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Üçüncü Basamak Bir Hastanede Yatan COVID-19 Hastalarında Sekonder Enfeksiyonlar

Secondary Infections in COVID-19 Patients Hospitalized in A Tertiary Hospital

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ÖZ

Amaç: Bu çalışmada hastanede yatan COVID-19 hastalarında sekonder enfeksiyonların oranları, etiyolojik ajanları ve klinik sonuçlara etkisinin belirlenmesi amaçlanmıştır.

Materyal ve Metot: RT-PCR yoluyla COVID-19 tanısı doğrulanmış hastanede yatan 150 yetişkin hasta arasında sekonder enfeksiyonu olan ve olmayan hastaların özelliklerinin retrospektif olarak karşılaştırmalı analizi yapıldı.

Bulgular: Dahil edilen hastaların 20'sinde (%13,3) en az bir sekonder enfeksiyon tespit edildi. Yoğun bakım hastalarında sekonder enfeksiyon oranı (%72) genel serviste yatan hastalardan (%1,6) anlamlı derecede yüksek bulundu (p<0,001). Ventilatör ilişkili pnömoni (VİP) prevalansı YBÜ hastalarında %52 idi. İzole edilen toplam 31 mikroorganizmanın çoğunluğunu gram negatif bakteriler oluşturmaktaydı. Genel olarak, 147 (%98) hasta, hastaneye yatışları esnasında en az bir kez antibiyotik tedavisi aldı. Sekonder enfeksiyonu olan hastalarda mortalite oranı, olmayanlara göre istatistiksel olarak anlamlı derecede yüksek bulundu (p<0,001).

Sonuç: Genel serviste yatan COVID-19 hastalarında sekonder enfeksiyon oranı çok düşük olduğu için, antibiyotiklerin akılcı kullanımı gereği, bu hastalara ampirik antibiyotik tedavisi başlanmaması gerektiğini düşünüyoruz. Ayrıca VİP enfeksiyonlarının hem ampirik hem de hedefe yönelik tedavisinde çoklu ilaca dirençli bakterilerin dikkate alınmasının önemli olduğunu düşünüyoruz.

Anahtar Kelimeler: Antibiyotik kullanımı, COVİD-19, sekonder enfeksiyonlar, ventilatör ilişkili pnömoni

ABSTRACT

Objective: In this study, it was aimed to describe rates, etiological agents of the secondary infections and its effect on clinical outcomes among hospitalized patients with COVID-19.

Materials and Methods: A retrospective comparative analysis of the characteristics of patients with and without secondary infection was carried out among 150 hospitalized adult patients with a confirmed diagnosis of COVID-19 via RT-PCR.

Results: Among included patients, 20 (13.3%) had at least one secondary infection. Secondary infection rate in ICU patients (72%) was significantly higher than patients in the general ward (1.6%) (p<0.001). The prevalence of ventilator-associated pneumonia (VAP) was 52% in ICU patients. The majority of 31 microorganisms isolated were gram negative bacteria. Overall, 147 (98%) patients received at least one antibiotic during their hospitalization. A significantly higher mortality rate was present in patients with secondary infection compared to those without.

Conclusion: Since the rate of secondary infection in hospitalized COVID-19 patients in the general ward is very low, we consider that empirical antibiotic therapy should not be initiated in these patients in accordance with the rational use of antibiotics. Besides, we recommend that multidrug-resistant bacteria be taken into account both in the empirical and targeted antimicrobial therapy of VAP infections.

Keywords: Antibiotic use, COVID-19, secondary infections, ventilator-associated pneumonia

