Etiology and Antimicrobial Resistance of Secondary Bacterial Infections in Patients Hospitalized With COVID-19 in Wuhan, China: A Retrospective Analysis

Jie Li
Union hospital, Tongji Medical College, University of Science and Technology
Junwei Wang
Union Hospital, Tongji Medical College, Huazhong University of Science and Technology
Yi Yang
Union Hospital, Tongji Medical College, Huazhong University of Science and Technology
Peishan Cai
Union Hospital, Tongji Medical College, Huazhong University of Science and Technology
Jingchao Cao
Union Hospital, Tongji Medical College, Huazhong University of Science and Technology
Xuefeng Cai (caiwhxh@163.com)
Union Hospital, Tongji Medical College, Huazhong University of Science and Technology
Yu Zhang
Union Hospital, Tongji Medical College, Huazhong University of Science and Technology

Research

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Abstract

Background: A considerable proportion of patients hospitalized with corona virus disease 2019 (COVID-19) have acquired secondary bacterial infections (SBIs). We report the etiology and antimicrobial resistance of bacteria to provide theoretical basis for appropriate infection therapy.

Methods: In the retrospective study, we reviewed electronic medical records of all the patients hospitalized with COVID-19 in the Wuhan Union hospital from January 27 to March 17, 2020. According to the inclusion and exclusion criteria, patients who acquired SBIs were enrolled. Demographic, clinical course, etiology and antimicrobial resistance data of the SBIs were collected. Outcomes were also compared between patients who were classified as severe on admission and those who were classified as critical.

Results: 6.8% (102/1495) of the patients with COVID-19 had acquired SBIs and almost half of them (50, 49.0%) died during hospitalization. Compared with the severe patients, the critical patients had a higher chance of SBIs. 159 strains of bacteria were isolated, 85.5% of which were Gram-negative bacteria. The top three bacteria of SBIs were *A. baumannii* (35.8%), *K. pneumoniae* (30.8%) and *Staphylococcus* (8.8%). The isolation rate of carbapenem-resistant *A. baumannii* and *K. pneumoniae* were 91.2% and 75.5%, respectively. Meticillin resistance was in 100% of *Staphylococcus*, and vancomycin resistance was not found.

Conclusions: SBIs may occur in patients hospitalized with COVID-19 and lead to high mortality. The incidence of SBIs was associated with the grade on admission. Gram-negative bacteria, especially *A. baumannii* and *K. pneumoniae,* were the main bacteria and the resistance rates of the major isolated bacteria were generally high.

Introduction

The epidemic of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has occurred in most countries around the world, and COVID-19 has progressed into a global pandemic. Globally, as of 15 July 2020, there have been more than 12 million confirmed cases of COVID-19, including over 570 thousand deaths [1]. According to previous researches [2, 3], secondary bacterial infection (SBI), about 10%~15% incidence, was a dangerous and common complication in patients hospitalized with COVID-19. These patients had a higher risk of mortality according to reports that 50% of COVID-19 deaths experienced secondary bacterial infections (SBIs) [3, 4]. SBIs had become the hidden threat lurking behind COVID-19. The effective antimicrobial regimen was still one of the key measures for successful treatment of COVID-19 [5].

Due to no controlled clinical trials evaluating the use of empiric antibacterial agents in COVID-19 patients, the current recommendations are based upon extrapolation of data from other viral pneumonia [5]. In a quick guide [6], it was recommended that empiric antimicrobial treatment covered all possible bacteria in severe COVID-19 patients with SBIs. Empiric use of third-generation cephalosporin combined enzyme

inhibitor for SBIs in severe patients was recommended in a consensus based on the experience in treating COVID-19 [7]. However, the SBIs caused by COVID-19 was different from others. During the outbreak, a large number of broad-spectrum antibacterial agents were used and the vast majority of patients hospitalized with COVID-19 were given empirical antimicrobial treatment before SBIs were confirmed [2, 3, 8]. The broader application of antibacterial agents may further lead to changes of etiology and antimicrobial resistance. The SBIs in patients hospitalized with COVID-19 should be treated according to further microbiological data. As of now, there is no report on the pathogenic spectrum of SBIs. Some cases of bacterial infections have been reported in the researches about the clinical characteristics of COVID-19, but they are not systematic studies about etiology of SBIs, and the number of positive cultures is small [8–12]. It is not enough to indicate the distribution of bacteria and guide reasonable empiric use of antibacterial agents.

