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The impact of COVID-19 on bacterial antimicrobial resistance: Findings from a narrative review

Bader S. Alotaibi[1]*

[1] *Department of Laboratories Sciences, College of Applied Medical Sciences, Alquwayiyah, Shaqra University, Shaqra, Riyadh, Saudi Arabia.*

Abstract

Background: Antimicrobial resistance was a major problem even before the current COVID-19 outbreak. The healthcare industry has been significantly impacted by the COVID-19 outbreak. Analysis of antimicrobial resistance rates, particularly bacterial antimicrobial resistance, is required due to the advent of novel COVID-19 variants. A narrative review of the studies was used to evaluate the effect of the COVID-19 virus on the rates and transmission of bacterial antibiotic resistance.

Methods: Since the start of the COVID-19 increase, this review has been carried out by searching databases including PubMed, Google Scholar, and EMBASE. Articles that examined how the COVID-19 virus affected the prevalence of antibiotic resistance in bacteria have been added since March 2020. Antimicrobial resistance was the key outcome of interest, and the COVID-19 pandemic was the main exposure. There were a total of 14 investigations, 9 of which were scheduled for 2021.

Results: Overall, the results suggest that there were more bacterial infections and cases of antibiotic resistance during COVID-19. Our results show that COVID-19 is associated with a rise in antibiotic-resistant microorganisms, notably in patients in intensive care units. Among the pathogens that represent a serious threat are methicillin-resistant Staphylococcus aureus, carbapenem-resistant Klebsiella pneumonia, and carbapenem-resistant Acinetobacter baumannii.

Conclusion: The widespread disruption in the healthcare system may have led to an increase in antimicrobial resistance. Although it is accepted that the COVID-19 virus has caught the attention of the healthcare system, it is crucial to combine COVID-19 management strategies with strategies for reducing antibiotic resistance. The larger health system's pandemic response should incorporate antimicrobial stewardship.

Keywords: Antimicrobial resistance; bacterial; COVID-19; pandemic; narrative review**.**

*Bader S. Alotaibi- Department of Laboratories Sciences, College of Applied Medical Sciences, Alquwayiyah, Shaqra University, Shaqra, Riyadh, Saudi Arabia; Email: balotaibi@su.edu.sa .

1. Introduction

Antimicrobial resistance has been recognized as one of the most serious worldwide health issues, with significant economic consequences [1]. In hospital settings where the use of prescription antibiotics is prevalent, such as intensive care units, there is an increase in the incidence of bacterial infections that are difficult to treat (ICUs)[2]. These infections may have catastrophic consequences, including septic shock or death, and they may place a heavy financial strain on the families [3]. Additionally, giving COVID-19 patients antibiotics or antifungals to prevent secondary infections may exacerbate antimicrobial resistance and related consequences [4]. Antimicrobial resistance was a top priority even before the current COVID-19 outbreak began, and it has remained so since 2015[5]. The evidence from European countries reveals that about 671 989 infections occur due to antibiotic-resistant bacteria and such infections lead to 33110 deaths and 874541 disability-adjusted life years [6].

E. coli, Pseudomonas aeruginosa, Enterococcus faecalis, Staphylococcus aureus, and Klebsiella pneumoniae are the most prevalent resistant bacteria [7]. For instance, E. coli, the most common bloodstream infection bacterium recorded globally, is responsible for 40% of infections resistant to third generation cephalosporins [8]. Additionally, the prevalence of carbapenem resistance varies by nation; for instance, in Europe, it ranges from 58 percent for Klebsiella to 100% for pneumoniae to 92% for A. baumannii [9, 10]. Methicillin-resistant S. aureus (MRSA), on the other hand, is relatively common among gram-positive bacteria [11]. The frequency of methicillin-resistant S. aureus (MRSA) varies over time, with significant concentrations in Europe, Latin America, and Japan. On the other hand, about 25% of S. aureus isolates are resistant to penicillin [12, 13].

The spread of the COVID-19 pandemic has had a significant impact on the health-care system [14, 15]. One way to lessen the spread of disease in a medical setting is to take preventive and hygienic measures, like limiting patient contact and maintaining social distance. On the other hand, if isolation rooms are given to COVID-19 patients, there may be more hospice transmissions as a result of the unavoidable rise in staffing needs. Higher antimicrobial resistance rates could result from this and administering more antibiotics could make the problem much worse. 62 percent of COVID-19 patients received antibiotics, according to a recent international survey [16]. While one rapid review was conducted in previous years, the review could not present the findings by type of pathogens such as gram positive or gram-negative bacteria [17]. In addition, another review included research articles before 2020 and did not include the recent studies [18]. Likewise, another review focused on the extent to which COVID-19 is complicated by bacterial or fungal infections with a little focus on antimicrobial resistance [19]. Hence, there is a need to update the existing literature to provide a comprehensive picture on the impact of COVID-19 on bacterial antimicrobial resistance.

