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Infection and Lupus: Which Causes Which?

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Abstract Infection is a leading cause of morbidity and mortality among patients with systemic lupus erythematous (SLE). Dysfunction of the innate and adaptive immune systems increases the risk of infection in patients with SLE. Infectious agents have also been theorized to play a role in the pathogenesis of SLE. This article summarizes our current knowledge of the infectious risk SLE patients face as a result of their underlying disease including abnormal phagocytes and T cells as well as the increased risk of infection associated with immunosuppressive agents used to treat disease. Pathogens thought to play a role in the pathogenesis of disease including EBV, CMV, human endogenous retroviruses (HERVs), and tuberculosis will also be reviewed, as well as the pathologic potential of microbial amyloids and the microbiome.

Keywords Systemic lupus erythematosus · Infection · Immunosuppression · Microbiome

This article is part of the Topical Collection on *Systemic Lupus Erythematosus*

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Introduction

Systemic lupus erythematosus (SLE) is an autoimmune disorder affecting virtually every organ system in the body that has a vast array of clinical manifestations. Infections are a major cause of mortality and morbidity in this patient population [1], and around 50 % of all SLE patients are hospitalized with infections during the course of their disease [2]. Complex interplay between the immune system, hormones, and environmental factors coupled with genetic susceptibility and epigenetic modifications are thought to be the factors responsible for pathogenesis of SLE, which in turn can make the patient more susceptible to various pathogens.

There is accumulating evidence to suggest that not only are patients with SLE more susceptible to certain organisms such as Epstein-Barr virus (EBV), cytomegalovirus (CMV), and tuberculosis (TB), but these organisms may play a role in the pathogenesis of SLE in genetically predisposed individuals [3•].

This article will review the current understanding of and recent developments in how the pathophysiology of SLE and its treatment make patients more susceptible to infection and the infectious agents that may play a role in the development or prevention of disease. While vaccination and infection prophylaxis are of general interest, this is not within the purvue of this review.

Background Infections

Bacterial

The majority of reported injections in lupus patients are bacterial [4••]. The most common infections in the patient with lupus, even in those who are on immunosuppressive medications, are the same infections and pathogens seen in the

general population: *Streptococcus pneumoniae* respiratory tract infections, *Escherichia coli* urinary tract infections, and *Staphylococcus aureus* skin and soft tissue infections [5••, 6].

Viral

Herpes zoster (HZ) is the most common viral pathogen in patients with lupus with rates higher than reported in age-matched populations with a particular risk for SLE patients on cyclophosphamide and azathioprine, and patients on more than 60 mg daily of prednisone are at higher risk for bacterial suprainfection [7]. Over 90 % of patients with SLE are seropositive for CMV as compared with 60–70 % of the general population [8]. Women with SLE have a high prevalence of human papilloma virus (HPV) and triple the prevalence of an abnormal pap smear as compared to healthy controls [9].

Fungal

The most common fungal infections, although rare, include *Candida* species, *Pneumocystis jirovecii*, and *Cryoptococcus neoformas* [5••]. (See Table 1.)

Impaired Immunity and Infectious Risk

Dysfunction of both the innate and adaptive immune systems leads to an increased risk for infection among patients with SLE.

Innate Immune System

Breakdown of epithelial barriers in patients with SLE due to rashes, ulcers, and cutaneous wounds can contribute to entry of infectious agents in the body. Studies have shown that there is accumulation of T gamma-delta cells in normal as well as abnormal skin of patients with SLE as compared to the skin of healthy subjects [10]. These cells have been implicated in skin epithelial breakdown, thus increasing propensity for infections, due to their cytotoxic properties [11]. Once pathogens breach physical barriers, they encounter a dysfunctional immune system in hosts with SLE.

Impairment of immune function with development of autoantibodies, immune complexes, and impaired clearance of apoptotic and necrotic material has been reported in patients with SLE [12–18]. Neutropenia is of various etiologies [19, 20]. Dysfunction of polymorphonuclear leukocytes (PMN), which are the first line of defense during infections, has been well described in the literature in patients with SLE. Production of interleukin 12 (IL-12), which links the innate and adaptive immune systems, crucial for fighting infections, is known to be impaired in PMNs of lupus patients [21]. Impaired IL-8 production [22], nitroblue tetrazolium reduction, and presence of anti-neutrophil antibodies in lupus patients all contribute to reduced PMN function [23].

