or monitoring ECGs are not required unless there are specific drug-drug interactions, especially with other therapies causing long-QT (2C) [97.0% (80–100)].

General recommendations for antimalarial therapies

Hydroxychloroquine (HCQ) is a cornerstone therapy for SLE. Multiple beneficial effects of HCQ in SLE have been demonstrated [226] with high quality of evidence as follows: (i) improved disease activity was reported in an SLR [227] that included three RCTs [228–230] and was supported by other large cohort studies including pregnant women and people with LN [231–235]; (ii) reduced concurrent GC dose was reported in an SLR [227] which included two RCTs [229, 236] and was supported by other large cohort studies [231, 233]; (iii) prevention of SLE flare was reported in an SLR [227] and five RCTs [228, 229, 236–238]; (iv) protection against accrual of organ damage was reported in large cohort studies [231, 239–244]; (v) improving remission rates as an adjuvant therapy in LN was reported in an SLR [227] and supported by other large cohort studies [231, 245, 246]; (vi) improved CLE reported in an SLR [247] and two RCTs [236, 248]; (vii) improved articular complaints reported in an SLR [227] and two RCTs [229, 230]; (viii) reduced risk of thrombosis reported in an SLR [227] and supported by other

large cohort studies including people with SLE and aPLs [239, 245, 249–253]; (ix) reduced infection risk reported in an SLR and meta-analysis of 39 cohort studies [254]; (x) reduced mortality risk reported in an SLR and meta-analysis of 21 cohort studies [255]; (xi) reduced lipid profile reported in two SLRs and meta-analyses of RCTs and cohort studies [256, 257] and one SLR [227]; (xii) reduced atherosclerosis reported in large cohort studies [258, 259]; (xiii) favourable pregnancy outcomes such as reduced risk of disease activity and flare during pregnancy, pre-term birth, intrauterine growth retardation, gestational hypertension, and pre-eclampsia reported in an SLR of 17 cohort and four case-control studies [260]; and (xiv) reduced the risk of CHB and neo-natal lupus in pregnant women with anti-Ro/SSA and/or anti-La/SSB antibodies reported in multicentre, open-label, single-arm, two-stage clinical trial [261] and cohort and case-control studies [262–264].

Owing to the wealth of benefits of HCQ in SLE, if people suffer persistent non-serious adverse effects with one product of HCQ, consider switching to an alternative product made by a different manufacturer. Plaquenil® was the originator for HCQ sulphate and Sanofi-Aventis lost its patent for this in 2015. Since then, generic versions have become available with different excipients/fillers added to the tablet. A single centre survey reported a higher gastrointestinal side effect rate with the Quinoric® brand (18%) compared with those on Plaquenil (4%) or other generic brands (0%) [265]. Therefore, clinicians need to be mindful of side effects possibly pertaining to excipients rather than the HCQ itself (particularly if non-serious) and recommend a trial of sourcing a product with different excipients instead of discontinuing HCQ altogether. Chloroquine can be used if HCQ is not available or not tolerated, although there is less evidence for effectiveness and there is a greater risk of retinal toxicity than HCQ [45, 227]. Another alternative to HCQ is mepacrine (also known as quinacrine), which is used predominantly for CLE (and sometimes in combination with HCQ) [45, 266–269]. Mepacrine is not generally associated with retinal toxicity [270].

Historically, the 2009 Royal College of Ophthalmologists (RCOphth) [271] and the 2011 American Academy of Ophthalmology (AAO) [272] guidelines each recommended a maximum safe dose of 6.5 mg/kg/day of ideal body weight (IBW) (up to a maximum of 400 mg daily) to minimise the risk of retinopathy. In 2016, the AAO updated their maximum daily dose recommendation to 5 mg/kg/day actual body weight (ABW) which was endorsed by the RCOphth in 2018. This was following a report of an overall prevalence of retinopathy of 7.5% in long-term (>5 years) HCQ users which increased to 20% after 20 years of therapy in the US [273], as opposed to ~0.5% [274, 275] when modern retinal imaging techniques were used in the former study. The retinopathy was more frequent using the IBW- as opposed to the ABW-based HCQ dosing [273]. Audits in the UK following the findings above showed slightly lower prevalence of retinopathy between 0.3% to 6.3% [276, 277].

The lower HCQ dose recommended by RCOphth and AAO was made specifically to reduce the risk of retinopathy, but the GWG also considered whether dose reduction may impact on the protective effect of HCQ on disease activity, thrombosis or cardiovascular disease. In a database study, odds of flare were inversely associated with HCQ dose for doses below 5 mg/kg/day. However, above a dose of 5 mg/kg/day, there was no

additional protection from flares with higher HCQ doses [278]. Until more high quality of evidence is available pertaining to benefit-risk relationship of different doses, we recommend HCQ is prescribed at a long-term target of 5 mg/kg/day (based on ABW, usual maximum 400 mg/day). This long-term target dose is contrary to its licensing dose, which is based on IBW, but in line with the recommendations by the 2023 EULAR [38], the 2020 RCOphth and the 2025 BSR conventional synthetic DMARDs [118] guidelines. The dose can be individualised based on risk of flare, risk of retinal toxicity (pre-existing macular or retinal disease) and other adverse events (2D). Consider dose reduction of 50% if estimated glomerular filtration rate (eGFR) <30 mL/min/1.73 m². Furthermore, in some people with SLE with moderate or severe disease, an initial HCQ dose higher than 5 mg/kg/day (but not exceeding 400 mg/day) may be used with appropriate monitoring as per the 2025 BSR conventional synthetic DMARDs guideline [118], followed by lowering of the dose to the usual long-term level once the disease has improved.

Another means to guide the optimal dose for each individual and assess for possible non-adherence to HCQ is by measuring HCQ blood levels. An SLR and meta-analysis of 13 observational studies and four intervention studies reported a strong relationship between low HCQ levels and reported non-adherence (defined as <80% medication adherence reported). The study also suggested HCQ levels of ≥ 750 ng/mL might be a potential therapeutic target since this was associated with lower disease activity [158]. At present, it is impractical to recommend HCQ blood level monitoring nationally since only a limited number of health services in the UK can offer this test, as well as the absence of its cost-effectiveness data. In services where it is available, it can nevertheless be used in selected patients.

For the management of mild non-organ threatening disease that is refractory to HCQ, to minimise GC use and exposure, consider adding methotrexate, mepacrine or azathioprine (azathioprine especially for those who may become pregnant). The evidence and rationale for these immunosuppressants is given in detail in the 2017 BSR SLE guideline [22].

Monitoring for antimalarial therapies

The GWG recommend following the RCOphth guideline [45] to monitor for possible ocular toxicity associated with HCQ in all people with SLE. Although there is only a small number of case reports published on HCQ retinopathy in JSLE [279], a similar HCQ monitoring algorithm should be followed since these individuals may accumulate exposure at a younger age and to a greater extent over their lifetime. From the perspective of care-delivery, each healthcare organisation should establish clear pathways to facilitate ocular toxicity monitoring. To facilitate effective referrals to ophthalmology, the date of commencement of HCQ and dosing should be clearly recorded and easily retrieved, as well as an up-to-date weight and height as per recommendation #16 in this guideline and renal function. This is especially important if people with SLE move to different healthcare services or transition from children to adult services.

Cardiac complications with HCQ may be a concern since it is a recognised cause of long-QT syndrome and through specific interactions with other concomitant drugs. During the height of the COVID-19 pandemic when HCQ was used in much larger

doses as a treatment, an SLR and meta-analysis of 19 cohort studies reported an increased risk of drug-induced QT prolongation and relatively higher incidence of torsades de pointes, ventricular tachycardia or cardiac arrest in people treated with HCQ or chloroquine [280]. However, data from the RECOVERY RCT which administered a total of 2400 mg of HCQ in the first 24 h, followed by 800 mg per day for 9 days with a total dose of 9600 mg HCQ in the study arm reported no significant difference in cardiac arrhythmias between HCQ and placebo groups [281]. This is reassuring since the HCQ dose for the treatment of SLE is much lower, with a usual maximum 400 mg daily.

Summary

All people with SLE should be treated with HCQ unless contraindicated at a long-term target dose of 5 mg/kg/day (based on ABW, usual maximum 400 mg/day). Follow the 2020 RCOphth guideline on monitoring for HCQ and chloroquine-associated retinopathy in all people with SLE. Since the risk of cardiotoxicity appears very low with the standard HCQ dose used in SLE, baseline or monitoring ECGs are not required unless there are specific drug-drug interactions, especially with other therapies causing long-QT syndrome.

Non-renal SLE: what is the best evidence for the management of inactive or low disease activity SLE?

Recommendation 44 Other treatments to be considered for the management of mild non-organ threatening disease that is refractory to HCQ include methotrexate (1B), mepacrine (2C) and azathioprine (2C) (azathioprine especially for those who may become pregnant) (2C) [97.4% (90–100)].

Conventional immunosuppressant

For the management of mild non-organ threatening disease that is refractory to HCQ, to minimise GC use and exposure, consider adding methotrexate, mepacrine or azathioprine (azathioprine especially for those who may become pregnant). The evidence and rationale for these immunosuppressants is given in detail in the 2017 BSR SLE guideline [22].

Recommendation 45 Glucocorticoids (GC) including topical preparations, intra-articular or intramuscular injections or intravenous methylprednisolone may be used depending on the type and severity of organ involvement, as a bridging therapy to settle a flare and/or while HCQ or a new or increased dose of an immunosuppressant takes effect (2C) [97.5% (85–100)].

(continued)

Recommendation 46 Long-term maintenance treatment with oral GC is not routinely recommended to treat disease activity. If used, target dose should be as low as possible aiming for ≤ 5 mg/day prednisolone (or equivalent) in adults (0.1 mg/kg/day, up to 5 mg/day in children) (1B) [97.4% (86–100)].

Glucocorticoids

GC have been used for three-quarters of a century for the treatment of SLE and other rheumatic diseases. With the advancement in therapies and owing to the detrimental effects of GC on longer-term health outcomes, the GWG members strongly advocate for minimisation of GC exposure. This is in line with the 2017 SHARE [40], the 2023 and the 2025 EULAR [38, 53], the 2024 and the 2025 ACR [52, 54] and the 2024 KDIGO guidelines/recommendations [39].

GC have a uniquely consistent and rapid effect on disease activity that makes them valuable as a bridging therapy to settle a flare and/or while HCQ or a new or increased dose of an immunosuppressant takes effect. The use of intravenous pulses of methylprednisolone of various doses (depending on disease severity and patient weight) may benefit on the non-genomic effects of GC [282, 283] and allow for a faster tapering of oral prednisolone [284, 285]. Nevertheless, we do not recommend long-term maintenance treatment with oral GC routinely to treat disease activity. We acknowledged that some people with SLE in remission and on low-dose prednisone could flare upon GC discontinuation [286–288]. However, in most situations there will be other therapeutic options to achieve the same. This has been formally demonstrated for belimumab and anifrolumab with reduction of flare rates in protocols that included GC tapering [289–291].

RCT evidence of different GC tapering regimens has been performed for LN demonstrating no difference in efficacy but worse safety with higher doses (discussed below). Although RCTs of different GC tapering regimens or maintenance doses are lacking in other features of SLE, some principles may be extrapolated to other scenarios. Specific guidelines relating to GC dosing and tapering are being developed by an international consortium but have not yet been published at the time of this BSR guideline. Long-term oral GC are not recommended but if they cannot be discontinued, the target dose should be as low as possible aiming for ≤ 5 mg/day prednisolone (or equivalent) in adults (0.1 mg/kg/day, up to 5 mg/day in children). This is in line with the EULAR and ACR guidelines, 2021 DORIS remission criteria and paediatric specific remission criteria [38, 54, 91, 125].

Summary

For the treatment of mild non-organ threatening disease, all people with SLE should be treated with HCQ unless contraindicated. GCs can be valuable short term, but exposure should be minimised, and long-term maintenance treatment with oral GC to treat disease activity is not routinely recommended. For mild non-organ threatening disease that is refractory to HCQ, to minimise GC use and exposure, consider adding methotrexate, mepacrine or azathioprine (azathioprine especially for those who may become pregnant).

Non-renal SLE: what is the best evidence for the management of moderate-to-severely active SLE?

Recommendation 47 In people with SLE with moderate disease activity but no evidence of organ or life-threatening disease, immunosuppression such as methotrexate (1B), mycophenolate (2B), azathioprine (2C) or ciclosporin/tacrolimus (2C), in addition to HCQ, should be started early [98.8% (92–100)].

Early use of a conventional immunosuppressant

A systematic review of evidence for conventional immunosuppressants in SLE was performed for the 2017 BSR SLE guideline and readers are referred to that paper for a detailed explanation [22]. Since the 2017 BSR SLE guideline search, there was one new published RCT pertaining to the efficacy of conventional immunosuppressants for the treatment of moderate-to-severe, and non-organ threatening SLE. In a multicentre, superiority, open label, RCT in Spain, people with moderate-to-severe non-renal active disease (SLEDAI-2K ≥ 6 or at least 1×BILAG A or 2×BILAG B scores) were assigned 1:1 to either enteric coated mycophenolate sodium (EC-MPS, myfortic) or azathioprine, in addition to antimalarials and/or oral GC. The study met its primary end point for which the proportions of participants who achieved clinical remission (clinical SLEDAI-2K=0 and/or absence of any BILAG A or B score) were greater in the EC-MPS group vs azathioprine group at both 3 months [32.5% vs 19.2% respectively; treatment difference, 13.3 (CI 2.3–24), $P=0.034$] and 24 months [71.2% vs 48.3%; treatment difference, 22.9 (CI 10.4–34.4), $P<0.001$]. Time to clinical remission and reduction in BILAG A/B flare rate also favoured EC-MPS vs azathioprine. EC-MPS was well-tolerated; adverse event (AE) rates were similar in both groups except for leukopenia which was more frequent in azathioprine [292]. Mycophenolic acid analogues (MPAA) may therefore be preferred to azathioprine, but choice of therapy will depend on individual patient features.

In new onset SLE, a multicentre, observer-blinded RCT in China sought to assess the effectiveness and safety of the early addition of MMF to HCQ and oral GC in treatment-naïve people with SLE with a high anti-dsDNA antibody titre and active disease but without major organ involvement. Participants were randomised 1:1 to either HCQ (5 mg/kg/day) + oral GC (0.5 mg/kg/day) or HCQ (5 mg/kg/day) + oral GC (0.5 mg/kg/day) + MMF 500 mg BD, with suggested oral GC tapering schedule after 4 weeks. The study met its primary end point; the rate of severe SLE flare (SELENA-SLEDAI) at week 96 was lower in the add-on MMF group (7 of 65 [10.8%]) vs the control group (18 of 65 [27.7%]) (relative risk [RR], 0.39 [95% CI, 0.17–0.87]; $P=0.01$). The incidence of LN also was lower in the add-on MMF group. No significant difference in AE was observed between groups with infections as the common AE for both groups [293]. This supports the value of early introduction of immunosuppressants, although a population of exclusively Chinese individuals

and use of lower MMF doses limits generalisability to UK populations.

