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COVID-19-related Secondary Bacterial Infections in Intubated Critical Illness

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What is known on this subject?

Bacterial common pathogens are frequently seen in viral respiratory diseases like influenza, and they are a major source of morbidity and mortality, necessitating prompt identification and antibacterial treatment.

What this study adds?

Antibiotic-resistant microorganisms render humans more vulnerable to bacterial infections while also reducing our ability to fight off viral pandemics. Preventing drug resistance and avoiding needless antibiotic treatment are two strategies that should be implemented today to prepare for future pandemics.

ABSTRACT

Objective: The prevalence, occurrence, and characteristics of bacterial infection in individuals with severe acute respiratory syndrome coronavirus-2 is primarily unknown. In this research, we examined the effects of secondary bacterial infections (SBI), antibiotic use, and mortality on coronavirus disease-2019 (COVID-19) patients who were observed in intensive care units (ICU) when intubated.

Material and Methods: Between October 1, 2020 and February 1, 2021, patients who were monitored because of COVID-19 in adult ICUs at tertiary healthcare facilities were included in this retrospective research. The study included The study included a total of 170 individuals with acute respiratory distress syndrome and COVID-19 pneumonia.

Results: Antibiotics were given to 154 (90.58%) patients. While all SBI-positive patients received antibiotic treatment, 78 (45.88%) SBI-negative patients were also treated. In addition, SBI-positive patients had a higher mortality rate ($p<0.001$). Time-SBI was 3.13±2.42/days in patients with catheters, and it was shorter and statistically significantly different compared with patients without catheters ($p<0.03$). Blood culture growths were discovered in 24 (14.1%) of patients and were the most common.

Conclusion: Antibiotic-resistant microorganisms render humans more vulnerable to bacterial infections while also reducing our ability to fight viral pandemics. Preventing drug resistance and avoiding needless antibiotic treatment are two strategies that should be implemented today to prepare for future pandemics.

Keywords: ARDS, coronavirus, critical care medicine intubation, secondary bacterial infection

Introduction

In viral respiratory illnesses like influenza, bacterial common pathogens are commonly present and are a significant cause of fatalities and morbidity, needing timely detection and antibacterial treatment (1,2).

Uncertainty regarding the prevalence, incidence, and characteristics of bacterial infection in patients with severe acute respiratory syndrome coronavirus type 2 (SARS-CoV-2) has emerged as a serious knowledge gap.

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Antibiotics are administered when bacterial co-infection cannot be ruled out if secondary bacterial infection (SBI) is present or probably present, even though they are useless for coronavirus disease-2019 (COVID-19) therapy. Some recommendations support the empirical use of antibiotics in severe COVID-19 patients due to the high mortality rate of patients with superinfection from bacteria throughout outbreaks of influenza (3,4). Nevertheless, misuse of antibiotics raises concerns about the risk of bacterial resistance.

In this research, we looked at how SBI, antibiotic use, and mortality impacted COVID-19 patients who were monitored in intensive care units (ICU) while intubated.

Material and Methods

Patients who underwent adult ICU follow-up because of COVID-19 between October 1, 2020 and February 1, 2021 in a tertiary healthcare center were included in this retrospective research. Following the University of Health Sciences Turkey, Başakşehir Çam and Sakura City Hospital Ethics Committee's authorization for the study (ethical permission number: 2021-58, date: 14.04.2021), the records of patients admitted to the ICU within the specified periods were retrospectively scanned.

The following cases met the inclusion criteria for the study: 1) COVID-19 instances in whom polymerase chain reaction (PCR) testing confirmed the test; 2) acute respiratory distress syndrome (ARDS) patients identified using the Berlin criteria; and 3) intubated patients who were 18 years of age or older.

Criteria for exclusion: 1) patients under the age of 18 years; 2) patients without ARDS; 3) patients who are pregnant; 4) patients with concurrent malignancy; 5) patients with a history of transplantation of an organ and/or immunosuppression medication; 6) patients with a radiological diagnosis and a negative COVID-19 PCR test; the study included 170 ARDS patients who also had COVID-19 pneumonia (Figure 1).