In view of the present COVID-19 outbreak and newly developing novel variants, antimicrobial resistance rates, particularly bacterial antimicrobial resistance, must be evaluated. This will let researchers assess how an ongoing pandemic has affected the public health issue of antibiotic resistance. As a result, they will be able to create backup plans to lessen the effects of COVID-19 on overall transmission, rates of bacterial drug resistance, and related morbidity and mortality. To ascertain the effect of the COVID-19 outbreak on bacterial antimicrobial resistance rates and transmission, we conducted a narrative assessment of the research.

2. Material and Methods

This narrative review has been undertaken by searching databases like Pubmed, Google Scholar, and EMBASE since the start of the COVID-19 epidemic. Since March 2020, we have included research studies that examined how the COVID-19 pandemic affected the prevalence of bacterial antibiotic resistance. The COVID-19 pandemic was the main exposure, and antimicrobial resistance was the main consequence of interest. We mainly focused on quantitative epidemiological studies and excluded qualitative studies, grey literature, and randomized controlled trials (RCTs). The RCTs were disregarded because the goal of this study was to determine how the COVID-19 pandemic affected rates of bacterial antibiotic resistance rather than to evaluate any therapies. Similar to this, the goal was to perform a quick examination of the literature, and the grey literature was excluded owing to a lack of time and resources. The studies were organized according to the pathogen type, region or country of study, study kind, key findings about the impact of the COVID-19 virus, key conclusion, study reference, and authors' names.

3. Results

A simultaneous outbreak of additional bacterial diseases is possible due to the current epidemic. The pandemic appears to have increased co-infections with many bacterial pathogens and the resulting antibiotic resistance, as seen in table 1. The information is arranged according to the types of bacterial diseases and environmental microorganisms that are common and may have contributed to antibiotic resistance.

3.1. Gram-Negative Bacterial pathogens

Carbapenem-resistant Enterobacteriaceae (CRE) and Pseudomonas aeruginosa, as well as carbapenem-resistant Acinetobacter baumannii, posed the most significant problem [20-22]. The results, for instance, show a significant prevalence of CRE co-infection, particularly with Klebsiella that is resistant to carbapenem. Pneumonia prevalence ranged from 0.35 to 53% of the population [23]. KPC was the most prevalent resistance gene, while bloodstream infections were the most common infection source [23]. On the other hand, skin, soft tissue, urinary tract, and gastrointestinal tract infections were less

frequent [23]. Numerous investigations conducted across the globe, including those in China, Peru, and the US, discovered a surprisingly high prevalence of Candida auris infections. For instance, retrospective research in China found that patients who underwent prone positioning-required surgery had a higher chance of CRE colonization than patients who did not. In comparison to patients who were not prone-positioned, patients who were prone-positioned saw a colonization rate of 67%. Furthermore, the risk of death increased with subsequent CRE infections [24]. Similar to this, studies in Peru revealed a Klebsiella pneumonia outbreak, and COVID-19 patients had an increased risk of developing multidrug-resistant bacterial infections. Likewise, a study conducted in Saudi Arabia demonstrated that COVID-19 patients are more prone to develop secondary bacterial infections [25]. More specifically, Klebsiella pneumoniae and Acinetobacter baumannii were found to be the most prevalent bacterial infections presenting with full resistance to all tested antibiotics except colistin [25].

During the pandemic, secondary infections brought on by carbapenem-resistant Acinetobacter baumannii pose a concern in addition to CRE [26]. Acinetobacter baumannii outbreaks resistant to carbapenem have so far been recorded in a number of COVID-19 patients. [22, 26-29]. According to a recent Italian report, infections brought on by carbapenem-resistant Acinetobacter baumannii climbed from 5.1/10,000 ICU patient days in 2019 to 26.4/10,000 ICU patient days in 2020 [30]. This demonstrates that there were more infections brought on by the bacteria during the pandemic. Acinetobacter baumannii colonization provides a risk of increased morbidity and death due to the bacterium's drug resistance. Similarly, studies conducted in Italy found that a larger percentage of carbapenem-resistant Acinetobacter baumannii infections were present in COVID-19 patients (63 percent compared to non-COVID-19 patients, 8 percent). Due to this illness, there was a nearly 8-fold increased risk of developing a multidrug-resistant infection and a roughly 7-fold increased risk of mortality, indicating a higher potential of both antimicrobial resistance and fatal consequences [26].

