Systemic Lupus Erythematosus

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Abbreviations

AZA	Azathioprine
CCR6	Chemokine receptor 6
CMV	Cytomegalovirus
CRP	C-reactive protein
CSF	Cerebrospinal fluid
cSLE	Childhood systemic lupus erythematosus
CW	Cutaneous warts
ESRD	End stage renal disease
HAI	Hospital-acquired infection
HBV	Hepatitis B virus
HLA	Human leukocyte antigen
HPV	Human papillomavirus
HR	Hazard ratio
HZI	Herpes zoster infection
IBLs	Infected brain lesions
IFI	Invasive fungal infection
IFN	Interferon
JCV	John Cunningham virus
LMP1	Latent membrane protein
LN	Lupus nephritis
LPS	Lipopolysaccharides
MMF	Mycophenolate mofetil
NETs	Neutrophil extracellular traps
NKs	Natural killer cells
PCT	Procalcitonin
PDC	Plasmacytoid dendritic cells
PMNs	Polymorphonuclear cells
PRRs	Pattern recognition receptors
RA	Rheumatoid arthritis
ROS	Reactive oxygen species
SBE	Subacute bacterial endocarditis
SFB	Segmented filamentous bacteria
SLE	Systemic lupus erythematosus
SLEDAI	Systemic lupus erythematosus disease activity index
SMR	Standardized mortality ratio
SMRs	Standardized mortality ratios
TB	Tuberculosis
Tfh	Follicular helper T cells
TLR	Toll-like receptors
Tregs	Regulatory T cells
UTI	Urinary tract infections

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Introduction

Systemic lupus erythematosus (SLE) is the epitome of autoimmune diseases. The pathogenesis, clinical manifestations, and management of SLE involve various aspects of microorganisms, either as potential triggers and perpetuators of disease, as infectious episodes, as complications from underlying immune dysregulation, or as adverse events from chronic immunosuppression. Despite significant progress that has been made in understanding the contributions of microorganisms to SLE, there are many questions that need to be answered.

Besides environmental factors, genetic risk factors have long been established to be important in the pathogenesis of autoimmune diseases including SLE. Several clinical case studies uncovered a family history of patients with either the same or closely related autoimmune diseases, which supports the possibility that a common genetic predisposition is at the core of autoimmune diseases [1]. Multiple genetic and genome-wide association studies have firmly established that HLA class II polymorphisms are a major genetic risk factor in many autoimmune diseases, as shown in detail for instance in rheumatoid arthritis (RA) [2, 3]. However, a genetically predisposed individual usually requires environmental exposures to initiate overt autoimmunity. With regard to potential triggers, infectious agents have long been implicated and are discussed herein.

The Role of Microorganisms in the Pathogenesis of SLE

The Microbiome

Chronic inflammatory disorders such as type 1 diabetes, Crohn's disease, or rheumatoid arthritis (RA) have been linked to gut microbial dysbiosis together with immune dysregulation. In addition, recent research suggests that early-life events and environmental factors play a significant role in the development of the adult immune system. In particular, diet and early-life exposures, e.g., infectious episodes or antibiotic exposures, influence immune cell numbers and functions. These factors are also influenced by the microbiota supporting an intricate interaction between environmental factors, the microbiota, and the host [4]. Additionally, the gut microbial communities change with increasing age, so another factor that contributes to dysbiosis is early-life perturbations [5]. Notably, several studies have shown that depletion of the gut microbiota in murine autoimmune models can affect autoantibody production as well as mortality [6]. Exact mechanisms through which the microbiota influences chronic immune-mediated diseases such as lupus remain to be established, but a multitude of effects on innate and adaptive immune cell functions are likely. In this chapter, we will focus on the effect of the microbiota on adaptive immune responses with implications for organ-specific and systemic autoimmunity and allude to potential roles in SLE.

Several groups have demonstrated in murine autoimmune models for multiple sclerosis or rheumatoid arthritis that Th17 cells, a subpopulation of CD4 T cells, are crucial in disease pathogenesis [7]. This subpopulation is characterized by expression of the chemokine receptor CCR6 as well as production of the inflammatory cytokine IL-17 [8, 9]. Th17 cells are, however, not the only cell type secreting IL-17. Voo et al. [10] have shown that there are a significant number of human $CD4^+$ $FOXP3^+$ regulatory T cells (Tregs) that have the capability to produce IL-17 upon activation, a subset that could not be found in the thymus. These are thought to be important in antimicrobial defense besides their regulatory function in autoimmunity and inflammation [10]. The differentiation of Tregs into an effector subset that is able to produce IL-17 may be mediated by epigenetic modifications [11]. This phenomenon may have evolved as a potent mechanism of the immune system to adapt to the vast variety of immune responses at different locations of the human body and at different stages of an immune response [12]. Th17 and Treg cells are the best-known counterparts in balancing the body's propensity to autoimmunity versus health and homeostasis.

Interestingly, both of the above CD4 helper subsets (Th17 and Tregs) are profoundly influenced by the microbiota. Induction of Tregs by certain microbiota has been reviewed in Chap. 5.

Herein, we summarize the role of gut commensals in the induction of Th17 cells. In mice, segmented filamentous bacteria (SFB), *Candidatus Arthromitus* or *Candidatus Savagella* are known as unique commensal bacteria that are able to stimulate maturation of the lymphoid cell compartments and to specifically induce Th17 cells in the small intestine [13]. Recently, a group in France succeeded for the first time in culturing SFB in vitro by mimicking their replicative niche, making it possible to study in detail its host interactions [13]. Importantly, SFB are capable of promoting pathogenic Th17 responses in mouse models of RA and multiple sclerosis. Thus, a possible influence of SFB on the pathogenesis of SLE seemed plausible, but studies using a lupus-prone mouse model suggest that SFB colonization might neither induce Th17 responses nor increase the incidence of disease [14].

Another important aspect of SFB biology is that these bacteria induce high levels of mucosal IgA and are highly IgA-coated. IgA is crucial for the homeostasis of the gut microbiota. Different levels of IgA coating of the microbiota have been exploited to identify pathogenic members of the human microbiota in inflammatory bowel disease [15]. It remains to be seen if extreme levels of IgA coating exist in non-gut diseases. An increased level of secretory IgA has been associated with intestinal dysbiosis in inflammatory bowel disease as well as psoriatic arthritis although the significance of this finding is unclear in the latter case [15, 16].