Patient files and the hospital's computerized records were both used to obtain data on the patients. The patients' age, gender, concomitant disease status, and laboratory results on the day of admission to the ICU and the day of intubation were all studied. The Sequential Organ Failure Assessment Score (SOFA) and the Acute Physiology and Chronic Health Evaluation (APACHE) scores were also recorded at the time of admission to the ICU. The diagnosis of SBI was made by the infection expert after evaluating clinical deterioration, increases in C-reactive protein, procalcitonin, and white blood cell, and culture growths that appeared 48 h after the patients had been taken into the ICU. The moment when the diagnosis of SBI was made was accepted as the "Time of Secondary Bacterial Infection". All the research participants were COVID-19-infected patients who underwent follow-up and treatment in inpatient internal medicine, infection, and/or pulmonology. Patients who experienced clinical and laboratory deterioration within the first 48 h of ICU admission were deemed to have co-infections that originated outside the ICU (in the ward or during outpatient treatment), and they were therefore excluded from the research. Positive cultures that emerged due to contamination or colonization were disregarded immunomodulatory and immunosuppressive treatments were administered to the patients as follows: depending on the patient's condition, tocilizumab was given intravenously (iv) at a maximum dose of 800 mg at 8 mg/kg, and 400 or 800 mg. Anakinra was given to patients at a dose of 2-10 mg/kg/iv over the course of 7-10

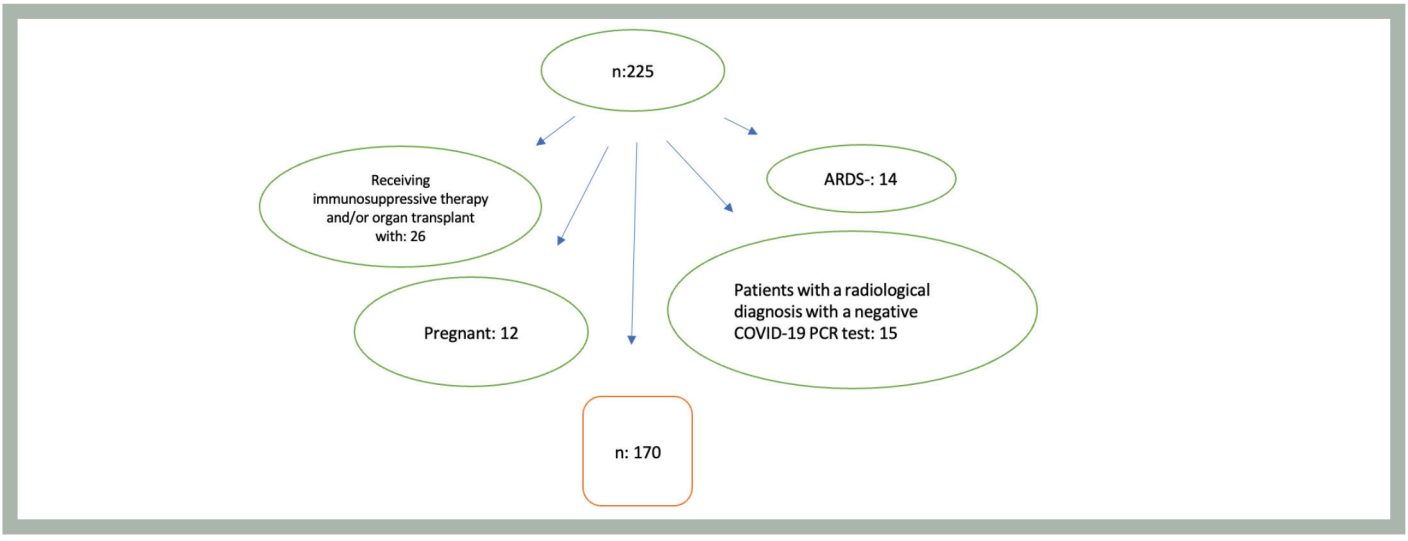

Figure 1. Flow chart

ARDS: Acute respiratory distress syndrome, COVID-19: Coronavirus disease-2019, PCR: Polymerase chain reaction

days, depending on their needs. The rheumatologist assessed the dosage and duration for each patient. iv immunoglobulin was administered at a total dose of 2 g/kg over the course of 2 days. Methylprednisolone pulse therapy was also given as 250 or 500 mg for 3-5 days, depending on the clinical condition of the patient. However, since these treatments were not used in all patients, the patients who used them were recorded.

