**OTJHS**
**Online Turkish Journal of Health Sciences**

**e-ISSN:** 2459-1467

**OTSBD**
**Online Türk Sağlık Bilimleri Dergisi**

*Online Turkish Journal of Health Sciences 2023;8(1):39-46* *Online Türk Sağlık Bilimleri Dergisi 2023;8(1):39-46*

# Secondary Bacterial Agents and Antibiotic Resistance Profiles in Respiratory Tract Specimens of Patients with COVID-19 Pneumonia

# COVID-19 Pnömonili Hastaların Solunum Yolu Örneklerinde Sekonder Bakteriyel Ajanlar ve Antibiyotik Direnç Profilleri

[1]Oya AKKAYA, [1]Ayşe Rüveyda UGUR, [1]Habibe OVET, [2]Feyza ALP, [3]Mustafa Onder GONEN

[1]Department of Medical Microbiology, Health Sciences University, Konya City Hospital, Konya Türkiye
[2]Department of Medical Microbiology, Konya Numune Hospital, Konya Türkiye
[3]Department of Emergency Medicine, Konya Meram State Hospital, Konya Türkiye

Oya Akkaya: https://orcid.org/0000- 0002- 1170- 3292
Ayşe Rüveyda Ugur: https://orcid.org/0000 0002 9622 6404
Habibe Ovet: https://orcid.org/0000 0001 8920 0612
Feyza Alp: https://orcid.org/ 0000 0001 8177 1947
Mustafa Onder Gönen: https://orcid.org/0000 0002 6059 4387

**ABSTRACT**

**Objective:** To assess secondary bacterial pneumonia agents and antibiotic resistance rates in patients with COVID-19 pneumonia and to compare findings with the pre-pandemic period.

**Materials and Methods:** Bacteria grown in endotracheal aspirate fluid and bronchoalveolar fluid samples of patients diagnosed with COVID-19 between January 2020 and December 2020, and antibiotic resistance rates were retrospectively compared with samples of the year before the pandemic. Isolates were identified at the species level with an automated system (VITEK 2, bioMérieux, France), and antimicrobial susceptibility was determined according to EUCAST criteria.

**Results:** A total of 900 culture results were examined in 2019. Acinetobacter baumannii was detected in 36%, Klebsiella pneumoniae in 23%, Pseudomonas aeruginosa in 14%, and Staphylococcus aureus in 8%. In 2020, 660 culture results were examined, and the same bacteria were detected in 43%, 23%, 16%, and 5%, respectively. K. pneumoniae's resistance to third-generation cephalosporins, and A. baumannii's resistance to gentamycin and tobramycin, were found to have increased significantly during the pandemic period.

**Conclusions:** The growth of multidrug-resistant Gram-negative bacteria was frequently detected in respiratory secretions obtained during the COVID-19 pandemic. Regional bacterial agents and antibiotic resistance profiles should be clarified, and empirical therapy should be selected accordingly in COVID-19.

**Keywords:** Antibiotic resistance, bacterial superinfection, COVID-19, intensive care unit, pneumoniae

**ÖZ**

**Amaç:** COVID-19 pnömonisi olan hastalardaki sekonder bakteriyel pnömoni etkenleri ve antibiyotik direnç oranlarının değerlendirilmesi ve sonuçların pandemi öncesi dönemle karşılaştırılmasıdır.

**Materyal ve Metot:** Ocak 2020-Aralık 2020 arasında COVID-19 tanısı konan hastaların endotrakeal aspirat sıvı ve bronkoalveolar sıvı örneklerinde üreyen bakteriler ve antibiyotik direnç oranları, pandemiden önceki yıl gelen hasta örnekleriyle retrospektif olarak karşılaştırılmıştır. Kültürde üremesi olan örnekler, otomatize sistemle (VITEK 2, bioMérieux, France) tür düzeyinde tanımlanmış ve antimikrobiyal duyarlılıkları EUCAST kriterlerine göre değerlendirilmiştir.

**Bulgular:** 2019 da mikrobiyolojik kültürlerinde üreme saptanan 900 hasta örneği incelendi. Acinetobacter baumannii %36, Klebsiella pneumoniae %23, Pseudomonas aeruginosa %14, Staphylococcus aureus ise %8 oranında saptandı. 2020 de ise 660 hasta örneği incelendi ve sırasıyla aynı bakteriler %43, %23, %16 ve %5 oranında saptandı. K. pneumoniae'nin 3. kuşak sefalosporin direncinde ve A. baumannii'nin gentamisin ve tobramisin direncinde pandemi öncesine göre anlamlı bir artış görüldü.

**Sonuç:** COVID-19 pandemisinde solunum sekresyonlarında çoğunlukla çok ilaca dirençli Gram negatif bakterilerin ürediği görüldü. COVID-19 hastalığı olanlarda, bölgesel bakteriyel etkenler ve antibiyotik direnç profilleri bilinip, uygun ampirik tedavi seçilmelidir.

