An observational study on bacterial infections in hospitalized coronavirus patients in a tertiary care center

Un estudio observacional sobre infecciones bacterianas en pacientes con coronavirus hospitalizados en un centro de tercer nivel de atención

Ilham Iqbal[1], Anjum Farhana[1], Syed Suraiya Farooq[1].

[1]Department of Microbiology, Govt. Medical College, Srinagar, J&K, India.

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Correspondencia a: *Ilham Iqbal, editcosmos123@gmail.com*

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ABSTRACT

Introduction: the latest global pandemic is caused by SARS-CoV-2 coronavirus. 6% of patients are admitted to the hospital, with 20% of those admitted to the intensive care unit due to acute respiratory distress syndrome. **Objective:** to characterise the bacterial infections in patients with coronavirus at an intensive care unit of North Indian Hospital. **Methods:** after receiving ethical approval from the institutional review board, a retrospective study was done on coronavirus subjects admitted to GMC Srinagar's intensive care units between January and June 2021. Data on demographics, comorbidities, and microbiology were obtained retrospectively. **Results:** overall, 394 COVID-19 patients were admitted to ICU. Median age was 58 years (IQR 51-69) and sex ratio (M/F) was 3. At admission the median SAPS II was 33 (IQR 24-49). Among patients, 232 had at least one co-morbidity and 162 were overweight (body mass index (BMI) = 27.8 kg/m2). In all, 358 patients received antibiotics (244/358 introduced before intensive care unit and 114/358 during intensive care unit stay). **Conclusions:** the current study is the first of its kind in our hospital setting to describe the bacterial persistence in the lungs despite adequate therapy, as well as frequent bloodstream infections possibly associated with bacterial translocations originating from the digestive or oropharyngeal microbiota, in COVID-19 intensive care unit patients.

Keywords: *Sepsis; Bacterial infection; Etiology; ICU.*

Palabras clave: *Sepsis; Infección bacteriana; Etiología; UCI.*

RESUMEN

Introducción: la última pandemia mundial está causada por el coronavirus SARS-CoV-2. El 6 % de los pacientes ingresan en el hospital, y el 20 % de ellos en la unidad de cuidados intensivos debido al síndrome de dificultad respiratoria aguda. **Objetivo:** caracterizar las infecciones bacterianas en pacientes con coronavirus en una unidad de cuidados intensivos de un hospital del norte de la India. **Métodos:** tras recibir la aprobación ética del consejo de revisión institucional, se realizó un estudio retrospectivo de los sujetos con coronavirus ingresados en las unidades de cuidados intensivos del GMC Srinagar entre enero y junio de 2021. Los datos sobre demografía, comorbilidades y microbiología se obtuvieron retrospectivamente. **Resultados:** en general 394 pacientes de COVID-19 fueron admitidos en la UCI. La mediana de edad fue de 58 años (IQR 51-69) y la proporción de sexos (M/F) fue de 3. En el momento del ingreso la mediana de SAPS II fue de 33 (IQR 24-49). Entre los pacientes, 232 tenían al menos una comorbilidad y 162 tenían sobrepeso (índice de masa corporal (IMC) = 27,8 kg/m2). En total, 358 pacientes recibieron antibióticos (244/358 introducidos antes de la unidad de cuidados intensivos y 114/358 durante la estancia en la unidad de cuidados intensivos). **Conclusiones**: el presente estudio es el primero de este tipo en nuestro entorno hospitalario que describe la persistencia bacteriana en los pulmones a pesar de la terapia adecuada, así como las frecuentes infecciones del torrente sanguíneo posiblemente asociadas a translocaciones bacterianas procedentes de la microbiota digestiva u orofaríngea, en pacientes de la UCI COVID-19.

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INTRODUCTION

The latest global pandemic, which began in December 2019, is caused by SARS-CoV-2 coronavirus. Six percent of patients are admitted to the hospital [1], with 20% of those admitted to the intensive care unit (ICU) due to acute respiratory distress syndrome (ARDS). Infections acquired in the hospital are common [2], although 2 meta-analyses found, "bacterial infection rates of 8.1 percent and 14 percent [3, 4] in COVID-19 ICU patients, there is currently a scarcity of research on bacterial infections in COVID-19 patients". In addition, numerous studies have highlighted the misuse of antibiotics in COVID-19 patients, as well as the global threat of antimicrobial resistance [5, 6]. To keep antibiotic prescriptions under control, it's crucial to understand the prevalence and epidemiology of bacterial infections in COVID 19 patients.