Statistical Analysis

Using the SPSS tool, the study results were statistically evaluated. If the continuous data in one sample met the normal distribution, it was determined using the Kolmogorov-Smirnov test. In this study, quantitative data were expressed as the mean and standard deviation or median, depending on their distribution. The categorical variables were represented by percentages and numbers. The Mann-Whitney U test was used for continuous data that did not fit a normal distribution, whereas the Student's t-test was employed to compare the two groups. Using the chi-square test, categorical data from two groups were compared. Mortality was also assessed using logistic regression analysis.

Results

The study involved 170 patients. Two groups of patients were created based on their SBI status: those positive for SBI (SBI-positive) and those negative for SBI (SBI-negative).

Table 1. Demographic data of patients and laboratory results

n=170	All patients	SBI-negative n=93 (54.70%)	SBI-positive n=77 (45.29%)	p
Age	68.35±11.76	67.87±2.34	68.94±12.49	0.45
Glucose (mg/dL)	192±112.29	186.54±158.02	200.64±133.15	0.86
BUN (mg/dL)	79.3±63.09	85.94±71.97	71.30±49.62	0.25
Creatinine (mg/dL)	1.6±1.54	1.68±1.66	1.52±1.39	0.95
AST (U/L)	54.9±66.83	64.30±79.16	45.54±45.90	0.06
ALT (U/L)	47.31±75.76	55.82±94.099	37.05±40.59	0.28
LDH (U/L)	494.75±265.93	502.72±300.89	460.98±213.42	0.23
Fibrinogen (mg/dL)	59.3±174.35	573.45±188.40	618.48±153.32	0.17
D-dimer (µg FEU/mL)	3.03±4.15	3.09±4.13	2.97±4.2	0.34
Ferritin (ng/mL)	1440.12±1833.21	1557.02±2082.45	1298.67±1480.21	0.45
INR	1.19±0.68	1.23±0.88	1.14±0.36	0.34
WBC (10^9/L)	11.13±6.59	11.94±7.46	10.15±5.23	0.28
HB (10^9/L)	12.63±10.33	11.69±2.34	13.77±15.11	0.11
Platelet (10^9/L)	233.99±124.06	223.41±119.48	255.61±128.00	0.10
Lymphocyte (10^9/L)	0.98±1.13	0.88±0.79	1.04±1.43	0.94
Neutrophil (10^9/L)	9.48±6.14	10.10±7.4	8.73±4.60	0.59
CRP (mg/L)	135.06±93.31	127.58±9.26	145.12±103.77	0.47
PCT	2.86±9.57	3.22±12.11	2.42±4.98	0.99
Mechanic ventilation days	9.03±8.57	8.74±9.26	9.37±7.7	0.26
LOS in ICU/day	14.07±10.32	13.76±10.42	14.4±10.25	0.41
LOS in hospital/day	18.32±12.21	17.27±11.83	19.58±12.62	0.16
SOFA	9.96±2.62	9.66±2.46	10.32±2.72	0.23
APACHE	18.37±7.03	18.52±7.09	18.19±7.00	0.7
NLR	18.64±21.09	19.88±22.28	17.15±19.6	0.64
PLR	339.12±233.88	327.32±247.27	353.32±217.35	0.20
Mortality	126 (74.1%)	54 (31.8%)	72 (42.4%)	0.000
Antibiotic therapy	154 (90.58%)	78 (45.88%)	77 (45.29%)	0.002
The catheter's existence	123 (72.4%)	57(33.5 %)	66 (38.8%)	0.001

SBI-negative: Secondary bacterial infection negativity, SBI-positive: Secondary bacterial infection positivity, BUN: Blood urea nitrogen, AST: Aspartate transaminase, ALT: Alanine aminotransferase, LDH: Lactate dehydrogenase, WBC: White blood cell, HB: hemoglobin, PCT: Procalcitonin, CRP: C-reactive protein, SOFA: Sequential Organ Failure Assessment Score, APACHE: The Acute Physiology and Chronic Health Evaluation, LOS: Length of stay in ICU, NLR: Neutrophil lymphocyte ratio, PLR: Platelet lymphocyte ratio, INR: International normalised ratio

