

# Systemic Lupus Erythematosus: A Review for Anesthesiologists

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Systemic lupus erythematosus (SLE) is a chronic autoimmune connective tissue disorder, with a heterogeneous presentation. Disease severity is wide ranging, with most suffering milder forms; however, it is potentially fatal depending on organ involvement. The disorder was recognized as early as the Middle Ages, with the 12th-century physician Rogerius being the first to apply the term *lupus* to the classic malar rash, and in 1872, Moric Kaposi first recognized the systemic nature of the disease. Perioperatively, SLE can present major challenges to the anesthesiologist because of accrued organ damage, coagulation defects, and complex management regimes. In this article I highlight adult SLE manifestations and treatments pertinent to the anesthesiologist and discuss perioperative management of these complex patients. (Anesth Analg 2010;111:665–76)

The prevalence of systemic lupus erythematosus (SLE) ranges from 7.4 to 159.4 per 100,000 of population, with the highest rates among United Kingdom residents of Afro-Caribbean descent, and non-White populations elsewhere.<sup>1</sup> A female:male ratio of 9:1 is reported, with peak age of onset between 15 and 40 years,<sup>2</sup> although cases may present anytime in childhood through advanced age, at which time female-to-male ratios are approximately 2:1.<sup>3</sup> Males and patients with later age of onset tend to have more severe disease and poorer prognosis.<sup>4,5</sup> Genetic factors are implicated in pathogenesis with a concordance rate for lupus of 24%–60% among monozygotic twins and 2%–5% among dizygotic twins.<sup>6</sup>

## PATHOGENESIS

The pathogenesis of SLE is complex and appears linked to autoimmunity against various native cellular components. Multiple genetic susceptibility loci have been identified in genomic studies, and specific major histocompatibility complexes are also linked to lupus.<sup>7</sup> It is possible that these major histocompatibility complexes bind antigens in such a way that they increase the likelihood of T-cells mounting an immune response to self-antigens. Implicated susceptibility genes include *IRF 5*, *STAT4*, *ITGAM*, and several deficiencies in complement components C1q, C4, and C2.<sup>8</sup> Damage subsequently results from autoimmunity-induced inflammation or tissue deposition of immune complexes.

Other factors have been implicated in the pathogenesis of SLE, but conclusive evidence is lacking. Factors implicated include current smoking,<sup>9</sup> exposure to crystalline silica,<sup>10</sup> Epstein–Barr virus seropositivity,<sup>11</sup> and hormones, with an association between early menarche and SLE<sup>12</sup> and a protective effect of breastfeeding.<sup>13</sup> Socioeconomic factors have been associated with poorer

outcomes and higher disease activity,<sup>14</sup> although it remains unclear whether it plays a role in disease susceptibility or subsequent progression.

Exposure to certain drugs may induce a lupus-like illness or exacerbate SLE. There are no standardized diagnostic criteria for drug-induced lupus erythematosus, but in such cases there must have been continuous exposure to a pharmacological trigger for at least a month, with resolution after discontinuation of the drug. The clinical manifestations of drug-induced lupus erythematosus are generally milder with arthralgias and serositis being the predominant symptoms, and major organ involvement is usually absent.<sup>15</sup>

## DIAGNOSIS

Consensus guidelines provided by the American College of Rheumatology (ACR) provide the basis for accurate and standardized diagnosis of SLE. The original recommendations published in 1982 were updated in 1997 and contain 11 diagnostic categories (Table 1). The presence of any 4 of these criteria, either concurrently or consecutively, confirms the diagnosis of SLE. The major change in the 1997 revision was the inclusion of newer immunological tests, namely, antiphospholipid (aPL) antibodies, anticardiolipin (aCL) antibodies, and lupus anticoagulant (LAC), and the removal of redundant histological preparations.

Serological biomarkers hold a significant potential in diagnosis and monitoring of SLE given that the pathogenesis is most likely the result of immune dysregulation. Anti-double -stranded DNA (anti-dsDNA) is highly specific for lupus, with 70% of SLE patients being positive in comparison with only 0.5% of the healthy population or those with other autoimmune diseases.<sup>16</sup> In contrast, antinuclear antibody is highly sensitive, being positive in 99% of SLE patients at some point in their illness, but is also found in 32% of the general population at a 1:40 dilution and in 5% at a 1:160 dilution.<sup>17</sup> The search for biomarkers with higher sensitivity and specificity continues with flow cytometric analysis of erythrocyte-bound complement activation product C4d and complement receptor 1 giving promising results.<sup>18</sup> Despite advances it must be recognized that there is no definitive laboratory test for the diagnosis or monitoring of SLE and that all results must be

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Accepted for publication May 9, 2010.

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DOI: 10.1213/ANE.0b013e3181e8138e

**Table 1. Diagnostic Guidelines for Systemic Lupus Erythematosus**

Criterion	Definition
Malar rash	Fixed erythema, flat or raised, over the malar eminences, tending to spare the nasolabial folds
Discoid rash	Erythematous raised patches with adherent keratotic scaling and follicular plugging; atrophic scarring may occur in older lesions
Photosensitivity	Skin rash as a result of unusual reaction to sunlight, by patient history or physician observation
Oral ulcers	Oral or nasopharyngeal ulceration, usually painless, observed by a physician
Arthritis	Nonerosive arthritis involving 2 or more peripheral joints, characterized by tenderness, swelling, or effusion
Serositis	(a) Pleuritis or (b) Pericarditis
Renal disorder	(a) Persistent proteinuria or (b) Cellular casts
Neurologic disorder	(a) Seizures or (b) Psychosis
Hematologic disorder	(a) Hemolytic anemia or (b) Leukopenia or (c) Lymphopenia or (d) Thrombocytopenia
Immunologic disorder	(a) Anti-dsDNA antibody or (b) Anti-Sm antibody or (c) Positive finding of antiphospholipid antibodies with either (i) abnormal serum IgG or IgM anti-cardiolipin antibody levels or (ii) positivity for lupus anticoagulant or (iii) false positive serological testing for syphilis
Antinuclear antibody	Abnormal ANA titer

Adapted from Tan EM, Cohen AS, Fries JF, Masi AT, McShane DJ, Rothfield NF, Schaller JG, Talal N, Winchester RJ. The 1982 revised criteria for the classification of systemic lupus erythematosus. *Arthritis Rheum* 1982;25:1271-7.

viewed in the context of each individual patient’s clinical course.

