Systemic lupus erythematosus and infections

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SUMMARY

Systemic lupus erythematosus (SLE) is an inflammatory and multi-systemic autoimmune disorder, characterized by an uncontrolled auto-reactivity of B and T lymphocytes, leading to the production of autoantibodies against self-directed antigens and tissue damage. The life expectancy in patients with SLE has improved tremendously in the last two decades, but the mortality rates still remain three times greater compared to those of the general population. Despite increased awareness and improved management, infections remain a major source of morbidity, mortality, hospitalization, and death in patients with SLE. The infections in SLE patients widely range from opportunistic to common bacterial and viral infections with typical or atypical presentations. Moreover, SLE patients exhibit an increased susceptibility to hospital-acquired infections. Factors associated with increased risk of infections include high disease activity, specific immune dysregulation, drug-induced immune deficiency, and organ failure with irreversible damage. Furthermore, immunosuppressive agents may make patients more susceptible to opportunistic infections. A big challenge faced by physicians in these patients is to distinguish between infections and flares of SLE, as infections may mimic them, leading to predicament in diagnosis and appropriate management. Immunosuppression used to treat severe flares of lupus can have catastrophic complications in patients with active infections. There is an urgent need for biomarkers to make an accurate differential diagnosis in this situation. In spite of increased understanding of SLE, many questions remain unanswered. Further research is needed to determine specific immune dysregulation underlying the increased susceptibility to specific infections, predictors of infection in SLE such as genetic markers, and biomarkers that discriminate between disease activity and active infections. Also, measures must be evaluated appropriately to prevent infections, and their complications in SLE.

Key words: Systemic lupus erythematosus; infections.

■ INTRODUCTION

Systemic lupus erythematosus (SLE) is an autoimmune inflammatory and multi-system disorder characterized by excessive auto-reactivity of B and T lymphocytes.

Infections are one of the most frequent causes of morbidity, hospitalization and death in patients with SLE. Immune dysregulation may play a role in the susceptibility of SLE patients to infections. Furthermore, immunosuppressive agents may increase the risk for infections.

In the EuroLupus cohort, 36% of patients had infections during follow-up, and approximately 30% of deaths were related to infections in the five-year-follow-up. (1) Infections have been well documented as cause for hospitalization and mortality in the Hopkins Lupus and British University College cohorts (2, 3). Infections remain a major source of morbidity and mortality among SLE patients (4). There is a bimodal curve of the mortality rate in these patients with an initial peak occurring at the early stage of the disease, related to disease activity, which is followed at a later stage by cardiovascular disease, damage accrual, and infections (5). The range of infections in lupus patients varies widely from bacterial and viral infections to opportunistic infections with normal or abnormal presentations. Moreover, SLE patients show a

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greater susceptibility to hospital-acquired infections.

Factors associated with an increased risk of infection include: high disease activity, immune dysregulation, drug-induced immune deficiency and organ failure due to irreversible damage. Infections may mimic SLE flares causing confusion in the diagnostic process and treatment selection. Fever, lymphadenopathy, confusion state, pulmonary infiltrates, skin and mucosal rashes/ulcer, coagulopathy and renal impairment pose diagnostic challenges. Evidence suggests that certain infections, particularly of viral nature, might contribute to the onset of this disease, and to flares or worsening of an active lupus (6).

■ EPIDEMIOLOGY OF INFECTIONS

The type of microorganisms involved is influenced by various environmental factors, *e.g.*
1) the patterns of disease arising from re-activated latent infections;
2) opportunistic infections;
3) invading pathogens.

Infection rates, organism presentation, and severity of infections vary between the developing and developed countries. Infections due to tuberculosis, *Staphylococcus aureus*, *Streptococcus pneumoniae*, *Pseudomonas aeruginosa*, *Escherichia coli* and *Candida,* with frequent mixed viral and bacterial infections and poor prognosis, are more common in developing countries while the incidence of tuberculosis is much lower in developed countries (7). Infectious diseases are reported to be more common and twice as dangerous in developing countries; in them an increase in infection rates with *Pneumocystis jirovecii* has been observed (8). This difference can be explained by poverty, overpopulation, malnutrition, poor water and food sanitation, decreased awareness and poor healthcare service infrastructures and availability in developing countries (7). In a nested case control study in 93 SLE patients, Gladman et al. (9) reported pneumonia (29.7%), skin (23.6%), genitourinary (18.2%) and gas-

trointestinal tract infections in 6% of patients. *S. aureus*, *E. coli* and *P. aeruginosa* were the most common pathogens (10-13). More suspicion of opportunistic pathogens, together with earlier evaluation and appropriate therapy, are required to decrease the infectious disease burden and its complications in patients with SLE.