**Anahtar Kelimeler:** Antibiyotik direnci, bakteriyel süperenfeksiyon, COVID-19, pnömoni, yoğun bakım ünitesi

**Sorumlu Yazar / Corresponding Author:**
Oya Akkaya
Health Sciences University, Konya City Hospital, Medical Microbiology, Akabe mah. Adana Çevreyolu Cad. 42020 Karatay/Konya, Türkiye
Tel: +90-505 2564333
E-mail: oyaakkaya12@gmail.com

**Yayın Bilgisi / Article Info:**
Gönderi Tarihi/ Received: 28/03/2022
Kabul Tarihi/ Accepted: 25/01/2023
Online Yayın Tarihi/ Published: 05/03/2023

**Atıf / Cited:** Akkaya O and et al. Secondary Bacterial Agents and Antibiotic Resistance Profiles in Respiratory Tract Specimens of Patients with COVID-19 Pneumonia. *Online Türk Sağlık Bilimleri Dergisi* 2023;8(1):39-46. doi: 10.26453/otjhs.1094238

## INTRODUCTION

COVID-19, caused by severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), has spread rapidly worldwide since 2019. It can lead to findings ranging from mild flu-like symptoms to severe pneumonia and multi-organ failure.[1] It is evident that only a portion of the population is vaccinated, and available vaccines also appear to have little effect on new variants. There is still no effective treatment for the disease, and patients may require prolonged hospitalization or treatment in intensive care units (ICUs); thus, these individuals with COVID-19 face the risk of secondary infection.[2]

There are many reasons for the development of secondary bacterial pneumonia in COVID-19. One of these is that the disease causes acute respiratory failure, leading to the need for mechanical ventilation.[3,4] Another reason is that SARS-CoV-2 can destroy the respiratory tract epithelium or can alter the normal respiratory tract microbiota due to microbial migration. These effects disrupt the flora and predispose patients to be secondary bacterial and/or fungal co-infections associated with high mortality.[5,6] According to recent reports, approximately 15-50% of deaths in COVID-19 are related to secondary infections.[7]

Antibiotic therapy has been frequently used during the COVID-19 pandemic. The rate of bacterial superinfection due to COVID-19 is between 3-15%, but up to 70% of hospitalized COVID-19 patients are believed to have received antibiotic therapy. Even mild pneumonia has often been treated with antibiotics, which can increase antibiotic resistance.[8,9]

Since the clinical management of severe COVID-19 is difficult, empirical initiation of anti-bacterial therapy was recommended by the WHO. It was included in the COVID-19 treatment guidelines of the Turkish Ministry of Health.[10,11] Empirical antibiotic use creates problems including side effects and antibiotic resistance.[1,12] To reduce these problems, it is important to identify the incidence and epidemiology of bacterial infections in such patients.

We aimed to determine which bacteria cause secondary infections in patients diagnosed with COVID -19, to assess the resistance rates of these bacteria to antibiotics, and to compare these results with pre-pandemic data.

## MATERIALS AND METHODS

***Ethical Statement:*** COVID-19 study approval was obtained from the Ministry of Health. on November 15, 2021, with Decision Number 2021/11-00-36. Ethics committee approval for the study was obtained from the Ethics Committee of Karatay University Faculty of Medicine (Date: 19/11/2021, decision no: 2021/005). The study was carried out according to the Helsinki Declaration.

***Study Design and Data Collection****:* This is a retrospective study in which the types and antibiotic resistance profiles of bacteria grown in endotracheal aspirate fluid (ETA) or bronchoalveolar fluid (BAL) samples from adult clinical wards and ICUs of our hospital were compared before and during the pandemic.

Pre-pandemic data were from samples received between January 2019 and December 2019. Pandemic data were from samples obtained between January 2020 and December 2020. All data were collected from electronic hospital records and included patient demographics, laboratory findings, and microbiology data (including ETA and BAL cultures and antimicrobial susceptibility). The ages of the patients were between 20-80 years (median age 56). Specimens were taken at least three days after the patients were hospitalized and included in the study. Pre-pandemic data were obtained from 880 ETA and 20 BAL samples. Pandemic data were obtained from 650 ETA and 10 BAL samples. Respiratory specimens without growth in culture were excluded from the study. Our hospital was a "pandemic center", so all samples obtained during 2020 were from patients with a proven diagnosis of COVID-19.

***Laboratory Procedures:*** All analyses were performed with a standardized routine methodology. Briefly, samples were seeded semi-quantitatively on 5% sheep blood agar, eosin methylene blue (EMB) agar, and chocolate agar, with incubations conducted at 37°C for 24-48 hours. If there were >25 leukocytes and <10 epithelial cells in the gram staining of ETA samples, the bacteria grown were considered secondary infection agents, and these samples were included in the study. If there was growth only in the first quadrant of the medium, the result was semi-quantitatively evaluated as "few". In the presence of growth in the second quadrant, it was assessed as "moderate". Whereas growth detection in the third quadrant was classified as "many". BAL samples were included in the study if there was $>10^4$ CFU/mL growth in the medium.