For the first time, a large sample size retrospective analysis of SBIs in patients hospitalized with COVID-19 had been conducted in our study. The aim was to obtain the etiology and antimicrobial resistance of SBIs for more accurate of antimicrobial use.

Methods

Study population

Wuhan Union hospital is one of the designated hospitals to treat patients with COVID-19 in Wuhan, China. From January 27 to March 17, 2020, a total of 1495 patients had been diagnosed COVID-19 and receive treatment in the West Campus of Wuhan Union hospital. According to the grade on admission, 1050 of them were classified as severe and 258 patients were critical. Demographic, clinical course, laboratory and treatment data were collected from electronic medical records.

Study design

SBIs were defined when patients showed clinical characteristics of bacterial infections and at least one positive etiology of bacteria was acquired from qualified microbiological specimens after infected with SARS-CoV-2 [3, 13]. We performed a retrospective review of medical records that met the criteria from January 27 to March 17, 2020. Inclusion criteria: (1) patients were diagnosed as COVID-19 according to the Guidance for COVID-19 (7^{th} edition) released by the National Health Commission of China [14]; (2) met the diagnostic criteria of SBIs. Patients were excluded if: (1) before being infected with SARS-CoV-2, patients had other infectious diseases; (2) the medical records were incomplete. Mild patients on admission rarely acquired SBIs. In our study, the patients enrolled were basically severe or critical ill. Therefore, according to the grade on admission, the patients enrolled were divided into severe group and critical group.

The study was approved by the Ethics Committee of Union Hospital, Tongji Medical College, Huazhong University of Science and Technology (Permission number: [2020]0104).

Pathogen detection and antimicrobial susceptibility

The qualified microbiological specimens of patients with COVID-19 from January 27, 2020 to March 17, 2020 were collected and cultured. Pathogen identification and antimicrobial susceptibility testing were carried out on the phoenix-100 automatic microbiological system (BD Corporation, USA). In some further antimicrobial susceptibility testing, international Kirby-Bauer method was also used. All the results were interpreted according to the criteria of the Clinical and Laboratory Standards Institute (CLSI 2015) [15]. The same strains of one patient were counted only once. The data was analyzed using WHONET 5.6 software.

Statistical Analysis

Continuous and categorical variables were presented as median (IQR) and percentages. Differences between the severe and critical groups were compared with Mann-Whitney U test, χ^2 test, or Fisher's exact test. P value less than 0.05 was regarded as statistically significant. All statistical analyses were performed by IBM SPSS Statistics 26.0.

Results

General information

A total of 102 inpatients (6.8%, 102/1495) were enrolled in the study. The mean age was 66.2 ± 11.2 years (30 ~ 93 years; Table 1) and 68 patients (66.7%) were males. The incidence in the severe was 3.1% (33/1050), much lower than in the critical (26.7%, 69/258). Almost half of the patients who acquired SBIs (49.0%, 50/102) died during hospitalization and the other patients were discharged. Compared with the severe group, the critical group had a significantly increased mortality (65.2% vs 15.2%, $P < 0.0001$).

Table 1
Demographic, clinical course and outcome data of patients who acquired SBIs during the COVID-19 hospitalization

	All patients (n = 102)	Severe group (n = 33)	Critical group (n = 69)	P value
Characteristics				
Age, years	66.2 (30 ~ 93)	64.9 (30 ~ 82)	66.1 (36 ~ 93)	0.686
Sex				0.178
Men	68 (66.7%)	19 (57.6%)	49 (71.0%)	
Women	34 (33.3%)	14 (42.4%)	20 (29.0%)	
Treatment before SBIs				
Antiviral therapy	96 (94.1%)	29 (87.9%)	67 (97.1%)	0.084
Antibiotic therapy	99 (97.1%)	31 (93.9%)	68 (98.6%)	0.244
Outcomes				< 0.0001
Discharge	52 (51.0%)	28 (84.8%)	24 (34.8%)	
Death	50 (49.0%)	5 (15.2%)	45 (65.2%)	

Data are median (IQR) or n (%). P values comparing severe group and critical group are from Mann-Whitney U test, χ^2 test, or Fisher's exact test.

