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Multidrug-Resistant Bacteria Related to Covid-19 Infection: A Minireview

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ABSTRACT

The World Health Organization recorded antimicrobial multidrug resistance as one of the biggest health risks in 2019. The inappropriate use of antibiotics results in their consequent ineffectiveness in the treatment of bacterial infections, hindering therapeutic alternatives and increasing the risk of poor prognosis. In late 2019, a single-stranded RNA zoonotic virus, SARS-CoV-2, was identified and caused the Coronavirus Disease-19 pandemic. The use of antibiotics prophylactically for secondary bacterial infections was one of the measures taken in the emergency scenario. The damage to the airways caused by these viruses and inhibition of the immune system favor bacterial adhesion and growth in the respiratory tract, the lack of knowledge of the disease and the initial symptomatic similarity between bacterial and viral infections, generating controversial diagnosis, causing concern about the impact on the worsening of the global condition of multidrug-resistant bacteria. More research aiming new treatments and control alternatives in cases of bacterial co-infection associated with COVID-19 and its possible markers is needed, as well as investigations of the possible impact of the pandemic on the global scenario of acquired multidrug resistance. Immunization of the population and individual respiratory stabilization effort and measures are still the only known protective measures. In the pandemic scenario characterized by a high use of biocidal agents, empirical and disordered use of antibiotics, decreased surveillance of resistance worldwide and overcrowding of health systems, lack of medical staff and personal protective equipment in some hospitals are factors that have contributed to the increase in antimicrobial resistance incidence. On the other hand, individual protective measures were identified as factors that reduce the incidence of infections in the community. In some countries, the increasing in the incidence of carbapenem-resistant bacteria and new genes and combinations have been reported, which may be related to the COVID-19 pandemic.

Keywords: Multidrug Resistance; Antibiotics; Bacterial; Co-Infection; COVID-19; Secondary Infections

Abbreviations: TLR4: Toll-Like Receptor 4; ARDS: Acute Respiratory Distress Syndrome; IL-6: Interleukin-6; ICU: Intensive Care Units; WHO: World Health Organization; HAI: Healthcare-Associated Infection; ESBL: Extended-Spectrum ***b***-Lactamase-Producing Klebsiella Pneumoniae; MRSA: Methicillin-resistant Staphylococcus Aureus; NLR: Neutrophil/Lymphocyte Ratio; PCT: Procalcitonin; CRP: C-Reactive Protein; ROS: Reactive Oxygen Species

Introduction

Native bacterial resistance to antibiotics is a natural selective pressure event that is currently a problem faced worldwide. Nevertheless, the inappropriate use of these classes of drugs results in treatment failure of infections, hindering therapeutic alternatives and increasing the risk of worsening the condition and spreading diseases. Multidrug-resistant bacteria is considered a pathogen that is not sensitive to three or more classes of antibiotics. The World Health Organization (WHO) recorded antimicrobial multidrug resistance as one of the biggest health risks in 2019. Some of the causes for this acquired resistance are misinformation about the function of antibiotics, leading part of the population to self-medicate to treat common viral infections, inadequate prescription due to inaccurate diagnosis,

pollution of the environment with antibiotics and their use in the treatment of animals in areas such as veterinary, and agriculture [1-4]. SARS-CoV-2 (Severe Acute Respiratory Syndrome Coronavirus 2) is a single-stranded, positive-sense RNA zoonotic virus identified in late 2019 in Wuhan, China, which spread around the world rapidly, causing a pandemic of the disease called Coronavirus Disease-19 (COVID-19). Immunization of the population is still the only known protective method, in addition to the individual respiratory support that was initiated and recommended as soon as the identification of disease. The world scenario has more than 700 million confirmed cases and more than 6 million deaths reported by WHO, as well as more than 13 billion vaccine doses applied to the population.