Production of high-affinity IgA is supported by a special subset of helper T cells, the T follicular helper (Tfh) cells, that have emerged as key players in the differentiation of memory B cells at several stages [17]. Interestingly, it has been suggested that Th17 cells act as progenitors for a subset of Tfh cells to promote the production of high-affinity IgA against commensal microbes [18]. This process is thought to occur via MyD88 signaling as loss of this pathway is accompanied by an inefficient IgA response as well as an altered commensal composition favoring a more inflammatory environment [19]. Several studies using lupus-prone animal models in addition to samples from human subjects demonstrated that these cells are involved in the production of pathogenic autoantibodies. A recent study showed increased Tfh-like cells ($CXCR5^+ICOS^+PD\text{-}1^+$) in SLE patient blood compared to healthy controls, which did not correlate with disease activity [20]. Thus, these cells may be considered as a marker of germinal center B-cell dysregulation. As detailed above, since Tfh cells are influenced by the gut microbiota, it is plausible to assume that the microbiota plays a role in the pathogenesis of human SLE. Over the last few years, exploratory studies on the contents of the microbiota in SLE have been published. A summary of four recent studies related to the human microbiota in SLE are listed in Table 21.1.

Various mechanisms have been ascribed to microbially triggered autoimmunity including molecular mimicry. As detailed also in Chap. 6, several studies in murine models of autoimmunity have established a role for commensal bacteria as potential chronic triggers, although the exact mechanisms remain unclear [25]. As the human gut microbiota provides an enormous source of persistent antigenic variation, it is plausible that molecular mimicry via cross-reactive antigen within the microbiome could be a chronic trigger of autoreactive lymphocytes, in particular those that are recognizing the earliest autoantigen in most lupus patients, the Ro60 protein, a conserved regulatory RNA-binding protein. Interestingly, certain human gut commensals encode Ro60 orthologs, which suggests that patients that are colonized with Ro60 ortholog-containing bacteria could develop cross-reactive responses to human Ro60 protein that eventually lead to pathogenic responses based on their HLA class II-related genetic predisposition. Indeed, experimental support for such a scenario is accumPulating [26].

In summary, many facets of the microbiota could influence the pathogenesis of SLE. Besides various innate immune interactions with the microbiota, adaptive immune responses described here—Treg/Th17 balances, Tfh, and IgA levels—are influenced by the microbiota and potentially dysregulated in lupus. It is important to note that there are likely even more host-microbiota interactions impinging on innate immunity that are

Table 21.1 Studies on the human microbiome in SLE patients

Source	Key findings	Comments
Intestinal dysbiosis associated with SLE [21]	16S rDNA sequencing of fecal samples from 20 SLE patients vs healthy donors revealed: (a) Comparable diversity between groups based on Shannon diversity index; significantly lower Firmicutes/Bacteroidetes ratio in SLE vs healthy as characterized in other autoimmune diseases (b) Decrease of some families within the Firmicutes, increase of Bacteroidetes opposite to obesity microbiota studies (c) In silico overrepresentation of oxidative phosphorylation and glycan utilization in SLE patient microbiota (d) Most abundant family in both subject groups was *Lachnospiraceae*	(a) Study examined only SLE patients in remission (1) Patients with more active disease are missing (2) Drug therapy prior to the study could have altered the microbiota (b) All patients were Caucasian
Ranking the impact of human health disorders on gut metabolism: Systemic lupus erythematosus and obesity as study cases [22]	(a) Statistically significant differences between patients and controls in composition of fecal metabolome (b) Mass spectroscopy (MS) signals were highly similar in all SLE patients regardless of age, BMI, disease duration, dietary intake, lifestyle, or medical history, while the MS signals of healthy subjects differed according to BMI status. SLE samples: decreased levels of components necessary for peptidoglycan cell wall synthesis; decreased molecules needed for heme synthesis (c) Conclusion: immune status of SLE is a dominant factor in the fecal metabolome, while in healthy subject BMI becomes driving factor determining microbial metabolism	– Healthy subjects but not SLE patients were selected based on BMI ranges, thereby possibly affecting the conclusions of this study
Th17 responses and natural IgM antibodies are related to gut microbiota composition in systemic lupus erythematosus patients [23]	(a) SLE fecal samples promoted lymphocyte activation and Th17 differentiation to a greater extent than healthy control microbiota (b) Enrichment of SLE microbiota with Treg-inducing bacteria reduced the Th17/Th1 balance; *Bifidobacterium bifidum* supplementation prevented $CD4^+$ lymphocyte overactivation (probiotics) (c) Ex vivo: increased Th17 and $Foxp3^+$ $IL\text{-}17^+$ populations (d) Negative correlation between $IL\text{-}17^+$ populations and Firmicutes in healthy controls (e) In SLE: proportion of Firmicutes correlated directly with serum levels of IFN-γ (f) Firmicutes/Bacteroidetes ratio reduced in SLE patients if anti-dsDNA titers increased; strong negative correlation with IL-6 serum levels; positive correlation with protective natural IgM antibodies against phosphorylcholine	– Significance of correlative findings unclear without in vitro or vivo studies to corroborate these findings
Association between *Staphylococcus aureus* nasal carriage and disease phenotype in patients affected by systemic lupus erythematosus [24]	(a) *S. aureus* colonization is frequent in patients with SLE and healthy subjects (21.4% vs 28.6%) (b) Presence of colonization associated with certain SLE phenotypes (renal involvement, autoantibody positivity) suggests that changes in the skin microbiota might be linked with SLE severity	(a) Study mainly based on questionnaires (b) No microbiome analyses performed

equally important in SLE pathogenesis, including activation of the inflammasome in lupus nephritis (LN) [27] or overstimulation of TLR signaling leading to an increased production of inflammatory cytokines and type I interferon (IFN) [28]. More research is needed to understand the multifaceted roles the microbiota may play in the pathogenesis of SLE.

