Infection in Southern Chinese Patients with Systemic Lupus Erythematosus: Spectrum, Drug Resistance, Outcomes, and Risk Factors

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ABSTRACT. ***Objective.*** To investigate the spectrum, antibiotic-resistant pattern, risk factors, and outcomes of infection in patients hospitalized with systemic lupus erythematosus (SLE).

Methods. We collected the clinical and microbiological data from hospitalized patients with SLE with infection between June 2005 and June 2015, and then conducted retrospective analyses.

Results. Among our sample of 3815 hospitalized patients, 1321 (34.6%) were diagnosed with infection. The majority (78.3%) of infection occurred within 5 years of SLE onset. Bacterial infection was predominant (50.6%), followed by viral infection (36.4%) and fungal infection (12.5%). The lungs (33.7%) and upper respiratory tracts (26.3%) were most commonly affected. Gram-negative bacteria (GNB) were predominant over gram-positive bacteria (178 isolates vs 90 isolates). The most frequently isolated bacteria were *Escherichia coli* (24.6%), followed by *Acinetobacter baumannii* (13.4%) and coagulase-negative *Staphylococcus* (13.4%). Multidrug-resistant (MDR) strains were detected in 26.9% of bacterial isolates. The most common fungus was *Candida spp*. (99 episodes), followed by *Aspergillus* (24 episodes) and *Cryptococcus neoformans* (13 episodes). The overall mortality rate for this cohort was 2.2%; 48 patients died of infection. Factors associated with bacterial and viral infection were higher Systemic Lupus Erythematosus Disease Activity Index, renal involvement, thrombocytopenia, accumulated dose of glucocorticoids (GC), and treatment with cyclophosphamide (CYC). Renal involvement, accumulated dose of GC, and treatment with CYC were associated with fungal infection.

Conclusion. Infection was the leading cause of mortality in patients hospitalized with SLE. There were some notable features of infection in Chinese patients including early onset, higher proportion of respiratory tract involvement, predominance of GNB with emergence of MDR isolates, and a variety of pathogens. (J Rheumatol First Release June 15 2016; doi:10.3899/jrheum.151523)

Key Indexing Terms:
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Systemic lupus erythematosus (SLE) is a chronic autoimmune disease with varied organ involvement. In recent decades, given the improvements in treatment, the leading cause of death in patients with SLE has changed from active disease to infection. The spectrum of infectious agents and predisposing risk factors of infection in patients with SLE varies significantly among different ethnic groups. Multiple drug-resistant (MDR) pathogens have become the biggest concern worldwide, and the situation is even more serious in China[1]. Analyzing the pattern of infection and drug resistance has helped to determine the optimal treatments and improve prognosis. To date, however, there are still limited data pertaining to infection prevalence and patterns in patients with SLE from south China.

We therefore conducted a retrospective study based on a large number of patients during the last 10 years. The objectives of our study were to (1) determine the prevalence and types of infection, (2) discover the infectious agents involved and their antibiotic-resistant pattern, and (3) identify the factors that might favor the onset of infection, as well as their probable influence on disease outcome.

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MATERIALS AND METHODS

Study design and patients. We performed a retrospective review of medical records from consecutive patients with SLE hospitalized in the First Affiliated Hospital of Sun Yat-Sen University from June 2005 to June 2015. All patients met at least 4 of the revised American College of Rheumatology criteria for SLE classification[2]. The infectious conditions of the patients were systematically checked. Patients with incomplete medical records or who were lost to followup were excluded.

Definition of infection. Bacterial infections were considered definite or probable according to culture results. A definite bacterial infection was diagnosed if an organism was identified on microscopy or culture. In the absence of an organism being identified, a probable bacterial infection diagnosis was made on the basis of a combination of clinical findings, review of imaging studies, laboratory findings such as raised C-reactive protein, white cell count, or procalcitonin, and a response to only antibiotic therapy. Isolated bacteria were identified to the species level and tested for their susceptibility to a variety of antimicrobial agents using the BD Phoenix Automated Microbiology System (BD Diagnostic Systems). MDR bacteria were defined as showing resistance to 3 different classes of antibiotics. Invasive fungal disease (IFD) was diagnosed according to the 2008 European Organization for the Research and Treatment of Cancer/Invasive Fungal Infections Cooperative Group and the National Institute of Allergy and Infectious Diseases Mycoses Study Group Consensus Group criteria[3].

