

ORIGINAL ARTICLE

Post Tocilizumab Secondary Infections in Covid-19 patients - Are we doing enough?

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ABSTRACT

Aim: To focus on the frequency of ICU-acquired infections in Sars Co-V2 Corona Virus disease (COVID 19) patients. **Method:** A retrospective observational study carried out in two tertiary care hospitals treating COVID 19 cases, Services Institute of Medical Sciences and Bahria International Hospital, Lahore. Data was collected from the medical records of the COVID 19 ICUs of both hospitals from May 1, 2020 to April30, 2021. All charts were reviewed for the evidence of positive cultures. The treatment given prior to positive cultures, after the availability of culture results and outcomes were also recorded.

Results: A total of 432 records were reviewed and 400 cases were included while 32 cases were excluded because of incomplete data. The frequency of infections per 1,000 days of ICU stay was calculated in 90 (22.5%) patients. Gram-negative bacteria accounted for 68 cases (75.5%) with Pseudomonas in 44 cases (48.8%), Acinetobacter in 23/90 (25.5%) while 17 cases (18.8%) had gram positive infection with Enterococcus in 14/18 (77.77%) or 14/90 (15.55%), MRSA in 4/18 (22.22%) 4/90 (4.44%), while 5/90 (5.5%) had more than 2 isolates at same time. Among these 3 had both pseudomonas and Acinetobacter while 2 patients had Pseudomonas and Stenotrophomonas Maltophilia.

Conclusion: There seems to be an increase in the infection rate among critically sick COVID 19 patients admitted in ICU. Use of steroids and Tocilizumab seems to play a role through their immunomodulatory effects.

Keywords: Tocilizumab, Secondary infections

INTRODUCTION

The novel coronavirus disease 2019 (COVID-19) caused by severe acute respiratory syndrome-coronavirus-2 (SARS-CoV-2) has led to a pandemic and caused public health emergency around the world. Most infections with SARS-CoV-2 are either asymptomatic or the disease is associated with mild symptoms, but in around 15–20% of patients it leads to hospitalization, of whom approximately 16% will need escalation to intensive care and ventilatory support^{1,2}. In this COVID-19 pandemic the healthcare systems around the world have faced serious dearth of medical staff and ICU beds due to overwhelming increase in critically ill patients. During the SARS outbreak of 2003, an increase in the rate of ICU acquired methicillin-resistant Staphylococcus aureus infections due to cross-transmission was noted, regardless the mandatory use of respiratory and contact precaution³. This calls for the need to uphold conventional practices of hospital infection control especially in the midst of this pandemic.

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There have been concerns raised over bacterial/ fungal co-infection during hospital admission in critically ill patients with COVID-19 disease, despite the wide use of antimicrobials⁴, but there is paucity in research and evidence. We observed that critically ill patients with SARS-CoV-2 admitted to ICU had increased incidence of bacterial/ fungal co-infection, we aimed this retrospective observational study to estimate the frequency of respiratory and blood stream co-infections and related microbiological patterns.

MATERIALS AND METHODS

Study Design & Study Settings: This retrospective observational study was carried out in two tertiary care hospitals treating COVID 19 cases, Services Institute of Medical Sciences and Bahria International Hospital, Lahore. The unit was created by converting the hospital's surgical ICU into a strictly isolated 9-bed ICU. The attending physicians, nurses and medical attendants were provided with PPE e.g., gloves, N95 masks, goggles/ face shields and Tyvek coveralls to attend the patients with COVID-19 disease and the use of personal protective equipment (PPE) was made mandatory. Each procedure, e.g., placement of indwelling catheters, was done after

ensuring use of aseptic measures and sterile fields. All operators were provided with separate sterile gloves and gowns for performing invasive procedures.

Participants: The study involved all of the COVID-19 patients admitted to the ICU between May 1, 2020 to April 30, 2021

Outcomes: The primary outcome was the increasing frequency of microbiologically verified BSIs. The secondary outcomes were the classification of the causative agents and the variations in the frequency of BSIs and the incidence of specific causative organisms between the study period (May 1, 2020 to April 30, 2020).

Operational Definitions: Blood stream infections (BSIs) were defined using the Center for Disease and Control criteria⁵. If the isolated BSI was a common skin organism associated with contamination, it had to be verified in two sets of blood cultures⁶. If the BSI was diagnosed more than or equal to 48 hours after admission to ICU, it was said to be ICU-acquired BSI. If more than one organism was isolated from a single or different sets of blood cultures it was called a polymicrobial BSI. In order to be considered a new episode, a BSI had to fulfill the criteria for an ICU-acquired BSI due to a different organism 48 hours after the initial infection; the isolation of the same microorganism in repeated sets of blood cultures was considered a recurrent BSI. The patients who stayed in the ICU during overlapping periods or for a maximum of 4 weeks were defined as being epidemiologically linked⁷ and the presence of nosocomial transmission was considered ascertained if genotypically related strains were detected in two or more epidemiologically linked patients.