Collectively, the body of evidence and expert agreement supports the add-on of a conventional immunosuppressant early in the treatment pathway to reduce the need for or dose of GC if there is moderate disease activity even without evidence of organ or life-threatening disease. In JSLE, MMF has generally become the initial immunosuppressant of choice [42].

It is important to note that these conventional immunosuppressants can be associated with side effects and toxicities. There can be other clinical challenges (e.g. attribution of cytopenia due to lupus or cytotoxic drugs, difficulties in distinguishing manifestations of lupus disease activity from damage and comorbidities). Methotrexate and MMF are teratogenic, hence alternative agents such as azathioprine, tacrolimus or ciclosporin are preferred in women trying to conceive or pregnant. Therefore, a personalised and shared patient-physician approach is required in the choice of therapies, that should consider the predominant features of their SLE, the most suitable route of administration and frequency, infection risk profile, pregnancy planning, complexity and risks for the individual.

Recommendation 48 In people with SLE with moderate-to-severe non-renal disease or the inability to withdraw GC despite the use of at least one immunosuppressant, discuss biological therapy and consider clinical trials with a specialised centre MDT (follow local processes for urgent cases) (2C) [98.2% (86–100)].

Consideration of biological therapy

We considered whether to recommend biologic therapies first-line or after other immunosuppressants in non-renal SLE. The licensing RCTs of belimumab and anifrolumab only required hydroxychloroquine and/or GC failure and not necessarily other immunosuppressants. In line with this, the 2023 EULAR guidelines include belimumab and anifrolumab as options after hydroxychloroquine only, alongside conventional immunosuppressants although with a higher grade of evidence [38]. However, no specific trial evidence has shown that biologics are more effective than other conventional immunosuppressants as first-line therapies. On the other hand, SLE is most severe and leads to most damage and death in the first year of disease [235, 294, 295], and individuals with markers of severity such as high SLEDAI or serological activity, who are at greatest risk of damage or death, also have the best responses to biologics [242, 296–300]. These latter observations suggest the potential value of first-line biologics at least in some people with SLE. We have recommended that in people with SLE with moderate-to-severe non-renal SLE, to introduce at least one conventional immunosuppressant early. If moderate-to-severe disease persists, or it is not possible to withdraw GC, despite the use of at least one immunosuppressant, physicians should discuss consideration for biological therapy or clinical trials with a specialised centre MDT at the earliest opportunity.

That said, there will be many exceptions or specific situations that will include biologics or other options as first-line therapies instead of conventional immunosuppressants. Indeed, real-world UK data show that rituximab is already prescribed relatively early; 14% of people in the BILAG Biologic Registry (BILAG-BR) for SLE [301] and 32% of people with JSLE in the British Paediatric Surveillance Unit study [9] received rituximab within the first year of diagnosis. These studies included individuals with a range of specific manifestations or severity of SLE, or where conventional immunosuppressants are contraindicated, and did not describe rituximab treatment according to mild, moderate and severe disease. These are described in detail below in the rituximab section. UK clinicians will also be bound by NICE and NHSE guidelines in England, that may restrict use of biologics in the treatment pathway. Although we emphasise MDT discussion for biologics in SLE, in line with NHSE guidelines, for urgent cases such as life-threatening disease, local processes (e.g. communication via phone, urgent emails, etc.) should be established and followed.

Recommendation 49 Belimumab is recommended as add-on treatment in autoantibody-positive people with SLE aged five or over with high disease activity [i.e. defined as at least one serological biomarker (positive anti-dsDNA or low complement) and a SLEDAI score of ≥ 10] despite standard treatment (1A) [96.9% (80–100)].

Belimumab

At the time of the last BSR guideline [22], belimumab was licensed for moderate-to-severe SLE based on two pivotal Phase III RCTs: BLISS-52 (289) and BLISS-76 [291]. Since that time, belimumab has been evaluated extensively in three other Phase III RCTs in non-renal adults with SLE: (i) BLISS-NEA (northeast Asia population) [302]; (ii) BLISS-SC (subcutaneous form of belimumab) [303], and EMBRACE (people of Black African ancestry) [304], as well as a Phase II RCT in JSLE: PLUTO [305]. BLISS-NEA and BLISS-SC met their primary endpoints (SLE Responder Index by ≥ 4 points, SRI-4). PLUTO was not powered for statistical hypothesis testing. SRI-4 responses were numerically more frequent with belimumab compared with placebo [52.8% vs 43.6%; OR 1.49 (95% CI 0.64–3.46)]. Differences were larger, and ORs did not include 0, for the secondary efficacy endpoints and SAEs were half as frequent with belimumab as with placebo. The EMBRACE study did not meet its primary end point of SRI-4 in people of Black African ancestry. However, nominally significant results were seen for several subgroups including individuals outside North America, suggesting that the ‘Black African ancestry’ criterion is too broad and finer ancestral specificity, socioeconomic or other factors were more important. SAEs were more common with placebo.

At the time of the last BSR guideline, the NICE Technology Appraisal recommended belimumab for the treatment of active autoantibody-positive adults with SLE, with a SLEDAI ≥ 10 points and active serological biomarkers (positive anti-dsDNA antibodies

and low complement) despite standard therapy. This decision was made following a pooled analysis of both BLISS RCTs that demonstrated greater therapeutic benefit with belimumab + SOC group over placebo + SOC, might be achieved in people with higher disease activity as well as greater serologic activity (i.e. anti-dsDNA positivity and low complement level) [299]. However, analysis of the BILAG-BR indicated that the immunological criteria were too restrictive and might have prevented uptake of this therapy. Together with the findings from the PLUTO trial above, NICE updated its recommendation for belimumab in 2021 as add-on treatment in autoantibody-positive people with SLE aged five or over with high disease activity [i.e. defined as at least one serological biomarker (positive anti-dsDNA or low complement) and a SLEDAI score of ≥ 10] despite standard treatment [50]. Belimumab can be continued beyond 24 weeks only if the SLEDAI score has improved by four points or more. For non-renal SLE, belimumab is administered either through intravenous infusion 10 mg/kg every 2 weeks for three doses, then 10 mg/kg every 4 weeks for people aged 5 years or older or subcutaneous injection 200 mg once weekly for adults.

An updated SLR and meta-analysis of seven RCTs [306] and an SLR and meta-analysis of seventeen cohort studies [307] consistently report that belimumab + SOC is effective in reducing disease activity, concurrent GC dose, preventing flare and improving HRQoL.

Pooled analyses of the RCTs demonstrate that belimumab is effective in treating mucocutaneous manifestations [308], musculoskeletal and immunological features (low C3/C4 levels and/or high anti-dsDNA antibodies) over SOC therapies [309]. For assessment of mucocutaneous manifestation, the RCTs used the mucocutaneous domain of classic BILAG (mcBILAG) and the mucocutaneous section of SLEDAI-2K (mcSLEDAI-2K). Cutaneous Lupus Erythematosus Disease Activity and Severity Index (CLASI) was not evaluated. Improvement was defined as a change in mcBILAG from a baseline score A to a score B, C or D, or a change from a baseline score B to a score C or D, or a ≥ 2 -point reduction in the total mcSLEDAI-2K score compared with baseline, respectively. At week 52, belimumab + SOC was superior to placebo + SOC in attaining mcBILAG (OR: 1.29 [95% CI: 1.07–1.57]; $P=0.008$) and mcSLEDAI-2K (OR: 1.37 [95% CI: 1.16–1.62]; $P<0.001$) responses. mcBILAG and mcSLEDAI-2K responses were observed from 12 and 16 weeks, respectively, and were sustained through week 52 [308].

For musculoskeletal disease, pooled analysis of BLISS-52 and BLISS-76 RCTs reported significantly more participants treated with either 10 mg/kg or 1 mg/kg belimumab + SOC achieved BILAG musculoskeletal improvement at week 52 (i.e. defined as a change from an A or B score to a B, C or D score) over placebo + SOC group, while significant major improvements of two to three letter scores (i.e. A to C or D, or B to D) were noted in the 10 mg/kg belimumab + SOC group for the musculoskeletal and in the 1 mg/kg belimumab + SOC group for the musculoskeletal domain over placebo + SOC group [309]. The magnitude of improvement in the number of swollen and/or tender joint counts was not reported. The vasculitis domain also improved more with belimumab than placebo.

For other non-renal SLE manifestations, pooled analysis of all Phase III RCTs of belimumab has not yet been published. It must be noted that data on efficacy in other organ systems are more

limited, especially neuropsychiatric SLE which was excluded from trials, which is why we recommend different therapies for some types of disease activity (see below). There were similar efficacy and safety in older people with SLE (aged >65 years) and the overall SLE population [310].

Long-term data over 8 years from RCTs and long-term extension studies (LTE) suggest that improvements in these outcomes, as well as in limiting organ damage accrual continue over time among people with SLE remaining on belimumab (the limitation being dropouts from long-term follow-up) [311, 312]. Belimumab showed a stable safety profile for over 8 years with no new safety signals based on data from RCTs and LTEs. There has been concern about risk of suicidal ideation with belimumab. Depression (including mood disorders), suicide and/or self-injury were reported in 11.7% of people with SLE in the study, with incidence decreasing over the course of the long-term observation. Most depression-related events (94.9%) were non-serious; serious depression was reported in 0.5% of individuals. No completed suicides were reported. Thus, as per recommendation by the Medicines and Healthcare products Regulatory Agency (MHRA), physicians should carefully assess the risk of depression and suicide when considering therapy with belimumab. The relationship between these factors may be complex as depression is not the only reason for suicidal ideation, improving physical health may help with mood, and treatment should not be denied to individuals with depression. People with SLE taking belimumab should be made aware of this potential side-effect and advised to seek medical attention promptly if they experience new or worsening depression, suicidal ideation or thoughts about injuring themselves.

Recommendation 50 Depending on specific patient presentation and situation, rituximab (2B) or anifrolumab (1A) may be more appropriate than belimumab or clinical trials in non-renal SLE [97.1% (80–100)].

Recommendation 51 Intravenous immunoglobulin could be considered for severe autoimmune thrombocytopaenia attributed to SLE (1B) [98.3% (87–100)].

Recommendation 52 In people with SLE with active and non-thrombotic neuropsychiatric disease attributed to SLE, GC and intravenous cyclophosphamide (2C), rituximab (2C) or combination of cyclophosphamide and rituximab (2C) should be considered [97.6% (80–100)].

Rituximab

Since the last BSR guideline [22], there has been no new fully published RCT of rituximab in SLE. A small RCT has been published as a conference abstract with the paper expected during the lifecycle of this guideline that was unpowered but supportive of efficacy in lupus arthritis [313]. NHS England updated their initial 2013 clinical commissioning interim policy in 2020 to continue commissioning rituximab for post-pubescent children or adults with moderate or severe refractory SLE [defined as at

least one BILAG A and/or two B scores or SLEDAI-2K score of six or more OR requiring unacceptably high levels of GC (e.g. ≥ 7.5 mg prednisolone per day in adults) to maintain a lower disease activity state], AND who have failed to respond or have had adverse events to two or more immunosuppressant (one of which must be either mycophenolate or cyclophosphamide, unless contraindicated). People with SLE should have been assessed and found not to be eligible for clinical trials or belimumab [49]. This position was supported by data relating to efficacy/effectiveness of rituximab from an updated SLR and meta-analysis of 31 studies (two RCTs and 29 observational studies, $N=1112$). The global response rates for people with refractory SLE in open-label studies of rituximab were 73% (95% CI 67% to 78%), complete response rates were 46% (38% to 55%) and partial response rates were 34% (28% to 40%) [314]. The effectiveness and safety of rituximab in JSLE were also reported in two SLRs of cohort studies and case series [315, 316]. Data from earlier UK studies reported that rituximab was used in some pre-pubescent children with SLE, with no concerning safety signals reported, despite the NHSE commissioning guidance relating to post-pubescent individuals [317, 318].

Of 178 people with SLE with paired baseline and 6-month data from the BILAG-BR registry, clinical response (i.e. defined as loss of all A and B BILAG scores to ≤ 1 B score with no new A/B scores in other organ domains) was achieved in 49%, while 18% achieved major clinical response (i.e. defined as BILAG-2004 score of C/D/E only, SLEDAI-2K ≤ 4 and daily oral glucocorticoid dose ≤ 7.5 mg). Median (IQR) daily oral prednisolone dose also reduced from 11.25 (8.4–20) mg to 7.5 (5–12) mg at 6 months post rituximab [301].

Regarding infection, data were reported from the BILAG-BR registry which included 746 people with SLE on rituximab, 119 people on belimumab and 183 people on standard of care. In the following 12 months of starting a therapy, 92 serious infections were recorded in 58 people on rituximab, eight serious infections in five people receiving belimumab, and 18 serious infections in 13 people on standard of care. Compared with standard of care, there was no significant difference in the risk of serious infection for rituximab [adjusted hazard ratio (HR) 1.68 (95% CI 0.60–4.68)] and belimumab [1.10 (0.21–4.80)] [319]. In RCTs of rituximab in SLE, serious infection rates have either been similar, or lower for rituximab compared with placebo [320]. Progressive multifocal leukoencephalopathy (PML) is a demyelinating disease of the central nervous system, caused by the reactivation of the John Cunningham (JC) virus. Although very rare, people with SLE are at increased risk for PML compared with other RMDs (i.e. incidence is about 10 times higher than people with RA) [321]. An SLR of four observational studies, two case series and 29 case reports in SLE reported incidence rates of PML between 1–2.4 cases per 100 000 person-years. Of the 35 cases of PML reported, three people were exposed to no immunosuppressant drugs at PML diagnosis while five had minimal immunosuppression. Thus, SLE itself might inherently predispose to JC reactivation, independent of immunosuppressive therapies [322, 323].

Repeat cycles of rituximab for treatment maintenance are effective in both JSLE and adults from longer-term data of observational cohort studies [317, 324–326]. However, up to 12% of people may develop a severe infusion reaction in repeat cycles

which is associated with anti-rituximab antibody [324, 327]. Factors associated with this anti-drug antibody phenomenon included lack of concomitant immunosuppressant and higher pre-rituximab plasmablasts [324]. In people with SLE with anti-drug antibody to rituximab, observational studies and case series suggested that switching to alternative humanised anti-CD20 mAb or a type 2 anti-CD20 mAb such as obinutuzumab restored B-cell depletion and clinical response [328–331]. Repeat cycles of rituximab in RMDs including SLE may also lead to secondary hypogammaglobulinaemia. A low IgG level is associated with an increased risk of serious infection [332–334]. Thus, immunoglobulin levels particularly IgG should be monitored at rituximab initiation and before each cycle to discern individuals at risk of serious infection and plan appropriate infection prevention and retreatment strategies.

Anifrolumab

Type I interferons (IFN-I) are anti-viral molecules that activate innate and adaptive immunity with causal roles in SLE pathogenesis [335, 336]. Overexpression of type I IFN-induced genes is associated with disease activity and subsequent flares in SLE [337–339].