Bacterial infection

About 80% of SLE infections are caused by bacteria. The most frequent sites of infection are respiratory tract, skin, and urinary tract, accounting for more than 60% of the infections seen in SLE patients. Most infections are caused by *S. aureus*, *S. pneumoniae*, *E. coli*, and *P. aeruginosa.*

Infection due to Salmonella species is more common in SLE patients than in the normal population, and is attributed to splenic dysfunction. Neutropenia caused by antigranulocyte antibodies through direct cytotoxicity and opsonization was found in approximately 50% of patients with SLE and predisposed them to bacterial infection in the Hopkins Lupus Cohort. In this cohort a significant difference in the SLEDAI scores was demonstrated between patients who developed bacteremia and those who did not. These authors concluded that SLE activity (SLEDAI) was a predictive factor for hospitalization due to infection (3).

Viral infections

Viruses such as cytomegalovirus (CMV), Epstein-Barr virus (EBV), and parvovirus B19, are environmental agents that may trigger the development of SLE. Moreover, SLE patients are at an increased risk for viral diseases.

Herpes zoster (HZ) is the most frequent infection in lupus patients with an annual incidence ranging from 6.4 to 32.5/1000 person-years, followed by other frequent infections like CMV, human papilloma virus (HPV), parvovirus B19, Hepatitis B, C and influenza (9, 14). HZ is the symptomatic reactivation of the Varicella-zoster virus (VZV), since the virus remains dormant in the dorsal root ganglia for long periods of time after primary infection. This latent virus is controlled predominantly

by cellular immune mechanisms and may be reactivated due to immune imbalance. The incidence rate of HZ reactivation is 2-3-fold greater in SLE patients than in the general population (15). Ten to 20% of lupus patients have more severe forms of infection, ocular involvement, post-herpetic neuralgia and disseminated disease (16). Higher incidence of CMV infections has also been reported in patients with SLE, often presenting with severe and atypical manifestations. CMV infection may mimic a lupus flare and cause pneumonia, arthritis, lymphadenopathy, gastro-intestinal bleeding or encephalitis, which is found to be more severe with immune-suppressants like cyclophosphamide (17, 18).

The majority of SLE patient are infected with EBV. A poor control of EBV infection could result in widespread latent infection and more frequent reactivation (17). The correlation of HCMV infection in the pathogenesis of SLE has not yet been established. Some studies have shown that the frequency of HCMV-specific CD69+, CD4+, T cells producing IFN-γ and TNF-α was similar in SLE patients and in healthy. Cassaniti et al. observed a significantly lower EBV and HCMV-specific T cell response in SLE patients, thus explaining the possible burden of these infections. Women with SLE have both a high prevalence of HPV infections and also an increased risk of squamous intraepithelial lesions (SIL). They show a three-fold increase in the rate of abnormal cervical cytology smears compared to the general population (19). The annual incidence of viral infections in SLE patients has not been studied much so far. The influenza vaccine has been shown to be associated with an increase in autoantibody formation in some patients. However, this does not correlate with clinical flares of lupus (20). Given the risk of potentially more severe influenza exposure in patients with SLE, annual vaccination is recommended (21).

In the HIV infected population the incidence of SLE is reported to be lower than in the general population. Some research suggested that the evolution of SLE can be suppressed by the immunosuppression re-

sulting from HIV infection. Conversely, a reactivation of SLE was observed in some HIV patients (22). The incidence of hepatitis B and C infection in SLE is reported to be same as in the general population. However, patients treated with MABs TNF inhibitors and rituximab may be at an increased risk of hepatitis reactivation.

Mycobacterial infection

In endemic countries, the incidence of *Mycobacterium tuberculosis* (TB) active infection in patients with SLE is approximately 5-7%, while 18-25% of them has latent tuberculosis (23). TB in SLE occurs commonly in extra pulmonary sites (CNS, joints, skin, and lymphnodes) and may be associated with more severe pulmonary and disseminated involvement (24, 25). The most important risk factors for TB reactivation is the use of biologics, like TNF inhibitors, and glucocorticoids. SLE patients have an increased incidence of both tuberculous mycobacterium (MTB) and nontuberculous mycobacterium (NTM) infections.

