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Proceeding Paper

The Impact of *Acinetobacter baumannii* Infections in COVID-19 Patients Admitted in Hospital Intensive Care Units †

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Abstract: Since the end of 2019, the Coronavirus Disease 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has spread globally, affecting people worldwide. Patients with severe COVID-19 require intensive care unit (ICU) admission for acute respiratory failure; over 10% need noninvasive and invasive mechanical ventilation. Acute respiratory distress syndrome (ARDS) severity and ventilation management determine a negative outcome and a 90-day mortality of 31%. During the COVID-19 pandemic, the impact of superinfections in ICUs has progressively increased, especially carbapenem-resistant *Acinetobacter baumannii* (CRAB). Infections caused by *A. baumannii* represent a significant concern for COVID-19 patients. The data about superinfections complicating COVID-19 are scant. A significant proportion of these patients are treated with empiric broad-spectrum antibiotic therapy, which increases the risk of developing infections caused by CRAB. Finally, drugs targeting cytokines, such as IL-1 and IL-6, might also increase the risk of superinfections in patients with COVID-19. Appropriate prescription and optimized use of antimicrobials according to the principles of antimicrobial stewardship, quality diagnosis, and aggressive infection control measures may help prevent CRAB infections during this pandemic. Recommended guidelines for antimicrobial stewardship in COVID-19 patient treatment are discussed regarding the minimization of empiric broad-spectrum antibiotic use. In this mini-review, we will present the impact of CRAB infections on the outcome of patients with COVID-19 requiring ICU admission. Subsequently, we will discuss the joint efforts needed to prevent and control the *A. baumannii* confection in the COVID-19 pandemic.

Keywords: COVID-19; antibiotic resistance; *Acinetobacter baumannii*; intensive care units; carbapenems;

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1. Introduction

Hospital-associated infections (HAIs) are a leading cause of morbidity and mortality in healthcare settings. These infections burden healthcare systems considerably, particularly due to bacterial infections that have developed resistance to currently available antimicrobial drugs [1]. Over the past decade, there has been a notable surge in the prevalence of multidrug-resistant (MDR) bacteria, sparking grave public health concerns on a global scale. Notably, Gram-negative bacteria (GNB), which are challenging to combat, have exhibited heightened resistance to currently employed antibiotics, severely limiting the therapeutic options available for treatment [2].

Among these species, *A. baumannii* strains hold a prominent position on the World Health Organization's list of critical priority pathogens that necessitate the development of new antimicrobial agents [3]. *A. baumannii* is an opportunistic pathogen that primarily affects critically ill patients. This bacterium is known for causing a range of infections, and its prevalence in healthcare settings, particularly in intensive care units (ICUs), has led to significant concern due to its ability to develop antimicrobial resistance [4–6] (Figure 1).