The Pathogenic Microorganisms

Several studies on experimental animal models demonstrated that infectious agents are capable of breaking immunological tolerance to self-antigen inducing autoimmunity [29]. The list of microorganisms associated with human SLE includes parvovirus B19 [30], CMV [31, 32], retroviruses [31, 33], dengue virus [34], HPV vaccination or infection [35], *Toxocara canis* [36], and *Mycobacterium tuberculosis* [31], but the most compelling evidence supports a role for Epstein-Barr virus (EBV). Many SLE patients negative for anti-dsDNA antibodies showed abnormal antibody responses to EBV: they produced IgG antibodies to EBV antigens to which healthy controls did not respond and failed to make antibodies to EBV antigens seen in healthy controls [37].

It was reported that the positive rate of EBV-encoded latent membrane protein 1 (LMP1) in the renal tissues was significantly higher in young patients with LN compared to controls [38]. The positive rate was similar between patients of initial onset and relapse, and there was no detectable difference between the patients with and without infection. The findings support the hypothesis that EBV reactivation is associated with SLE induction with a potential role of EBV-encoded LMP1 in this process.

Rasmussen et al. [39] studied 57 SLE patients and 29 healthy controls using plasma galectin-3-binding protein as a surrogate marker of type I IFN activity. They showed that the marker's concentrations were significantly higher in SLE patients and associated positively with EBV early antigen diffuse (EBV EA/D)-directed antibodies and the presence of antibodies against extractable nuclear antigens [39].

In addition, Draborg et al. [40] demonstrated that there was an impaired regulation of the immune response against latent and lytic cycle EBV infection in SLE, even in the absence of lymphopenia, which further supported the proposed general dysfunction of leukocytes and their cytokine regulation in SLE patients. Reviewing the numerous experimental studies on EBV establishing an association with SLE, Draborg et al. [40] theorized that the interplay between an impaired immune system and the cumulative effects of EBV and other viruses results in frequent reactivation of EBV and enhanced cell death, leading to autoreactivity and development of SLE.

Type I INF family comprises 12 IFN-α subtypes and IFN-β, IFN-ε, IFN-κ, and IFN-ω. Normally, IFN-α and IFN-β production is strictly controlled but starts rapidly when viral or bacterial nucleic acids are sensed by pattern recognition receptors (PRRs) [41]. Two cell types capable of secreting large amounts of IFN-α and IFN-β are plasmacytoid dendritic cells (PDC) and monocytes. Monocytes respond mainly to dsRNA, certain RNA viruses such as Sendai and influenza virus, whereas PDCs can be triggered to secrete type I IFN by almost all viruses and some bacteria [42].

As microbial RNA and DNA can be recognized by multiple nucleic acid sensors and thereby induce production of type I IFNs, this may be the mechanism by which several microorganisms can contribute to the development and relapse of SLE [43]. An increase in the expression of long interspersed nuclear element 1 (LINE-1) was reported in kidney biopsies from patients with LN and transcript expression correlated with the tissue expression of type I IFN [44]. This connection may suggest that endogenous retroviruses may play a role in the initiation or amplification of the autoimmune process [43].

A recent study implicated one additional specific organism, *Enterococcus gallinarum*, as an etiologic agent of lupus. Manfredo Vieira et al. [45] studied the (NZW × BXSB)F^1 lupus model, demonstrating a role for the microbiota as evidenced by diminished disease following antibiotic therapy. Antibiotics also strengthened the gut wall barrier, preventing translocation of bacteria into the mesenteric lymph nodes, mesenteric veins, and liver. *E. gallinarum* specifically was able to weaken the barrier defense and induce pro-inflammatory intestinal changes in mice, and its translocation specifically upregulated lupus-associated autoantibody production, and vaccination against *E. gallinarum* was protective against the diseaes in mice. Finally, in humans, this

organism was present in the livers of 3/3 lupus patients who underwent biopsy, compared to 0/6 healthy liver transplant donors.

The Protective Role of Infectious Agents and Parasites

Contrary to this, there are other studies that support the notion of a protective role of other organisms. Experimental animal studies showed that hepatitis B virus plays a protective role against SLE [46]. Gamma-irradiated *Plasmodium chabaudi* infection of lupus-prone BWF1 mice ameliorated the histopathological changes attributed to renal involvement in lupus [47]. Another study showed that infection of female BWF1 lupus mice with malaria parasites attenuated B-cell autoreactivity [48]. Chen et al. demonstrated that *Toxoplasma gondii* infection may prevent the progression of SLE-related nephritis in New Zealand Black/New Zealand White F1 mice and was associated with downregulated intracellular expression of IFN-γ and IL-10 [49]. Fischer et al. evaluated the seroprevalence of anti-*T. gondii* antibodies in European patients with rheumatoid arthritis (RA) and SLE. They found a higher prevalence of anti-*T. gondii* antibodies in those with RA than in SLE patients (63% vs 36%, respectively) and that the rates of seropositivity of IgG against other infectious agents were comparable between the two groups [50].

Sowalha and his group investigated the prevalence of *Helicobacter pylori* seropositivity in a cohort of 466 patients with SLE, finding a low rate of specific *H. pylori* antibodies suggesting that *H. pylori* might exert a protective role on the risk of developing SLE [51]. Furthermore, it has been reported that in filarial endemic areas in India, patients with SLE do not suffer from concomitant filariasis. Filarial infestation was found to be associated with a low plasma level of IL-17A, which may contribute to protection from the development of autoimmune disorders like SLE [52].

Many pathogens have developed efficient methods to overcome adaptive immune mechanisms, and there is growing evidence that they are capable of insinuating their own anti-immune strategies into a susceptible host. They can block antigen presentation interference with Toll-like receptor signaling and alter the cytokine milieu, which is crucial for an effective immune response. They may also cause antigenic competition, the tendency of strong antigens, particularly from infectious agents, to impair antibody responses to weaker ones, which would dampen immune responses against self-antigens [53, 54].

Risk Factors for Infection in SLE

SLE patients have an increased frequency of severe bacterial and viral infections, possibly due to inherited genetic and immunological defects as well as due to chronic immunosuppressive therapies [55].