Specimens with growth in culture were identified at the species level by conventional methods, such as gram staining and colony morphology, using an automated system (VITEK2 automated system, bioMérieux, France). Antimicrobial susceptibility was determined with the same system according to EUCAST criteria.

Susceptibility to levofloxacin and ceftazidime for *S. maltophilia* was evaluated according to Clinical Laboratory Standards Institute (CLSI) criteria because these particular susceptibilities are not included in EUCAST criteria. The tigecycline MIC results for *A.*

*Baumannii* were evaluated according to the Food and Drug Administration (FDA) recommendations (> 8 µg/mL, resistant). Resistant strains were confirmed by the agar gradient test (bioMérieux, France) method. Over two years, the bacteria growth in BAL and ETA samples and the data containing the antibiotic resistance rates of these bacteria were recorded in a Microsoft Excel worksheet. Data before and after the pandemic were compared.

***Statistical Analysis:*** The data obtained during the study were assessed via the SPSS v21 software (SPSS Inc., Chicago, IL, USA) with a predetermined significance threshold of $p< 0.05$. Categorical descriptive data were given with frequency (number and percentage). Between-group categorical distribution analyses were conducted via Pearson chi-square or Fisher's exact tests.

## RESULTS

A total of 1560 BAL and ETA culture samples with bacterial growth were examined. In 2019, a total of 900 culture results with growth were examined: *Acinetobacter baumannii* was yielded in 328 (36%), *Klebsiella pneumoniae* in 205 (23%), *Pseudomonas aeruginosa* in 125 (14%), *Staphylococcus aureus* in 76 (8%), *Escherichia coli* in 47 (5%), *Streptococcus pneumoniae* in 27 (3%), *Enterobacter cloacae* in 15 (2%), *Serratia marcescens* in 18 (2%), *Stenotrophomonas maltophilia* in 10 (1%), *Haemophilus influenzae* in 10 (1%), and other bacteria in 39 (4%) cases. In 2020, 660 culture results with growth were examined: *A. baumannii* was reproduced in 286 (43%), *K. pneumoniae* in 150 (23%), *P. aeruginosa* in 105 (16%), *S. aureus* in 30 (5%), *E. coli* in 15 (2%), *S. pneumoniae* in 17 (2.5%), *E. cloaca* in 3 (0.5%), *S. marcescens* in 27 (4%), *S. maltophilia* in 10 (1.5%), *H. influenzae* in 8 (1.2%), and other bacteria were detected in 9 (1.3%) cases. The most common bacteria before the pandemic were *A. baumannii* (36%), *K. pneumoniae* (23%), and *P. aeruginosa* (14%). Although the order did not change during the pandemic, the positivity rate for *A. baumannii* increased, and this increase was significant ($p= 0.006$) (Figure 1).

