

# A Framework to Overcome Challenges in the Management of Infections in Patients with Systemic Lupus Erythematosus

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**Abstract:** Infections remain one of the leading causes of death in systemic lupus erythematosus (SLE), despite awareness of factors contributing to increased susceptibility to infectious diseases in SLE. Clinicians report challenges and barriers when encountering infection in SLE as certain infections may mimic a lupus flare. There are no evidence-based practice guidelines in the management of fever in SLE, with suboptimal implementations of evidence-based benefits related to infectious disease control and/or prevention strategies in SLE. Vigilance in identifying an opportunistic infection must be stressed when confronted by a diagnostic challenge during a presentation with a febrile illness in SLE. A balanced approach must focus on management of infections in SLE, and reduction in the glucocorticoids dose, given the need to control lupus disease activity to avoid lupus related organ damage and mortality. Clinical judgement and application of biomarkers of lupus flares could reduce false positives and overdiagnosis and improve differentiation of infections from lupus flares. Further precision-based risk and screening measures must identify individuals who would benefit most from low dose immunosuppressive therapy, targeted immune therapy, and vaccination programs.

**Keywords:** systemic lupus erythematosus, infections, challenges, management, lupus flares

## Plain Language Summary

Patients with systemic lupus erythematosus (SLE) are at considerable risk of serious infections. Clinical providers report an ongoing challenge during an encounter with a febrile illness in SLE patients, by way of the varied types of infections mimicking lupus disease flare. Misdiagnosis of an infection for lupus flare will lead to complications and death if not treated. Lupus patients must seek medical attention when a febrile illness occurs. Providers should initiate prompt antibiotic treatment and reduce the dose of steroids during a febrile illness in SLE. In addition, providers should apply infectious disease controls and vaccine preventive measures during low disease activity state to prevent life-threatening conditions and death.

## Introduction

Infectious diseases and their causative agents pose considerable challenges for the management of patients with systemic lupus erythematosus (SLE).<sup>1,2</sup> Despite awareness of factors contributing to increased susceptibility to infections in SLE, and having the knowledge of vaccinations and pre-exposure prophylaxis, infections remain one of the leading causes of death in SLE across all times.<sup>3,4</sup>

The poor clinical outcome of infection in SLE reflects the complex interplay of infectious pathogens and the highly dysregulated nature of the immune system in SLE. Infections are at times coupled with lupus disease activity states where glucocorticoids and cytotoxic immune suppressive therapy may trigger infections. The major burden is that there are no evidence-based practice guidelines in the management of fever, or evidence-based benefits related to implementation of infectious disease controls and/or prevention strategies in SLE. In addition, the lack of specific

biomarkers of lupus flare or lupus related infections and the near absence of clear principles on the use of preventive measures with their insufficient evidence are barriers implied in the poor outcome.

To reduce the risk of infections in SLE and their complications, providers should apply strategies of glucocorticoids dose reduction and judicious use of immunosuppressive and targeted biological therapies with treatment to target approaches.<sup>5</sup> Novel therapeutics in SLE, though safer and efficacious in controlling disease activity and in achieving disease remission, must also prevent infections, damage accrual and death.

Importantly, providers should apply diverse therapeutic strategies including general hygienic methods, vaccinations, recognition of latent and opportunistic infections and antibiotic prophylaxis.<sup>6,7</sup> However, implementation of these measures and their use in clinical practice is inconsistent and rarely applied.<sup>8,9</sup>

In this manuscript we analyzed the burden, the types of infection, the factors related to higher risk of infection, and highlight certain tools used in predicting infection in SLE. We propose a framework to overcome challenges in the management of infections in SLE patients and explore opportunities that can benefit the therapeutic and preventive plan of care.

## Methods and Materials

We performed a semi-structured systematic review of the literature of adults (age  $\geq 18$  years) with infections in SLE between January 1985 and June 2022, using search words such as, “systemic lupus erythematosus”, “infection”, “viral syndrome”, “bacterial infections”, “fungal”, “opportunistic infections”, “parasites”, and “prevention” were reported. Sources of literature from which full-length clinical studies in humans were extracted were published in Medline, PubMed Clinical Queries and Embase, Cochrane library, and the database from CINHALL.

