Original Article

Bacterial Superinfection and Antibiotic Management in Patients with COVID-19 Admitted to Intensive Care Medicine in Central Iran: A Follow-Up Study

Zary Nokhodian[1], Soodabeh Rostami[2], Parisa Zeraatei[2], Marzieh Rahimkhorasani[1], Saeed Abbasi[3], Somayeh Sadeghi[4]

[1]Infectious Diseases and Tropical Medicine Research Center, Isfahan University of Medical Sciences, Isfahan, Iran, [2]Nosocomial Infection Research Center, Isfahan University of Medical Sciences, Isfahan, Iran, [3]Anesthesiology and Critical Care Research Center, Isfahan University of Medical Sciences, Isfahan, Iran, [4]Acquired Immunodeficiency Research Center, Isfahan University of Medical Sciences, Isfahan, Iran

Abstract

Background: Bacterial superinfections are one of the crucial challenges in patients with coronavirus disease 2019 (COVID-19) that are associated with a high mortality rate. The current study was designed to assess bacterial superinfections and antibiotic management in COVID-19 patients admitted to intensive care unit (ICU).

Material and Methods: Seventy-three adult intubated patients with COVID-19 were included in a cross-sectional study. The lung aspirate samples were collected in two stages and assessed for bacterial growth by standard methods. Antimicrobial susceptibility testing was performed using the Kirby-Bauer method as recommended by the Clinical Laboratory Standard Institute guideline (2021 edition). Also, demographic and clinical data were collected. The statistical analysis was done by chisquare test and Student's *t*-test, and a *P* value <0.05 was considered significant.

Results: Forty men and thirty-three women with a mean age of 64.78 ± 13.90 have included in our study. The mean length of hospitalization and stay in ICU were 18.77 ± 12.94 and 13.51 ± 9.83 days, respectively; 84.9% of cases died. Thirty-three patients had a bacterial superinfection mainly caused by *Klebsiella* spp and *Acinetobacter* spp; 21.2% of piperacillin/tazobactam consumers' patients survived that; the differences were significant (p = 0.034). A significant relationship was seen between superinfection and length of hospital stay until intubation (p = 0.033).

Conclusion: Bacterial superinfection and mortality rates were relatively high in COVID-19 patients admitted to ICU. According to the results, using beta-lactam/beta-lactamase inhibitors antibiotics in hospitalized patients in ICU can effectively control superinfection.

Keywords: Anti-bacterial agents, bacterial infections, COVID-19, intensive care units, superinfection

Address for correspondence: Dr. Soodabeh Rostami, Infectious Diseases and Tropical Medicine Research Center, Alzahra Hospital, Isfahan University of Medical Sciences, Isfahan, Iran.
E-mail: srostami1876@gmail.com
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Introduction

Severe acute respiratory coronavirus 2 (SARS-CoV-2) first appeared in China in December 2019.[1] Since then, the virus has created a global pandemic that threatens the lives of billions of people on the earth. The advent of SARS-CoV-2 has presented severe challenges to health systems and physicians worldwide.[2-4] In this situation, Iran, like other countries in the world, with 6,175,782 cases of a definite diagnosis of the disease and 131,167 cases of death (till 22 December 2021), experiences a super-acute condition.[5]

SARS-CoV-2 is an RNA beta-coronavirus that, based on the phylogenetic tree, is related to SARS-CoV-1.[6,7] The most

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prevalent symptoms are cough and fever.[4] However, the more serious outcomes, such as hospitalization in the intensive care unit (ICU) and the need for a ventilator are accompanied by a high mortality rate.[8,9] It is estimated about 5 to 15% of patients with coronavirus disease 2019 (COVID-19) require hospitalization in the ICU and use of a ventilator due to severe respiratory problems.[1,10] Studies in China and the United States show a high mortality rate in patients with COVID-19 admitted to the ICU.[2,11,12]

Insignificant outbreaks of respiratory infections and superinfections' role and importance are not clear. Patients with SARS-CoV-1, Middle East respiratory syndrome (MERS) coronavirus, and pandemic and seasonal influenza have various bacterial superinfections.[13] Bacterial superinfection has been repeatedly reported in influenza disease. While superinfection has been rarely seen in patients with SARS-CoV-1, and evidence show that superinfection does not occur in patients with MERS-CoV.[14-17] The limited studies have assessed superinfection in patients who suffer from SARS-CoV-2, showing different results. The prevalence of bacterial superinfections varies among patients with COVID-19 admitted to the ICU from 28% to 100% in different countries.[18-20] A meta-analysis study reported that the prevalence is 14% in ICU.[13] *Staphylococcus aureus*, *Haemophilus influenza*, *Streptococcus pneumonia*, *Enterobacteriaceae, Moraxella catarrhalis,* and *Acinetobacter baumannii* were the most common bacteria identified in samples.[18-20]

