Hospital-acquired bacterial infections in COVID-19 intensive care unit: A retrospective cross-sectional study

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ABSTRACT

Background: The aim of this study was to determine the incidence of hospital-acquired infections (HAIs) in patients with SARS-CoV-2 coronavirus (COVID-19) infection admitted to the intensive care unit (ICU), and the most common causing pathogenic microorganisms.

Methods: This retrospective study included 535 patients admitted to the COVID-19 ICU of University Clinical Hospital Mostar from July 2020 to December 2021. The results of blood culture, urine culture, and bronchial aspirate samples were analyzed for each patient who met the inclusion criteria.

Results: Of a total of 535, 194 (36.2 %) patients had 313 confirmed HAIs at the COVID-19 ICU. The predominant infection was hospital-acquired pneumonia (HAP) (56.2 %), following bloodstream infections (BSI) (23.6 %) and urinary tract infections (UTI) (20.2 %). The most common isolate was multidrug-resistant (MDR) Acinetobacter baumannii causing 50.5 % of HAPs, 33.6 % of BSIs, and 9.6 % of UTIs. Furthermore, Klebsiella pneumoniae was the cause of 22 % of BSI, 22.9 % of UTI, and 17.5 % of HAP. Enterococcus species were the most common isolates of UTIs (43.4 %). Patients with HAIs stayed on average significantly longer in the ICU in comparison with patients without HAIs (12.1 ± 5.5 vs 6.7 ± 3.1 days, p < 0.001).

Conclusion: Hospital-acquired infections are common complications in critically ill COVID-19 patients with a predominance of respiratory infections and are also associated with a significantly longer stay in the ICU.

1. Introduction

Severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) is the novel coronavirus first reported in 2019 in Wuhan, China, responsible for the illness named Coronavirus disease 2019 (COVID-19) that has rapidly spread worldwide. As of 12 February 2023, over 755 million confirmed cases and over 6.8 million deaths have been reported globally.

The first COVID-19 patient was admitted to the University Clinical Hospital Mostar in March 2020 and new patients soon followed. Over time, it has become apparent that a separate ICU is needed for COVID-19 patients. At the beginning of the pandemic, the COVID-19 ICU with a capacity of 13 beds was formed. During the increased influx of patients, an additional COVID-19 ICU was periodically active at another hospital location.

The reported secondary bacterial infections and associated microorganisms during prior viral pandemics have varied. Most deaths associated with the influenza pandemic of 1918 were not caused by the influenza virus alone, but by subsequent bacterial pneumonia, particularly caused by S. pneumoniae. Secondary bacterial infections were also reported in the 2009 H1N1 influenza pandemic, and also during the 2002 severe acute respiratory syndrome (SARS) and the 2012 Middle East respiratory syndrome (MERS), both caused by the coronavirus of zoonotic origin SARS-CoV and MERS-CoV, respectively. Secondary bacterial infections were common in hospitalized, especially in critically ill COVID-19 patients, and are linked to prolonged mechanical ventilation and central venous line placement, hence increasing the disease’s mortality.

Reports on the incidence of secondary bacterial infections in COVID-19 critically ill patients vary up to 86.8 % in China. Given the significant differences in these reports, we conducted a retrospective observational study to evaluate the incidence of hospital-acquired infections...
(HAIs), the main bacterial pathogens, and their antibiotic resistance in critically ill COVID-19 patients admitted to our ICU.

2. Methods

2.1. Study design and population

A total of 535 patients (362 males and 173 females) who were admitted to the COVID-19 ICU of University Clinical Hospital Mostar, Bosnia and Herzegovina from July 2020 to December 2021 were recruited into this cross-sectional retrospective study. All included patients had COVID-19 infection confirmed by polymerase chain reaction (PCR) in nasal or respiratory tract samples, were older than 18 years, and were treated in the ICU for more than 48 h. Exclusion criteria were: age <18 years, ICU length of stay <48 h.

2.2. Data collection and definitions

Key data (demographics, admission to ICU, type of oxygen support, source of infection, isolated bacterial species, antimicrobial resistance) were collected from the electronic medical records and analyzed. In the study were included cases with confirmed infection, defined by the presence of a positive culture of a significant clinical sample, associated with clinical signs of infection. Specimens for isolation of bacterial pathogens included sputum for non-intubated patients and endotracheal aspirates either for intubated or tracheotomy patients, blood, and urine samples.

Upon admission to the ICU, the ordinating ICU physician examined all patients and diagnostic and therapeutic options were assessed. Following internal protocols, a urinary catheter was inserted to all patients on non-invasive ventilation (NIV), if not inserted earlier for specific reasons (difficulty/inability to urinate in a supine position, etc.). Invasive mechanical ventilation (IMV) was an indication for central venous catheter placement.