Anifrolumab is a fully human IFN-I receptor mAb that inhibits the biological activity of all IFN-I. It is administered intravenously at 300 mg every 4 weeks. Anifrolumab was approved for the treatment of adult people with moderate-to-severe SLE, who are receiving standard therapy by the United States Food and Drug Administration (FDA) in July 2021 and the European Medicine Agency (EMA) in February 2022. This is following the results from a Phase IIb RCT (MUSE) [340] and two Phase III RCTs (TULIP-1 and TULIP-2) [341, 342] in autoantibody positive, moderate-to-severe non-renal SLE, despite being on standard treatment (at least one of either GC, an antimalarial or immunosuppressant). At the time of writing, NICE is unable to make a recommendation about the use of anifrolumab in the UK because evidence submission has not yet been undertaken by AstraZeneca.

In TULIP-1, participants were randomly assigned (2:1:2) to receive placebo, anifrolumab 150 mg or anifrolumab 300 mg for 48 weeks. The primary end point was the proportion of participants who achieved an SRI-4 at week 52 in the anifrolumab 300 mg group vs placebo group. The results showed no difference in SRI-4 between the treatment and placebo groups; anifrolumab 300 mg (65/180 [36%]) and placebo [74/184 (40%); difference -4.2 (95% CI -14.2 – 5.8) percentage points; $P=0.412$], thus the primary end point was not met. However, several secondary endpoints including reduction in oral GC dose, CLASI responses and BICLA responses, suggested clinical benefit of anifrolumab 300 mg dose compared with placebo [342]. In TULIP-2, participants were allocated in a 1:1 ratio to receive intravenous anifrolumab 300 mg or placebo every 4 weeks for 48 weeks. The primary end point of BICLA response at week 52 was met; significantly more participants achieved a BICLA response in the anifrolumab 300 mg group vs the placebo group (86/180 [47.8%] vs 57/182 [31.5%], respectively, difference 16.3 (95% CI 6.3–26.3) percentage points; $P=0.001$). Furthermore, three of the five key secondary endpoints (adjusted for multiple comparisons) were also attained in the anifrolumab vs placebo group. These endpoints were (i) BICLA response at week 52 in

participants with a high interferon gene signature at baseline; (ii) a reduction in the GC dose to ≤ 7.5 mg per day, sustained from week 40 to week 52, among those with a baseline dose of ≥ 10 mg per day; and (iii) a reduction of $\geq 50\%$ in the CLASI score at week 12 among those with moderate-to-severe cutaneous activity (CLASI ≥ 10) at baseline [341].

Three-year safety data have been reported in a blinded, placebo-controlled LTE study [343]. Participants completing the TULIP studies either continued anifrolumab 300 mg, switched from anifrolumab 150 mg to 300 mg or were re-randomised from placebo to receive either anifrolumab 300 mg or to continue placebo. In the LTE phase (years 2–4), the exposure-adjusted incident rates per 100 patient-years (EAIRs) of serious adverse events (SAEs) were 8.5 for anifrolumab 300 mg compared with 11.2 for placebo, while EAIRs of AEs leading to treatment discontinuation were 2.5 vs 3.2, respectively.

Regarding herpes zoster, EAIRs for anifrolumab 300 mg, placebo, anifrolumab 150 mg to 300 mg and placebo to anifrolumab 300 mg were 3.4, 2.8, 6.6 and 4.9, respectively. In all anifrolumab group (i.e. participants who had ever received at least one dose of anifrolumab), EAIRs of herpes zoster decreased over time and were lower during the LTE period than during the first year of treatment; 6.8 for year 1; 5.7 for year 2; 3.9 for year 3; and 2.9 for year 4. Zoster vaccination was not required for these trials and was not commonly used in routine practice for most participants at the time. EAIRs of COVID-related AEs, including asymptomatic infections, were higher in the anifrolumab group (15.5) compared with the placebo group (9.8). No COVID-related AEs occurred in fully vaccinated individuals and all COVID-related SAEs including three deaths in the anifrolumab group occurred during the first 6 months of the pandemic, prior to availability of vaccinations or treatments for COVID-19 [343]. Overall, this blinded LTE showed no new major safety signals and highlighted the importance of vaccination against COVID-19 and other viral infections such as influenzae and herpes zoster in people with SLE treated with anifrolumab. Phase III RCTs of anifrolumab in children and young people with moderate-to-severe, non-renal SLE [NCT05835310] and adults with active proliferative lupus nephritis [NCT05138133] are still ongoing.

Preference for specific biologics or other induction therapies

NICE and NHSE guidelines may restrict the choice of biologics in the treatment pathway for people with SLE living in England. There may be different guidelines in the devolved nations. However, there is no head-to-head late phase RCT comparing the efficacy and safety between biologics in non-renal SLE. Our SLR and the SLR informing the 2023 EULAR recommendations [344] demonstrated lack of high-quality evidence to recommend specific drugs for specific organ manifestations outside LN. Factors that may influence the choice of therapies for remission induction could include the type of lupus manifestations, the extent and severity of organ involvement, adherence concerns, fertility and family planning, and concurrent comorbidities (like cardiovascular disease, diabetes mellitus or infections).

Depending on specific disease manifestation and severity, rituximab or anifrolumab may be more appropriate first-choice biologics than belimumab or clinical trials. Although most of the evidence in support of the efficacy of rituximab is from open-

label case series, these case series include a large number of people with SLE with various manifestations and with the most refractory disease. One example where rituximab may be indicated is moderate-to-severe autoimmune cytopenia [i.e. autoimmune haemolytic anaemia (AIHA) or thrombocytopenia]. The EULAR 2023 recommendations also prioritise rituximab over other biologics in cases of immune cytopenia [38]. Although not specific for SLE, NHSE commissioned rituximab for people with primary immunodeficiency with intractable cytopenia who have failed to respond to standard therapies [GC and higher doses of intravenous immunoglobulin (IVIG)] or are contraindicated for standard therapies [345].

Since the last BSR search, we did not note a major advancement in the field of autoimmune cytopenia attributable to SLE. In 2020, an international expert consensus recommended rituximab as second-line therapy for the management of GC refractory or GC dependent SLE-associated warm AIHA (wAIHA) [346]. This was supported by evidence from a multicentre retrospective cohort study of the French AIR registry where 14/16 (88%) people with SLE and haemoglobin < 100 g/l pre-rituximab had improvement in their haemoglobin to > 100 g/l with at least a 20 g/l increase from the pretreatment level and without the need for blood transfusion [347], as well as an SLR of small case series of four studies ($N = 25$) which reported around 84% of haemoglobin response or 100% improvement [348]. To comply with the NHSE clinical commissioning policy for rituximab in SLE [49], a BILAG score A requires haemoglobin of < 80 g/l while a BILAG B score requires haemoglobin level between 80–89 g/l AND another B score in other domain OR if requiring unacceptably high levels of oral GC (e.g. > 7.5 mg prednisolone in an adult per day) to maintain a lower disease activity state.

For the management of autoimmune thrombocytopenia, major advancement has been seen in the field of idiopathic thrombocytopenia purpura (ITP). For first-line therapy, the 2019 International Consensus recommend high dose GC (including intravenous methylprednisolone) with or without intravenous immunoglobulin G (IVIG) in children and adults with ITP [349]. In the UK, the updated 2025 NHSE clinical commissioning policy outlines that IVIG may be considered in four situations for the treatment of ITP: (i) life-threatening bleeding; (ii) where an immediate increase in platelet count is required (e.g. before emergency surgery or other procedure); (iii) where the individual is refractory to all other treatment to maintain the platelet count at a level to prevent haemorrhage. It may need to be given every 2–3 weeks during a period where other second line treatments are being tried; or (iv) moderate severity bleeding in individuals at higher risk of subsequent severe bleed. Individuals with mucosal bleeding or bleeding from multiple sites or a previous history of severe bleeding are at a higher risk of a subsequent severe bleed [350]. Since the publication of the 2019 international consensus [349], an RCT reported superior response of mycophenolate mofetil + GC as first-line therapy compared with GC with regards to primary end point (treatment failure) in people aged 16 years old or older with ITP [351]. For second-line therapy, high quality evidence (SLR and meta-analysis of RCTs or at least one RCT) are available for thrombopoietin receptor agonists (TPORAs) (e.g. eltrombopag [352–354], avatrombopag [355, 356] and romiplostim [357, 358]), spleen tyrosine kinase inhibitor (fostamatinib) [359] and rituximab in people with relapsing

or refractory ITP [360]. Treatment with TPORAs and fostaminitib are endorsed by NICE while NHSE commissions rituximab as off-label therapy for ITP.

For the management of moderate-to-severe autoimmune thrombocytopaenia attributable to SLE, some treatment strategies from ITP could be considered. The 2023 EULAR recommendations recommend high dose GC (including methylprednisolone), with or without IVIG, and/or rituximab, and/or high-dose intravenous cyclophosphamide, followed by maintenance therapy with rituximab, azathioprine, mycophenolate or ciclosporin [38]. The BSR GWG concurred with the above recommendation. Evidence from non-RCT studies for the agents above were provided in the last BSR guideline [22]. Since the last search, data from the French AIR registry also reported a high degree of effectiveness of rituximab; 40/44 (91%) people with SLE with a platelet count $<50 \times 10^9/l$ improved to a minimum platelet count $>30 \times 10^9/l$ with at least a doubling of the initial (i.e. pretreatment) count following rituximab therapy [347]. It is worth noting that RCTs in the field of ITP included participants with a platelet count $<30 \times 10^9/l$. However, to comply with the NHSE clinical commissioning policy for rituximab in SLE [42], a BILAG score A requires a platelet count of $<25 \times 10^9/l$ while a BILAG B score requires a platelet count between $25\text{--}50 \times 10^9/l$ AND another B score in other domain OR if requiring unacceptably high levels of oral GC (e.g. >7.5 mg prednisolone in an adult per day) to maintain a lower disease activity state.

Since the last BSR guideline search, a few more small uncontrolled cohort studies have reported the effectiveness of IVIG in refractory SLE-associated thrombocytopenia [361, 362] and could be considered. Its use will need to be agreed in an MDT, as well as liaison with haematologists and the local Immunology Assessment Panel since the updated NHSE clinical commissioning policy does not routinely commission IVIG for SLE with secondary immunocytopenia [350].

Limited uncontrolled cohort studies have published on the effectiveness of TPORAs in refractory SLE-associated thrombocytopaenia [363, 364]. One cohort study reported that of 18 individuals treated with TPORAs, four arterial thromboses (including one catastrophic APS) and two venous thromboses occurred in five individuals of whom four out of five had either a history of APS or aPLs. Thus, for individuals with APS or positivity for aPLs and particularly those with suboptimal adherence to anti-coagulation therapy, TPORAs should be used with caution or alternative second-line therapy to be considered in refractory SLE-associated thrombocytopenia. The BSR GWG could not make a recommendation on the routine use of TPORAs for SLE-associated thrombocytopenia due to their main approvals for ITP and limited current evidence or experience. In refractory SLE-associated thrombocytopenia, individual consideration for TPORAs should be made with haematologists.

Another manifestation where rituximab may be indicated as a first-choice biologic is neuropsychiatric disease attributed to SLE. This manifestation was excluded from the pivotal trials of belimumab and anifrolumab. The 2023 EULAR recommendations recommend GC and immunosuppressive agents for inflammatory manifestations and antiplatelet agents/anticoagulants for atherothrombotic/antiphospholipid antibodies (aPL)-related manifestations [38]. In this guideline, the

BSR GWG decided to focus on the management of non-thrombotic neuropsychiatric disease attributed to SLE (NPSLE). Management of thrombotic disease should be managed according to national and international guidelines of APS [80, 82, 365]. Evidence for GC and cyclophosphamide which included a small RCT of 32 people with SLE [366] and a Cochrane SLR [367] were presented in the last BSR guideline [22]. No new high-quality studies pertaining to the efficacy of cyclophosphamide have been published since the last BSR guideline search. For rituximab, since the last search, a meta-analysis of RCTs and observational studies in refractory SLE including NPSLE reported a pooled complete response rate with rituximab of 90% (95% CI 53% to 99%) for the treatment of NPSLE [314]. For NPSLE in JSLE, small case series on the effectiveness of rituximab have been published [368–370] and summarised in an SLR of new treatment [42] since the publication of the SHARE guideline [40]. An example includes a retrospective study of 144 children with autoimmune and inflammatory disorders of the central nervous system (CNS, 18/144 with NP-SLE) treated with rituximab that reported ‘definite’ clinician-defined improvement with rituximab in 5/18 patients, ‘probable’ in 7/18, ‘possible’ in 5/18 and ‘no improvement’ in 1/18 patients [368]. New data since the last BSR guideline search relating to combination therapy of cyclophosphamide and rituximab were more limited. Data from BILAG-BR which evaluated short-term effectiveness of rituximab for the treatment of NPSLE reported that none of the nine individuals who were treated with concomitant cyclophosphamide had persistent NP disease while 11 of 41 (27%) individuals who received rituximab alone had persistent NP disease [371].

In certain situations, anifrolumab (if commissioned in the UK) may be indicated for the treatment of moderate-to-severe mucocutaneous SLE. In anifrolumab RCTs, CLASI-A which measured disease activity in CLE across several anatomical locations, based on five clinical sub-components: (i) erythema; (ii) scale/hypertrophy; (iii) mucous membrane lesions; (iv) recent hair loss (preceding 30 days); and (v) non-scarring alopecia was used as an end point. Post-hoc analyses of both Phase III TULIP RCTs and the Phase IIb MUSE RCT showed percentage differences in CLASI-A 50 (i.e. 50% reduction from baseline) response of $>20\%$, almost reaching 30% in MUSE, in favour of the anifrolumab-treated group compared with placebo [300, 372, 373]. Real-world cases series also supported the use of anifrolumab particularly in the most refractory CLE, discoid lupus erythematosus (DLE) where rapid improvement in CLASI-A could be observed as early as 4 weeks post-treatment [374–377].

Anifrolumab may be indicated also for SLE-associated arthritis. Post-hoc analyses of the Phase III TULIP RCTs reported that a greater proportion of participants in the anifrolumab group achieved $\geq 50\%$ reduction in active swollen and tender joints compared with the placebo group [treatment difference: 12.6% (95% CI 2.4% to 22.9%)] [300]. A significant reduction favouring anifrolumab over placebo was also noted in a similar analysis of the Phase II MUSE RCT; mean (SD) swollen and tender joint reductions -5.5 (6.3) vs -3.4 (5.9), respectively; $P=0.004$ [373]. Moreover, post-hoc analyses of the Phase III TULIP RCTs also reported greater improvement in the

anifrolumab group compared with the placebo group with regard to haematological and immunological domains as assessed by SLEDAI-2K [372].

Recommendation 53 For remission induction of people with SLE with organ-threatening or life-threatening non-renal disease attributed to disease activity, high-dose GC with intravenous cyclophosphamide (2C), rituximab (2C) or combination of cyclophosphamide and rituximab (2C) should be considered. Plasma exchange and intravenous immunoglobulin could be considered (2D) [97.0% (81–100)].