Diagnosis of superinfections in patients with COVID-19, particularly in ICU, is challenging. The clinical symptoms, radiologic imaging, and inflammatory markers sometimes do not support each other and lead to misunderstanding and misdiagnosis. Information such as the prevalence of bacterial coinfections, essential risk factors, the frequent micro-organisms involved, and their antibiotic resistance can help physicians diagnose early and suitable treatment. This research aimed to identify respiratory tract bacterial superinfections in COVID patients admitted to the ICU in a referral hospital.

Materials and Methods

A cross-sectional study was conducted at AL-Zahra hospital in Isfahan, Iran, from April 11 until May 17, 2021. Al-Zahra hospital is a 700-bed university referral hospital that provides medical services for Isfahan province and the central region of Iran. All adult intubated patients over 18 years who suffered from COVID-19 and were admitted to three ICUs were included in the study. The COVID-19 was confirmed by a positive real-time-PCR (Polymerase chain reaction) test on a nasopharyngeal swab and/or clinical signs. The tracheal aspirate samples were collected in sterile tubes and immediately transferred to the laboratory. Sample collection was done in two stages: stage 1, when the patient was intubated in ICU or arrived intubated at the ICU, and stage 2, one week later if the patient was still intubated and alive. Superinfection was detected according to proper guidelines and clinical and para-clinical signs and symptoms.

The tracheal samples were cultures on the blood Agar, MacConkey Agar, and Chocolate Agar to identify the type of bacteria. Standard microbiology methods were used to confirm colonies grown on the plates. Antimicrobial susceptibility testing was performed using the Kirby-Bauer method for gram-positive and gram-negative bacteria, as recommended by the Clinical Laboratory Standard Institute (CLSI) guideline (2021 edition).

A checklist was completed for all cases from patients' electronic records, including demographic information (sex and age), laboratory test results including white blood cell count (WBC), C-reactive protein (CRP), Procalcitonin test (PCT), Erythrocyte sedimentation test (ESR), drugs including antibiotics and antivirals, corticosteroids, anticoagulants, mouthwashes, proton pump inhibitors, opioids and anesthetics, and length of stay in ICU and hospital.

Statistical analysis

Analyzes were performed using SPSS software (version 21, 2007, SPSS Inc., Chicago, IL, USA). Continuous and categorical variables were reported using mean with standard deviation (SD) and percentage, respectively. The Chi-square test and Student's t-test were used to analyze the data. $P < 0.05$ was statistically considered significant.

Results

From April 11 till May 17, 2021, 299 patients with COVID-19 were admitted to AL Zahra hospital ICUs, of whom 73 patients had inclusion criteria to enter the study. Twenty-two individuals had two samples. Forty men with a mean age of 66.20 ± 14.09 and thirty-three women with a mean age of 63.06 ± 13.69 years were included in our research. At the end of the study, 62 (84.9%) patients were died. The mean length of hospitalization was 18.77 ± 12.94 days, and the mean length of stay in ICU was 13.51 ± 9.83 days. There was a significant relationship between the duration from hospitalization to intubation in survived and dead patients (p = 0.033) [Table 1].

Seventy-one participants received at least one antimicrobial drug during ICU stay, mostly with piperacillin/tazobactam (71.2%), meropenem (54.8%), and linezolid (42.5%). 21.2% of piperacillin/tazobactam consumers survived, that the differences were significant (p = 0.034). Corticosteroids (94.3%), Remdesivir (58.9%), anticoagulants (94.3%), mouthwash (68.6%), proton pump inhibitors (74.3%), opioids (98.6%), and anesthetics (100%) were used for patients.

Sex, age, length of hospitalization, length of hospital stays until intubation, and inflammatory markers did not show significant differences between patients with bacterial superinfection and without that [Table 2].

