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Coronavirus Pandemic

Secondary bacterial infections of the respiratory tract in COVID-19 patients

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Abstract

Introduction: Secondary Bacterial Infections (SBIs) of the respiratory system are one of the biggest medical concerns in patients undergoing hospitalization with a diagnosis of COVID-19. This study aims to provide relevant data for the initiation of appropriate empirical treatment after examining the etiology and antimicrobial resistance of SBIs in COVID-19 patients under care in the Intensive Care Units (ICUs) in the largest pandemic hospital of our country.

Methodology: Between March 16, 2020 and December 31, 2021, 56,993 COVID patients were hospitalized, of which 7684 were admitted to ICUs. A total of 1513 patients diagnosed with SBIs have been included in this study. During the course of the study, demographic data, clinical course, etiology and antimicrobial resistance data of all patients were collected.

Results: The most common causative agents of SBIs were inferred as *Acinetobacter baumanii* (35.1%), *Staphylococcus aureus* (15.2%), *Klebsiella pneumoniae* (12.3%) and *Pseudomonas aeruginosa* (10.4%). The isolation rates of carbapenem-resistant and colistin-resistant *A. baumannii*, *K. pneumoniae* and *P. aeruginosa* were 83.7%; 42.7%, 79.2%, and 5.6%, 42.7%, 1.7%, respectively. *Acinetobacter pittii* clustering was seen in one of the ICUs in the hospital. Multidrug resistant 92 (5.4%) *Corynebacterium striatum* isolates were also found as a causative agent with increasing frequency during the study period.

Conclusions: SBI of the respiratory system is one of the major complications in patients hospitalized with COVID-19. The antimicrobial resistance rates of the isolated bacteria are generally high, which indicates that more accurate use of antibacterial agents is necessary for SBIs in patients hospitalized with COVID-19 diagnosis.

Key words: Secondary bacterial infections; respiratory tract; COVID-19.

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Introduction

Since December 2019, the COVID-19 pandemic has spread extensively around the world, infecting more than 430 million people and causing more than 5.9 million deaths [1]. While some patients are hospitalized due to serious respiratory disease caused by COVID-19, severe cases require hospitalization in the Intensive Care Units (ICU) with mechanical ventilation support [2]. Although deaths associated with COVID-19 occur mainly in elderly patients with serious underlying diseases, healthcare-associated pneumonia, particularly in intubated patients continues to remain a significant risk factor in ICUs [3]. Notably, patients of all age groups who do not have an underlying disease may also be at risk of secondary bacterial infection [4].

Viral pathogens can cause secondary bacterial pneumonia. Some studies have shown that viral agents damage ciliary cells and can cause increased bacterial colonization in the respiratory tract [5]. It is also been inferred that the acute inflammatory reaction caused by viral infections causes pulmonary tissue damage, which may result in an increased susceptibility to secondary bacterial infections [6]. However, it is still unclear as to how coronavirus contributes to the development of Secondary Bacterial Infections (SBIs).

According to reports, SBIs are responsible for 0.6-50.0% of COVID-19 deaths [7,8]. Effective antimicrobial therapy is the key measure for the successful treatment of SBIs in COVID-19 cases [7]. The World Health Organization and Turkish Ministry of Health COVID-19 guides do not recommend the use of prophylactic antibiotics in cases of COVID-19 unless bacterial infection is clinically suspected or established [9,10]. The use of broad-spectrum antibacterial agents

may further lead to changes in etiology and antimicrobial resistance. They may also cause unnecessary side effects and adversely affect the clinical course. On the other hand, in clinical cases where bacterial coinfection is clinically suspected, antibiotics can be added to the treatment. Empirical antibiotic selection is based on the patient's clinical condition (i.e., sepsis status, comorbidities, immunosuppression, previous antibiotic use), local epidemiological data, and treatment guidelines.

Since the first days of the pandemic, most of the ICUs of the hospital under study have been reserved for the follow-up of COVID-19 patients. In this study, the researchers performed a retrospective analysis of SBIs in the respiratory systems of COVID-19 patients hospitalized in ICUs. The primary study aim was to evaluate SBIs agents causing respiratory tract infection and their antibiotic susceptibility for more accurate antimicrobial use in COVID-19 patients.

