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Research Article

Comparative Study of Antibiotic Resistance Pattern for Gram-positive Bacteria Pre and Post-COVID-19 Pandemic

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A B S T R A C T

Background: Antimicrobial resistance (AR) is a universal crisis that requires emergent attention and solution. The coronavirus disease 2019 (COVID-19) has provided a real danger to global health. In a try to surround the spread of COVID-19, a large quantity of antibiotics (AB) has been used. During COVID-19 there are real threats that could affect AB activity and potentiate AR.

Patients and Method: The study was done in eleven hospitals in Baghdad taking a time of eight months from 1 November 2019 to 30 June 2020. Seven types of AB discs were utilised; those are amoxicillin-clavulanate, azithromycin, ceftriaxone, gentamicin, levofloxacin, meropenem and vancomycin. In the current study, 1324 samples were isolated and tested to detect AR toward AB pre and post COVID-19 pandemic. The microbial isolates were confirmed by the standard microbiological tests.

Results: The study revealed that the main bacterial isolates pre-pandemic were *Staphylococcus aureus*, whereas post-pandemic isolates were Streptococcus species. The AR of *Staphylococcus aureus, Streptococcus pneumonia, and B-hemolytic streptococci* to amoxicillin-clavulanate, ceftriaxone, and gentamicin was higher in COVID than non-COVID patients. While the AR was variable for the other four AB (Azithromycin, levofloxacin, meropenem, and Vancomycin).

Conclusion: Azithromycin, levofloxacin, vancomycin less resisted than amoxicillin-clavulanate, ceftriaxone, gentamycin by Gram-positive bacteria in COVID patients. Meropenem represents a golden standard AB in treating infections during the pandemic attack.

Keywords: COVID-19, Bacterial Resistance, Pandemic Coinfection, Antibiotic Sensitivity

Introduction

Antibiotics (AB) have been reported to enable health improvement during the last decades. However, the presence of antimicrobials resistance (AR) decreases the ability to cure diseases and curbs efforts to achieve global medical coverage and the medical-related development

goal. AR is a forgotten universal problem that requires serious action and attention.[1]

AR may significantly impair the immune defence system of the host, increase AB therapy intolerance, and have a negative impact on the prognosis of the disease. AR development is a multifactorial phenomenon in which all factors converge in a common trend, that is, selective AB pressure on microbes. AB attack susceptible microbes, so that any bacteria having or getting genes that provide AR to those AB are selected in a Darwinian-like manner.[2] Bacteria, that carry AR genes, can survive and persist in environments contaminated by AB. The AR genes spread among other bacteria, namely "horizontal gene transformation", which induced the enrichment effects of the AR genes in AR bacteria through the uptake of naked DNA material and mobile genetic elements such as plasmids, integrons, transposons, gene cassettes, and bacteriophages.[3]

Although COVID-19 is a viral infection yet, the pandemic is strongly fueling direct AB load on microbes. It has been documented that 72% of COVID-19 cases admitting medical centres have received AB, although 8% only are co-infected by bacteria or fungi.[1] Also, many AB have been explored or proposed to treat COVID-19.[4] Therefore, serious co-infections by strong drug-resistant and pan-resistant microbes have been reported in COVID-19 cases.[5] The World Health Organization (WHO) has documented exaggerated use of broad-spectrum AB during COVID-19 raising warnings of increasing AR.[6]

The current panoramic view requires strongly reinforcement of AB control measures. In this aspect, researches concentrated on determining the development of AR levels pre and post-pandemic are of special relevance to accurately establish the effects on medical schedules for microbial infections during COVID-19 and are important to design strategies to mitigate these negative impacts. It cannot be afforded to further relax the control and containment measures of AB use.

Patients and Method

In a cross-sectional study, extended for eight months between 1 November 2019 and 30 June 2020, blood, urine, sputum, ear swap, cerebrospinal fluid and endotracheal aspirate samples for 1324 patients of both genders were cultured in medical labs of eleven Iraqi health institutions in Baghdad. Of those, 745 samples were obtained before pandemic spread (non-COVID-19) and 579 were obtained after pandemic from laboratory-confirmed positive patients for SARS-CoV-2 by use of quantitative RT-PCR (qRT-PCR) on throat-swab specimens. The microbial isolates were confirmed by the standard microbiological tests.