According to internal treatment protocols, all patients received on average 12 mg dexamethasone daily for 6–8 days with a tapering dose after. No other immunosuppressants were used. Of antiviral agents, only remdesivir was sporadically used. In most cases, antibiotic treatment started only when bacterial infection was suspected. The diagnosis of hospital-acquired infection (HAI) was based on the standard definitions of the Centers for Disease Control and Prevention (CDC). The HAI was considered as an infection manifested at least 48 h upon admission to the ICU.

Fig. 1. Flow diagram showing patient enrollment; ICU – Intensive Care Unit; HAI – Hospital-acquired infection; HAP – Hospital-acquired pneumonia; BSI – Bloodstream infection; UTI – urinary tract infection.
informed consent was not required, and any potentially identifying
amendments. Because this was a retrospective database analysis,
ards laid down in the 1964 Declaration of Helsinki and its later
(BSI) was defined as the presence of bacteria in blood detected on blood
before mentioned methods but without meeting the criteria for HAP
ICU. Hospital-acquired pneumonia (HAP) was defined as the presence of
HAI
Baseline patients

<table>
<thead>
<tr>
<th>Baseline characteristics</th>
<th>Patients with HAI</th>
<th>Patients without HAI</th>
<th>Total number of patients</th>
<th>P - value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients, N (%)</td>
<td>194 (36.2 ± 10.7)</td>
<td>341 (63.8 ± 11.2)</td>
<td>535 (100 %)</td>
<td>P &lt; 0.001</td>
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<td>Age (year), M ± StD</td>
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<td>64 ± 10.7</td>
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<td>Male, N (%)</td>
<td>130 (67 %)</td>
<td>232 (68 %)</td>
<td>362 (67.7 %)</td>
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<td>Female, N (%)</td>
<td>64 (33 %)</td>
<td>109 (32 %)</td>
<td>173 (32.3 %)</td>
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Hospital days

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<tr>
<th>Range</th>
<th>Mean (M) ± StD</th>
<th>Total</th>
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<tr>
<td>4-38</td>
<td>12.1 ± 5.5</td>
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<tr>
<td>3-20</td>
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<tr>
<td>3-38</td>
<td>8.5 ± 4.9</td>
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</table>

Respiratory support during ICU treatment

| Oxygen therapy only, N (%) | 25 (7.4 %) | 25 (4.7 %) | P < 0.001 |
| NIV ± oxygen therapy, N (%) | 123 (36 %) | 130 (24.3 %) | P < 0.001 |
| IMV, N (%)                 | 193 (56.6 %) | 380 (71 %) | P = 0.001 |

HAI – hospital-acquired infection; N(%) – number (percentage); M – mean; StD – standard deviation; NIV – non-invasive ventilation; IMV – invasive ventilation.

a Chi-square test.
b t-test.

ICU. Hospital-acquired pneumonia (HAP) was defined as the presence of a new lung infiltrate plus clinical evidence that the infiltrate is of an infectious origin, which includes the recent onset of fever, purulent sputum, leukocytosis, and decline in oxygenation at least 48 h upon admission to the ICU. To confirm HAP, we also used a chest x-ray, which proved the presence of new changes in the lung parenchyma or pleural effusion, and the isolation of an infectious organism from bronchoalveolar lavage, endotracheal aspirates or sputum samples. Patients who had evidence of an infectious organism acquired with before mentioned methods but without meeting the criteria for HAP were defined as having a colonizing organism. Bloodstream infection (BSI) was defined as the presence of bacteria in blood detected on blood cultures. BSIs with organisms known to cause contamination such as coagulase-negative Staphylococci were considered to be contaminants unless accompanied by signs and symptoms of genuine BSI that couldn’t be explained by any other means. Urinary tract infection (UTI) requires the presence of ≥ 10^5 UCf/mL of bacteria in a urinary sample from a newly inserted urinary catheter with clinical signs congruent with an infectious process.

2.3. Ethical considerations

All procedures followed were in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments. Because this was a retrospective database analysis, informed consent was not required, and any potentially identifying patient information was omitted. The collection of patient data was approved by the Ethics Committee of University Clinical Hospital Mostar (903/21; 24.05.2021).

2.4. Statistical analysis

Statistical analysis of the collected data was performed using IBM SPSS Statistics, version 23.0. (IBM Corp., Armonk, NY, IBM Corp.), and Microsoft Excel (version 2016, Microsoft Corporation, Redmond, WA, USA). The results of the categorical variables are presented as numbers (n) and percentages (%), and the Chi-squared test (χ² test) was used to test the significance of the differences. The results of the numerical variables are presented as the mean (M) and standard deviation (SD), and a t-test was used to test the significance of the differences. The level of statistical significance was set at p < 0.05.