Doaty et al. [31] in their review of literature cited innate immunity disturbance in SLE patients that included:

(a) Breakdown of epithelial barriers in SLE patients caused by rashes, ulcers, and wounds allowing entry of infectious agents in the body.
(b) Accumulation of gamma delta T cells in skin of SLE patients as compared to healthy subjects [56]. These cells are implicated in epithelial breakdown, further increasing the risk of infection [57].
(c) Impaired production of IL-8 and IL-12 by PMNs with disruption of the links between the innate and adaptive systems mediated by IL-12 [58].
(d) Deficiencies of the early components of the classical pathway of the complement system (C1q, C4, and C2). A higher prevalence of these genetic defects has been established in SLE, but acquired complement deficiency because of consumption due to immune complex disease may also play a role in predisposing SLE patients to infection by encapsulated organisms [59–61]. Furthermore, single nucleotide polymorphisms have been reported associated with mannose-binding lectin deficiency in SLE patients, further increasing their susceptibility to infection [62, 63].

(e) Decreased levels of complement receptors CR1 and CR2 on B cells, PMNs, and RBCs in SLE patents [64].
(f) Suppressed natural killer (NK)-cell cytotoxicity with fewer NK cells [65] and weaker NK response to IL-2 stimulation [66].

Inappropriate or dysfunctional antigen presentation by DCs might promote the breakdown of T-cell and B-cell tolerance in SLE and other autoimmune diseases. Patients with SLE show multiple DC abnormalities, including a reduced number of circulating conventional DCs but increased numbers of PDCs [67].

Neutrophils show several facets of dysregulation in SLE. Impaired phagocytosis by neutrophils in SLE has been described in multiple reports and might contribute to the increased susceptibility to infection associated with this disease [68]. In one study, neutrophils from patients with SLE showed reduced production of reactive oxygen species (ROS), which correlated with disease severity and end-organ damage [69]. Patients with chronic granulomatous disease, in which ROS production is defective, have a high incidence of SLE [70, 71]. Patients with SLE have an abnormal subset of neutrophils (termed low-density granulocytes) with an increased propensity for NETosis [72]. NETosis is a mechanism of cell death that occurs in response to various stimuli, including infectious organisms and oxidative stress. NETosis involves the extrusion of chromatin and other nuclear, cytoplasmic, and granular material from the cell. This extruded material, called neutrophil extracellular traps (NETs), contains proinflammatory cytokines, antimicrobial peptides, enzymes such as myeloperoxidase, and potentially antigenic citrullinated histones and dsDNA [73].

Other workers reported that leukopenia, in particular lymphopenia, was a common finding in SLE. In their work, however, it was not persistent [74]. SLE patients can also develop granulocytopenia due to anti-granulocyte antibodies or complications from chronic immunosuppression. If neutropenia is severe enough, the impaired function of PMNs in SLE predisposes to severe bacterial infections. It was reported [68] that regardless of infection status, medication, or disease activity, pediatric-onset SLE patients have impaired phagocytic ability against *Salmonella*-specific lipopolysaccharides (LPS) which is not influenced by the use of immunosuppressants. The same study [68] did not find deficiency of peroxidase production and chemotaxis activity in SLE patients; however, serum complement levels were not reported.

In the earlier review by Doaty et al. [31], they also reported adaptive immunity disturbances such as:

(a) Impaired production of IFN-γ, IL-1, IL-2, and TNF-α contributing to T-cell dysfunction [75]
(b) Reduced numbers and dysfunction of all B-cell lines: naïve, memory, and plasma cells

Hypogammaglobulinemia has been attributed to immunosuppressive therapy in SLE patients even in the absence of therapy with B-cell-depleting agents. Isolated IgM [76] and IgA [77] were reported in SLE patients; however their contribution to an increased risk of infection was not shown. Therefore, it has been recommended in one report to measure immunoglobulin levels during the course of SLE treatment [78].

More than 80 genetic loci are reported to show robust genetic associations with SLE [79–82]. More than half of these loci are connected to the type I IFN system [83]. Genome-wide association studies have revealed single nucleotide polymorphisms in the STAT4 gene, which codes for a protein involved in type I interferon receptor signal transduction, that are associated with enhanced protein production [84]. The NCF1 gene encodes the p47phox/Ncf1 protein of the NADPH oxidase (NOX2) complex, which is critical for the induction of ROS. The NCF1 gene is highly complex and has excluded SNPs in NCF1 in genome-wide association studies. It has been recently reported that an amino acid replacement in NCF1, leading to a lower capacity of inducing oxidative burst, is strongly associated with SLE [85, 86]. This observation aligns with the previously reported association of an ROS-reducing SNP in the NCF2 gene with SLE [87]. Also, some rare monogenic SLE

diseases are now categorized as type I interferonopathies because of the prominent type I IFN signature [43].

In a study by Danza and Ruiz-Irastorza [88], risk factors for infection in SLE included disease activity, prednisone doses over 7.5–10 mg/day, high doses of methylprednisolone, as well as use of chemotherapeutic agents such as cyclophosphamide and multiple courses of rituximab treatment. It is difficult, however, to tease apart the therapeutics from the underlying disease severity that prompted use of these medications. Indeed, lupus patients present with multiple features that pose an increased infection risk, including hypocomplementemia, lymphopenia, and hyposplenism, and data from the 1970s prior to the introduction and widespread use of newer therapies indicated a high risk of mortality from infections early in the disease course, attesting again to the infectious risk associated with active SLE [89].

Lupus Nephritis

Renal involvement occurs in up to 60% of SLE patients [90] and remains a major determinant for morbidity and mortality among these patients [90, 91]. We will focus on this particular organ as a notorious example of the interplay between the disease and infection.

Feldman et al. [92] studied serious infections among adult Medicaid beneficiaries with SLE and LN over the years 2000–2010. They identified 33,565 patients with SLE, of whom 7113 had LN. There were 9078 serious infections reported in 7078 SLE patients, whereas in 1825 LN patients, there were 3494 reports. Infection incidence rate per 100 person-year was 10.8 in the SLE cohort and 23.9 in the LN sub-cohort.