Ninety-five respiratory tract secretion samples from 73 patients with COVID-19 cultured to detect of bacterial superinfection that 33 (45.2%) patients had positive culture. In total,

Table 1: The main characteristic and biologic of patients with COVID-19 hospitalized in ICU

Variables	Total (*n*=73)	Survivors (*n*=11)	Dead (*n*=62)	*P**
Age, year (mean±SD)	64.78±13.90	57.27±13.57	66.11±13.64	0.051
Sex *n* (%)				
male	40	7 (17.5)	33 (82.5)	
female	33	4 (12.1)	29 (87.9)	0.523
Mean length of hospitalization (Days±SD)				
In ICU	13.51±9.83	11.91±3.89	13.80±10.55	0.560
Totally	18.77±12.94	23.09±13.27	18.00±12.84	0.232
Duration from hospitalization to intubation	8.27±6.048	4.73±7.74	8.93±6.07	**0.033**
Inflammatory markers				
Lab data (mean±SD)				
WBC >11000	31 (64)	2 (6.5)	29 (93.5)	0.08
CRP >6	65 (89)	11 (16.9)	54 (83.1)	0.207
ESR >10	65 (90.3)	11 (16.9)	(54 (83.1	0.237
PCT >0.5	50 (82)	8 (16)	42 (84)	0.860

n=number, SD=standard deviation, WBC=white blood cell, CRP=C-reactive protein, ESR=erythrocyte sedimentation rate, PCT=Procalcitonin Test. The bold items were considered significant. * *P*<0.05 was significant

Table 2: Demographic and clinical data of patients with and without bacterial superinfection

Variables	Bacterial superinfection		
	Negative (*n*=41)	Positive (*n*=32)	*P**
Age, year (mean±SD)	63.15±14.986	66.88±12.291	0.258
Sex *n* (%)			
Male	22 (55)	18 (45)	
Female	19 (57.6)	14 (42.4)	0.825
Mean length of hospitalization (Days±SD)			
In ICU	12.27±7.99	15.16±11.78	0.219
Totally	17.17±10.70	20.81±15.28	0.235
Duration from hospitalization to intubation	7.39±5.11	9.31±6.94	0.188
Inflammatory markers			
Lab data (mean±SD)			
WBC >11000	19 (61.3)	12 (38.7%)	0.867
CRP >6	37 (56.9)	28 (43.1%)	0.723
ESR >10	37 (56.9)	28 (43.1)	0.692
PCT >0.5	27 (54)	23 (46)	0.560
Survivors	7 (63.6)	4 (36.4)	0.588
Death	34 (54.8)	28 (45.2)	

n=number, SD=standard deviation, WBC=white blood cell, CRP=C-reactive protein, ESR=erythrocyte sedimentation rate, PCT=Procalcitonin test. * *P*<0.05 was considered significant

8 *Klebsiella* spp., 8 *Acinetobacter* spp., 6 *S. aureus*, 6 *E. coli*, 5 *K. pneumoniae*, 3 *Acinetobacter calcoaceticus-baumannii* complex, 1 *S. epidermidis*, 1 *enterococcus* spp., and 1 *P. aeruginosa* were detected [Table 3]. Of 15 patients who had two samples, in 6 patients, the bacterium isolated in the second sample was different from the bacteria isolated in the first sample. In seven cases, no bacteria were detected.

Of the 31 gram-negative isolates, 21/31; 68% were resistant to Ceftazidime, 24/31; 77.4% to cefepime, 21/31; 68% to imipenem and meropenem, 17/31; 54.8% to amikacin, and 20/31; 64.5% to levofloxacin. Also, 21/31; 68% of gram negative bacteria were multidrug-resistant (MDR).

Of the 8 gram positive bacteria 4 MRSA and one Vancomycin-resistant enterococci (VRE) were isolated [Table 3].

Discussion

COVID-19 is a new infection that weakens the patient's immune system and paves the way for more disorders. In the current study, bacterial superinfection was assessed among COVID-19 patients hospitalized in the ICU. Our results documented that 43.8% of patients with COVID-19 suffered from bacterial superinfection and the leading involved bacteria were *Klebsiella* spp and *Acinetobacter* spp. In a similar study in France, bacterial superinfection was reported in 28% of patients, and MRSA was the most frequent pathogen.[18] In the study by Lehmann *et al*.[21], bacterial superinfection among patients admitted to ICU was 41%. In a study in Iran, all patients were positive for bacterial superinfections; the most common organism was *A. baumannii*.[20] Fu *et al*.[22] reported that 13.9% of patients with COVID-19 admitted to ICU suffer from secondary bacterial infection. A meta-analysis showed that 14% of COVID-19 patients admitted to ICU suffer from bacterial superinfection.[13]

The most frequently involved bacteria in our study were *Klebsiella spp*. and *Acinetobacter* spp. In 2016, in a survey conducted in ICU within the same hospital, the common pathogens causing pneumonia were *A. baumannii* and *K. pneumonia*.[23] Sharifipour *et al*.[20] documented that the causative agent of infection in patients with COVID-19 in the ICU was *A. baumannii* and *S. aureus*. In another study in Iran, *K. pneumonia* and *Acinetobacter* were the most common organism in ICU.[24]

