

Different microbiological and clinical aspects of lower respiratory tract infections between China and European/American countries

Xin Zhang¹, Rui Wang², Xiuzhen Di², Bin Liu¹, Youning Liu¹

¹Department of Respiratory Diseases, ²Department of Clinical Pharmacology, Chinese PLA General Hospital, Beijing 100853, China

Corresponding to: Youning Liu, MD. Department of Respiratory Diseases, Chinese PLA General Hospital, Beijing 100853, China. Email: liuyn301@126.com.

Background: National treatment/diagnosis guidelines for lower respiratory tract infections (LRTIs) are generally based on local epidemiological data. Etiology and drug-resistance patterns could differ between China and European/American countries, and simply following their respective guidelines might cause problems in clinical practice. Therefore, we need to summarize the microbiology and clinical manifestations of LRTIs in China and develop our own guidelines.

Methods: Three major national multicenter epidemiology surveillance studies on LRTI were completed recently. The data were compared in detail with those from European/American studies.

Results: Clinical and microbiological differences were observed in community-acquired pneumonia (CAP), hospital-acquired pneumonia (HAP), and pulmonary mycosis between our country and European/American countries.

Conclusions: The microbiological and clinical characteristics of the major LRTIs in China differ in many respects from those in European/American countries. Patients should have personal treatment plans instead of simply following the guidelines from foreign countries

Keywords: Pathogens; epidemiology; antimicrobial resistance; lower respiratory tract infections (LRTIs)



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Introduction

Lower respiratory tract infection (LRTI) is one of the most common diseases in humans and a long-term global public health concern. Worldwide, it places considerably more strain on health budgets than do cancer, cardiovascular diseases, and malaria (1). In the United States, the incidence of LRTI and its mortality rates are higher than for any other infectious diseases. According to a 2002 WHO report, LRTIs accounted for 6.9% of all deaths in that year (2). High rates of LRTI incidence and the high medical cost involved are found worldwide, and the importance of their diagnosis and treatment is accordingly emphasized. Since the 1990s, European/American countries have developed guidelines for diagnosis and treatment of LRTI. These guidelines have been subject to regular evaluations and revisions on the basis of repeated evidence-based medical

research and epidemiological investigations. The most comprehensive and influential guidelines are currently presented by the American Thoracic Society (ATS), the Infectious Diseases Society of America (IDSA), and the British Thoracic Society (BTS). Compared with European/American countries, China has diverging socioeconomic models, different medicare systems, and varying LRTI etiology and drug-resistance patterns. Therefore, simply copying the existing European/American guidelines is inappropriate and might cause serious problems in clinical practice. In recent years, large epidemiological investigations of community-acquired pneumonia (CAP), hospital-acquired pneumonia (HAP), and pulmonary mycosis were carried out in several large/middle-sized cities in China, and preliminary data on LRTI were obtained.

This paper summarized these results and discussed the differences in the microbiological and clinical features of