Therapeutic modalities used in LN management, either as induction therapy or for maintenance treatment, influence the prognosis of LN. An Egyptian study retrospectively analyzed records of 928 SLE patients with biopsy-confirmed LN seen between 2006 and 2012 at Cairo University hospitals [93]. The reported complications included pneumonia requiring hospitalization in 93/575 (16.1%) patients who received intravenous cyclophosphamide as induction therapy, compared to 22 of 321 (6.9%) patients in the group that received mycophenolate. However, the difference between these two groups was not statistically significant ($p = 0.270$). Herpes zoster infection (HZI) was reported in 12 (1.3%) patients. The 5-year mortality was 7.4%. Sepsis was responsible for death in 68.1%, which was higher than the percentages reported in Europe (25%) [94] and China (60%) [95].

In India, Srivastava et al. [96] studied the outcome of LN in childhood-onset SLE (cSLE) retrospectively from 1989 to 2013. Among 205 children with cSLE, 134 had evidence of LN. During the follow-up period, 11 (8.2%) children died, and infections were the leading cause of death.

Lin et al. [97] conducted a nationwide cohort study of 7326 patients with newly diagnosed SLE and no history of end-stage renal disease (ESRD). They derived their data from Taiwan's National Health Insurance claims database from 2000 to 2011. Among all SLE patients, 316 (43%) developed ESRD. Multivariate Cox regression analysis indicated that the risk of ESRD increased with the number of infection-related hospitalizations. For patients with three or more infection-related admissions, the hazard ratio (HR) for ESRD was 5.08 (99% CI: 3.74–6.90) relative to those with no infection-related admissions. Analysis by type of infection indicated that bacteremia patients had the greatest risk for ESRD with a HR of 4.82 (95% CI: 3.40–6.85) highlighting the impact of infection on LN outcome.

In South China [98], a group of investigators studied hospital-acquired infections (HAI) in SLE patients. In a multivariate analysis, they found that a history of LN or a higher SLE disease activity index SLEDAI score correlated with HAI [OR: 3.7 ($p < 0.001$) and 1.1 ($p < 0.001$), respectively]. Moreover, treatment with high doses of glucocorticoids or cyclophosphamide was the main risk factor for HAI [OR: 2.7 ($p < 0.001$) and 2.9 ($p < 0.001$), respectively].

Murray et al. [99] studied hospitalization trends for SLE from 2000 to 2011. They identified 361,337 hospitalizations for SLE that were

derived from the United States (US) Healthcare Cost and Utilization Project National Inpatient Sample (NIS). A diagnosis of SLE was associated with increased severe and opportunistic infections, including bacteremia, pneumonia, opportunistic fungal infections, herpes zoster (HZ), CMV, and *Pneumocystis jirovecii* pneumonia (PJP). They also found that among SLE hospitalization, rates of all these infections significantly rose between 2000 and 2011, with the exception of PJP which significantly declined. HZ was the only infection that disproportionally increased over time among SLE hospitalizations when compared with non-SLE hospitalizations. They attributed this to the increasingly widespread use of mycophenolate mofetil for induction and maintenance of LN and for severe non-renal lupus. It has been demonstrated that medications used to treat SLE, including prednisone, azathioprine, and cyclophosphamide, increase the risk of HZ [100–104]. In a prospective cohort study of 1485 patients with SLE, the hazard ratio for an incident diagnosis of HZ was greatest in SLE patients treated with mycophenolate mofetil (HR 5.00, 95% CI 1.40–17.60) followed by prednisone [100].

Murray et al. [99] attributed the reduction of PJP in their study to the declining use of cyclophosphamide and increasing use of mycophenolate. Even among patients receiving cyclophosphamide as induction therapy, cumulative doses may be declining over time. The Euro-Lupus Nephritis trial demonstrated equivalent efficacy and a favorable side effect profile for low-dose intravenous cyclophosphamide compared with a previously standard high-dose regime [105, 106]. Also, the American College of Rheumatology recommended mycophenolate or cyclophosphamide for induction of LN with lower cumulative doses of cyclophosphamide ("Euro-Lupus" dosing schedule), followed by mycophenolate or azathioprine for maintenance therapy [107]. Interestingly, animal studies and data from renal transplant trials suggest that mycophenolate may have antimicrobial properties against *P. jirovecii*, although data specific to lupus patients are lacking [108, 109].

Based on the Medicaid Analytic Extract database (2000–2010); Feldman et al. [92] found no difference in the rates of serious infection and mortality among new users of mycophenolate, azathioprine, or cyclophosphamide when examining the 29 most populated US states. Strikingly, antimalarial treatment of SLE patients was associated with an additional benefit in protection against serious infection [110]. In summary, patients with severe lupus, as evidenced by LN, have a high risk of serious infections, including death. It remains unclear the extent to which this higher risk is mediated by the underlying disease severity, versus its therapy. One favorable trend in recent years has been a lower incidence of PJP, potentially attributable to lower cumulative doses of cyclophosphamide and/or more widespread usage of mycophenolate.

The Heavy Burden of Infection on Morbidity and Mortality in SLE

It is well established that infection contributes significantly to the morbidity and mortality of SLE patients. In a South African study [111], the authors reviewed the records of hospitalized SLE patients admitted over a 79-month period. They found that infections accounted for 35.2% of admissions. Among those, pneumonia, cutaneous sepsis, urinary tract infections, and septicemia were the most common types of infection. Organisms commonly isolated were *Staphylococcus aureus*, *Escherichia coli*, and *Klebsiella* species, as well as *Mycobacterium tuberculosis*. The incidence rate ratio for infection in SLE was 1.49 compared to matched controls emphasizing its burden as a comorbidity in the disease [112]. It was found that infection-related hospitalizations are associated with an increased risk of end-stage renal disease in SLE, especially the juvenile-onset type [97]. Souza et al. reported that renal failure and infectious diseases were the most frequent causes of death in Brazilian SLE patients [113]. A Chinese study reported that over time (1986–2012) infections have increased gradually and have become the most frequent cause of death in SLE

[114]. Richie et al. extensively reviewed the literature and reported a total of 17 maternal deaths in women with LN within 6 weeks postpartum. In all cases where mortality was attributed to SLE and nephritis, the patients had active disease, and infection was responsible for 41.2% of deaths [115]. In a meta-analysis that included 26,101 SLE patients with 4640 deaths, the cause-specific standardized mortality ratios (SMRs) were assessed in SLE patients. The SMR for infection was reported as 4980 with a highly significant *p*-value [116]. In a multicenter Southern Chinese study that included 3815 hospitalized patients, infection was the leading cause of death. Features of infection in this group included early disease onset, higher percentage of respiratory tract involvement, and predominance of Gram-negative bacteria with emergence of multidrug-resistant strains and a variety of pathogens [117].