These conclusions were supported by an Iranian investigation that found Acinetobacter baumannii, which is carbapenem-resistant, was responsible for over 90% of the co-infections in COVID-19 positive people and had a similar mortality risk (95 %) [29]. Similarly, a study in India (n = 17,534) discovered that 3.6 percent of patients contracted bacterial or fungal illnesses [31]. About 78 percent of the patients had gram-negative bacteria, with Klebsiella pneumonia being the most common illness (29 percent), and 92.6 percent of the patients had carbapenem resistance. This suggests that there was a higher incidence of superinfection and antibiotic resistance during COVID-19 [31]. Acinetobacter baumannii, which is resistant to carbapenem, has been linked to an outbreak of five cases in Israel, with the use of contaminated equipment or hands by healthcare workers as a likely mode of transmission [22]. Another

study conducted in Iran revealed that Acinetobacter baumannii was commonly found bacterium in the blood and respiratory tract and E. coli was the commonly reported infection in urine [32].

Additionally, numerous investigations have demonstrated that COVID-19 infections in seriously ill patients are brought on by carbapenem-resistant P. aeruginosa [33, 34]. For instance, a study of 118 patients admitted to the ICU in Italy during a pandemic was carried out [35]. Carbapenem-resistant P. aeruginosa colonized and infected 10.2% of these individuals [35]. Contrary to CRE and carbapenem-resistant Acinetobacter baumannii, there isn't any indication in the literature that carbapenem-resistant P. aeruginosa significantly increased or became more common during the COVID-19 crisis. The health workforce must be vigilant and take precautions to avoid such diseases and their effects because there may be a big worry in the future.

3.2. Vancomycin-resistant bacteria

Numerous retrospective case series or case-control studies have been carried out to examine the prevalence and trends of vancomycin-resistant enterococcus species. There is a growing pre-pandemic tendency in these illnesses, according to these studies, which are primarily from Italy, Germany, and Spain. For instance, in 91 cases of co-infections examined in Spain, Enterococcus faecium was the most often identified infection in the bloodstream (43 percent) [36]. Of the total infections, multidrug resistance was found in about 75% of the cases [36]. This could result in a rise in co-infections and consequent resistance due to Enterococcus species during pandemics [36]. Similar to this, an Italian study found an unexpected rise in bloodstream infections, with an incidence of 87/1000 day for ICU stays [37]. The majority of infections (79.6%) were caused by gram-positive bacteria, with Enterococcus species being the most prevalent and responsible for 55.8% of cases [37]. Furthermore, 27.3 percent of the isolates had multidrug resistance [37]. Retrospective research conducted in Germany found similar results [38].

3.3. Methicillin-resistant bacteria

Other methicillin-resistant bacteria investigations, including their corresponding meta-analyses, have been carried out in the United States, France, Italy, and Germany. Even though pre-pandemic infection rates were dropping in all of these nations except for Germany, where they were rising, they surged during the COVID-19 pandemic. A retrospective multicenter case series in New York City, for example, reported methicillin-resistant Staphylococcus aureus bacteremia in 1.6 percent of patients during COVID-19[39]. Methicillin-resistant Staphylococcus aureus was present in 45.2 percent of those affected, and lung infections accounted for 19 percent of those infections [39]. This may suggest that although Staphylococcus aureus was not a common pathogen during COVID-19, it was associated with higher fatality rates [39].

Likewise, a case-control study was conducted in Italy on 40 patients admitted to ICU [30]. In Italy, a case-control study of 40 patients hospitalized to the ICU was done (27). Regardless of their COVID status, these patients were mostly admitted to the ICU for ventilator-associated pneumonia (27). Contrarily, patients with COVID-19 infection were found to have a statistically significant increased risk of developing Methicillin-resistant Staphylococcus aureus (65%) compared to those without COVID-19 infection (27.5%). (30). These conclusions are supported by the findings of a meta-analysis of 18 studies, which discovered that Methicillin-resistant Staphylococcus aureus accounted for 53.9% of COVID-19 infections and that S. aureus co-infections affected nearly a quarter of COVID-19 infections (25.65%), indicating a higher rate of Methicillin-resistant Staphylococcus aureus co-infections among COVID-19 patients [40]. Besides, an alarming high mortality at 2 weeks (54.8%) and one month (66.7%) was reported in one of the case series on Stahplococcus aureus bloodstream infections.