Genetic or acquired deficiency of the early components of the complement system (C1q, C4, and C2) has been established in SLE and predisposes these patients to infections by encapsulated organisms [24–26]. Decreased levels of complement receptors CR1 and CR2 have been reported on B cells, PMNs, and RBCs in patients with SLE [27, 28].

Adaptive Immune System

The adapative immune system is also impaired in patients with SLE. Studies show increased autoreactivity of helper T cells, cytotoxic T cells, B cell differentiation, and autoantibody production [29]. Impaired production of interferon gamma, IL-1, IL-2, and TNF alpha also contribute to T cell dysfunction [8]. Park et al. [30] studied blood samples from 108 SLE patients and found that cytotoxicity of natural killer (NK) cells was suppressed, there were fewer NK cells, and, as demonstrated in other studies [31], there was a reduced response of NK cells to IL-2.

In a study by Odendhal et al., 13 SLE patients were examined for B cell dysfunction. They found that all three B cell lines, naïve, memory, and plasma cell, were altered in SLE patients along with B cell lymphocytopenia [32]. Hypogammaglobulinemia can be found in SLE patients and can be associated with increased risk of infections [33]. IgM [34] and IgA [35] deficiencies have been described in patients with SLE, although no association with increased infectious risk was proven.

Genetics

High concordance rates of SLE in monozygotic twins points to genetic inheritance and modifications in SLE patients [36]. Mannose-binding lectin (MBL) is an acute phase protein which plays a key role in innate immunity [37]. Single nucleotide polymorphisms (SNPs) have been associated with MBL deficiency in SLE which can lead to increased infectious susceptibility [38].

Table 1 Common infections in patients with SLE

Bacterial [5••, 6]
•*Streptococcus pneumonia*
•*Escherichia coli*
•*Staphylococcus aureus*
Viral [7–9]
•*Herpes Zoster*
•*Cytomegalovirus*
•*Human Papilloma Virus*
Fungal [5••]
•*Candida species*
•*Pneumocystis jirovecii*
•*Cryptococcus neoformans*

Patients with SLE have higher infection rates than the general population

Genes located on HLA loci which are involved in the regulation of the immune system have been associated with SLE along with impaired STAT4 protein production and interferon release, leading to an increased risk of infections [39].

SLE Treatment and Infectious Risk

It is clear that defects in the immune system of hosts with SLE predispose them to infection. This risk is increased when immunosuppressive agents are used to treat disease.

Glucocorticoids

Glucocorticoids (GC) exert a powerful anti-inflammatory effect and therefore have been a mainstay in the treatment of SLE since their discovery in 1949 [40]. Long lasting suppression of T lymphocyte-mediated immunity begins after about 21 days of continuous GC use [41]. In addition to duration of therapy, there is a clear dose response relationship. A 2011 case control study of 16,207 patients with rheumatoid arthritis found that doses below 5 mg/day of prednisone equivalent did not significantly increase the risk of nonserious infections while the adjusted relative risk was 1.1 for the 5–9.9 mg/day dose and 1.85 for doses >20 mg/day [42]. A nested case–control study within the prospective Lupus Cruces cohort found that the risk of a major infection (defined as disseminated, organ-affecting, requiring hospitalization, or resulting in death) increased by 12 % with each milligram per day of prednisone. The other immunosuppressive agents analyzed in the study included azathioprine, methotrexate, cyclophosphamide, mycophenolate, and cyclosporine, but they were not linked to major infections [43]. Methylprednisolone pulses show a similar dose response effect with regards to infection. A retrospective evaluation of 55 patients with SLE given less than 1500 mg IV over 3 days versus 3000 mg IV over 3 days found significantly fewer infections in the lower dose group (7 vs 20, $p<0.05$) with equal efficacy [44]. Both common and less common infections such as *Listeria monocytogenes*, *Nocardia*, nontuberculous mycobacteria, and *Strongyloides stercoralis* have been associated with GC use [45].

Aside from increasing the risk of infection, GC may blunt the normal physiologic response to infection, such as fever, pain, and erythema [46•] They may also cause a rise in peripheral leukocyte counts making it difficult to differentiate between drug effect and underlying infection [40].

Furthermore, GC diminish the reliability of the PPD and QuantiFERON Gold screening tests for TB [47].

