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ACINETOBACTER SPP. INFECTIONS AMONG COVID-19 CRITICALLY-ILL PATIENTS: SHIFTING UP THE CURRENT AND FUTURE THREATENING LEVELS OF THE VERSATILE OPPORTUNISTIC PATHOGEN

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ABSTRACT

Acinetobacter spp. are bacteria responsible for hospital infections, especially among patients submitted to medical devices like mechanical ventilation and catheters. Severe-ill patients with COVID-19 require hospital care, often in Intensive Care Units. These patients are vulnerable to nosocomial or secondary infections as a consequence of immune system imbalance as a consequence of the acute infection by the SARS-CoV-2. This manuscript aims to analyse the current scientific literature on the impact of infection by species of the genus *Acinetobacter* concomitant to COVID-19 severe-ill patients. Carbapenem-resistant strains of *Acinetobacter* spp. are prevalent almost worldwide, and strains with resistance to Polymyxin, Colistin and other antibiotics emerge as new threats to critically-ill COVID-19 patients. The context of the SARS-CoV-2 pandemic, particularly the use of empirical antibiotic therapy, may contribute to the selection of opportunistic pathogens and promote an increase of multidrug-resistance profiles, leaving as a legacy the proliferation of populations of *Acinetobacter* spp. hard to control in the hospital environment for the near future.

KEYWORDS: COVID-19, SARS-CoV-2, *Acinetobacter* spp., Secondary infections, Multidrug-resistant pathogens.

INTRODUCTION

Multidrug-resistant bacteria are responsible for approximately 700,000 deaths per year worldwide and some studies estimate that this mortality rate will reach 10 million individuals per year by 2050 if new technologies against these pathogens are not developed.[1,2,3,4,5,6,7,8,9] In 2007, the Infectious Diseases Society of America (IDSA) identified five bacterial species with high virulence and multidrug-resistance capacity that are of most concern to public health worldwide, grouping these pathogens under the acronym ESKAPE - *Enterococcus faecium*, *Staphylococcus aureus*, *Klebsiella pneumoniae*, *Acinetobacter baumannii*, *Pseudomonas aeruginosa* and *Enterobacter spp*. These bacteria are responsible for major nosocomial infections in immunocompromised patients or affected by severe diseases, being responsible for bad prognosis and most of the mortality causes to these individuals.[8,10,11,12,13,14] For this same reason, the WHO has included *A. baumannii* in the list of most dangerous bacteria for human health, being classified in the priority group 1, referring to pathogens that pose a critical threat to global public health.[15] *Acinetobacter baumannii* is, among the bacteria in this group, the species more efficient on developing environmental adaptability and multidrug resistance profiles.

Acinetobacter is a genus of small, pleomorphic, Gram-negative, strictly aerobic, catalase-positive, oxidase-negative, non-fermenting and immobile cocobacilli.[12,16,17,18,19] The original studies on *Acinetobacter* spp. found these microorganisms in soil samples collected in 1911 and this bacterium was named *Micrococcus calcoaceticus*. In 1971, the analysis of particular biochemical properties led taxonomists to recognize the genus *Acinetobacter*, whose etymology originates from the Greek A-kinetos-bacter, meaning immobile bacteria.[12]

Acinetobacter spp. are responsible for nosocomial infections, mainly among patients who need the use of medical devices like mechanical ventilation and catheters. Infection by these bacteria can cause pneumonia, septicaemia, urinary tract infection, endocarditis and meningitis.[10] By March 2021, molecular analyses allowed to recognise 65 valid species for the genus *Acinetobacter*.[12] at least 20 of them acknowledged as human pathogens.[20] The species that most frequently cause clinically relevant infections are *Acinetobacter baumannii*, *A. pittii* and *A. nosocomialis*, accounting for 90% to 95% of infections human infections.[20] In the last decade, *A. seifertii*, A. *variabilis*, A. *proteolyticus*, *A. vivianni*, *A. modestus*[20] and *A. ursingi*[21] were identified as pathogens for humans and this fact suggest that a greater number of species of the genus *Acinetobacter* have been acquiring pathogenic properties, pointing to potential public health problems in a near future. Species of the *Acinetobacter calcoaceticus-baumannii* complex are the most prevalent in humans, represented by *A. baumannii*, *A. pittii* and *A. nosocomialis*. Species precise identification through laboratorial methods is quite problematic and many scientific papers refer generically to these three species as *A. baumannii* due to the difficulty in accessing genomic sequencing methods required for the correct species determination.[16]