**CLINICAL FEATURES**

A variety of disease manifestations are exhibited by SLE patients (Table 2), with the heterogeneity of presentations often delaying diagnosis. Common manifestations include rashes, photosensitivity, arthritis, pleuritis, pericarditis, nephritis, neuropsychiatric disorders, and hematological disorders. There is also an array of less common but potentially hazardous complications.

**Cardiovascular**

Pericarditis is well recognized in lupus and is included as a diagnostic criterion by the ACR. One-quarter of lupus patients develop symptomatic pericarditis, while >50% have evidence of asymptomatic pericardial involvement.<sup>19</sup> Pericardial tamponade is a rare but well-documented complication with a rate of <2%.<sup>20</sup> Pericarditis usually occurs at disease onset (rarely as the presenting symptom) and during flare-ups of the disease and is often found in conjunction with pleural effusions as part of a generalized serositis.<sup>21</sup> Nonsteroidal anti-inflammatory drugs (NSAIDs) and corticosteroids are standard management, but pericardiocentesis or

**Table 2. Estimated Lifetime Prevalence of Major Systemic Lupus Erythematosus Manifestations**

Condition	Estimated prevalence
<b>Dermatologic</b>	
Malar rash	50%
Chronic discoid lesions	25%
<b>Neurologic</b>	
Seizures	7%–20%
<b>Cardiovascular</b>	
Symptomatic pericarditis	25%
Pericardial tamponade	<2%
Myocarditis	5%–10%
Libman–Sacks endocarditis	10%
Valvular dysfunction	3%–4%
Raynaud’s phenomenon	30%–40%
<b>Pulmonary</b>	
Pleuritis	35%
Pneumonitis	1%–10%
Diffuse alveolar hemorrhage	1%–5%
Pulmonary arterial hypertension	0.5%–14%
<b>Renal</b>	
Lupus nephritis	60%
End-stage renal disease	3%–12%
<b>Hematology</b>	
Anemia of chronic disease	40%
Autoimmune hemolytic anemia	5%–10%
Autoimmune thrombocytopenia	10%
<b>Gastrointestinal</b>	
Oral ulcers	7%–52%
Sjorgen’s syndrome	10%
Dysphagia	1%–13%
Acute abdominal pain	40%
Abnormal liver function tests	Up to 60%
Autoimmune hepatitis	2%–5%
<b>Musculoskeletal</b>	
Arthritis	15%–50%
Osteoporosis	23%
Fractures	12.5%
Asymptomatic atlantoaxial subluxation	8.5%

pericardial window procedures may be required for treatment of tamponade.

Myocarditis is characteristic of myocardial involvement in SLE, with 5%–10% of patients experiencing clinically evident disease,<sup>22</sup> and up to 80% of these have decreased left ventricular ejection fraction.<sup>23</sup> The pathological process is probably immunological with immune complexes and complement deposition evident in perivascular myocardium. SLE myocarditis can progress to arrhythmias, ventricular dysfunction, dilated cardiomyopathy and heart failure, although other factors may be responsible such as hypertension, accelerated atherosclerosis with ischemia, valvular disease, renal failure, and treatment toxicity from cyclophosphamide or hydroxychloroquine.

In 1976 the bimodal pattern of mortality in SLE patients was established.<sup>24</sup> More recently the impact of cardiovascular disease (CVD) as a cause for late complications has been confirmed. Epidemiological studies highlight the significant risk in some populations; women ages 44 to 50 years with SLE had a 50-times increased likelihood of myocardial infarction when compared with controls from the Framingham study.<sup>25</sup> SLE is clearly an independent risk factor for the development of CVD, and as a result, traditional risk factor models perform less well in this population<sup>26</sup>; thus, the clinician must have a lower threshold for suspicion of CVD in these patients, despite the

absence of classical risk factors. Cohort studies identified specific risk factors associated with development of CVD in SLE patients, including older age at diagnosis of SLE, longer disease duration, longer duration of steroid use, and hypercholesterolemia.<sup>25,27</sup>

The overlapping inflammatory and immune-mediated nature of both SLE and atherosclerosis is being increasingly recognized, and is seen as part of the mechanistic cause of the premature CVD noted in lupus patients. Activated immune-mediating cells are typical of atherosclerotic plaques<sup>28</sup> and elevated C-reactive protein has been associated with CVD risk in the general population<sup>29</sup> and more specifically in SLE patients as well.<sup>30</sup> SLE patients develop a typical dyslipidemia characterized by increased very-low-density lipoprotein (LDL), increased triglycerides, and reduced high-density lipoprotein,<sup>31</sup> which is aggravated by flares,<sup>32</sup> suggesting that SLE activity promotes a proatherogenic lipid profile, including increased circulating oxidized LDL (oxLDL). B-2-glycoprotein 1 ( $\beta$ 2GPI), the protein recognized by most aCL antibodies, binds stably to oxLDL,<sup>33</sup> and these oxLDL/ $\beta$ 2GPI complexes may be recognized by aCL in SLE patients, thus enhancing their uptake into macrophages via  $\gamma$ -FC (fragment, crystallizable) receptors and accelerating the process of foam cell formation. Additional proatherogenic processes include dysfunctional proinflammatory high-density lipoprotein, which increases levels of oxLDL,<sup>34</sup> impaired lipid metabolism by lipoprotein lipase,<sup>35</sup> possibly due to autoantibodies against lipoprotein lipase,<sup>36</sup> and inflammatory cytokines predisposing to atherosclerosis such as tumor necrosis factor,<sup>37</sup> monocyte chemoattractant protein-1,<sup>38</sup> and interleukin-6.<sup>39</sup>

