Bacterial etiology of lower respiratory tract infection in a Chinese large teaching hospital from 2015 to 2019

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Research

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Abstract

Background Sputum is the most common specimen type of lower respiratory tract in China, but its cultivation result is easily confused by the bacteria colonized in the oral cavity and pharynx. And it is very difficult to evaluate the clinical significance of sputum culture results both for clinicians and microbiologists. Bronchoscope alveolus lavage fluid (BALF) is a good specimen, which can accurately reflect the situation of lower respiratory tract infections (LRIs).

Methods The accumulated data of BALF culture and antimicrobial susceptibility test in our hospital from January 2015 to October 2019 were reviewed and analyzed.

Results The positive rate of BALF culture in our hospital was 18.3% (3467/18935) in 2015-2019. The most common pathogens were *Klebsiella pneumoniae* (18.1%, 627/3467), *Pseudomonas aeruginosa* (16.9%, 587/3467) and *Acinetobacter baumannii* (14.0%, 485/3467). For the eight most common pathogens, 40-70 years old was the highest age of distribution, but for *Escherichia coli* and *Streptococcus pneumoniae*, 0-5 years old was also the higher age of distribution. The antibiotic resistance rate of *K. pneumoniae* to imipenem and meropenem was 30.6% and 30.8%, respectively. The sensitivity of *P. aeruginosa* to antibiotics other than minocycline and ticarcillin clavulanic acid was all more than 60%. However, the resistance rate of *A. baumannii* to antibiotics other than tegacyclin and minocycline was all more than 80%.

Conclusions 40-70 years old was the high incidence age of lower respiratory tract bacterial infection. *K. pneumoniae* resistant to carbapenems (CR-*K. pneumoniae*) and *A. baumannii* were a great challenge to clinical treatment and bacterial resistance control.

Background

Lower respiratory tract infections (LRIs) were a leading cause of illness and death in people of all age according to a systematic analysis for the Global Burden of Disease Study 2015 in 195 countries. [1] Bacteria were the main pathogenic factors of LRIs, and the SENTRY surveillance project had carried out etiology and antimicrobial resistance surveillance of LRIs in North America, Europe, Asia Pacific and Latin America. [2] The surveillance results of SENTRY also showed that the etiology of LRIs was different in different regions all over the world. [2] Therefore, the analysis of antimicrobial resistance monitoring data accumulated over many years is of great practical significance for the empirical treatment in this region.

Sputum was the most common specimen type of lower respiratory tract in China. Data from China Antimicrobial Resistance Surveillance System (CARSS) in 2015 indicated sputum accounted for 81.6% of the major specimens from inpatients of respiratory departments in 91 general hospitals in seven regions of China. [3] However, the evaluation of LRIs by sputum smear or sputum culture has been controversial. Results of sputum culture are easy to be confused by the colonized bacteria in the oral cavity and throat, so it is difficult to judge whether the culture result is infection or colonization, so the evaluation of sputum culture has always been a difficult problem for clinicians and microbiologists. As early as the 1970s,

microbiologists developed many standards to evaluate the quality of sputum samples. [4] Only qualified sputum samples have the value of culture. Even for qualified sputum samples, the results of culture were influenced by the use of antibiotics in the evaluation of LRIs. [5] Therefore, sputum specimen is not a good specimen type to evaluate LRIs. Bronchoscope alveolus lavage fluid (BALF) is a good specimen, which can accurately reflect the situation of LRIs. [6] In order to accurately analyze the pathogenic bacteria and antimicrobial resistance of LRIs in this region, the BALF data accumulated from 2015 to 2019 were analyzed retrospectively, so as to guide clinicians to reasonably select antibiotics for empirical treatment.

Methods

Study design and data collection

The inspection results of BALF from January 2015 to October 2019 in our hospital were analyzed retrospectively. The differences of age distribution, seasonal distribution and antimicrobial resistance of main pathogens were analyzed. Tongji Hospital is one of the largest teaching hospitals in Central China, including more than 7000 beds in three hospital districts. Most of the patients came from six provinces in Central South China, including Hubei, Hunan, Jiangxi, Anhui, Henan and Shanxi. The clinical laboratory of Tongji Hospital is one of the first laboratories recognized by International Organization for Standardization (ISO) 15189 and College of American Pathologists (CAP) certification in the United States. The standardized operation and accumulated data analysis of the laboratory are of great significance to understand the distribution and antimicrobial resistance of pathogens in Central China.