The Clinical Presentations of Infections in SLE

Serious infections are defined as those that lead to hospitalization or death or require intravenous antibiotic treatment [118].

Shen et al. [119] studied the temporal trends among SLE patients in the intensive care unit (ICU) as part of a national population-based study in Taiwan between 1999 and 2008. The incidence of infection rose from 39.1% to 47.2%. The study reported three poor prognostic factors (i.e., older age, infection, and organ dysfunction) that were thought to potentially lessen the temporal improvement of short-term survival in ICU patients with SLE. The authors suggested that improved treatment of SLE reduces and postpones the occurrence of acute critical illness. Their study showed that the median time for SLE diagnosis to ICU admission had increased by 4 years during the 10-year study period. However, the improved survival was achieved at the costs of immune-suppression and accrual of organ damage.

Han et al. [120] studied the clinical presentations and outcomes of SLE patients with infection admitted to the ICU. They demonstrated that SLE patients with infections in the ICU have a higher mortality rate, and a higher APACHE II score compared to SLE patients without infections. SLE with infections also had a higher maximum temperature, higher minimum and maximum systolic blood pressure compared to SLE patients with noninfectious causes of admission.

Musculoskeletal System

Odd presentations of musculoskeletal infections at unusual anatomical sites like the sacroiliac joint [121] and uncommon organisms like *Candida albicans* involving the joints [122] are frequently reported in SLE patients. One rare and frequently misdiagnosed infection in SLE is tropical pyomyositis, primary muscle abscesses most frequently due to *Staphylococcus aureus* and frequently following trauma [123]. Also, hematogenous salmonella osteomyelitis can be encountered in immunocompromised SLE patients, a finding that can be complicated by septic arthritis if not managed promptly [124]. Infection should also be considered when dealing with cases of osteonecrosis [124, 125].

Mucocutaneous and Genital Manifestations

In a retrospective multicenter cohort study involving ten pediatric rheumatology services in São Paulo, Brazil, that included 852 childhood-onset SLE patients, the researchers reported a frequency of 14% of herpes zoster infection (HZI). Hospitalization took place in 61% of these cases, and secondary bacterial infection was reported in 13%. Postherpetic neuralgia occurred in 5%. Lymphopenia and immunosuppressive therapy seemed to be the major factors underlying this complication [126].

There is a special interest concerning human papillomavirus (HPV) in SLE patients. In a meta-analysis, the authors found that cutane-

ous warts (CW) were present in a higher frequency in SLE patients compared to healthy controls. It is of interest that most of the articles they cited showed that the presence of CW did not correlate with the use of immunosuppressive drugs [127].

SLE female patients have also been shown to have a higher prevalence of genital HPV infection (80.7%) compared to healthy women (35%). The odds ratio (OR) for genital HPV infection in women with SLE was 7.2 [128]. There was no evidence that the use of immunosuppressive drugs was associated with a higher prevalence of HPV infection. This finding together with the study of Silva et al. [127] suggests that the high prevalence of HPV may be due to defects in immune mechanisms that are independent of immunosuppressive drugs. Another study found that in a subset of women diagnosed with SLE in the eastern Brazilian Amazon, 75% of them were HPV positive in the 1–5 years preceding the study [129].

The Urinary Tract

Lupus patients are likely to have urinary tract infections (UTI), with a prevalence of 36%. They usually manifest in the lower tract. They are community acquired, and the most frequently isolated uropathogen is *E.coli* [130].

In an Egyptian cohort of 200 SLE patients who were followed up for one year, the urinary tract was the most common site of infection (31.8%) with 74/230 infectious episodes. *E.coli* was the most common isolated bacterial organism (26/230), followed by *Klebsiella* species (11/230) and *Proteus mirabilis* (8/230), whereas nine cases had mixed infections [131].

Hematological Involvement

Lupus patients with episodes of bacteremia suffer from poor long-term outcome. *E. coli* and *S. aureus* are the leading pathogens reported in this setting. Community-acquired bacteremia and C-reactive protein levels lower than 8 mg/dl during bacteremic episodes are associated with lower long-term mortality [132]. A Danish study involving 5102 patient-years of follow-up [133] reported an increased incidence of arterial and venous thrombosis within 1 year after infection (2.18% and 2.56%, respectively) compared to patients who never had either a hospitalized infection or herpes simplex virus. Infections can also trigger catastrophic antiphospholipid syndrome [134] (see Chap. 22).

The Respiratory System

Respiratory tract infection is a common problem in SLE. Luijten et al. [135] reported the incidence of invasive pneumococcal infections to be 13 times higher in SLE patients than in the general Dutch population. The prevalence of latent tuberculosis infection was reported to be 26.5% in SLE patients [136]. The authors of the study cautioned that higher SLE disease activity index (SLEDAI) and increased glucocorticoid dose were associated with indeterminate results in interferon-gamma release assays. Fungal infections including aspergillosis can occur and may be associated with cavitary lesions that can lead to pneumothorax [137] (Fig. 21.1).

Studying the incidence of diffuse alveolar hemorrhage (DAH) in SLE patients [138], researchers reported 57 episodes of DAH of 50 patients including seven recurrences. They detected infection in 22 episodes (38.6%): 8 invasive fungal infections and 16 bacterial infections, including two patients with both types. These infections were associated with treatment for SLE, requirement for mechanical ventilation, hypocomplementemia, and high CRP levels.

