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Clinical Characteristics and Antibiotic Resistance of Bacterial and Fungal Isolates from the Lower Respiratory Tract of Patients Infected by COVID-19

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Abstract

Background: Analysis of the antibiotic resistance and clinical features of clinical bacterial and fungi isolates from the lower respiratory tract of patients infected with COVID-19.

Methods: Collected the qualified lower respiratory tract 397 strains of patients infected with COVID-19 between 10 December 2022 and 10 January 2023.The isolated strains were identified and tested for antimicrobial susceptibility. Colloidal gold enzyme type assays for carbapenem-resistant *Klebsiella pneumoniae*; analyzed procalcitonin interleukin 6,C-reactive protein and neutrophils. The Whonet 5.6 software was used to analyse the results.

Results: A total of 123 strains were isolated, of which 97 were bacterial and 26 were fungal, respectiveley. *Pseudomonas aeruginosa* strains showed lower resistance to cefoperazone/sulbactam and imipenem（22% and 6. 5%), the resistance rates of fungi to fluconazole and voriconazole were 7.7% and 3.8% respectively, the isolation rate of carbapenem-resistant Klebsiella pneumonia is 12% (3/25), the enzyme type is all KPC-2. The drug resistance rate of *Acinetobacter baumannii* to most antibiotics is more than 50%, still, the drug resistance rate to cefoperazone/sulbactam is 27%, which also maintains a lower drug resistance level.No staphylococcal strains were found resistant to vancomycin, ceftaroline, and Linezolid. There are 98 strains isolated from the people, especially 80 to 96. Clinical data showed that at least one index of PCT, IL-6, CRP, or neutrophil increased in 120 patients.

Conclusion: There is an excellent possibility that the elderly infected with COVID-19 may suffer from secondary bacterial and fungal infections. Improve surveillance and laboratory testing for inflammatory factors for a comprehensive assessment.

Keywords: Lower respiratory tract; COVID-19; Resistance analysis; Novel coronavirus

Introduction

The First discovered in Southern Africa in November 2021, the Omicron variant of SARS-CoV-2 has spread swiftly across the world, spread quickly, and strong concealment; the strains currently prevalent in China, are also dominated by the Omicron variant [1,2]. Accompany by the adjustment of prevention policy in China, the number of hospitalized patients infected with COVID-19 increased sharply. These are the elderly and patients with underlying diseases, when the virus invades the respiratory tract, it can cause acute respiratory distress syndrome, perhaps secondary the bacterial and fungal infection, there are few reports on drug resistance monitoring of secondary bacterial and fungal infection in patients with COVID-19 [3]. We are a general hospital with 800 beds, all are used to treat patients with COVID-19 infection. We collected the lower respiratory tract from patients infected with COVID-19, then analyzed the antibiotic resistance and clinical characteristics. Meanwhile, we analyzed the procalcitonin, interleukin-6, C-reactive protein, and neutrophils. To provide a reference for secondary bacterial and fungal infection with COVID-19.

Materials and Methods

Materials

Collection of strains: A total of 397 eligible sputum specimens were collected from patients hospitalized in our hospital with positive nucleic acid gene amplification for COVID-19 infection from 10 December 2022 to 10 January 2023. There are 123 strains.Repeat isolates of the same species from the same patient were excluded.

Quality control strains: *S. aureus* ATCC 25923 (Kirby-Bauer method) and ATCC 29213 (automated systems), *Escherichia coli* ATCC 25922, *Pseudomonas aeruginosa* ATCC 27853, and *Enterococcus faecalis* ATCC 29212 were used as quality control strains.

Instruments and reagents: Identified Strains and antimicrobial susceptibility test used MALDI-TOF MS and VITEK-2 COMPACT respectively (Mérieux, France); Cefoxitin paper (30 μg/tablet) and cefazolin (30 μg/piece) paper are produced by Oxoid; carbapenem enzyme test kit (colloidal gold method) is made by Dana BiotecŠology Co., Ltd.