## The Burden of Infections in SLE

Mortality and hospitalization rates related to infections in SLE have increased dramatically over the past decade compared to the general population.<sup>6</sup> Researchers suggest a change in the trend and the pattern in SLE mortality where infection is the biggest reason for mortality compared to lupus related disease activity, lupus nephritis or cardiovascular diseases.<sup>10</sup> Similar observations have appeared in not just the United States, but in Japan, South Korea, Canada, China, Hong Kong, Malaysia, Jamaica, Columbia, Mexico, Chile, Brazil, United Kingdom, Spain, Denmark, France, and Sweden. The impact of infection in SLE is even more pronounced in developing countries.<sup>2,11</sup>

Infections account for 20% to 55% of all deaths in SLE patients and are the leading cause of deaths within the first year after the diagnosis of SLE.<sup>12</sup> Bacterial infections contribute to a higher relative risk of hospitalization which could be serious requiring high level care. Pulmonary infections and septicemia had the largest positive effect on increased mortality in SLE.<sup>13</sup>

## Types of Infections in SLE

### Bacterial Infections

Around 60% to 75% of all reported infections in SLE are common bacterial infections.<sup>14</sup> The systems of respiratory, urinary tract, skin and soft tissue are the most common sites of infection in SLE. Respiratory tract infections are common in hospitalized patients, whereas urinary system, skin and soft tissue infections are more frequent in the outpatient setting.<sup>15</sup>

*Escherichia coli* causing urine tract infections and streptococcal pneumonia causing bronchopneumonia, bacteremia, and sepsis represent the most frequent pathogens.<sup>16,17</sup> Streptococcal infections are severe in SLE related to reduction in opsonization with complement factor 3b/inactive C3b (C3b/iC3b) as compared to other rheumatic syndromes and the healthy population.<sup>18</sup>

*Staphylococcus aureus* causes skin and soft tissue infections, bone and joint infections, as well as bacteremia. *Klebsiella* and *Pseudomonas* species may cause urine tract infections related bacteremia in SLE that are associated with shortened survival rate.<sup>19</sup>

*Salmonella enterica* infections are more frequent among SLE subjects as compared to the general population causing a spectrum of syndromes including gall bladder infection and bacteremia.<sup>20</sup> Atypical presentations of *Salmonella* species infections in SLE patients include osteomyelitis of long bones, septic arthritis, soft tissue abscess, meningitis, typhoid

fever, and sepsis syndrome. Risk factors for salmonella infection in SLE are associated with splenic dysfunction and opsonization defects as well as high disease activity and use of immune suppressive therapy.<sup>21</sup>

### Mycobacterial Infections

Various mycobacterial species infections are common in SLE and may disseminate leading to serious and lethal disease.<sup>22</sup> The prevalence of *Mycobacteria tuberculosis* ranges from 5% to 30% depending on the specific geographic region which is higher in SLE subjects than the general population.<sup>23</sup> Clinical presentations of mycobacteria may mimic lupus clinical syndrome, with features that involve severe extrapulmonary disease, extensive pulmonary syndromes, and high relapse rates.<sup>24</sup> non-tuberculosis mycobacterial infections cause skin and soft tissue infections with skin nodules and skin abscesses. Higher cumulative doses of glucocorticoids and renal disease are associated with increased risk of mycobacterial species in SLE.<sup>25</sup>

### Viral Infections

Herpes zoster (HZ) represents the most common viral infection in SLE patients, followed by cytomegalovirus (CMV) and human papilloma virus (HPV).<sup>26,27</sup> Other viruses with high frequency in SLE include, parvovirus B19, hepatitis B and C, influenza, and SARS-COV-2.<sup>28,29</sup>

HZ infections occur at the age of 30 to 40 years in SLE with higher prevalence in the Asian population than in the US population.<sup>30</sup> Risk factors include increasing age, lymphopenia, major organ disease, multi morbidities, glomerulonephritis, high dose glucocorticoids and non-glucocorticoid therapy such as mycophenolate mofetil and cyclophosphamide.<sup>31</sup> HZ infection and reactivation occurring even during a low disease activity state is associated with serious morbidity, inferior quality of life and death. The use of high-dose glucocorticoids is associated with bacterial superinfection.

CMV infection in SLE may present as gastrointestinal bleed, colitis, hepatitis, retinitis, or encephalitis, with a high incidence of pneumonitis.<sup>32</sup> High dose of glucocorticoids, cyclophosphamide, plasma exchange, pancytopenia and concurrent infections have been associated with serious CMV clinical syndrome. High CMV viral loads are associated with the development of CMV infection in patients with SLE.<sup>33</sup>

The rate of cervical HPV infections is higher in SLE patients than in the general population, with an increased risk for high grade squamous interepithelial lesions.<sup>34</sup> This may be due to delayed clearance of infections or greater reactivation of latent infections, in addition to higher rates of HPV coinfection. The association between immunosuppressive medications and risk of HPV infection needs additional evaluation.