The proportion of SBIs in lungs, bloodstream and urinary tract was 86.3% (88/102), 34.3% (35/102) and 7.8% (8/102), respectively. The SBIs were lung infections mixed with bloodstream infections in 27 (26.5%) patients, and with urinary tract infections in 2 (2.0%) patients. There was no secondary infection in other sites.

Etiology of the secondary infection

A total of 159 strains of bacteria were isolated from the cultures in the 102 patients. Among the isolated bacteria, Gram-negative bacteria were the main bacteria, accounting for 85.5%. The top three bacteria of SBIs were *Acinetobacter baumannii* (*A. baumannii*, 35.8%), *Klebsiella pneumoniae* (*K. pneumoniae*, 30.8%) and *Staphylococcus* (8.8%). The distribution and composition ratio of bacteria were shown in Table 2. Among them, 46 patients had infections with mixed bacteria, mostly *A. baumannii* mixed with *K. pneumoniae* (41.3%) (Table 3).

Table 2
Etiological distribution of SBIs in patients hospitalized with COVID-19

bacteria	N (%) in different sites			
	Lungs	bloodstream	Urinary tract	Total
Gram-negative	105(95.5)	27(62.8)	4(50.0)	136(85.5)
A. baumannii	47(42.7)	9(20.9)	1(12.5)	57(35.8)
K. pneumoniae	34(30.9)	15(34.9)	0(0)	49(30.8)
Stenotrophomonas maltophilia	10(9.1)	0(0)	0(0)	10(6.3)
Pseudomonas aeruginosa	7(6.4)	0(0)	0(0)	7(4.4)
Escherichia coli	4(3.6)	1(2.3)	3(37.5)	8(5.0)
others	3(2.7)	2(4.7)	0(0)	5(3.1)
Gram-positive	5(4.5)	16(37.2)	2(25.0)	23(14.5)
Staphylococcus aureus	2(1.8)	1(2.3)	0(0)	3(1.9)
Staphylococcus epidermidis	0(0)	2(4.7)	0(0)	2(1.3)
Staphylococcus hominis	0(0)	5(11.6)	0(0)	5(3.1)
Staphylococcus haemolyticus	0(0)	2(4.7)	0(0)	2(1.3)
Enterococcus faecium	0(0)	4(9.3)	2(25.0)	6(3.8)
others	3(2.7)	2(4.7)	0(0)	5(3.1)
Total N (%)	110(100)	43(100)	6(100)	159(100)

Table 3
Etiological distribution of SBIs caused by multiple bacteria in patients hospitalized with COVID-19

Mixed infection	N (%)
Two bacteria	
A. baumannii + K. pneumoniae	9(19.6)
A. baumannii + staphylococcus	4(8.7)
Other combination	17(37.0)
Three and more bacteria	16(34.8)
Total N (%)	46(100)

Antimicrobial susceptibility

The antimicrobial resistance rate of bacteria isolated from patients with SBIs was generally high. The isolation rates of carbapenem-resistant *A. baumannii* and *K. pneumoniae* were 91.7% and 76.6%, respectively. Meticillin resistance was in 100% of *Staphylococcus*, and vancomycin resistance was not found. The isolation rate of extended-spectrum beta-lactamase (ESBL)-producing *Escherichia coli* (*E. coli*) was 75%. The results of antimicrobial susceptibility testing for the major bacteria were shown in Table 4 and Table 5.