Remission induction in organ-threatening or life-threatening non-renal SLE

In people with SLE with organ-threatening or life-threatening non-renal disease attributed to disease activity, evidence for high-dose GC with intravenous cyclophosphamide or rituximab was provided in the last BSR guideline [22]. Cyclophosphamide is gonadotoxic and can lead to infertility, haemorrhagic cystitis and bladder cancer, is teratogenic and is contra-indicated in females trying to conceive, or who are pregnant or breast-feeding, and males should not father children while on therapy [30]. For this reason, despite its high degree of efficacy, it should be reserved for severe cases of SLE with organ- or life-threatening situations. In this current BSR guideline, evidence for rituximab in severe SLE was further supported by an updated SLR and meta-analysis of RCTs and cohort studies [314]. To minimise the cumulative exposure of cyclophosphamide, the BSR GWG recommend combination therapy of cyclophosphamide and rituximab for the treatment of organ- or life-threatening SLE. This approach has been used in earlier studies of rituximab in both JSLE and adults with SLE [317, 369, 378–381]. Using this combined therapy approach, continuation of cyclophosphamide beyond the initial two pulses can be decided based on the initial response, the extent of organ involvement, comorbidities and infection risk. This recommendation also applies to some LN cases as discussed below.

In people with SLE with organ-threatening or life-threatening non-renal disease attributed to disease activity who have not responded to the therapies above, evidence is highly limited but plasma exchange or IVIG could be considered. Since the last BSR guideline search, an SLR of cohort studies and case reports to support the use of plasma exchange or IVIG in severe and refractory SLE have been published [382, 383].

Recommendation 54 Following remission induction for organ-threatening or life-threatening non-renal disease attributed to SLE, maintenance therapy with belimumab (1A), anifrolumab (1A) mycophenolate (1B), rituximab (2C), azathioprine (2C), methotrexate (2C) or ciclosporin/tacrolimus (2C) should be considered [98.3% (87–100)].

Maintenance therapy following remission induction for organ-threatening or life-threatening non-renal disease attributed to SLE

Following remission induction for organ-threatening or life-threatening non-renal disease attributed to SLE, maintenance therapy should be considered to allow tapering and/or cessation of GC. For people with SLE who received treatment with biological agents for remission induction for non-renal SLE, continuation of those agents should be considered.

Since the last search, long-term efficacy and safety of belimumab up to 13 years from LTE studies (i.e. those who completed the main Phase II or III trials and subsequently enrolled into open-label studies) have been published. Continuation of belimumab leads to control of disease activity, reduced flare episodes, reduced GC dose requirement, minimal organ damage progression, treatment is well tolerated, and with a stable safety profile [311, 312, 384, 385].

For rituximab, long-term data from observational cohort studies since the last BSR search relating to the effectiveness and safety of repeat cycles for treatment maintenance in both JSLE and adults have been published [317, 324–326]. Details and practical considerations are described in the rituximab section above. The NHSE clinical commissioning policy outlines that retreatment with rituximab is permitted if the clinical assessment suggests that some improvement in scores has occurred, but response is incomplete, or a flare is now beginning (e.g. the recurrence or persistence of one or more BILAG B scores without waiting for recurrence or development of a BILAG A score or another B score). In people with SLE with severe organ threatening disease, the clinician should follow these individuals carefully with clinical and serological markers, monitor for signs of an impending flare (e.g. rising anti-dsDNA antibodies, returning of B cells particularly plasmablasts) [324, 386] and use their clinical judgement and knowledge of the patient's history to inform the timing and dose of any repeat infusion [49].

Long-term efficacy and safety data from a 3-year blinded, placebo-controlled LTE study [343] have been described in the 'Anifrolumab' section above.

Evidence to support the use of conventional oral immunosuppressants such as mycophenolic acid analogues, azathioprine, methotrexate and calcineurin inhibitors (ciclosporin or tacrolimus) for maintenance therapy has been provided in the last BSR guideline [22] and in the 'Early use of conventional immunosuppressant' section above.

Summary

For the treatment of moderate-to-severe SLE, early use of conventional immunosuppressant is recommended. Biological agents or participation in a clinical trial should be considered and discussed in an MDT meeting if moderate-to-severe disease persists, or if it is not possible to withdraw GC, despite the use of at least one immunosuppressant. The choice of biological therapies should be personalised to the individual with SLE based on the type of lupus manifestations, the extent and severity of organ involvement, adherence concerns, fertility and family planning, and concurrent comorbidities (like cardiovascular disease, diabetes mellitus or infections), as well as commissioning policy.

Organ-specific approach: what is the best evidence for the management of cutaneous lupus erythematosus in SLE?

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- Recommendation 55 In people with SLE with cutaneous manifestations, consider drug-induced lupus as a cause (2C) [97.4% (80–100)].
- Recommendation 56 Scarring and/or refractory cutaneous involvement in SLE should be managed in a timely manner in conjunction with dermatologists (1D) [98.3% (80–100)].
- Recommendation 57 Offer very potent/potent topical GC as a first-line therapy in cutaneous involvement (non-facial) attributed to SLE, for up to 4 weeks (1B) [95.9% (80–100)].
- Recommendation 58 Consider topical GC on the face with appropriate dermatology guidance (2C) [94.0% (80–100)].
- Recommendation 59 Offer topical calcineurin inhibitors in cutaneous involvement (non-facial) attributed to SLE for up to 4 weeks and longer if agreed with dermatologists (1B) [96.8% (80–100)].
- Recommendation 60 Offer very potent/potent topical GC and/or calcineurin inhibitors as an adjuvant to systemic therapy when there is widespread cutaneous involvement in SLE (1B) [96.2% (80–100)].
- Recommendation 61 Consider concomitant short-term systemic GC alongside other systemic and topical therapies, especially in people with SLE at high risk of scarring with appropriate guidance by dermatologists (2D) [94.9% (80–100)].
- Recommendation 62 In refractory cutaneous SLE, optimise hydroxychloroquine by adding mepacrine (2B) and refer to dermatology to consider other therapeutic options; for example, intralesional GC (2D), retinoids (2C), dapsone (2C), clofazimine (2C), thalidomide (2C), lenalidomide (2C) or ciclosporin (2C) [95.2% (81–100)].
- Recommendation 63 For refractory cutaneous involvement in SLE, the best evidence is for anifrolumab and this should be used as first-line biologic if available (1B). If not available, other biologics can be considered as per management of non-renal SLE (2B) [97.0% (80–100)].
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Rationale

The recommendations for this BSR guideline draw from the 2021 BAD guidelines for the management of CLE [34]. We also performed a further search from the date of their last search (Dec 2020) to update evidence and inform our

recommendations. When reviewing recommendations by the BAD guidelines, the BSR GWG identified the need to distinguish evidence and recommendations for the assessment and management of CLE with SLE and CLE only. The former is applicable to our BSR guideline. CLE can occur ‘alone’ as an isolated skin condition without the involvement of SLE in other organs.

For cutaneous involvement attributed to SLE, rheumatologists can start very potent/potent topical GC as a first-line therapy for up to 4 weeks. An overarching principle is to seek timely guidance or manage CLE with SLE in conjunction with dermatologists particularly when the lesions affect the face, are at high risk of scarring or refractory to conventional immunosuppressant or biologics. This is important to access other agents that are usually beyond the scope of rheumatologists including intralesional GC injection, retinoids, dapsone, clofazimine, thalidomide and lenalidomide. Although rheumatologists are experienced in using ciclosporin in non-CLE features of SLE, due to its low quality of evidence in CLE [387, 388] and the potential other options available to dermatologists, the GSG recommended for this decision to be made in conjunction with dermatologists.

Since the last search by the BAD guidelines committee, new evidence supports the use of anifrolumab for refractory CLE based on the subgroup analyses of the Phase III TULIP RCTs. Details of the cutaneous response to anifrolumab in RCTs [300, 372, 373] and real-world use [374–377] have been described in the ‘Preference for specific biologics or other induction therapies’ section above. A Phase III RCT of anifrolumab in adults with chronic and/or subacute CLE is in progress [NCT06015737]. Thus, based on current evidence, the 2023 EULAR recommendations [38] and expert consensus, if commissioned, anifrolumab should be used as the first-line biologic for the treatment of CLE with SLE. If not available, other biologics can be considered as per management of non-renal SLE.

Summary

For the management of non-facial and facial CLE attributed to SLE, rheumatologists can start very potent/potent topical GC as a first-line therapy for up to 4 weeks. If the lesions affect the face, are at high risk of scarring or refractory to combined anti-malarials (e.g. hydroxychloroquine and mepacrine), conventional immunosuppressant or biologics, it is advised to seek timely guidance or manage CLE with SLE in conjunction with dermatologists. For refractory CLE attributed to SLE, anifrolumab (if commissioned) should be used as the first-line biologic. If not available, then consider the use of other biologics as per management of moderate-to-severe non-renal SLE.

Organ-specific approach: what is the best evidence for the general management of lupus nephritis?

Rationale

The previous BSR guideline did not undertake an SLR for LN, instead referring to the 2012 EULAR-ERA-EDTA guidelines [389]. There have been several recent changes to evidence in LN including new therapies with NHS England Commissioning statements or NICE technology appraisals. In addition, there is emerging evidence regarding the importance of care delivery for

Table 3 Summary of pivotal randomised controlled trials in lupus nephritis induction therapy and their salient outcomes.

Trial	Design		Therapies			Primary endpoint			Outcome				
	Objective	N	Power	Recruitment	Pure class V included	Placebo arm	Active arm	Proteinuria	Serum Creatinine or GFR	Other Components	1° endpoint placebo	1° endpoint active	1° endpoint different
ALMS [83]	Superiority	370	90%	Global	Yes	NIH CYP	MMF 3 g	uPCR <300 if baseline ≥300, ≥50% decrease if baseline <3	Stabilization (±25%) or improvement	None	53.0%	56.2%	No
AURORA 1 [27]	Superiority	357	80%	Global	Yes	MMF 2 g	MMF 2 g+ VOC	uPCR ≤50	eGFR ≥60 mL/min/1.73 m² or no decrease from baseline >20%	No rescue therapy; no >10 mg prednisone for 3 or more consecutive days or for 7 or more days during weeks 44–52	23%	41%	Yes
BLISS-LN [28]	Superiority	448	80%	Global	Yes	MMF or EuroLupus CYP→AZA	MMF or EuroLupus CYP→AZA+BEL	uPCR ≤70	eGFR no worse than 20% below the pre-flare value or ≥60 ml/min/1.73 m²	No rescue therapy	32%	43%	Yes
REGENCY [29]	Superiority	271	90%	Global	No	MMF	MMF + OBI	uPCR <50	eGFR ≥85% of baseline value	No intercurrent event (rescue therapy, treatment failure, death, or early trial withdrawal)	33.1%	46.4%	Yes
Multitarget [84]	Superiority	362	80%	China	Yes	NIH CYP	MMF 1 g + TAC 4 mg	24-h urinary protein ≤0.4 g	Normal	No active urine sediments; serum albumin ≥35 g/L	25.6%	45.9%	Yes
EuroLupus [85]	Non-inferiority	90	22%	Europe	No	NIH CYP→AZA	EuroLupus CYP→AZA	For patients with nephrotic syndrome, proteinuria < 3 g	If baseline creatinine 1.3–2.6 mg/dl, decrease to ≤1.3; if baseline >2.6, >30% improvement	No glucocorticoid-resistant flare; no doubling of serum creatinine	80%	84%	+/-

LN, with substantial variation in practice across the UK, often deviating from EULAR-ERA-EDTA guidelines. For these reasons, we developed BSR guidelines for LN for the first time. We addressed aspects that we felt were incomplete in the updated 2025 EULAR [53], the 2024 ACR [52], the 2024 KDIGO [39] and the 2017 SHARE [41] guidelines in LN, providing more up-to-date guidance on pharmaceutical therapies for induction and maintenance therapy, as well as adding greater detail on the selection of these options and a whole life-course approach. Unlike international guidelines, we discuss best practice for delivery of care in the NHS, and the increased role of rituximab in the UK. We considered it unnecessary to replicate items on diagnosis, monitoring and treatment targets and have reproduced or referred to other guidelines for these topics [33, 39, 41]. Management of LN in this BSR guideline is illustrated in Fig. 1.

Recommendation 64 All people with lupus nephritis should be managed in combined services with rheumatology and renal expertise for use of adjunctive therapies in addition to immunosuppression, and to ensure optimal management of acute kidney injury and CKD. Consult the KDIGO, EULAR, ACR and SHARE guidelines as appropriate (2D) [97.8% (80–100)].

Overall care of people with lupus nephritis

Overall outcomes of LN are suboptimal with continued incidence of end-stage kidney disease (ESKD) despite standard therapy. Even well-treated episodes of nephritis result in nephron loss, which may not be clinically manifest for years or decades until ageing and co-morbidities further affect renal function [390, 391]. LN care is becoming increasingly complicated with more choices of immunosuppressive therapy options as well as non-immunosuppressive management of chronic kidney disease (CKD). This requires combined expertise from rheumatology (to guide immunosuppressive therapy, assessment of non-renal disease, and provide continuity of care) and nephrology (to guide diagnosis and biopsy, CKD management including use of adjunctive therapies, management of other renal pathologies, management of blood pressure and cardiovascular risk, assessment of response and resistant disease). The nature of combined services may vary according to local service. A combined clinic with both consultants at once can be ideal but seeing both specialties separately is reasonable. Specialized MDT meetings and local referral networks can be helpful.

Recommendation 65 A timely kidney biopsy should be included in the initial diagnosis of lupus nephritis (2B) [98.5% (81–100)].

Kidney biopsy

A recent survey of UK rheumatologists and nephrologists treating LN revealed that 25% do not routinely include a kidney biopsy at the time of diagnosis [392]. Biopsy is extremely valuable to management decisions in LN, even if the decision to use

immunosuppression has already been made. Apart from confirmation of LN, the biopsy provides information such as baseline assessment of scarring, presence of crescents or tubulointerstitial lesions that might warrant a more aggressive treatment and monitoring approach, presence of class V that can influence choice of therapies and expected proteinuria response, and other renal pathologies. Statements about cyclophosphamide, calcineurin inhibitors, GC doses and speed of proteinuria response in our guidelines depend on knowledge of histological features. Biopsy is also important as a baseline comparison whenever a repeat biopsy is required. We have emphasized that repeat biopsies may be required in cases of incomplete response, and knowledge of the change in scarring or class since treatment was attempted is crucially important in interpreting these [393].

Recommendation 66 For detailed guidance on monitoring for proteinuria, the role of biopsy and other diagnostic tests in adults and children, consult the KDIGO, EULAR, ACR and SHARE guidelines, respectively (2B) [98.1% (80–100)].