Valvular abnormalities are common among SLE patients, with verrucous noninfective vegetations, also termed *Libman-Sacks endocarditis*, being the characteristic lesion.<sup>40</sup> Echocardiography evidence reveals that about 1 in 10 SLE patients have Libman-Sacks vegetations and that they are associated with longer disease duration, higher disease activity, and aPL antibodies with the mitral valve most frequently involved followed by the aortic valve, and the predominant lesion being regurgitation.<sup>41</sup> Progression of lesions occurs over time, especially aortic valve stenosis. Patients with Libman-Sacks endocarditis more frequently develop cerebral ischemia, possibly due to the association between aPL antibodies and valve disease, with a high prevalence of lesions among antiphospholipid syndrome (APS) patients with or without SLE,<sup>42</sup> and in those with aPL antibodies alone,<sup>43</sup> with 1 study finding cardiac involvement in 84% of primary APS patients.<sup>44</sup> An immune-mediated pathogenesis is suggested by the presence of immunoglobulin (Ig) complexes within these vegetations.<sup>19</sup> Clinically significant valvular dysfunction occurs in 3%–4% of SLE patients, with about half requiring surgery.<sup>45</sup> Bioprosthetic valves may be susceptible to valvulitis relapse, making the use of mechanical valves a potentially more appropriate option.<sup>46</sup>

Rhythm and conduction abnormalities are noted in SLE patients, most commonly sinus tachycardia, atrial fibrillation, and atrioventricular block,<sup>47</sup> although these may be due to contributing factors such as premature CVD and medications. QT prolongation may occur as a result of hydroxychloroquine therapy.<sup>48</sup>

## Pulmonary

Lupus can affect all pulmonary tissues, and abnormalities are common among lupus patients. Significant lung pathology was found in 18% of patients in 1 autopsy study,<sup>49</sup> and two thirds of patients had subclinical defects on lung function testing, most commonly a deficit in the diffusing capacity of carbon monoxide.<sup>50</sup> Radiological changes often seen with high-resolution computed tomography include the following: ground-glass and reticular opacities; features of interstitial lung disease present in one third; airway abnormalities noted in one fifth of asymptomatic patients; and frequent mediastinal lymphadenopathy.<sup>51,52</sup>

Pleural disease is the most likely clinical manifestation of SLE, with up to 35% of patients presenting with pleuritis. Pleural effusions when present are usually only mild, but large and clinically relevant effusions may develop.<sup>53</sup>

Parenchymal manifestations include interstitial lung disease, diffuse alveolar hemorrhage, and acute lupus pneumonitis. High-resolution computed tomography provides diagnostic support to clinical suspicion, while tissue sampling commonly reveals cellular, fibrotic, or mixed nonspecific interstitial pneumonia.<sup>54</sup> Diffuse alveolar hemorrhage is a potentially severe complication occurring in 1%–5% of SLE patients and carrying a 50% mortality.<sup>53</sup> It should be suspected in any case of new dyspnea, ground-glass opacities, or decreasing hematocrit with or without hemoptysis, with diagnosis being confirmed on bronchoalveolar lavage. Patients often require supportive intensive care, aggressive immunosuppression, and plasmapheresis with or without mechanical ventilation.

Pulmonary arterial hypertension is an uncommon but well-documented complication of SLE, with a reported prevalence of 0.5%–14%.<sup>55</sup> Diagnosis is often delayed because usual symptoms of dyspnea, fatigue, and impaired exercise tolerance are nonspecific. Several processes contribute to development of pulmonary arterial hypertension, including thromboembolism, pulmonary vasculitis, and fibrosis secondary to interstitial lung disease; treatment involves a combination of immunosuppression and standard therapies.

## Laryngeal Involvement

Laryngeal complications in SLE have been recognized for >50 years,<sup>56</sup> with an incidence ranging from 0.3% to 30%.<sup>57,58</sup> Findings include mild inflammation, vocal cord paralysis, subglottic stenosis, and laryngeal edema with acute obstruction.<sup>59</sup> Most cases arise in patients with pre-existing SLE, although laryngeal manifestations may rarely be the presenting feature. There exist case reports of vocal cord paralysis, and an association with pulmonary hypertension has been found, presumably due to right atrial/pulmonary artery enlargement causing compression of the recurrent laryngeal nerve.<sup>60</sup> Epiglottitis, rheumatoid type nodules, inflammatory masses,<sup>59</sup> and cricoarytenoiditis<sup>61</sup> have been described as well. Most cases respond to immunosuppressive therapy, although emergent endotracheal intubation or surgical tracheostomy has rarely been required. There is also some suggestion that active SLE may also predispose to postintubation subglottic stenosis even after relatively brief periods of tracheal intubation.<sup>62</sup>

## Renal

Lupus nephritis is common and carries a high burden of morbidity in SLE patients, both directly and as a result of treatment complications. Clinically relevant nephritis develops in 60% of patients, often within the first 3 years of lupus diagnosis.<sup>63</sup> One third of SLE patients present with lupus nephritis within the first year of diagnosis.<sup>4</sup> Renal complications have a standardized mortality ratio estimated at 4.3<sup>64</sup> and also independently predict mortality in damage accrual indexes.<sup>65</sup> Notably, minority populations suffer lupus nephritis more commonly, and this likely contributes to poorer outcomes in these groups.<sup>66</sup>