The most severe cases of infection require mechanical ventilation and intensive care treatment, with prolonged stays in the hospital environment, which characterizes a very increased risk and predisposition to secondary and opportunistic infections [2,5,6]. In the first phase of the pandemic, from December 2019 to June 2020, antibiotic prescription reached 82.3%, in contrast to 39.7% in the second phase, between June 2020 and March 2021, according to a study by Cong et al. published in 2022 [7]. These data can be explained by the prophylactic use of antibiotics for secondary bacterial infections, which can be corroborate by increased mortality rates from co-infections described after analysis of autopsy data and case studies of the influenza pandemic in 1918. The lack of knowledge of the disease and the initial symptomatic similarity between bacterial and viral infections cannot be ruled out, generating diagnostic misunderstanding, in addition to the high mortality rate 3, [8-10]. As the COVID-19 pandemic gradually accelerated, the investigation of highly effective drug therapies became a major debate in the scientific community. Azithromycin, for example, became one of the antibiotic alternatives raised to combat the syndrome caused by SARS-CoV-2 due to its immunomodulatory properties that were considered promising. Another possibility investigated was hydroxychloroquine, which is used for rheumatoid arthritis, lupus and malaria. Subsequently, studies concluded that both drugs did not have beneficial properties in the treatment of the disease [11-13].

The study by Rawson et al., published in May 2020, describes that 72% of patients were prescribed with antibiotics, although only 8% had confirmed bacterial co-infection after analyzing cases of predominantly Asian infections. It is still difficult to determine whether the conditions of patients infected with COVID-19 who died worsened before or after the bacterial infection acquired during hospitalization in Intensive Care Units (ICU). The interaction of SARS-CoV-2 with other pathogens is still poorly defined in the literature, as well as the impact of acquired resistance in the general public7, [14,15]. The aim of this review is to identify and correlate cases of infection of multidrug-resistant bacteria and the SARS-CoV-2 virus. In particular, addressing the effects of the use of antimicrobials empirically in patients with severe respiratory syndrome infected by antibiotic-resistant pathogens associated with COVID-19. The investigation of diagnosis methods and therapeutic approaches can contribute to a better understanding of the impact on the global scenario of bacterial multidrug resistance.

Materials and Methods

The present work is a narrative review of the literature relating multidrug-resistant bacteria and COVID-19, considering the co-infection scenario, as well as the impact on the development of acquired resistance of these bacteria. The following descriptors were used to carry out this study: "COVID-19", "bacterial", "co-infection", "SARS-CoV-2", "resistant", "resistance", "antibiotic", "antimicrobial". At first, the exclusion was made by the titles, resulting in 286 selected and, by eliminating the duplicates, 190 articles were obtained. Of the selected publications, 7 were paid articles. In the end, 81 articles were read partially, 109 in full, and 54 were included in this study.

Results and Discussion

Studies with humans and published in the period from 2020 to 2023 in the PubMed database, obtained 1290 results. Of these, 835 articles were found in the time frame between January 2022 and May 2023 SARS-CoV-2 is responsible for several systemic complications and injuries, differentiating it from other members of the Coronoviridae family, such as: Pulmonary, renal, pancreatic, cardiac, brain, hepatic, and coagulation disorders. Epithelial cells infected by this virus produce inflammatory cytokines such as interleukin-6 (IL-6) and interleukin-8 (IL-8). The activation of these cytokines is linked to lungs infiltration by inflammatory cells and induction severe lung injury [16]. Co-infection Bacterial infections are related to an increased mortality rate of respiratory viral primary infections. The study by Na and colleagues revealed a rate of more than doubled in-hospital mortality in patients with severe COVID-19 and secondary infections. The damage to the airways caused by the viruses added to the inhibition of the immunology favors the adhesion and bacterial growth in the airways. The inflammation resulting from the cellular damage caused by SARS-CoV-2 infection in lung epithelial cells promotes severe tissue detriment due to bacterial adhesion, invasion, and proliferation. The SARS-CoV-2 spike protein binds to the bacteria's lipopolysaccharides, increasing anti-inflammatory activity. Acute Respiratory Distress Syndrome (ARDS) is a systemic inflammatory reaction found in severe infections, pneumonia, COVID-19 and activation of the Toll-Like Receptor 4 (TLR4) by lipopolysaccharide stimulation during ARDS causes the pro-inflammatory phase, with high releases of cytokines, acute-phase proteins, and reactive oxygen species [17-20].