Proteinuria monitoring and diagnostic tests

Other guidelines, especially KDIGO, have provided detailed evidence-based guidance on proteinuria thresholds and targets, as well as the use of adjunctive therapies that we considered appropriate [39]. Regular monitoring of urine dipstick at all assessment appointments is essential for detection of nephritis. A threshold of proteinuria ≥ 0.5 g/24 h (or uPCR ≥ 50 mg/mmol in morning first void urine) or a reduction in eGFR help to indicate when nephrology review and biopsy are required, considered alongside blood pressure, clinical disease activity, serology and haematuria. The EULAR proteinuria treatment targets [33] are described further in recommendation 78.

Recommendation 67 Before deciding treatment, identify important prognostic factors including first episode of nephritis or a relapse, prior therapy failures, patient understanding and potential adherence concerns, histological LN class, baseline kidney function and degree of chronicity on the biopsy, presence of crescents or tubulointerstitial lesions, renal function, level of proteinuria, non-renal SLE features, relevant renal and non-renal co-morbidities and GC toxicity (prior or future risk) (2B) [98.0% (80–100)].

Initial assessment

Evidence-based treatment options now include a range of GC and immunosuppressive options as first-line, second-line, refractory disease and maintenance. There are several choices to be made regarding intensity of GC therapy, the most appropriate immunosuppressive combination, the use of

hospital-delivered or oral treatments, adherence support such as education, drug level monitoring, specialist nurse, patient group and psychological support. Before deciding treatment, physicians should identify important prognostic factors including those listed above. Some of these have been highlighted in the individual therapy recommendations.

Outcomes with repeat episodes of nephritis are significantly worse than an initial episode in terms of clinical response and long-term renal outcome [394]. Although detailed data on sequential therapy are limited, it may be logical to switch therapy class in many people with LN. Patient understanding and adherence are strong negative predictors of outcome in LN [152]. Histological class may influence choice of immunosuppressant and expected responses, but additionally scarring, crescents and tubulointerstitial lesions are independent predictors of poor prognosis [395, 396]. People with LN with eGFR under 30 mL/min/1.73 m² are at higher risk of ESKD but were excluded from the pivotal trials for our first-line therapy recommendations. Further, those trials were powered for a primary end point of proteinuria response rather than ESKD. For this reason, more intensive therapy may need to be considered in the most severely affected people with LN (recommendation 77). Although the factors listed have been associated with worse long-term outcomes, in practice these must be interpreted in combination and with qualitative interpretation. Therefore, there is not a single definition of 'high risk' features, but we instead emphasize considering all the factors mentioned and final decisions by highly experienced clinicians.

Organ-specific approach: what is the best evidence for active lupus nephritis induction treatment?

Recommendation 68 For adults with LN requiring induction therapy, start GC therapy with 250–500 mg intravenous methylprednisolone/day for 1–3 days. For children and young people with LN, 10–30 mg/kg/day up to 500 mg total for 1–3 days (2B). Higher doses, up to 1000 mg/day, may be used for adults, children or young people under expert guidance (e.g. severe renal failure or multi-organ involvement) [98.2% (90–100)].

Intravenous glucocorticoids

GC were included in all treatment regimens we reviewed. They have uniquely rapid and reliable anti-inflammatory effects so are especially valuable in the early phase of treatment. During longer-term treatment, benefits are less unique and toxicity more significant. For this reason, many clinical trial protocols favour more intensive intravenous GC initially but increasingly rapid tapering of oral GC [27–29, 397]. Intravenous GC have additional non-genomic effects on inflammation compared with oral

prednisolone [398], as well as better bioavailability and adherence. In contrast, sustained doses of oral GC over ~40 mg prednisolone induce transactivation of genes that lead to gluconeogenesis, insulin resistance, skin atrophy and inhibition of bone formation [399], while genomic anti-inflammatory effects are already saturated, limiting increased efficacy. Although formal comparisons of IV and oral-based GC induction are not available, protocols that successfully reduced overall GC burden usually included IV methylprednisolone for 1–3 days, including a UK study using no oral GC with combination immunosuppressants [400].

In childhood SLE, the Childhood Arthritis and Rheumatology Research Alliance (CARRA) provided consensus for three different dosing regimens combining oral GC with intravenous methylprednisolone-pulses based on expert opinion for induction therapy of proliferative LN. These were supported by evidence that intravenous methylprednisolone pulses, but not oral prednisolone, could eliminate the interferon-alpha gene expression signature in JSLE [401, 402]. Methylprednisolone has typically been dosed at 30 mg/kg up to a maximum of 1000 mg. We did not identify any clear reason for a higher maximum dose in JSLE other than a higher frequency of severe disease in this population.

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- Recommendation 69** Following IV methylprednisolone, adults with LN should be treated with one of the KDIGO GC regimens with the taper planned from the outset (2B) [96.3% (80–100)].
- Recommendation 70** In adults with LN without severe histology or high-risk features, and while treatment response remains acceptable, the KDIGO GC reduced-dose regimen is preferable and is especially suitable with combination immunosuppressants and/or those with high risk of GC toxicity (2B) [96.6% (81–100)].
- Recommendation 71** In adults with LN with severe histology, severe extra renal disease, not able to take combination immunosuppressants or poor initial response, the KDIGO moderate (or rarely high dose) GC regimen may be preferable (2B) [95.3% (80–100)].
- Recommendation 72** For children and young people with SLE, a similar principle should be followed for oral GC prescription in LN induction therapy (prescribing proportionate to patient characteristics and planning GC taper in advance) using weight-based dosing as appropriate (2B) [96.6% (80–100)].
- Recommendation 73** Planned GC tapering should be supervised by a physician and adjusted as appropriate to response (2B) [98.7% (90–100)].
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Oral glucocorticoids

Several different GC regimens have been published. Evidence supporting these varies and they can be stratified according to the patient profile. The MYLUPUS trial compared IV methylprednisolone followed by a higher (start at 45–70 mg prednisolone and taper to 5 mg by 6 months) and lower (start at 22.5–35 mg prednisolone and taper to 2.5 mg by 6 months) GC regimen, each combined with oral mycophenolic acid analogues (i.e. mycophenolate mofetil or mycophenolic acid, MPAA) [397]. The lower dose was found to be non-inferior although it is important to note that this study only had 19% power to detect a difference (i.e. an 81% chance of missing a real difference) and only 6 months follow up (recent trials of other therapies required >12 months to differentiate treatment groups). That said, the lower GC dose was substantially safer, with 19% vs 10% serious infections and 17% vs 0% zoster infections for the higher and lower dose regimens, respectively. Results from a retrospective propensity analysis of the ALMS and AURA-LV trials suggested that doses of GC and MPAA lower than those in ALMS result in better long-term safety [403]. Accordingly, a lower dose GC regimen was used in the AURORA trial [27]. A second retrospective propensity analysis including the Phase III AURORA trial supported the conclusion that lower GC and MPAA doses were acceptable when used in a combination with voclosporin [404]. A UK open-label study used no oral GC as part of a combination of rituximab, MPAA and IV methylprednisolone [400]. Finally, the expert opinion of the group stressed the importance of a full planned GC taper from the outset rather than relying on ad hoc decisions on dose changes at each review. This increases patient understanding, tapers according to published evidence and is helpful when people with LN see more than one doctor.

For JSLE, such detailed regimens and comparisons have not been published. Oral prednisolone has typically been dosed 1–2 mg/kg/day (maximum 60 mg/day) tapered by 10–20% at 1-week or 2-week intervals based on clinical improvement. Overall, this led to a similar but less specific recommendation for JSLE: to include methylprednisolone, use a planned oral GC taper, stratify doses to initial severity features and adjust according to response.

Although we recommend a planned taper, it is important to note that this should be continually reviewed. It may need to be adjusted if renal response targets are not met and therapy changes are required, or for extra-renal disease activity.

Recommendation 74 People with SLE with new or relapsing class III or IV LN (with or without class V), should be offered combination immunosuppressant regimen including GC, HCQ and one of these combinations of immunosuppressants:

- mycophenolic acid analogues (MPAA) and obinutuzumab (1A, 2D for JSLE);
- MPAA and calcineurin inhibitors (CNI) (voclosporin 1A for adults, 2D for JSLE, tacrolimus 1B for adults, 2C for JSLE);
- MPAA and belimumab (1A for adults, 2C for JSLE) [95.6% (82–100)].

Induction therapy: first-line recommendation

The most important evidence for our first- and second-line recommendations is summarized in Table 3.

Over recent years, usual practice has been to use a single immunosuppressant agent; mycophenolate mofetil or EuroLupus-dose cyclophosphamide (along with GC, hydroxychloroquine and adjunctive therapies). These regimens were the first-line choices for induction immunosuppression in the 2012 and 2019 EULAR-ERA-EDTA guidelines [33, 389] and retained among first-line options in the 2024 KDIGO [39] and the 2023 EULAR SLE guidelines [38]. However, since 2020, we have three Phase III RCTs that demonstrate the superiority of combination immunosuppressants over these single agents. Moreover, in these trials, the outcomes of the placebo arms (i.e. single agent immunosuppression with MPAA or EuroLupus-dose cyclophosphamide) were poor with only 20–33% of participants achieving complete renal response (CRR) [27–29]. Failure to achieve CRR is associated with substantially worse long-term survival [405]. We therefore do not recommend single immunosuppressant regimens any longer as routine first-line therapy. We do note that observational data have shown higher response rates from single agent immunosuppressants [406–410], but those studies do not offer any comparison with combination therapies.

We recommend that one of three combination immunosuppressant options is used; obinutuzumab, voclosporin and belimumab each combined with mycophenolate mofetil. This is in line with the 2025 EULAR recommendations for LN [53]. Each of these agents was found to be superior to mycophenolate mofetil alone in Phase III RCTs in people with proliferative LN (REGENCY, AURORA and BLISS-LN trials, respectively) [27–29]. Although BLISS-LN also allowed EuroLupus cyclophosphamide as a standard of care, we considered that this is less convenient and more poorly tolerated for most people with LN, although it will be suitable as one of the second-line options for some individuals, particularly when MPAA is not tolerated and fully intravenous route of administration is required.

Obinutuzumab combined with MPAA in adults with LN

Obinutuzumab is a type II anti-CD20 monoclonal antibody that achieves better B-cell depletion than rituximab through enhanced antibody-dependent cytotoxicity mechanism [411]. It was shown to be effective in LN in the Phase II NOBILITY trial [412]. In the Phase III REGENCY trial, people with LN were enrolled with class III or IV nephritis with or without class V. Obinutuzumab combined with standard therapy (mycophenolate mofetil and GC) achieved a higher rate of CRR at 76 weeks compared with placebo plus standard therapy (46.4% vs 33.1%, adjusted difference, 13.4 percentage points; 95% CI 2.0–24.8; $P=0.02$). Secondary endpoints were met for CRR with prednisolone taper and uPCR < 80 mg/mmol with no intercurrent event. Subgroup analyses indicated consistent efficacy across racial and histological classes, though data in adolescents are emerging from ongoing trials. Safety was favorable. There were increased serious adverse events with obinutuzumab compared with placebo, but these related to the COVID-19 pandemic at the time the trial was conducted. This effect would not be expected outside that time, and vaccination has been shown to be

protective in anti-CD20 monoclonal antibody-treated individuals with rituximab [413].

Belimumab combined with MPAA in adults with LN

The Phase III BLISS-LN trial found that intravenous belimumab plus mycophenolate mofetil was superior to placebo plus mycophenolate mofetil. People with LN were enrolled with class III or IV nephritis with or without class V. This RCT included 16% of participants with pure class V nephritis. At week 104, significantly more people with LN in the belimumab group than in the placebo group had a primary efficacy renal response (43% vs 32%; odds ratio, 1.6; 95% CI 1.0–2.3; $P=0.03$) and a CRR (30% vs 20%; odds ratio, 1.7; 95% CI 1.1–2.7; $P=0.02$). The risk of a renal-related event or death was lower among individuals who received belimumab than those who received placebo (hazard ratio, 0.51; 95% CI 0.34–0.77; $P=0.001$). There was no increase in adverse or serious adverse events with belimumab compared with placebo [28].

Voclosporin combined with MPAA in adults with LN

The Phase III AURORA 1 trial reported that voclosporin added to mycophenolate mofetil and low-dose GC yielded a superior CRR rate at 52 weeks compared with placebo. The primary end point of CRR at week 52 was achieved in significantly more people with LN in the voclosporin group than in the placebo group (73 [41%] of 179 participants vs 40 [23%] of 178 participants; odds ratio 2.655; 95% CI 1.64–4.27; $P<0.0001$). This trial included 14% of participants with pure class V nephritis. There was no increase in adverse or serious adverse events with voclosporin compared with placebo [27].

Tacrolimus compared with MPAA in adults with LN

Tacrolimus combined with a low dose of mycophenolate mofetil has been compared with National Institutes of Health (NIH)-dose cyclophosphamide in an RCT [84]. The combination therapy was associated with higher complete response rates than cyclophosphamide alone at 6 months (45.9% vs 25.6% respectively; difference of 20.3 percentage points; 95% CI 10.0–30.6 percentage points; $P<0.001$). Tacrolimus has a preferable pill burden compared with voclosporin. However, a limitation with this trial is that all participants were recruited in China where some characteristics of LN appeared different, perhaps reflected in higher overall response rates than other trials. The trial also only had 24 weeks follow up. For this reason, our level of recommendation for a calcineurin inhibitor in adults with LN is stronger for voclosporin.

Therapy in children with LN

Belimumab combined with MPAA was evaluated in 93 children aged over five with active SLE with an end point of SRI-4 in the PLUTO RCT [305]. Although the trial was designed for SLE in general, 53 participants had LN at baseline and subgroup analyses showed positive trends in renal outcomes, such as improved proteinuria. A pharmacokinetic study supports use of the intravenous 10 mg/kg dose for children with LN [414]. Based on these data, belimumab combined with MPAA for children with LN is approved by the FDA but not MHRA or EMA [415]. RCTs of tacrolimus in

children with LN have not been performed and its use is supported only by case series [416, 417]. Tacrolimus is widely prescribed for children with a wide range of indications for kidney transplantation including LN, so it is known to be safe. Trials of voclosporin and obinutuzumab in children in LN are in late stages but no results are available at the time of writing. The results from the paediatric trials are expected imminently and until that time, the other options in the BSR guideline would be recommended until further evidence is available. In severe and refractory cases or in those where other treatments have failed or cannot be used (e.g. anaphylaxis), then the use of voclosporin or obinutuzumab could be considered based on expert advice at this time, as well as strong adult evidence and reassuring safety profile.

Relevance to major subgroups

Although these trials did not report major efficacy differences between most subgroups analysed, there may be some basis to customize treatment to patient characteristics. Calcineurin inhibitors have independent beneficial effects on T-cell function to suppress immunity and podocyte stability to reduce proteinuria in nephrotic individuals, but transient negative effects on GFR. For this reason, they may be best suited to individuals with a nephrotic presentation or class V histology but preserved renal function. On the other hand, there is less evidence for calcineurin inhibitors in extra-renal manifestations. There is additional long-term safety monitoring required for tacrolimus, discussed below. Both belimumab and B-cell depletion therapies have more substantial evidence in extra-renal SLE. In addition, they are intravenously administered so may be well suited where there are concerns about adherence, especially with the lower frequency of infusions with obinutuzumab.