The pathogenesis of lupus nephritis is complex but may reflect either the deposition of circulating immune complexes, such as anti-dsDNA, into the glomerulus and subsequent activation of complement, or a direct pathogenic mechanism whereby autoantibodies react with proteins in the kidney such as  $\alpha$ -actinin.<sup>16</sup> Additional mechanisms of damage are being recognized, including renal vasculitis, thrombotic microangiopathy, injury to podocytes, and dysregulation of inflammatory mediators.<sup>67,68</sup>

Proteinuria is the hallmark of renal disease in lupus and is extremely common, though hematuria is less common. Urinary casts are often seen, reflecting renal tubular dysfunction, and hyperkalemic renal tubular acidosis has been associated with lupus. About 5%–20% of nephritic patients will progress to end-stage renal disease,<sup>63</sup> although rates appear to be decreasing and survival improving as a result of improved treatment regimens.

Kidney biopsy is the “gold standard” for the diagnosis and classification of lupus nephritis. The 2004 revision of the World Health Organization system by the International Society of Nephrology identifies 6 categories based on histological findings.<sup>69</sup> Focal proliferative (Class III) and diffuse proliferative (Class IV) disease have a poor prognosis for renal survival and are associated with severe hypertension. Two thirds of Class III patients progress to Class IV, and it is widely accepted that Class IV lupus nephritis carries the worst prognosis.<sup>70</sup> Biopsy is indicated in patients with evidence of underlying pathology such as increased creatinine, proteinuria, hematuria, or abnormal urinary sediments, but it is increasingly recognized that even in the absence of such findings, patients may have significant pathology on biopsy. One retrospective review found no correlation between serum creatinine or proteinuria and biopsy findings, and a large proportion of patients with normal renal function were found to have Class IV diffuse proliferative lupus nephritis on biopsy.<sup>71</sup> It would therefore be appropriate to take precautions for renal protection in lupus patients even in the presence of normal serum creatinine and urinary analysis.

## Neurological

SLE causes central nervous system (CNS), peripheral nervous system, autonomic nervous system, and psychiatric complications and is reported to affect between 37% to 95% of patients.<sup>72</sup> The ACR recommends the term *neuropsychiatric SLE* (NPSLE) to encompass all possible manifestations. Nineteen separate categories were created, classifying manifestations on the basis of pathological location, but inclusion of some categories remains controversial. When

neurological symptoms arise, it is essential to consider differential diagnoses that may coexist. There is controversy because much of the healthy population exhibits at least 1 manifestation listed in the ACR definition for NPSLE. Ainiola et al. studied 46 SLE patients and 46 controls and found at least 1 NPSLE manifestation in 91% and 54% of patients, respectively, but after the exclusion of the most common manifestations (headache, anxiety, mild depression, mild cognitive impairment, and polyneuropathy without electrophysiological confirmation), the prevalence of NPSLE decreased to 54% and 7%, respectively.<sup>73</sup>

Headaches have been reported in >50% of SLE patients, often of the migraine or tension type, but a 2004 meta-analysis failed to confirm an association between SLE and headaches.<sup>74</sup> Seizures are reported by 7%–20% of patients and may be the result of direct antibody activity against neural elements.<sup>75</sup> Seizures secondary to SLE represent a diagnosis of exclusion and require full investigation for alternate causes.

Cerebrovascular disease is increased most significantly in those with aPL antibodies with an odds ratio between 2.3 and 6.7, although SLE patients without such antibodies are also at higher risk of stroke.<sup>75</sup> Psychosis, movement disorders, acute confusional states, and demyelinating disease are also reported. Transverse myelitis or a demyelinating process resembling multiple sclerosis can complicate SLE. SLE myelitis presents with spinal cord injury with paralysis, sensory deficits, and smooth muscle dysfunction. Additionally, several studies show higher rates of dysautonomia in SLE patients,<sup>76–78</sup> but the clinical significance remains unclear.

## Hematological

Hematological derangements in SLE are widely recognized, with lymphopenia being the most common, although anemia and thrombocytopenia are also seen. Anemia is found in about half of SLE patients with the most common cause being anemia of chronic disease; however, other causes include autoimmune hemolytic anemia, iron deficiency anemia, anemia of chronic renal failure and cyclophosphamide myelotoxicity. Autoimmune hemolytic anemia occurs in about 5%–10% of SLE patients, although positive Coombs' tests without actual hemolysis are found in a much higher proportion. Antierythrocyte antibodies are implicated in the pathogenesis of autoimmune hemolytic anemia, and there is also a strong correlation between aCL antibodies and Coombs' positive hemolytic anemia,<sup>79</sup> which may contribute to the pathogenesis of cytopenia rather than simply being induced as a result of cellular breakdown. This would explain combined anemia/thrombocytopenia better than specific antibodies to respective cell types. Most cases of anemia are mild, but severe cases with hemoglobin below 8.0 g/dL do occur, often coexisting with significant renal or CNS disease.<sup>80</sup>

Thrombocytopenia occurs either in isolation or as part of a broader hematological disturbance. The prevalence of autoimmune thrombocytopenia has been reported as 9.5% of SLE patients,<sup>81</sup> and its occurrence may precede the

diagnosis of SLE, with 3%–16% of idiopathic thrombocytopenic purpura patients eventually developing SLE.<sup>82</sup> Immunosuppression is the initial therapeutic option, but up to one fifth of patients do not respond and require splenectomy.<sup>80</sup>

### Gastrointestinal

The gastrointestinal (GI) and hepatobiliary systems are susceptible in their entirety to SLE-related complications. GI symptoms are very common and may result from SLE, treatment, or non-SLE etiologies, and differentiating the true cause of symptoms may herald a diagnostic nightmare for clinicians and delay institution of the appropriate intervention.