Strain identification and antimicrobial sensitivity testing

The culture of strains was carried out by conventional methods in strict accordance with the standardized operation procedures of the department. The identification of strains was carried out by biochemical experiments, automatic identification system (Vitek-2-compact, BioMerier Products) and/or IVD-MALDI Biotyper (Bruker, Germany). Antimicrobial susceptibility test was carried out according to CLSI by disk diffusion method and E test method.

Statistical analysis

All strain information and patient information were stored in WHONET 5.6 software. The results of antimicrobial sensitivity, age distribution and seasonal distribution of the strains were analyzed by whonet5.6 software. The analysis of antimicrobial sensitivity data was based on CLSI 2019 standard. [7] For the same strain from the same patient, only the first isolated strain was analyzed according to CLSI M39 in order to avoid the influence of repeatedly isolated strains on antimicrobial resistance statistics.[8]

For the antimicrobial sensitivity results of Enterobacteriaceae to carbapenems, when result of disk diffusion method was not sensitive, the method of E test was used to confirm the results and the results of antimicrobial sensitivity test were analyzed according to the results of E test.

Results

BALF submission and culture positive rate

Data from January 2015 to October 2019 showed that the numbers of BALF specimens and culture positive specimens were increasing year by year. The positive rate of culture was between 16.8% and 21.9%. (fig 1)

Distribution of common pathogens responsible for LRIs

From 2015 to 2019, the strains more than 100 isolates were *K. pneumoniae*, *P. aeruginosa*, *A. baumannii*, *Staphylococcus aureus*, *Haemophilus influenzae*, *Stenotrophomonas maltophilia*, *E. coli* and *S. pneumoniae* in order of quantity. (fig 2)

Age demographic affected by LRIs

Individuals aged 40–70 years old were the major demographics at risk of infection by these eight pathogens, while individuals aged 0–5 years were also the major demographics at risk of infection by *E. coli* and *S. pneumoniae*. (fig 3)

Seasonal distribution of LRIs pathogens

Different strains had different epidemic seasons. *S. aureus* isolated most in spring (February to April), while *A. baumannii*, *H. influenzae* and *S. pneumoniae* isolated most in summer (May to July). For *K. pneumoniae*, *P. aeruginosa* and *S. maltophilia*, autumn (August to October) was the season with the most isolates, while *E. coli* was in winter (November to January) with the most isolates. (fig 4)

Antimicrobial susceptibility testing

For *K. pneumoniae* isolates, sensitivity rates to cefotaxime, ceftazidime and cefepime were 56.5%, 52.6% and 54.9%, respectively. But resistance rates to imipenem and meropenem were 30.6% and 30.8%, respectively. (fig 5a) The sensitivity of *P. aeruginosa* to minocycline and ticarcillin clavulanic acid was 35% and 40.6% respectively, and the sensitivity to other commonly used antibiotics was all more than

60%. (fig 5b) The sensitivity rates of *A. baumannii* to tegacyclin and minocycline were 42.2% and 32.9% respectively, and the resistance rates to other antibiotics were all higher than 80%. (fig 5c) The sensitivity rates of *MRSA* to vancomycin, teicoplanin and linezolid were all 100%, to tegacyclin, rifampicin and Trimethoprim Sulfamethoxazole were 92.7%, 72.5% and 96.7%, respectively, but resistance rates to other antimicrobial agents were more than 50%. (fig 5d) The resistant rate of *MSSA* to penicillin was 90.9% and the sensitive rates to erythromycin and clindamycin were 56.9% and 78.4%, respectively. The sensitivity rates to other antibiotics were more than 85%. (fig 5e) The sensitivity rate of *H. influenzae* to ampicillin was 57.9%. The resistance rate to Trimethoprim Sulfamethoxazole was 54.5% and the non-sensitivity rates to azithromycin, ciprofloxacin and cefotaxime were 18.2%, 3.7% and 4%, respectively. (fig 5f) The sensitivity rates of *S. maltophilia* to Trimethoprim Sulfamethoxazole, minocycline and levofloxacin was more than 80%. (fig 5g) For *E. coli* isolates, sensitivity rates to cefotaxime, ceftazidime and cefepime were 50.4%, 24.4% and 26.0%, respectively. But resistance rates to imipenem and meropenem were both 2.4%. (fig 5h) The sensitivity of *S. pneumoniae* to penicillin was 41.8% and 94.5% according to the breaking points of meningitis and non-meningitis, respectively. And the sensitivity rate to ceftriaxone was 66.4% and 89.1% according to the breaking points of meningitis and non-meningitis, respectively. The non-sensitivity rate of *S. pneumoniae* to oxacillin was 56.4%. (fig 5i)