The increasing concentrations of antibiotics in the natural environment exert a selective pressure and the horizontal gene transfer of antibacterial resistance factors between microorganisms that survive the action of these substances contributes to the perpetuation of multidrug-resistant bacteria. The intrinsic genetic organisation and the fast evolution dynamics of *Acinetobacter* spp. through induced mutation and horizontal gene transfer contributes decisively to the ecological success of their species in an evolutionary way to opportunistic pathogens.[10] *Acinetobacter baumannii* has a wide assortment of multi-drug resistance genetic elements and its genome displays great plasticity. Recent researches show that these species have acquired and accumulated antimicrobial resistance factors from other Gram-negative bacterial species of the genera *Escherichia*, *Salmonella* and *Pseudomonas.* The diversity of biochemical processes and cellular adaptations that ensure resistance to antimicrobial agents has transformed a large number of strains of *Acinetobacter* spp. into hard-to-kill pathogens.[20] *Acinetobacter* has shown successive patterns of adaptability and multi-drug resistance over the years, narrowing the possibilities for treatment with antimicrobial drugs.[10]

An important characteristic of *A. baumannii* is its tendency to cause outbreaks due to its resistance to antimicrobials and its ability to survive in dry environments for a long period. Outbreaks of multidrug-resistant *A. baumanni* have been associated with contamination of healthcare workers' hands and medical devices, as well as hospital environments colonised by this bacterium.[15] Despite being opportunistic pathogens, the mortality rate among hospitalized patients who acquired *A. baumannii* infection is high, ranging from 23% to 68%. Higher mortality rates are associated with an increasing prevalence of Carbapenem and Colistin resistant strains.[12] Overall, *A. baumannii* is considered accountable for more than 12% of cases of nosocomial infections in Intensive Care Units.[15]

Severe-ill COVID-19 patients require hospital admission, often in Intensive Care Units. These patients are vulnerable to nosocomial or secondary infections as a consequence of immune system imbalance as a consequence of the acute infection by the SARS-CoV-2. Co-infections and superinfections generally play an important role in worsening COVID-19, promoting bad prognosis and higher mortality rates.[22] The use of mechanical ventilation can lead to infections associated with this medical device, particularly by multidrug-resistant bacteria such as *A. baumannii*.

This manuscript aims to analyse through the current scientific literature the impact of infections by species of the genus *Acinetobacter* among severe-ill COVID-19 patients.

DISCUSSION

In a review on co-infections and superinfections among patients with COVID-19, Norberg *et al.*[22] revealed that *Staphylococcus aureus*, *Klebsiella pneumoniae*, *Escherichia coli*, *Pseudomonas aeruginosa* and *Acinetobacter baumannii* are the most frequent pathogens causing secondary infections in these patients. Concerns about the increasing levels of *Acinetobacter baumannii* infections in hospital settings were evinced in the last decade. However, the advent of the SARS-CoV-2 pandemic raised the alerts for infection by this bacterium, since it shows multi-drug resistance attributes, easy environmental colonization, increasing virulence patterns and tropism for respiratory tract infections. Further, the deregulation of the immune system of patients who develop the severe forms of COVID-19 is the critical moment for the establishment of opportunistic pathogens such as species of the genus *Acinetobacter*. Beyond the concurrent infection, *Acinetobacter baumannii* and *Acinetobacter nosocomialis* can impair the clinical status of patients with SARS-CoV-2 through inflammatory mechanisms in the epithelial tissue triggered by the extramembranous vesicles bordering the cells of these bacterial species.[23]

Patel *et al.*[6] described an outbreak of multidrug-resistant Gram-negative bacteria in an Intensive Care Unit dedicated to COVID-19 patients of a hospital in Maryland, United States of America. Between May and June 2020 there was a quick increase in cases of this group of bacteria in superinfection, being *Acinetobacter baumannii* the most prevalent, reaching a total of 27 cases in the thirteenth week of the outbreak, and representing 34% of the total Gram-negative bacteria.