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INTRODUCTION

The coronavirus disease 2019 (COVID-19) caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has spread worldwide, and due to severity of the disease, some patients need to be hospitalized and some severe cases may require intensive care with non-invasive or invasive respiratory support.[1,2] Patients with moderate or severe COVID-19 often have serious comorbidities, prolonged hospitalizations, and need for mechanical ventilation, which may pose a high risk for secondary infections.[3,4] Although rates of these infections in hospitalized COVID-19 patients are generally low (10-15%), it was emphasized in many studies that the presence of these infections is associated with unfavorable outcomes in critically ill ICU-patients.[5-7] Therefore, microbiological data are valuable in guiding evidence-based treatment of secondary bacterial infections in patients with COVID-19. International guidelines regarding antimicrobial stewardship recommend clinicians to collect blood cultures as well as respiratory samples for bacterial cultures to confirm the secondary infection.[8,9] However, in some studies, it has been reported that routine microbiological examinations cannot be performed due to the risk of exposure of healthcare workers to SARS-Cov-2 during sample collection and processing, which may cause serious disruptions in the diagnosis and treatment of secondary infection.[3,5,10] Furthermore, due to the difficulty of ruling out bacterial co-infection on presentation and also secondary infection during the course of the illness, empiric antibiotics, including broad spectrum agents, are frequently prescribed for patients both in the general wards and in the ICU.[11] However, recent World Health Organization (WHO) guidelines, and most researchers report that antibiotic prescription should be limited only to severe COVID-19 patients in order to avoid the widespread use of empirical antibiotics that could lead to the development of multidrug-resistant bacteria.[7-9,12]

Although there are studies on the clinical management of COVID-19 in our country, data on the secondary infections are scarce. In this study, performing a comparative analysis of the characteristics of patients with and without secondary infection, we aimed to describe rates, etiological agents of the secondary infections, and its effect on clinical outcomes among hospitalized patients with COVID-19.

MATERIALS AND METHODS

***Ethics Committee Approval*:** A retrospective observational analysis was carried out on hospitalized adult patients admitted to a tertiary hospital between 11/03/2020 and 31/05/2020 with a confirmed diagnosis of COVID-19 via reverse transcriptase-polymerase chain reaction assay (RT-PCR) performed on nasopharyngeal throat swab specimens. Approvels were received by the Ministry of Health and the ethics committee of Haydarpaşa Numune Research and Training Hospital (Date: 29/06/2020, decision no:115).

***Study Design, Participants, and Data Collection*:** A total of 150 patients with complete data of white blood cells (WBC), neutrophil-to-lymphocyte ratio (NLR), C-reactive protein (CRP), and procalcitonin (PCT) results were included in the study. All data were collected from the hospital electronic record and included patient demographics, comorbidities, clinical parameters, laboratory findings, microbiology data (including culture of blood samples, endotracheal aspirate (ETA), urine, and antimicrobial susceptibility), ICU admission, mechanical ventilation (MV), patterns of antibiotic use, and outcome (length of hospital stay, discharge, and died). Secondary infection was determined by the presence of characteristic clinical features, and at least one positive blood, sputum/endotracheal aspirate, and urine culture results after 48 h of admission. Ventilator-associated pneumonia (VAP) was defined as the sum of infectious ventilator associated condition and a quantitative pulmonary infection (endotracheal aspiration growing $>10^5$ CFU/mL) in patients exposed to invasive mechanical ventilation for at least 48 h.[13]

***Laboratory Procedures*:** Laboratory confirmation of SARS-CoV-2 was achieved by RT-PCR (Biospeedy, Turkey) using nasopharyngeal throat samples at an authorized central laboratory. Routine blood examinations consisted of white blood cells (WBC), neutrophil-to-lymphocyte ratio (NLR), C-reactive protein (CRP), and procalcitonin (PCT). For blood culture, blood was inoculated into aerobic and anaerobic media and culture bottles were incubated in an automated blood culture system (BactAlert, Biomerieux, France) for 5 days according to the manufacturer's recommendations. Blood cultures positive for skin flora [coagulase-negative staphylococci (CoNS), gram-positive bacilli, micrococci e.g.,] that did not grow in multiple cultures or on separate dates were excluded. For ETA culture, microorganisms grown $\geq 10^5$ CFU/mL in ETA samples showing on gram stain >25 neutrophils and <10 epithelial cells per low power field were considered as etiological agents for secondary infection. Pathogen identification was performed by matrix assisted laser desorption ionisation-time of flight mass spectrometry (MALDI-TOF VITEK MS, bioMerieux, France). Antimicrobial susceptibility testing was carried out on VITEK-2 automated system (bioMerieux, France), and all the results were interpreted according to the criteria of the European Committee on Antimic-

robial Susceptibility Testing (EUCAST 2020).[14]

***Statistical Analysis*:** Descriptive statistics of the obtained data were given in tables as mean, standard deviation (SD), median, number and % frequencies. The compliance of numerical data to the normal distribution was examined using the Shapiro-Wilks test. While the relationship of secondary infection status with numerical type features was examined with the Mann-Whitney U test, its relationship with the categorical features was evaluated with the Pearson chi-square test. $p < 0.05$ was accepted as the statistical significance level and Statistical Package for the Social Sciences (SPSS ver. 23) program was used in calculations.