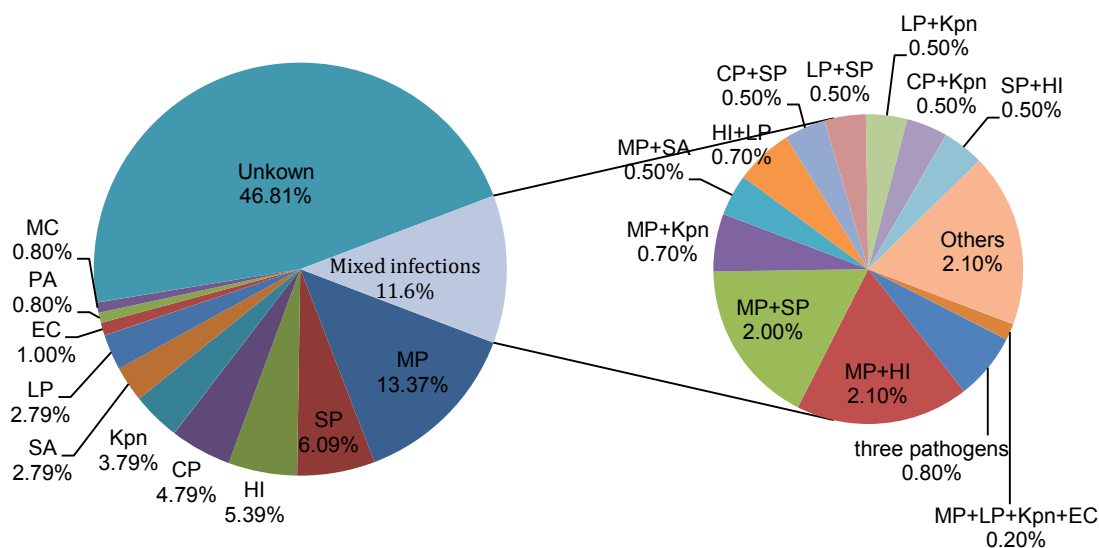


Figure 1 The pathogen distribution of 610 adult CAP cases in China. Unknown, No detectable pathogens; SP, *Streptococcus pneumoniae*; HI, *Haemophilus influenzae*; Kpn, *Klebsiella pneumoniae*; MP, *Mycoplasma pneumoniae*; LP, *Legionella pneumophila*; CP, *Chlamydia pneumoniae*; EC, *Escherichia coli*; SA, *Staphylococcus aureus*; PA, *Pseudomonas aeruginosa*; MC, *Moraxella catarrhalis*.

LRTIs between China and European/American countries.

CAP

CAP is one of the most common LRTIs. The overall incidence rate is 5-11 per 1,000 people per year, accounting for 5-12% of all LRTIs (3). The pathogens causing CAP include viruses, bacteria, and other atypical pathogens. The pathogen composition is complicated and varies according to geographic area, population, and seasonal changes. The national pathogenic epidemiological investigation of CAP in 2006 indicated the following major characteristics in China.

(I) The infection rate of *Mycoplasma pneumoniae* surpassed that of *Streptococcus pneumoniae* and became the leading cause of adult CAP in our country. Whereas *S. pneumoniae* and *Haemophilus influenzae* are still two kinds of the most common CAP pathogens (Figure 1). A high proportion of adult cases of CAP are derived from mixed infection with bacteria and atypical pathogens (4).

Regular sputum sampling was done with most (590/610) inpatients enrolled in the study, and blood samples were taken if patients had a fever of $>38.5^{\circ}\text{C}$. Sputum was Gram-stained. Representative sputum originated from the lower respiratory tract was defined as that containing >25 granulocytes and <10 epithelial cells per low power field microscopic view. Validated sputum and blood samples were

cultured.

(II) High resistance to macrolides among *S. pneumoniae* in China is another characteristic difference compared with European/American countries. The Alexander Project Group showed that in European/American countries, rates of erythromycin resistance (resistant + intermediate resistance) in *S. pneumoniae* are $<30\%$, with 6.9% in Germany, 13.0% in the UK, and 28.8% in the USA (5). The resistance is mainly mediated by the *mef(A)* gene, and the common resistance phenotype is M-type (low level resistance to 14- or 15-membered macrolides and susceptibility to 16-membered macrolides and clindamycin) (6,7) (Table 1). Therefore, in those countries, macrolide antibiotics are recommended as the first-line empirical therapy in the clinic for CAP patients without risk factors (9). In contrast, in our country, the level of macrolide resistance in *S. pneumoniae* is higher. For example, the rate of azithromycin resistance is as high as 79.4%; mainly as constitutive resistance mediated by the *erm(B)* gene (cMLS_B, highly resistant to erythromycin) (8,10). Considering the high divergence in drug resistance to macrolides in different areas, the CAP guidelines from ATS/IDSA (2007 edition) still recommended macrolides as the drug of first choice for previously healthy patients. However, they also pointed out that in areas with high rates of macrolide resistance, alternative antibiotics should be selected (11).