Oral ulcers are the only GI manifestation to be included in the ACR diagnostic guidelines for SLE, and occur in 7%–52% of patients.<sup>83</sup> They are mostly painless and appear unrelated to systemic disease activity. Sjogren's syndrome has a consistently reported prevalence of approximately 10%.<sup>84</sup>

Esophageal symptoms are commonly reported, with 1%–13% and 11%–50% of SLE patients experiencing dysphagia and heartburn, respectively.<sup>83</sup> Manometry studies have revealed a frequent prevalence of peristaltic dysfunction, particularly within the upper third of the esophagus, which may explain some symptoms. However, no studies have shown lower esophageal sphincter abnormalities, and it appears SLE patients are not at an increased risk of gastroesophageal reflux.<sup>85</sup> Gastric disease resulting from SLE is controversial. Peptic ulcer disease or gastric perforation may occur as a consequence of NSAID and corticosteroid usage, rather than directly from SLE itself.

Acute abdominal pain (AAP) is reported by up to 40% of SLE patients,<sup>83</sup> some of whom go on to present to hospital. Immunosuppressive drugs mask symptoms and signs, making accurate diagnosis difficult with resultant treatment delays. The treatment of most SLE-related causes of AAP is with high-dose corticosteroids or other immunosuppressive drugs, while non-SLE causes may require surgery. SLE causes of AAP include serositis, vasculitis, ischemic gut, pseudo-obstruction, pancreatitis, acalculous cholecystitis, and protein-losing enteropathy. Treatment-related causes include peptic ulcer disease, intra-abdominal sepsis, infective enteritis or colitis, and pancreatitis. Most recent studies attribute the majority of AAP to non-SLE related causes,<sup>86–88</sup> and of SLE causes, intestinal vasculitis is the main culprit.<sup>89,90</sup> In the study by Medina et al., patients with inactive SLE were more likely to have non-SLE causes of AAP, while those with active SLE and delays in surgical exploration had higher mortality.<sup>89</sup> Lee et al. did not find any correlation between SLE activity and SLE versus non-SLE causes.<sup>90</sup> Vegara-Fernandez et al. conducted the largest prospective study to date in SLE patients presenting with AAP. Of 73 patients, 55 (75%) underwent surgical procedures, the majority being for non-SLE pathologies. Overall morbidity was 57%, with the most common complications being intra-abdominal abscesses and pneumonia, and there were 8 perioperative deaths. In a multivariate analysis, mortality was associated with an Acute Physiology and Chronic Health Evaluation II score >12, but not with any index of disease activity or damage accrual.<sup>86</sup>

Hepatobiliary involvement in SLE is predominantly manifested as subclinical increases of liver function tests

(LFTs) and may be attributable to drug treatment, including herbal medicines.<sup>91</sup> Up to 60% of SLE patients have abnormal LFTs at some point in their illness, and of these approximately one fifth have no cause found except for the concomitant presence of SLE.<sup>92</sup> Autoimmune hepatitis is rarely associated with SLE, with a lifetime prevalence of 2%–5% among SLE patients and is treated with high-dose corticosteroids. Hepatic thromboembolic complications have also been reported.

Pancreatitis has an unclear association with SLE, and when it does occur, it appears to be more commonly of the idiopathic type and associated with disease activity.<sup>93</sup> In patients with SLE and pancreatitis, active lupus has been associated with increased mortality.<sup>94</sup>

### Musculoskeletal

Nonerosive arthritis is a hallmark of SLE, but other significant musculoskeletal complications are noteworthy. Osteoporosis is a major cause of morbidity and is probably related to a combination of treatment complications and disease mechanisms, and secondary behavior, such as reduced physical activity and sunlight avoidance, may also contribute. The prevalence of osteoporosis has been reported to be as high as 23%,<sup>95</sup> and 1 study reported a prevalence of fracture risk of 12.5%.<sup>96</sup> Interestingly, the relationship between corticosteroid usage and bone loss is not straightforward. Multiple studies have failed to show a relationship between corticosteroid usage and bone mineral density, whereas a stronger correlation is found with damage accrual scores, regardless of corticosteroid use. This supports the theory of disease-dependent loss of bone marrow density and that corticosteroid usage that suppresses SLE activity may be beneficial.<sup>97</sup>

Atlantoaxial subluxation has been reported in several case reports.<sup>98,99</sup> Babini et al. prospectively assessed 59 patients, and 5 (8.5%) were found to have anterior atlantoaxial subluxation in full flexion cervical radiographs.<sup>100</sup> Four of the 5 patients had neck pain, which was severe in only 1 person with concomitant paresthesia and hypoesthesia of the fingers. The patients with cervical subluxation had longer disease duration, chronic renal failure, and higher serum parathyroid levels. The issue of cervical spine instability has never been fully studied in any large studies and remains an area of concern for anesthesiologists.

### Infection

SLE patients suffer a higher rate of infections, which appears related to both an intrinsic susceptibility and treatment-related immunosuppression. Immunological dysfunction may be due to functional asplenia, impaired complement system, and mannose-binding lectin deficiency, a serum protein that binds mannose in the bacterial wall and activates the complement system,<sup>101</sup> although data are conflicting.<sup>102</sup>

The majority of infections are bacterial and primarily affect the skin, respiratory system, and urinary tract.<sup>103</sup> SLE patients who develop infections require significantly longer hospitalization, and long-term survival is dramatically impacted by a single episode of bacteremia.<sup>104</sup> Factors predictive of infection in SLE patients include active disease,

duration of disease, cytopenia, hypocomplementemia, renal involvement, CNS involvement, and immunosuppressive therapy.<sup>103</sup> Multiple factors may contribute to the innate infection susceptibility among these patients, including depressed production of interleukin-12,<sup>105</sup> reduced serum complement,<sup>106</sup> and antigranulocyte antibodies.<sup>107</sup>