Acute viral infections were diagnosed on the basis of a combination of manifestations: (1) clinical features (e.g., prolonged fever, pharyngitis, arthralgia, cutaneous rash, acute hepatitis, or gastroenteritis) and/or specific imaging (e.g., interstitial pneumonia) suggestive of acute viral infections in the absence of positive bacterial cultures; (2) nonresponse to increased doses of corticosteroids or even immunosuppressive agents, or response to only antiviral treatment without any evidence of active SLE; and (3) positive results of antiviral immunoglobulin (Ig) M antibodies and subsequent specific IgG antibodies, replicating of some virus confirmed by molecular methods such as PCR. A diagnosis of herpes zoster was clinically established by the presence of a typical vesicular eruption developing in a dermatomal distribution. Because the clinical presentation of herpes zoster was typical, virology confirmation was not required.

Data collection. Information was obtained from patients' recorded data at admissions, including sex, age, SLE duration, SLE disease activity measured with Systemic Lupus Erythematosus Disease Activity Index (SLEDAI) scores according to the medical records[4], organ involvement, laboratory examinations, and treatments. Details of glucocorticoids (GC) and immunosuppressants within 1 month of hospitalization were also recorded. We categorized GC exposure according to the average daily dose and accumulated doses for each patient. The average GC doses were separated into 4 groups: 0–10 mg/day, 11–30 mg/day, 31–60 mg/day, and ≥ 61 mg/day. We calculated "dose equivalents" of prednisolone as follows: 1 mg of prednisolone = 0.8 mg of methylprednisolone = 0.15 mg of dexamethasone.

Statistical analysis. Analyses were performed using SPSS 16.0 (SPSS Inc.). Mean ± SD and median (interquartile range) were presented for numeric values with normal or non-normal distribution, respectively. Categorical data were presented as the absolute count and percentage. The Student t test or the Mann-Whitney U test were used to compare the differences of continuous variables with normal or non-normal distribution between the 2 groups, respectively. Two-by-two tables were analyzed by chi-square or Fisher's exact test as appropriate. Factors related to infectious outcomes at $p < 0.10$ in univariate analyses were entered into a multivariate logistic model. A p value < 0.05 was considered statistically significant.

RESULTS

Demographic data. In total, records for 3815 patients were reviewed. The sample had a mean age of 35.0 ± 13.2 years. All of the subjects were of Chinese Han nationality, and 3167 patients (83.0%) were women. Of the patients, 1321 (34.6%) had 1452 episodes of infection during the whole course of SLE (Table 1). The mean (± SD) interval between SLE diagnosis and infection was 3.5 ± 5.2 years. The majority of infections (78.3%) occurred within 5 years of SLE onset.

Frequency and types of infection. There were 1040 patients (78.7%) who had 1 infection episode each, and 173 and 22 patients who had 2 and 3 infection episodes each, respectively. A nosocomial infection occurred in 76.5% of the episodes, and a community-acquired infection in 23.5%. The most commonly affected sites were the lung and upper respiratory tracts, identified in 33.7% and 26.3%, respectively; the next most commonly affected sites were the multisite in 9.0%, urinary tracts in 8.8%, skin/soft tissue in 7.9%, gastrointestinal (GI) tracts in 5.4%, mucosa in 4.4%, sepsis in 2.4%, central nervous system in 1.1%, pleura in 0.83%, and bone/joints in 0.27%.