The authors related an increased incidence of multidrug-resistant Gram-negative bacteria related to the overcrowding of hospital wards and contamination of medical devices and inert surfaces. Patient redistribution and the adoption of stricter measures to control hospital infection drastically reduced the number of superinfections.

Perez *et al.*[24] investigated a nosocomial outbreak of Carbapenem-resistant *Acinetobacter baumannii* in a hospital in New Jersey, United States of America. Thirty-four cases were reported at the peak of the outbreak and the chronological progression of *A. baumannii* and COVID-19 incidences displayed a statistical symmetry between February and August 2020, suggesting a possible relationship between these infections.

To study the variables related to bacterial superinfection in COVID-19 patients hospitalised in Mexico, Durán-Manuel *et al.*[25] performed a genetic analysis of bacteria of the ESKAPE group in patients, healthcare professionals, medical devices and inert surfaces of an Intensive Care Unit. *Acinetobacter baumannii* was the bacterium with the highest distribution throughout the hospital environment and exhibited clonal affinity in all 64 isolated samples. This *Acinetobacter baumannii* strain was considered multidrug-resistant.

Although the *Acinetobacter* spp. tendency to appear as outbreak events is known since before the SARS-CoV-2 pandemic, this bacterium infects much easier patients with Severe Acute Respiratory Syndrome, by translocation of existing microorganisms in the oral microbiota or by nosocomial contamination through the use of catheters and mechanical respiratory devices colonized by multidrug-resistant strains, turning these microorganisms especially threatening to patients with COVID-19. The outbreak events described by Patel *et al.*[6] and Perez *et al.*[24] and the ubiquity of *A. baumannii* at the hospital environment discovered by Durán-Manuel *et al.*[25] in North America highlight this risk.

An investigation on infections in patients with COVID-19 admitted to Intensive Care Units in a hospital in Rio de Janeiro, Brazil, was conducted by Costa *et al.*[26] Among 191 patients confirmed for COVID-19, 57 (29.8%) developed secondary infections. The pathogen most frequently found was *Acinetobacter baumannii* (28.9%), followed by *Pseudomonas aeruginosa* (22.7%) and *Klebsiella pneumoniae* (14.4%). The researchers highlighted that 96% of the *Acinetobacter baumannii* strains were multidrug-resistant.

The evaluation of infections concomitant to COVID-19 and the mortality rate among critically-ill patients due to this acute viral disease in a hospital in the Province of Minas Gerais, Brazil, was the object of study by Silva *et al.*[27] Among the investigated 221 patients, 64 had infections by several bacterial genera, including *Acinetobacter* spp. in 21 individuals, which corresponds to 32.8% of the total number of secondary infections among COVID-19 patients. It was calculated that the increased risk of death among patients who had secondary *Acinetobacter* infection in severe COVID-19 had an odds ratio of 6.88 compared to the control group. This rate was only lower than that of the group with secondary infections caused by *Staphylococcus* spp.

Lutz et *al.*[28] examined patients admitted to Intensive Care Units of the Hospital das Clínicas in Porto Alegre, Brazil. Among patients admitted to the ICU, 84% revealed colonization by Carbapenem-resistant *Acinetobacter baumannii* and, among these, 79.4% were patients with COVID-19. The multidrug-resistance profile of *A. baumannii* was considered high because 72.8% of the isolated samples were resistant to all the tested antibiotics, and 60.4% of this total came from critically ill SARS-CoV-2 positive patients. When the 30-day mortality rate was measured, 44.1% of the patients infected by *A. baumannii* died, 76.6% of whom were patients with COVID-19.

Oliveira-Sá *et al.*[29] examined the bronchotracheal lavage of patients with COVID-19 submitted to mechanical ventilation who developed pneumonia associated with this medical device in an Intensive Care Unit in Campina Grande, Brazil. Among the 22 examined patients, the most frequent bacteria found was *Acinetobacter* spp. in 39.1% of those examined. The epidemiological findings of Costa *et al.*[26] Silva *et al.*[27] Lutz *et al.*[28] and Oliveira-Sá *et al.*[29] prove an important role of *Acinetobacter* spp. as one of the most frequent secondary infections agents among patients with COVID-19 in Intensive Care Units in Brazil.