Methods

Antimicrobial susceptibility test methods: Antimicrobial susceptibility testing for Gram-positive and Gram-negative bacteria was carried out using the VITEK 2-Compact automated system card GP67 and GN13, respectively. The fungus drug sensitivity test uses ATB Fungus 3, supplementary susceptibility test for cefazolin against MRSA using the K-B method. Results were interpreted were conducted according to Clinical and Laboratory Standards Institute standards M100, 32th and M60, 26th [4,5].

Detected the enzyme of carbapenem-resistant *Klebsiella pneumoniae*: Carbapenem-resistant *K. pneumoniae* (CR-KP) is a severe threat to human health, and it is defined as resistance to imipenem, meropenem, or ertapenem [6]. We use an immunochromatographic colloidal gold method to detect the CR-KP enzyme type that allows

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rapid reporting of results to the doctors.

Analysis of inflammatory factors: We retrospectively analyzed the PCT, IL-6, CRP , and neutrophil that were positive for isolated pathogens.

Statistical analysis: Statistical analysis of the data obtained was performed using WHONET 5.6 software.

Results

The distribution of strains

There are 123 strains are isolated from 397 sputum specimens who infected with COVID-19, including 97 bacterial (24.4%, 97/397) and 26 fungal strains (6.5%, 26/397). The results were shown in Table 1.

Analysis of drug resistance of the top five isolated strains

The top five pathogens are *P. aeruginosa*, fungi, *K. pneumoniae*, *A. baumannii*, and *S. maltophilia*. The antimicrobial resistance is shown in Table 2.

CR-KP enzyme type and supplementary trial of cefurolin against MRSA

Of the 25 *K. pneumoniae* strains isolated, 3 were CR-KP, all of which were tested for enzyme type KPC-2, and no cefurolin-resistant MRSA was found (Table 3).

Organism	Number of strains	%
P. aeruginosa	33	26.9
Fungi (C. albicans 19, C. tropicalis 5, C. glabrata 2)	26	21.2
K. pneumoniae	25	20.3
A. baumannii	11	8.9
S. maltophilia	6	4.9
E. coli	6	4.9
S. aureus	4	3.3
S. marcescens	2	1.6
P. mirabilis	2	1.6
K. aerogenes	2	1.6
P. rett	1	0.8
E. cloacae	1	0.8
H. influenzae	1	0.8
E. aerogenes	1	0.8
P. fluorescens	1	0.8
P. putida	1	0.8
Total	123	100

Table 1: Distribution of bacterial and fungal organisms.

***P. Aeruginosa*(n=33)**		**Fungi (n=26)**		***K. pneumoniae* (n=25)**		***A. baumannii* (n=11)**		***S. maltophilia* (n=10)**	
Antimicrobial agent	**Resistance rates**	**Antimicrobial agent**	**Resistance rates**	**Antimicrobial agent**	**Resistance rates**	**Antimicrobial agent**	**Resistance rates**	**Antimicrobial agent**	**Resistance rates**
Aztreonam	52.9	Fluconazole	7.7	Ampicillin sulbactam	55.2	Ampicillin	76.9	Trimethoprim/ sulfamethoxazole	16.7
Ceftazidime	47.1	Voriconazole	3.8	Furantoin	51.7	Ampicillin sulbactam	61.5	Minocycline	0
Piperacillin/ tazobactam	35.3	Amphotericin B	0	Cefazolin	48.3	Piperacillin/ tazobactam	53.8	Levofloxacin	0
Cefepime	32.4	5-fluorocytosine	0	Ciprofloxacin	48.3	Ceftazidime	53.8	Cefoperazone/ sulbactam	0
Cefoperazone/ sulbactam	22	Itraconazole	0	ceftriaxone	44.8	cefatriaxone	53.8		
Imipenem	7.5			Aztreonam	37.9	Cefepime	53.8		
Ciprofloxacin	5.9			Cefepime	37.9	Imipenem	53.8		
Levofloxacin	5.9			Levofloxacin	31	Gentamicin	53.8		
Amikacin	2.9			Ceftazidime	31	Tobramycin	53.8		
Gentamicin	2.9			Piperacillin/ tazobactam	27.6	Ciprofloxacin	53.8		
Tobramycin	2.9			Gentamicin	24.1	Levofloxacin	53.8		
				Tobramycin	24.1	Trimethoprim/ sulfamethoxazole	53.8		
				Trimethoprim/ sulfamethoxazole	17.2	Amikacin	30.8		
				Imipenem	17.2	Cefoperazone/ sulbactam	27		
				Amikacin	12				
				Ertapenem	6.9				

Table 2: Drug resistance analysis of isolates located in the top five pathogens.