3.4. Multidrug resistant Entercocucus

The increased use of antibiotics (such cephalosporins and glycopeptides) by COVID-19 patients as well as a disruption in the healthcare system are associated to an increase in the prevalence of ampicillin- and vancomycin-resistant infections. In a retrospective cohort examination of 89 ICU patients, for instance, an alarmingly high frequency of primary and catheter-associated diseases was described [37]. In a cohort of 140 patients in Spain, these infections were largely brought on by Enterococcus faecium and E. faecalis, and the incidence of bloodstream infections brought on by multidrug-resistant infections (Enterococci) increased mortality and ICU stay [36].

Table (1) Characteristics of the included studies with main findings and conclusion

Author	Year	Study design	Study setting	Type of bacteria	Key findings
Sharifipour et al[41]	2020	Prospective study	Iran	*Carbapenem-resistant Acinetobacter baumannii*	*Carbapenem-resistant Acinetobacter baumannii* was responsible for roughly 90% of the co-infections, with a similar death rate (95 percent). *Carbapenem-resistant Acinetobacter baumannii* and methicillin-resistant infections have increased.
Magnasco et al[35].	2021	Prospective study	Italy	*Carbapenem-resistant pseudomonas aeruginosa*	*Carbapenem-resistant Pseudomonas aeruginosa* was found in 10.2 percent of the 118 patients admitted to the ICU. Secondary infections have increased as a result of multidrug-resistant bacteria.

Yang et al[24].	2020	Retrospective study	China	*Carbapenem-resistant Enterobacteriaceae*	The percentage of colonization in prone-positioned patients was 67 percent, compared to 37 percent in non-prone-positioned patients. There was a greater rate of CRE infections and mortality as a result.
Bonazzetti et al[37].	2021	Retrospective study	Italy	*Vancomycin-resistant Enterococcus spp*	A rate of 87 per 1000 days in the ICU. The majority of infections (79.6%) were caused by gram-positive bacteria, with Enterococcus species being the most common, accounting for 55.8% of cases and 27.3 percent of isolates showing multidrug resistance.
Punjabi et al[42].	2021	Retrospective cohort study	USA	*Methicillin-resistant staphylococcus aureus*	At the end of one month, the prevalence of *methicillin-resistant staphylococcus aureus* climbed from 0.6 to 5.7 percent. Methicillin-resistant Staphylococcus aureus (MRSA) is on the decline.
Elabbadi et al[43].	2021	Prospective study	France	*Methicillin-resistant Staphylococcus aureus*	*Staphylococcus aureus* was responsible for 44% of the infections, with *Methicillin-resistant Staphylococcus aureus* accounting for 20% of those. *Staphylococcus aureus* is a kind of bacteria.
Arteaga-Livias et al[44]	2021	Retrospective cohort study	Peru	*Carbapenem resistant Enterobacteriaceae*	COVID-19 patients are more likely to develop several drug-resistant illnesses. There was a *Klebsiella pneumonia* outbreak in which no resistant patients had been reported earlier.
Vijay et al[34].	2021	Retrospective study	India	*Carbapenem-resistant Acinetobacter baumannii*	Infections caused by bacteria or fungi struck 3.6 percent of the patients. *Klebsiella pneumoniae* was the most prevalent pathogen (29%) among the 78 percent of patients that were identified with gram-negative bacteria, with carbapenem resistance found in 92.6 percent of the patients.
Russo et al[26].	2021	Case-control study	Italy	*Carbapenem-resistant Acinetobacter baumannii*	COVID-19 patients had a greater rate (63%) of *carbapenem-resistant Acinetobacter baumannii*

					infections than non-COVID-19 patients (8 percent). This infection raised the likelihood of multidrug-resistant illness by nearly 8 times, with a 7-fold increase in related mortality.
Bardi et al[36]	2021	Case-control study	Spain	*Vancomycin-resistant enterococcus spp*	Out of 91 patients, the most common blood stream infection was *Enterococcus faecium* (43%), whereas multidrug resistance was found in 75% of the cases.
Adeiza et al[40].	2020	Meta-analysis	Mixed countries	*Methicillin-resistant Staphylococcus aureus*	A quarter of COVID-19 infections (25.65%) were affected by *S. aureus* co-infections and 53.9% of those infections were contributed by *Methicillin-resistant Staphylococcus aureus*, indicating a higher rate of *Methicillin-resistant Staphylococcus aureus* co-infections among COVID-19 patients
De Pascale et al[30]	2021	Case-control study	Italy	*Methicillin-resistant Staphylococcus aureus*	Out of 40 patients with and without COVID-19, patients with COVID-19 were at higher risk of developing Methicillin-resistant infections (65%) than patients without COVID-19 (27.5%).