RESULTS

A total of 150 hospitalized patients with confirmed COVID-19 were analyzed. Among them 95(63.3%) patients were males and the mean age was 56 years (21-92). Among included patients, 20 (13.3%) had at least one microbiologically documented secondary infection and 130 (86.7%) had no secondary infection. The study population was divided into two subgroups as patients with and without secondary infection. The median age in patients with secondary infection (71.5 vs 54.5) was significantly higher than those without ($p<0.001$). When laboratory values examined, median WBC (10.3 versus 5.5), NLR (11.3 versus 2.3), CRP (18 versus 2.4), and PCT (1.8 versus 0.05) levels were significantly higher among patients with secondary infection compared to those without ($p<0.001$). Thirteen of the 25 ICU-patients received MV for at least 48 hours had significant bacterial growth, indicating a 52% prevalence of ventilator-associated pneumonia (VAP) in these patients. The mean time of total MV duration was 9 days in patients with bacterial growth, and the mean time of ETA positivity after tracheal intubation was found to be 6.8 days. In comparison to patients who underwent invasive mechanical ventilation, and did not have secondary infection, patients with secondary infection received significantly longer mechanical ventilation with a median duration of 9 (5.75–17.5) days ($p<0.001$). Overall, 147 (98%) patients received at least one antibiotic during their hospitalization, regardless of the presence of any secondary infection. The median antibiotic days of therapy was 12 days (9.25–21) for the patients with secondary infection. Besides, patients with secondary infection had a median duration of hospital stay for 12 days (10-24.75), which was significantly higher than those without ($p<0.001$) (Table 1).

Table 1. Comparison of numerical properties between patients with and without secondary infection.

Parameters	Secondary infection	N	Mean±SD	Percentiles			p*
				25th	Median	75th	
Age	No	130	54.14±15.03	44.00	54.50	65.00	**<0.001**
	Yes	20	68.30±11.17	58.50	71.50	77.75	
WBC	No	130	6.39±3.36	4.50	5.55	7.33	**<0.001**
	Yes	20	13.18±7.33	9.00	10.30	18.75	
NLR	No	130	3.99±5.86	1.58	2.35	3.80	**<0.001**
	Yes	20	13.10±8.83	4.85	11.30	19.50	
CRP	No	130	4.90±5.19	0.80	2.45	7.73	**<0.001**
	Yes	19	19.61±9.70	11.00	18.00	29.00	
PCT	No	99	0.472±.03	0.05	0.05	0.08	**<0.001**
	Yes	19	5.93±7.42	0.61	1.80	9.30	
Length of antibiotic therapy (day)	No	130	7.35±3.88	5.00	7.00	8.25	**<0.001**
	Yes	20	14.65±7.41	9.25	12.00	21.00	
Length of hospital stay (day)	No	130	9.27±4.58	6.00	8.00	11.25	**<0.001**
	Yes	20	16.20±9.23	10.00	12.00	24.75	
Length of ICU stay (day)	No	7	8.57±4.20	6.00	9.00	13.00	0.523
	Yes	18	13.22±9.59	7.00	10.00	18.25	
Length of mechanical ventilation (day)	No	4	7.00±2.70	4.25	8.00	8.75	**0.005**
	Yes	18	12.67±9.94	5.75	9.00	17.50	

WBC: white blood cells; NLR: neutrophil-to-lymphocyte ratio; CRP: C-reactive protein; PCT: procalcitonin; ICU: intensive care unit