Trends of multi-drug resistance (MDR) strains

The detection rate of *MRSA* was decreasing year by year. The detection rate of *A. baumannii* resistant to carbapenems was always at a high level, all of which were more than 80%. Different from *A. baumannii*, the detection rates of carbapenem resistant *P. aeruginosa* has been lower than 25% from 2015 to 2019. The detection rate of carbapenem resistant *E. coli* was lower than 6%, but the detection rate of carbapenem resistant *K. pneumoniae* was 15% - 40%. (fig 6)

Discussion

Our surveillance data showed that *K. pneumoniae*, *P. aeruginosa* and *A. baumannii* were the most common pathogens of LRIs. Our data was different from the results of a global multi center report from the SENTRY Antimicrobial Surveillance Program (1997–2016), which showed in Latin America, the most common pathogens were *P. aeruginosa*, *S. aureus* and *Acinetobacter*, while in Europe, Asia Pacific and North America, the most common pathogens were *S. aureus*, *P. aeruginosa* and *K. pneumoniae*. [2] *S. aureus* ranked fourth in our area. Our pathogenic spectrum was consistent with the data reported by CHINET (China antimicrobial surveillance network) of China in 2018. [9] In the developed world, the United States a study indicated *S. pneumoniae*, *S. aureus* and *Legionella pneumophila* were the most common pathogens of community-acquired pneumonia in adults (≥ 18 years old) from 2010–2012. [10] However, the most common pathogens of adult community-acquired pneumonia in Malawi, a developing country in Africa were *S. pneumoniae*, *Mycobacterium tuberculosis* and *non-Mycobacterium tuberculosis*. [11] We found that in different regions of the world, the pathogenic bacteria of LRIs were significantly different.

Therefore, it was of great significance to analyze the distribution of local pathogens for epidemiological research and clinical experience.

This study found that the main population of LRIs was 40–70 years old, for the eight most common pathogens *K. pneumoniae*, *P. aeruginosa*, *A. baumannii*, *S. aureus*, *H. influenzae*, *S. maltophilia*, *E. coli* and *S. pneumoniae*. For *E. coli* and *S. pneumoniae*, the age range of 0–5 years was also a major distribution. According to data from 195 countries around the world, *S. pneumoniae* and *H. influenzae* type b were the main pathogens of LRIs in children under 5 years old.[1] With the global promotion of *S. pneumoniae* and *H. influenzae* b vaccine, their incidence had decreased significantly. [12] Among all infectious diseases, vaccines were the most effective means of control. Our study found that the age distribution of pathogens in LRIs was different from that in bloodstream infection. Studies from Malawi, Africa, have shown that *K. pneumoniae*, which caused bloodstream infection, mainly came from the ages of 0–5 and 75–79.[13] To understand the age distribution of the main pathogens was helpful for clinicians to choose the appropriate antibiotics when they took experiential treatment. For example, in the treatment of children, fluoroquinolones should be avoided because of their influence on bone development. For the elderly patients with poor liver and kidney function, the liver and kidney toxicity of antibiotics should be considered in the empirical treatment.

A systematic analysis on global patterns in monthly activity of influenza virus, respiratory syncytial virus, parainfluenza virus, and metapneumovirus found influenza virus had clear seasonal epidemics in winter months in most temperate sites but timing of epidemics was more variable and less seasonal with decreasing distance from the equator and other viruses had obvious epidemic seasons.[14] In our data, *S. aureus* had the highest isolation rate in spring, *A. baumannii*, *H. influenzae* and *S. pneumoniae* had the highest isolation rate in summer, *K. pneumoniae*, *P. aeruginosa* and *S. maltophilia* had the highest isolation rate in autumn, while *E. coli* had the highest isolation rate in winter. It is of great significance to understand the seasonal prevalence of pathogens in LRIs for disease prevention and control as well as vaccination. [15]

This study showed that *K. pneumoniae* was the main pathogen of LRIs. Cephalosporin was often used in the treatment of LRIs because of its small side effects. This study showed that the sensitivity rates of *K. pneumoniae* to ceftazidime and cefotaxime were 56.5% and 52.6% respectively, and the sensitivity rate to cefepime was 54.9%. The main resistance mechanism of *K. pneumoniae* to cephalosporin was the expression of extended spectrum β -lactamase. (ESBLs). [16] When cephalosporins were resistant, carbapenems were often considered in clinical experience. Our data showed that the resistance rates of *K. pneumoniae* to imipenem and meropenem were 30.6% and 30.8%, respectively. Large data analysis from China's multi centers shows that the antimicrobial resistance rate of *K. pneumoniae* to imipenem and meropenem increased year by year from 2005 to 2018, and the resistance rates of meropenem and imipenem increased from 2.9% to 26.3% and 3% to 25%, respectively.[9] However, the situation in Germany was different from that in China. Monitoring data from the German Antimicrobial Resistance Surveillance (ARS) show that the isolation rate of *K. pneumoniae*, which was not sensitive to carbapenems, in Germany in 2011–2016 was only 0.63%. [17] In addition, *K. pneumoniae*, which was not