4. Discussion

This narrative evaluation sought to determine the impact of the COVID-19 pandemic on the rates and dissemination of bacterial drug resistance. Overall, the data indicate an increased risk of bacterial infections and antibiotic resistance during COVID-19, with the latter most frequently happening in people with compromised immune systems because of the virus. The problem is made more complicated by additional risks associated with using immunosuppressive medications, such as corticosteroids, well-known immune system suppressors that may promote secondary bacterial infections or adversely affect the body's response to bacterial illness. It's probable that colonization by multidrug-resistant gram-negative bacteria has injured ICU patients and is to blame for several problems. Early in the pandemic, there was a major emphasis on treating COVID-19 patients, which changed the focus of therapy and infection control to COVID-19 patients. As a result, the healthcare system was upset, potentially resulting in a rise in the colonization of multidrug-resistant gram-negative bacteria.

As a result of this pervasive disruption in the healthcare system, antimicrobial resistance is increasing globally. In the wake of the COVID-19 pandemic, the prevalence of this resistance has increased [41]. Three elements including emergence, transmission, and population-level infection determine the antimicrobial resistance [5]. The increase in antibiotic prescriptions as a result of co-infections, a heavier workload for the medical workforce, and inadequate laboratory capacity in underdeveloped nations could all be contributing factors to the development in antimicrobial resistance. Additionally, a change in attention from routine infection control procedures to COVID-19 infection control procedures might have contributed to the spread of resistant microorganisms and an increase in antibiotic resistance [42]. Additionally, COVID-19-related hospital admissions have increased the requirement for antibiotic prescriptions and the spread of infections that are multi-drug resistant, which has led to a rise in antimicrobial resistance. Only 54% of patients in ICUs in 88 different nations were found to have bacterial illnesses, although 70% of those patients had at least one antibiotic prescription [43].

Additionally, COVID-19 symptoms are comparable to those of bacterial pneumonia. As a result, it might be challenging to stop doctors from prescribing unnecessary antibiotics. This may be yet another excuse for administering medicines ineffectively, perhaps raising the risk of antibiotic resistance. The European Society of Clinical Microbiology and Infectious Diseases has released new guidelines on how to prescribe antibiotics to patients during the pandemic as a result of the rise in antimicrobial resistance, which are comparable to the guidelines on how to treat seriously ill COVID-19 patients while awaiting test results [44].

Due to time and resource constraints, we didn't thoroughly search the publications. Because of this, it's likely that some pertinent studies were disregarded, producing distorted results. Furthermore, the majority of the included studies took place in acute care facilities and industrialized nations. This does not rule out the possibility that COVID-19 has had an impact on antibiotic resistance in regular hospital wards, even if we acknowledge that the majority of the findings came from hospital settings like ICUs. We do realize that most of the studies were retrospective in nature and lacked a potential control group. This review may provide a framework for physicians, microbiologists, and decision-makers to set reasonable standards and take the required action to battle antibiotic resistance and prevent the spread of this resistance once more.

5. Conclusion

Antibiotic-resistant microorganisms have increased as a result of COVID-19, particularly in patients in intensive care units. The most common bacteria that provide a risk are carbapenem-resistant Klebsiella pneumoniae, carbapenem-resistant Acinetobacter Baumannii, and methicillin-resistant

Staphylococcus aureus, according to the findings of the current review. Although it is acknowledged that the COVID-19 pandemic has moved the focus of the healthcare system, it is crucial to combine COVID-19 management efforts with antibiotic resistance mitigation strategies throughout this pandemic. The World Health Organization's most recent interim guideline on the clinical management of COVID-19 includes concepts of antibiotic stewardship and specific recommendations (45). According to the recommendations, antibiotic therapy or prophylaxis is not advised for those with mild or moderate COVID-19 until signs and symptoms of bacterial infection appear.

6. Declarations

6.1 Conflict of Interest Statement

The author has no conflict of interests to declare.

6.2 Funding Disclosure

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