Mycophenolate Mofetil and Azathioprine

Mycophenolate mofetil exerts anti-inflammatory effects by depleting guanosine nucleotides in T and B lymphocytes thus inhibiting their proliferation and antibody formation and by inhibiting the expression of adhesion molecules and the recruitment of lymphocytes and monocytes. It is used as part of induction and maintenance therapy for patients with lupus nephritis as well as in the organ transplant patient population [48]. A 2015 study from the Hopkins lupus cohort analyzed 244 patients who had recently started mycophenolate mofetil and found a significant increase in the risk of bacterial (but not viral) infections over a median of 47 days follow-up [49]. In a longer-term randomized, controlled study in patients with lupus nephritis intended to compare mycophenolate mofetil and azathiproine (the Mycophoneolate Mofetil Versus Azathiproine for Maintenance Therapy of Lupus Nephritis (MAINTAIN) trial), all patients received 0.5 mg/kg/day of GC in addition to cyclophosphamide and then subsequently were randomized to azathioprine or mycophenolate. After a mean of 48 months, there was a slighter higher but nonsignificant number of infections [50]. Similar results were found in the Aspreva Lupus Management Study (ALMS) which followed lupus nephritis patients who had been randomized to azathiproine or mycophenolate after cyclophosphamide or mycophenolate induction for 36 months [51]. Mycophenolate mofetil has rarely been associated with invasive fungal infections such *Aspergillus* sp., *Mucor* sp., *Cryoptococcus* sp., *Histoplasma capsulatum*, and *Coccidioides immitis* [52]. Interestingly, some studies have found a protective effect of mycophenolate mofetil against *P. jirovecii* pneumonia and *Coxsackievirus* infections in the transplant population [53].

Cyclophosphamide

Cyclophosphamide, an alkylating agent commonly used for severe manifestations of SLE, is also commonly linked to infectious complications. In a retrospective study of 100 lupus patients treated with cyclophosphamide, 45 infections were reported with the majority being bacterial. The patients who developed infections had a mean cumulative dose of 9.3 g CYC and white blood cell counts less than 3000 cells/mm^3. They also received higher doses of GC as compared to those patients who did not develop infections [54]. There does appear to be a relationship to the cumulative dose of CYC. In another retrospective study of 90 patients, half received "low dose" cyclosphophamide, 2.5 g or less; they reported significantly fewer infectious complications than those receiving >2.5 gm cumulative dose with equivalent efficacy [55]. The problem with these studies of course is the high likelihood of a selection bias, so the results should be interpreted cautiously. The risk of infection appears to be highest among leukopenic patients, especially with concomitant GC use [5••]. Along with high-dose GCs, cyclophosphamide use has been associated with severe and atypical CMV manifestations and *P. jirovecii* respiratory tract infections [3•].

Rituximab

Rituximab is an anti-CD20 monoclonal antibody used off label in lupus patients with severe or refractory organ-threatening disease. As is often the case with adverse effects in general, most serious infections occurred during the first 3 months. Also common for adverse effects in general, higher doses may lead to a higher infection rate. An example of the dose effect is found in Gurwitz et al. [56] while the often-noted early occurrence of side effects is seen in Migita et al. [57]. Data from rheumatoid arthritis trials showed more serious infections in patients who received rituximab as two 1000-mg doses 2 weeks apart (DANCER and REFLEX trials) versus those who received two 500-mg doses (IMAGE trial). However, a meta-analysis of the three trials did not show an increased risk of serious infections in those treated with rituximab as compared to placebo [58]. Rheumatoid arthritis registry data suggests that an IgG level of less than 600 mg/dL prior to therapy and concomitant GC use may increase the risk of infections [58]. The most frequent infections include bacterial pneumonia, HZ, and urinary tract infections [59]. Data shows that progressive multifocal leukoencephalitis (PML), a rare but often fatal disease caused by reactivation of the JC virus, occurs more often in patients with SLE compared to those with other rheumatic diseases [60]. Rituximab, while not FDA-approved for SLE, is often used off label as mentioned above. A 2015 review by Calabrese et al. reports that of eight cases of PML seen in off-label use of the drug, five of those cases occurred in patients with SLE [61••].

Belimumab

Belimumab, a monoclonal antibody against the soluble B lymphocyte stimulator (BLyS), effects B cell function and survival [11]. In a large multisite clinical trial, the rate of serious infection was similar in the belimumab and placebo groups (6 % as compared to 4 %) and the rate of all infections were not significantly different with 69 % in the placebo group and 74 % in the treatment group [62]. Of note, two cases of PML have been reported in lupus patients treated with belimumab [63, 64].