Table 4
Antimicrobial susceptibility of major Gram-negative bacteria

Antibacterial	Major Gram-negative bacteria, N (%) of resistant strains				
	A. baumannii(n = 57)	*K. pneumoniae*(n = 49)	*S. maltophilia*(n = 10)	*P.aeruginosa*(n = 7)	*E. coli* (n = 8)
Ampicillin	-	49(100)	-	-	7(87.5)
Ampicillin sulbactam	53(93.0)	44(89.8)	-	-	2(25.0)
Piperacillin	53(93.0)	43(87.8)	-	1(14.3)	7(87.5)
Piperacillin tazobactam	52(91.2)	38(77.6)	-	1(14.3)	1(12.5)
Amoxicillin clavulanate	57(100)	42(85.7)	-	-	1(12.5)
Cefazolin	57(100)	48(98.0)	-	-	7(87.5)
Cefuroxime	-	43(87.8)	-	-	6(75.0)
Ceftriaxone	52(91.2)	41(83.7)	-	-	6(75.0)
Ceftazidime	52(91.2)	41(83.7)	9(90.0)	1(14.3)	3(37.5)
Cefoperazone sulbactam	45(78.9)	39(79.6)	-	-	-
Cefepime	53(93.0)	41(83.7)	-	1(14.3)	5(62.5)
Aztreonam	57(100)	41(83.7)	-	2(28.6)	2(25.0)
Cefoxitin	-	41(83.7)	-	-	0(0)
Meropenem	52(91.2)	37(75.5)	-	3(42.9)	0(0)
Imipenem	52(91.2)	37(75.5)	-	3(42.9)	0(0)
Amikacin	48(84.2)	36(73.5)	-	0(0)	0(0)
Gentamicin	52(91.2)	39(79.6)	-	0(0)	2(25.0)
Tobramycin	50(87.7)	32(65.3)	-	-	2(25.0)
Levofloxacin	52(91.2)	39(79.6)	3(30.0)	2(28.6)	6(75.0)
Ciprofloxacin	52(91.2)	43(87.8)	-	2(28.6)	6(75.0)
Sulfamethoxazole trimethoprim	48(84.2)	36(73.5)	0(0)	-	4(50.0)
Minocycline	16(28.1)	23(46.9)	0(0)	-	2(25.0)

Antibacterial	Major Gram-negative bacteria, N (%) of resistant strains				
	A. baumannii(n = 57)	*K. pneumoniae*(n = 49)	*S. maltophilia*(n = 10)	*P.aeruginosa*(n = 7)	*E. coli* (n = 8)
Tigecycline	0(0)	1(1.7)	-	-	0(0)
ESBL	-	43(87.8)	-	-	6(75.0)
Note: -, not detected					

Table 5
Antimicrobial susceptibility of major Gram-positive bacteria

Antibacterial	Major Gram-positive bacteria, N (%) of resistant strains	
	Staphylococcus(n = 14)	*Enterococcus faecium*(n = 6)
Penicillin G	14(100)	6(100)
Oxacillin	13(92.9)	-
Ampicillin	-	6(100)
Erythromycin	13(92.9)	6(100)
Clindamycin	7(50.0)	-
Minocycline	0(0)	0(0)
Levofloxacin	-	5(83.3)
Ciprofloxacin	11(78.6)	6(100)
Gentamicin	4(28.6)	2(33.3)
Vancomycin	0(0)	0(0)
Teicoplanin	0(0)	0(0)
Linezolid	0(0)	0(0)
Note: -, not detected		

Discussion

Respiratory failure or multiple organ failure is the direct cause of death in patients with COVID-19, and SBIs play an important role in this process [16]. Among the 1495 patients with COVID-19, the incidence of SBIs was 6.8%. Perhaps because of the larger sample size in our study, the incidence of SBIs was lower than the data in previous studies (10%~15%, Wuhan, China) [2, 3]. The incidence in critical patients was much higher than in severe patients, which was consistent with the higher rate of central catheter placement and invasive mechanical ventilation in critical patients [2]. Almost half (49.0%) of the patients with SBIs died during hospitalization, in agreement with the previous study (50%) [3]. Compared with the

severe group, the critical group had a significantly increased mortality. Recent studies related to COVID-19 reported that male was a risk factor for disease severity status, and age 65 or older was a risk factor related to death [3, 17, 18]. In our research, no differences in gender and age were found between the severe and critical groups. It revealed that gender and age were not risk factors for death in patients with SBIs. The risk factors for death in patients with SBIs needed to be explored in the next study.

According to the sites of SBIs, lung infections were the main type, which may be related to the decrease of airway defense function after infected with SARS-CoV-2 [19]. Invasive operations such as trachea intubation and ventilator-assisted breathing during hospitalization may also be the causes of SBIs in the lungs. There were 35 patients with bloodstream infections, 27 of which were bloodstream infections mixed with lung infections. We compared the bacteria of mixed infections and found that 21 patients had the same bacteria in lungs and bloodstream, including *K. pneumoniae* (66.7%, 14/21) and *A. baumannii* (33.3%, 7/21). We inferred that the migration of *K. pneumoniae* or *A. baumannii* from the lungs resulted in bloodstream infections in these patients.