*Mann-Whitney U test

Considering all patients, most common comorbidities included hypertension, diabetes mellitus, and coronary heart disease, respectively. Patients with hypertension, coronary heart disease, and malignancy have had significantly higher secondary infection rate. Overall, 125 (83.3%) patients were treated in the general ward, and 25 (16.7%) patients were in the ICU. Secondary infection rate in ICU patients [18, (72%)] was significantly higher than patients in the general ward [2, (1.6%)] ($p<0.001$). Among 130 patients without secondary infection, 123 (94%) of whom in the general service, the antibiotic regimen most commonly used was azithromycin with or without ceftriaxone with a median duration of 7 (5–8.25) days. Among twenty patients with secondary infection, the most common antibiotics used were teicoplanin (12, 60%), meropenem [10, (50%)], and piperacillin-tazobactam (5, 25%), except of ceftriaxone and azithromycin administered before ICU admission. Generally, 127 (84.7%) of 150 patients were discharged, and 23 (15.3%) were died. A significantly higher mortality rate [18, (78.3%)] was present in patients with secondary infection compared to those without ($p<0.001$) (Table 2).

Table 2. Comparison of categorical properties between patients with and without secondary infection.

			Secondary infection		
		Total	**No (n=130)**	**Yes (n=20)**	
		n (%)	n (%)	n (%)	p*
Sex	Male	95 (63.3)	81 (85.3)	14 (14.7)	0.506
	Female	55 (36.7)	49 (89.1)	6 (10.9)	
Service	General	125 (83.3)	123 (98.4)	2 (1.6)	**<0.001**
	ICU	25 (16.7)	7 (28.0)	18 (72.0)	
Comorbidities					
Hypertension	No	110 (73.3)	99 (90.0)	11 (10.0)	**0.046**
	Yes	40 (26.7)	31 (77.5)	9 (22.5)	
Diabetes	No	119 (79.3)	103 (86.6)	16 (13.4)	0.937
	Yes	31 (20.7)	27 (87.1)	4 (12.9)	
Coronary heart disease	No	133 (88.7)	121 (91.0)	12 (9.0)	**<0.001**
	Yes	17 (11.3)	9 (52.9)	8 (47.1)	
Chronic obstructive pulmonary disease	No	136 (90.7)	120 (88.2)	16 (11.8)	0.078
	Yes	14 (9.3)	10 (71.4)	4 (28.6)	
Chronic renal failure	No	140 (93.3)	123 (87.9)	17 (12.1)	0.109
	Yes	10 (6.7)	7 (70.0)	3 (30.0)	
Malignancy	No	142 (94.7)	126 (88.7)	16 (11.3)	**0.002**
	Yes	8 (5.3)	4 (50.0)	4 (50.0)	
Antibiotics					
Azithromycin	No	34 (22.7)	23 (67.6)	11 (32.4)	<0.001
	Yes	116 (77.3)	107 (92.2)	9 (7.8)	
Ceftriaxone	No	41 (27.3)	29 (70.7)	12 (29.3)	<0.001
	Yes	109 (72.7)	101 (92.7)	8 (7.3)	
Cefixime	No	139 (92.7)	121 (87.1)	18 (12.9)	0.623
	Yes	11 (7.3)	9 (81.8)	2 (18.2)	
Piperacillin-tazobactam	No	138 (92.0)	123 (89.1)	15 (10.9)	0.003
	Yes	12 (8.0)	7 (58.3)	5 (41.7)	
Colistin	No	146 (97.3)	130 (89.0)	16 (11.0)	<0.001
	Yes	4 (2.7)	0 (0.0)	4 (100.0)	
Meropenem	No	138 (92.0)	128 (92.8)	10 (7.2)	<0.001
	Yes	12 (8.0)	2 (16.7)	10 (83.3)	
Teicoplanin	No	129 (86.0)	121 (93.8)	8 (6.2)	<0.001
	Yes	21 (14.0)	9 (42.9)	12 (57.1)	
Vancomycin	No	149 (99.3)	130 (87.2)	19 (12.8)	0.011
	Yes	1 (0.7)	0 (0.0)	1 (100.0)	
No antibiotic administered	No	147 (98.0)	127 (86.4)	20 (13.6)	0.493
	Yes	3 (2.0)	3 (100.0)	0 (0.0)	
Mechanical ventilation	No	128 (85.3)	126 (98.4)	2 (1.6)	**<0.001**
	Yes	22 (14.7)	4 (18.2)	18 (81.8)	
Outcome	Discharge	127 (84.7)	125 (98.4)	2 (1.6)	**<0.001**
	Died	23 (15.3)	5 (21.7)	18 (78.3)	