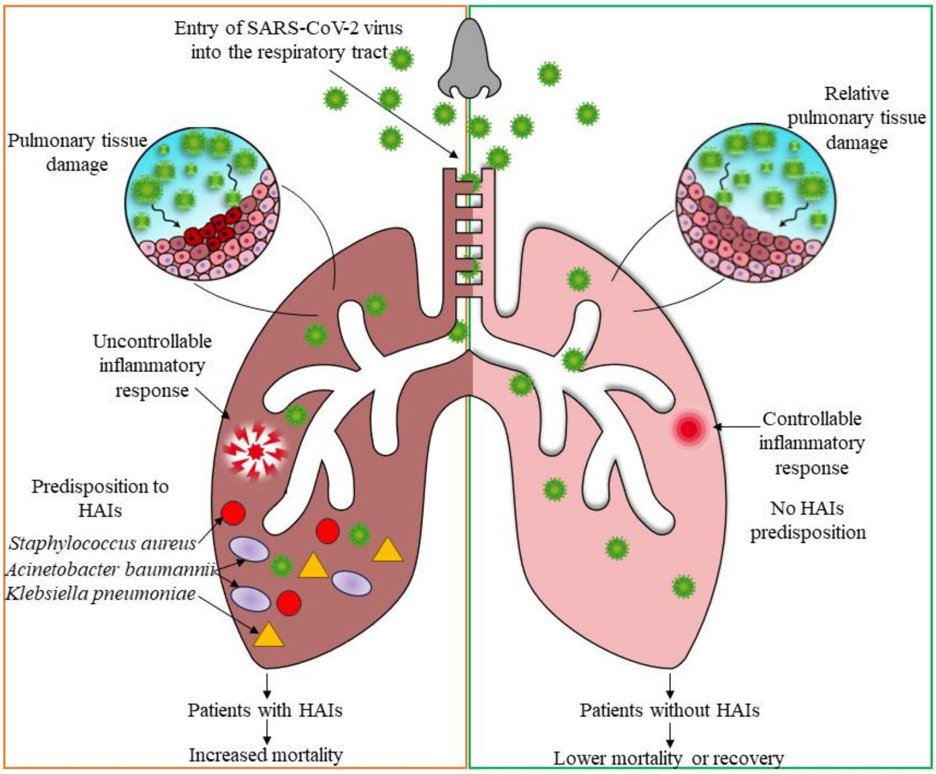

Figure 1. The schematic view of the SARS-CoV-2 virus influence on HAIs outcome**.**

Since the close of 2019, the pandemic caused by the severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) has significantly strained healthcare systems worldwide, primarily attributed to the substantial number of infected individuals necessitating extended hospital stays and intensive care [7]. A recent pilot study conducted in Spain highlighted the potential of gut microbiota profiling as a predictive biomarker for colonizing MDR bacteria in patients with SARS-CoV-2 infection [8]. Among GNB, *A. baumannii* and *Klebsiella pneumoniae* have emerged as the most commonly isolated species in COVID-19 patients who experience hospital-acquired superinfections [9].

In this mini-review, we will present the impact of *A. baumannii* infections in healthcare settings and on the outcome of patients with COVID-19 requiring ICU admission. Subsequently, we will discuss the joint efforts to prevent and control the *A. baumannii* confection in the COVID-19 pandemic.

2. *A. baumannii* Healthcare Associate Infections

A. baumannii strains has become a significant concern in global public health due to its frequent involvement in HAIs, particularly in individuals who are critically ill or immunocompromised. Abassi and collaborators conducted a study to investigate the presence of *A. baumannii* strains in 546 clinical patient samples using conventional culture methods and PCR. The results revealed that out of 546 samples, 87 were *A. baumannii* isolates, most of them extensively drug-resistant or carbapenem-resistant [6]. An extended retrospective matched cohort study of 2213 patients with *A. baumannii* HAIs was conducted to understand these infections' impact on mortality and morbidity. The excess one-year mortality was 27.2% in patients with carbapenem-resistant *A. baumannii* (CRAB) strains, compared with uninfected patients, resulting in a mortality of 11.8%. The excess risk associated with carbapenem resistance for new-onset chronic ventilator dependence was 5.2%. Also, the carbapenem resistance was associated with an extra cost of $2511 per case of *A. baumannii* HAIs compared with patients with susceptible infections. The authors concluded that carbapenem resistance significantly impacts the disease burden regarding excess mortality, long-term ventilator dependence, and medical cost [10]. Recently, Doughty and collaborators conducted a three-month cross-sectional observational study in a 28-bed ICU in China. This study aimed to observe the impact of CRAB infections on the outcome of critically ill patients admitted to the ICU. They collected 5068 samples from the hospital environment and characterized these isolates through whole-genome sequencing. The results revealed that CRAB strains were dominated by OXA-23-producing global clone 2 isolates and were persistently present in the ICU. The hospital environment was heavily contaminated with CRAB isolates, spread to adjacent bed units and rooms following the re-location of patients within the ICU. The authors also observed three horizontal gene transfer events between CRAB strains in the ICU involving three different plasmids [11].

The epidemiological aspects of CRAB strains in healthcare settings underscore the significance of CRAB within ICUs and the urgent need to control the spread of this highly drug-resistant pathogen. Further studies on the effects of antimicrobial stewardship programs in decreasing this burden are warranted.