(III) Many recent studies suggest that China has the

Table 1 Comparative prevalences of erythromycin resistance in *S. pneumoniae* between China and European/American countries

References	The main resistance gene type and phenotype	Country	n, isolates (intermediate + resistant)
Tiemei Z <i>et al.</i> (8)	erm(B), cMLS _B -phenotype	China	149/192*
Michael R <i>et al.</i> (5)	mef(A), M-phenotype	Germany	22/321
		UK	31/238
		USA	700/2,432

*, multiple comparisons of erythromycin resistance rates in *S. pneumoniae* isolates from different countries are based upon chi-square analog of Scheffé's theorem. The rate of erythromycin resistance in *S. pneumoniae* isolates between China and any of other West countries are all significantly different ($P \leq 0.05$).

Table 2 Comparative prevalences of macrolide resistance in *M. pneumoniae* between China and European/American countries

Country	%, isolates (intermediate + resistant)	References
China	69.0*	Cao B, <i>et al.</i> (17)
Japan	30.6	Morozumi M, <i>et al.</i> (13)
France	9.8	Peuchant O, <i>et al.</i> (14)
USA	20.7	Dumke R, <i>et al.</i> (15)

*, multiple comparisons of macrolide resistance rates in *M. pneumoniae* isolates from different countries are based upon chi-square analog of Scheffé's theorem. The rate of macrolide resistance in *M. pneumoniae* isolates between China and any of the other three countries are of significances in statistics ($P \leq 0.05$).

highest rates of macrolide resistance of *M. pneumoniae*. Since the first macrolide-resistant *M. pneumoniae* strain was isolated from the lower respiratory tract of a Japanese child in 2001 (12), more macrolide-resistant strains have been obtained from other countries and the prevalence is increasing annually. In 2006, this resistance rate in Japan was 30.6% (13); from 2005 to 2007, it was 9.8% in France (14); it was 3% in Germany in 2009 (15) and from 2006 to 2007, it was 20.7% in USA (16). The surveillance data from our country indicated an even worse situation (17) (Table 2). Two clinical studies in Japan showed that the pneumonia derived from macrolide-resistant strains when treated with macrolides alone did not cause deaths from significant deterioration or treatment failure. However, the recovery from fever took longer. In such cases, alternative antibiotics had to be administered when clinical symptoms aggravated (13,18). These factors lead to new difficulties for treatment of *M. pneumoniae* infections. *In vitro* culture and susceptibility testing for *M. pneumoniae* take long, and alternative antibiotics should be used to treat *M. pneumoniae*-derived pneumonia before the laboratory results become available if macrolides are not effective. For children and young adults, there are no safe and effective antibiotics that can completely replace the macrolides. Therefore, tetracycline can be used for children aged >8 years, and

respiratory quinolones or tetracyclines can be used for adults. For adult patients with severe infection, respiratory quinolones alone or combined with other drugs can be used for initial treatment.

(IV) CAP caused by methicillin-resistant *Staphylococcus aureus* (MRSA) is still rare in China. In 1993, the first community-acquired MRSA (19) was reported in Australia. Since then, a large number of cases have also been reported in the USA, and their severity and high mortality have attracted worldwide attention (20-22). It is generally accepted that community-acquired MRSA causes more infections of the skin and soft tissues than the respiratory tract. A study from Prof. Wang H in China suggests that MRSA-derived skin and soft tissue infections only accounted for 1% of cases (23). Therefore, except for patients with a high suspicion of MRSA infection, empiric anti-MRSA drugs are not necessary.