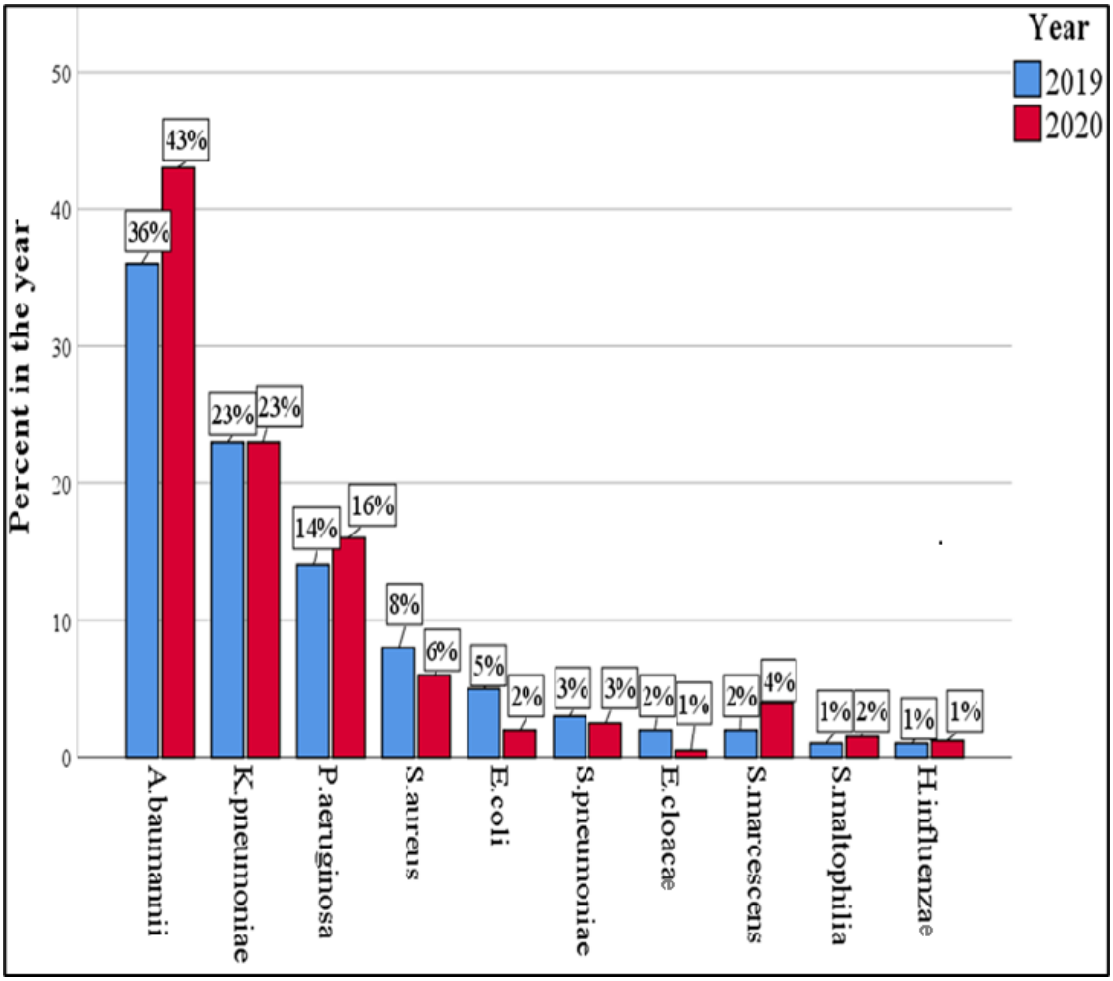


**Figure 1.** Percentage of bacteria detected with regard to years.

The positive rate for *K. pneumoniae* remained at 23%. Meropenem resistance for *K. pneumoniae* increased from 64% in 2019 to 70% in 2020. There was no significant increase in carbapenem resistance. Resistance to third-generation cephalosporins increased from 83% to 94%. Compared to 2019, *K. pneumoniae* strains from 2020 were found to be significantly more resistant to amoxicillin-clavulanate (p= 0.002), ceftazidime (p< 0.001), cefotaxime (p= 0.002), ceftriaxone (p= 0.002), ciprofloxacin (p< 0.001), cefepime (p< 0.001), ertapenem (p< 0.001), and gentamycin (p< 0.001) (Table 1). The positivity rates of *E. coli* decreased during the pandemic (p= 0.003), but extended-spectrum beta-lactamase (ESBL) frequency increased from 45% in 2019 to 60% in 2020. The frequency of *S. marcescens* increased from 2% to 4%, and this increase was significant (p= 0.015) (Table 1).

**Table 1.** Positive Rates of Fermentative Gram-Negative Bacteria and Antibiotic Resistance Rates in BAL and ETA Samples Before and During the Pandemic.

| | **K. pneumoniae** | | | **E. coli** | | | **E. cloacae** | | | **S. marcescens** | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | **2019 Number n (%)** | **2020 Number n (%)** | **p** | **2019 Number n (%)** | **2020 Number n (%)** | **p** | **2019 Number n (%)** | **2020 Number n (%)** | **p** | **2019 Number n (%)** | **2020 Number n (%)** | **p** |
| **Ampicillin** | - | - | - | 37 (7) | 15 (100) | N/A | - | - | - | - | - | - |
| **Amoxicilin-clavulanicacid** | 172 (84) | 142 (95) | **0.002** | 33 (70) | 12 (80) | 0.459 | - | - | - | - | - | - |
| **Amikacin** | 135 (66) | 102 (68) | 0.672 | 4 (9) | 1 (7) | 0.819 | 2 (14) | 0 (0) | N/A | 2 (12) | 1 (4) | 0.952 |
| **Ceftazidime** | 170 (83) | 142 (95) | **0.001** | 16 (34) | 10 (67) | **0.026** | 2 (14) | 1 (34) | 0.396 | 4 (22) | 10 (37) | 0.293 |
| **Cefotaxime** | 170 (83) | 141 (94) | **0.002** | 23 (49) | 10 (67) | 0.231 | 2 (14) | 1 (34) | 0.396 | 13 (72) | 11 (40) | **0.038** |
| **Ceftriaxone** | 170 (83) | 141 (94) | **0.002** | 21 (45) | 10 (67) | 0.138 | 2 (14) | 1 (34) | 0.396 | 5 (28) | 11 (40) | 0.373 |
| **Ciprofloxacin** | 168 (82) | 142 (95) | **0.001** | 19 (40) | 10 (67) | 0.076 | 2 (14) | 1 (34) | 0.396 | 0 (0) | 2 (7) | N/A |
| **Cefepime** | 164 (80) | 140 (93) | **0.001** | 13 (28) | 6 (40) | 0.367 | 2 (14) | 1 (34) | 0.396 | 2 (12) | 3 (11) | 1 |
| **Ertapenem** | 157 (77) | 138 (92) | **0.001** | 2 (4) | 1 (7) | 0.704 | 2 (14) | 1 (34) | 0.396 | 0 (0) | 2 (7) | N/A |
| **Gentamycin** | 137 (67) | 148 (99) | **0.001** | 10 (21) | 5 (34) | 0.342 | 2 (14) | 1 (34) | 0.396 | 2 (12) | 2 (7) | 0.669 |
| **Meropenem** | 131 (64) | 105 (70) | 0.229 | 3 (6) | 1 (7) | 0.968 | 2 (14) | 1 (34) | 0.396 | 0 (0) | 0 (0) | NA |
| **Piperacillin-tazobactam** | 166 (81) | 141 (94) | **0.001** | 16 (34) | 4 (27) | 0.595 | 2 (14) | 1 (34) | 0.396 | 4 (22) | 4 (15) | 0.524 |
| **Trimethoprim-sulfamethoxazole** | 166 (81) | 130 (87) | 0.155 | 12 (25) | 7 (47) | 0.122 | 0 (0) | 1 (34) | N/A | 0 (0) | 2 (7) | N/A |
| **TOTAL PATIENTS** | 205 (23) | 150 (23) | 0.981 | 47 (5) | 15 (2) | **0.003** | 15 (2) | 3 (0.5) | 0.057 | 18 (2) | 27 (4) | **0.015** |