Age range	Cases	Proportion%	Bacterial species
<60	8	6.5	*K. pneumoniae*
60-70	6	4.9	*K. pneumoniae*
71-80	31	25.2	*P. aeruginosa*
>80	78	63.4	*P. aeruginosa*

Table 3: Age distribution and a corresponding distribution of major pathogenic bacteria.

Analysis of clinical characteristics

Age distribution: The 397 COVID-19 infected patients, the youngest being five months old and the oldest 97 years old, but of the 123 positive specimens isolated from them, only eight patients were below 60 years, 78 patients over 80 years old that accounting for 63.4% of the number of positives.

Analysis of inflammatory factors: One or more of PCT, IL-6, CRP, and neutrophils were elevated in 120 of the 123 positive culture specimens, supporting a clinical respiratory infection. In comparison three samples had decreased leucocyte markers, as shown in Table 4.

Inflammatory factor*	Cases	Percentage%
Neutrophils	120	97.6
PCT	27	22
II-6	9	7.3
CRP	15	12.2
Note: For PCT, IL-6, and CRP, except for the number of elevated cases shown in the table, the remaining patients were not elevated because the relevant indicators were not queried.		

Table 4: The inflammatory indicators of 123 patients.

Discussion

Since the first outbreak of novel coronavirus in Wuhan, China, in 2020, the Chinese government has taken various measures to control it. Currently, the primary virus strain prevalent in China is Omicron with a prevalence rate is 93%. Omicron spreads rapidly and comprehensively against the body's immune system, especially for people who are elderly, immunocompromised, and accompanying, with underlying diseases [7]. We should be careful the secondary bacterial and fungal infections.

In previous influenza epidemics, coinfection with bacteria secondary to viral infection was thought to be a significant contributor to lethality [8]. Accompaning or secondary bacterial infection in COVID-19 is also a critical factor contributing to lethality,and there, reports of between 14% and 100% infection in patients admitted to intensive care units [9-11].With the adjustment of China's epidemic prevention policy on 8 December 2022, there was a surge of hospitalized patients with novel coronavirus infection in a short period. In this period, there were 908 patients in our hospital, and 803 species (some patients have no sputum). What exactly is the secondary bacterial and fungal respiratory infection after COVID-19 virus infection needs to be supported by relevant data. In this study, 123 strains were isolated from 397 qualified sputum specimens from 10 December 2022 to 10 January 2023 in our hospitalized patients who were infected with COVID-19 were analyzed, and their clinical characteristics were determined to provide an individual reference basis for the doctors.

There are 123 pathogenic strains isolated from 397 eligible sputa, and the separation rate was 30.9%. In contrast, a metal analysis [12], found that the infection rate of secondary bacterial infection in patients with novel coronavirus infection in the data analyzed was around 7%, but the rate in ICU patients was about 14%. The high number of older adults in this study means that whether patients develop secondary bacterial or fungal infections after COVID-19 infection needs to be monitored on time in the context of the patient's condition.

The 123 strains included Gram-negative bacilli (24.4%,97/397) and fungi (6.5%,26/397). Gram-positive cocci (1%,4/397) have a significant reduction compared to the 28.6% isolation rate of Gram-positive cocci in our Chinet surveillance network [13]. Although Gram-negative bacilli had the highest isolation rate, fungi were the second highest among the top five pathogens. In the available literature on fungal infections secondary to COVID-19 infection, the occurrence of fungal infections was reported to be in the second position [14]. Another report, also from China, analyzed fungal isolation rates secondary to COVID-19 in the second position of isolated pathogens, both of which were isolated from *Candida albicans*, which is consistent with the results reported here. It has also been reported that patients with COVID-19 infections in the ICU have a predominance of *S. aureus* in the early stages of infection and P.aeruginosa in the late stages, so the time of admission after patient onset should also be included in the analysis [15,16].Therefore, secondary fungal infections following COVID-19 infection should be taken seriously, especially as a large proportion of these fungi are from older adults, and dynamic monitoring should be performed with additional serological tests, if necessary, combined with clinical information to determine whether antifungal treatment is indicated.