The Gastrointestinal System

In a large prospective cohort study of 2258 SLE patients from the Hopkins Lupus Cohort, Fangtham et al. [139] reported 53,548 cohort visits. Oral candidiasis was diagnosed at 675 visits

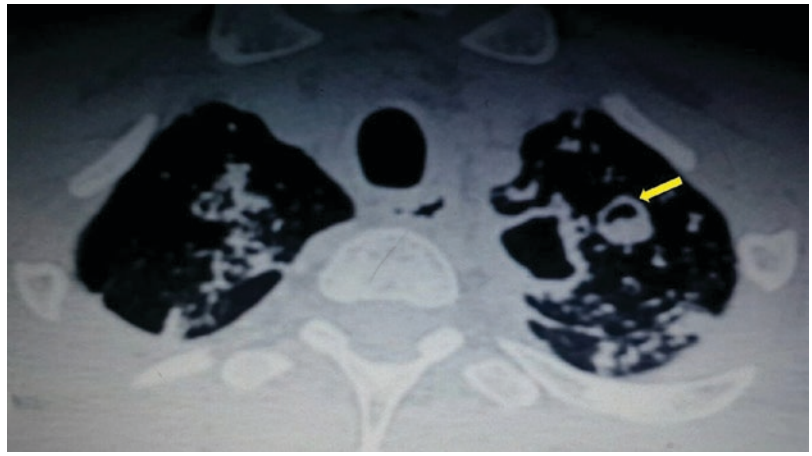

Fig. 21.1 High-resolution chest CT scan with contrast showing a case of SLE with multiple pulmonary fungal cavitary lesions. Arrow: intracavitary mycosis. Microbiological studies diagnosed the case as aspergillosis. *SLE* systemic lupus erythematosus. Courtesy of Dr. Hala El-Guendy, Professor of Internal Medicine, Cairo University

(1.25%), in 325/2258 (14%) of SLE patients. The authors recommended inspection of the oral cavity for signs of oral candidiasis, especially in patients with active disease, proteinuria, high white blood cell count, and intake of prednisone, immunosuppressive drugs, or antibiotics.

Fawzy et al. [140] reported an increase of *Giardia lamblia* infection in SLE patients: 30% in SLE patients compared to 3.3% in healthy, age- and sex-matched controls from the same geographic area. This number was even higher in those who had GI symptoms (52.9%). In acute pancreatitis, the presence of concomitant infections was associated with a poor prognosis in SLE patients [141].

Opportunistic CMV colitis can lead to colonic perforation with life-threatening consequences [142, 143]. In case of significant gastrointestinal symptoms, CMV infection should be considered in SLE patients who are immunosuppressed. SLE was also found to be significantly associated with chronic hepatitis C infection [144].

The Nervous System

Infectious brain lesions (IBLs) are rare presentations in SLE patients. They can, however, be life-threatening in this context. Xu et al. [145] described 15 patients with IBLs. They reported the following characteristics: fever in 80% of cases, headache and focal neurological signs (73.3%), associated pulmonary infection (66.7%), and associated meningitis (40%). There were ring-enhancing lesions in enhanced magnetic resonance imaging in all patients (100%) (Fig. 21.2).

Progressive multifocal leukoencephalopathy (PML) has been reported in SLE patients treated with various immunosuppressive therapies including biological drugs (e.g., rituximab or belimumab). It was suggested that severe lymphopenia may be responsible for John Cunningham virus (JCV) reactivation, the causative agent of PML. Early infection screening, antiviral therapy, and effective management of lymphopenia are important in this setting [146]. Diagnosis of PML is generally made by identification of the virus in CSF by PCR along with consistent imaging and clinical features [147]. CSF lactate is a good single indicator and a better marker, compared to other conventional markers, to distinguish bacterial meningitis from aseptic meningitis [148, 149].

Cryptococcal meningitis [150] and meningoencephalitis [151] can be fatal in SLE patients. Epidural infection, an uncommon condition, can be caused by *Salmonella enteritidis*, which was also reported in SLE [152]. An early diagnosis and prompt treatment is essential to prevent mortality.

Invasive and Disseminated Infections

Miliary TB with fatal consequences has been reported in juvenile SLE patients in Brazil. The authors stressed the importance of routine

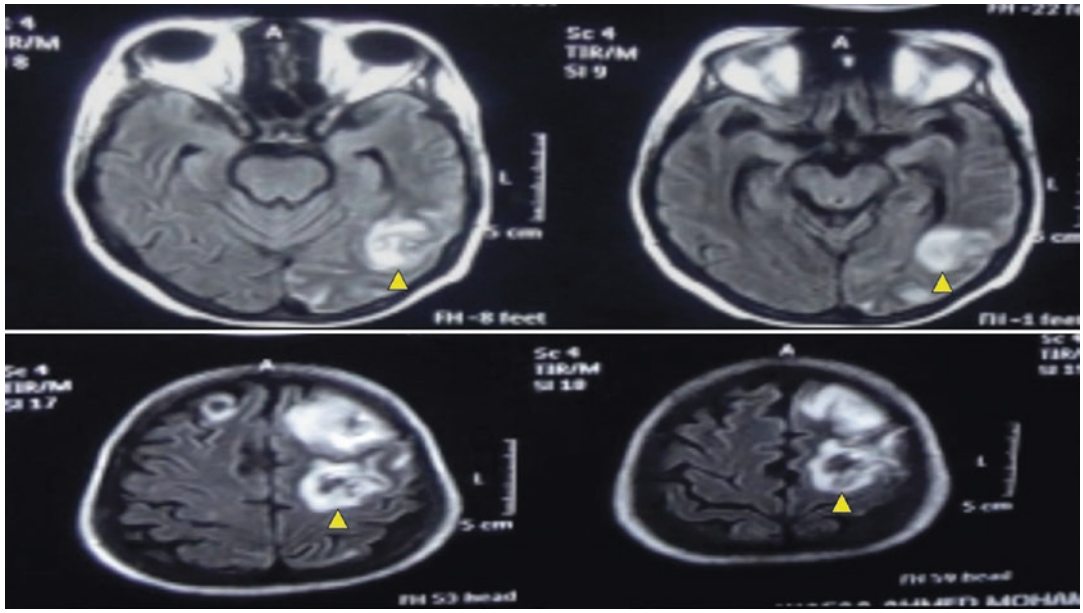

Fig. 21.2 Cranial MRI with IV contrast, T2 weighted, showing an SLE patient whose condition was complicated with subacute bacterial endocarditis (SBE) and multiple infected emboli of the brain. Arrow heads: ring-enhancing lesions. Courtesy of Dr. Hala El-Guendy, Professor of Internal Medicine, Cairo University

screening for TB in this patient population [153]. Also, the prevalence of disseminated CMV infection is rising as a complication of active treatment of SLE [154].