A higher proportion of hepatitis C infection is frequent in patients with SLE compared to healthy controls.<sup>35</sup> However, there appears to be a lower risk of hepatitis B infection in patients with SLE (possible protective role of overexpressed cytokines in these patients). Nonetheless, the risk of reactivation of hepatitis B virus is higher in SLE patients receiving a daily steroid dose of >10 mg/day and patients over the age of 40. Rituximab, to treat SLE, is associated with a higher risk of reactivation of hepatitis B and patients should be screened prior to therapy.

Parvovirus B19 and SLE share certain similarities in terms of presentation, including fevers, malaise, lymphadenopathy, anemia, and rash.<sup>36</sup> This viral infection is also able to induce the production of autoantibodies specific to SLE, like anti-dsDNA and soluble nuclear antigens. It has been proposed that parvovirus B19 can induce pathogenic autoimmunity through a variety of mechanisms, including molecular mimicry.<sup>37</sup> However, it is difficult to estimate the prevalence of this parvovirus infection in SLE patients as immune therapy inhibits immunoglobulin (IgM and IgG) seroconversion.

The COVID-19 Global Rheumatology Alliance and OpenSAFELY databases provide data that suggest that patients with SLE are at a higher risk of severe disease, hospitalization and death from COVID-19 compared to the general population.<sup>38</sup> The risk is highest in patients on prednisone dose >10 mg/day, and those on rituximab, as compared to those patients maintained on belimumab, hydroxychloroquine, azathioprine, methotrexate, or mycophenolate mofetil.<sup>39</sup>

### Opportunistic Infections

Opportunistic infections like *Listeria monocytogenes*, *Nocardia* species, *Aspergillus fumigatus*, and others may present as neurologic syndromes that mimic neuropsychiatric lupus and behave more aggressively to cause severe disease leading to death.<sup>40</sup> *Cryptococcus neoformans* presents in SLE as meningitis, meningoencephalitis, lung nodules and pneumonia/bronchiolitis driven by long term use of glucocorticoids and cytotoxic drugs and is associated with higher mortality rates.<sup>41</sup>

*Candida albicans* is a usual form of candidemia in SLE and usually involves the gastrointestinal and genitourinary system and may become invasive at times.<sup>42</sup>

## Why are Lupus Patients at Substantial Risk for Infections?

### Aberrant Immune Functions in SLE

The aberrant immune response in SLE, low serum complement levels, functional asplenia, and abnormal host response of neutrophils and macrophages to pathogens have contributed to the rise in infectious rates in SLE (Table 1). The impaired inflammatory response with decreased chemotaxis, membrane recognition and attachment to microorganisms, phagocytosis, oxidative metabolism could also predispose to infection.

Lymphopenia and neutropenia are common hematologic manifestations in SLE and can have poor clinical outcomes with predisposition to infection given decreased T-cell activity and dysfunctional macrophages and monocyte systems.<sup>43</sup> Prior studies have shown that a decrease in phagocytic function and the impaired handling of immune complexes due to the presence of autoantibodies against Fc gamma receptors (FcγR) which belong to the tumor necrosis factor (TNF) alpha superfamily contribute to the risk of infections.<sup>44</sup>

Complement dysfunction is frequent in SLE, reflected by inherited complement deficiency, and hypocomplementemia during SLE disease activity. SLE patients with complement dysfunctions show an increase in risk to capsulated organisms such as *Streptococcal pneumonia*, *Neisseria meningitis* and *Neisseria gonorrhoea*. Hypogammaglobulinemia encountered in SLE contributes to an increased risk of recurrent and severe bacterial infections, although polyclonal hypergammaglobulinemia is common in SLE. Whether immunoglobulin replacement therapy decreases the risk of infection in those patients requires further investigation.<sup>45</sup>

In addition, the risk of infection in SLE is higher in the presence of comorbidities and when using glucocorticoids, immunosuppressive and immune modulatory therapy. The incidence of kidney involvement, diabetes, and higher lupus damage index (SDI/SLE international collaborating clinic) scores were dramatically higher in SLE patients with an infection compared to SLE patients without an infection. In fact, the use of aggressive immunosuppressive therapy is a serious risk factor for the development of infections in SLE.<sup>46</sup>