3. *A. baumannii* Co-Infection in COVID-19 Positive Patients

Amongst the plethora of potential coinfections during COVID-19 pandemic, the interest directed towards *A. baumanii* was due to the efficiency of the pathogen in avoiding antibiotic treatments coupled with the potential in taking advantage of the already weakened immune system of the patients infected with the COVID-19 virus. A recent study conducted in a Serbian hospital aiming to assess the MDR profile and virulence potential of *A. baumannii* isolates from COVID-19 patients admitted to the ICU revealed an increased risk of developing MDR bacterial infections in patients on mechanical ventilation [12]. Therefore, antimicrobial stewardship programs are mandatory in this population. Despite identifying a predominant pulsotype through PFGE analysis, individual *A. baumannii* strains exhibited variations in antibiotic resistance, biofilm formation, binding to mucin, and motility, which may be due to horizontal gene transfer, mutations, or physiological adaptations. Hence, the study highlighted that *A. baumannii* isolates recovered from male patients display higher mucin adhesion ability than isolates originating from females, associated with increased bacterial virulence and poorer outcomes for affected patients [12]. In contrast, an Italian study involving 96 isolates and utilizing both short- and long-read sequencing technologies identified two endemic clones of multidrug-resistant *A. baumannii* responsible for a hospital outbreak during the initial wave of the COVID-19 pandemic. This underscores how the emergency created by COVID-19 disrupted the effectiveness of standard infection prevention procedures [13]. Finally, several studies have identified serum lactate levels, white blood cell count, *A. baumannii* colonization, BSI, and steroid therapy as potential mortality indicators in COVID-19 patients.

Therefore, for COVID-19 patients with prolonged stays in the ICU, the administration of steroids and immunomodulatory drugs should be approached with caution, as they may increase the risk of secondary infections [14]. During the pandemic it has been noted that a co-infection between *A. baumanii* and the COVID-19 virus resulted in a number of complications which brought most ICUs to overload. The most notable would be respiratory infections that would increase the time needed for a patient's treatment, the increased need for trained personnel and infrastructure capable of managing the increased influx of patients. It is to be noted here that the mortality rate during a coinfection was significantly higher than in patients infected with either pathogen on a standalone basis [15,16]. Akgün Karapınar and collaborators conducted a study to assess the microorganisms present in blood cultures from a substantial sample of 22,944 patients, both SARS-CoV-2-positive and SARS-CoV-2-negative. Their primary focus was on understanding patterns of antimicrobial resistance. Within this extensive sample, 1630 samples were found to be culture-positive, indicating the presence of microorganisms responsible for BSI. Out of the patients studied, 652 were identified as having positive cultures. It's worth noting that some patients had multiple positive cultures. Notably, the research revealed that *A. baumannii* and *K. pneumoniae* strains were more frequently detected in patients who tested positive for SARS-CoV-2 than those who tested negative. This implies a potential connection between the presence of the SARS-CoV-2 virus and the distribution of these particular bacterial strains in BSI. The study's findings underscore the significance of ongoing monitoring of the microorganisms responsible for BSI and their susceptibility to antibiotics during a pandemic such as COVID-19. This information is critical for optimizing treatment strategies and ensuring patients receive appropriate care [17].

4. Conclusions

This concise review aims to provide insights into the occurrence of *A. baumannii* coinfections in individuals with COVID-19, utilizing the most up-to-date available information. Patients with COVID-19 may encounter a formidable health risk in the hospital environment: antimicrobial-resistant bacteria like *A. baumannii*, with its carbapenem resistance pattern. Identifying and isolating *A. baumannii* in COVID-19 patients underscores the importance of implementing proper prevention and control measures. This microorganism could potentially have profound and severe implications for the clinical outcomes of these COVID-19 patients. Further research is imperative to explore the characteristics of COVID-19 coinfections and the distribution of microbiological agents, especially *A. baumannii*, to alleviate the socio-economic and psychological burdens associated with these conditions.

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