OBJETIVES

The aim of this study is to characterise the bacterial infections in patients with coronavirus at an ICU of North Indian Hospital.

METODHS

After receiving ethical approval from the institutional review board, retrospective analysis was done on coronavirus subjects admitted to GMC Srinagar's ICUs between January and June 2021. Data on demographics, comorbidities, and microbiology were obtained retrospectively.

A positive result for the SARS-CoV-2 virus based on a reverse transcriptase-polymerase-chain-reaction (RT-PCR) test on a nasopharyngeal swab or respiratory material and/or characteristic parenchyma infiltrates on a chest CT scan was selected as a COVID-19 verified case. The presence of microbials in a respiratory sample (broncho-alveolar lavage - BAL), blocked telescoping catheter (PTC), tracheal aspiration, or sputum) was used to diagnose bacterial pneumonia, according to clinical Infectious Diseases Society of America (IDSA) guidelines [7]. The specimens were subjected to quantitative cultures in the laboratory and Antimicrobial susceptibility was carried out in line with Clinical and Laboratory Standards Institute (CLSI) guidelines. A bacterial infection was classified as co-infection if the bacteria and SARS-CoV-2 were discovered at the same time during hospital admission and as super-infection, if the bacterium was found more than two days after admission for COVID-19. A Bloodstream Infection (BSI) was defined as the presence of bacteria in blood cultures that were not considered contaminants and resulted in the start or adjustment of antibiotic treatment. The breakpoints for early- and late-onset Ventilator-associated pneumonia (VAP) or BSI were defined at five days of mechanical ventilation for VAP and ICU stay for BSI [8].

Statistical analysis "For univariate analysis, categorical data were analyzed using Pearson's chi-squared analysis or Fisher test, and continuous data were analyzed using non-parametric Wilcoxon test. All statistical analyses were 2-tailed with a significance level of 5%.

RESULTS

Overall, "394 COVID-19 patients were admitted to ICU. Median age was 58 years (IQR 51-69) and sex ratio (M/F) was 3.02. At admission the median SAPS II was 33 (IQR 24-49). Among patients, 232 had at least one co-morbidity and 162 were overweight (body mass index (BMI) = 27.8 kg/m2). In all, 358 patients received antibiotics (244/358 introduced before ICU and 114/358 during ICU stay). The characteristics and comorbidities of COVID-19 ICU patients are shown in table 1 and table 2, respectively.

Table 1. Characteristics of COVID-19 ICU patients.

Characteristics	ALL	With BSI	Without BSI	Univariate analysis P	Intubated patient	Intubated patient with VAP	Intubated patient without VAP	Univariate analysis P
	n = 394	n = 62	n = 332	-	n = 258	n = 130	n = 128	-
Age	58 [51–69]	57 [50–65]	51[58–69]	1	57 [50–68]	57 [49–67]	57 [47–68]	1
Male sex	296	46	250	0.79	186	96	90	0.79
BMI(kg/m2)	27.8 [24.2–31.3]	29 [26–32]	29 [23–33]	0.008	28.0 [24.5–32.1]	28.5 [25.0–32.2]	27.7 [24.2–31.5]	0.19

Table 2. Comorbidities.

Comorbidities	ALL	With BSI	Without BSI	Univariate analysis P	Intubated patient	Intubated patient with VAP	Intubated patient without VAP	Univariate analysis P
Smoker	28	2	26	0.29	16	8	8	0.29
Chronic alcoholism	10	0	10	0.29	6	4	2	0.29
Diabetes mellitus	118	24	94	0.29	82	38	44	0.68
Chronic kidney disease	48	10	38	0.68	36	16	20	0.78
Chronic pulmonary disease	48	16	32	0.059	34	22	12	0.29
Liver dysfunction	12	2	10	0.59	6	2	4	1
Cardiac trouble	90	20	70	0.29	64	32	32	0.88
Immunosuppression	62	4	58	0.18	38	16	22	0.59
Intubation	258	62	196	**<0.001**	258	70	128	1
Anti-inflammatory treatment before infection	202	42	160	0.19	136	72	64	0.39

Almost half of patients (176/394) had at least one bacterial infection during their ICU stay; 154 had pneumonia, 62 BSI, 8 urinary tract infection and 2 a surgical site infection. Patients with bacterial infections were more severe at ICU admission than those who weren't infected. Patients with bacterial infections had a longer ICU stay and a higher mortality rate. The outcome and bacterial resistance is shown in table 3 and table 4.