Pathogenic NTM affects skin, lungs, lymphnodes, soft tissues, and bones, and rarely disseminate. NTM presentation may be subtle with multiple sites of involvement, is more commonly found in patients with longer lupus disease duration, in older patients, patients with concomitant diabetes and higher cumulative doses of prednisolone. The possible route of transmission is the penetration of the pathogen through a skin abrasion. *M.chelonae*, *M.avium* complicated (MAC) and *M.haemophilum* cause cutaneous infections in SLE (26). Synovitis is mainly monoarticular and also the periarticular tissue may be involved. *M.fortuitum*, MAC, and *M.marinum* are common NTM causing synovitis. A tissue culture is often required for a definitive diagnosis (27).

Fungal infection

Invasive fungal infection (IFI) is a life-threatening condition occurring occasionally in SLE patients. IFI is mainly caused by opportunistic pathomycetes, including *Candida*, *Aspergillus* and *Cryptococcus*, which may affect lungs, spleen, CNS,

pharynx, esophagus, urinary tract, or may present as fungemia. The use of glucocorticoids or other immunosuppressants, several antibiotics and steroid-induced diabetes contribute to the immune dysfunction which increases the susceptibility to IFI. Fan et al. (28) studied 1534 SLE patients of whom 20 patients had IFI. The affected sites included the lungs in nine patients and the central nervous system in five. Five cases of disseminated IFI were also reported. *Aspergillus* (33.3%) and *Cryptococcus neoformans* (33.3%) were the most common species, followed by *Candida albicans* (22.2%), thus confirming the results of previous studies. Six (30%) patients expired: two from lung IFI, two from central nervous system IFI and two from disseminated IFI. These patients were taking significantly higher prednisone doses and had significantly higher serum C reactive protein (CRP), erythrocyte sedimentation rate (ESR), thrombocytopenia and systemic lupus erythematosus disease activity index (SLEDAI) scores (29-32).

Pneumocystis jiroveci

This pathogen is recognized as a frequent cause of severe pulmonary involvement in immunosuppressed patients. SLE patients have shown higher severity and mortality rates. Higher disease activity, higher dose of prednisolone, renal involvement, lower absolute lymphocyte count and lower CD4+ count are risk factors for *P. jiroveci* pneumonia infection.

Parasites

Toxoplasmosis may complicate the clinical picture of SLE patients, presenting as cerebritis and pericarditis, mimicking disease flares and causing significant morbidity and mortality. Interestingly, Toxoplasma infection can also occur in patients with low disease activity and low steroid dosage (33, 34).

Infections that mimick SLE

It is sometime difficult to distinguish between viral infection and SLE manifestations. Human parvovirus B19 (HPV-B19) infection and Lehismania are common infections with SLE-like characteristics. The similarities between these infections and SLE include arthralgia, photosensitivity, fever, fatigue, lymphadenopathy and serological abnormalities. In these cases it is important to identify diligently any potential contact with individuals affected by erythema infectiosum.

■ MORBIDITY AND MORTALITY DUE TO INFECTIONS

Diagnostic and clinical considerations

Fever in SLE patients presents often a dilemma in the differential diagnosis between a flare of the disease and a superimposed infection. Therefore, it is necessary to understand if there is an infection in progress and if and when to start empirical antibiotics, and to decide whether to change the immunosuppressive treatment.

Fever associated with SLE presents more frequently with serositis, kidney damage, cytopenia, lymphadenopathies, or thrombosis. Kidney involvement and anti-Ro positivity are associated with SLE fever, although with low odd ratios. Conversely, discoid lesions are not associated with SLE fever. This could help in the differential diagnosis. Considering the effect of treatment is of importance in SLE patients with infection. Because of the impaired inflammatory response, signs and symptoms of infection may be subtle, especially in patients receiving cytotoxic drugs. Furthermore, SLE is associated with false positive serological tests, such as those for syphilis, HIV, Lyme disease, toxoplasmosis, and several other common infections, explained by the underlying polyclonal hyperglobulinemia.

Additionally, glucocorticoid treatment may result in false negative skin tests *e.g.* tuberculin skin testing. C reactive protein (CRP) is an acute phase reactant that is found to be elevated in infections and many autoimmune states. However, CRP levels are normal in SLE patients and do not reflect disease activity. It was suggested that increased CRP can be considered as a surrogate marker of infection in SLE to distinguish between disease activity and infec-

tion. However, available studies reported conflicting results (35-40).

In SLE patients receiving prednisone at maintenance doses or greater, SLE fever is rare. When fever does develop, it is usually due to infection. A mean dosage of prednisone of 28 mg/day (range 20 to 40 mg/day) completely suppresses SLE fever within 24 h. Lower serum C3 and higher SLEDAI scores are associated with SLE fever. Immunotherapy especially with azathioprine is a risk factor for infection fever. Furthermore, SLE reactivation and infection may co-occur (8%).