### Impact of Immune Therapy and Risk of Infections

The use of immunosuppressive therapy will induce difficulty in mounting an immune response to viral and bacterial infections in SLE, including the exposure to immunosuppressive agents including high-dose glucocorticoids, alkylating agents such as cyclophosphamide, in addition to mycophenolate mofetil, azathioprine, cyclosporin, and hydroxychloroquine.<sup>4,6</sup>

Importantly, glucocorticoid use is a significant risk factor for serious infections requiring hospitalization. Indeed, the risk for infection in SLE patients is a 10-fold increase in patients at a prednisone dose over 20 mg daily. Thus, the emphasis on keeping the prednisone dose below 7.5 mg daily or the use of pulses of intravenous methylprednisolone to control disease activity.<sup>47</sup>

Intravenous cyclophosphamide use has been associated with an increased risk in infection in particular HZ infections as described in SLE population studies, whereas the infection rates are similar among users of azathioprine, mycophenolate, and methotrexate.<sup>46,48</sup> Further, mycophenolate use is associated with a lower risk of infection in non-Asian

**Table 1** Risk Factors for Infection in SLE

Sociodemographic	Young age at onset of SLE The first 5 years of SLE diagnosis Ethnicity- minority race/ Black and Native American
Lupus disease activity	High disease activity Lupus nephritis/ renal involvement
Laboratory studies	Low serum albumin Low serum complements Lymphopenia

patients with lupus nephritis as compared to cyclophosphamide. However poor clinical outcomes with related deaths appeared to be more frequently observed among the Asian population.

Mycophenolate is a protective against *Pneumocystis jirovecii* pneumonia and Coxsackie virus infections in transplant patients; however, this protective effect in SLE patients requires confirmation. Antimalarial agents are the major anchor medication in lupus and studies have supported fewer infection rates with their exposure.<sup>49</sup>

Effective and targeted biological therapy with their steroid-sparing effects, are becoming available, yet many had adverse events, including serious infections. Infections either mild or severe do not seem to be a major concern in patients treated with belimumab as indicated in the post marketing data. On the other hand, rituximab's (an anti-CD-20 monoclonal antibody) use has been associated with severe infections, including bronchopneumonia followed by sepsis, the frequent organisms involved during rituximab therapy include *S. pneumonia*, followed by *E. coli* and *S. aureus*. While severe infections are associated with rituximab exposure occurring within the first 6 months of treatment, these patients have been receiving high doses of glucocorticoids.<sup>50</sup>

Like immunosuppressive therapy, biological therapy in SLE is associated with infectious comparable incidence rates including opportunistic infections. However, Janus kinase targeted therapy has a slightly higher rate of herpes zoster infections, with a dose dependent pattern of infectious risk.<sup>51</sup>

## Infections May Trigger the Development of SLE

The SLE disease process is triggered by genetic, immunological, and environmental factors including the possible role of certain microbial agents (viral, bacterial, parasitic, or fungal). Through molecular mimicry, bacterial DNA can also stimulate autoreactive B cells leading to an autoimmune response.<sup>52</sup>

Viruses associated with SLE onset include, human endogenous retroviruses (HERV), Epstein-Barr virus (EBV), parvovirus B19, CMV and human immunodeficiency virus (HIV-1).<sup>53,54</sup>

The relationship between tuberculosis and SLE suggests an increased risk of SLE in patients exposed to tuberculosis based on molecular and epidemiologic data.<sup>22,55</sup>

Exposure to *Helicobacter pylori* has been linked to a lower risk of SLE or delay in its onset like the protective role of helminth infections in SLE, attributed to the activation of lymphocytes and secretion of interleukin 10. *Toxoplasma gondii* appears to protect against progression of SLE, while Leishmania infection may trigger polyclonal activation of B cells and activation of ribonucleoproteins. Controversy remains about the role of *Plasmodium falciparum* in reducing the risk of SLE onset.<sup>56</sup>

The onset of SLE is associated with exposure to certain vaccines including Bacillus Calmette- Guérin, and BNT162b2 mRNA, with varying degrees of severity from cutaneous lupus to lupus nephritis.<sup>57</sup> A recent systematic review meta-analysis study has emphasized the safety of HPV vaccination in SLE, given the low-level evidence of the temporal relationship between SLE development following the exposure of HPV vaccine.<sup>58,59</sup>