(V) We found that the probability of infection with *Escherichia coli* and *Klebsiellapneumoniae* were significantly higher in patients aged >50 years (10). In China, the drug-resistance rates in these two bacteria are as high as 50% (24), and the approximate rate of production of extended-spectrum β -lactamase is also high (~30%) (25). The drugs recommended by foreign guidelines, for instance, respiratory quinolones alone or third-generation

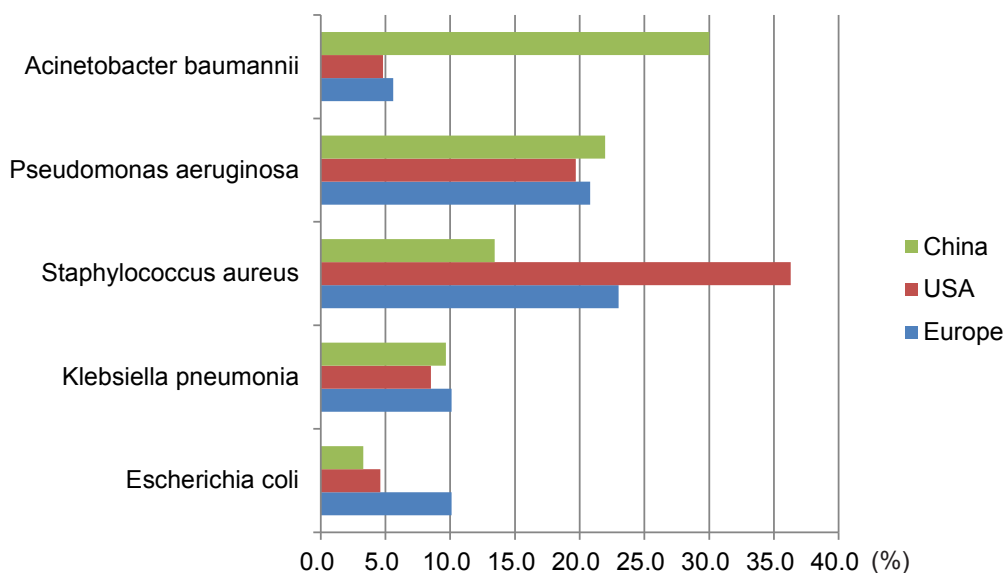


Figure 2 Regional incidence (%) of pathogens isolated from patients with hospital-acquired pneumonia (HAP).

cephalosporins combined with macrolides or respiratory fluoroquinolones, might result in treatment failure. For elderly patients with CAP caused by *E. coli*, β -lactam/ β -lactamase inhibitors or carbapenems should be selected.

HAP

HAP, including ventilator-associated pneumonia, is the most common nosocomial infection worldwide, with a high incidence and mortality (26). In the USA, HAP is the second most common nosocomial infection with an incidence rate of 0.5-1%, which might lengthen hospital stay by 7-9 days and increase hospital cost by >\$40,000. The HAP incidence rate in patients who receive mechanical ventilation can reach 6-20% (27,28). In 2012, we carried out a nationwide multicenter, prospective epidemiological survey of HAP.

In that study, we isolated the three most common pathogenic bacteria for HAP: *Acinetobacter baumannii*, *Pseudomonas aeruginosa*, and *Staph. aureus* (MRSA accounted for 87.8% of *Staph. aureus*) (29). In European/American countries, the most common HAP bacterium is *Staph. Aureus* (30) (Figure 2).

In addition to the differences in pathogen distribution, the drug resistance in non-fermentative bacteria is also more severe in China than that in European/American countries. The rates of non-susceptibility to carbapenems are nearly 80% for *A. baumannii* (Figure 3) and >70% for *P. aeruginosa*

(Figure 4), indicating the reduced value of these drugs for treatment of HAP in our country. This might be associated with the uncontrolled usage of these drugs in our clinical practice. *P. aeruginosa* still has relatively high susceptibility to some carbapenems such as β -lactams, aminoglycosides, and quinolones. However, for *A. baumannii*, the drug options are relatively few and only polymyxin, sulbactam/ β -lactam agents and tetracycline can be considered. The means to obtain polymyxin in China are still limited.