Table 1 summarizes the laboratory results and clinical features of these patients, and there was no statistical difference in the SOFA and APACHE scores between the two groups. Antibiotics were given to 154 (90.6%) of the patients. While all SBI-positive patients received antibiotic treatment, 78 (45.88%) SBI-negative patients were also treated. In addition, SBI-positive patients had a higher mortality rate ($p<0.001$). Table 2 summarizes the treatments used and the problems that occurred during ICU follow-up. In Table 3, the time of SBI (time-SBI) in patients with and without catheters is presented. Time-SBI was 3.13±2.42/days in patients with catheters, and it was shorter and statistically significantly different compared to patients without catheters ($p<0.03$).

Table 4 shows how culture growths were classified, with blood culture growths being discovered in 24 (14.1%) of patients and being the most common. In addition, in Table 4, 24 (14.1%) of the patients with SBI were informed that there was growth in the blood culture, that is, bacteremia. Catheter-related bloodstream infection was detected in 6 (3.53%) patients (5). In addition, SBI was found to predict mortality in binary logistic regression analysis ($p<0.001$) (Table 5).

Discussion

In this study, 77 (45.29%) of the COVID-19 patients followed in the ICU developed SBI-positive, and those with SBI-positive had a higher mortality rate. Time-SBI was also detected early in those who had a catheter. Bacterial infections aggravating viral diseases have been observed in earlier outbreaks and pandemics of viral respiratory diseases. Bacterial co-infection was recorded in up to 30% of critically ill individuals during the 2009 A (H1N1) influenza pandemic (2,6,7).

Based on studies on other coronaviruses, co-infections affect 11% of patients, with secondary infections being the most prevalent in the largest SARS-CoV-1 cohort (8) and bacterial infections having a negligible impact on Middle East respiratory syndrome (MERS) (9). Co-infection was noted

Table 2. Treatments and complications

All patients n=170	SBI-negative n=93 (54.70%)	SBI-positive n=77 (45.29%)	p
Male (n=91)	50 (54.9%)	41 (53.2%)	0.94
Female (n=79)	43 (46.2%)	36 (546.8%)	
Diabetic ketoacidosis	23 (12%)	16 (13.2)	0.89
Acute renal failure	51 (26.6%)	35 (28.9%)	0.64
Elevated liver enzymes	11 (5.7%)	8 (6.6%)	0.94
Deep vein thrombosis	2 (1%)	0 (0)	0.5
Pulmonary embolism	3 (2.5%)	3 (2.5%)	0.68
Tocilizumab	8 (4.2%)	7 (5.7%)	0.7
Anakinra	29 (15.1%)	13 (10.7%)	0.35
Plasmapheresis	16 (6.8%)	11 (9.1%)	0.97
IVIG	13 (6.8%)	6 (5%)	0.68
Methylprednisolone pulse therapy	76 (39.6%)	48 (39.7%)	0.98

SBI-negative: Secondary bacterial infection negativity, SBI-positive: Secondary bacterial infection positivity, IVIG: Intravenous immunoglobulin

Table 3. Time of secondary bacterial infection with and without central venous catheter

	Without catheterized group (n=11)	Catheterized group n=66)	p
The time of secondary bacteria infection/day	7.6±4.97	3.13±2.42	0.03

Table 4. Culture results

	n (%)
Blood culture	24 (14.1%)
Deep tracheal aspirate culture	18 (10.6%)
Urine culture	6 (3.5%)
Catheter culture	8 (4.7%)
Multiple growths	14 (8.2%)

Table 5. The logistic regression analysis of clinical and laboratory factors for predicting secondary bacterial infection

	Beta	OR	95% CI for EXP (B)		
			Lower	Upper	
APACHE	0.031	1.031	0.971	1.095	0.316
SOFA	-0.129	0.879	0.741	1.044	0.141
NLR	0.006	1.006	0.988	1.025	0.513
PLR	0.000	1.000	0.999	1.002	0.691
CRP	-0.001	0.999	0.994	1.004	0.717
PCT	-0.002	0.998	0.953	1.046	0.948
LOS in ICU	-0.027	0.974	0.889	1.066	0.563
Mechanic ventilation days	0.013	1.013	0.915	1.120	0.806
The catheter's existence	0.769	2.157	0.905	5.140	0.083
SBE	-2.189	0.112	0.039	0.320	0.000