## Existing SLE May Undergo an Exacerbation Following an Infection

Multiple factors are known to cause SLE flares, including exposure to UV light, certain hormones, and drugs, but infections also worsen existing SLE, leading to poor outcomes.<sup>60</sup> Infections may trigger a worsening lupus disease process leading to a feedback loop that may reinforce autoimmunity. The exposure to influenza infection is associated with lupus flares leading to hospitalization within seven days of infection, regardless of patients' age, gender, underlying illnesses, or immunosuppressive therapies.<sup>61</sup>

Others have confirmed the association of infection and high disease activity in hospitalized lupus patients independent of prednisone dose, comorbid conditions, or disease duration.

A better understanding of the interactions between viral proteins, bacterial microbiome and lupus related nuclear autoantigens and the host immune system in SLE could help improve the therapeutic management of challenging SLE patients with infections. Thus, vigilance should be borne in mind when challenged by infection in SLE and use of clinical predictors of infection is then fundamental.

## Clinical Predictors of Infections in SLE

A major challenge in the care of SLE patients is how to differentiate between a clinical presentation of an infection from a lupus flare. Investigators have suggested certain laboratory biomarkers that are indicative of infections, yet these biomarkers remain nonspecific and at times misleading. Further atypical presentation of infectious clinical syndromes in SLE may vary with the array of symptoms that mimic a lupus flare, and individual infections may present concurrently during a lupus flare. A predictor marker must then have high specificity and sensitivity for determining whether the patient is presenting an infection or a lupus flare.<sup>62</sup>

Shaking chills, leukocytosis, and neutrophilia with normal dsDNA were associated with infection in SLE.<sup>63</sup> Yet leukopenia is common in severe sepsis, and pneumococcal pneumonia, and neutropenia in typhoid infections and brucellosis.

Certain clinical predictors of infections outlined below are applicable in clinical practice:

### Serum C-Reactive Protein (CRP)

C-reactive protein (CRP) is a key acute phase protein synthesized by the liver and secreted in response to interleukin-6 stimulation. CRP has also the ability to opsonize bacteria, activate the complement pathway, and bind FcR on phagocytes, facilitating elimination of pathogens.<sup>64</sup>

CRP has been an unreliable measure for lupus disease activity (except for serositis).<sup>65</sup>

Elevated CRP (in the absence of serositis) is higher in SLE patients with bacterial infections. The cut-off value of 19.2 mg/l has a sensitivity of 81.2% and a specificity of 73.9% during an infectious event.<sup>66</sup> However, limitations remain for the application of CRP in the diagnosis of bacterial infections in SLE and other rheumatic diseases.

### Elevated Procalcitonin (PCT)

Procalcitonin (PCT) a protein consisting of 116 amino acids and the precursor of calcitonin, has a better diagnostic performance than CRP in differentiating bacterial infections from lupus flares. However, the diagnostic value of PCT and CRP in the identification of bacterial infection in SLE remains unsettled.<sup>67,68</sup>

### Mannose Binding Lectin (MBL)

Mannose binding lectin (MBL) is a protein produced by the liver that activates the complement system by an associated protease, the MBL-associated serine protease. MBL polymorphisms have been associated with SLE development in multiple populations and high MBL levels are predictive of disease activity especially lupus nephritis.<sup>69</sup>

### CD64

CD64 is a receptor observed on monocytes, macrophages and on neutrophils (nCD64). Peripheral nCD74 index combined with elevated CRP improves the ability to predict bacterial infections.<sup>70</sup>

### High Mobility Group Box Chromosomal Protein 1 (HMGB1)

High mobility group box chromosomal protein 1 (HMGB1) is a nuclear non-histone protein and a damage associated molecular pattern protein.<sup>71</sup> Their levels are notably higher in SLE patients, especially those with renal involvement. However, their levels are elevated after onset of sepsis and septic shock.

### 2'5'-Oligoadenylate Synthetase (OAS)

2'5'-oligoadenylate synthetase (OAS) is an enzyme activated by Type I IFN which leads to the degradation of RNA and is important for the protection from viral infections.<sup>72</sup> High OASL expression levels negatively correlate with the presence of certain infections and may provide useful information in differentiating disease lupus flare.