Low soluble Fcgamma receptor III levels and elevated G-CSF levels are proposed as novel indicators infection (41) in SLE patients with sepsis. In another study, elevated levels of sE-Selectin and sICAM-1 were reported by Egerer et al. (42). They observed elevated concentrations of sCD14 in sera from SLE patients, which rapidly decreased after effective antibiotic therapy. A continuous elevation of these three parameters was associated with a fatal outcome in both sepsis and SLE patients (42). Recently evidence suggests that serum procalcitonin has negative predictive value for bacterial infection in active SLE.

Anti-CRP antibody is found in one third of lupus patients to be associated with anti DsDNA antibodies and Lupus nephritis. However, the presence of the anti-CRP antibody was not associated with disease activity in SLE.

Vaccination

Vaccination is an attractive method to prevent certain infections. It was suggested that efficacy of vaccinations may be reduced in patients with SLE. However, the majority of these patients develop protective levels of antibodies after vaccination. There is also a concern of disease flares after vaccinations, which, however, was not found to be significant (43-52). It is recommended to avoid live attenuated vaccines and vaccines to be given in stable disease, preferably 2-4 weeks before initiating the immunosuppressant/biological therapy. Vaccination is a safe procedure for secondary prophylaxis. Pneumococcal and influenza vaccinations are routinely recommended (53).

Susceptibility to infections in SLE patients

The susceptibility to infections in SLE patients might also be defined based on various intrinsic and acquired defects in the immune system associated with this disease or with immunosuppressive therapies. A summary of infective agents involved in SLE (Table I), of the relevant studies examined in this review (Table II), of infection-related mortality (Table III), and of the risk factors for infection (Table IV) is reported (9-13, 35, 36, 45-60).

Table I - Pathogenic organisms responsible for infections in SLE.

Bacteria	*Staphylococcus aureus* *Pseudomonas* spp *Escherichia coli* *Streptococcus pneumonia* *Neisseria* spp *Salmonella species* *Non-typhoidal salmonella* *Haemophilus influenza* *Klebsiella* spp *Acinetobacter* spp *Listeria monocytogens* *Mycoplasma* spp
Mycobacterium	*M. tuberculosis* *Nontuberculous mycobacterium* *Mycobacterium chelonae* *M. avium complex* (MAC) *M. Haemophilum* *M. Fortuitum* *M. Marinum*
Virus	Parvovirus B19 Cytomegalovirus Epstein-Barr virus Herpes simplex/varicella zoster Human papillomavirus Hepatitis A Hepatitis B Hepatitis C
Fungus	*Candida* spp *Aspergillus* spp *Cryptococcus Neoformans* *Pneumocystis jiroveci* *Histoplasma Capsulatum* *Nocardia* spp *Coccidoides immitis*
Parasite	*Toxoplasma Gondi* *Strongyloides Stercoralis*

Table II - Studies on infections in SLE.

Author/Year	Number of patients observed	Number of patients had infections	Main Site/Pathogens
Costa-Reis et al., 2013 (13)	120	44	*S. aureus* - 5 (11.4%) *E. coli* - 6 (13.6%) *Pseudomonas* - 2 (4.5%) *Herpes simplex* - 4 (9%) *Herpes zoster* - 8 (18.1%) *S. pneumoniae* - 2 (4.5%)
Navarro-Zarza et al., 2010 (35)	473	268 (Confirmed 96)	*Mycobacterium tuberculosis* 6 (4.5%) *Staphylococcus* sp. 21 (15.0%) *Streptococcus* sp. 16 (12.1%) *Escherichia coli* 64 (48.4%) *Candida* sp 8 (23%)
Ruiz-Irastorza et al., 2009 (36)	249	83	*E. coli* - 7 (16%) *S. aureus* - 6 (14%) *M. tuberculosis* - 6 (14%) *S. pneumoniae* - 5 (12%) *Salmonella* - 4 (9%) *Candida* sp. 3 (7%)
Al-Rayes et al., 2007 (10)	199	117	*Staphylococcus aureus* - 37 (18.59%) *Escherichia coli* - 21 (10.55%) *Pseudomonas aeruginosa* - 17 (8.54%) *Salmonella* - 12 (6.03%) *Mycobacterium tuberculosis* - 11 (5.52%) *Streptococcus* sp. - 11 (5.52%) *Candida albicans* - 37 (18.59%)
Bosch et al., 2006 (12)	110	39	*E. coli* - 10 (21.3%) *S. aureus* - 7 (14.9%) *Candida* sp. - 6 (12.7%) *H. zoster* - 5 (10.6%) *Salmonella* sp. - 4 (8.5%) *S. pneumonia* - 3 (6.4%)
Khalifa et al., 2007 (11)	75	43	*Staphylococcus aureus* - 16 (19.5%) *Escherichia coli* - 13 (15.8%) *C. albicans* - 11 (13.4%) *Streptococcus* - 9 (10.9%) *Proteus mirabilis* - 4 (4.8 %) *M. tuberculosis* - 4 (4.8%) *Herpes zoster* - 3 (3.6%) *Enterobacter* - 2 (2.4 %) *Klebsiella* - 1 (1.2 %) Hepatitis C virus - 1 (1.2%)
Gladman et al., 2002 (9)	363	93	*Staphylococcus* - 21 (14.2%) *E. coli* - 17 (11.5%) HPV - 14 (9.4%) *Streptococcus* - 12 (8.1%) *Herpes simplex* - 5 (3.4%) *Candida albicans* - 5 (3.4%) *Herpes Zoster* - 2 (1.3%) *Pseudomonas* - 1 (0.7%) Atypical mycobacterium - 1 (0.7%)