Bacterial infection was confirmed in 325 episodes based on positive culture and classified as probable in 410 episodes based on clinical judgment. Among the confirmed cases, 64.0% were nosocomial infections. In terms of isolated microorganisms, gram-negative bacteria (GNB) were predominant over gram-positive bacteria (GPB; 178 isolates vs 90 isolates). In the GNB, *Escherichia coli* (24.6%) was the most common isolate, followed by *Acinetobacter baumannii* (13.4%) and *Klebsiella pneumoniae* (9.0%). For GPB, coagulase-negative *Staphylococcus* (CNS; 13.4%) was most commonly documented, followed by *Staphylococcus aureus* (11.2%) and other GPB (Table 2). Overall, MDR was detected in 26.9% of bacterial isolates. Extended-spectrum β-lactamase (ESBL) producers were expressed mainly in *E. coli* (30/66, 45.5%) and *K. pneumoniae* (7/24, 29.2%). The proportion of MDR *A. baumannii* (MDRAB) in the sample was 36.1%. Eight of *S. aureus* (8/30, 26.7%) were found to be methicillin-resistant *S. aureus* (MRSA), and 14 of CNS (14/36, 38.9%) were considered methicillin-resistant CNS (MRCNS). The pattern of resistance of the 5 most commonly isolated bacteria are listed in Table 3.

Nonspecific viral infection was diagnosed 349 times. Eighty-six patients developed herpes zoster, 48 had cytomegalovirus (CMV) infection, and 40 and 12 patients had influenza and herpes simplex, respectively. Among the 86 patients who had herpes zoster, 12 had cutaneous dissemination and post-herpetic neuralgia each. The general symptoms of CMV infection included fever (n = 43), cough or dyspnea (n = 38), and abdominal pain (n = 5). The main involved organs included pulmonary (n = 38), GI (n = 5), and liver-related (n = 5).

There were 182 fungal infections identified, and 140 fungi were isolated. As shown in Table 2, the most common fungus was *Candida spp*., followed by *Aspergillus* and *C. neoformans*. The clinical spectrum of *Candida spp*. infections included oral mucosa (56 episodes), lower respiratory tract (11 episodes), esophageal mucosa (20 episodes), and urinary tract (12 episodes). There were 24 patients who developed *Aspergillus*

Table 1. Demographic and clinical features of patients with SLE. Values are n (%) unless otherwise specified.

Features	SLE, n = 3815	Infected, n = 1321	Noninfected, n = 2494	p
Male:female, n	648:3167	224:1097	424:2070	1.0
Age, yrs, mean ± SD	35.0 ± 13.2	35.0 ± 15.8	34.9 ± 9.6	0.9
SLE duration, mos, median (IQR)	12 (58)	12 (58)	12 (58)	0.1
ANA+	3783 (99.2)	1311 (99.2)	2472 (99.1)	0.9
Anti-dsDNA+	2440 (97.8)	1287 (97.4)	2440 (97.8)	0.4
Disease duration, mos	779 (20.4)	255 (19.3)	524 (21.0)	0.2
Leukopenia	819 (21.5)	287 (21.7)	532 (21.3)	0.8
Anemia	2406 (63.1)	868 (65.7)	1538 (61.7)	**0.01**
Thrombocytopenia	827 (21.7)	360 (27.3)	467 (18.7)	**< 0.001**
Hypoproteinemia	2536 (66.5)	929 (70.3)	1607 (64.4)	**< 0.001**
Renal involvement	2364 (62.0)	926 (70.1)	1438 (57.7)	**< 0.001**
Neuropsychiatric manifestations	171 (4.5)	65 (4.9)	106 (4.3)	0.3
Gastrointestinal tract involvement	87 (2.3)	37 (2.8)	50 (2.0)	0.1
Low C_3C_4, and/or CH_{50}	2607 (68.3)	907 (68.7)	1700 (68.1)	0.1
CRP, mg/dl, median (IQR)	2.1 (9.7)	6.5 (18.1)	1.4 (5.4)	**< 0.001**
SLEDAI, median (IQR)	8 (10)	10 (11)	8 (9)	**0.001**
Methotrexate	768 (20.1)	245 (18.5)	523 (21.0)	0.7
Cyclophosphamide	1074 (28.2)	573 (43.4)	501 (20.1)	**< 0.001**
Azathioprine	65 (1.8)	19 (1.4)	46 (1.8)	0.9
Cyclosporine	125 (3.3)	40 (3.0)	85 (3.4)	0.5
Tacrolimus	181 (5.1)	55 (4.2)	126 (5.1)	0.2
GC use	3761 (98.6)	1305 (98.8)	2456 (98.5)	0.4
Average GC dose, mg/day, median (IQR)	20 (30)	40 (30)	15 (10)	**< 0.001**
0–10	1218 (31.9)	154 (11.7)	1064 (42.7)	**< 0.001**
11–30	1295 (33.9)	281 (21.3)	1014 (40.7)	
31–60	1152 (30.2)	736 (55.7)	416 (16.7)	
> 61 mg/day	150 (3.9)	150 (11.4)	34 (1.4)	
Average GC dose, mg/kg/d, median (IQR)	0.4 (0.6)	0.8 (0.6)	0.3 (0.2)	**< 0.001**
Accumulated GC doses, g, median (IQR)	0.6 (0.9)	1.2 (0.9)	0.45 (0.3)	**< 0.001**