Of the 394 COVID-19 patients, 132 had at least one positive blood culture, among which 62 had BSI. The remaining cases were considered to have contaminated blood cultures, predominantly with coagulase negative staphylococci. Patients with BSI had higher BMIs, were more severe at ICU admission and during ICU stay.

Among the BSI, all were super-infections, and 52 out of 62 were late onset. Gram-positive cocci were prominent in BSI with Enterococci (22 out of 62) and Staphylococci (20 out of 62). Enterobacterales were only detected in 8 samples (8 out of 62).

In 24 out of 62 samples, the origin of the bacteremia was identified: ten from the lungs and 14 from catheter with positive respiratory sample or catheter tip culture. Of the 38 samples without proven origin, 34 out of 62 were considered to originate from a digestive or oro-pharyngeal translocation. Indeed, the isolated bacterial species are known to belong to the digestive or oropharyngeal microbiota, and all other potential sources were excluded

Among the 394 ICU COVID-19 patients, 154 had at least one bacterial pneumonia. First episodes were: 10 community-acquired pneumonia, 14 non-ventilated hospital acquired pneumonia and 130 VAP. This represents 10 out of 154 pneumonia co- infections (present since admission) and 142 out of 154 pneumonia super-infection (acquired during hospitalization). Before the first VAP, median ICU stay and ventilation duration were 10 (IQR, 6-14) and 9 (IQR, 6-14) days respectively; 102 out of 130 VAP were late-onset. The length of hospitalization was longer for patients with VAP than in ventilated patients without VAP.

The most frequent bacteria involved in VAP were Staphylococcus aureus (34 out of 130), Pseudomonas aeruginosa (22 out of 130), Klebsiella pneumoniae (18 out of 130), and Escherichia coli (16 out of 130). No difference was observed in the distribution of bacteria between early- and late-onset VAP. Among Enterobacterales, 22 out of 74 were resistant to third-generation cephalosporins but susceptible to carbapenems, and 10 out of 74 were resistant to carbapenems (all harboring an NDM-type carbapenemase).

Strikingly, we observed an unusual persistence of bacteria in the respiratory samples of patients with VAP despite an adequate antibiotic therapy. Among patients still hospitalized seven days following the initial VAP, the responsible bacteria was still detected in culture in 54 out of 94 of cases. Presence of the bacteria, was 12 out of 52 among those who were still hospitalized 16 days following initial VAP".

Table 3. Outcome.

Outcome	ALL	With BSI	Without BSI	Univariate analysis P	Intubated patient	Intubated patient with VAP	Intubated patient without VAP	Univariate analysis P
Transfer to medicine services	166	4	162	<0.001	58	22	36	0.19
Death	142	38	104	0.0029	124	68	56	0.38

Table 4. Bacterial and antibiotic resistance.

Bacteria & antibiotic resistance	Total bacteria: 70	BSI source documented	BSI source	Total bacteria: 87
Enterobacteriaceae				
Escherichia coli	4	0	0	16
Klebsiella pneumoniae	0	0	0	18
Enterobacter cloacae	2	0	0	10
Klebsiella aerogenes	2	0	0	10
Others	0			20
Total	8			74
ESBL & HCASE	2			22
CPE	0			10
Non-fermenting bacteria				
Pseudomonas aeruginosa	6	4	KT / Lung	22
Acinetobacter baumannii	0			8
Others	0			10
Total	6			42
R_carbapenems	0			10
Other Gram-negative rods				
Haemophilius influenzae	0			4
Staphylococcacae				
Staphylococcus aureus	8	6	KT / Lung	34
MRSA	0			2
CoNS	12	10	KT	2
Enteroccoccus				
Enterococcus faecalis	18	2	Lung	4
Others	4	0		0
Streptococcacae				
Streptococcus viridans group	6	2	Lung	8
Streptococcus milleri group	2	0		4
Anaerobes	6	0		0

There can be several bacteria in a single sample BSI, Blood stream infection; BMI, Body mass index; ICU, Intensive care unit; ESBL, Extended Spectrum Beta-Lactamase; HCASE, Hyperproduction of cephalosporinase; CPE, Carbapenemase-producing Enterobacteriaceae; R_ carbapenems, Resistante to carbapenems; CoNS, Coagulase-negative staphylococci; MRSA Methicillin-resistant Staphylococcus aureus; KT, Catheter.