Table III - Infection-related mortality in SLE.

Authors/Year	Number of patients	Site of Infections	Pathogens	Deaths due to infection
Fei et al., 2014 (45)	3,831	Meningitis - 41.5% Pulmonary - 24.6% Peritonitis - 20.7% Urinary Tract - 10.4%	Fungal - 10 (62.5%), Bacterial - 4 (25.0%), Tuberculosis - 2 (12.5%)	101/268 (37.3%)
Voss et al., 2013 (46)	215	Sepsis - 66% Gastrointestinal - 33%		3/38 (8%)
Zhen et al., 2013 (47)	1,958	Pulmonary - 64.7% Extrapulmonary - 35.3%		51/165 (30.9%)
Sharma et al., 2013 (48)	17	Sepsis - 40% Ventilator associated pneumonia - 20% CNS - 10% Skin& Soft Tissue - 10% Pancreatitis - 10% Cysytitis - 10%	Aspergillus - 30% Escherichia coli - 20% Candida - 20% Tuberculous Meningitis - 10% MRSA - 10% Pseudomonas aeruginosa - 10%	10/17 (58.8%)
Teh et al., 2013 (49)	251	Pneumonia - 10.5% Sepsis - 6.7% Cellulitis - 6.7 % Urinary tract infections - 2.1% Meningitis - 0.4% Septic arthritis - 0.2%	Gram-negative organisms 66.7% Gram-positive organisms - 6.1% Mycobacterium tuberculosis - 1.5% Cryptococcal meningitis - 0.7% Mycoplasma pneumoniae - 0.7% Total 130	17/26 (65.3%)
Kang et al., 2011 (50)	1010	Pneumonia - 65.2% 15/23 Sepsis - 13% Abscess - 8.7% Peritonitis - 4.3% Meningitis - 4.3%	Bacterial	52% Total 44
Souza et al., 2012 (51)	3133	Pneumonia - 25.7% Sepsis - 22.8% Meningitis - 0.3% Tuberculosis - 0.6%	Bacterial	51.3%

Table IV - Risk factors for infection in patients with systemic lupus erythematosus.

Disease related	Disease activity Nephritis CNS Lupus Lymphopenia/Leucopenia/ Neutropenia Irreversible organ damage/failure
Genetics	Complement deficiency MBL polymorphism TLR polymorphism FCGR polymorphism TNFR polymorphism Osteopontin polymorphism
Laboratory	High anti-dsDNA titers Low complements Anti-phospholipid antibodies
Therapy related	Biologics (Anti CD 20 Ab, TNF Blockers) Cyclophosphamide high-dose regimens Methyl prednisolone high-dose pulses Prednisone-equivalent doses >7.5 - 10 mg/day Immunosuppressants-Azathioprine, MMF, Methotrexate, Leflunamide etc.
Coexistent Immunodeficiency	Common variable immunodeficiency Selective IgA deficiency Selective IgM deficiency Hematological malignancy-Myeloma, Lymphoma, Leukemia

■ GENETIC SUSCEPTIBILITY

Defects in the complement system

The complement system is composed of a complex cascade of plasma proteins that leads to deposition of C3b fragments and formation of immune complexes that leads to the activation of a lytic complex on the bacterial surface. Increased pyogenic infection rates are observed in patients with complement deficiencies. Congenital deficiency of early complement components associated with lupus may involve C1q, C1r, C2, C4 and C1-Inhibitor (61, 62). C1q plays an important role in the classical pathway activation through the recognition of apoptotic material, antibodies and bacteria/viral proteins (13, 14). There is also a decreased expression of CR1 on neutrophils, causing defective phagocytosis (63-66). The expression of CR1 and CR2 (C3d receptor) is also likely to be significantly low on B lymphocytes in lupus patients (67). Autoantibodies against the CR1 and CR3 (CDllb/CD18) has also been recognized in lupus. In addition, the consumption of complement proteins by immune complexes (IC) also limits the amount of complement available for normal defense against pathogens (68, 69).