Cytokine release syndrome or cytokine storm, defined as the elevated release of pro-inflammatory cytokines, resulting from the activation of dendritic cells, lymphocytes (T), neutrophils, macrophages. Cytokine storm is an excessive response to SARS-CoV-2 and has been recognized as a cause of death in COVID-19. It results from the association of molecules such as interleukins, interferons, chemokines, and TNF-α in patients with COVID-19. A significant elevation of inflammatory markers were observed in patients who received antibiotics,

which Have been pointed out as a possible aggravation of the cytokine storm caused by COVID-19 [16,21,22]. Bacteria are able to successfully cause secondary infections in COVID-19 by their virulence factors, such as membrane proteins, secretory systems, adhesins, and glycoconjugates. Bacteria are considered resistant to a specific antimicrobial when the recommended dose is unable to kill it or inhibit its proliferation.

The mechanisms of bacterial resistance can be summarized as follows:

1. Alteration of the site of action of the antibiotic,

2. Drug inactivation,

3. Expulsion of substrates from the interior of the bacterium to the external environment by an efflux system and

4. Alteration in membrane permeability. Acquired resistance is characterized as the alteration of the microbial cell site, antibiotic inactivation, and efflux system.

Gram-positive bacteria mostly adopt the method of decreasing membrane permeability, while gram-negative bacteria can use all four mechanisms. In addition, gram-negative bacteria have a layer of lipopolysaccharides that promotes innate resistance to several groups of antibiotics [20,23]. Bacterial co-infections are often common complications of respiratory infections and are associated with prolonged hospital permanence and increase in ICU admittance and mechanical ventilation. In the study by Patton et al., a high mortality rate of 24% for bacterial co-infections was observed compared to the 5.9% mortality rate for community-acquired pneumonia (CAP) in the pre-pandemic times. Community-acquired bacterial infections confer even greater risks of ICU admission and mechanical ventilation than advanced age and comorbidities, which have been identified as risk factors for COVID-19 mortality. The study by Tiseo et al. conducted in Italy found higher comparative rates of chronic obstructive pulmonary disease (20% vs. 10.2%), chronic kidney disease (24.4% vs. 7%), cerebrovascular disease (22.2% vs. 11.8%), higher sputum frequency (11.1% vs. 2.8%), and PaO2/FiO2 ratio <200 (17.8% vs. 5.4%) between patients with and those without respiratory co-infections, respectively. The rate of co-infections in hospitalized patients with COVID-19 was 8% in this study and was associated with a high risk of progression to severe disease [24-26]. The prevalence rate of co-infection varies in published articles, but it is as high as 50% among non-COVID-19 survivors. Studies show that the risk of acquiring bacterial infection increases according to the severity of COVID-19 and the length of hospital permanence, in which case it is called Healthcare-Associated Infection (HAI). In addition, microbiology differs between HAIs and community-acquired infections [27,28].

Bacterial Species Related to Covid-19

The study by Gu et al. published in 2020 points out that the diversity of the gut microbiota is reduced in patients infected with SARS-CoV-2, with an increase in opportunistic pathogens such as *Streptococcus, Rothia, Veillonella,* and *Actinomyces*. In addition, a significant increase in *Enterococcus sp*. in the gut microbiota, blood infections after ICU admission, especially *E. faecalis and E. faecium* in studies in Italy [27]. In HAIs, the antibiotic-resistant pathogens found in association with COVID-19 were: carbapenem-resistant *Acinetobacter baumannii*, Extended-Spectrum β-Lactamase-Producing *Klebsiella* Pneumoniae (ESBl), vancomycin-resistant Enterococcus, and other members of the New Delhi-producing Enterobacteriaceae family Metallo-β-lactamase (NDM) that confers resistance to carbapenem, and *Methicillin-Resistant Staphylococcus Aureus* (MRSA). *S. aureus* was associated with both HAIs and community-acquired infections in the 2021 study by Garcia-vidal et al., as was *Escherichia coli* and *Klebsiella pneumoniae* in the urinary tract. In this study, the species *Streptococcus pneumoniae, Pseudomonas aeruginosa, Enterococcus faecium* and *Haemophilus influenzae* were also identified, with the former and latter being associated only with community-acquired infections [27]. The prevalence of *Acinetobacter baumannii* and *Klebsiella pneumoniae* is remarkable and has been reinforced by several studies. The acronym ESKAPE encompasses the pathogens *Enterococcus faecium, Staphylococcus aureus, Klebsiella pneumoniae, Acinetobacter baumannii, Pseudomonas aeruginosa* and species of the genus *Enterobacter spp.* which are known for their association with nosocomial infections and mechanisms of multidrug resistance to antibiotics [29].