Viral infections in SLE are more likely to mimic a lupus flare and are often diagnosed after failure to respond to SLE-targeted therapy.<sup>108</sup> Typical viral features of arthralgia, rash, fever, malaise, lymphadenopathy, and cytopenia are easily confused with lupus flares. Parvovirus B19 and cytomegalovirus are the most common viral infections, although many other viruses also cause morbidity. In those with SLE, parvovirus preferentially affects immunocompetent patients, whereas cytomegalovirus affects the immunosuppressed.<sup>103</sup>

### Cancer

A variety of cancer types are increased among SLE patients. Previous evidence had been suggestive but inconclusive, but the study by Bernatsky et al. in a cohort of >9500 patients provided clear evidence for the association between SLE and cancer risk.<sup>109</sup> The strongest association appears to be between non-Hodgkins lymphoma, with a standard incidence ratio of 3.64, but other studies have shown small increases in the risk of breast, lung, and cervical cancer.<sup>110</sup> The exact cause of the association between SLE and malignancy remains unknown but may be the result of genetic predisposition, drug exposure, or conventional risk factors.

### Antiphospholipid Antibodies and Antiphospholipid Syndrome

APS is classified as a primary disorder, or a secondary disorder if in the presence of an autoimmune process such as SLE. Diagnosis requires documented vascular thrombosis or recurrent adverse pregnancy outcomes with laboratory evidence of LAC or aCL IgG or IgM antibodies measured on 2 or more occasions at least 6 weeks apart. The frequency of aPL antibodies is higher among SLE patients than among the general population, and of those with aPL antibodies and SLE, there is a considerably higher incidence of thrombosis than is in SLE patients without aPL antibodies. Love and Santoro reviewed the literature and found a prevalence of 34% for LAC and 44% for aCL antibodies in SLE patients and that thromboembolic complications occurred in 53% of SLE patients with LAC versus 12% without LAC, while of those with aCL antibodies, 40% had thromboembolism in comparison with 18% of antibody-negative patients.<sup>111</sup> Additionally, evidence does suggest that LAC carries a significantly higher risk of thrombosis than do aCL antibodies.<sup>112</sup>

The presence of LAC can complicate the management of any SLE patient. Although LAC is prothrombotic, the clinician must be aware that it can falsely prolong activated partial thromboplastin time (aPTT), and conversely any increased aPTT result in a patient with SLE should prompt investigation for the presence of LAC. An elevated aPTT in SLE should be tested with a 1:1 mixture of patient and normal pooled plasma to correct for coagulation deficiencies, and if the result remains elevated, it is suggestive of

the presence of an inhibitor such as LAC, with further testing being directed by a hematologist. Standard dosing protocols for unfractionated heparin are unreliable in the presence of an elevated baseline aPTT resulting from LAC, and anti-Xa heparin activity assays may be required as an alternative.

SLE with aPL antibodies seems to carry an even higher risk of thrombosis than does primary APS.<sup>113</sup> Aung et al. compared lung perfusion scintigraphy in patients with SLE, SLE-APS, and APS alone and found that 43% of SLE-APS patients had uptake defects, whereas none of the patients in the other groups had similar defects.<sup>114</sup> The presence of aPL antibodies alone carries an increased thrombosis risk, with low IgG aCL antibody titers carrying a 1% per year risk of a thrombotic event, and high titers having a 6% per year risk, in contrast to the 0.1% risk per year in the general population.<sup>115</sup> The most common manifestation is venous thrombosis, especially of the deep veins of the legs. Arterial thrombosis is less common, and of these, half are within the brain; coronary occlusions account for about 25%, and the rest are spread throughout the main vascular beds of the body.<sup>116</sup> A subset of patients may experience catastrophic APS when thrombotic events affect 3 or more organ systems over a period of days or weeks. Precipitating factors include cessation of anticoagulant therapy, infection, surgery, or oral contraceptives, and mortality may be as high as 50%. Catastrophic APS appears to have a higher mortality in SLE patients than in primary APS patients.<sup>117,118</sup>

After venous thromboembolism, expert consensus recommends indefinite anticoagulation with standard intensity warfarin to a target internationalized ratio (INR) of 2 to 3, and patients with SLE and aPL antibodies but no thrombotic events are recommended low-dose aspirin.<sup>119</sup> Management of patients postarterial thromboembolic events is less clear, but high-intensity anticoagulation (INR 3.0 to 4.0) is recommended.<sup>120</sup> During pregnancy, heparin or low-molecular-weight heparin may be used.

## MANAGEMENT

### Pharmacotherapy

The mainstay of SLE treatment is based on symptomatic treatment of manifestations with NSAIDs, antimalarials, or aspirin, combined with the use of immunosuppressive drugs to achieve disease remission. Various regimens have been advocated for immunosuppression, depending on organ involvement, but most involve the use of corticosteroids, cyclophosphamide, azathioprine, methotrexate, and mycophenolate mofetil either as single drugs or in combination. Other specific drugs are used to manage end-organ damage, for example, in pulmonary hypertension, dyslipidemia, or accelerated CAD.

It is important to understand the toxicity profiles of these drugs and their implications on perioperative management (Table 3). It is difficult to ascertain whether manifestations are the result of SLE activity or of drug toxicity, but such differentiation combined with consultation with the patient's rheumatologist allows better management decisions.