* Pearson chi-square test

A total of 86 samples, including 54 blood, 25 ETA, and 7 urine were obtained for microbiological culture from 43 of 150 COVID-19 patients. While no ETA samples were sent from 8 out of 22 mechanically ventilated patients in the ICU, a total of 25 ETA samples were collected from the remaining 14 patients during their hospital stay. A total of 21 bacteria were isolated from 18 ETA samples with significant growth. Among the detected twenty-one microorganisms, gram negative bacteria accounts for 19 (90.4%), and the most common bacteria isolated was *Acinetobacter baumannii* (n=11), followed by *Pseudomonas aeruginosa* (n=5), and *Klebsiella pneumoniae* (n=3), respectively. All of *A. baumannii* isolates were multi-drug resistant, and susceptible only against colistin. Any mold that could cause invasive pulmonary aspergillosis was not detected by Gram/Giemsa staining or by ETA culture. For diagnosis of bacteremia, no growth was occurred in any of the blood cultures from patients in the general wards, while in 10 (32%) of the blood cultures from ICU patients growth was detected. The microorganisms isolated were *Staphylococcus epidermidis* (n=3), *Enterococcus faecalis* (n=3), *Acinetobacter baumannii* (n=2), *Klebsiella pneumoniae* (n=1), and *Candida glabrata* (n=1) in order of frequency. As for gram positive bacteria, methicillin resistance was present in all *Staphylococcus epidermidis* isolates, and no vancomycin resistance was found in *Enterococcus spp*. While no growth was observed in urine samples sent from the ICU, *E.coli* was isolated in a sample from the general service.

DISCUSSION AND CONCLUSION

Secondary infection is a serious complication in patients hospitalized with COVID-19, which is associated with worse outcomes and high mortality.[6,15] So far, many studies have been published reporting frequency and the features of these infections from different countries around the world.[7,11] As stated in some studies,[16,17] we also observed that patients with secondary infections were older and had multiple underlying comorbidities, mostly hypertension and coronary heart disease, compared to those without secondary infection. Overall, 127 of 150 hospitalized COVID-19 patients were discharged, and 23 were died in our study. We found that patients with secondary infection had significantly prolonged length of hospital stay and a higher mortality rate, compared to those without infection, which was consistent with previous studies.[2,18]

In the current literature, the rate of secondary infection in hospitalized COVID-19 patients varies widely between 3.8% and 83.3%, by emphasizing that it is noticeably more often in ICU-patients than those in the general service.[2,6,11,18] In accordance with this data, we found the secondary infection rate to be 13.3% among all 150 hospitalized COVID-19 patients. In service-based evaluation, we observed that this rate was very high as 72% in ICU patients, while it was very low as 1.6% in non-ICU-patients. Besides, compared with patients without secondary infection, use of MV were more common in patients with secondary infections (81.8% vs 18.2%) and these patients received significantly longer mechanical ventilation with a duration of 12 versus 7 days. Given that secondary infections closely related with the use of mechanical ventilation, it is expected that the majority of secondary respiratory infections reported in critically ill COVID-19 patients are ventilator-associated pneumonia.[11,16,19,20] We also observed that 21 of 31 secondary infection episodes were lower respiratory tract infections, mostly VAP. In recent studies,[18,19,21] the rate of VAP in COVID-19 patients was reported being as high as 25–54%. Similarly, we found the prevalence of VAP as 52% (13) in mechanical ventilated COVID-19 patients. Our data indicated a significant rate of VAP, with a predominance of Gram-negative bacteria, mostly non-fermenters (*A.baumannii*, *P.aeruginosa*), compatible with previous studies of COVID-19 patients in ICU. [1,6,20-22] However, in contrast to a current study,[23] which reported that there have been several cases of COVID-19-associated pulmonary aspergillosis (CAPA), we didn't observed such a case, possibly due to the small number of ICU patients in our study population. Besides, we should state that the frequency of VAP may be slightly higher and secondary respiratory tract infection may have been overlooked, since respiratory samples were not sent from eight patients who were mechanically ventilated and died, and microbiological examination could not be performed. This observation is in agreement with previous studies which indicated that respiratory cultures from COVID-19 patients were obtained on a limited basis due to extreme workloads and risk for aerosolization, and thus the rates of secondary infection potentially affected.[3,5] Therefore, we recommend performing respiratory samples from mechanically ventilated COVID-19 patients with suspected secondary respiratory infection, taking all precaution to prevent possible transmission, due to provide an effective treatment and better prognosis of the patients.