For most people with SLE in these trials, concomitant immunosuppressant used is usually mycophenolate mofetil. Mycophenolate mofetil and mycophenolic acid are pharmacologically equivalent. Mycophenolic acid is better tolerated from the perspective of gastrointestinal side effects than mycophenolate mofetil in some individuals. We see no reason to differentiate between these forms of MPAA in any of the combinations listed and consider it inappropriate to deny first-line recommendations to people able to tolerate the mycophenolate mofetil form of this drug. We have used the term ‘mycophenolic acid analogues, MPAA’ to indicate interchangeability throughout. This term was also used in KDIGO [39].

Recommendation 75 If the regimens in #74 are not suitable or available as remission induction for LN, then alternative immunosuppressant options with substantial evidence but lower efficacy are as follows:

- EuroLupus dose cyclophosphamide combined with belimumab (1A);
- MPAA combined with rituximab (2B);
- MPAA alone (1A);
- EuroLupus dose cyclophosphamide alone (2B) [76.5% (80–100)].

Induction therapy: second line or special case recommendations

Our recommended first-line treatments may be subject to NICE technology appraisals or NHSE clinical commissioning policies and not always available, or unsuitable for particular people with LN especially if they cannot tolerate MPAA. We have provided second-line options in order of preference. At the time of writing, there is a NICE TA approval for belimumab that was based on evidence in non-renal SLE trials (NICE TA572) [50]. Voclosporin (TA 882) [25] and obinutuzumab (GID-TA11478) [26] also have NICE approvals.

EuroLupus dose cyclophosphamide with belimumab

Belimumab combined with EuroLupus dose cyclophosphamide was evaluated in the same trial as belimumab combined with MMF [28]. The different combinations were compared in a subgroup analysis. While limited by smaller numbers of belimumab + EuroLupus cyclophosphamide participants compared with belimumab + MMF, primary end point attainment appeared similar between both agents as standard of care while CRR was numerically more frequent with the belimumab + MMF combination. Treatment tolerability and preference is also likely to be better with belimumab + MMF, but where there is intolerance of MPAA, adherence concerns or other reasons for parenteral administration, then belimumab + EuroLupus cyclophosphamide combination may be more appropriate.

MPAA with rituximab

MPAA combined with rituximab does not have RCT evidence of efficacy but is commonly used in the UK and has multiple real-world evidence and an SLR to support this [418, 419]. The mechanism of action is similar to obinutuzumab. Depth of B-cell depletion is superior with obinutuzumab so that is the preferred therapy, but some people with SLE achieve good depletion with rituximab (e.g. in the presence of certain Fc gamma receptor genotypes) [420]. The LUNAR RCT compared rituximab or placebo in combination with MMF and GC. Although it was negative for its primary and secondary endpoints, the design, power and duration of that trial were suboptimal [421]. Exploratory clinical endpoints such as later partial clinical response, requirement for rescue cyclophosphamide and GC dose all favoured the rituximab arm. Although subgroups were small, the primary end point was met numerically more frequently with rituximab compared with placebo in people of Black African ancestry (who usually have worse outcomes in LN). There is substantial open-label evidence for the efficacy of rituximab. This includes greater numbers of people with LN that were refractory to MMF or cyclophosphamide than in the Phase III trials of licensed therapies [422], as also reflected in the 2023 EULAR SLE recommendations [38]. Much of the evidence was generated in UK populations, including the RituxiLup study that used our recommended combination of rituximab and MPAA but excluded concomitant oral GC [301, 324, 386, 400].

MPAA alone

MPAA as a single immunosuppressant agent was regarded as the most common standard therapy before publication of the combination therapy trials. It is now rated lower because those

combinations were superior. Some people with LN achieve CRR with MPAA and GC alone (23–30% in the comparator arms of AURORA 1 and REGENCY RCTs) [27, 29]. While single agent immunosuppression with MPAA may be effective in some people with LN, unfortunately we do not know how to reliably identify these individuals in advance. Since assessment of response takes 3–6 months, this may allow renal damage if therapy proves to be insufficient. Given the known imprecision of renal endpoints based on uPCR and GFR, we do not know whether CRR achieved with combination immunosuppression confers a better histological response or carries a better long-term prognosis than CRR achieved with MPAA alone. For this reason, we recommend combination therapy initially in all people with LN. However, single agent therapy with MPAA may be appropriate in some cases, especially later in the induction therapy phase if other agents need to be discontinued, or during maintenance (see below).

EuroLupus dose cyclophosphamide alone

Minimisation of cyclophosphamide dose was essential prior to 2000 when there were no other effective first-line immunosuppressants for LN and multiple cycles might be required over an individual's lifetime leading to severe cumulative toxicity. The EuroLupus trial was performed to evaluate a lower cyclophosphamide dose (500 mg × six doses, given 2-weekly) than used in the original 1970 NIH cyclophosphamide protocol (0.5–1.0 g/m² BSA monthly), and reported no difference, leading to the lower dose becoming a common standard of care [85]. Now that there are many other well evidenced first-line options as detailed above, cyclophosphamide is reserved for specific scenarios, often because disease is more severe or refractory rather than first-line induction therapy. For this reason, the evidence in support of the EuroLupus must be re-evaluated for this context.

The primary end point of EuroLupus was remaining free of treatment-failure. Achieving this required participants with raised creatinine to show normalization and those with nephrotic syndrome to improve in that aspect. If the participants did not have raised creatinine (i.e. >50% of participants in the trial) and were not nephrotic (i.e. ~50% of participants in the trial), then they were considered to have met the primary end point (no treatment failure) unless creatinine doubled or a GC-resistant flare occurred. A total of 82% of participants did not have treatment failure in the final results. Some of these 82% might have been considered partial or non-responders by the endpoints in other trials described here. This may make the comparison of groups within the trial insensitive to real treatment differences and makes comparison with other trials more difficult.

A further significant issue in the EuroLupus trial is that the statistical power was only 0.22. This means that if the EuroLupus dose were truly inferior to the NIH dose, this trial design would have a 78% chance of failing to detect the difference. A ten-year follow-up study was published, again showing no differences between treatment groups in longer-term outcomes [423]. This is far stronger long-term follow-up than other trials. However, the majority of this follow-up applied the same non-randomized CKD care and immunosuppression to both of the original treatment arms, which would dilute any real differences. A total of 36% of participants had received new MMF or

cyclophosphamide, introducing a significant element of cross-over that further reduces power. Lastly, the EuroLupus trial included only 14 participants who were not of European ancestry, with only three people of Black African ancestry (who usually have the highest chance of developing ESKD) randomized to the low-dose cyclophosphamide group. This is a serious limitation of evidence to justify lowering treatment intensity for the individuals susceptible to the most severe and resistant LN.

Other evidence may also introduce uncertainty about the efficacy of EuroLupus. In the placebo arm of the BELONG trial (a trial which active arm was the abandoned therapy ocrelizumab), participants could receive either EuroLupus or MMF as standard of care. CRR was achieved in 40% of participants on MMF, but only 25% of participants on EuroLupus [424]. In the ALMS trial, even the NIH dose of cyclophosphamide appeared inferior to MMF in a non-European non-Asian subgroup that mostly consisted of people of Black African ancestry and mixed ethnicity participants [83].

Overall, EuroLupus may be appropriate in some situations, such as people of European ancestry and milder LN and few risk factors who are either: unable to tolerate MPAA, have a high cumulative lifetime dose of cyclophosphamide, or in whom long-term fertility is a concern. For most people with LN, other options in this guideline will be more appropriate. For people with LN with more severe disease requiring cyclophosphamide, a higher dose regimen should also be considered as below.

Recommendation 76 People with SLE with new or relapsing pure class V LN with proteinuria >100 mg/mmol should receive a combination immunosuppression regimen consisting of oral GC using the reduced-dose KDIGO regimen and MPAA and calcineurin inhibitor (1A). If not appropriate or tolerated, consider alternative therapies including oral GC + MPAA + anti-CD20 therapies (2B), oral GC + MPAA + belimumab (2C) or oral GC + EuroLupus dose cyclophosphamide + belimumab (2C) [96.1% (83–100)].

Pure class V

Of our first-line induction therapy options, the RCTs for voclosporin, tacrolimus and belimumab permitted entry of people with pure class V disease [27, 28, 84]. Other trials permitted class V disease only when co-existent with class III or IV. For this, and theoretical reasons, in the case of pure class V nephritis, a calcineurin inhibitor (voclosporin or tacrolimus)-based combination therapy is preferred.

Podocyte foot processes become effaced in class V lupus nephritis, leading to nephrotic syndrome that is often severe [425, 426]. In addition to their immunosuppressive effects, calcineurin inhibitors stabilize podocyte structure, which may be more effective in controlling the nephrotic syndrome. Since pure class V disease does not initially impact on renal function, the potential negative effects of calcineurin inhibitors on GFR are less concerning. Although class V nephritis does not usually affect renal

function in the short term, over a sustained period, heavy proteinuria is a significant risk factor for progressive CKD, as well as the associated complications such as hyperlipidemia and hypercoagulability that require active management, further emphasizing the importance of choosing the agent expected to best improve proteinuria.

The lowest dose GC regimen is expected to be most appropriate for people with class V disease (unless required for extra-renal disease) due to their lower initial risk of scarring and renal failure, as well as the use of the lower dose regimen in the AURORA trial of voclosporin [27]. Two trials of MMF vs intravenous cyclophosphamide induction in LN included people with pure membranous lesions. In a pooled analysis of these participants, remissions, relapses and overall clinical course were similar in the membranous individuals treated with either oral MMF and NIH-dose cyclophosphamide [83, 427, 428]. Open-label data support the use of rituximab in class V LN [418, 429]. Overall, we considered that the totality of the evidence supported combinations of MPAA with rituximab or belimumab if a calcineurin inhibitor could not be used. Combined care with nephrology is essential to manage nephrotic syndrome, with agents such as angiotensin-converting enzyme (ACE) inhibitors, angiotensin-II receptor blockers, diuretics, statins, anticoagulation and sodium-glucose linked transporter 2 (SGLT2) inhibitors.

Recommendation 77 In cases of exceptionally severe or life- or organ-threatening LN, initial therapy should be discussed with a specialist centre as the National Institute for Health (NIH) regimen of IV cyclophosphamide (2B), with or without anti-CD20 agents (2C), may be more appropriate than standard LN induction therapy initially. In such cases, the number of cyclophosphamide infusions should be limited and therapy switched to options with lower toxicity once disease activity improves [93.8% (80–100)].

Exceptionally severe disease

People with the most severe renal involvement were either under-represented or excluded from the trials for our first-line options and many second line options. For BLISS-LN, AURORA, REGENCY and EXPLORER, respectively, people with LN were excluded if they had $eGFR <30$, <45 , <30 , 25 and $mL/min/1.73 m^2$. Although this exclusion was not present in the EuroLupus, the numbers of people with $eGFR <30 mL/min/1.73 m^2$ was low. The NIH trial of cyclophosphamide included many people with severe disease. Further, the NIH trials had the harder end point of doubling serum creatinine, which may be more appropriate for more severe people with LN than endpoints based on uPCR improvement with stable $eGFR$ as used in later trials. Higher dose cyclophosphamide also has advantages such as assured adherence and efficacy in extra-renal disease activity.

Although NIH dose cyclophosphamide may have efficacy and evidence advantages in severe people with LN, this must be balanced against significant toxicity in short-term (neutropenia,

nausea, infection) and long-term (infertility, bladder cancer proportionate to lifetime exposure). Cyclophosphamide is increasingly used alongside rituximab in severe and refractory disease [381]. This combination may limit total dose of cyclophosphamide required. Therefore, although evidence will always be limited in the most complex and unstable people with LN, the expert opinion of the renal working group was that in exceptionally severe and life- or organ-threatening SLE cases, higher dose cyclophosphamide may still be appropriate in short-term use, but in these cases the duration of higher dose cyclophosphamide should be limited, which may be achieved by combination with rituximab. We recommend switching to less toxic options once improvement occurs. The NIH protocol dose of cyclophosphamide was 0.5 g–1.0 g/m² body surface area (start at 0.75 g and adjust by 0.25 g according to tolerability and day 10 leucopenia), repeated monthly. In practice, variation of this is often used according to individual patient characteristics, including shorter intervals between doses if tolerated.

eGFR alone should not be used to identify the most severe individuals, as this may be due to prior damage rather than inflammation, and people with LN with a higher eGFR may also be considered severely high risk; for example, with severe histological features such as crescents and tubulointerstitial inflammation, or with prior therapy failures or intolerances of key medications such as mycophenolate.

Recommendation 78 Therapy should be reconsidered early if people with LN are not meeting these treatment targets (2C):

- at 3 months, 25% reduction in urinary protein to creatinine ratio (uPCR);
- at 6 months, 50% reduction in uPCR;
- at 12 months, uPCR less than 70 mg/mmol;

with preserved or improving kidney function. In those with class V LN, slower reduction of proteinuria is acceptable as long as improving [95.6% (80–100)].

Recommendation 79 In people with LN with a partial response to the induction regimen treatment but not meeting treatment targets, expert opinion, or more specialist advice, should be used to decide on repeat biopsy and whether further induction regimen required or a change of maintenance therapy (2B) [98.4% (85–100)].

Recommendation 80 In people refractory to the initial treatment for LN, reasons for suboptimal response should be fully re-assessed including checking adherence, optimising doses of immunosuppressants and checking drug levels, and considering a repeat renal biopsy. Expert opinion, or more specialist advice, must be used to decide therapy (2B) [81.7% (80–100)].

Recommendation 81 Treatment options for refractory LN include clinical trials (2B), switching to one of the other induction immunosuppressant combinations in #74 (2B), and/or restarting induction GC (2B) [96.6% (88–100)].

Induction therapy: assessing response and switching

There is good evidence from several studies that a 12-month proteinuria target of <50–70 mg/mmol with stable or improved eGFR predict a good overall long-term renal outcome in terms of harder endpoints such as doubling creatinine, ESKD and death [430–432]. Not reaching this threshold does not necessarily equate to a poor prognosis but is an indication for further assessment such as causes for glomerular hyperfiltration including a high salt intake, poorly controlled blood pressure, diabetes mellitus or obesity and possibly a repeat biopsy.

It is important to detect suboptimal response at earlier time-points since change in therapy would be important, especially as more therapy options and combinations are available if switches are required to overcome this. The EULAR-ERA-EDTA recommendations suggested targets of 25% and 50% reduction at 3 and 6 months (with preserved or improving GFR) [33]. Although the evidence for these is weaker, we agreed these are reasonable targets. It should be noted these are approximations and the complete clinical and laboratory assessment should be considered, including extra-renal disease, serology and haematuria. In people with LN and higher risk features, such as reduced GFR or adherence concerns, the threshold for switching or escalating therapy may be lower.