DISCUSION

Nearly half of the subjects had a microbial infection, according to our findings. Our research uncovered two microbial anomalies: (i) epidemiological bloodstream infection that might indicate gastrointestinal tract or oropharynx translocation, (ii) the presence of microbes in pulmonary system of subjects who had received appropriate VAP treatment.

Positive blood cultures were found at a greater incidence than previously reported in the literature (3.8 percent to 12 percent) [9, 10]. More than half of them were deemed contaminants, possibly as a result of modifications in nursing staff rules and safety equipment as a result of the COVID-19 pandemic. In our study, Enterococcus, Staphylococcus, and Streptococcus were the bacteria that caused bloodstream infection, which is rare in ICU patients. Surprisingly, in half of the cases, the source of the bloodstream infection could not be established, bacteria from the gut or oropharynx were implicated. One of the theories is COVID-19 patients' hyper-inflammatory state increases the permeation of GIT or oropharynx barriers, resulting in microbial translocations. Understanding the genesis of these atypical BSIs would benefit from a description of the makeup of GIT and oropharynx microbiota [11].

We also discovered that about half of coronavirus intensive care unit intubated patients acquired a Ventilator associated pneumonia, which is greater than the rate reported (varying from zero percent in the United States [12], seven percent in Spanish population [13], thirty percent in French population) [14]. The bacteria causing Ventilator associated pneumonia was not unusual, but we did see a greater prevalence of drug resistant microbes. This might be due to a 91 % rise in antibiotic usage in COVID-19 patients. Antimicrobial prescription is frequently difficult because it must consider the pathologies, susceptibility of bacteria to antimicrobial, patient's signs/symptoms, and danger of bacterial resistance. With a complex illness like COVID-19 and in a crisis scenario, all of these requirements are considerably more challenging to meet [15].

One of the observations in our study was that the clearance of ventilator associated pneumonia from pulmonary system was extremely slow despite appropriate antimicrobials. The etiology of these antibacterial failures is unknown. The major reasons are, "(i) pharmacodynamic alterations due to frequent glomerular hyperfiltration, even though in our study we did not find any difference in renal function between the patients, (ii) pharmacodynamic alterations due to a high BMI, which seems to be the case in this study, (iii) a probable decrease in the antimicrobial lung concentration associated with pulmonary emboli and obstruction of the pulmonary vasculature frequently observed in ICU COVID-19 patients [15, 16], and/or (iv) an impaired immune response". However, the time duration of microbiological persistence in relation to clinical outcome is unclear. Research found a microbiological failure (bacterial persistence) in forty-six percent of pneumonia cases [16]. In our investigation, however, "microbial failure was found to be consistently linked to clinical failure, necessitating a repeat sample. A case-control study would be required to investigate the microbiological outcome in COVID-19 patients with VAP. With a limited sample size, this retrospective observational study was done in a single center. Multi-center case-control research and experimental confirmation are needed to corroborate our findings".

In conclusion, "the current study is the first of its kind in our hospital setting to describe the bacterial persistence in the lungs despite adequate therapy, as well as frequent bloodstream infections possibly associated with bacterial translocations originating from the digestive or oropharyngeal microbiota, in COVID-19 ICU patients".

CONFLICTS OF INTEREST

The authors declare no conflict of interest.

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AUTHOR´S CONTRIBUTION

Conceptualization: II and SS.
Methodology: AF.
Software: AF.
Validation: II, SS and AF.
Formal Analysis: SS.
Investigation: AF.
Resources: AF, II.
Data Curation: SS.
Writing - Original Draft Preparation: II, AF, SS.
Writing - Review & Editing: AF, SS.
Visualization: SS, II.
Supervision: II.
Project Administration: SS

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