Among the systemic infections verified in critically ill patients by COVID-19 in an Intensive Care Unit in Greece, Kokkoris *et al.*[30] pointed out *Acinetobacter baumannii* as the most incident pathogen species. This species accounted for 35% of the superinfection cases with 7 cases: 4 patients infected by multidrug-resistant *A. baumannii* and 3 patients infected by a pandrug-resistant strain.

Protonotariou *et al.*[31] investigated the characteristics of bacterial infections of patients with COVID-19 in a hospital in Greece during the second epidemic wave. Among 1160 hospitalised patients, 122 (10.47%) developed bacteraemia. *Acinetobacter baumannii* was the pathogen most frequently found, in 41.8% of this group of patients, followed by *Klebsiella pneumoniae* (36.88%) and *Enterococcus faecium* (25.41%). The isolated strains of *Acinetobacter* spp. revealed resistance rates higher than 90% for Amikacin, Gentamicin and Sulfamethoxazole-Trimethoprim, and 29.41% for Colistin.

Despotovic et *al.*[32] explain that as the pandemic of COVID-19 progresses, both mortality as a consequence

of secondary infections and the profile of antimicrobial resistance by bacteria in the hospital environment increases, notably in Intensive Care Units. These authors conducted a retrospective survey on medical records of patients admitted to Intensive Care Units due to COVID-19 in Belgrade, Serbia, and analysed the impact of secondary infections on the clinical course of these patients. *Acinetobacter* spp. were the pathogens most frequently identified as the causative agent of superinfections (37.6%), and 72.2% of samples of these bacteria were isolated from the respiratory tract. The pathogen distribution analysis among ICU patients (with and without COVID-19) allowed a flagrant association between *Acinetobacter* spp. as a cause of hospital infection and a affirmative diagnosis for COVID-19 with bad prognosis. Despite demonstrating multi-drug resistance since before the COVID-19 pandemic, *Acinetobacter* spp. did not show significant changes in antimicrobial resistance patterns in the retrospective analysis of the last five years in this health care unit.

Research involving 196 patients admitted with COVID-19 in an Intensive Care Unit of a hospital in Rome, Italy, was conducted by Ceparano *et al.*[33] *Acinetobacter baumannii* samples were isolated from 74 patients (38%). These patients had a mean hospital stay of 24.6 days, slightly more than twice as long as other patients with COVID-19. Phylogenetic analysis disclosed the existence of two strains in the hospital, both multidrug-resistant and sensitive only to Colistin.

Karruli *et al.*[34] investigated coinfection by multidrug-resistant bacteria among patients with COVID-19 in an Intensive Care Unit in Naples, Italy. Among the 32 patients examined, half presented coinfection by multidrug-resistant bacteria, and among them, 19% were positive for *Acinetobacter baumannii*. The isolated samples of this bacterium were resistant to Carbapenem and displayed genomic expressions indicative of high resistance to antimicrobial drugs.

An investigation by Cultrera *et al.*[35] among patients admitted to Intensive Care Units with or without COVID-19 in Ferrara, Italy, showed that among 49 patients without COVID-19 there was no coinfection by *Acinetobacter baumannii* in the year 2020. In the same period, among the 28 COVID-19 inpatients, 17 samples of *Acinetobacter baumannii* were isolated, representing the second most frequent bacterial infection.