A. baumannii resistant to carbapenems (CRAB) is on the WHO list of greatest threats to human health. *A. baumannii* is intrinsically resistant to penicillin and may acquire resistance to all antibiotics used to treat gram-negative drugs, including fluoroquinolones, aminoglycosides, and cephalosporins, as reported in studies in Table 1. Carbapenems are widely used in the treatment of *A. baumanii*, but some mechanisms of resistance against these antibiotics have been extensively reported and, for that reason polymyxins have been considered the first choice for the treatment of infections caused by CRAB [29]. Infections caused by *K. pneumoniae* and *E. coli* are associated with high mortality risks, possibly due to a lack of effective treatments. The main species carrying carbapenemase are *K. pneumoniae, E. coli*, and *Enterobacter spp* and have been linked to infections in the COVID-19 pandemic. *K. pneumoniae* is the most common enterobacterium related to the spread of ESBL and is responsible for the majority of human infections [29]. *P. aeruginosa* has several virulence factors, in addition to bacterial resistance genes possibly conferred by plasmids, and adaptability to numerous adverse conditions including the immune response. This pathogen has been reported to be significantly elevated in the nasal microbiota of patients infected with SARS-CoV-2. It causes a high risk of mortality, despite its variable resistance in different regions and the high incidence colistin-sensitive diseases caused by *P. aeruginosa* in hospitals around the world [29]. *S. aureus* has a marked virulence factor called coagulase, which is used for laboratory identification and is the main agent of blood, cutaneous, and lower respiratory tract infection. Some patients had *S. aureus* co-infection

after hospitalization for COVID-19, some were infected with methicillin-resistant S. aureus (MRSA) and also methicillin-sensitive *S. aureus* (MSSA). The resistance of *S. aureus* seems to be due to several mechanisms, such as horizontal gene transfer by plasmids, changes in the target site, and enzyme production [29].

Table 1: Most Frequent Bacterial Species and Multidrug Resistance Rates in COVID-19 Patients.

Most Frequent Species	Total	MR rate	Resistance	Study
P. aeruginosa; S. aureus, K. pneumoniae, E. Coli	55	31%	NOT	29
Klebsiella spp., E. Coli	38	42%	CKD; fluoroquinolones; aminoglycosides; colistin	30
K. pneumoniae; A. baumannii. E. coli; P. aeruginosa; ECN (S. haemolyticus e S. epidermidis); S. Aureus	457	NOT	Carbapenem (meropenem); ESBL; third- generationcephalosporin; oxacillin (MRSA); aminoglycoside; lincosamide; fluoroquinolones; macrolides	31
K. pneumoniae; E. coli. A. baumannii; S. aureus. S. Pneumoniae	87	65,5%	ESBL; aminoglycoside; fluoroquinolones; beta- lactamic; cefepime; gentamicin	32
A.baumannii; K. pneumoniae; P. aeruginosa; Enterobacter spp.	115	43%	ESBL; beta-lactamic; ciprofloxacin; gentamicin	33
A. baumannii,K. pneumoniae, Enterococcus faecium, S. aureus, P. aeruginosa, and Enterobacter spp.	93	74.2%	NOT	34
K. pneumoniae; A. baumannii; E. faecium	38	NE	NE	28

Note: Legends - MR RATE: Multidrug resistance rate among total bacterial infections; TOTAL: Bacterial infections occurring in COVID-19 patients; NE: Not specified; ERC: Carbapenemase-resistant Enterobacteriaceae; NEC: Coagulase-negative staphylococci; ESBL: Stretched-Spectrum Beta-Lactamase; MRSA: *Staphylococcus aureus* resistant to meticilina.