Total number of patients with growth in respiratory secretions in 2019: 900
Total number of patients with growth in respiratory secretions in 2020: 660

N/A: not applicable.

Tigecycline resistance (strains with MIK> 8) for *A. baumannii* increased during the pandemic, and this increase was significant (p< 0.001). Compared to 2019, the resistance of *A. baumannii* strains to gentamycin (p= 0.005), tobramycin (p= 0.012), and tigecycline (p< 0.001) antibiotics were significantly higher in 2020. Ceftazidime resistance for *P. aeruginosa* increased during the pandemic, and this increase was also significant (p= 0.028) (Table 2).
The positivity rates for *S. aureus* decreased during the pandemic (p= 0.003). The frequency of methicillin-resistant *S. aureus* (MRSA) remained unchanged during the pandemic. (Table 3)

**Table 2.** Positive rates of gram-negative non-fermentative bacteria and antibiotic resistance rates in BAL and ETA samples before and during the pandemic.

| Antibiotics | A. baumannii | | | P. aeruginosa | | | S. maltophilia | | |
|---|---|---|---|---|---|---|---|---|---|
| | 2019 Number n (%) | 2020 Number n (%) | p | 2019 Number n (%) | 2019 Number n (%) | p | 2019 Number n (%) | 2019 Number n (%) | p |
| **Ceftazidime** | - | - | - | 33 (27) | 42 (40) | **0.028** | 6 (60) | 6 (60) | 1.0 |
| **Cefepime** | - | - | - | 45 (36) | 38 (36) | 0.976 | - | - | - |
| **Piperacillin** | - | - | - | 57 (46) | 42 (40) | 0.393 | - | - | - |
| **Piperacillin-tazobactam** | - | - | - | 53 (43) | 38 (36) | 0.337 | - | - | - |
| **Amikacin** | 216 (66) | 188 (66) | 0.975 | 5 (4) | 4 (4) | 0.941 | - | - | - |
| **Gentamycin** | 288 (88) | 270 (94) | **0.005** | - | - | | - | - | - |
| **Tobramycin** | 291 (89) | 270 (94) | **0.012** | 6 (5) | 5 (5) | 0.989 | - | - | - |
| **Ciprofloxacin** | 325 (99) | 286 (100) | 0.104 | 30 (24) | 30 (28) | 0.432 | - | - | - |
| **Levofloxacin** | 325 (99) | 286 (100) | 0.104 | 53 (43) | 40 (38) | 0.507 | 6 (60) | 6 (60) | 1.0 |
| **Imipenem** | 325 (99) | 284 (99) | 0.767 | 58 (47) | 50 (47) | 0.854 | - | - | - |
| **Meropenem** | 325 (99) | 284 (99) | 0.767 | 42 (33) | 37 (35) | 0.794 | - | - | - |
| **Tigecycline (MIK >8)** | 19 (6) | 72 (25) | **0.001** | - | - | - | - | - | - |
| **Trimethoprim-sulfa-methoxazole** | - | - | - | - | - | - | 5 (50) | 5 (50) | 1.0 |
| **Total Patients** | 328 (36) | 286 (43) | **0.006** | 125 (14) | 105 (16) | 0.266 | 10 (1) | 10 (1.5) | 0.483 |
| Total number of patients with growth in respiratory secretions in 2019: 900 | | | | | | | | | |
| Total number of patients with growth in respiratory secretions in 2020: 660 | | | | | | | | | |