The investigation of co-infections among COVID-19 patients at San Raffaele Hospital in Italy showed that 731 patients, 68 (9.3%) had bacterial secondary infections. Among these, 23 were infected by Gram-negative bacteria, with *Acinetobacter baumannii* representing the most frequent species. This bacterium accounted for 30.4% of the incidence of Gram-negative species and 10.3% of the total number of bacterial infections concomitant with COVID-19.[36]

A study on Carbapenem-resistant bacteria in Intensive Care Units of three hospital centres in Italy was conducted by Pascale *et al.*.[37] These researchers indicated that the rate of colonisation by *Acinetobacter baumanni* in patients before the pandemic was 5.1 per 10000 attendances, while in the COVID-19 epidemic the incidence rose to 36.8 per 10000 patients. Among COVID-19 patients requiring mechanical ventilation, the incidence was 11.2 per 10000 patients, and the incidence of *Acinetobacter* infection was 7.2 per 10000 patients, while in the pre-pandemic period no colonisations or infections were reported in the same hospital centres. The researchers further detected that there was an increased incidence of *Acinetobacter baumannii* among critically ill patients by COVID-19 throughout the pandemic. Three strains of *Acinetobacter baumannii* were identified, one for each hospital involved in the research, whose clonal affinity suggests nosocomial superinfections. The profile of resistance to antimicrobial drugs showed that all strains isolated were resistant to Carbapenem, Fluoroquinolone and aminoglycosides; 61.9% were resistant to Sulfamethoxazole-Trimethoprim, but all strains were sensitive to Colistin.

Researchers Leli *et al.*[38] performed a retrospective analysis of infections and colonization by *Acinetobacter baumannii* between 2011 and 2020 and compared it with the prevalence of concomitant infections by this bacterium and SARS-CoV-2 in the General Hospital of Alessandria, Italy. The comparison between the pre-pandemic period and that of the pandemic by SARS-CoV-2 in the year 2020 pointed out that in the pandemic context the incidence of patients colonized by *Acinetobacter baumannii* was almost triple (2.8 times higher). Compared to the previous period. Considering the period from 2011 to 2020, the Meropenem resistance profile had an increasing trend over the years, while Colistin sensitivity remained stable. The researchers concluded that the SARS-CoV-2 pandemic directly influenced the number of multidrug-resistant *Acinetobacter baumannii* isolates.

Duployez *et al.*[39] stated that coinfection by *Acinetobacter* spp. is underestimated and that the viral pandemic of SARS-CoV-2 may hide possible outbreaks of other pathogens. These authors investigated an outbreak of *Acinetobacter baumannii* that occurred in five Intensive Care Units in a teaching hospital in France between March and May 2020. A total of 21 patients were diagnosed with *Acinetobacter baumannii* and all samples examined showed the same pattern of antibiotic resistance (beta-lactamase resistant, including Imipenem, aminoglycosides and quinolones, with sensitivity only to Colistin). This homogeneity in the antibiotic resistance profile suggests superinfections of nosocomial origin, reinforced by the fact that all these patients required mechanical ventilation. The main site of infection was the respiratory tract (71.4%) and 12 patients developed generalised infection (57.2%). The total of patients with

concomitant infection by *Acinetobacter baumannii* was 28.6%.

Acinetobacter spp. strains in Europe mostly exhibit sensitivity to Colistin[33,34,37,38,39] and Despotovic *et al.*[32] affirm that sensitivity to Colistin remained constant since the pre-pandemic period. However, research by Protonotariou *et al.*[31] demonstrating that almost one-third of *Acinetobacter* spp. samples isolated from patients with COVID-19 in Greece in the second wave of the pandemic is resistant to Colistin alert to a possible change in the resistance profile in the continent. The bacterial sensitivity profile of species of the genus *Acinetobacter* can experience changes soon with the spread of Colistin-resistant strains by the ease of cross-border transit of individuals from the European Union and the transfers of critically ill patients by COVID-19 between hospital units of the block countries under the Emergency Support Instrument program to avoid the collapse of national health systems.[40]

According to Li et *al.*[41] a considerable number of patients hospitalised for COVID-19 acquire secondary microbial infections. These researchers examined 1495 patients hospitalised with COVID-19 in Wuhan City, China, of whom 102 (6.8%) acquired secondary infections and the most frequently isolated bacterium was *A. baumannii*, with 35.8% incidence. Among the isolated strains, 91.2% were resistant to Carbapenem.