Invasive fungal infections (IFI) describe a group of diseases caused by cryptococcus, histoplasma, aspergillus, and candida [155]. Their frequency was 4.8% in hospitalized SLE patients in Argentina [155] and 3.9% in juvenile SLE in Brazil [156]. A Mexican study [157] found the risk of IFI in SLE to be associated with high CRP levels, high disease activity, mechanical ventilation, antibiotic treatment, hemodialysis, high dose of glucocorticoids, and treatment with mycophenolate mofetil. The mortality was four times higher in patients with IFI than in those without. *Cryptococcus neoformans* is the most frequent agent in Argentina and East Asia [155, 158], while *Candida* spp. are more common in North America [155].

IFI should be suspected in hospitalized SLE patients undergoing immunosuppressive therapy. We suggest that clinicians have a high index of suspicion for IFI in hospitalized SLE patients who have unexplained organ-specific symptoms and imaging abnormalities (e.g., neurologic, pulmonary, dermatologic, musculoskeletal, and elevated CRP with or without elevated WBC or fever). Additionally, hospitalized SLE patients who do not improve rapidly with antibiotics should undergo thorough diagnostic procedures (e.g., CSF sampling, bone marrow/tissue biopsies and/or bronchoalveolar lavage with culture, histopathology, serum antigen and antibody levels, and PCR testing) and consideration for prompt empiric antifungal treatment.

Differentiating Flare from Infection in SLE Patients

SLE follows a chronic course with intermitting flares [159]. Symptoms such as fever, fatigue, and rash may be seen in an SLE flare or as a result of infection [160]. The differentiation of SLE activity and infection in febrile or otherwise acutely ill SLE patients is extremely difficult, and several biomarkers have been recognized as potential tools to differentiate between these two conditions [161].

Serum procalcitonin (PCT) and CRP are markers with strong supportive evidence. Song et al. [162] performed a meta-analysis of published studies and found that procalcitonin is more specific and has better diagnostic accuracy than PCR for bacterial infection in systemic rheumatic diseases. Bador et al. [163] conducted a study to determine predictive values of PCT and CRP for bacterial infections in SLE patients. Bacterial infection was defined as positive culture results. PCT and CRP were measured by automated immunoassays. The areas under the receiver operating characteristic curves for PCT and CRP were not significantly different (0.797 (CCI 0.614–0.979) vs 0.755 (CI 0.600–0.910)). They found that PCT but not CRP was higher in flaring lupus patients with infection ($p = 0.019$ vs 0.195), as compared to flaring SLE patients without infection. A PCT of <0.17 ng/ml ruled out infection with a negative predictive value (NPV) of 94%. In patients in remission, CRP but not PCT was elevated during infection ($p = 0.036$ vs 0.103); a CRP <0.57 ng/dl had a NPV of 96%. They concluded that PCT may be a better marker to rule out bacterial infection in lupus flares but not in remission or general screening. Serio et al. [164] conducted a systematic review on this topic and concluded that PCT levels detected during disease flares were lower than those observed during bacterial infection and that elevated PCT levels ≥0.5 μg/l strongly suggest bacterial infection. SLE patients, including patients in remission, tend to have higher CRP baseline levels when compared with controls. CRP response during flares seems to be incomplete and did not always correlate with disease activity. Values greater than 1.0 mg/dl can indicate severe flare if neither serositis nor arthritis is associated, while higher CRP levels above 5–6 mg/dl may be associated with infection [165].

Other potential biomarkers have been identified but have limited usage to date. One is the delta neutrophil index, an index which reflects the fraction of circulating immature granulocytes associated with infection [166]. The activity of adenosine triphosphate produced by $CD4^+$ T cells was also found to be lower in patients with LN with infection compared to non-infected LN patients [167]. The ratio of erythrocyte-bound C4d to complement receptor 1 (C4d/CR1) was also studied. Febrile patients with disease flares had higher ratios and lower CRP levels than those with infection [168]. Ospina et al. [161] suggested that new scores, which include different biomarkers, might represent a better solution for differentiating infections from flares.

Prevention of Infections in SLE

Various strategies can be applied to reduce the risk of infections in SLE patients. These include vaccinations, antibacterial or antiviral prophylaxis, and intravenous immunoglobulins [169] (see also Chaps. 32 and 33).

Most non-live vaccines are immunogenic and safe in SLE patients, although antibody titers are frequently lower than those of healthy controls [170]. HPV vaccines can be given safely to SLE patients to avoid the increased incidence of anogenital warts and cervical epithelial dysplasia or carcinoma associated with high-risk viral genotypes [170]. Several experts [171] have recommended annual examinations of the cervical cytology in immunosuppressed patients.

Influenza vaccination is well tolerated and conveys a moderate protection against influenza infection in SLE. Considering that influenza runs a more severe course in SLE patients with a higher risk of disease exacerbation, influenza vaccination is recommended in patients with a low-to-moderate SLEDAI score or in those with stable disease. However, there were limited data and concern of the vaccine triggering a flare in severe disease [172]. Pneumococcal vaccination, however, is recommended for patients at any stage of their disease [171].

Live attenuated vaccines should generally be avoided in immunosuppressed patients. Recent studies, however, suggest that they can be considered in mildly immunosuppressed patients [171]. Serological screening for hepatitis B virus infection before starting immunosuppressive therapy is recommended for SLE patients to avoid viral reactivation [173].

Conclusion In summary, microbial agents are involved in various aspects of lupus including the pathogenesis, treatment complications, and long-term sequelae. Further studies are needed to fully delineate the role of commensal microbiota in the pathogenesis of SLE and the entire spectrum of acute and chronic infections (bacterial, viral, parasitic) during the lifespan of lupus patients, particularly those on chronic immunosuppressive therapies.

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