AR was confirmed by utilising the disk diffusion method. To differentiate bacteria, swabs and blood samples were cultured on MacConkey and blood agar plates and incubated at 37°C for 18-24 hrs. Identification of the isolated microbe was done by using standard microbiological tests.[7] For all isolated strains, antibacterial susceptibility was tested by using the standard Kirby-Bauer disk-diffusion test on Mueller Hinton agar (Merk Co., Germany) in accordance with the laboratory and clinical standards institute guidelines (CLSI; 2019, M100-S29). Seven AB disc kinds were used which are azithromycin, amoxicillin-clavulanate, ceftriaxone, levofloxacin, gentamicin, meropenem and vancomycin. All procedures conducted in this study involving human materials were approved by the official ethical committee of the health institution prior to accomplishing the study. A written consent was obtained from each participant prior to specimen collection.

Results

The samples were grouped into two main groups: non-COVID and COVID patients. The rate of distribution of gram-positive microorganisms in the two groups was represented as per cent in Figure 1 for non-COVID and in Figure 2 for COVID patients. The rate of *Staphylococcus aureus* infection was the highest in non-COVID patients (70%) while *Streptococcus pneumonia* with *B-hemolytic streptococci* collectively represent only 30% of the total samples, as shown in Figure 1.

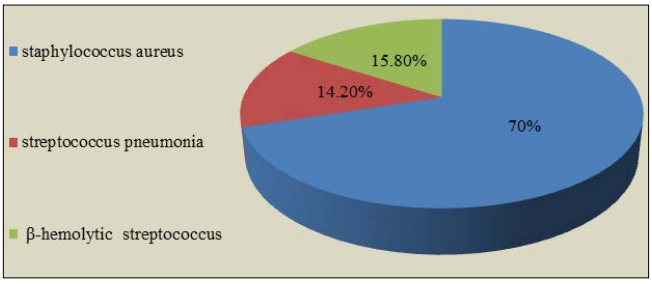

Figure 1.Rate of Distribution of Different Gram-positive Bacteria in Non-COVID Patients

The rate of distribution of *Staphylococcus aureus* decreased in COVID patients to 33%. In contrast, the rate of distribution of *Streptococcus pneumonia* and *B-hemolytic streptococci* collectively increased to represent 67%, as presented in Figure 2.

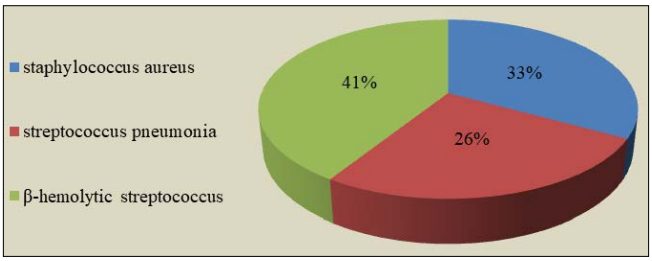

Figure 2.Distribution of Different Gram-positive Bacteria in COVID Patients

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Generally, the resistance of *Staphylococcus aureus, Streptococcus pneumonia, and B-hemolytic streptococcus* to amoxicillin-clavulanate, ceftriaxone, and gentamicin was higher in COVID than in non-COVID patients. While the resistance was variable for the other four AB (azithromycin, levofloxacin, meropenem, and vancomycin) as presented in Table 1. The resistance of *Staphylococcus aureus* and *B-hemolytic streptococcus* to azithromycin decreased in COVID than that in non-COVID isolates. This observation was repeated in meropenem in which *Staphylococcus aureus* and *Streptococcus pneumonia* showed less resistance to this AB in COVID samples, while *B-hemolytic streptococcus* showed no resistance to meropenem in both COVID and non-COVID isolates. *Streptococcus pneumonia* showed no resistance to vancomycin in both COVID and non-COVID isolates. At the same time, it was less resisted by *B-hemolytic streptococcus* isolates in COVID isolates but highly resisted by *Staphylococcus aureus* isolates.

Staphylococcus aureus was found to be completely resistant to Amoxicillin-Clavulanate in COVID and non-COVID patients (100%). The rate of resistance was higher for ceftriaxone (28.5% vs 22%), levofloxacin (16.6% vs 7.7%) and vancomycin (18% vs 11%). Gentamycin has no activity against *Staphylococcus aureus* in COVID samples, but 60% of non-COVID samples were resistant to it. The resistance was lower to azithromycin (43% vs 50%) in COVID than in non-COVID patients. *Staphylococcus aureus* was found to be not resistant to meropenem in COVID patients but 11% of non-COVID samples were resistant to it, as shown in Figure 3.

All samples containing *Streptococcus pneumonia* was found to be completely resistant to Amoxicillin-Clavulanate in COVID in comparison to 75% of them which was found to be resistant in non-COVID patients. Higher resistance rate was seen to azithromycin (60% vs 50%), ceftriaxone (22% vs 20%), Gentamycin (33% vs 20%), and Levofloxacin (28.5% vs 25%). *Streptococcus pneumonia* had lower resistance to Meropenem (20% vs 25%) in COVID than non-COVID patients. In contrast, *Streptococcus pneumonia* had no resistance to Vancomycin (0%) in both groups, as seen in Figure 4.