3. Results

A total of 552 patients were admitted to the COVID-19 ICU of the University Clinical Hospital Mostar between July 2020 and December 2021. 17 patients met one or more of the exclusion criteria (Fig. 1). Thus, 535 patients (362 males and 173 females) with a mean age of 64 ± 10.7 were included in this analysis. The flowchart in Fig. 1 shows the total number of analyzed patients with HAIs and the total number and distribution of HAIs in the COVID-19 ICU. HAI was identified in 194 (36.3 %) patients, 33 % (n = 64) were females and 67 % (n = 130) were men with a mean age of 64 ± 9.8 years (Table 1).

In comparison, 96.4 % (n = 187) of patients with HAIs and 56.6 % (n = 193) of patients without HAI (Table 1) were on IMV (p < 0.001). Likewise, 3.6 % (n = 7) of patients with HAIs have received oxygen and/or non-invasive ventilation (NIV) support. Furthermore, patients with HAIs stayed in the ICU significantly longer than patients without co-infections (12.1 ± 5.5 vs 6.7 ± 3.1 days respectively, p < 0.001, CI 95 %) (Table 1).

Table 2 showed the total number of confirmed hospital infections with an infection rate of 68.6/1000 hospital days (HD). The most commonly diagnosed HAIs were HAPs (n = 176, 56.2 %), followed by BSIs (n = 74, 23.6 %) and UTIs (n = 63, 20.2 %) (Table 2).

Bacterial pathogens isolated in patients with HAIs are shown in Table 3. Acinetobacter baumannii was the most commonly isolated pathogen in patients with HAIs (n = 139, 50.5 %) and BSIs (n = 36, 33.6 %). Other isolated pathogens included Klebsiella pneumoniae Enterococcus species and Pseudomonas aeruginosa. Enterococcus species were the most frequently identified pathogen in patients with UTIs (n = 36, 43.4 %). Gram-negative bacteria (GNB) with predominance Acinetobacter baumannii and Klebsiella pneumoniae were identified in 82 % (n = 381) samples and showed multidrug resistance (MDR) in 77.9 % isolates. Among Gram-positive bacteria (GBP), 30.9 % showed MDR phenotype (Table 3). Pathogen resistance on selected antibiotics is shown in Table 4. Acinetobacter baumannii as the most common cause of HAIs showed a high resistance rate to crucial antibiotics (Table 4).

4. Discussion

In the COVID-19 pandemic worldwide health systems were exposed to organizational challenges, followed by a lack of health personnel, as well as large influxes of patients to ICUs. However, HAIs were an additional problem faced by the health system during the pandemic.

In our study, we analyzed the incidence of HAI and etiologic factors in critically ill COVID-19 patients. The incidence of HAIs in our COVID-
19 ICU was relatively high (36.2 %) similar to other studies that registered incidence from 44.6 % up to 86.6 % in the first wave of the pandemic. We also noticed an increase in the incidence of patients with HAIs during the COVID-19 period in comparison with previously reported HAIs incidence in the non-COVID multidisciplinary ICU in our institution which is also in accordance with the results of other authors. Among potentially relevant factors, the large influx of critically ill patients and increased length of stay in ICU, as well as lack of professional staff could be contributing factors to the increased incidence of HAIs during the COVID-19 pandemic. Furthermore, a study by Reyes et al. showed that patients with severe COVID-19 infections admitted to the ICU and treated with dexamethasone had a higher risk of developing respiratory hospital infections. IMV is another potentially relevant factor as almost every patient with HAI was at some point of treatment on IMV (96.4 %). Likewise, our results showed that COVID-19 patients with HAIs have stayed significantly longer in the ICU in comparison with the patients without HAIs, similar to previous findings. Also, protective measures during the pandemic were strongly directed at avoiding the spread of airborne viral pathogens, and during the peak of the pandemic, less attention could have been paid to ordinary infection control practices, and care bundles when handling IV lines or tracheal tubes.

HAP (56.2 %) was the most common HAI with a higher incidence in comparison with pre-pandemic ICU-acquired HAPs at our institution, and it is similar to the results of other studies. The possible reasons could be impaired immune cell function and damage of the alveolar membrane as prolonged exposure to invasive ventilation. According to our results, 96.4 % of patients with HAIs were at one point in their treatment on IMV. Acinetobacter baumannii, Klebsiella pneumoniae, and Pseudomonas aeruginosa were the most commonly isolated GNB pathogens. Our results are consistent with those of Chong et al. who reported that Pseudomonas aeruginosa and Klebsiella spp. were the cause of nearly 40 % of secondary pulmonary infections.

BSI were registered in 23.6 % of HAIs which was higher in comparison with the pre-COVID infection rate. The occurrence of BSI in COVID-19 patients admitted to ICU increased to 29.6 % according to a recent meta-analysis. There are conflicting results about the main etiologic factor of ICU-BSI. Gram-negative Acinetobacter baumannii and Klebsiella pneumoniae were the most commonly isolated pathogens in our study. Another author reported a frequent occurrence of BSI due to GPB as an etiologic factor.