Methodology

Study population

This single-center, retrospective study was conducted at the Ankara City Hospital which served as the main pandemic response center in Ankara with 4066 beds of which 1000 are intensive care beds. Neonatal and pediatric ICUs were excluded from the study. Ethical approval was obtained from Ankara City Hospital Ethical Committee (No: E1-20-803).

Between 14 March 2020 and 31 December 2021, 56,793 patients with positive COVID-19 Reverse Transcription Polymerase Chain Reaction (RT-PCR) test were hospitalized and followed up in Ankara City hospital. Of these patients, 7684 were treated in the ICUs. Criteria for admission to ICU according to the COVID-19 guide of the Turkish Ministry of Health was: having dyspnea and respiratory distress, respiration rate ≥ 30/min, $PaO_2/FiO_2 < 300$, increasing oxygen need, $SpO_2 < 90\%$ or $PaO_2 < 70$ mmHg despite 5 L/min oxygen therapy, hypotension, tachycardia > 100/min, acute kidney damage, impaired liver function tests, patients with acute organ dysfunction such as confusion, acute bleeding diathesis and immunosuppression, troponin elevation and arrhythmia, lactate > 2 mmol, skin disorders such as capillary return disorder and cutis marmaratus. The decision of ICU admission was made by intensive care specialists [10].

In this study, the inclusion criteria were: COVID-19 diagnosis, ICU hospitalization, intubatation, and mechanical ventilation of > 48 h in ICUs. The diagnosis of SBI was defined when patients showed clinical features of bacterial infections and at least one causative bacterium was isolated from qualified microbiological specimens (i.e., qualified sputum, endotracheal aspirate or bronchoalveolar lavage fluid). None of the patients received empirical antibacterial therapy before clinical diagnosis of SBI. The demographic, clinical course, laboratory, and treatment data were collected from the hospital information management system.

Reverse transcription real-time polymerase chain reaction (RT-PCR) for the detection of COVID-19

Nasopharyngeal samples were obtained using a specific swab and then placed in a collection tube containing viral transport medium (VTM, various manufacturers) and immediately sent to the Molecular Microbiology department. RNA extraction from swab samples was performed using Biospeedy Viral Nucleic Acid Isolation Kit (Bioeksen, Istanbul, Turkey), according to the manufacturer's instructions. Swab samples in VTM were vortexed for 15 seconds and then 100 µL sample was transferred to a 1.5 mL microcentrifuge tube containing 100 µL viral nucleic acid extraction buffer supplied by the manufacturer. After repeated vortexing, the tube was ready for PCR reaction. Detection of SARS-CoV2 in swab samples was performed by RT-PCR method targeting RNA-dependent RNA polymerase (RdRp) gene. RT-PCR was performed by using Bio-Speedy COVID-19 RT-qPCR Detection Kit (Bioeksen, Istanbul, Turkey). A 20 µL reaction contained 5 µL of RNA, 5 µL of Oligo Mix (RdRp gene for SARS-CoV-2 detection, Rnase P gene for internal control), and 10 µL of 2x Primer Script Mix containing Taq Polymerase, each deoxyribose triphosphate, reverse transcriptase, and ribonuclease inhibitor. Thermal cycling was performed at 45 °C for 10 minutes for reverse transcription, followed by 95 °C for 3 minutes, and then 45 cycles of 95 °C for 5 seconds, 55 °C for 35 seconds in Rotor-Gene Q device (Qiagen, Manheim, Germany). Cycle threshold (Ct) values of less than 40 were defined as positive.