APACHE: The Acute Physiology and Chronic Health Evaluation, SOFA: Sequential Organ Failure Assessment Score, NLR: Neutrophil lymphocyte ratio, PLR: Platelet lymphocyte ratio, CRP: C-reactive protein, PCT: Procalcitonin, LOS: Length of stay, ICU: Intensive care unit , CI: Confidence interval, OR: Odds ratio

in 3.5% [95% confidence interval (CI): 0.4-6.7%] of COVID-19 patients, and secondary infection was noted in 14.3% (95.5% CI: 9.6-18.9%) of COVID-19 patients, referring to a meta-analysis by Langford et al. (10). Over 70% of patients received antibiotic prescriptions, the majority of which were broad-spectrum antibiotics such as fluoroquinolones and cephalosporins of the third generation (10), although the overall risk of bacterial infections. SBI rates have been found to range between 5% and 30% in numerous cohort studies (11,12,13,14,15,16,17). SBI was found in 77 (45.29%) of the patients in our study, which was greater than the current rates.

Current recommendations are based on data from other viral pneumonia and lack randomized clinical trials on the use of empirical antibiotics in COVID-19 patients (18). In our study, all SBI-positive patients were given antibiotics, while 78 (45.88%) of SBI-negative patients and 154 (90.58%) of all patients were given antibiotics. In patients with COVID-19, drugs that inhibit the immune system are commonly used to reverse the immune system's irregular activation (19,20).

Secondary infection susceptibility is believed to be increased by a combination of virus and drug-induced immunosuppression. Furthermore, the finding of primarily *Streptococcus pneumonia* and *Staphylococcus aureus* (1) growths in hospitalized patients justify antibiotic treatment in patients with COVID-19. Rawson et al. (8) analyzed eighteen full-text reports of bacterial/fungal confections, of which nine (50%) were COVID-19, 5/18 (28%) SARS-1, 1/18 (6%) MERS, and 3/18 (17%) were about other coronaviruses. Although there is limited evidence for bacterial coinfection, it was reported that 62/806 (8%) of COVID-19 patients had bacterial/fungal co-infection at hospital admission and 1450/2010 (72%) received antimicrobial therapy. Patients who also had fungal or bacterial infections and broad-spectrum antibiotic usage were recorded in 89/815 (11%) of non-COVID-19 cases (8).

Clinicians still have trouble distinguishing between viral and bacterial infections. This diagnostic ambiguity has contributed to the well-acknowledged misuse of antibiotics in viral illness patients (21,22). Antibiotic use was shown to be extremely prevalent in our study. Broad-spectrum antibiotics weaken and impair the immune system's ability to manufacture antibodies (by decreasing gut bacteria). Furthermore, research shows that antibiotic use affects bile acid metabolism and triggers inflammatory reactions (23).

According to World Health Organization recommendations, antibiotic therapy or prophylaxis should be avoided in patients with mild COVID-19 symptoms or suspected or confirmed intermediate COVID-19 disease unless there is clinical evidence of bacterial infection (24).

Study Limitations

The study's limitations are that bacteria produced as a result of antibiotic treatments and patient culture growth were excluded from the data, and non-intubated patients were not included. In addition, the retrospective design of the study is another limitation of our study.

Conclusion

As a result, antibiotic-resistant microorganisms render humans more vulnerable to bacterial infections while also

reducing our ability to fight viral pandemics. Preventing drug resistance and avoiding needless antibiotic treatment are two strategies that should be implemented today to prepare for future pandemics.

Ethics

Ethics Committee Approval: University of Health Sciences Turkey, Başakşehir Çam and Sakura City Hospital Ethics Committee's authorization for the study (ethical permission number: 2021-58, date: 14.04.2021).

Informed Consent: Retrospective study.

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: D.T., G.H.A., G.T., O.Ö., Concept: D.T., G.H.A., G.T., O.Ö., Design: D.T., G.H.A., G.T., O.Ö., Data Collection or Processing: D.T., G.H.A., G.T., O.Ö., Analysis or Interpretation: D.T., G.H.A., G.T., Literature Search: D.T., G.H.A., G.T., Writing: D.T., G.H.A., G.T.

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