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Pathogen characteristics reveal novel antibacterial approaches for interstitial lung disease

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ABSTRACT

Interstitial lung disease (ILD) is a clinical disorder associated with changes of lung structure. Concurrent infection is a serious complication and one of the major factors that exacerbates ILD. Pathogen screening is a critical step in early diagnosis and proper treatment of ILD with secondary infection. Here we analyzed distribution and drug susceptibility of pathogens isolated from hospitalized ILD patients from January, 2007 to December, 2008 and compared them to bacterial drug resistance data in CHINET during the same period. The main specimens were from sputum culture, lavage fluid culture, lung biopsy tissue culture, and pleural effusion culture and bacterial or fungal cultures were performed on these specimens accordingly. Drug susceptibility was tested for positive bacterial cultures using disk diffusion (Kirby–Bauer method) and E Test strips in which results were determined based on the criteria of CLSI (2007). A total of 371 pathogen strains from ILD patients, including 306 bacterial strains and 65 fungal strains were isolated and cultured. Five main bacterial strains and their distribution were as follows: *Klebsiella pneumoniae* (31.7%), *Pseudomonas aeruginosa* (20.6%), *Acinetobacter* (12.7%), *Enterobacter cloacae* (8.2%), and *Staphylococcus aureus* (7.8%). The results showed that ILD patients who had anti-infection treatment tended to have Gram-negative bacteria, whether they acquired an infection in the hospital or elsewhere. Drug resistance screening indicated that aminoglycosides and carbapenems had lower antibiotic resistance rates. In addition, we found that the usage of immunosuppressants was associated with the increased infection rate and number of pathogens that were isolated. In conclusion, aminoglycosides and carbapenems may be selected as a priority for secondary infection to control ILD progression. Meanwhile, the use of anti-MRSA/MRCNS drugs may be considered for *Staphylococcus* infection.

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1. Introduction

Interstitial lung disease (ILD) is a clinical entity associated with multiple connective tissue diseases (CTDs), resulting in significant morbidity and mortality [1–3]. CTDs are a group of inflammatory and immune-mediated disorders. Those associated with ILD include rheumatoid arthritis (RA), systemic sclerosis/scleroderma (SSc), polymyositis (PM)/dermatomyositis (DM), Sjögren syndrome, and systemic lupus erythematosus (SLE) [4–8].

Despite the fact that therapies for some CTD-ILD patients are effective for immunosuppressive use, the management and treatment of patients with ILD secondary infection remain suboptimal [9–11]. Furthermore, most patients with ILD have immune deficiencies and easily acquire various infections that exacerbate the condition. The infection rate of ILD patients is much higher than that of the healthy population. Glucocorticoids are the primary drugs used to treat ILD. During hormone therapy, ILD patients are more vulnerable to invasion by pathogens due to suppressed immune function [6], which is marked by high fever, cough, increased sputum, and shortness of breath. Some patients' pulmonary lesions expand rapidly and gradually become aggravated, and may even cause death. Many studies suggest that infection is an important factor in the induction of acute ILD [12]. Therefore, there is an urgent need to better understand the characteristics of pathogens acquired by ILD patients in order to develop effective therapeutic interventions [13]. We evaluated the following factors: pathogen strains from ILD patients, Gram-staining bacteria and fungi with or without hospital infection, response to anti-MRSA/MRCNS drugs,

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and resistance surveillance compared to CHINET. In this study, we present new information regarding the characteristics of ILD-associated pathogens and the treatment of ILD patients with secondary infection.

2. Materials and methods

2.1. Patients

We collected different categories of samples, then cultured and analyzed 1362 cases of hospitalized patients with ILD who were diagnosed idiopathic pulmonary fibrosis (IPF), connective tissue disease-related ILD (CTD-ILD), pulmonary vascular disease-related ILD (PVD-ILD), pulmonary alveolar proteinosis (PAP), sarcoidosis, extrinsic allergic alveolitis (EAA) and other ILD of unknown etiology from 01/2007 to 12/2008. The diagnosis and details of patients were listed in Table 1. All patients with ILD's were classified based on disease diagnosis and whether or not they had at least two-week treatment with immunosuppressive agents (including corticosteroids, azathioprine, cyclophosphamide, hydroxychloroquine, methotrexate or others). While 20.9% of patients used immunosuppressant before admission to our hospital, the majority of patients (79.1%) were admitted due to lung shadows or respiratory symptoms such as cough and shortness of breath and did not use immunosuppressants before the isolation of pathogens.