Antimalarials

Chloroquine and hydroxychlorquine have multiple actions responsible for anti-inflammatory properties including affecting MHC Class II expression and antigen presentation, accumulation in lysosomes, and decreased production of pro-inflammatory cytokines [65]. Studies suggest a protective effect with antibacterial properties against *S. aureus, M. tuberculosis, S. typhi*, and *E.coli,* antifungal properties against *Histoplasma, Cryptococcus*, and *Aspergillus*, and antiviral effects against Hepatitis A, B, and C, human immunodeficiency virus (HIV), and influenza [5••].

Pathogens and the Pathogenesis of SLE

Infectious agents have been implicated in the pathogenesis of SLE in genetically predisposed individuals. This includes exogenous viruses, such as EBV, CMV, and parvovirus B19 [3•], *and human endogenous viruses (HERV)* [66•]. *Tuberculosis* [67] *and Helicobacter pylori* [68] *have also been studied. Bacterial infections have long been reported to trigger disease flares in SLE patients* [69]*, and now new reports also suggest that bacterial byproducts may play a role in the development of autoimmunity* [70••].

Epstein Barr Virus

The link between EBV and the pathogenesis of SLE is perhaps the most studied of all suspect infections. Hanlon et al. reported that patients with SLE had a higher frequency of antibodies to a marker of viral replication (EBV early antigen diffuse) than did healthy controls [71•]. Draborg and colleagues suggested that the increased rate of EBV infection and reactivation may be the result of abnormal T cell response to infection [72]. Proposed mechanisms for the induction of SLE include EBV RNA/SSB protein complexes inducing type 1 interferon via Toll-like receptor 3 (TLR-3) [73] and molecular mimicry [74].

Cytomegalovirus

Cytomegalovirus, another member of the human herpes virus family, is well known to be associated with disease flares in SLE with increased levels of anti-CMV IgM detected in the serum of patients during an SLE flare [75, 76]. However, some authors have postulated that elevated levels of anti-CMV Ab were the result of nonspecific activation of B lymphocytes and SLE autoantibodies [77]. A recent study by Rasmussen et al. demonstrated significantly increased levels of antibody specific to CMV pp52 (a protein necessary for the lytic cycle of viral replication) in SLE patients versus healthy controls. This implicates CMV as a contributor to the development of SLE, but further studies are needed to assess for correlation between elevated early antigen-directed antibodies and disease activity or remission [78].

Human Endogenous Retroviruses

Compared to EBV, CMV, and *Parvoviruses*, which are exogenous pathogens, HERVs are endogenous viruses which were incorporated into DNA 30–40 million years ago, are now inheritable, and are subject to epigenetic phenomena influenced by DNA hypomethylation, UV light exposure, and

estrogens [3•, 66•]. HERVs are thought to induce autoimmunity via molecular mimicry and have been shown to stimulate production of interferon and anti-dsDNA antibodies [66•, 79]. HERV-encoded proteins may be targets of autoimmunity with antibodies to *gag* and *env* regions of HERVs being reported in patients with SLE [80].

Parvovirus B19

Acute parvovirus B19 infection may mimic aspects of SLE, with the production of autoantibodies including anti-double-stranded DNA, rheumatoid factor, and antiphospholipid antibodies [81–83]. However, these patients generally fulfill fewer than four American College of Rheumatology Criteria for SLE [84]. Parvovirus B19 was associated with antiphospholipid antibodies and their clinical manifestations including thrombocytopenia and prolonged aPTT [85, 86] as well as worsening of disease in lupus-prone mice exposed to viral protein [87]. A mechanism of autoimmunity has been proposed in which anti-ssDNA antibodies induce hydrolyzed viral ssDNA, which then translocates into the nucleus of the host cell and perpetuates a cycle of disease flares [88].

Mycobacterium Tuberculosis

Antinuclear antibodies and rheumatoid factor have been detected in the serum of patients with TB [89, 90], and isoniazid, a drug used to treat TB, can cause drug-induced SLE. Tuberculosis has also been implicated in the pathogenesis of SLE in endemic areas of the world. A study by Lin et al. reviewed the National Health Insurance Research Database in Taiwan and found that, after controlling for other risk factors, TB patients were at increased risk for the development of SLE (OR 2.11, CI 1.49–3.00) compared to controls. They also found that the incidence of prior TB infection was higher among patients with SLE (1.8 %) versus the general population (0.9 %, $p < 0.0001$) [67]. The underlying mechanism of this association is not clearly defined and warrants further investigation given the high prevalence of TB worldwide.