Regarding blood cultures, culture positivity was detected as 16.5% (9/54), all of them in ICU patients. Among isolated microroganisms, gram positive pathogens were the most frequent cause of bacteremia, being coagulase negative *Staphylococcus* (*CNS)* and *Enterococcus spp.* the most common detected. This pathogen distribution was similar to some COVID-19 studies, which reported that *Enterococcus* strains especially may have been selected in bacteremia detected in intensive care patients due to previous

empirical use of ceftriaxone, as in our ICU-patients.[18,22,24]

Evaluating the antimicrobial resistance data of isolated microorganisms, it was remarkable that all *A. baumannii* isolates, which are the main bacteria of VAP infections, were resistant to all antibiotics except colistin. Therefore, for centers with similar epidemiological features to our hospital, in cases considered to develop possible or probable VAP, empirical treatment adequately covering the multidrug-resistant *A. baumannii* strains should be implemented. Swithcing to targeted antibacterial treatment upon microbiological results is highly appreciated. As stated in previous studies[3,5,9,11,18] conducted at the onset of the pandemic, oral or i.v empirical antibiotic therapy was initiated for all hospitalized COVID-19 patients. However, most researchers subsequently emphasized that there is a significant discrepancy between antibiotic use and bacterial infections in these patients. Similarly, almost all patients (98%) in our study routinely received ceftriaxone and azithromycin, but only 13% of them had a microbiologically proven bacterial infection. The WHO also currently recommends that antibiotics should not be prescribed unless there is clinical suspicion of a bacterial infection, and the use of empiric antimicrobials should be limited only for patients with severe COVID-19, based on patient host factors and local epidemiology.[8]

In our study, when laboratory values examined, it was found that median WBC (10.3 vs 5.5), NLR (11.3 vs 2.3), CRP (18 vs 2.4), and PCT (1.8 vs 0.05) levels were significantly higher among patients with secondary infection compared to those without. Thus, the fact that these parameters are within the normal range can help the clinician to predict that patients are unlikely to have secondary infection, even if it cannot be completely ruled out. Given that the incidence of secondary bacterial infection is very low (1.6%) for patients hospitalized in the general wards in our study, we consider that the widespread use of antibiotics is not necessary, and antibiotic stewardship programmes should be implemented among all COVID-19 patients to avoid both the side effects of antibiotics and the spread of antimicrobial resistance in hospital.

In conclusion, the rate of secondary infection in hospitalized COVID-19 patients differs widely among patients in the general ward and in the ICU. We consider that empirical antibiotic therapy should not be initiated in patients hospitalized in the general ward, as the rate of secondary infection is very low. On the other hand, due to the high rate of VAP, we recommend sending respiratory samples regularly from COVID-19 patients hospitalized in the ICU for targeted antimicrobial therapy, and considering multidrug-resistant bacteria in empirical treatment. Our study have several limitations. First, we performed a single-centre retrospective study with a small sample size, which may limit generalizability. Second, in the diagnosis of secondary infection, we could not perform any additional tests other than culture, such as respiratory RT-PCR techniques or detection of pulmonary aspergillosis by galactomannan. Besides, although it is known that the use of steroids increases the risk of secondary infection, we could not comment on this issue in our study, since steroids were not used in the treatment of COVID-19 patients at the time of the study.

Ethics Committee Approval: Our study was approved by the Haydarpaşa Numune Training and Research Hospital Ethics Committee (Date:29/06/2020, decision no: 115).

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

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