2.2. Cultured samples

The methods used to obtain specimens included sputum culture, bronchoalveolar lavage fluid culture, artificial airway aspirate culture, lung biopsy tissue culture, pleural effusion culture, blood culture, and urine culture.

2.3. Bacterial and fungal culture and drug susceptibility

Bacterial and fungal cultures were performed for all specimens according to the requirements. When a bacterial culture was positive, drug susceptibility of these bacteria was tested by the disk diffusion method (Kirby–Bauer method) and by E Test strip. The results were determined using CLSI standards (2007 edition). We excluded *Candida albicans* in fungal culture results because of its high positive rates and colonization rates.

3. Results

3.1. Pathogens and their distribution

We reviewed disease diagnosis and the usage of immunosuppressants for 371 patients from whom pathogens were isolated (Table 1). The results showed that the classification of pathogens is directly associated with the usage of immunosuppressive agents. Pathogens were isolated in 48.4% of patients who were treated with immunosuppressants. In contrast, pathogens were isolated in only 21.6% of patients who did not have immunosuppressant treatment ($X^2 = 81.59$, $P = 0.000$). Notably, the pathogen isolation rate in IPF patients treated with immunosuppressants was 65.1% compared to 23.1% in untreated patients (Table 1), suggesting the use of immunosuppressive drugs in IPF patients markedly increased the risk of secondary infection ($X^2 = 37.07$, $P = 0.000$). In addition, the effect of smoking was investigated. Among the total 1362 patients in this study, 395 patients were current or former smokers. Among the 371 patients in whom pathogens were isolated, 122 patients were smokers. Smokers and non-smokers had roughly similar proportion of infection rates and there was no statistically significant difference between them ($X^2 = 2.099$, $P = 0.15$). This indicates that infection is not directly correlated with smoking in this group of patients (data not shown).

We cultured and isolated 371 pathogen strains from ILD patients, including 306 strains of bacteria and 65 strains of fungi. *Candida* was excluded from this study because it grew mainly in sputum culture for colonization. An important way to obtain pathogens is from respiratory secretions, which comprised 86.5% of specimens, including 206 sputum specimens (55.5%) and 68 BALF samples (18.3%). Culture-positive specimens are shown in Table 2.

Among 306 strains of bacteria isolated, 49 were Gram-positive (16%) and 257 were Gram-negative (84%). The five most highly represented were: 97 strains of *Klebsiella pneumoniae* (31.7%), 63 strains of *Pseudomonas aeruginosa* (20.6%), 39 strains of *Acinetobacter* (12.7%), 25 strains of *Enterobacter cloacae* (8.2%), and 24 strains of *Staphylococcus aureus* (7.8%); followed by 13 strains of *Stenotrophomonas*, 12 strains of *coagulase-negative staphylococci*, 9 strains of *Escherichia coli*, 7 strains of *Enterococcus*, 7 strains of other *Pseudomonas*, 4 strains of *Streptococcus pneumoniae*, and 6 strains of other bacteria (Table 3).

The top five bacteria in the 2007 China study (CHINET) by Wang et al. were *E. coli*, coagulase-negative *Staphylococci*, *P. aeruginosa*, *S.*

Table 1
The diagnosis and pathogens isolation from patients involving this study.

Diagnosis	Previous immune inhibitor treatment	Patients amount ($N = 1362$)	Percentage (n/N)	Pathogens amount ($N = 371$)	Pathogens isolation rate (%)
IPF	+	63	4.6	41	65.1
	–	186	13.7	43	23.1
CTD-ILD	+	146	10.7	51	34.9
	–	127	9.3	31	24.4
PVD-ILD	+	17	1.2	3	17.6
	–	47	3.5	9	19.1
PAP	+	5	0.4	2	40
	–	75	5.5	23	30.7
Sarcoidosis	+	46	3.4	5	10.9
	–	113	8.3	3	2.7
EAA	+	21	1.5	8	38.1
	–	85	6.2	17	20
Other ILD	+	57	4.2	28	49.1
	–	374	27.5	107	28.6
Total	**+**	**285**	**20.9**	**138**	**48.4**
	–	**1077**	**79.1**	**233**	**21.6**

IPF = idiopathic pulmonary fibrosis, CTD-ILD = connective tissue disease-related ILD, PVD-ILD = pulmonary vascular disease-related ILD, PAP = pulmonary alveolar proteinosis, EAA = extrinsic allergic alveolitis, other ILD = other ILD of unknown etiology.

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