sensitive to carbapenems, was often resistant to other antibiotics, such as gentamicin, Sulfanilamide and tegacyclin. [17] Some studies had shown that carbapenem-resistant hypervirulent *K. pneumoniae* may have a clonal distribution in the hospital.[18] The increase of resistance rate of carbapenems may be related to the unreasonable use of carbapenems.[19] Therefore, the control of carbapenem resistant *K. pneumoniae* in our hospital was the top priority for infection control.

This study found that in addition to *K. pneumoniae*, another strain with high resistance rate was *A. baumannii*. In addition to tegacyclin and minocycline, the resistant rates to other commonly used antibiotics of *A. baumannii* were more than 80%. Data from CHINET in 2018 shows that *A. baumannii* isolates from blood, cerebrospinal fluid and lower respiratory tract had a very high resistance rate to commonly used antibiotics (almost all more than 50%, even more than 80%).[9] At present, the antimicrobial resistance of *A. baumannii* in China had reached a very serious level. The high resistance of *A. baumannii* may be related to the expression of carbapenemase ox-23, ox-24 and ox-51. [20] The formation of biofilm was beneficial to the long-term existence of *A. baumannii* in the environment and it was found that there was homology between the infection strains of patients and the colonization strains in the environment, indicating that the highly resistant strains were cross transmitted between patients and the environment. [21] Therefore, the control of *A. baumannii* must rely on the strengthening of hospital infection control measures.

There are several limitations in this study. First of all, the types of LRIs such as community acquired, hospital acquired and ventilator related infection types were not distinguished in this study. Secondly, the molecular epidemiology of carbapenem resistant *K. pneumoniae* and *A. baumannii* were not analyzed.

Conclusions

At present, the primary task of LRIs is to control the spread of *K. pneumoniae* which are resistant to carbapenem and *A. baumannii*.

Abbreviations

BALF: bronchoscope alveolus lavage fluid; LRIs: lower respiratory tract infections, CR-*K. pneumoniae*: *K. pneumoniae* resistant to carbapenems, CARSS: China Antimicrobial Resistance Surveillance System, ISO: International Organization for Standardization, CAP: College of American Pathologists, MDR: multi-drug resistance, CHINET: China antimicrobial surveillance network, ESBLs: extended spectrum β -lactamase, ARS: German Antimicrobial Resistance Surveillance

Declarations

Ethics approval and consent to participate

The study protocol was approved by the Tongji Hospital ethics committee for research in health. The Tongji Hospital ethics committee also approved the waiver of informed consent to participate in this study due to its retrospective design. All patient data were anonymous prior to the analysis.

Consent to publish

Not applicable.

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interest.

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Author Contributions

Ziyong Sun designed the study. Lei Tian analyzed the data and wrote the article. Zhen Zhang and Feng He helped to revise the manuscript. All authors reviewed the manuscript prior to submission.

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Figures

Fig 1. Number of BALF specimens and positive rate of culture in 2015-2019

Figure 1

Number of BALF specimens and positive rate of culture in 2015-2019

Fig 2. Distribution of main pathogens in lower respiratory tract infection (n > 100)

Figure 2

Distribution of main pathogens in lower respiratory tract infection (n > 100)

Figure 3

The main pathogens isolated from lower respiratory tract infection stratified by age

Fig 4. The distribution proportion in the four seasons of the main pathogens isolated from LRIs

Figure 4

The distribution proportion in the four seasons of the main pathogens isolated from LRIs

Figure 5

Results of antimicrobial susceptibility test of main pathogens. A. (*Klebsiella pneumoniae*) B. (*Pseudomonas aeruginosa*) C. (*Acinetobacter Bauman*) D. (MRSA) E. (MSSA) F. (*Haemophilus influenzae*) G. (*Stenotrophomonas maltophilia*) H. (*Escherichia coli*) I. (*Streptococcus pneumonia*)

Figure 6

Distribution of common multi-drug resistance strains from 2015 to 2019. A. Number distribution of multidrug resistant strains B. Isolation rates distribution of multidrug resistant strains