A survey on fungal and bacterial infections simultaneous to COVID-19 among patients admitted to Intensive Care Units in China was performed by Yang *et al.*[42] These authors stated that the most prevalent bacteria among patients entering Intensive Care Units after 12 days of admission were *Staphylococcus aureus* and *Acinetobacter baumannii*. *A. baumannii* was identified by RT-PCR in 20% of the coinfection cases. The higher incidence among patients with late admission in Intensive Care Units when compared to the group of patients with shorter hospital stays indicates the probability of superinfection by *Acinetobacter baumannii* in the hospital environment.

According to Endraputra and Khoendori,[43] the prevalence of Carbapenem-resistant *Acinetobacter baumannii* in January 2020 was 43%, and as the COVID-19 pandemic progressed it reached 50% in June 2020 in a hospital in the city of Surabaya, Indonesia. Retrospective analysis showed a significant and steady upward trend from April 2020, one month after the COVID-19 outbreak hit the locality. The authors point out that the antimicrobial drug resistance profile is alarming among the isolated *Acinetobacter baumannii* samples in superinfections in this hospital.

Sharifipour *et al.*[44] examined 19 patients admitted for COVID-19 in an Intensive Care Unit in Iran. All patients were positive for secondary bacterial infections, of which 17 (90%) were positive for *Acinetobacter baumannii*. Antimicrobial drug sensitivity testing demonstrated a high level of resistance to these drugs. The strains were resistant to all the antibiotics tested, except for a parcel of 48% of the isolated strains that were sensitive to Colistin. All patients who presented *Acinetobacter baumannii* infection during COVID-19 treatment evolved to death. The results presented by Sharifipour *et al.*[44] are extremely worrying since the emergence of Colistin-resistant strains in Iran,[45] one of the last therapeutic alternatives to multidrug-resistant *Acinetobacter* spp. may extinguish therapeutic options to the treatment of this microorganism especially disturbing in concurrent infection in severe SARS-CoV-2 infections.

The clinical profile of generalized infections in patients with COVID-19 in 750 patients admitted to Intensive Care Units of a hospital in Rajasthan, India, was investigated by Palanisamy *et al.*[46] Of the total examined, 8.5% developed systemic infections, mostly by Gram-negative bacteria (82.8%). *Acinetobacter baumannii* accounted for one-third of the total systemic infections (32.8%), being the most incident pathogen. The profile of bacterial resistance to Ceftriaxone (76.2%) and Piperacillin-Tazobactam (76.2%) was considered high.

A retrospective data analysis of 600 patients hospitalised for COVID-19 in India was evaluated by Krithika-Varshini *et al.*[47] for secondary infections. A total of 37 patients had bacterial coinfection to COVID-19, and among the 21 individuals with respiratory tract infection, the most frequent pathogen was *Acinetobacter baumannii* (45.8%). All strains of *A. baumannii* were considered multidrug-resistant.

Saini *et al.*[48] analysed antimicrobial resistance profiles in bacteria isolated from COVID-19 inpatients at a hospital in Delhi, India. The researchers compared microorganisms isolated between March 2019 and December 2019 with isolates obtained from COVID-19 patients between March 2020 and December 2020. The authors pointed to an increased incidence of *Acinetobacter baumannii*, which was the predominant bacterium in the pandemic period in coinfection with SARS-CoV-2. Analysis of the antimicrobial sensitivity profile displayed a trend towards a reduction in the number of strains susceptible to Gentamicin, Amikacin and Ciprofloxacin, and an alarming decline in susceptibility to Cotrimoxazole and Piperacillin-Tazobactam. *Acinetobacter baumannii* infections in COVID-19 critically ill patients were associated with the use of mechanical ventilation in Intensive Care Units and a high mortality rate.

Halder *et al.*[49] evaluated bacterial isolates among patients admitted to a hospital in Kolkata, India. Eighteen patients with COVID-19 and 12 uninfected with SARS-CoV-2 were examined. Among patients with COVID-19, 5 (27.8%) exhibited colonization by

Acinetobacter spp. while in the group not infected with SARS-CoV-2 only 1 individual (8.3%) was colonized by this bacterial genus.