Bacterial Amyloids

The formation of a biofilm is a major pathogenic mechanism for many bacteria, including *E. coli* and *Salmonella typhimurium* [91]. It plays a role in the development of many types of infections including urinary tract infections and catheter-associated sepsis [92] by protecting the invading organism from host immune defenses. Amyloid fibers, called curli, are a major proteinacious component of the extracellular matrix produced by the bacterial cell. A study by Gallo et al. found that curli have the ability to bind extracellular host DNA (eDNA) [93••]. Perhaps through interaction with TLR1-TLR2 heterocomplexes [94], dendritic cells exposed to curli/eDNA complexes (formed in the context of *S. typhimurium* infection) induced elevated levels of inflammatory cytokines (IL6, IL-12) as well as type 1 interferons and anti-DNA and anti-chromatin antibodies [31, 93••]. Furthermore, lupus-prone and nonlupus-prone mice injected with the curli/eDNA complex tested positive for antibodies within 2 weeks after exposure, while those injected with a sham substance did not test positive for SLE. These findings raise the question of whether or not biofilm-producing bacteria within our microbiome might also be able to bind eDNA in curli complexes and induce autoimmunity [70••].

Certain Organisms Have a Potential Protective Effect Against the Development of SLE

Helicobacter Pylori

H. pylori has been studied as a trigger for the onset of various autoimmune diseases, including SLE [68]. A study by Theander et al. showed that mice treated with *H. pylori* urease produced anti-dsDNA antibodies [95]. However, other studies showed that exposure to *H. pylori* may actually be protective in a subset of female African American patients at risk for developing SLE [96, 97]. In a study by Sawalha et al., African American patients who were seronegative for *H. pylori* had earlier onset of disease [97].

Toxoplasma gondii

Exposure to *Toxoplasma gondii* showed a protective effect in the progression of SLE in a New Zealand mouse cohort via downregulation of intercellular expression of interferon gamma and IL-10 [98].

The Microbiome and SLE

The role of the microbiome in the development of autoimmunity is an emerging field of research. Hevia et al. showed that there may be an imbalance of certain gut flora in patients with SLE compared to healthy controls [99••] A recent study looking at the impact of environmental factors on the development of SLE-prone mice showed that in mice drinking neutral versus acidic pH water, there was a significant difference in the composition of their gut flora during pre-nephritic stages and that mice drinking acidic water showed slower progression of nephritis and had lower levels of SLE-associated antibodies [100•]. These studies suggest that as we continue to investigate the pathogenesis of SLE, it may be just as

important to analyze the bacteria within us as those in the environment around us.

Differentiation of SLE Flare from Infection

SLE mimickers, including infections, medication effects, and vaccine-induced reactions may make it difficult to differentiate between a true flare of disease compared to the infection itself [101•]. Symptoms such as fever, fatigue, and rash may be seen in a SLE flare or as a result of infection. Biomarkers can be used to help distinguish between infection and SLE flares when the clinical presentation is not clear. High-sensitivity C-reactive protein (hsCRP) has long been regarded as a good discriminatory biomarker with significant elevation in infection when compared to disease flare [102]. A recent meta-analysis showed that procalcitonin is a more accurate and sensitive biomarker for the detection of bacterial infection when compared to CRP [103••]. Duration of fever and dsDNA titers have also been used to help distinguish between flare and infection [104•].

Conclusions

The pathogenesis of SLE remains an area of intense research, but it is clear that the underlying immune dysregulation that propagates disease also increases a patient's risk for infection. Likewise, treatments used in the management of SLE further increase this risk, except for anti-malarials, which may provide a protective effect. Infectious agents have also been shown to play a role in the pathogenesis of and increased disease activity in SLE. As we continue to explore the pathogenesis of SLE, it may be just as important to examine the microorganisms within us, the microbiome, and the bacterial by-products these bacteria produce, as it is to study the microorganisms in our external environment, so that one day we can answer the question, infection and lupus, which causes which?

Compliance with Ethics Guidelines

Conflicts of Interest Sarah Doaty, Harsh Agrawal, and Erin Bauer declare they have no conflicts of interest.

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