Pathogen detection and antimicrobial susceptibility

The qualified microbiological specimens of patients with COVID-19 were collected and immediately transferred to the Microbiology Department. While the first samples were taken during the admission of the patients to the ICU, the later samples were taken upon the manifestation and observation of signs of infection. The samples were cultured on blood agar, chocolate agar, and MacConkey agar and then incubated at 37 °C for 24–72 h under standard conditions. Pathogen identification was performed by Vitek MS, MaldiTof

system (bioMerieux, Lyon, France) and antimicrobial susceptibility testing was carried out on the Vitek II automated microbiological system (bioMerieux, Lyon, France). Broth microdilution method was performed for detecting the colistin and vancomycin susceptibility. Disc diffusion method was used for antimicrobial susceptibility test of *C. striatum* and *Stenotrophomonas maltophilia* isolates. Ceftazidime-avibactam susceptibility test was performed for the pan-resistant Enterobacterales and *P. aeruginosa* by disc diffusion method. Results were interpreted according to the criteria of the European Committee on Antimicrobial Susceptibility Testing [11]. The same strains from one patient were counted only once. *Escherichia coli* ATCC 25922 and *Staphylococcus aureus* ATCC 25923 were used as standard strains for quality control.

Results

General information

A total of 7684 patients were diagnosed with COVID-19 and treated in ICU between March 2020 and December 2021. A total of 1716 isolates from 1513 patients with SBIs (19.7%) were included in the study. A total of 998 (66%) of the patients were male and 515 (34%) were female, with a mean ± standard deviation (SD) age of 66.7 ± 12.9 years (range: 38–96 years). The mean ± SD length of pre-ICU stay for patients was 3.6 ± 4.4 days, while the average time in our ICU was 12.1 ± 9.1 days. It was inferred that 997 patients who acquired SBI (65.9%) died during hospitalization, and 516 (34.1%) were discharged. The number of patients who had underlying diseases such as cancer, diabetes, heart diseases, hypertension, kidney disease or autoimmune diseases were 1161 (76.7%).

Table 1. Etiological distribution of SBIs in patients hospitalized with COVID-19.

Organisms	N (%)
Gram-negative bacteria; 1302 (75.9%)	
Acinetobacter baumannii	603 (35.1)
Klebsiella pneumoniae	211 (12.3)
Pseudomonas aeruginosa	178 (10.4)
Stenotrophomonas maltophilia	129 (7.5)
Escherichia coli	87 (5.1)
Other Enterobacterales	44 (2,6)
Other non-fermentative bacteria	19 (1.1)
Acinetobacter pittii	19 (1,1)
Haemophilus influenzae	12 (0.7)
Gram-positive bacteria; 414 (24.1%)	
Staphylococcus aureus	261 (15.2)
Corynebacterium striatum	92 (5,4)
Enterococcus faecium	27 (1.6)
Streptococcus pneumoniae	19 (1.1)
Enterococcus faecalis	15 (0.9)
Total	1716 (100)

Table 2. Etiological distribution of secondary bacterial infections caused by multiple bacteria in patients hospitalized with COVID-19.

Mixed infection	N (%)
Acinetobacter baumanii+ K. pneumoniae	31 (17)
Acinetobacter baumanii + Pseudomonas aeruginosa	26 (15)
Acinetobacter baumanii+Staphylococcus aureus	26 (15)
Klebsiella pneumoniae + Pseudomonas aeruginosa	14 (8)
Acinetobacter baumanii + Corynebacterium striatum	13 (7)
Other two bacteria combination	43 (24)
Three bacteria combination	25 (14)
Total	178

Etiological distribution of SBIs in patients hospitalized with COVID-19

A total of 1716 strains were isolated from the cultures in the 1513 patients. As many as 83 (5.5%) of the samples were sputum, 56 (3.7%) were bronchoalveolar lavages and 1374 were endotracheal aspirates. In 171 (11.3%) patients, the causative pathogen was isolated in cultures taken at the time of admission to the ICUs, while other agents were isolated in the following days. Among the 1716 isolates from the SBIs, 1302 strains (75.9%) were Gram-negative bacteria and 414 (24.1%) were Gram-positive bacteria. The most common agents of SBIs were 603 (35.1%) *Acinetobacter* spp., 261 (15.2%) *S. aureus*, 211 (12.3%) *K. pneumoniae*, 178 (10.4%) *P. aeruginosa*, 129 (7.5) *S. maltophilia*, 92 (5.4%) *C. striatum* and 87 (5.1%) *Escherichiae coli*. The distribution of all isolated bacteria is shown in Table 1. Mixed bacterial infections were observed in 178 (11.8%) patients. Of these, two agents were found in 153 (10.1%) patients and three agents were found in 25 (1.7%) patients. It was observed that mostly *A. baumanii* strains caused mixed infections with *K. pneumoniae, P. aeruginosa, S. aureus* or *C. striatum* strains (Table 2).