Significant values are in bold face. SLE: systemic lupus erythematosus; IQR: interquartile range; ANA: antinuclear antibody; CRP: C-reactive protein; SLEDAI: Systemic Lupus Erythematosus Disease Activity Index; GC: glucocorticoid.

Table 2. Organisms identified in patients with SLE.

Types	Organisms (n)
Bacteria, n = 325	
Gram-negative, n = 178	*Escherichia coli* (66), *Acinetobacter baumannii* (36), *Klebsiella pneumoniae* (24), *Pseudomonas aeruginosa* (20), *Haemophilus influenzae* (10), *Salmonella sp*. (7), *Enterobacter aerogenes* (5), *Stenotrophomonas maltophilia* (5), *Citrobacter freundii* (3), *Proteus mirabilis* (2)
Gram-positive, n = 90	*Staphylococcus aureus* (30), *Staphylococcus epidermidis* (13), *Staphylococcus hominis* (12), *Staphylococcus haemolyticus* (3), *Streptococcus pneumonia* (2) *Streptococcus viridians* (4), *Enterococcus faecalis* (6), *Enterococcus faecium* (4), *Streptococcus gallolyticus* (2), *Gram-positive Rods* (14)
Other, n = 57	*Mycobacterium tuberculosis* (56), *Mycobacterium leprae* (1)
Fungus, n = 140	*Candida albicans* (99), *Aspergillus fumigatus* (24), *Cryptococcus neoformans* (13), *Candida tropicalis* (10), *Candida glabrata* (10), *Penicillium marneffei* (1), *Saccharomycetes* (1), *Pityrosporum orbiculare* (2)
Virus, n = 136	Herpes zoster (86), cytomegalovirus (48), influenza (40), herpes simplex (12)

pneumonia, while 10 patients developed *C. neoformans* meningitis and 3 developed pulmonary cryptococcosis. Forty-eight cases with a diagnosis of IFD were identified.

Outcome of infection. The overall mortality of this cohort was 2.2% (n = 80). The mortality of infected patients was higher than that of noninfected patients (4.8% vs 0.6%, p < 0.001).

Table 3. Drug resistances of the main isolated bacteria.