A survey involving 144 patients admitted with severe COVID-19 in an Intensive Care Unit in Pakistan was conducted by Tayyab *et al.*[50] Blood culture analysis was positive for bacteria in 44.7% of patients. The most frequent species was *Acinetobacter baumannii* (51.16%), followed by *Klebsiella pneumoniae* (23.25%) and *Enterococcus faecium* (13.9%). The antibiogram showed that strains of *Acinetobacter baumannii* were resistant to all the tested antibiotics, except Minocycline, Colistin/Polymyxin E and Tigecycline, which resistance rates were 9.2%, 33.3% and 66.6% respectively.

Sharma *et al.*[51] bacterial secondary infections among 814 patients admitted with COVID-19 in a hospital in the north of India. A total of 17.9% of cultures were positive for bacteria. In this group, 74% of patients were found to have secondary bacterial infection after 48 hours of hospitalization and 26% were diagnosed with bacterial infections on admission to hospital. Among the pathogens isolated, species of the genus *Acinetobacter* were the most incident (35.6%), followed by *Klebsiella pneumoniae* (18.1%). *Acinetobacter* spp. was the most frequent pathogen in both respiratory tract infections and systemic infections. Carbapenem-resistant strains of *Acinetobacter baumannii* constituted 65.4% of the isolates of this bacterium, while Colistin-resistant strains were 17.3%. The authors related that the infection patterns among COVID-19 patients follow the same profiles observed in patients admitted to other Intensive Care Units not dedicated to COVID-19 in the same hospital.

Secondary infections by species of the genus *Acinetobacter* can be considered frequent in the Indian subcontinent and Iran, and although heterogeneous antimicrobial drug resistance profiles are possible among the various regions that make up this geographic cluster, all research demonstrates the prevalence of multidrug-resistant strains.

The complexity of the control of the *Acinetobacter* spp. in the hospital environment involves patients, health professionals, equipment and colonized inert surfaces, imposing the urge of measures of better effectiveness in the disinfection, people circulation and personal contact, periodicity of control of secondary infections and the adoption of protocols of verification of the sensibility to the antibacterial drugs of the circulating strains of this bacteria in the environment of attention to the health. The standard of prophylaxis measures to *Acinetobacter* spp. already tried out before the COVID-19 pandemic provides for the use of a closed tracheal suction system for patients receiving mechanical ventilation, hand decontamination using alcohol gel, frequent and effective disinfection of the environment, and the inhaled use of Polymyxin B for patients with evidence of pneumonia.[52] These measures should be reinforced in the basic protocols in the use of mechanical ventilation equipment in patients with SARS-CoV-2, based on the evidence pointed out by Sharma *et al.*[51] Despotovic *et al.*[32] and Karatas *et al.*[53] that *Acinetobacter* spp. was the most incident species among SARS-CoV-2 infected and in control group patients, considering that a large part of the strains of this bacterium isolated in hospital settings present high rates of multidrug resistance and easy environmental dispersion, characterized by the local phylogenetic homogeneity observed in patients in several studies.[25,33,37,53] The isolation of patients with colonization by *Acinetobacter* spp. in separate wards from other patients with COVID-19 and the redistribution of patients to avoid overcrowding of hospital environments were measures indicated by Patel *et al.*[6] that, together with stricter controls in asepsis, were successful in controlling an outbreak of *Acinetobacter* spp. and should be replicated in similar occasions.

The literature review indicates that most strains of *Acinetobacter* spp. circulating in hospitals and Intensive Care Units that treat patients with COVID-19 have high levels of bacterial resistance, especially to Carbapenem. Although a reasonable number of isolated strains show sensitivity to Colistin, mainly in Europe[33,37,39,50] the emergence of strains resistant to this antibiotic[12,31,44,45,50,51] further narrows the possibilities for treatment and control of secondary *Acinetobacter* spp. infections in the context of COVID-19.