Mannose-binding lectin

Mannose-binding lectin (MBL) is a serum protein that is considered a recognition particle in the lectin pathway of complement activation. Besides, MLB may directly opsonize pathogenic microorganisms and activate phagocytes. Mok et al. reported an increase by 34.2% in the risk of bacterial infection for every decline in serum MBL level by one log, and by 22.8% for every increase in the number of major lupus exacerbations (70).

Osteopontin (SPP1)

It is a soluble ligand with pleomorphic immunologic activities, which is also involved in activation of macrophage chemotaxis, stimulation of Th1 responses and activation of B1 B-cells.

It has been associated with the development of murine lupus, and is overexpressed in humans with SLE. Forton et al. demon-

strated that a silent polymorphism (707C >T, rs1126616) of osteopontin was significantly associated with SLE. Additional associations with renal disease and opportunistic infections were also found (71).

PTPN22 gene polymorphisms

Protein tyrosine phosphatase non-receptor type 22 (PTPN22) gene was found to be related to SLE. The missense R620W polymorphism, rs 2476601, in PTPN22 gene at the nucleotide 1858 in codon 620 (620Arg >Trp) proved to be significantly associated with SLE (72). The PTPN22 (1858T, G788A) locus was also found to be associated with an increased risk of pulmonary tuberculosis and chronic infections (73).

Fcgamma receptor polymorphisms

The G Immunoglobulin Fc Receptors (FcγR) belong to the TNFR5 receptors family of the immunoglobulin superfamily and are generally expressed in the immune system. They play an important role in the clearance of immune complexes. Several studies have shown an impaired handling of immune complexes in SLE due in part to the dysfunction of the FcγR. Among all types of Fc receptors, the FcγRIIA, FcγRIIB, FcγRIIIA and FcγRIIIB have well characterized polymorphisms that produce an alteration in the receptor function, which is associated with SLE, lupus nephritis and infection risk (74, 75).

■ DEFECTS OF THE INNATE IMMUNE SYSTEM

Macrophage defects

There are multiple defects of the macrophage/monocyte system that affect its antigen-presenting function and diminish the phagocytic activity of lupus monocytes (76). Decreased tumor necrosis factor (TNF) and superoxide generation by Fc'y receptor by mononuclear cells may also contribute to a deficient phagocytic ability and predisposition to bacterial infections (77). Circulating immunoglobulin IgM and IgG autoantibodies against this receptor (Fc'yRI, Fc'yRII, and Fc'yRIII) may interfere with its function (78).

Neutrophil defects

Both the number and functions of PMN can be defective in lupus patients. Antibodies against the neutrophil cytoplasmic components, which correlate with neutropenia and can have an antibacterial activity (*i.e*. lactoferrin, elastase and lysozyme), were also found in SLE. However, their clinical importance has not yet been completely understood (79, 80). The deficiency of lactoferrin, a bacteriostatic protein, is associated with recurrent infections (81). Anti-neutrophil cytoplasmic antibodies (ANCA) activate neutrophils by occupying and cross-linking the Fc-/RIIa receptors (82). Neutrophil chemo taxis is also defective in SLE (83).

Natural killer cell defects

NK cells are an important part of innate immunity. Decreased numbers of NK cells have been reported in active SLE patients, in particular in the presence of infection. Anti-NK cells and antilymphocyte autoantibodies may contribute to decreased NK cell activity (38, 39).

Spleen/reticuloendothelial system dysfunction

CR1 on erythrocytes transport IC to the reticuloendothelial system (RES) organs. The spleen is the main organ of the RES. Spleen dysfunction has already been shown in SLE patients. The defective clearance of IgG-sensitized erythrocytes from the blood circulation by the RES is associated with disease activity (84-89). High incidence of bacterial sepsis has been frequently reported in SLE patients with functional asplenia (90).