**Table 3.** Positive rates of gram-positive bacteria and antibiotic resistance rates in BAL and ETA samples before and during the pandemic.

| Antibiotics | S. aureus | | | S. pneumoniae | | |
|---|---|---|---|---|---|---|
| | 2019 Number n (%) | 2020 Number n (%) | p | 2019 Number n (%) | 2020 Number (%) | p |
| **Penicillin** | 60 (79) | 25 (83) | 0.609 | 3 (11) | 0 | 0.155 |
| **Cefoxitin** | 27 (36) | 11 (36) | 0.912 | - | - | - |
| **Erythromycin** | 16 (21) | 6 (20) | 0.904 | 10 (37) | 6 (38) | 0.906 |
| **Clindamycin** | 5 (7) | 2 (7) | 0.987 | 12 (45) | 7 (42) | 0.831 |
| **İnd. Clindamycin resistance** | 9 (12) | 3 (10) | 0.787 | - | - | - |
| **Ciprofloxacin** | 3 (4) | 0 | 0.270 | - | - | - |
| **Levofloxacin** | 2 (3) | 0 | 0.370 | 7 (26) | 4 (24) | 0.858 |
| **Cefotaxime** | - | - | - | 10 (37) | 6 (35) | 0.907 |
| **Ceftriaxone** | - | - | - | 10 (37) | 6 (35) | 0.907 |
| **Vancomycin** | 0 | 0 | - | 0 | 0 | - |
| **Teicoplanin** | 0 | 0 | - | 0 | 0 | - |
| **Linezolid** | 0 | 0 | - | 0 | 0 | - |
| **TOTAL** | 76 (8) | 30 (6) | **0.003** | 27 (3) | 17 (2.5) | 0.617 |
| Total number of patients with growth in respiratory secretions in 2019: 900 | | | | | | |
| Total number of patients with growth in respiratory secretions in 2020: 660 | | | | | | |

## DISCUSSION AND CONCLUSION

Many studies have explored factors affecting the prognosis of COVID-19, and it has been observed that co-morbid diseases and advanced age are the leading factors.[13] If respiratory failure develops in a patient with COVID-19 infection, a need for intubation and mechanical ventilation may arise. Hospital-associated or ventilator-associated pneumonia may develop due to these invasive procedures.[14] Data on causative agents and antibiotic susceptibility in these pneumonia cases secondary to COVID-19 are still insufficient, but they are usually caused by multi-drug-resistant bacteria and have very high mortality rates.

In our study, culture analyses were used. Before the pandemic, the most common bacteria in BAL and ETA samples were *A. baumannii* (36%), *K. pneumoniae* (23%), and *P. aeruginosa*. Although the ranking did not change during the pandemic, the positivity rate of *A. baumannii* increased significantly. We attributed this increase to long-term hospitalization and a higher frequency of steroid use in COVID-19 patients. Of note, *E. coli, E. cloacae*, and *S. aureus* frequency decreased during the pandemic, while *S. marcescens* and *S. maltophilia* frequencies increased slightly. Although the number of patients admitted to the hospital decreased due to the COVID -19 pandemic, findings related to the types of bacteria causing hospital infections and their antibiotic resistance profiles appeared to be unchanged. This was attributed to the fact that healthcare personnel contacted many patients due to high workloads.

It is well established that 20-30% of influenza infections are accompanied by secondary bacterial pneumonia with the most common causative bacteria identified as *S. pneumoniae* and *S. aureus.*[15] The association between COVID-19 and bacterial pneumonia is less apparent, and the most common bacteria appear to be gram-negative and antibiotic-resistant bacteria, such as *A. baumannii* and *K. pneumoniae.*[13] Around 7% of patients with a diagnosis of COVID-19 were hospitalized in wards, and 14% of those hospitalized in ICUs are suggested to have secondary bacterial pneumonia.[16,17]

Various studies have examined the respiratory tract samples of patients with COVID-19 using multiplex PCR and culture methods. In France, Camelana et al. detected bacterial infection in 35% of BAL samples and found *P. aeruginosa* and *S. aureus* to be the most common bacteria.[18] In a study conducted in Korea using multiplex PCR and culture methods together, *A. baumannii* was found to be present in 33% and *P. aeruginosa* in 30% as secondary bacterial pneumonia agents in COVID-19 patients.[19] A similar study from the USA reported that *Enterobactericea* and *P. aeruginosa* were the most common bacteria.[20] Rapid and reliable multiplex PCR assays have been recommended for the assessment of respiratory tract samples during the pandemic. In cases where bacterial agents could not be detected, discontinuation of antibiotic treatment was recommended, particularly when the radiological imaging findings were in favor of viral pneumonia.[1,21]

The frequencies of resistant bacteria in clinical services and ICUs differ between countries and hospitals. In a study from China, bacterial pneumonia was observed in 7% of patients with COVID-19, and 75% of them were determined to have *A. baumannii* and carbapenem-resistant *K. pneumoniae*. It has been emphasized that bacterial pneumonia caused by these factors is the most important cause of death in patients with COVID-19.[14] In our study, the increase in carbapenem resistance for *K. pneumoniae* was not significant, but the increase in resistance to third-generation cephalosporins was found to be significant. We only included samples with growth among COVID-19 patients, which may explain these relatively high rates.