The most commonly isolated HAP-associated bacterium in European/American countries, *Staph. aureus*, is only the third most common in China, and MRSA accounts for most cases. MRSA in China still has ideal susceptibility to several anti-MRSA drugs, such as vancomycin, teicoplanin, linezolid, and tigecycline (Figure 5). The ineffectiveness of the treatments with commonly used glycopeptides in clinical practice might result from low dosage or no loading dosage. Vancomycin-resistant MRSA has not yet been found in China.

It is generally believed that the distribution of pathogenic bacteria differs significantly between early- and late-onset HAP, with the former mainly caused by susceptible bacteria and the latter by drug-resistant bacteria (31,32). In the present study, we applied a variety of tests including *S. pneumoniae* urinary antigen test for diagnosis. However, no significant differences were revealed between pathogens associated with early- and late-onset HAP (29). The possible explanation is that >90% of patients with either

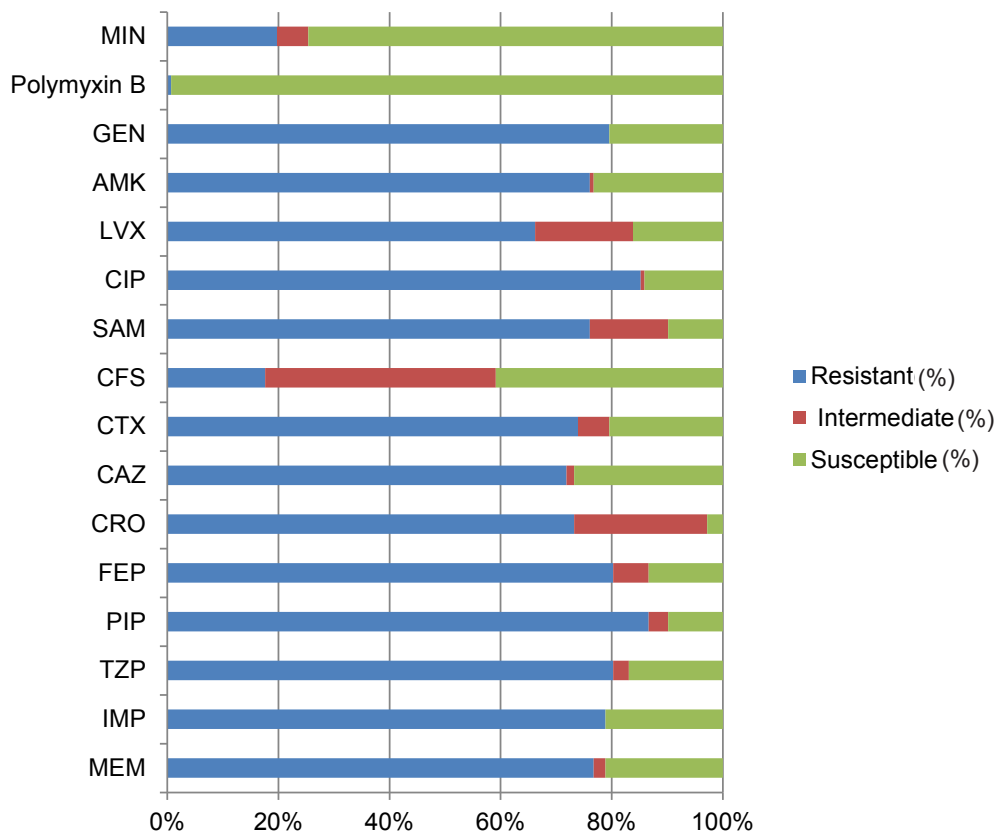


Figure 3 The antibiotics susceptibility of Acinetobacter baumannii isolates.