Moreover, 104 (6.9%) patients had bloodstream infection along with respiratory tract infection with the same causative agents.

A. pittii strains were unexpectedly isolated as the causative agent in tracheal aspirate samples of 19 patients hospitalized in the same ICU between 19 August 2020 and 8 September 2020. Since the antimicrobial susceptibility patterns of the isolates were the same, they were considered as cumulation. Surveillance cultures were taken and patients were admitted to the service after necessary cleaning.

Table 3. Major Gram-negative bacteria. N (%) of susceptible strains.

Antibacterials	*A. baumanii* (n = 603)	*K. pneumoniae* (n = 211)	*P. aeruginosa* (n = 178)	*S. maltophilia* (n = 129)	*E.coli* (n = 87)
Ampicillin	-	-	-	-	28 (32.2)
Piperacillin/tazobactam	51(8.5)	65 (30.8)	145 (81.5)	-	59 (67.8)
Amoxicillin/clavulanate	-	34 (16,1)	-	-	32 (36,8)
Cefazolin	-	26 (12,3)	-	-	28 (32,2)
Cefuroxime	-	26 (12.3)	-	-	28 (32.2)
Ceftriaxone	-	30 (14.2)	-	-	28 (32.2)
Ceftazidime	47 (7.8)	30 (14.2)	142 (79.8)	-	40 (46.0)
Cefepime	-	34 (16.1)	145 (81.5)	-	63 (72.4)
Cefoxitin	-	69 (32.7)	-	-	36 (41.4)
Ertapenem	-	92 (43.6)	-	-	71 (81.6)
Meropenem	60 (10)	90 (42.7)	149 (83.7)	-	67 (77.0)
Imipenem	60(10)	90 (42.7)	117 (65.7)	-	67 (77.0)
Amikacin	291 (48.3)	99 (46.9)	157 (88.2)	-	63 (72.4)
Gentamicin	103 (17.2)	99 (46.9)	-	-	63 (72.4)
Ciprofloxacin	0	56 (26.5)	125 (70.2)	-	52 (59.7)
Trimetoprim/Sulfamethoxazole	154 (25.5)	69 (32.7)	-	117 (90.7)	59 (67.8)
Tigecycline	-	52 (24.6)	-	-	75 (86.2)
Colistin	569 (94.4)	121 (57.3)	175 (98.3)	-	83 (95.4)
ESBL	-	151 (71.6)	-	-	48 (54.0)
Carbapenemase positivity	505 (83.7)	90 (42.7)	141 (79.2)	-	12 (13.8)

Interestingly, multidrug resistant 92 (5.4%) *C. striatum* isolates were also found as a causative agent with increasing frequency. All isolates were found to be susceptible only to vancomycin and linezolid.

Notably, during the study period, 27 *Candida* spp. (20 *C. albicans*, 3 *C. lusitaniae*, 1 *C. parapsilosis*, 1 *C. glabrata*, 1 *C. tropicalis*, 1 *C. kefyr*) were identified as secondary respiratory tract infection agents. A total of 20 (13 *C. albicans* and all non-albicans) were together with other bacterial agents while 7 C. albicans were primary infectious agents. It had been observed that all candida infections occurred during or after the course of broad-spectrum antimicrobial therapy.

Antimicrobial susceptibility results

The antimicrobial resistance rate of bacteria isolated from patients with SBIs was found to be generally high. The results of antimicrobial susceptibility testing for the most common Gram-negative and Gram-positive bacteria are shown in Table 3 and Table 4. Carbapenem-resistance was higher in *A. baumannii* (83.7%) and *P. aeruginosa* (79.2%), than *K. pneumoniae* (42.7%) and *E. coli* (13.8%). *K. pneumoniae* showed highest colistin-resistance (42.7 %) followed by *A. baumanii* (5.6 %). The isolation rate of ESBL producing *K. pneumoniae* and *E. coli* were 71.6% and 54.0%, respectively. Meticillin resistance was present in 34.1% of *S. aureus* and all patients (n = 89) infected with MRSA died. *C. striatum* isolates were

Table 4. Major Gram-positive bacteria. N (%) of susceptible strains.