Empirical antibiotic use is life-saving due to the prevention of these infections, and national and international guidelines already recommend this approach.[22] But antimicrobial therapy has undesirable effects including toxicity, diarrhea, and the spread of antimicrobial resistance. Therefore, appropriate empirical antibiotic selection should be kept in mind during the management of such patients. Antibiotic therapy should be rapidly terminated after bacterial pneumonia is excluded.[23]

The reason for the development of secondary bacterial pneumonia in COVID-19 is likely to be associated with prolonged hospitalization, the use of steroids, or the need for mechanical ventilation.[6,22] Many antibiotics have been used in COVID-19 to prevent the development of secondary bacterial pneumonia and to treat bacterial co-infections. Antibiotics were selected for empirical treatment based on data from cases of bacterial pneumonia developing in pre-COVID-19 viral infections.[24] However, since COVID-19 cases are hospitalized for a long time, and the disease is often very severe, more antibiotics have been used compared to previous viral pneumonia cases, causing increased antibiotic resistance.

In this study, COVID-19 patients with suspected secondary bacterial pneumonia were assessed, and all samples that the laboratory received were evaluated and included in the study. However, we did not have access to the clinical data of the patients or other clinical information concerning the presence/ absence of secondary infection. This is a limitation of our study.

Additionally, due to COVID-19-related lockdowns, the number of patients admitted decreased during the pandemic; therefore, the frequency of infectious

bacteria and antibiotic resistance may have been overestimated. The study may become more meaningful if it is combined with data from other hospitals, and the number of samples increases.

In conclusion, in hospitalized patients with COVID-19, secondary bacterial pneumonia agents are mostly Gram-negative bacteria with high pathogenicity and mortality, demonstrating resistance to most drugs. Unfortunately, antibiotic resistance rates were found to have increased during the pandemic. To prevent this increase, laboratory parameters that can aid physicians in distinguishing between bacterial and viral infections should be used. Appropriately empirical treatment should be selected by accurately describing local/regional bacterial agent types and antibiotic resistance profiles.

***Ethics Committee Approval:*** Ethics committee approval for the study was obtained from the Ethics Committee of Karatay University Faculty of Medicine (Date: 19/11/2021, decision no: 2021/005). The study was carried out according to the Helsinki Declaration.

***Conflict of Interest:*** No conflict of interest was declared by the authors.

***Author Contributions:*** Concept- OA developed the concept; Supervision- OA, ARU, HO, FA, MOG; Materials- OA, AR; Data collection and/or processing- OA, ARU, HO, FA; Analysis and/or interpretation- OA, ARU, HO, FA; Writing- OA.