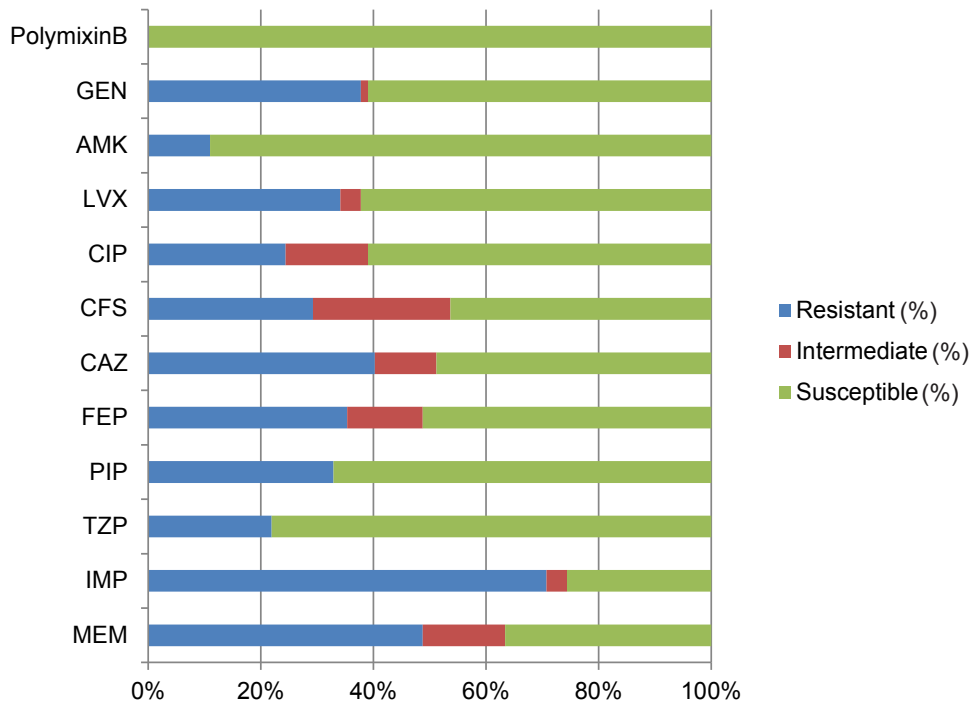


Figure 4 The antibiotics susceptibility of Pseudomonas aeruginosa isolates.