Markers for Detection of Secondary Infections

One of the obstacles encountered is determining whether the bacterial infection occurred before or after admission, mainly due to the inability of most patients to produce sputum for culture at the time of arrival at the hospital. In addition, it is difficult to detect secondary infections or co-infections or to easily identify the exact pathogen because the symptoms of COVID-19 are similar to those of bacterial pneumonia [30]. The average time described for detection of secondary infections is 10 days. The most effective method was bronchoalveolar lavage cultures, but it is commonly avoided by the production of aerosols. Thus, sputum cultures and endotracheal aspirates are performed, although studies report that there is no increase in risks to health professionals when performing bronchoscopy [31]. Lymphocytopenia usually occurs within two weeks of the onset of COVID-19 and can result in immune dysregulation and immunodeficiency promoting secondary infections. The study by Chong et al. found a mean value of three to four days for the lowest lymphocyte levels and pointed out that the use of corticosteroids may have contributed to lymphocytopenia. Alnimir et al. found lymphocytopenia in 39 (57.4%) non-survivors. Wu et al. also pointed out that severe immunosuppression marked by low lymphocyte count is associated with mortality risk [28,32-34]. In addition, the administration of medications such as steroids, immunomodulatory agents, and antibiotics can also increase the occurrence of secondary hospital-acquired infections.

The use of corticosteroids to control local inflammation was mentioned and related to consequent immunosuppression in the studies by Gottesman et al. and Wu et al and Ceballos et al. In those studies, authors described that patients who used corticosteroids before admission to the hospital and were exposed to dexamethasone during hospitalization were associated with a higher risk of secondary infections than those who were not exposed in a bivariate analysis [25,34-37]. The Neutrophil/Lymphocyte Ratio (NLR) is a simple and

low-cost marker of systemic inflammation, with its desirable values averaging below 2. It is obtained by dividing the absolute values of neutrophils by the absolute count of lymphocytes used in the prognostic evaluation of clinical conditions. NLR increases due to reduced lymphocyte count associated with increased neutrophil count. Levels above 2 suggest a reduction in lymphocyte count or a progressive increase in neutrophil count, which is a marker of worsening of the clinical condition of patients. The likelihood of bacterial co-infection is increased in patients with ≥ 15 NLR within 48 h of hospital admission [24,38-40]. Procalcitonin (PCT) is a peptide or prohormone precursor to calcitonin normally synthesized by the thyroid and, in case of bacterial infection, by other tissues. It is used to screen for bacterial infections and sepsis because it is a biomarker that is generally higher in bacterial infections compared to viral infections, in which the elevation is minimal, and is promising for differentiation.

Normal PCT levels are below 0.1 ng/mL and studies support that an increase above 0.25 ng/mL indicates elevated chances of bacterial infection of the respiratory tract. Increased procalcitonin may indicate bacterial co-infection in patients with COVID-19. The study by Carbonell et al. found that values of up to 0.3 ng/mL of PCT could help rule out bacterial co-infection on admission with a NPV (Negative Predictive Value) of 91.1%. This finding is also supported by the studies of Dolci et al. and May et al. who found the threshold to be up to 0.25 ng/mL with a NPV of 91.7% and 99%, respectively. The study by Alnimr et al. points out that PCT levels were higher at hospital admission among non-survivors compared to survivors 39,43,46. However, approximately 36% of patients with chronic kidney disease have an elevated PCT value of 0.5 ng/mL or above. Some studies also suggest the relationship between elevated PCT and elevated IL-6 release as a result of the cytokine storm caused by SARS-CoV-2, decreasing the discriminatory capacity of PCT. ARDS in patients with COVID-19 can also increase the levels of this marker, as well as clinical conditions of biliary pancretitis, fungal infections, lung carcinoma, among others. However, although PCT is not a reliable marker of the presence of bacterial co-infection, its dosage of up to 0.25 ng/mL is indicative of its absence and is an aid to avoid inappropriate treatment with antibiotics in patients infected with SARS-CoV-2 [38,41-43]. Among the advantages of using procalcitonin as an inflammatory marker, it can be also considered the absence of interference of its levels with the use of corticosteroids, rapid elevation after induction, high sensitivity, and simple dosing through a blood sample [38].