■ **DEFECTS OF ADAPTIVE IMMUNE SYSTEM**

T cell defects

T-cell lymphopenia and especially CD4 + lymphopenia are the most commonly observed hematological abnormalities in lupus (79). Lymphopenia may contribute to increased susceptibility to infections and also correlates with disease flares. An inadequate production of cytokines (*e.g.* IL-2, IFN-γ) is responsible for the defective

cytotoxic T cells (84). There is also a reduced delayed hypersensitivity response in patients with SLE. Many patients with SLE have altered in-vitro immune responses to alloantigens and memory response and such dysfunction correlates with higher disease activity (77).

B cell and immunoglobulin defects

Abnormalities include defects in the negative selection of auto reactive B cells at certain stages, pre-naive, transitional, pre-naive memory B cells and in particular plasma blast/plasma cells (85), although immunization produces reasonable immune response (86). Transient or permanent hypoglobulinemia with low IgG levels has also been described in SLE patients, who, in some cases, experienced repeated infections (35). An imbalance in the IgG sub-classes with a change in the IgGl:IgG2 ratio and low IgG2 is reported in few patients; it is mainly aimed against polysaccharide antigens and encapsulated bacteria (36, 37).

■ **CONCOMITANT IMMUNODEFICIENCIES IN SLE**

Common variable immunodeficiency

The development of common variable immunodeficiency (CVID) or hypogammaglobulinemia in SLE is rare.

SLE evolves into a low activity state after development of CVID in most cases. CVID should be suspected in any patient who has SLE with recurrent sinopulmonary infections in the absence of SLE activity or immunosuppressive treatment. Although SLE-associated CVID is not common, it should be considered in any SLE patient with hypogammaglobulinemia (at least 2 standard deviations below the mean age in serum concentration of IgG and IgA), absent or poor response to immunization (two-fold or less increase in antibody titer), and acute, chronic, or recurrent infections, specifically, pneumonia, bronchitis, sinusitis, conjunctivitis, and otitis media.

The clinical and bacterial spectrums of infections are similar in patients of CVID with or without SLE and include recurrent infections with encapsulated organisms,

such as *Streptococcus pneumoniae* and *Hemophilius influenzae*. These patients also show an unusual susceptibility to Mycoplasma infections (89). Other unrelated causes of hypogammaglobulinemia in patients who have SLE are lymphoproliferative disorders, including myeloma, chronic lymphocytic leukemia, and lymphoma.

IgA deficiency

Mantovani et al. investigated the occurrence of IgA deficiency and reported a prevalence of 6.17% in 199 SLE patients, observing that it had no particular laboratory or clinical effects (90). Cassidy et al. calculated that the prevalence of IgA deficiency is 2.6% in adults (n=152) and 5.2% in children (n=77) with SLE. These patients have a similar clinical course compared to patients who have SLE without IgA deficiency (91).

IgM deficiency

Selective IgM deficiency has been described in patients who have SLE and was found more often in long-standing and less severe SLE cases (92). The most common clinical manifestations of selective IgM deficiency are infections with extracellular and intracellular bacteria, viruses, and fungi, that respond to conventional antibiotics/antiviral/antifungal agents, without a need for prolonged antibiotic therapy, and occasional intravenous immunoglobulin (Ig) therapy (93).

■ THERAPY-RELATED RISK FOR INFECTION IN SLE

SLE treatment includes glucocorticoids, immunosuppressive agents such as cyclophosphamide, azathioprine, methotrexate, mycophenolate mofetil and cyclosporine, and biologics (Anti CD 20, Anti BLyS, Anti TNF). SLE patients treated with corticosteroids, immunosuppressive, and biologic agents have shown to be more susceptible to infections (9, 14).

Glucocorticoids

Glucocorticoids are the main drugs in the therapeutic armamentarium in SLE. They have a wide range of impacts on the immune system (94). Glucocorticoids have various anti-inflammatory and immunosuppressive effects triggered by several mechanisms, including interference with leucocyte, fibroblast and endothelial cell function. Glucocorticoids suppress cell-mediated immunity and also reduce the number of circulating monocytes and macrophages, thus increasing the risk for opportunistic infections (95, 96). They increase the risk of infection in SLE in a dose-dependent manner (95). The infection risk is considered greater, if prednisolone dose is >15 mg. However, it is not clear whether there is a threshold below which glucocorticoids can be considered safe (46, 47).

Cytotoxic drugs

Cytotoxic drugs, including cyclophosphamide, mycophenolate mofetil (MMF), azathioprine and cyclosporine, are frequently used in combination with glucocorticoids for the treatment of severe SLE and can lead to a greater risk of infection.