Table 1.Difference of AR between COVID and Non-COVID Patients

Bacterial Isolate/ AB Disc Tested	*Staphylococcus aureus* % of Resistance		*Streptococcus pneumonia* % of Resistance		*B-hemolytic streptococci* % of Resistance	
	COVID	Non-COVID	COVID	Non-COVID	COVID	Non-COVID
Amoxicillin-clavulanate	100	100	100	75	60	14.2
Azithromycin	43	50	60	50	33	60
Ceftriaxone	28.5	22	22	20	72	55.5
Gentamicin	100	60	33	20	66.6	33.3
Levofloxacin	16.6	7.7	28.5	25	33	50
Meropenem	0	11	20	25	0	0
Vancomycin	18	11	0	0	33	55

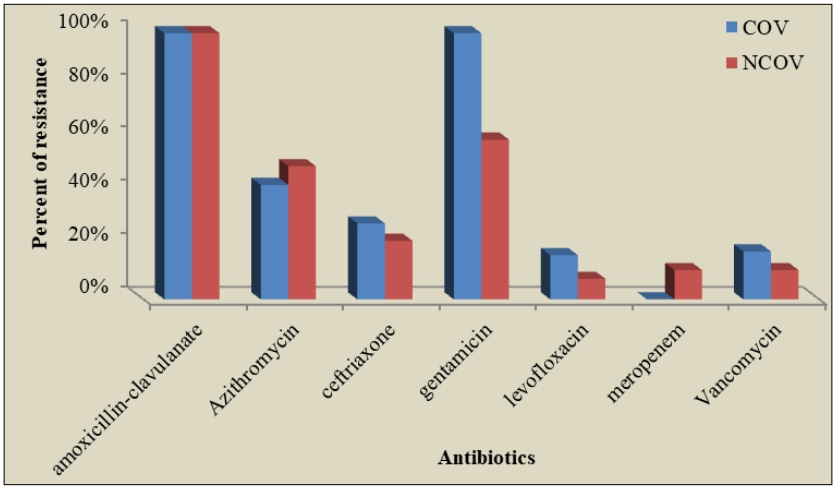

Figure 3.Difference between COVID and Non-COVID Patients in *Staphylococcus aureus* Resistance to AB

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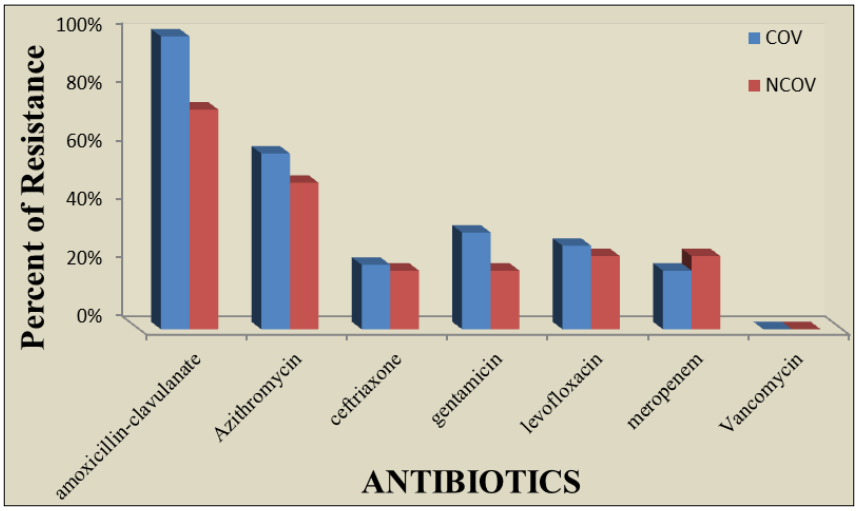

Figure 4.Difference between COVID and Non-COVID Patients in *Streptococcus pneumonia* Resistance to different AB