P. aeruginosa is less than 25% resistant to Cefoperazone/sulbactam, imipenem, ciprofloxacin, levofloxacin, gentamicin, and tobramycin. The main population infected with COVID-19 was older people, requiring rational selection of antimicrobial drugs in conjunction with clinical presentation and laboratory information.Fungal infections are not a negligible problem in patients with COVID-19 infection. Of the 26 fungal strains isolated in this study, 7.7% and 3.8% were resistant to fluconazole and voriconazole, respectively.

Ten ESBLs-producing and three Carbapenem resistance *K. pneumoniae* strains were isolated from 25 strains, and three CR-KP strains were tested for enzyme type KPC-2. Therefore, these factors should be fully considered in the using of antimicrobial drugs for COVID-19 secondary pathogenic infections, and enzyme-type testing should be performed when necessary. Cefurolin, vancomycin, and linezolid -resistant strains were not found in *S. aureus*.

Antibiotic resistance of more than 50% about 11 strains of A.baumannii, the susceptibility to amikacin and cefoperazone/sulbactam was maintained at 30.8% and 27%, so that priority consideration could be given to the selection of antimicrobial medications, and the use of antimicrobial drugs could be adjusted later based on drug sensitivity tests. *S.maltophilia* has a low resistance to commonly used antimicrobial drugs, except for 16.7% resistance to compound sulfamethoxazole, and no resistant strains of levofloxacin, cefoperazone sulbactam, and minocycline.

The average age of the subjects of this pathogenic isolation is 79 years old, especially those aged 80-90 years old. These patients have many basic diseases and low resistance. However, the average age of COVID-19 secondary bacterial or fungal infection reported in previous literature is 61 years old, which is far lower than the age of this report [14]. Therefore, with the adjustment of the vaccination policy, the follow-up of COVID-19-infected patients with secondary respiratory

infections focuses on the elderly population [17].

To find additional pathogenic evidence, 123 positive specimens were retrospective analysis for calcitonin gene, interleukin 6, C-reactive protein , and neutrophils. 123 patients all analyzed for blood cells, 120 had elevated neutrophils , and three had decreased total leucocytes. Not all patients were tested for PCT, IL-6, and CRP, but based on available data, an elevation in one or more of these may be evidence of infection. All opinions agree that PCT is a good indicator that can distinguish bacterial infection from viral infection and distinguish early disease from late disease [18,19]. In our study, only 27 patients were examined for PCT, but the PCT of these 27 cases was all increased. PCT plays an essential, a vital role in COVID-19 infection [20,21]. It can reduce the abuse of antibiotics in COVID-19 infection. There are 72% of patients with COVID-19 will use broad-spectrum antibiotics, and some organizations recommend to use of drugs with full coverage, including atypical pathogens.

Conclusion

According to this study, secondary respiratory infections are predominantly in the elderly, therefore for hospitalized elderly patients with COVID-19 infection, and patients younger than 60 years with underlying disease, to prevent secondary bacterial infections, broad-spectrum antibiotics can still be used empirically, while sputum cultures are sent for examination and inflammatory indicators are checked, and antibiotics are adjusted promptly according to the results. Secondary fungal infections also require attention, dynamic observation of indicators , and antifungal treatment in conjunction with clinical information. There is an excellent possibility that the elderly infected with COVID-19 may suffer from secondary bacterial and fungal infections. This study improve surveillance and laboratory testing for inflammatory factors for a comprehensive assessment.

ICMJE Statement

Contributors Yin Di Zhou are responsible for article writing and data collection. Xiao Qin Yu was responsible for the organization and coordination of the trial. Done Mei Gao was responsible for English editorial work.Ethics declarations. This study protocol was approved by the institutional review broad of the Kao Corporation (K0141-2209). These studies were performed in accordance with the Declaration of Helsinki.

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