Cyclophosphamide

Infection with a range of common and opportunistic pathogens is a frequent complication. Illei et al. reported higher frequency of infection in lupus nephritis patients treated with cyclophosphamide compared with patients treated with methylprednisolone alone (26% *vs* 8%) (97-100).

Azathioprine

The effect of azathioprine on the susceptibility to infection does not appear to be as strong as with cyclophosphamide, However, an increased frequency of infection in patients with SLE receiving azathioprine was reported in several studies (101-103).

Mycophenolate mofetil

Increased incidence of infection in patients with SLE receiving MMF was also noticed in several studies. However, the MAINTAIN and ALMS trials reported no significant difference in infection rates between MMF and azathioprine (102-104). Several controlled studies were performed comparing MMF and cyclophosphamide and dem-

onstrated that the frequency of infection in patients treated with MMF (17-19%) was similar or lower compared to patients treated with cyclophosphamide (105-107).

Chloroquine/Hydroxychloroquine

Hydroxychloroquine (HCQ) and chloroquine (CQ) have an anti-parasitic activity. They also have anti-bacterial, antifungal as well as anti-viral effects. These effects are exerted by pH-dependent iron deprivation and increasing lysosomal pH, leading to growth inhibition of intra-cellular organisms. Antibacterial effects are effective against *S. aureus*, *tuberculosis*, *S. typhi* and *E. coli*, while antifungal activity against *Histoplasma*, *Cryptococcus* and *Aspergillus* has also been reported (108, 109).

Biological therapies

Rituximab is an anti-CD20 monoclonal anti-body used in severe or refractory manifestations of SLE. The rate of infections in SLE patients treated with rituximab was reported as 19.5 per 100 patient/years. Infections were more frequent within the first six months of treatment (110-112).

The Spanish BIOGEAS study group recently described the rate and risk factors for severe infections in patients treated with biological agents. Biological therapies included were rituximab in 264 (77%) patients, infliximab in 37 (11%), etanercept in 21 (6%), adalimumab in 19 (5%), and *other* agents in 3 (1%). Four deaths and forty-five severe infections were reported. The gross rate of severe infections was 90.9 events/1000 person-years (112.5 for rituximab, 76.9 for infliximab, 66.9 for adalimumab and 30.5 for etanercept respectively). The most frequent microorganisms seen were *S.pneumonia* followed by *E.coli* and *S.aureus*. The most common sites of severe infection were the lower respiratory tract (39%), bacteremia/sepsis (20%) and the urinary tract (16%). Infections develop within the first six months (63%) or after one year (24%) after the administration of rituximab. The risk for severe infections was associated with the number of rituximab cycles received (113). Belimumab is a monoclonal antibody targeted against the

soluble B lymphocyte stimulator (BLyS), which is a co-stimulator for B-cell function and survival. It has been recently approved in Europe and America for treating SLE patients who are clinically and serologically active, despite the standard therapy. At the recommended doses of 10 mg/kg, the rate of serious infections is comparable with placebo (114-116).

Progressive multifocal leukoencephalopathy (PML) is a rare, potentially fatal, central nervous system (CNS) opportunistic infection of oligodendrocytes and astrocytes by John Cunningham virus (JC virus). JC virus reactivation occurs during periods of immunosuppression. Severe lymphopenia and a significant use of immunosuppressants, specifically rituximab and cyclophosphamide, were identified as potential risk factors. B cells may act as a potential viral reservoir or contribute to the immune response controlling JCV infection. Rituximab can achieve a robust peripheral blood B cell depletion (117-125).

■ CONCLUSIONS

Infections are a major and important cause of morbidity and mortality in patients with SLE due to the underlying immune dysregulation. SLE patients have a higher infection rate than the general population. High-dose glucocorticoids, high disease activity, organ dysfunction and use of biologics and immunosuppressants are the main risk factors for the development of an infection in SLE. Distinguishing between infections and flares of SLE is a significant challenge, as infections may mimic flares of SLE, leading to a predicament in diagnosis and appropriate management.

There is an urgent need for biomarkers for an appropriate differential diagnosis in this situation. However, in spite of increased understanding of SLE, many questions remain unanswered. Further research is needed to understand specific immune dysregulation underlying the increased susceptibility to specific infections, predictors of infection in SLE such as genetic markers, and biomarkers that discriminates between disease activity and active infec-

tions. There is also a need to evaluate more appropriate measures to prevent infections and their complications in SLE patients.

Contributions
The authors contributed equally.

Conflict of interest
The authors declare no conflict of interest.

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