Variables	Gram-negative Bacteria, Percentage Resistance					Gram-positive Bacteria, Percentage Resistance		
	Escherichia coli		*Klebsiella pneumoniae*		*Acinetobacter*	Variables	*Staphylococcus*	*Staphylococcus*
	ESBL+	ESBL–	ESBL+	ESBL–	*baumannii*		*aureus*	coagulase-negative
n	30	36	7	17	36	n	30	36
Antibiotic						Antibiotic		
Imipenem	0	0	0	0	13.9	Vancomycin	0	0
Ertapenem	0	0	0	0	22.2	Linezolid	0	0
Amikacin	33.3	22.2	42.9	23.5	33.3	Rifampicin	6.7	8.3
Gentamicin	90.0	58.3	71.4	29.4	65.6	Amikacin	23.3	11.1
Ceftazidime	13.3	5.6	14.3	5.9	27.8	Gentamicin	73.3	25.0
Ceftriaxon	43.3	11.2	42.9	11.8	100	Levofloxacin	26.7	47.2
Cefepime	12.2	11.2	14.3	5.9	80.6	Ciprofloxacin	26.7	41.7
Aztreonam	26.7	11.2	57.1	29.4	—	Clindamycin	30.0	30.6
Levofloxacin	53.3	16.7	14.3	5.9	44.4	Oxacillin	100.0	100.0
Ciprofloxacin	56.7	52.8	57.1	47.1	66.7	Erythromycin	73.3	75.0
Ampicillin	100.0	80.6	71.4	58.9	100	Penicillin	96.7	88.9
Piperacillin/tazobactam	3.3	2.8	0	0	27.8			
Cefoperazone/sulbactam	13.3	8.3	14.3	5.9	11.1			
Amoxicillin/clavulanic	73.3	52.8	57.1	23.6	—			
Sulfamethoxazole trimethoprim	63.3	66.7	57.2	52.9	—			
Colistin	0	0	0	0	0			

ESBL: extended-spectrum β-lactamase.

No significant differences were observed between the 2 groups in terms of age or disease duration. In the infected group, 26 died from infection complications, 22 from active SLE combined with infection, and 16 from active SLE. The lungs were the most common infection site (n = 20), followed by multiple sites (n = 18), sepsis (n = 7), meningitis (n = 2), and brain abscess (n = 1). Among 48 cases of death caused by infection, there were 36 patients infected with definite pathogens, including 16 cases of single pathogen and 20 cases of mixed infection. Details regarding the isolated pathogens and infection sites are listed in Table 4.

Factors associated with infection in patients with SLE. In the

Table 4. Affected sites and pathogens in patients with SLE who died of infection.

Pathogens	Infection Sites	n
Single pathogen		16
Aspergillus fumigatus	Lung	5
Cytomegalovirus	Lung	3
Klebsiella pneumoniae	Lung	2
Staphylococcus aureus, MRSA	Lung	2
Cryptococcus neoformans	CNS	2
Escherichia coli, ESBL	Bloodstream	1
Penicillium marneffei	Disseminated	1
Mixed pathogen		20
E. coli, ESBL + *Enterococcus faecium*	Urinary tract	2
E. coli, ESBL + *E. faecium*	Urinary tract + bloodstream	2
Acinetobacter baumannii, MDRAB + *Pseudomonas aeruginosa*	Lung	1
A. baumannii + *E. coli*	Bloodstream + urinary tract	2
A. fumigatus + *Candida albicans*	Lung	2
A. fumigatus + *E. coli*	Lung + bloodstream	2
P. aeruginosa, ESBL + *C. albicans*	Bloodstream + oral mucosa	1
A. fumigatus + herpes zoster + *E. coli,* ESBL	Lung + skin + bloodstream	2
Cytomegalovirus + *A. fumigatus*	Lung	2
E. coli + herpes zoster + *C. albicans*	Bloodstream + skin + esophageal mucosa	2
Cytomegalovirus + MRSA	Lung + skin + bloodstream	2
Generalized infection		12
Total		48

SLE: systemic lupus erythematosus; MRSA: methicillin-resistant *S. aureus*; ESBL: extended-spectrum β-lactamase; MDRAB: multidrug-resistant *A. baumannii*; CNS: coagulase-negative *Staphylococcus*.

multivariate analysis, these factors were associated with the presence of bacterial infections and viral infection in patients with SLE: active disease measured by SLEDAI score, renal involvement, thrombocytopenia, treatment with cyclophosphamide (CYC), and average dose of GC. The predictive factors for fungal infections were renal involvement, treatment with CYC, and average dose of GC (Table 5). Other immunosuppressive agents, including methotrexate, azathioprine, cyclosporine, and tacrolimus, did not confer risk for infections.