The use of the CURB-65 score to discern between intermediate-risk patients who may need early antibiotic administration to standardize treatment was suggested by Giannella et al. This marker have already been reported to be higher in patients with secondary infections than in those not infected at the time of hospital admission in the study by Na et al. In the study by Giannella et al., leukocyte counts, TSPs, and the Charlson index were also used to guide diagnostic tests and antibiotic use. It is recommended to use antibiotics in patients with CURB-65 >2 [40,44]. C-reactive protein (CRP) is an acute inflammatory protein synthesized mainly in the liver after IL-6 stimulation. It plays an important role in the response to infections and can stimulate the inflammatory process through mechanisms such as activation of complement life, induction of phagocytosis and apoptosis, regulation of nitric oxide synthesis, stimulation of inflammatory cytokine production, and leukocyte chemotaxis and recruitment. It is a nonspecific biochemical marker of the acute phase and has little specificity because it is elevated in several pathologies, and is not very useful for differentiating inflammation from infection. Among the factors that can cause changes in serum CRP levels are age, gender, weight, smoking, dyslipidemia, liver damage, and hypertension. The use of corticosteroids is associated with lower induction of CRP by Carbonell et al. and Schouten et al. while PCT remains unchanged, in addition to the slower elevation of CRP levels compared to PCT.

In healthy patients, the blood concentration of CRP is less than 5 mg/L. Its serum levels are directly associated with the severity of COVID-19 and worse clinical outcome. Patients with elevated CRP levels at the time of admission were associated with a higher risk of disease severity and of developing secondary pulmonary infections [31,38,41,43]. Several studies have demonstrated the correlation between CAP severity and PCT and CRP. In the study by Schouten et al., secondary increases in CRP and PCT were associated with superinfections such as COVID-19 complications, but the use of tocilizumab is associated with a reduction in these markers. On the other hand, a study by Kooistra et al. conducted with patients admitted to the Radboud University Medical Center in the Netherlands demonstrates data from 190 ICU patients who received treatment with immunomodulators such as dexamethasone and tocilizumab had their CRP levels suppressed even after a secondary infection, while these drugs did not affect PCT [41,43,45]. Presepsin serves as a bacterial lipopolysaccharide (LPS) receptor and is the soluble form of CD14, a glycoprotein expressed in monocytes and macrophages. It has been demonstrated as a tool to indicate severity in sepsis diagnoses because it rises early, within the first two hours after infection, surpassing PCT and CRP. Carbonell's study points to presepsin as a non-specific biomarker for diagnosing pneumonia and its etiology, but several studies have described this marker as reliable for the severity of viral pneumonia and COVID-19 [41,45].

Possible Treatment Alternatives

The development of new therapeutic agents to prevent mortality of patients co-infected with SARS-CoV-2 and bacteria is necessary. Laboratory tests are the tools used during the clinical management of diagnosis and direction of antimicrobial treatment in order to reduce cases of bacterial resistance and prevent mortality 51.

Serial PCT measurement provides follow-up of inflammatory dynamics, and can be used to shorten the duration of treatment after antibiotic administration begins. If PCT levels remain low at dosage after 24 and 48 hours from the start of antibiotic treatment in the uncertainty of co-infection, in that case, discontinuation is recom-

mended. If bacterial co-infection has been proven or its presence is very likely, PCT reduced by 80% of the baseline value or below 0.5 µg/L after 48 hours or 72 hours, stopping antibiotic administration is reasonable [38]. Finally, phages are very target-specific, have low toxicity and resistance to them are rare, in addition to reducing the synthesis of reactive oxygen species (ROS), whose levels are elevated in COVID-19 patients [46,47].