### Soluble Triggering Receptor Expressed on Myeloid Cells Type 1 (sTREM-1)

The receptor TREM-1 expressed on the surface of mature neutrophils and monocytes in response to bacterial and fungal infections lead to a higher level of the soluble form (sTREM-1) in lupus patients with flares and in those with infections, compared to quiescent disease or the general population.<sup>73</sup>



## CD27

CD27 protein is a TNF receptor expressed on T- and B-lymphocytes where high expression of CD27 corresponds with high disease activity.<sup>74</sup>

## Delta Neutrophil Index (DNI)

Delta neutrophil index (DNI) is a measure of immature granulocytes and is determined by subtracting the number of mature polymorphonuclear leucocytes from myeloperoxidase reactive cells. When compared to CRP, a high DNI correlates better with sepsis and aids in early diagnosis.<sup>7</sup>

## Cerebrospinal Fluid (CSF) Biomarkers

Patients with neuropsychiatric lupus have elevated levels of interleukin-6 (IL-6), prostaglandin E2 (PGE2) and immunoglobulin G (IgG) in their cerebrospinal fluid (CSF).<sup>75,76</sup> However, in central nervous system (CNS) infections, there are elevated levels of IL-6 and PGE2 but not significantly elevated CSF or IgG.

## Sepsis Scores in SLE

The high mortality of SLE patients with sepsis in the intensive care units (ICU) used sepsis scores as good predictors of mortality. These include, Simplified Acute Physiology Score II (SAPS II), Sequential Organ Failure Assessment (SOFA) and Acute Physiology and Chronic Health Evaluation II (APACHE II).<sup>77</sup>

Despite the discovery of new biomarkers to verify the infections in SLE, none of these biomarkers alone confirm or exclude an infection. A mixture of these tests may be more accurate in predicting the diagnosis and monitoring of infections in SLE patients.<sup>78</sup>

Nonetheless, these biomarkers require further reliability and validity studies in different SLE populations and long-term data in SLE patients with distinct types of infections. An optimal biomarker or combination of biomarkers of infections or lupus flares should be accurate and reproducible and should enhance the approach to early diagnosis, effective treatment, and improved clinical outcome.

## Proposed Steps to Take When Challenged with Infection in SLE

Assessment of SLE patients remains crucial when confronted by a major diagnostic challenge of having a presentation with a febrile illness. The need to control lupus disease activity that requires suppression of the immune system to avoid lupus related organ damage and death complicates the care of lupus patients. Yet, crucial, and appropriate evaluation of infectious etiology and prompt initiation of antibiotics will evade serious life-threatening complications.

Proposed steps to adopt when challenged by an infection in SLE are outlined and depicted in [Table 2](#).

Fever in SLE is infectious until proven otherwise. While the prevalence of fever in SLE has declined over the past decades related to the intake of non-steroidal anti-inflammatory drugs, glucocorticoids and broad-spectrum antibiotics, the source of fever must be identified. Thus, vigilance warrants efforts in identifying a latent or an opportunistic infection in febrile patients with SLE.

Initial assessment should focus on risk indices based on age, multi-morbidities, use of glucocorticoids, cytotoxic immune suppressive and immune modulatory therapy. High-risk lupus patients require hospitalization. It is vital to deal with evolving sepsis and its complications in the setting of quantitative or qualitative neutropenia be it related to SLE or a complication of cytotoxic immunosuppressive therapy or immune modulatory treatment.

Frameworks in the diagnostic work up of fever emphasize ongoing evaluations guided by cultures and clinical data including awareness of antimicrobial resistant infections. Applying the abovementioned clinical predictors of infection including CRP, procalcitonin and others is helpful. Molecular diagnostic assays may be useful if available including those combined with <sup>18</sup>F-fluorodeoxyglucose positron-emission tomography and computed tomography (FDG PET-CT) and next-generation sequencing. Nevertheless, the diagnostic yield of these tools in autoimmune disorders remains limited.<sup>79</sup>

On the other hand, fever, in systemic autoimmune disorders like SLE is linked to adaptive immunity driven by interferon response during the lupus disease activity state and must be suspected when having negative infectious work-ups or