DISCUSSION

Our study showed that about one-third of patients with SLE developed infection during their hospitalization. The prevalence observed in our present study was similar to that found in Malaysia[5], Mexico[6], and Korea[7], but higher than that in Canada and Britain[8,9]. The increased prevalence of infection in our patients with SLE might reflect the poor living and public health conditions in developing countries. Several key characteristics of infection were noted in the Chinese patients with SLE. First, infection occurred early, with peak occurrence around 5 years after SLE diagnosis. Second, lungs and upper respiratory tracts were the most common infection sites, with more documented cases than those identified in other countries[5,6,7,8]. Third, GNB was predominant over GPB, with a high proportion of MDR. Fourth, a variety of new pathogens including fungi and virus emerged.

As to the bacteria isolated in patients with SLE, there was a significant variation across various countries. Most European studies demonstrated a predominance of GPB[9], while most studies from the Asian region demonstrated a predominance of GNB[5,10]. GNB predominated with *E. coli* while CNS and *S. aureus* were the most common GPB. These data were comparable to the national surveillance study from the China Antimicrobial resistance surveillance network in 2013[1]. This similar trend of bacteria epidemiology was also observed in other immunosuppressed hosts in China[11,12,13].

As for the drug resistance of GNB, in our series, the most common resistant isolates were observed in ESBL producing *E. coli* and *K. pneumoniae*, and MDRAB. The domestic reports revealed that the prevalence of ESBL-producing strains was 54.0% in *E. coli* and 31.8% in *Klebsiella spp.*[1]. The ESBL-producing strains were only highly sensitive to carbapenems, β-lactamase inhibitor compound families, and certain cefalosporin *in vitro*. However, cefalosporin was not a preferred empirical therapy *in vivo*. It was surprising that about 20% of the *A. baumanniian* were resistant to carbapenems. This observation was significantly higher than the report from other hospitals in China[11,13]. In our present study, the proportion of CNS surpassed *S. aureus*, ranking first among GPB. CNS became an important opportunistic pathogen in China[14]. The isolated frequency of MRSA and MRCNS was 26.7% and 38.9%, respectively; both were lower than the national average[1]. The MRSA/MRCNS were resistant to commonly used antibiotics, extensively resistant to penicillin and erythromycin, rarely resistant to amikacin and rifampicin, and not resistant at all to linezolid or vancomycin. In the clinical setting, the first-class selection for infection caused by MRSA/MRCNS should be linezolid or vancomycin and could be combined with amikacin or rifampicin in severe cases.

Herpes zoster was the most frequent specific viral

Table 5. Risk factors for specific types of infections in patients with SLE. The average dose of GC (mg/kg/d), different dose range of GC, and accumulated dose of GC (g) were all significant factors in the univariate analysis. The accumulated dose of GC was chosen to enter into the multivariate analysis.

Variables	Bacterial Infection				Fungal Infection				Viral Infection			
	Univariate Analysis		Multivariate Analysis		Univariate Analysis		Multivariate Analysis		Univariate Analysis		Multivariate Analysis	
	OR (95% CI)	p	OR (95% CI)	p	OR (95% CI)	p	OR (95% CI)	p	OR (95% CI)	p	OR (95% CI)	p
SLEDAI	1.2 (1.1–1.2)	< 0.001	1.1 (1.1–1.2)	< 0.001	NS	NS	NS	NS	1.2 (1.2–1.3)	< 0.001	1.2 (1.2–1.3)	< 0.001
Renal involvement	1.4 (1.2–1.7)	< 0.001	1.4 (1.1–1.8)	0.003	1.7 (1.2–2.3)	0.002	8.0 (5.2–12.2)	< 0.001	1.6 (1.3–2.0)	< 0.001	5.6 (4.1–7.7)	< 0.001
Thrombocytopenia	1.5 (1.3–1.9)	< 0.001	2.1 (1.7–2.7)	< 0.001	1.6 (1.1–2.3)	0.007	NS	NS	1.4 (1.1–1.8	< 0.001	2.4 (1.8–3.3)	< 0.001
Treatment of CYC	3.0 (2.5–3.6)	< 0.001	6.0 (4.8–7.4)	< 0.001	3.5 (2.6–4.7)	< 0.001	2.7 (1.9–2.9)	< 0.001	2.8 (2.3–3.4)	< 0.001	2.4 (1.8–3.2)	< 0.001
Average dose of GC, mg/kg/d	30.4 (23.3–39.7)	< 0.001	—	—	144.6 (80.1–260.9)	< 0.001	—	—	34.8 (25.8–46.7)	< 0.001	—	—
Different dose range of GC, mg/day												
0–10												
11–30	2.4 (1.8–3.1)	< 0.001			1.7 (0.7–4.1)	0.2			2.6 (1.8–3.6)	< 0.001		
31–60	13.1 (10.1–17.2)	< 0.001			50.0 (24.2–102.5)	< 0.001			15.8 (11.5–21.7)	< 0.001		
≥ 61 mg/day	34.8 (22.1–54.8)	< 0.001			70.4 (28.6–173.2)	< 0.001			43.1 (26.5–71.5)	< 0.001		
Accumulated dose of GC, g	10.4 (7.7–14.1)	< 0.001	14.2 (10.2–19.7)	< 0.001	15.8 (11.2–22.3)	< 0.001	32.7 (21.7–49.1)	< 0.001	9.0 (7.5–11.0)	< 0.001	15.0 (11.4–19.8)	