In published investigations on hospital-acquired infections in COVID-19 patients, urinary tract infections (UTI) and catheter-associated urinary tract infections (CAUTI) have not been adequately documented. According to Fakih et al., overall CAUTI rates within the ICU did not show any significant difference between the pre–COVID–19 and COVID-19 periods. The incidence of UTIs in our ICU was 20.2 %. That is lower than in the pre-COVID-19 period, although still somewhat higher than in a majority of similar studies. Enterococcus species were the most common isolates in urinary tract cultures (43.4 %), similar to other results. This could be in line with the fact that it has been previously shown that urine Enterococcal isolates are more frequently pronounced after therapy by cephalosporine antimicrobials, and one of the most frequently used antibiotics in the pandemic were cephalosporins.

We also analyzed the antimicrobial resistance of pathogens isolated in patients admitted to the COVID-19 ICU. Overall, 82 % of isolated strains were GNB with MDR phenotype. Acinetobacter baumannii as the most commonly isolated pathogen in patients with HAI showed a high resistance rate to crucial antibiotics in our study. Of special importance is carbapenem-resistant Acinetobacter baumannii (CRAB). While carbapenem antibiotics are the last line of defense in the treatment of infections caused by MDR GNB, Zhang et al. found that 55.6 % of COVID-19 patients were infected with CRAB in ICU. CRAB contaminates the hospital environment and health workers’ hands. It can survive for prolonged periods on dry surfaces and can be spread by asymptomatic colonization. It is also resistant to many common disinfectants, leading to outbreaks that are hard to contain affecting the most vulnerable and critically ill patients. Compared to the pre-COVID-19 period, some authors reported a decreased antibiotic susceptibility during the first wave, while others observed an increased risk of CRE in patients hospitalized with COVID-19. Interestingly, we observed an increased incidence of Acinetobacter infections compared to the pre-COVID-19 period which is similar to data reported from Brazil. Our results also showed an increased incidence of infections caused by MDR Klebsiella pneumoniae. Similar results were also reported in Italy which showed an increase in Klebsiella infections by up to 50 % during the period March–April 20, 20.

There are several possible reasons for an increased incidence of infections with these pathogens. The mechanism of CRAB acquisition is the microbe cross-transmission, with the presence of microbes in a patient, transfer of this organism to health care workers (HCW), and cross-transmission to another patient. Incorrect hand cleaning during patient care has been demonstrated to facilitate the cross-transmission of GNB. The COVID-19 ICU patients demanded a high intensity of care,
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*a* Resistance on selected antibiotic is expressed as a percentage; /- Pathogen not tested on selected antibiotic.
with a continuous need for assistance, and thus a continuous need to be touched by the HCWs. Extended and prolonged contact of HCWs in full personal protective equipment, especially those without work experience in an ICU setting, with patients can contribute to increased infections by these pathogens. Another possible reason is the use of corticosteroids in high doses. The use of dexamethasone resulted in lower 28-day mortality, especially in patients receiving IMV, but some authors hypothesized that patients who received corticosteroids, with their immunomodulatory effects, survived longer and were, therefore, more likely to develop an infection with MDR pathogens during ICU stay. Additionally, lower funding allocated for antibiotic stewardship and infection prevention programs in low/middle-income countries such as Bosnia and Herzegovina could be also the causative factor.

Our study has several limitations that should be considered. The main limitation of our study was its retrospective design. Second, due to organizational difficulties in the first year of the pandemic, some of the patients’ data might be missing, meaning there could be patients not included in this study. Third, we did not record patients’ mortality and HAIs’ effects on it. We believe that, due to the organization of health care in that period, with numerous COVID-19 wards and the existence of other periodic ICU in different hospital location, any mortality data from only our ICU would not be relevant in this context. Also, we included only infections that were documented by culture samples and, therefore, some episodes may be missing. Finally, this study was limited to a single institution.

The main strength of our study is the identification of pathogens involved in HAIs with their antimicrobial resistances. Also, HAIs were strictly defined.

In conclusion, the higher rate of MDR strains, as well as the workload of HCWs, employment of personnel without previous ICU experience, and prolonged contact with patients in full personal protective equipment, could play a significant role in the higher incidence of HAIs than in the pre-pandemic period. Rational use of antibiotics could also reduce the circulation of resistant strains that cause HAIs in COVID-19 patients in ICUs. In this context, there are many lessons to be learned for future pandemics, and measures to reduce bacterial infection are fundamental in order to provide adequate critical care.

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Data sharing statement

Individual participant data that underlie the results reported in this article, after deidentification will be available beginning 3 months and ending 5 years following article publication to achieve aims in the approved proposal or for individual participant data for meta-analysis. Proposals for data access should be directed to the corresponding author email.

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