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Letter to the Editor

Threat of multidrug resistant bacterial pathogens in COVID-19 pandemic

Sir,

Coronavirus disease 2019 (COVID-19) is caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). The disease first emerged in Wuhan, China in December 2019 and since then, has been spreading worldwide.[1] On March 11, 2020, the World Health Organization (WHO) declared the disease a pandemic.[2] This pandemic has been described as the greatest threat to global health since the Spanish Influenza pandemic in the 20th century.[3]

The Presentations of COVID-19 range from asymptomatic/mild symptoms to severe illness. Common symptoms include fever, cough, shortness of breath and malaise but the infection may lead to complications such as pneumonia, acute respiratory distress syndrome, cardiac injury, arrhythmia, septic shock, liver dysfunction, acute kidney injury, and multi-organ failure in some patients.[4]

As of March 12, 2022, WHO has reported a total of 452,201,564 confirmed cases of COVID-19.5 There is no miracle cure for COVID-19. Though number of vaccines were developed in short time and are currently on use with around 56% full vaccination coverage, the infection still continues with over 11 million cases every week.[5] Reports obtained from the early phase of the pandemic suggest that among those with COVID-19, up to 20 percent develop severe disease requiring hospitalization.[6] Among those who are hospitalized, up to 25% need intensive care unit (ICU) admission, representing approximately 5 to 8 percent of the total infected population.[6] However, rates of ICU admission vary, reflecting differences in practice, admission criteria, and population characteristics in the region served by the ICU.[6] Rates may change as the pandemic progresses. The current case fatality rate reported by WHO is 1.33%.[5]

Severe COVID-19 usually leads to respiratory failure, often requiring hospitalization in critical wards and respiratory support.[7] The critically ill patients with COVID-19 have been found to be at risk of developing secondary infections. Secondary infections include pneumonia (eg, bacterial, fungal), vascular catheter infections, urinary tract infections, and rarely Strongyloides reactivation.[3,6] The overall rate of secondary bacterial infection is about 3.2% -15%.[8] Many studies have found the high incidence of multidrug resistant (MDR) bacterial pathogens such as *Acinetobacter baumannii, Pseudomonas aeruginosa, Staphylococcus aureus, Enterococcus species, Klebsiella pneumoniae* and *Clostridium difficile* in patients with COVID-19.[9,10] It is highlighted that the incidence of co-infections is low, affecting about 3.5% of hospitalized patients, while the majority are secondary or hospital acquired infections, developed later, generally 10–15 days after ICU admission.[10]

In an Italian study involving 774 critically ill patients with COVID-19, 46% had hospital acquired infections, of which one third were caused by MDR bacterial pathogens.[11] Fifty percent of hospital acquired infections were ventilator-associated pneumonia (mostly Gram-negative bacteria and *Staphylococcus aureus*) and one-third were bloodstream infections. In another study, Karruli et al reported 50% of MDR infections among ICU admitted 32 patients. The most common MDR pathogens were carbapenem-resistant *Klebsiella pneumoniae* and *Acinetobacter baumannii*, causing bloodstream infections and pneumonia.[12] A Brazilian study reported that 29.7% health care associated infections were multidrug resistant infections and the overall incidence of MDR infections increased by 23% during COVID-19.[3] In another study by Costa et al, a total of 191 patients with laboratory-confirmed COVID-19 were included and 57 patients had 97 secondary infectious events.[13] The most frequent agents were *Acinetobacter baumannii* (28.9%), *Pseudomonas aeruginosa* (22.7%) and *Klebsiella pneumoniae* (14.4%); multi-drug resistance was present in 96% of *A. baumannii* and in 57% of *K. pneumoniae*. The most prevalent infection was ventilator-associated pneumonia in 57.9% of patients. It remains unknown whether the infection rate has increased with the more widespread use of dexamethasone and other immunomodulating agents.

The secondary infections with MDR pathogens in COVID-19 have been found to prolong the hospitalization of the patients, increase the severity of organ dysfunction and also increase the mortality of the patients. Therefore, those infections create worrisome situations.[6]

The important risk factors that have been associated with the secondary infections caused by the MDR pathogens in patients with COVID-19 include long hospital stay, prolonged mechanical ventilation and peripheral and central venous access, use of steroid therapy, intensive use of broad-spectrum antibiotic agents in patients with SARS-CoV-2 infection since the first day of admission in ICUs.[3,8-10] A meta-analysis of 3,338 hospitalized and critical COVID-19 patients across 24 studies reported an

antibiotic prescription prevalence of 74%, with fluoroquinolones, macrolides, cephalosporins and β-lactam-β-lactamase inhibitor combinations being the most commonly used antimicrobial families. Literature has indicated that treatment for real and feared co-infection and health care associated infection have all contributed to a substantial increase in antibiotic prescribing globally, often using broad-spectrum antimicrobials.[3] This practice has a major impact on the emergence of MDR bacterial infections worldwide.

WHO has warned against any indiscriminate use of antibiotics (broad-spectrum) in the management of COVID-19 and recommends that antibiotic therapy or prophylaxis should not be used in patients with mild/moderate COVID-19 unless it is justifiable.[15]

Since there may not be any therapeutic options remaining to treat infections caused by MDR pathogens, judicious use of antibiotics in patients in COVID-19, improved adherence to hand hygiene and implementation of infection control measures play very important role to limit the infections associated with MDR pathogens.

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