Impact of the COVID-19 Pandemic on Bacterial Resistance

The increase in the use of biocidal agents, disorderly use of antibiotics and their empirical use, decreased surveillance of resistance due to the focus on COVID-19, and overcrowding of health systems are factors that may contribute to the increase in antimicrobial resistance. The systematic review study by Langford et al. found no association between COVID-19 and changes in antimicrobial resistance of gram-positive bacteria. However, a possible increase in resistance was found in gram-negative patients, suggesting an important role due to the high use of beta-lactams and third generation cephalosporins in patients with COVID-19 [48,49]. The study by Elton and colleagues at two hospitals in Africa observed an increase in the total number of HAIs caused by multidrug-resistant bacteria in COVID-19 patients. The lack of medical staff and personal protective equipment in some hospitals may have counteracted the possible effect of reducing the transmission of antimicrobial resistance caused by the factors of social distancing, improved hand hygiene, and the use of personal protective equipment. The same was pointed out by Serapide et al., in addition to the overcrowding of patients and failure to quickly isolation of patients colonized by multidrug-resistant bacteria upon admission to hospitals. Protection against COVID-19, such as the quarantine established in early 2020, have been identified as non medicament factors extremely useful in reducing the incidence of infections in the community by the respiratory bacteria *S. pneumoniae, Haemophilus influenzae,* and *Neisseria meningitidis*.

Mentions of the incidence of MRSA colonization, reduced by 65.2%, and minimally in resistance rates were related to organized responses to the COVID-19 pandemic, while overloaded environments are directly related to the opposite effect [48,50-52]. A study conducted in Serbia found a statistically relevant difference in carbapenem resistance when COVID-19 patients were compared with patients without COVID-19. Resistance to imipenem was 56.8% vs. 24.5% ($p < 0.001$), meropenem 61.1% vs. 24.3% ($p < 0.001$), and ertapenem 26.1% vs. 21.7% ($p = 0.03$). Another study conducted in Spain reported that patients with COVID-19 revealed an increased risk of nosocomial infection by carbapenemase-producing Enterobacteria, associated with a high risk of mortality and being severe. In Brazil, there was an increase in the incidence of carbapenemase-resistant *A. baumannii* correlated with COVID-19 both in the ICU and outside. A change in the sequencing of *K. pneumoniae* and its virulence type (from ST11 to ST15) from 2015 to 2020, which may be related to COVID-19 [48]. The study by Thomas et al. reported an emerging in carbapenemase-resistant Enterobacteriaceae isolates by 42.8% in Brazil, and an increase from 73.6% to 88.4% in the total number of carbapenemase genes detected. The emergence of new genes that have not been identified yet has been reported in Chile, Dominica and Belize, while Peru, Ecuador, Venezuela and Costa Rica have reported the emergence of new combinations of carbapenemase [53-58].

Conclusion

Infections caused by multidrug-resistant bacteria are related to the worsening prognosis and increased mortality in patients with COVID-19. The empirical and prophylactic use of antibiotics has been widely reported in patients with COVID-19 and is one of the main causes for acquired resistance. Studies indicate that PCT levels in SARS-CoV-2 infected patients of up to 0.25 ng/mL are indicative of the absence of bacterial co-infections and are a support to avoid inappropriate antibiotic treatment. In the pandemic scenario characterized by a high use of biocidal agents, empirical and disordered use of antibiotics, and decreased surveillance of resistance worldwide and overcrowding of health systems, lack of medical staff and personal protective equipment in some hospitals were factors that have been pointed out as contributing to the increase in antimicrobial resistance. On the other hand, protective strategies against COVID-19, such as quarantine, improved hand hygiene, and the use of personal protective equipment were identified as factors able to reduce the incidence of infections in the community. In some countries, increasing in the incidence of carbapenem-resistant bacteria and new genes and combinations have been reported, which may be related to the COVID-19 pandemic. More research in the field of therapeutics and alternatives management in cases of bacterial co-infection associated with COVID-19 and its possible markers is needed, as well as investigations of the possible impact of the pandemic on the global scenario of acquired multidrug resistance.

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