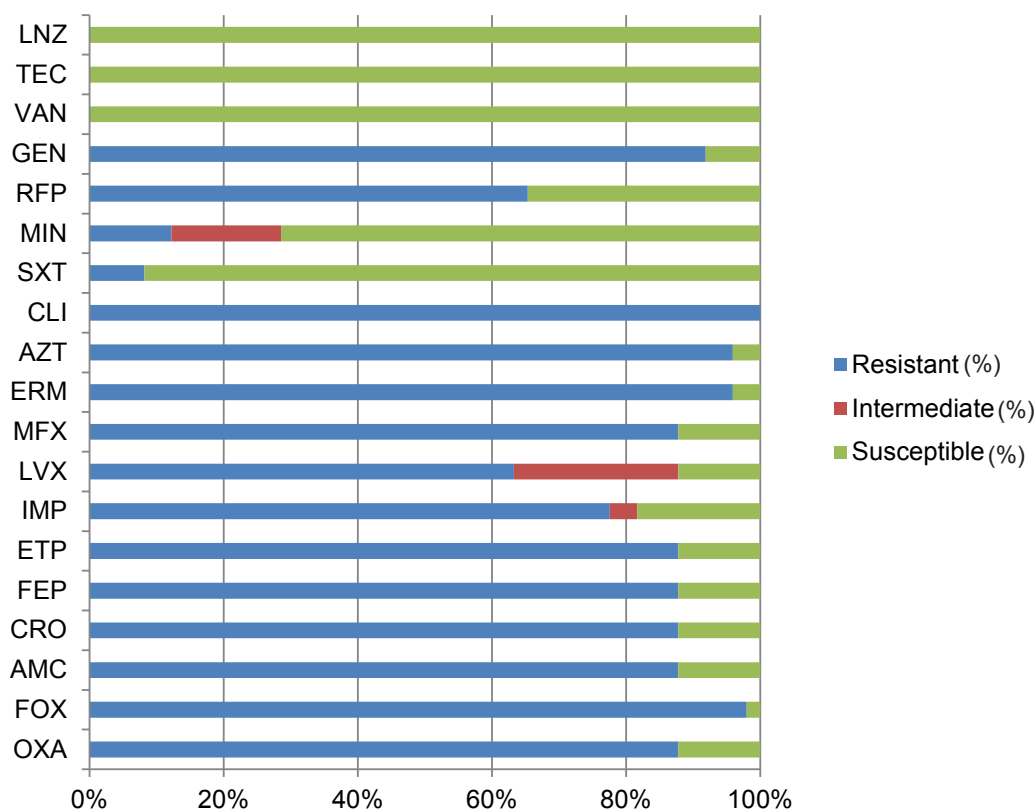


Figure 5 The antibiotics susceptibility of methicillin-resistant *Staphylococcus aureus* (MRSA) isolates.

early- or late-onset HAP have been exposed to antibiotics within 90 days of the first symptom. Compared with the timing of HAP onset, the application of the antibiotics may be more relevant to the type of the pathogenic bacteria and drug resistance of pathogens. This is another difference between China and European/American countries.

Pulmonary mycosis

The number of cases of pulmonary mycosis is growing. This results from the increased number of immunocompromised hosts, and widespread application of broad-spectrum antibiotics, immunosuppressive agents, and invasive diagnostic/therapeutic technologies. Compared with bacterial LRTI, pulmonary mycosis is more difficult to treat and has poorer prognosis. Most recent foreign pulmonary mycosis guidelines are evidence-based. They are valuable for correct clinical diagnosis and proper treatment, although they might not be applicable in our country. Therefore, a national multicenter 10-year retrospective study provides more useful information for our clinicians.

In the survey, we found in the past ten years in China

that the three most common types of pulmonary mycoses were pulmonary aspergillosis, pulmonary candidiasis and pulmonary cryptococcosis (*Figure 6*). IDSA guidelines suggest that invasive pulmonary candidiasis is rare and lung histopathology evidence must be provided for its diagnosis. Positive sputum/bronchoalveolar lavage fluid culture cannot be used as a diagnostic criterion for pulmonary candidiasis and patients do not receive antifungal therapy in such cases (33). We included comparison of blood/pleural fluid culture with sputum culture as a criterion and found that the incidence of candidiasis was almost the same as that of aspergillosis. There were no less than 54 cases of candidiasis confirmed only by lung biopsy (34). This suggests that it is not as rare as indicated by the IDSA guidelines, which is consistent with studies in other countries. Kontoyiannis *et al.* performed autopsies on 676 cancer patients and found that 38% of them (254/676) had mixed pneumonia. Histopathology results showed that 14% (36/254) of cases were caused by candidiasis (35). Therefore, the description about the fungal distribution in the European/American guidelines is not applicable in China.