Factors such as the quality of care in ICU, the high workload of nurses in pandemic COVID-19, ICU type, and rate and type

Table 3: The list of isolated bacteria according to sex and age

Sex	Age	Output	Stage 1	Stage 2
Cases with two samples (Total Number=22)				
Male	77	Death	*S. aureus* (MRSA*)	*Acinetobacter* spp.
Female	54	Death	Negative	*E. coli*
Female	44	Alive	*Acinetobacter* spp.	*Enterococcus* spp. (VRE**)
Male	77	Death	*E. coli*	*Klebsiella* spp.
Male	91	Death	Negative	*E. coli*
Male	64	Alive	*S. aureus* (MRSA)	*Acinetobacter calcoaceticus-baumannii* complex
Male	65	Death	Negative	*E. coli*
Male	69	Alive	Negative	*K. pneumoniae*
Male	64	Death	Negative	*K. pneumoniae*
Male	82	Death	Negative	*Klebsiella* spp.
Male	55	Alive	*E. coli*	*Acinetobacter* spp.
Female	61	Death	*P. aeruginosa*	Negative
Female	75	Death	*S. epidermidis*	*K. pneumoniae*
Male	49	Death	*K. pneumonia*	Negative
Female	78	Death	Negative	*Acinetobacter calcoaceticus-baumannii* complex
Cases with one sample (Total Number=51)				
Male	73	Death	*S. aureus*	
Female	57	Death	*Klebsiella* spp.	
Male	71	Death	*Acinetobacter* spp.	
Female	58	Death	*Acinetobacter* spp.	
Male	77	Death	*Klebsiella* spp.	
Female	75	Death	*Klebsiella* spp.	
Female	62	Death	*S. aureus* (MRSA)	
Male	78	Death	*Klebsiella* sp	
Male	38	Death	*E. coli*	
Female	74	Death	*Acinetobacter* spp.	
Male	81	Death	*Klebsiella* spp.	
Female	49	Death	*Acinetobacter* spp.	
Female	75	Death	*Klebsiella* spp.	
Male	77	Death	*K. pneumonia*	
Female	76	Death	*Acinetobacter calcoaceticus-baumannii* complex	
Male	77	Death	*S. aureus* (MRSA)	
Male	66	Death	*S. aureus*	
Male	53	Death	*Acinetobacter* spp.	

*MRSA, Methicillin-resistant *Staphylococcus aureus*, ** VRE, Vancomycin-resistant Enterococci

of used equipment can explain different results. However, the important things are that various studies document that bacterial superinfection can frequently occur in COVID-19 patients and be a severe threat to the patient's life.

It is possible that bacterial superinfection has developed in the ICU, and these were considered Intensive care unit acquired nosocomial infections. According to the results, the duration from hospitalization to intubation of patients was almost more than eight days. This data supports the occurrence of nosocomial infection for most of our patients. Another critical issue is that despite the frequency of bacterial superinfection in 43% of patients, antibiotic was used for 97.3% of subjects.

Unfortunately, in our study, 64.5% MDR gram-negative bacilli were isolated. Other studies do not support our results.[18,20,25] One of the reasons for the high prevalence of antibiotic resistance in these patients may be the using antibiotics for most of them (71/73; 97.3%) through ICU stay. During the COVID-19 pandemic, antibiotic stewardship programs (ASPs) became difficult to implement in the hospital. Therefore, one of the emergency measures of hospital managers should be the robust implementation of the ASP.

Our study has some limitations: I) Due to financial problems, we could not assess other superinfections in these patients. II) We did not have information about antibiotic therapy before ICU admission, which can prevent the growth of bacteria in the culture medium and potentially influence the real superinfection rate. III) Our research was done at a hospital, which influenced our results. Although, Al Zahra hospital is the biggest hospital in central Iran, we think the actual rate is near our results.

Conclusion

Bacterial superinfection and mortality rates were relatively high in COVID-19 patients admitted to ICU. According to the results, using beta-lactam/beta-lactamase inhibitors antibiotics in hospitalized patients in ICU can effectively control superinfection.

Ethical issues

The ethics Committee of Isfahan University of Medical Sciences, Isfahan, Iran, approved this study (approval number: IR.MUI.MEDREC.1399.065, Date of approve: 11/March/2021).

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Conflicts of interest

There are no conflicts of interest.

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