Cardiotoxicity is a recognized complication of high-dose cyclophosphamide therapy, with acute decompensation and

**Table 3. Systemic Lupus Erythematosus (SLE) Pharmacotherapy and Significant Side Effects**

Drug	Indication	Anesthetic implications
Anti-malarials (hydroxychloroquine)	Cutaneous SLE Pleuritis/pericarditis Arthritis Reduced renal flares	Retinotoxicity Neuromyotoxicity Cardiotoxicity
Corticosteroids (prednisone, methylprednisone, topical preparations)	Cutaneous SLE Arthritis Nephritis Pleuritis/pericarditis Diffuse alveolar hemorrhage NPSLE Mesenteric vasculitis SLE pancreatitis	Hyperglycemia Hypercholesterolemia Hypertension Osteoporosis
Aspirin/NSAIDs	Antiphospholipid syndrome SLE arthritis	Peptic ulceration Platelet inhibition Renal impairment Fluid retention/electrolyte disturbance Hepatic dysfunction Bronchospasm
Cyclophosphamide	Nephritis NPSLE	Myelosuppression Pseudocholinesterase inhibition Cardiotoxicity Leucopenia Hemorrhagic cystitis
Azathioprine	Arthritis	Myelosuppression Hepatotoxicity
Methotrexate	Arthritis Cutaneous SLE	Myelosuppression Hepatic fibrosis/cirrhosis Pulmonary infiltrates/fibrosis
Mycophenolate mofetil	Nephritis Hemolytic anemia, thrombocytopenia	GI upset Pancytopenia

NPSLE = neuropsychiatric SLE; NSAID = nonsteroidal anti-inflammatory drugs; GI = gastrointestinal.

reversible declines in systolic function being reported,<sup>121,122</sup> although rare cases are also documented with hydroxychloroquine.<sup>123</sup> In the case of hydroxychloroquine, cardiac dysfunction may be due to myotoxicity consistent with a broader neuromyotoxicity noted in case reports in which the predominant finding is a proximal myopathy with or without peripheral neuropathy or cardiomyopathy.<sup>124</sup>

Azathioprine and methotrexate both have potential hepatotoxicity with derangement of LFTs, with methotrexate having a tendency to produce hepatic fibrosis and cirrhosis in severe cases. Methotrexate-induced pulmonary toxicity has also been documented; usually in the form of a drug-induced pneumonitis with pulmonary infiltrates.<sup>125,126</sup> Mycophenolate mofetil, a lymphocyte-selective immunosuppressant acting via inhibition of purine synthesis, is a newer drug increasingly being used in the treatment of lupus nephritis. It has a favorable toxicity profile in comparison with older drugs but, as with the majority of other treatment drugs, it has the potential to cause clinically significant myelosuppression.

Glucocorticoids have well-documented adverse effects. Consideration needs to be given to patients who may have hypothalamic–pituitary–adrenal axis suppression from prolonged glucocorticoid treatment. In these patients, abrupt cessation of glucocorticoids or the stress response associated with surgery could precipitate an Addisonian crisis. Additionally, glucocorticoids cause hyperglycemia, hypercholesterolemia, osteoporosis, and hypertension.

### Monitoring

Monitoring of SLE in clinical practice is based upon differentiating disease activity from organ damage accrual. A

variety of disease activity indices have been formulated, including the SLEDAI (Systemic Lupus Erythematosus Disease Activity Index), SLAM (Systemic Lupus Activity Measure), BILAG (British Isles Lupus Assessment Group), and the ECLAM (European Community Lupus Activity Measure). The BILAG index provides an index of activity based on 8 organ systems involved, whereas the others provide a more global index of activity. Assessment is based on patient responses to detailed questionnaires and the results of routine laboratory investigations. The SLICC/ACR (Systemic Lupus International Cooperating Clinics/American College Rheumatology) damage index records the cumulative damage in 12 organs or systems. Changes must have been present for at least 6 months to warrant inclusion.

Routine laboratory testing is recommended for monitoring of SLE patients. Full blood count, erythrocyte sedimentation rate, C-reactive protein, urea and creatinine, liver function tests, and urinalysis are all indicated. There is intense interest in identification of lupus biomarkers correlating with disease activity, although findings have been inconsistent. However, increasing anti-dsDNA titers may predict lupus flares, especially when coupled with decreasing complement levels.<sup>127,128</sup> Usually C3/C4 and anti-C1q are measured,<sup>129</sup> but testing for complement breakdown products, such as C3d or C4d, may be increasingly used in the future. Recent appreciation of the increased risk of CVD in these patients has resulted in more focus being placed on monitoring and treatment of modifiable risk factors such as hypertension and hypercholesterolemia.