**Table 2** Proposed Strategies to Manage an Infectious Challenge in Systemic Lupus (SLE)

Management of infection guidance	Increase awareness that fever in SLE is infectious until proven otherwise, where diagnostic tools must be applied to confirm infection diagnosis. Initiate antibiotic therapy promptly and reduce time to antibiotic therapy administration when an infection is suspected. Determine SLE disease activity and avoid overdiagnosis of lupus disease flare. Reduce exposure to glucocorticoids, cytotoxic immunosuppressive and immune suppressive therapy during concurrent antibiotics use. Continue hydroxychloroquine with its safety profile in all SLE patients without convincing contraindications and improve strategies to advance adherence.
Deliver person-centered and coordinated care	Apply multi-disciplinary approaches among rheumatologists, primary care providers, infectious disease experts, and other specialty teams caring for SLE patients to optimize screening (hepatitis, tuberculosis, etc), diagnostic practices, and management of infections in SLE.
Guidance for elective surgery	Perform elective procedures during inactive disease state. Balance the benefit of low-dose glucocorticoids with the potential risk of infection.
Improve patient safety through open and clear communication	Communicate with SLE patients clearly about the crucial role of hygiene, high risk exposure to infection and knowledge of febrile illness characteristics and signs and symptoms of infection.
Reduce the risk of contracting infections	Boost patient confidence in immunization to increase vaccination coverage rates and prevent leading infections in SLE that are vaccine preventable Review vaccination status at every healthcare encounter given vaccinations are substantially under-utilized in SLE.
Personalized patient education and engagement	Discuss treatment goals and preventive strategies related to SLE with patients, caregivers, and care partners at all times of the decision-making process.

microbiological control of infections.<sup>80</sup> It is imperative to determine disease activity in febrile illnesses in SLE and avoid possible overdiagnosis of lupus disease flare.

There are few examples of overdiagnosis of SLE and lupus flares, but it is important to approach those patients with the understanding of the risk of treatment with immune suppressive therapy and the risk of undertreatment.<sup>81</sup>

The diagnosis of SLE and lupus flare should be based on diagnostic criteria that include patients with mild disease activity. SLE disease activity must be determined clinically employing clinical questionnaires including SLE disease activity index (SLEDAI), British Isles Lupus Assessment Group disease activity index (BILAG-2004), Systemic Lupus Activity Measure (SLAM), the Systemic Lupus Activity Index (SLAI), European Consensus Lupus Activity Measurements index (ECLAM) and the Systemic Lupus Activity Questionnaire (SLAQ) for Population Studies.<sup>82</sup>

Clinical features like the presence of scleritis, cytooid bodies on eye examination, lupus dermatitis, splinter hemorrhages, cutaneous vasculitis or livedo pattern, friction rub of pericarditis and leg edema suggesting myocarditis, and pulmonary hypertension or renal disease of glomerulonephritis are clues to advocate for lupus disease activity.

Biomarkers like anti-dsDNA antibodies, complement C3 and complement C4, cardiolipin antibodies, ESR, CRP, anti-C1q antibodies, and activity on urinary sediment, added to clinical disease activity scales will help in favor of increased immune therapy treatment. However, these biomarkers are often nonspecific and lack the precision to differentiate disease activity from infection. At times serological activity may persist and not reflect adequate treatment response, though biomarker levels may decrease with immune suppression. Nonetheless, the quest for new and reliable biomarkers of lupus disease activity remains a challenge.

Determining lupus disease activity remains complicated as certain organs may respond to treatment while others get worse within the same patient. Serum cytokines, soluble cytokine receptors, markers of endothelial activation, cell markers in plasma cells, among others are informative, yet the interpretation of these markers may require long-term data at a larger scale. To be safe, caution is encouraged with careful use of immune therapy and a balanced approach to control lupus disease activity during infection events.



Reducing immune therapy during antibiotics use, in conjunction with glucocorticoid reduction plans are the primary goal for SLE treatment during an infectious event. Indeed, novel therapeutic trials have examined serious infection and hospitalization related to infection and death. In the systematic review of clinical trials in the treatment of lupus nephritis, high dose of glucocorticoids therapy was associated with increased rate of infections compared to cytotoxic and immune modulatory therapy.<sup>6,83</sup>

The use of safer immune therapy with lower infectious adverse events such as intravenous immunoglobulin must be prudent given the importance of controlling disease activity. The use of hydroxychloroquine (HCQ) must be universal in lupus patients without compelling contraindications given its association with a decrease in the incidence of infections.