Laboratory Procedures: The species causing BSIs were identified by means of Vitek MS matrix-assisted laser desorption/ionization time-of-flight mass spectrometry (bioMérieux, Marcy l'Etoile, France). Antimicrobial susceptibility and resistance detection of the clinical isolates were determined using the automated Vitek 2 system (bio-Mérieux). The interpretation of susceptibility patterns was performed according to the European Committee on Antimicrobial Susceptibility Testing⁸. In accordance with local multidrug resistance (MDR) surveillance policy, all of the MDR bacteria isolated from blood cultures are routinely collected and stored at -80°C . The genetic relationships of the vancomycin-resistant Enterococcus species strains isolated from COVID-19 patients were explored by means of automated repetitive extragenic palindromic polymerase chain reaction (DiversiLab Enterococcus kit, bioMérieux)^{9,10}. The amplified fragments were separated by means of capillary electrophoresis and their band patterns were compared using an Agilent 2100 Bioanalyzer (Agilent Technologies, Palo Alto, CA). The isolates whose band patterns were greater than 95% similar were considered to be genetically related⁹.

RESULTS

A total of 432 cases were reviewed and 400 cases were included in the study. 32 cases were excluded because of incomplete data. The frequency of infections per 1,000 days of ICU stay was calculated in 90 (22.5%) patients. Sixty-eight patients (75.5 %) had one of the 90 episodes of

culture positive infection with a frequency of 90 per 1,000 days of ICU stay (95% CI, 65–115). All the patients who had infection had prolonged median ICU stay (18 days; IQR 12–30 as compared to those who did not IQR 4–10; $p < 0.001$), and required invasive mechanical ventilation (90.4 % than those who did not 34.6%; $p = 0.013$). The median time from ICU admission to the first infection episode was 09 days. Gram-negative bacteria accounted for 68 cases (75.5%) while 17 cases 18.8 % had gram positive infection, while 5 cases (5.5%) had more than 2, gram negative species isolated. Pseudomonas species was the most prevalent and was seen in 44 cases (48.8 %). Second most prevalent gram-negative bacteria were Acinetobacter which accounted for 23 isolates (25.5 %). 5 patients had multiple gram-negative bacteria 3 had both pseudomonas and Acinetobacter while 2 patients had Pseudomonas and Stenotrophomonas Maltophilia. Among gram positive bacteria Enterococcus species were more prevalent and accounted for 14/18 (77.77 %) while Methicillin resistant Staphylococcus Aureus (MRSA) was isolated from 4 cases (22.22%). 66 cases (73.33%) showed multidrug resistance. Out of these 90 cases 29 (32.2 %) had respiratory tract infection, 45(50%) had blood stream infections while 16 cases (17.77%) had both respiratory and blood stream infections.

Variables	Descriptive Statistics
Culture +Ve Infection	68 (17)
Patients with infection and ICU Stay median IQR (days) 18-12	90(6)
Bacteria	
Gram negative	68(75.5)
Pseudomonas	44(48.8)
Acinetobacter	23(25.5)
Gram positive	18(18.8)
Enterococcus	14(77.77)
MRSA	4(22.22)
Multidrug resistance Isolates	66(73.3)
Respiratory tract infection	29 (32.2)
Bloodstream Infection	45 (50)
Both URTI [#] & BSI [*]	16(17.77)

[#]Methicillin resistant staphylococcal aureus, [#] Upper respiratory tract infection, ^{*}Blood stream infection

DISCUSSION

Although COVID-19 associated deaths have mainly occurred in the elderly with serious underlying diseases⁸, Nosocomial pneumonia (NP) poses a major threat to the patients in intensive care units. Among microorganisms, the bacteria including Staphylococcus spp., Enterococcus spp., Klebsiella pneumoniae, Enterobacter spp., Escherichia coli, Acinetobacter spp., and Pseudomonas spp. are the most frequently detected causative agents of NIs⁹. In hospitalized patients with viral pneumonias, these opportunistic pathogens can cause superinfections not only in patients with serious underlying disease but also in patients without underlying diseases and in all age group^{10,11}.