**Table 4. Recommended Guidelines for the Perioperative Management of Systemic Lupus Erythematosus (SLE) Patients**

Management issue	Comment
<b>Preoperative</b>	
History	Review disease activity index, accrued organ damage, and drug history.
Examination	Thorough examination of cardiovascular, respiratory, and neurological systems, including testing for atlantoaxial subluxation symptoms and signs.
Full blood count	Test for anemia, thrombocytopenia, and leucopenia. Consider further testing for hemolysis if anemia is present.
Serum electrolytes, creatinine, urea	Any abnormality requires further investigation for lupus nephritis.
Liver function tests	Abnormalities should prompt review for autoimmune or drug hepatotoxicity.
Coagulation studies	Elevated aPTT requires investigation for the presence of lupus anticoagulant.
Anti-dsDNA, complement levels	May reflect lupus activity after comparison with previous baseline measurements.
Urinalysis	Proteinuria, red cells, white cells, and cellular casts may indicate clinically silent disease and prompt further investigation.
Electrocardiogram	Silent ischemia, myocarditis, pericarditis, and conduction abnormalities may be identified.
Chest radiograph	Pleural effusion, interstitial pneumonitis, pericardial effusion, or subglottic stenosis may be seen.
<b>Intraoperative</b>	
5-lead electrocardiography	Accelerated coronary artery disease, conduction abnormalities.
Intra-arterial blood pressure monitoring	Case dependent, consider in presence of myocarditis, conduction abnormalities, valvular abnormalities, or autonomic dysfunction. Special care to be taken in the presence of Raynaud's phenomenon.
Laryngeal mask airway if appropriate	Minimize airway manipulation due to risk of inflammation and postextubation airway edema.
Difficult airway precautions with immediate access to smaller-size endotracheal tubes	Vocal cord paralysis, subglottic stenosis, or laryngeal edema may make intubation difficult.
Standard antibiotic prophylaxis	Innate susceptibility to infection and immunosuppressive therapy predispose to infection risk.
Caution with muscle relaxants	Azathioprine and cyclophosphamide may interact with muscle relaxants.
Renal protective strategies	Maintain urine output, avoid hypoperfusion and hypotensive states, and use nephrotoxic drugs cautiously because of possibility of subclinical lupus nephritis.
Careful patient positioning	Predisposition to peripheral neuropathies and osteoporosis.
Antithrombotic prophylaxis	Institute mechanical and pharmacological measures early, especially in the presence of antiphospholipid antibodies. Patients with confirmed lupus anticoagulant and previous thromboembolic events warrant therapeutic anticoagulation in discussion with a hematologist. Sjogren's Syndrome may predispose to corneal abrasions despite adequate eye taping.
Eye protection and artificial tears/lubrication	
Temperature monitoring	Hypothermic states may induce vasospasm in patients with Raynaud's phenomenon.
Pain management	Consider side effects of systemic analgesics; regional techniques may be helpful if neuropathies, myelitis, and coagulopathies are excluded.
Corticosteroid cover	Adrenal suppression may have resulted from long-term corticosteroid therapy with the need for a "stress dose" perioperatively.
<b>Postoperative</b>	
Pain management	Regular review and input by a specialist pain service to minimize systemic side effects.
Antithrombotic prophylaxis	Early institution of mechanical and pharmacological prophylaxis dependent on surgical factors.

aPTT = activated partial thromboplastin time; dsDNA = double-stranded DNA.

**ANESTHETIC CONSIDERATIONS**

The impact of SLE on provision of anesthesia has never been investigated, and the lack of evidence combined with the heterogeneity of disease manifestations makes it difficult to establish definitive management protocols. Anesthesiologists require an understanding of potential manifestations of SLE and that these manifestations may be overt or subclinical (Table 4). The need to assess the patient for consequences of acute flares and accrual of organ damage is a priority. Preoperative consultation with the patient's rheumatologist will provide accurate information on disease flares, organ damage, and drug history. Although the study by Vegara-Fernandez failed to show a link between disease activity or damage accrual and mortality,<sup>86</sup> it would be prudent to delay nonurgent surgery until after recovery from disease flares. Obstetric and cardiac anesthesia, especially in those with aPL antibodies or APS, requires multidisciplinary management at a specialist center, and an increasing body of literature has documented safe anesthesia in this high-risk group.<sup>130</sup>

Preoperative assessment should particularly address the need for perioperative continuation of immunosuppressants and steroid replacement. A thorough physical examination should be conducted and may reveal cardiac valvular abnormalities, pericarditis, pleural effusions, interstitial lung disease, or peripheral neuropathies. Unexpected cardiac murmurs or findings consistent with endocarditis should prompt referral for preoperative transesophageal echocardiography. Laboratory testing is indicated in all patients, with antibody or complement levels being useful if reviewed in the context of previous values and their relation to disease activity. Ascertaining the presence of aPL antibodies is warranted to identify whether there is an increased risk of thrombosis, and thromboprophylaxis is indicated especially in procedures with a significant risk of thrombotic complications, such as orthopedic or vascular surgery.<sup>131</sup> A baseline 12-lead electrocardiogram is indicated, given the increased risk of myocardial ischemia.

Perioperative management must be tailored to the individual patient. Appropriate monitoring should include a

5-lead electrocardiogram because unexpected intraoperative myocardial ischemia in SLE patients has been reported.<sup>132</sup> A low threshold for the insertion of an arterial catheter is warranted in major cases, given the increased cardiac risk in this population. Choice of anesthetic technique should account for the potential drug interactions with immunosuppressants, an unexpected difficult airway with subglottic stenosis or laryngeal edema, unrecognized myocardial ischemia, and thrombotic risk. If the patient is anticoagulated, regional techniques may be contraindicated, and reintroduction of anticoagulation postoperatively is a priority. Attention to infection risk is warranted with appropriate antibiotic prophylaxis, as is careful intraoperative positioning to prevent fractures of osteoporotic bones and peripheral nerve compression. Strategies for renal protection are advisable even in the absence of overt kidney impairment.

Pharmacological interactions between anesthetic drugs and immunosuppressant drugs should warrant consideration. Azathioprine, an antimetabolite immunosuppressor, may interact with muscle relaxants, and dose increases of 37% with atracurium, 20% with vecuronium, and 45% with pancuronium were required in one study.<sup>133</sup> In the case of pancuronium and vecuronium, the increases were offset in the presence of renal insufficiency. Cyclophosphamide acts as a pseudocholinesterase inhibitor, and this may explain the risk of prolonged apnea after succinylcholine use.<sup>134</sup> Coadministration of NSAIDs with methotrexate has known deleterious effects, with several case reports describing acute renal failure and pancytopenia; additionally, administration in proximity to nitrous oxide exposure may precipitate bone marrow suppression.<sup>135</sup>

## SUMMARY

SLE is a multisystem autoimmune disorder with a complex pattern of disease manifestations and damage accrual. Prognosis has steadily improved, with longer survival resulting in more patients presenting for surgery; this results in a need for anesthesiologists to understand the potential complications that they may encounter when caring for a SLE patient. Given the heterogeneity of this disease and its ability to affect any organ in the body, anesthetic and perioperative management remains dependent on clinical acumen and understanding of the medical issues at play in these patients. ■■

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