Infection control strategies and prevention of infection guidelines are crucial in SLE patients receiving prednisone higher than 20 mg daily. The rheumatology and infectious disease societies' clinical practice guideline recommendations emphasize the administration of preventive vaccines during low disease activity state and prior to the initiation of cytotoxic immunosuppressive and immune modulatory therapy. Yet, preventive vaccinations are under-utilized in SLE, and improved coverage is crucial. While the importance of preventive vaccinations must be a priority, clear communication, and education of SLE patients about hygiene, substantial risk exposure to infection and awareness of febrile illness characteristics and signs and symptoms of infection are nonetheless critical for preventive approaches.

Despite the safety and efficacy of immunization against common pathogens, controversies remain regarding concerns of inadequate immune response to vaccination in SLE patients. The fear of immunization lingers with matters of de novo development of autoimmune disorder, perceived risk of autoimmune reactions and adjuvant related autoimmune syndrome, exacerbation of lupus flare triggered by the administration of vaccines.<sup>84</sup> Educating physicians and skilled counseling of patients about the importance of immunization against pathogens in SLE will improve attitudes towards combating vaccines hesitancy.

While mortality-related infection is a major concern, most SLE patients survive their infections thanks to infection control policies and successful control strategies. Nonetheless, the spread of infectious diseases remains unpredictable, and the emergence of antibiotic-resistance and troubling new viruses are on the rise. Anticipation and measurements of risk factors involved in infectious diseases can be useful to control the exposure of infections in SLE.

The frontier infectious control measures observed during the COVID-19 pandemic have promoted high quality infectious control measures across autoimmune disorders.<sup>29,85</sup> The timing of elective procedures vital to patient's health must be during inactive lupus disease phases and while using low doses of glucocorticoids. To achieve high quality results, multi-disciplinary approaches among rheumatologists and infectious disease teams must optimize screening (hepatitis, tuberculosis, etc), diagnostic practices, and management of infections in lupus. Discussions with patients, caregivers, and care partners about treatment goals are fundamental.

## Discussion and Conclusion

Over the last few years, substantial progress has been made with the understanding of lupus pathogenic mechanisms and novel treatment strategies in terms of control of disease activity, and prevention of damage. Yet, infection in SLE is still a major burden globally and in the United States.

Clearly SLE patients are at a substantial risk for infections given the nature of the disease and its related immune dysregulation, but most importantly the use of glucocorticoids, cytotoxic immunosuppressive and immune modulatory therapy. Providers caring for lupus patients must address the challenging task of differentiating infections from lupus flares. Fever in SLE is infectious in origin until proven otherwise, even though fever is an element in the classification criteria for SLE diagnosis.

We propose a framework to overcome challenges in the management of concurrent infections in SLE. Certain biomarkers are recognized to help distinguish infections from flares, including CRP and procalcitonin, but remain insufficient to confirm the diagnosis of infections. Clinical judgement with the use of simple scoring systems that predict infections or lupus disease activity remain useful in the decision-making of clinical care. Avoiding overdiagnosis of lupus flare and lowering the glucocorticoids dose might represent a better approach for dealing with fever in SLE. Nonetheless, research gaps remain.

Robust efforts must identify causal risk factors for infection among SLE patients including patients with low disease activity as well as high disease activity and identify effective screening programs for infections in SLE. Data from novel immune therapies in SLE about risk of infections during clinical trials remain scanty as interruption of biological therapy could be related to toxicity and not to infections. Tight control of disease activity and reduction of glucocorticoid doses must be target goals of low disease activity and clinical remission and aim at tapering or discontinuation of high-risk medications. Prophylactic therapy and screening for salient infections in SLE is a priority prior to the use of biological and immunosuppressive therapy.

From a prevention standpoint, additional research to identify potential agents can reduce infectious risk especially among non-steroid using patients. Precision-based risk and drug screening platforms for lupus patients should classify individuals who would benefit most from entering an infection screening and vaccination program. Further research on the feasibility and efficacy of providing vaccination programs in SLE is valuable.

Advancements in discovery of biomarkers of lupus flares could reduce false positives and overdiagnosis and improve differentiation of infections from lupus flares. Biomarkers that are highly predictive of negative responses to targeted immune therapies are a significant unmet clinical need. This is particularly relevant in the subsets of patients that may experience treatment resistance requiring aggressive and multiple immune suppressive therapies which can encourage exposure to infections and associated infection-related complications. Personalized treatment plans which minimize the risk of infections and ensure the safety of SLE patients must address survival rates, prevention of hospitalization, economic benefits, and enhancement of quality of life.

## Disclosure

The authors report no conflicts of interest in this work.

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