Antibacterials	*S. aureus* (n = 261)	*C. striatum* (n = 92)	*E. faecium* (n = 27)	*S.pneumoniae* (n = 19)	*E. faecalis* (n = 15)
Penicillin	4 (1.5)	0	-	15 (78.9)	-
Ampicillin	-	-	0	-	15 (100)
Erythromycin	171 (65.5)	-	-	14 (73.7)	-
Clindamycin	234 (89.7)	0	-	15 (78.9)	-
Ciprofloxacin	220 (84.3)	0	15 (55.6)	-	-
Moxifloxacin	-	-	-	19 (100)	-
Gentamicin	234 (89.7)	0	-	-	-
Vancomycin	261 (100)	92 (100)	20 (74.1)	19 (100)	15 (100)
Teicoplanin	261 (100)	-	20 (74.1)	-	15 (100)
Linezolid	261 (100)	92 (100)	26 (96.3)	19 (100)	15 (100)
Daptomycin	240 (92.0)	-	-	-	-
Tetrasiklin	186 (71.3)	0	-	19 (100)	-
Trimethoprim/sulfamethoxazole	240 (92.0)	-	-	14 (73.7)	-
Cefoxitin screen positive	89 (34.1)	-	-	-	-
Inducible Clindamycin resistance	75 (28.7)	-	-	-	-
High level gentamicin resistance	-	-	4 (14.8)	-	2 (13.3)

only sensitive to vancomycin and linezolid while resistant to other tested antimicrobials. All *A. pittii* strains were resistant to piperacillin-tazobactam, imipenem, and meropenem, while they were sensitive to other antibiotics.

Discussion

SBI has emerged one of the main complications leading to high mortality in patients hospitalized with COVID-19 diagnosis [8]. In this study. SBI frequency of respiratory system was found to be 19.7% in COVID-19 patients hospitalized in the ICUs. The incidence of SBIs in the current study was inferred to be higher than the data in previous studies. Zhou *et al.* in their study reported a 6.3% SBI incidence rate and Li *et al.* reported that 15% of their patients had SBIs [9,12]. This may be due to the fact that these studies were carried out in the early days of the pandemic and the present study considered a comparatively larger sample size.

In this study, while the mortality rate was 51.0% in patients admitted to the ICUs due to COVID-19, this rate increased to 65.9% in patients with SBI. One of the reasons for the increase in mortality rate among these patients could be attributed to the synergetic affect of the virus and bacteria. Even though further studies are still warranted to gain an improved understand the interaction between COVID-19 and bacteria, several investigators emphasised that the damage that viruses cause to the respiratory epithelium, as well as their effects on innate and adaptive immunity, antagonising IFN responses that enhance bacterial adherence, colonisation, growth, and invasion into healthy sites in the respiratory tract, are important mechanisms [5,12].

Furthermore, Li *et al*. reported that the mortality rate of SBI was 49.0% in patients with COVID-19 [13]. In addition, Sharifipour *et al.* in their study inferred a 95.0% mortality rate in the ICU patients [14]. The reason for the difference in infection and death rates between hospitals could be affected by several factors including, the type of ICU, the frequency of equipment used, admission and/or discharge criteria. High workload/staff rate may also affect the quality of care, particularly in pandemic.

The current study sample reported that 66.0% of patients who had SBI were male, the mean age was 66.7 years and 76.7% of all patients had underlying diseases. Similar to this data, recent studies have reported that the male gender constitutes a risk factor for the disease severity status. Having underlying diseases and age 65 or older are risk factors related to death in COVID-19 patients [8,9].

In a total of 171 (11.3%) patients, the causative pathogen was isolated in cultures taken at the time of admission to the ICUs. The mean ± SD length of pre-ICUs stay for patients was 3.6 ± 4.4 days. This duration is sufficient for bacteria to infect patients with underlying diseases. Although some researchers did not detect any secondary bacterial infection at the time of admission, they reported that the infection rate rises as the length of stay in hospital increases [9,15].