Species of the genus *Acinetobacter* own unique evolutionary characteristics, such as high levels of induced mutation and horizontal gene transfer.[10] Their genome plasticity and fast adaptability to hostile conditions, accumulating antibiotic and disinfectant resistance genes, was already of concern before the COVID-19 pandemic. The pandemic context added extra elements to the challenge that *Acinetobacter* spp. represents: greater movement and rotativity of patients in hospital units, more intense use of invasive equipment such as mechanical ventilation and catheters, little time for ambient disinfection due to the high turnover of patients and the sudden increase of critically ill patients by SARS-CoV-2 infection whose hallmark characteristic is the deregulation of the immune system, paving the way for opportunistic infections. Moreover, the transfer of patients between hospital units is a known factor of diffusion of multidrug-resistant strains,[54,55,56,57] and in the case of microorganisms that show high intrinsic adaptability for resistance to chemical aggression such as *Acinetobacter* spp. this problem is even more serious since bacterial conjugation mechanisms add and accumulate resistance patterns among communicating strains and local strains can present different genomic patterns.[37] The transfer of patients for various reasons is a common and unavoidable event in the care of individuals who need medical attention, even more pronounced during a pandemic. This conjuncture drives

the increased rate of infections by opportunistic pathogens, and empirical antibiotic therapy used to prevent infections secondary to COVID-19 results in increasing selection of multidrug-resistant strains in the hospital environment and among hospitalized patients.

Bassetti *et al.*[58] alert that the urgency in facing a new viral pathogen, little known and with impact on the world population, focusing scientific efforts on the processes of clinicopathological evolution of SARS-CoV-2, and neglected the role of secondary infections in the clinical analysis. Pemán *et al.*[59] also alerts to the low number of bronchoscopies and necropsies performed after the death of patients with COVID-19 due to the production of aerosols during these procedures, since it may disseminate the virus in the environment, but makes the post-mortem diagnosis of the extension of secondary infections that may have contributed to the death unfeasible. It is possible that the real impact of secondary infection by *Acinetobacter* spp. in patients with COVID-19 is underestimated, although it is one of the pathogens most frequently associated with hospital infections even before the SARS-CoV-2 pandemic.

Although the distribution of the incidence of *Acinetobacter* spp. infections is unequally distributed in different regions of the world[15] and seasonal climatic factors influence infection rates,[60] there is the possibility of geographic expansion of more adapted strains and the expansion of incidence rates in places little impacted by these bacteria in public health. *Acinetobacter* spp. share potential attributes of virulence, adaptability, environmental colonization and resistance to antibiotic drugs comparable to the observed in the fungus *Candida auris*,[61] another opportunistic pathogen that has expanded its incidence explosively in recent years in parallel to the pandemic of COVID-19, with a confirmed presence today in all continents.

CONCLUSIONS

Several factors contributed to the dissemination of *Acinetobacter* spp. in hospital environments in the context of the pandemic of COVID-19. Overcrowding of wards with hospitalized patients due to the increased number of cases of SARS-CoV-2 infection, with special attention to Intensive Care Units, may have favoured the communication of strains among patients. Empirical antibiotic therapy in patients with COVID-19 may have selected multi-drug resistant strains that colonize the hospital environment, medical equipment, patients and healthcare professionals. The delay of bacteriological diagnosis and antibiogram tests - or even the non-performance of these diagnostic methods - may contribute to the late or ineffective use of antibiotics, supporting the persistence of bacterial infection in hospitalized patients and increasing the chance of environmental dissemination of these strains during treatment of COVID-19.

Clinical management protocols for patients with severe COVID-19 indicate preventive antibiotic therapy as part of the optimal treatment routine. We emphasise that these measures have diminished effectiveness in the case of secondary infections by multidrug-resistant bacteria in patients with COVID-19 and that efforts should be more focused on early detection and determination of the aetiology of concomitant infections, determination of the antibiotic susceptibility profile for appropriate drug therapy, and improved disinfection of the hospital environment.

Characteristics of the genus *Acinetobacter*, such as quick evolution through induced mutation and high rates of horizontal gene transfer, especially of multidrug resistance factors, raise the level of concern about this pathogen. Carbapenem-resistant strains are prevalent in several regions of the world and strains with resistance to Polymyxin, Colistin and other antibiotics emerge as new threats. The progressive pattern of antimicrobial drug resistance, reducing therapeutic options, is a current challenge. The conjuncture of the pandemic of COVID-19, however, may contribute to an acceleration of multidrug resistance profiles and leave as a legacy the proliferation of populations of *Acinetobacter* spp. difficult to control in the hospital environment in a near future.

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