In this study, we found that the incidence of BSI in critically ill patients admitted to ICU with COVID disease was quite high. The main factors responsible for causing at least one BSI episode in patients were a severe COVID

disease leading to a compromised clinical state at the time of ICU admission, a prolonged ICU stay, a need for mechanical ventilation during their ICU stay¹², and the use of steroids and tocilizumab through their immunomodulatory effects.

The simultaneous infection of the virus and bacteria is also a factor for increased incidence of BSI. Viruses can facilitate the attachment and colonization of the bacteria in the respiratory tract by damaging the ciliated cells and thus resulting in decreased mucociliary clearance and increased adhesion of bacteria to mucin¹³, however, the interaction of SARS-CoV2 and other bacteria needs further research.

The disruption of the gut barrier caused by SARS-CoV-2 is another possible mechanism for the high incidence of BSIs. It has been shown that SARS-CoV-2 can infect human gut enterocytes¹⁴, this increases the possibility that infection with this virus can increase the intestinal permeability and bacterial translocation, which is a known risk factor for the development of BSIs.

The unprecedentedly high incidence of BSIs (90/1,000 d of ICU stay) is much higher than that reported in other studies conducted in China and the United States (1–11.9%)^{15–17}, one reason for this difference is the observation period of our study which is longer than these and the incidence of BSIs is subject to the duration of observation¹⁸. Another important characteristic that may be responsible for the increased incidence of BSI is the need for mechanical ventilation which in turn is associated with increased risk of BSI¹². More than 83% of our patients underwent mechanical ventilation, whereas the proportion of ICU-treated COVID-19 patients requiring mechanical ventilation in studies conducted in China and the United States varies from 37.6% to 67.4%^{15–18, 21–23}.

In this study, the secondary infections of the lower respiratory tract were focused and it was found that *P. aeruginosa* was the most common organism followed by *A. baumannii*. In recent years, it has been seen that both species have shown emerging strains and have acquired additional genetic features and are frequently associated with hypervirulence and resistant to many types of antibiotics^{19,20}. The secondary infections were also associated with other bacteria including *Escherichia coli*, *Klebsiella pneumoniae*, *Staphylococcus aureus*, *Enterobacter* spp., *Serratia marcescens*, and *Stenotrophomonas maltophilia*, etc. that were previously isolated from the ICU wards and non COVID-19 patients admitted to our ICUs. In 2014, the most common ICU-acquired strains were *Acinetobacter baumannii*, *Pseudomonas aeruginosa*, *Stenotrophomonas maltophilia*, *Staphylococcus aureus*, *Enterococcus* spp., and *Klebsiella pneumoniae* in Shanghai, China²⁴.

In this study, MRSA was also identified as one of the organisms which is known to complicate infections in ICU environments. The incidence of acquiring MRSA increases (> 2.5–4 times) in patients with longer stays in the ward, i.e. more than one week²⁵. In multiple studies it has been shown that lower respiratory tract infections caused by MRSA increases level of mortality in the patients admitted to ICUs significantly^{26,27}.

In this study, the first samples were taken in the patients who were admitted to ICUs for ≥9 days. The extended duration of admission to ICU was an excellent opportunity

for bacteria to infect the patients, and thus all of our first cultures were positive with secondary infection (19/19, 100%). This incidence rate is higher than similar recently published articles. In Fu et al. study, 13.9% (5 of 36) of the patients in the ICU that were diagnosed with SARS-CoV-2 had subsequently developed secondary bacterial infections. In another report that was published from a UK secondary care setting, amongst 836 patients identified as SARS-CoV-2, 27 cases (3.2%) were identified to have early secondary bacterial infection (0–5 days post admission) rising to 51 cases (6.1%) during the admission^{28,29}.

Except for colistin, *A. baumannii* strains showed widespread resistance to all different classes of antibiotics and no inhibition zone was observed in the disk diffusion method. The hospital-acquired infections have become a major concern to health care systems worldwide and multi-drug resistant bacteria, especially *A. baumannii*, are common in patients admitted to the hospitals. Wang et al. revealed that *A. baumannii* isolates were approximately >98% resistant to piperacillin, imipenem, ceftriaxone, ciprofloxacin, and ceftazidime³⁰. Castilho et al. also reported that in Goiânia, Brazil *A. baumannii* isolates from ICUs, had a high incidence of resistance to carbapenems and were classified as multi-drug resistant (MDR). One of the common factors responsible for the development of resistance to carbapenems and other β-lactams is the production of the MBLs that can inactivate a wide range of β-lactam antibiotics³¹. However, the bacteria may use other mechanisms to resist the effects of antibiotics^{32,33}.

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