Cryptococcosis is the third leading form of pulmonary

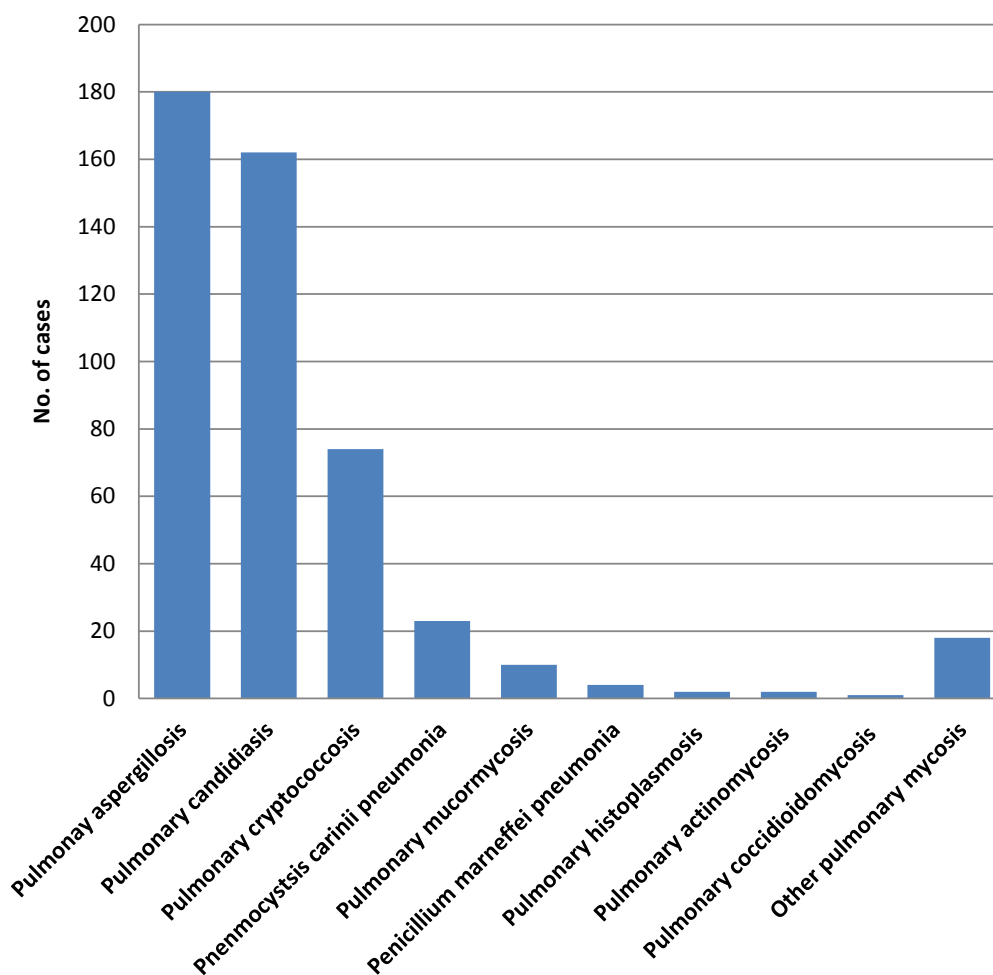


Figure 6 Type distribution of pulmonary mycoses diagnosed.

Characteristics	Pulmonary cryptococcosis	Other pulmonary mycoses	P-value
Age ≤ 44	44/74 (58.7)	129/400 (31.8)	<0.01
Acquired in the community	71/74 (94.7)	243/400 (59.9)	<0.01
Without underlying diseases	53/74 (70.7)	110/400 (27.1)	<0.01
Without immunodeficiency	66/74 (88.0)	259/400 (63.8)	<0.01
All-cause mortality	3/74 (4.0)	98/400 (21.0)	<0.01

mycosis in China. Compared with other pulmonary mycoses, pulmonary cryptococcosis is characterized by high community incidence, less combined immunodeficiency or underlying diseases, and good prognosis (*Table 3*). Compared with foreign countries, its cure rate is higher in China (36,37), which might be related to the presence of different *Cryptococcus* subtypes (38).

In summary, the nationwide multicenter epidemiological studies on LRTIs revealed differences in microbiology and clinical practice between China and European/American countries. This suggests that the diagnosis/treatment guidelines should be developed based on local research results. China is a vast country and information from remote areas or medium-sized/small hospitals is still

missing because of resource limitations. Further studies are needed to improve the present findings. In clinical practice, when following empirical guidelines, it is important to apply individualized treatment plans while considering the patterns of endemic pathogens, differences in hospitals.

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