SLE: systemic lupus erythematosus; GC: glucocorticoid; SLEDAI: SLE Disease Activity Index; CYC: cyclophosphamide; NS: nonsignificant.

infection, followed by CMV. So far, very few studies are available on CMV infection in patients with SLE. Ramos-Casals, *et al* reported that the majority of CMV infection cases (68%) occurred in non-white (overwhelmingly Asian) patients[15]. The total prevalence of CMV infection was 1.3% in our study, which was similar to a study from Japan (1.0%)[16]. CMV infection often presented with fever, severe dyspnea, and digestive symptoms in our patients. The mortality of CMV interstitial pneumonia was very high in our study (5/12, 41.7%). Our study reminds us that CMV infection was not unusual and severe in patients with SLE. To diagnose early and obtain satisfactory prognosis, suspicions of CMV infection should be considered in patients with SLE presenting with fever or organ-specific symptoms, and particularly those who had no response to anti-SLE treatment.

Although superficial fungal diseases were still frequent, an increased rate of IFD was noted in our present study. The prevalence of IFD in our study sample was 1.3%, which was similar to that in Asia[17,18,19], but lower than that in Mexico and Argentina[20,21]. Our data indicated that the lungs and central nervous systems were the most common sites; *Aspergillus* was the most frequent pathogen of IFD. Pathogens varied by geographic region; for instance, *Aspergillus* was predominant in reports from China and Korea[17,18] while *Cryptococcus* was more frequent in Argentina and Taiwan[19,21].

The overall mortality rate of our cohort was 2.2%, with infection being the top cause of death. We found that mixed infection was more frequent than single pathogen infection in death cases. Fungal infection was the most frequent pattern of the single pathogen infection, accounting for over one-third of the isolation, in which *Aspergillus fumigatus* was the most common pathogen. Among 20 cases of mixed infections, *E. coli* and *A. fumigatus* mixed infection were the most common pathogens. This could be explained by greater isolation of *E. coli* and *A. fumigatus* in Asia[17].

Our data indicated that critical organ involvement (renal involvement or thrombocytopenia) and clinically active SLE as defined by the SLEDAI were independent risk factors predisposing to infections. This finding was comparable to that obtained in previous studies[7,22]. As for drug administration, a significant association was found between the onset of infection and the treatment of CYC and the accumulated dose of GC. Other groups have reported similar trends[23,24]. Our study highlights the importance of disease control to reduce the onset of infection. How to choose an optimal treatment to balance immunosuppression between disease activities remains a challenge.

Infection was common in hospitalized patients with SLE, which was the top cause of mortality. There are some notable features of infection in Chinese patients with SLE, including early complication, higher proportion of respiratory tract involvement, predominance of GNB with emerging of MDR isolates, and a variety of pathogens. Mixed infections were the most common pathogens causing death. Empirical antibiotic therapy should be guided by the local bacteriological surveillance and drug sensitivity data.

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