A total of 1716 strains of bacteria were isolated in this study and the most common bacteria include *A. baumannii, S. aureus, K. pneumoniae, P. aeruginosa, S. maltophilia, C. striatum* and *E. coli*. The etiologic distribution was observed to be very similar to the hospital-acquired pneumonia agents previously reported in the hospital (annual cumulative data, unpublished).

In recent years, hypervirulent bacteria resistant to several antibiotics have been reported with increasing frequency all over the world [16]. In February 2017, the World Health Organization (WHO) published a list of multidrug resistance pathogens for which new antimicrobial development is urgently needed. Within this broad list, ESKAPE pathogens (*E. faecium, S. aureus, K. pneumoniae, A. baumannii, P. aeruginosa*, and *Enterobacter* spp.) were designated a "priority status" [17]. In the present study, the most common bacteria in the hospital under study were found to be ESKAPE pathogens. These bacteria showed extremely high resistance to most antibacterial agents. *A. baumannii* strains showed > 90% resistance to all different classes of antibiotics except for colistin. *K. pneumoniae* strains were found to be the most resistant pathogens including 42.7% resistance to colistin. Extended spectrum beta lactamases (ESBL) and carbapenemases were also high. Ceftazidime-avibactam was tested by disc diffusion method for all multidrug resistant Enterobacterales and *P. aeruginosa* strains and these demonstrated to have 95% and 100% susceptibility, respectively.

The antimicrobial susceptibility tests showed that the isolated Gram-negative bacteria were mostly multi-drug resistant. This could not only delay the process of treatment and recovery of COVID-19 patients but also increase the mortality rate. Thus, the choice of antimicrobial program could be more suitable to treat the infections of multidrug resistant Gram-negative bacteria.

In this study, 34.1% of the strains of *S. aureus* were identified as MRSA. All patients (n = 89) infected with MRSA died during the study period. Different studies have reported that respiratory tract infections caused by

MRSA strains not only delay the process of treatment and recovery but also increase the mortality rate in the patients admitted to ICUs [18,19].

Antibiotics were not given to the patients until signs of infection were observed. Patients with suspected infection were treated according to Turkish guide [10]. However, the treatment protocols were adapted based on the results of the cultures and the pattern of antibiotic resistance.

A mix of bacterial infections were observed in 178 (11.8%) patients in this study. Li *et al*. in their study reported 46 patients had infections with mixed bacteria, mostly *A. baumannii* mixed with *K. pneumoniae* (41.3%). In this study, researchers found 104 (6.9%) patients had bloodstream infection mixed with respiratory tract infection with the same causative agent including *A. baumanni, K. pneumoniae, P. aeruginosa,* and *S. aureus* and in these patients, lung infections occurred first, followed by bloodstream infections.

Acinetobacter pittii strains were isolated from tracheal aspirate samples of 19 patients between 19 August 2020 to 8 September 2020. Antimicrobial susceptibility patterns of the isolates were same and they were considered as cumulation. Surveillance cultures were taken and necessary cleaning was performed. Multidrug resistant *A. pitti* strains have also been reported as hospital-acquired infectious agents in previous studies [20,21].

Another emerging Gram-positive bacterium, *C. striatum* has been observed with increasing frequency in recent years [22,23]. In the current study, all isolated *C. striatum* strains were sensitive to vancomycin and linezolid while resistant to other tested antimicrobials (Table 4). This suggests that vancomycin can be used as the empirical choice for both *S. aureus* and *C. striatum*.

This study, like any other academic study, presents several limitations. The etiology and antimicrobial resistance may be different in other medical institutions or regions. In addition, since the beginning of the pandemic, the priority in the study site laboratory was to study COVID-19 tests, detailed resistance gene analysis and phenotypic confirmatory tests for evaluating carbapenemases or ESBLs, from isolated bacteria could not be performed.

Conclusions

Secondary bacterial infections may develop during or following COVID-19 in ICU patients. *A. baumannii, S. aureus, P. aeruginosa, K. pneumoniae, S. maltophilia* and *E. coli* are the main causative bacteria and they were also seen as mixed infections in combination. The antimicrobial resistance rates against 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 diagnosis.

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