These targets become less reliable in people with class V lesions (with or without other classes). These individuals often have nephrotic syndrome in which heavy proteinuria and its complications may be difficult to manage. The reduction in proteinuria may be much slower, requiring renin-angiotensin-aldosterone (RAAS) blockade and SGLT2 inhibitors, as well as immunosuppression escalation (see recommendations 79–81). The EULAR-ERA-EDTA recommendations suggest that an additional 6–9 months may be required to reach the same targets, and that slower but progressive reduction in proteinuria with preserved renal function may also be acceptable [33].

We do not consider partial responses to be acceptable. Older studies are informative for the consequences of incomplete remission. It is notable that, compared with people with complete remission, long-term renal survival and survival without ESKD were significantly worse in individuals with either partial or no remission. In a 10-year US study, the renal survival at 10 years was 94% for people with LN who had achieved complete remission on therapy, 45% for partial remission and 19% for no remission, and the survival without ESKD at 10 years was 92% for complete remission, 43% for partial remission and 13% for no remission [405]. These outcomes emphasize the importance of monitoring response and optimizing therapy to the highest quality of early remission.

The reasons for partial or non-response to induction therapy may be complex and there are several potential therapy options. It is not possible to protocolize these decisions based on RCT evidence. Treatment choice will require review of original biopsy

(continued)

features as well as consideration of a repeat biopsy to assess for change in histology or degree of scarring. The individual features mentioned in Recommendation #67 above should be re-assessed. Care must be discussed with a specialist centre or at a specialized MDT meeting. Clinical trials should be considered. Obinutuzumab has been used in a small study of highly refractory lupus in the UK, including those with secondary non-response to rituximab [329]. In this study, seven out of nine people with SLE had clinical response including two out of four (50%) with LN.

Organ-specific approach: what is the best evidence for lupus nephritis maintenance treatment?

Recommendation 82 Maintenance therapy should be continued for at least 3 years (1A). Longer durations may be advantageous in many people with LN and the decision should be individualised based on quality of response, prior relapses, risk associated with relapse, tolerability, biomarkers, extra-renal disease activity and patient preference (2C) [97.5% (87–100)].

Rationale for maintenance treatment for lupus nephritis

Relapse is associated with significantly worse outcomes than an initial episode of LN, so prevention of relapse is equally important as achieving the best response to initial induction therapy. A long-term observational study in 441 patients followed from 2008 to 2018 showed that a second episode of nephritis was associated with 31% lower rates of CRR, 31% lower rates of partial response, 50% higher rates of a 30% reduction in GFR and 93% higher mortality. With a third episode of nephritis, the rates of complete and partial renal response were 62% and 40% lower, and the rates of a 30% reduction in GFR or death were 69% and 285% higher [394].

Relapse rates are substantial, even if good response to initial induction therapy is achieved. Relapse rates are especially high if MPAA monotherapy (i.e. the historic standard of care) was used for maintenance in the standard-of-care arms of the long-term extensions of randomized trials. In AURORA-2, 26% (19/73) had a relapse over 3 years. In BLISS-LN trials, 26% (51/196) over 2 years [433, 434].

A non-inferiority RCT compared stopping vs continuing azathioprine or MMF maintenance at a median of 2.8 years. Despite relatively low numbers of participants leading to a lack of statistical power, relapse of proliferative LN occurred in 5/40 (12.5%) participants with immunosuppressive therapy (IST) continuation and in 12/44 (27.3%) participants with IST discontinuation, a difference of 14.8% (95% CI –1.9–31.5) and non-inferiority was not demonstrated. Further, severe SLE flares (renal or extrarenal) were less frequent in participants with IST continuation (5/40 vs 14/44 patients; $P=0.035$), while adverse events did not differ between the groups [435]. Hence, we advise that maintenance therapy should be continued for a minimum of 3 years with regular monitoring for signs of relapse before and

especially after discontinuation of therapy. Longer duration of therapy will be appropriate in many people with LN based on risk profile and quality of response. In an observational study, remission duration of >48 months was associated with a lower risk of relapse on discontinuation of maintenance therapy, as were fulfilling DORIS of LLDAS criteria and gradual discontinuation [436].

Recommendation 83 In people with LN meeting the 12-month treatment targets after induction therapy using regimens in #74, the following treatment maintenance should be continued for at least 3 years:

- MPAA + obinutuzumab (1B);
- MPAA + belimumab (1A);
- MPAA + CNI (1A) [96.2% (85–100)].

Recommendation 84 In people with LN who received a different induction option to regimens in #74, combination therapies in #83 could be added for maintenance if appropriate (2B) [95.2% (80–100)].

Recommendation 85 If rituximab and MPAA were used for induction with good response, then this combination could be continued for maintenance, individualising retreatment interval (2C) [97.8% (90–100)].

Recommendation 86 If combination therapy cannot be used, then MPAA should be used for maintenance therapy (1A) [97.3% (87–100)].

Recommendation 87 If MPAA cannot be taken or pregnancy is planned, then azathioprine (or combination of azathioprine and tacrolimus) can be used for maintenance with closer monitoring for LN flare (1A) [98.3% (84–100)].

Recommended maintenance treatment in lupus nephritis

Several RCTs have compared maintenance therapy options. When NIH or EuroLupus cyclophosphamide were standard first-line induction therapy, the usual maintenance was azathioprine. Two RCTs have shown the superiority of MPAA in maintaining remission, which therefore became standard of care for maintenance therapy in previous EULAR-ERA-EDTA recommendations [33]. Since these trials, combination maintenance therapy has been shown to be superior in maintaining remission.

Extensions to the trials of the recommended combination therapies in [74] have shown that these combinations are superior to MPAA alone in maintaining remission and preventing relapses.

For belimumab, the initial study was 104 weeks with a 28-week open-label extension and post-hoc analyses demonstrated reduction in rates of renal flare in the belimumab arm with HR 0.5–0.6 across subgroups of initial response [28, 437, 438]. In an SLR and meta-analysis of 6 RCTs, belimumab reduced the risk of renal flare (RR, 0.51; 95% CI, 0.37–0.69; $P<0.001$) and renal function worsening or progression to ESKD (RR, 0.56; 95% CI, 0.40–

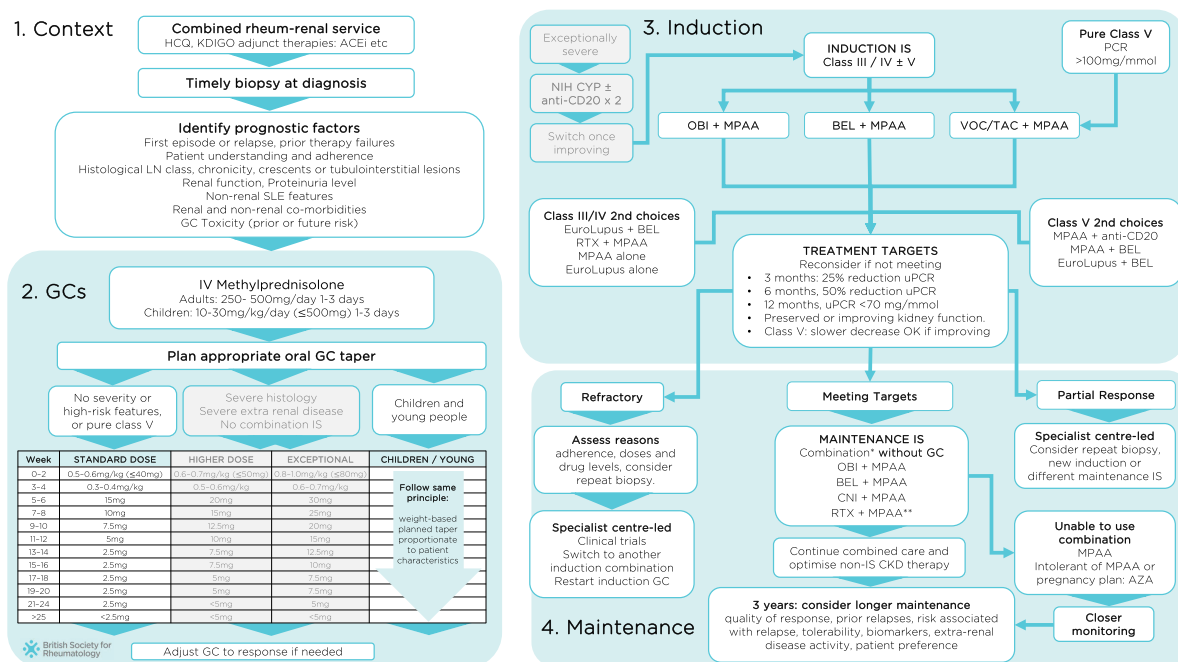


Figure 1 Lupus nephritis management algorithm. Management of lupus nephritis is broadly divided into four main sections: (a) context, general approach and the delivery of care; (b) glucocorticoids for remission induction and suggested tapering schedule; (c) evidence-based first-line and second-line combination immunosuppressant therapies for remission induction of lupus nephritis and treatment targets; and (d) therapies for maintenance of lupus nephritis, duration of therapy and monitoring approaches. ACEi, angiotensin-converting enzyme inhibitors; BEL, belimumab; CKD, chronic kidney disease; CNI, calcineurin inhibitor; CYP, cyclophosphamide; GC, glucocorticoids; IS, immunosuppressant; KDIGO, Kidney Disease Improving Global Outcomes; MPAA, mycophenolic acid analogues; NIH, National Institute of Health; OBI, obinutuzumab; RTX, rituximab; TAC, tacrolimus; uPCR, urinary protein creatinine ratio; VOC, voclosporin

0.79; $P=0.001$) as compared with SOC alone. Serious adverse events were also less frequent with belimumab.

There are concerns regarding the duration of long-term tacrolimus as it can lead to nephrotoxicity and eGFR decline. In a long-term extension of the Multitarget trial of tacrolimus combination therapy as remission induction, there was no difference in renal relapse rate between tacrolimus and MMF combination and azathioprine monotherapy as maintenance over 18 months (5.47% vs 7.62%, respectively; adjusted hazard ratio, 0.82; 95% confidence interval, 0.25–2.67; $P=0.74$) although adverse events were less frequent with Multitarget [439].

For voclosporin, however, 3-year data from the long-term AURORA-2 study demonstrated stable levels of eGFR throughout the 3-year period [433]. Rates of renal relapse were numerically lower with voclosporin compared with placebo [23.8% vs 26.0%, respectively, OR 0.85 (0.42–1.73), $P=0.662$].

For obinutuzumab, currently available follow-up data extends to 104 weeks (NOBILITY) and 76 weeks (REGENCY). Treatment failure, rescue therapy and clinically significant worsening of proteinuria or eGFR were all higher in the placebo group compared with the obinutuzumab group [29, 412].

For rituximab, formal long-term RCTs are not available but there is extensive experience of its use over 20 years in routine practice. Clinicians are experienced in customizing retreatment intervals for both B-cell depleting therapies according to clinical response and B-cell biomarkers [324]. The greatest issues are loss of response due to development of anti-rituximab antibodies, and development of hypogammaglobulinaemia. The former can be managed by switching to obinutuzumab [329].

Hypogammaglobulinaemia can be prevented by checking IgG as part of each retreatment decision and considering switch of therapy if there is a progressive trend to below-normal levels [332].

Recommendation 88 Following the GC induction regimen for LN, full withdrawal of GC should be attempted; use of GC is not recommended for long-term control of disease activity after either full or partial response (2B) [97.4% (82–100)].

Full withdrawal of GC should be attempted following remission induction

Historically there has been limited evidence that withdrawal of GC could lead to increased rates of flares in people with SLE in general. For example, the CORTICOLUP trial compared continuation of prednisone 5 mg daily against discontinuation in a multi-ethnic French population with stable and quiescent SLE (history of LN in 34% and 41%, respectively) [440]. Although an increased flare rate occurred in the discontinuation group (HR: 0.2 for continuation, $P=0.002$), these flares were mild, mostly non-renal, and 45 of 63 patients in the discontinuation group remained GC-free. Moreover, the withdrawal was abrupt, and people with LN were not receiving the combination immunosuppressants that we recommend here, with many not on MMF. Doses of GC above 7.5 mg/day have substantial long-term toxicity leading to organ damage in up to 80% of patients over 5–10 years, and slower

withdrawal in clinically quiescent individuals has been reported to be safe. Long-term damage has not been shown to result from doses under 7.5 mg/day [441]. However, we still prefer withdrawal where possible to avoid hypoadrenalism and reduce pill burden. Overall, we advise that an attempt to withdraw GC is made in all people with LN provided individual risk is assessed and managed and appropriate maintenance therapy is used.

Recommendation 89 During maintenance therapy, people with LN should continue to be managed by renal services, combined with rheumatology if necessary, to ensure appropriate chronic kidney disease (CKD) management using adjunctive therapies (2B) [97.0% (83–100)].

Management of chronic kidney disease

People with LN all have chronic kidney disease and, even after a good response to induction therapy and prevention of relapses, have likely sustained loss of nephrons and increased risk of decline. In addition to appropriate immunosuppression, long-term maintenance of renal function as well as cardiovascular and bone health and non-renal SLE still requires active and complex management. This may include blood pressure control, use of reno-protective medications, management of dyslipidaemia and management of bone health. Additionally, long-term supervision for adherence and proteinuria monitoring, and management of non-renal SLE is required. For non-immunosuppressive management we again refer to KDIGO [39].

Delivery of care: how should care be delivered to optimise the management of people with SLE?

Rationale

The recommendations in this delivery of care section build on the 2017 BSR SLE guideline [22] and aim to harmonise care within the UK system and define auditable standards. The recommendations are based on SLR of studies evaluating multidisciplinary or integrated care for people with SLE, grey literature (NHS reports) focusing on e-referral, advice and guidance, qualitative studies focusing on barriers and facilitators to (optimal) care, national audits reporting on quality of care in SLE, and expert consensus.

Recommendation 90 Where there is complex multisystem disease, people with SLE should be co-managed with relevant specialties in joint clinics or if not, at least with regular multispecialty/multiprofessional MDT meetings that enable rapid communication (1D) [99.8% (95–100)].

Recommendation 91 Every healthcare organisation treating SLE should be part of a regional specialised network/regional MDT meetings

so that people with SLE can receive access to additional specialised care and advice, combined with ongoing local hospital care, regardless of geography (1C). Such services are still in development for JSLE but should be used when available [98.1% (82–100)].

Recommendation 92 All people with SLE with severe, complex or refractory disease including those with lupus nephritis, especially those being considered for biologic drugs must be discussed with and/or managed by a specialist lupus centre (1D) [98.4% (84–100)].

Multispecialty/multiprofessional MDT meetings, regional specialised networks and specialist lupus centres

The BSR GWG recommend that where there is complex multisystem disease, people with SLE should be co-managed with relevant specialties in joint clinics or if not, at least with access to regular multispecialty/multiprofessional MDT meetings. This is supported by other related guidelines (e.g. the 2021 BAD guideline for the management of CLE [34] and the 2024 KDIGO guideline for the management of LN [39]). Moreover, this is also in line with Recommendation 12 of the 2021 GIRFT Programme National Rheumatology Specialty Report that states people with rare RMDs should have rapid access to specialist expertise and effective treatments to ensure equity of outcomes regardless of geography and reduce the risks of morbidity and mortality, as well as Recommendation 12 b of the GIRFT report (i.e. to ensure effective co-ordination of care across all specialties as required) [48].