A total of 159 strains of bacteria were isolated in this study and mainly were Gram-negative bacteria. The top three bacteria of secondary lung infections were *A. baumannii, K. pneumoniae and Stenotrophomonas maltophilia* (*S. maltophilia*). The etiological distribution was different from the previously reported bacteria of hospital-acquired pneumonia (HAP) [20, 21]. The proportion of *A. baumannii and K. pneumoniae* was significantly increased and the proportion of *Pseudomonas aeruginosa* (*P. aeruginosa*) and *Staphylococcus aureus* (*S. aureus*) was decreased. It suggests that the initial empirical antimicrobial program of HAP should not be completely copied if SBIs in the lungs occur. The lower proportion of *P. aeruginosa* and *S. aureus* indicates that it is not necessary to first choose antimicrobial with antibacterial activity of *P. aeruginosa* and *S. aureus* for SBIs in the lungs. The choice of antimicrobial program should be more inclined to treat the infections of *A. baumannii and K. pneumoniae.* The antimicrobial susceptibility tests showed that most of *A. baumannii and K. pneumoniae* were multi-drug resistant bacteria. The isolation rate of carbapenem-resistant *A. baumannii* and *K. pneumoniae* were 91.7% and 76.6%, respectively. When the patients suffer SBIs, the possibility of infections by drug-resistant strains should be adequately considered. The resistance rate of tigecycline and cefoperazone sulbactam was relatively lower and the combination can be considered for the initial empirical treatment of SBIs in the lungs. According to reports [22, 23], avibactam compound has a better effect on carbapenem-resistant *K. pneumoniae*, but systematic research in patients with COVID-19 has not been launched.

Although the bacteria of secondary bloodstream infections were mainly Gram-negative bacteria, the proportion of Gram-positive bacteria was relatively higher than lung infections. If the bacteria derived from lung infections were excluded in the statistics, Gram-positive bacteria would be the main bacteria for bloodstream infections. 80.0% (16/20) of patients infected with Gram-positive bacteria were given central venous catheter implantation during hospitalization. We analyzed that the bloodstream infections of Gram-positive bacteria were associated with central venous catheter implantation. Therefore, we suggest that the management of venous catheter in severe patients should be strengthened to avoid

bloodstream infections. According to antimicrobial susceptibility tests, methicillin resistance was in 100% of Staphylococcus, and vancomycin resistance was not yet found. It suggests that vancomycin can be used as the empirical choice for Gram-positive bacteria if secondary bloodstream infections occur.

The number of secondary urinary tract infections was relatively small and *E. coli* was still the main bacterium. According to antimicrobial susceptibility tests, the isolation rate of ESBL-producing *E. coli* was 75%. As the initial empirical choice, β-lactams combinations with β-lactamase inhibitors can be recommended, rather than levofloxacin and ceftriaxone.

This was a single center study in the Wuhan Union hospital. The etiology and antimicrobial resistance in different medical institutions or different regions may be different.

Conclusions

In conclusion, SBIs is one of the main complications in patients hospitalized with COVID-19, with a high mortality. Gram-negative bacteria, especially *A. baumannii* and *K. pneumoniae*, are the main bacteria. The antimicrobial resistance rates of the major isolated bacteria are generally high, which indicates that more accurate use of antibacterial agents is necessary for SBIs in patients hospitalized with COVID-19.

Abbreviations

COVID-19: corona virus disease 2019; SBIs: secondary bacterial infections; HAP: hospital-acquired pneumonia. SARS-CoV-2: severe acute respiratory syndrome coronavirus 2; CLSI: Clinical and Laboratory Standards Institute. *A. baumannii*: *Acinetobacter baumannii*; *K. pneumoniae*: *Klebsiella pneumoniae*; *E. coli*: *Escherichia coli*; *S. maltophilia*: *Stenotrophomonas maltophilia*; *P. aeruginosa*: *Pseudomonas aeruginosa*; *S. aureus*: *Staphylococcus aureus*.

Declarations

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Informed consent

Not applicable.

Authors' contributions

JL, JW, YY, JC, XC collected, analyzed, and interpreted the clinical and laboratory data. JW and YY processed data analysis. JL and JW drafted the manuscript. XC and YZ revised the final manuscript and take responsibility for all data.

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Availability of data and materials

The supporting data are available with the corresponding author and

laboratory depositories.

Ethics approval and consent to participate

The study was approved by the Ethics Committee of Union Hospital, Tongji Medical College, Huazhong University of Science and Technology (Permission number: [2020]0104).

Consent for publication

The researchers have full right to publish the findings.

Competing Interests

We declare that we have no conflicts of interest.

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