***Peer-review:*** Externally peer-reviewed.

## REFERENCES


1. Liu HH, Yaron D, Piraino AS, Kapelusznik L. Bacterial and fungal growth in sputum cultures from 165 COVID-19 pneumonia patients requiring intubation: evidence for antimicrobial resistance development and analysis of risk factors. Ann Clin Microbiol Antimicrob. 2021;20 (1):1-13. doi:10.1186/s12941-021-00472-5
2. Khurana S, Singh P, Shara N, et al. Profile of co-infections & secondary infections in COVID-19 patients at a dedicated COVID-19 facility of a tertiary care Indian hospital: Implication on antimicrobial resistance. Indian J Med Microbiol. 2021;39(2):147-153. doi:10.1016/ j.ijmmb.2020.10.014
3. Zhang H, Zhang Y, Wu J, et al. Risks and features of secondary infections in severe and critical ill COVID-19 patients. Emerg Microbes Infect. 2020;9(1):1958-1964. doi:10.1080/22221751.2020.1812437
4. Ceballos ME, Nuñez C, Uribe J, et al. Corticosteroids use and risk of respiratory coinfections in mechanically ventilated patients with COVID-19. Research Square 2021. doi:10.21203/rs.3.rs-966047/v1
5. Soltani S, Zakeri A, Zandi M, et al. The role of bacterial and fungal human respiratory microbiota in COVID-19 patients. BioMed Research International 2021. doi:10.1155/2021/6670798
6. Bengoechea JA, Bamford CG. SARS-CoV-2, bacterial co-infections, and AMR: the deadly trio in COVID-19? EMBO Mol Med. 2020;12 (7):e12560. doi:10.15252/emmm.202012560
7. Rollas K, Ersan G, Zincircioğlu C, et al. Septic shock in patients admitted to intensive care unit with COVID-19 pneumonia. Eurasian J Pulmonol. 2021;23(2):95-100. doi:10.4103/ ejop.ejop_101_20
8. Guo M, Gao M, Gao J, et al. Identifying risk factors for secondary infection post-SARS-CoV-2 infection in patients with severe and critical COVID-19. Frontiers in Immunology 2021;3601. doi:10.3389/fimmu.2021.715023
9. Mutlu TA, Bozok T. COVID-19 Hastalarının alt solunum yolu örneklerinden izole edilen bakteriyel etkenlerin identifikasyonu ve antibakteriyel direnç paternlerinin incelenmesi. Türk Mikrobiyol Cemiy Derg. 2022;52(1):48-55. doi:10.54453/TMCD.2022.98105
10. Rollas K, Şenoğlu N. Management of Covid-19 patients in intensive care unit. The Journal of Tepecik Education and Research Hospital. 2020;30:142-55. doi:10.5222/terh.2020.77044
11. Elabbadi A, Turpin M, Gerotziafas GT. Bacterial coinfection in critically ill COVID-19 patients with severe pneumonia. Infection 2021; 49(3): 559-562. doi:10.1007/s15010-020-01553-x
12. Işık SA, Şaylan B, Yenilmez E. Ağır Covid-19'da bakteriyel pnömoni riski artıyor mu? Mersin Univ Saglık Bilim Derg. 2021;14(2):291-297. doi:10.26559/mersinsbd.900945
13. Senok A, Alfaresi M, Khansaheb H, et al. Coinfections in patients hospitalized with COVID-19: a descriptive study from the United Arab Emirates. Infect Drug Resist. 2021;14:2289-2296. doi:10.2147/IDR.S314029
14. Li J, Wang J, Yang Y, et al. Etiology and antimicrobial resistance of secondary bacterial infections in patients hospitalized with COVID-19 in Wuhan, China: a retrospective analysis. Antimicrobial Resistance & Infection Control. 2020;9 (1):1-7. doi:10.1186/s13756-020-00819-1
15. Morris DE, Cleary DW, Clarke SC. Secondary bacterial infections associated with influenza pandemics. Front. Microbiol. 2017;8:1041. doi:10.3389/fmicb.2017.01041
16. Lansbury L, Lim B, Baskaran V, Lim W. Co-infections in people with COVID-19: a systematic review and meta-analysis. J Infect. 2020;81 (2):266-275. doi:10.1016/j.jinf.2020.05.046
17. Langford BJ, So M, Raybardhan S, et al. Bacterial co-infection and secondary infection in pati-

ents with COVID-19: a living rapid review and meta-analysis. Clin Microbiol Infect. 2020;26 (12):1622-1629. doi:10.1016/j.cmi.2020.07.016
18. Caméléna F, Moy AC, Dudoignon E, et al. Performance of a multiplex polymerase chain reaction panel for identifying bacterial pathogens causing pneumonia in critically ill patients with COVID-19. Diagn Microbiol Infect Dis. 2021;99 (1):115183. doi:10.1016/ j.diagmicrobio.2020.115183
19. Yoo IY, Huh K, Shim HJ, et al. Evaluation of the BioFire FilmArray Pneumonia Panel for rapid detection of respiratory bacterial pathogens and antibiotic resistance genes in sputum and endotracheal aspirate specimens. Int J Infect Dis. 2020;95:326-331. doi:10.1016/j.ijid.2020.03.024
20. Timbrook TT, Hueth KD, Ginocchio CC. Identification of bacterial co-detections in COVID-19 critically ill patients by BioFire® FilmArray® pneumonia panel: a systematic review and meta-analysis. Diagn Microbiol Infect Dis. 2021;101 (3):115476. doi:10.1016/ j.diagmicrobio.2021.115476
21. Zhu X, Ge Y, Wu T, et al. Co-infection with respiratory pathogens among COVID-2019 cases. Virus Res. 2020;285:198005. doi:10.1016/ j.virusres.2020.198005
22. Grasselli G, Cattaneo E, Florio G. Secondary infections in critically ill patients with COVID-19. Critical Care. 2021;25(1):1-6. doi:10.1186/ s13054-021-03672-9
23. Rawson TM, Moore LS, Zhu N, et al. Bacterial and fungal coinfection in individuals with coronavirus: a rapid review to support COVID-19 antimicrobial prescribing. Clin Infect Dis 2020;71(9):2459-2468. doi:10.1093/cid/ciaa530
24. Aydemir O, Aydemir Y, Şahin EO, Şahin F, Koroglu M, Erdem AF. Secondary bacterial infection in patients with coronavirus disease-2019 associated pneumonia. Revista da Associação Médica Brasileira. 2022;68:142-146. doi:10.1590/1806-9282.20210745