Every healthcare organisation treating people with SLE should be part of a regional specialised network/regional MDT meetings. This is in line with Recommendation 12 of the 2021 GIRFT Programme National Rheumatology Specialty Report as stated above and Recommendation 13 that states the structure, operation and geographic reach of specialised rheumatology networks should be reviewed and improved to ensure this across and between regions [48]. We acknowledge that such services may not be feasibly delivered on a regional level for JSLE, but a monthly national JSLE MDT has recently been developed and should be utilised where possible.

In line with the 2017 BSR SLE guideline [22] and the 2020 NHSE clinical commissioning policy for rituximab [49], all people with SLE with severe, complex or refractory disease including those with LN, especially those being considered for biologic drugs must be discussed with and/or managed by a specialist lupus centre. These biologic drugs can be given at nonspecialised centres (with reimbursement of those centres) if the appropriate use of therapies has been ratified at/by a specialised centre.

Recommendation 93 Shared care within secondary care and between primary and secondary/tertiary care should be funded, supported and standardised (1D) [99.6% (95–100)].

(continued)

Recommendation 94 A coordinated transition plan including paediatric and adult specialists should be put in place to manage this high-risk period of SLE in a young person's journey (1C) [97.9% (80–100)].

Shared care and a coordinated transition plan

The BSR GWG recommend shared care within secondary care and between primary and secondary/tertiary care should be funded, supported and standardised. This is in line with Recommendation 20 of the 2021 GIRFT report that states disease-modifying anti-rheumatic drug (DMARD) monitoring processes should be standardised across the integrated care system (ICS)/sustainability and transformation partnership (STP) footprints and medical specialties, linked to an interoperable electronic monitoring system [48]. Our recommendation is also in keeping with the NHS 10-Year Health Plan with a shift from hospital to community focus to provide continuous, accessible and integrated care [442]. Effective communication between primary and secondary/tertiary care is required to prevent duplication of resources and investigations (e.g. blood monitoring tests and lack of visibility of bloods results done in primary care out of area and vice versa).

Transition of care, defined as the process of moving from children's to adults' services, represents a high-risk period in a young person's journey. This full process includes the initial planning, the actual transfer between services and continuous provision of patient centred support throughout the process. A coordinated transition plan including paediatric and adult specialists therefore should be put in place in each centre, involving all relevant specialties. To refer to the 2016 NICE guideline on Transition from children's to adults' services for young people using health or social care services [443] and the 2017 EULAR/PreS standards and recommendations for the transitional care of young people with juvenile-onset rheumatic diseases [444].

Recommendation 95 People with SLE should be seen in dedicated/cohorted clinics with specific clinic templates adjusted for complexity to allow adequate time for a full multi-system holistic assessment (1C) [98.6% (82–100)].

Recommendation 96 Services should consider and develop ways to address potential health inequalities particularly those faced by minoritised and underserved groups and from low socioeconomic backgrounds to ensure equitable access to optimal management (1D) [97.4% (82–100)].

Recommendation 97 Where there are communication barriers including where interpreters are required, longer clinic appointment times are recommended (1D) [96.7% (80–100)].

Recommendation 98 Each healthcare organisation should have a lead clinician for the delivery of service for people with SLE, with recognition in job plan for this activity (1D) [96.8% (80–100)].

Recommendation 99 Every individual with SLE should have access to a specialist nurse with understanding and expertise in management of lupus with dedicated time within their job plan, including access to a telephone and/or email advice line (1C) [97.7% (82–100)].

Recommendation 100 People with SLE with disease flares or possible drug-related side effects should be able to receive timely advice (ideally within 1–2 working days) of contacting their hospital service (1C) [98.4% (86–100)].

Organising lupus care in healthcare organisations

The BSR GWG recommend that people with SLE should be seen in dedicated/cohorted clinics with specific clinic templates adjusted for complexity to allow adequate time for a full multi-system holistic assessment. The benefits of dedicated clinics (cohorting) for people with SLE, as opposed to general rheumatology clinics, include better patient care as highlighted in the UK multicentre audit of the last BSR 2017 guideline [86]. Furthermore, a mixed-methods study in UK and Ireland also reported that cohorted clinics, nurse-led clinics and specialist vasculitis multi-disciplinary team meetings were associated with fewer serious infections in patients [445]. In terms of clinic templates, our recommendation is in line with the 2024 Modern outpatient care: using resources to add value guideline published by the Royal College of Physicians (i.e. that the length of an individual patient contact should take into account the complexity of that contact). Factors influencing complexity that are related to SLE include multisystem disease, multiple health conditions, outpatient procedure required and requirement of an interpreter [446].

There are health inequities including socioeconomic, educational, geography and ethnicity/ancestry across the UK in terms of access to good care, treatment provision, treatment response and outcomes. For example, data from the BILAG Biologics Register of people with moderate-to-severe SLE who required biological therapy showed that almost half were from a non-white background [301]. In addition to the difference in disease severity according to ancestry, people with SLE from more deprived backgrounds had higher rates of morbidity and mortality [447, 448]. Thus, services should consider and develop ways to address potential health inequalities, particularly those faced by minoritised and underserved groups and from low socioeconomic backgrounds to ensure equitable access to optimal management. An example could include where there are communication barriers including where interpreters are required, longer clinic appointment times are recommended. This is in line with the 2024 RCP guideline of modern outpatient care [446].

The BSR GWG also recommend that each healthcare organisation should have a lead clinician for the delivery of service for people with SLE, with recognition in their job plan for this activity. In addition, people with SLE should have access to a specialist nurse(s) with understanding and expertise in the management of lupus including access to a telephone and/or email advice line. Similarly, they should have dedicated time in their job plans to perform this function. This is in keeping with Recommendation 12a of the 2021 GIRFT report to identify responsible clinicians and lead nurses/allied health professionals in each trust offering care for rare RMDs, to co-ordinate care for each main category of specialised rheumatology: autoimmune connective tissue diseases, vasculitis, heritable connective tissue diseases and rare metabolic bone diseases [48].

The BSR GWG recommend that people with SLE with disease flares or possible drug-related side effects should be able to receive timely advice (ideally within 1–2 working days) of contacting their hospital service. A mixed-methods study showed that nurse-led advice lines were associated with fewer serious infections (OR 0.76 [95% CI 0.58–0.93]) and fewer emergency hospital admissions (0.85 [0.74–0.96]) [445]. The provision for 1–2 working days response to queries pertaining to SLE disease flares or possible drug-related side effects is in line with the 2020 BSR Evidence-based recommendations for rheumatology advice lines [449] and the 2006 Royal College of Nursing guidance on using telephone advice lines for patients with long-term conditions [450].

Recommendation 101 All people with SLE should be given the opportunity of taking part in observational research studies, and if treated with biologic drugs, with their consent should be registered with the National BILAG Biologics Register (BILAG BR) and/or UK Juvenile SLE (JSLE) Cohort Study (1D) [98.8% (80–100)].

Recommendation 102 All departments should collect the required data for national audits and registries. Healthcare organisations should ensure that there is appropriate administrative support for audit participation. Clinical and operational teams should review their audit data and take any required action (1D) [97.3% (80–100)].

Opportunity to take part in research, registry and national audits

The BSR GWG recommend that people with SLE should be given the opportunity of taking part in observational research studies to provide an evidence base aimed at improving the care and understanding of SLE. This is in line with Section 6: Choosing to take part in health research of the 2024 Department of Health and Social Care guidance on NHS Choice Framework [451]. If treated with biologic drugs, with their consent, people with SLE should be registered with the National BILAG Biologics Register (BILAG BR) and/or UK JSLE Cohort Study and Repository, as per the 2020 NHSE clinical commissioning policy for rituximab [49].

Pertaining to national audits and registries, Recommendation 11 of the GIRFT report stated that all rheumatology units providing care for rare RMDs should collect data on care, caseload and outcomes for people with rare RMDs, using routinely collected data where possible to reduce burden of clinician data collection and submission. In addition, Recommendation 11c stated that to use audit, and dashboard data where appropriate, to understand how care is being delivered and develop quality improvement tools to improve outcomes [48]. An example of a non-exhaustive list includes all units must enter the required data on newly diagnosed people with SLE to the National Early Inflammatory Arthritis Audit (NEIAA) portal. Thus, healthcare organisations should ensure that there is appropriate administrative support for audit participation.

Summary

This new section of the BSR SLE guideline provides guidance on the optimal strategies on how care should be coordinated and delivered in the UK for people with SLE. It includes the use of multispecialty/multiprofessional MDT meetings, shared care between primary and secondary/tertiary care, organisation of clinics and services in a healthcare organisation and offering the opportunity for people with SLE to take part in research, audits and registries.

Applicability, utility and limitation

This updated life-course guideline provides an overview of evidence-based management and current best practice for the management of SLE with a particular focus on delivering care within the NHS in England and the devolved nations. It is important to consider other guidelines and expert consensus regarding some aspects of SLE management that are not included in our guideline scope. This guideline also highlights the limited high-quality evidence base available particularly for non-renal SLE, non-pharmacological approaches and JSLE with relative absence of RCTs or head-to-head comparison of treatments. It is important to note that our search for studies evaluating the effectiveness of treatments were limited to RCTs only since multiple RCTs with consistent findings, adequate precision and low risk of bias would be needed to underpin treatment recommendations with high certainty. It was not feasible within the Guideline timeline to search systematically for other study designs (e.g. exceptionally strong observational cohort studies) across all statements for such a broad scope, especially noting a whole life-course approach. However, it is expected that the GWG would bring all their expertise to bear on each question, including all forms of evidence they know during draft formulation. We also explicitly reviewed other related guidelines and by these processes, we were able to incorporate observational evidence.

There should be no barriers to implementation, apart from limitations on the funding or commissioning criteria for belimumab, rituximab, voclosporin and obinutuzumab discussed in the relevant sections, as well as impending submission/approval for newer therapies including anifrolumab.

Paediatric evidence for SLE remains limited compared with adult data, largely due to the rarity of juvenile-onset disease and

Table 4 Research agenda.

- 1) Research is needed to demonstrate the value of dedicated treat-to-target clinics compared to usual care in a cohorted SLE clinic or general rheumatology clinic. This should include analysis of the cost-effectiveness given additional clinic time and appointments required, and the treatment policy followed.
- 2) Formal clinical trials or similar systematic prospective studies should be conducted to evaluate the value of the non-pharmacological interventions identified in our literature review. These should include analysis of quality of life and other patient-reported outcomes as well as usual disease activity and damage measures.
- 3) Clinical trials should be undertaken to evaluate the role of biologics as first-line immunosuppressants given in the first year after SLE diagnosis (when disease activity is worst), compared with reserving them for refractory disease. Such trials would need an end point that would capture worsening, glucocorticoid exposure and other therapy use, not simply response compared with baseline. A time-on-target design would be suitable.
- 4) Research should be conducted to evaluate the effect of licensed biologics (such as belimumab, anifrolumab and obinutuzumab) on rare lupus manifestations that were not included in randomised trials, such as neuropsychiatric disease, cardiorespiratory disease and severe haematological involvement. Given the challenges in these patients, pragmatic or observational designs may be needed.
- 5) Therapies licensed for the treatment of lupus nephritis in adults (e.g. obinutuzumab, voclosporin) should be evaluated in randomised trials in children and adolescents with sufficient follow-up duration to capture the full impact of combination therapy.
- 6) A review will be required of numerous agents currently in Phase III clinical trials to determine their positioning in the treatment pathway. With an increasingly complex field of therapeutics, this will need to include meta-analysis, real-world evidence and expert opinion.
- 7) Head-to-head studies are required to decide the most appropriate biologic for each patient. These studies would need to enrol a broader spectrum of demographics and lupus manifestations than were included in the original licensing trials with appropriate endpoints and standard of care in line with this. Given the challenges of large randomised trials in SLE, alternative designs should be considered.
- 8) The importance of glucocorticoid tapering has been stressed at several points in our guidelines as well as others. However, real-world trials of the feasibility, efficacy, safety and patient acceptability of these strategies is lacking.
- 9) We have recommended more extensive investment in specialist clinics, specialist nurses, AHPs and psychological care and MDTs. These services are expensive and evidence of their impact on real-world outcomes is required.

the logistical challenges of conducting adequately powered trials. This gap is compounded by the typical delay in initiating paediatric studies until adult trials are complete. Yet, children often

present with more severe disease and face greater risks from steroid toxicity, making them prime candidates for novel therapies. The only randomised trial in JSLE (PLUTO assessing belimumab), supported regulatory approval of belimumab but was intentionally underpowered for efficacy because of feasibility constraints, regulatory design and disease heterogeneity [305].

Throughout this guideline, paediatric evidence has been presented wherever possible; however, the expert working group emphasises that the absence of paediatric-specific data should not be interpreted as recommendations being inapplicable to children. Given the rarity of JSLE, it may never be feasible to generate fully powered paediatric trials, and inequity in research access persists. Without pragmatic application of adult-derived evidence, children risk receiving substandard care and experiencing worse outcomes.

The guideline will be widely presented at local, regional, national and international meetings for healthcare professionals, people with SLE and their carers, stakeholders and patient partners. The final guideline and the executive summary will be disseminated by publication in *Rheumatology (Oxford)* and will be freely available on the BSR website.

Mechanism of audit of the guideline

To assess adherence with this guideline, an audit proforma is provided as [Supplementary Material](#), available at *Rheumatology* online. We would also strongly recommend that new cases of SLE are recorded in the NEIAA (New Early Inflammatory Arthritis Audit <https://arthritisaudit.org.uk/>) database to provide information on the incidence and demographics of the condition, as well as collect evidence on diagnostic delays and route of referral.

Research recommendations

There is a need for more evidence to support decision making and a personalised approach in the management of people with SLE. There is particular inequity in access to research for people with JSLE, and where possible life-course studies and trials should be promoted. The BSR GWG have identified certain priorities for research into SLE to help address this issue, and these are shown in [Table 4](#).

Conclusion

The field of therapeutics in SLE has advanced significantly since the last BSR SLE guideline. However, there remain unmet needs including inconsistency in diagnostics, persistent disease activity, frequent flares, toxicities from immunosuppressants including GC, health inequalities and significant burden from comorbidities like cardiovascular disease and infections. This guideline will provide a framework for health professionals and people with SLE in providing evidence- and eminence-based, good-quality care across the life course to manage/self-manage effectively and proactively.

Supplementary material

[Supplementary material](#) is available at *Rheumatology* online.

Data availability

Data are available in the guideline and its [Supplementary Material](#), available at *Rheumatology* online. Extracted data for some RCTs are available in Excel format and can be shared upon justifiable request to the corresponding author.

Author contributions

M.M., E.M.D.S. and E.M.V. drafted this article. All authors contributed to developing the guideline scope, provided critical manuscript editing and revision, and approved the final submitted version.

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