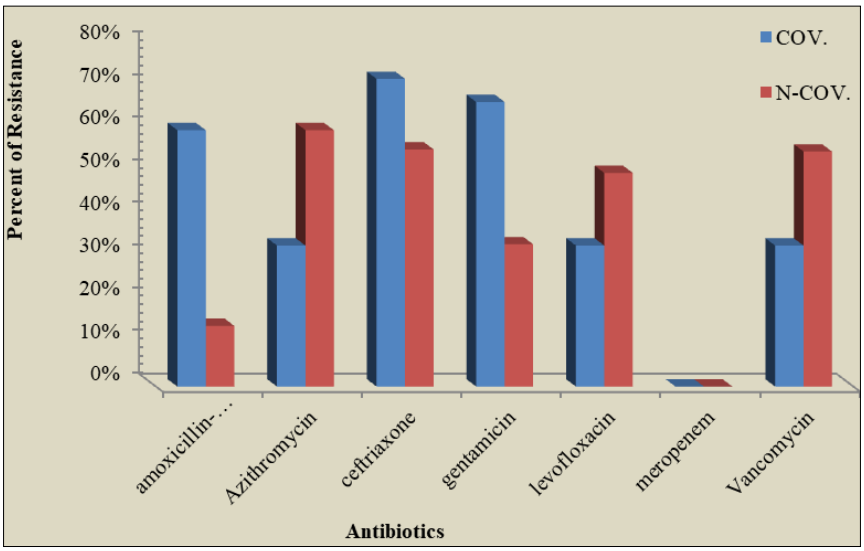

Figure 5.Difference between COVID and Non-COVID Patients in *B-hemolytic streptococci* Resistance to different AB

The rate of resistance of *B-hemolytic streptococci* was found to be higher in COVID than non-COVID patients to amoxicillin-clavulanate (60% vs 14.2%), ceftriaxone (72% vs 55.5%), and gentamycin (66.6 vs 33.3%). The resistance was lower to azithromycin (33% vs 60%), levofloxacin (33% vs 50%), and vancomycin (33% vs 55%) in COVID than non-COVID samples. *B-hemolytic streptococci* were not resistant to Meropenem in both groups, as depicted in Figure 5.

A number of isolates showed lower AR in COVID than non-COVID samples as in the case of *Staphylococcus aureus* resistance to azithromycin (43% vs 50%) and *Staphylococcus aureus* resistance to meropenem (0% vs 11%) (Figure 3), *Streptococcus pneumonia* resistance to meropenem (20% vs 25%) (Figure 4), *B-hemolytic streptococcus* resistance to azithromycin (33% vs 60%), *B-hemolytic streptococcus* resistance to levofloxacin (33% vs 50%) and *B-hemolytic streptococcus* resistance to vancomycin (30% vs 55%) (Figure 5).

B-hemolytic streptococcus showed no resistance to meropenem in the case of COVID and non-COVID isolates. *Streptococcus pneumonia* showed no resistance to vancomycin in both COVID and non-COVID isolates.

Discussion

In this study, the rate of distribution of *Staphylococcus aureus* bacteria was higher in non-COVID than COVID samples, that may be due to the fact the number of endotracheal aspirate and sputum samples increased after the pandemic as a result of increasing the cases of chest infection in the general population. The predominant Gram-positive bacteria in COVID samples were *Streptococcus pneumonia* reflecting higher cases of chest infection presented by

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COVID patients. This result agreed with Bahadur J,[8] who reported that 86.4% of Gram-positive bacteria detected in sputum and endotracheal aspirates were Streptococcus pneumonia and 13.6% were *Staphylococcus aureus*. Also, it was consistent with Chertow DS et al.,[9] who mentioned that the most encountered microorganism during the epidemic of influenza was *Streptococcus pneumonia*.

The resistance of *Staphylococcus aureus*, *Streptococcus pneumonia* and *B-hemolytic streptococci* to amoxicillin-clavulanate, ceftriaxone, and gentamicin was higher in COVID than non-COVID patients. This higher resistance rate may be due to the common use of disinfectants (e.g., hydrogen peroxide, ethanol and sodium hypochlorite) which are applied on objects, especially on usual touch surfaces in common situations, as a means of decreasing virus spread. The continuous usage of these disinfectants can enhance the production of AR bacteria on those objects and permit their direct transmittance to the population. The community are most impacted severely by regular and intensive disinfecting use during the COVID pandemic, and because of their proximity to the population, AR bacterial isolates that emerged in such situations may constitute a risk of transfers directly to the public, especially in dense population developing countries. This explanation was agreed with Chen B et al.,[10] who reported an increased rate of AR because of the effect of common use of disinfectants.

Another suggestion that increases the possibility of infections associated with healthcare staff and the spread of AR microorganisms is hospital admissions, which in turn lead to raised AB use that resulted in a negative circle of AR increment. This finding was consistent with Saleem Z et al.[11], who reported that medical-care-associated infections are considered serious community health issues that substantially contribute to the universal burden of morbidity and mortality with respect to such types of diseases.

Another suggested reason for AR emergence was the increased demand applied to clinical situations. The information or details about how to use an AB for the treatment of COVID-19 is easily accessible to most people on newspapers, web pages and TV programmes. Actually, two things play a significant role in this aspect. Firstly, the fear of the pandemic which harvested a large number of victims. Secondly, there is not enough knowledge about the use of AB which has a direct effect on over the counter (OTC) accessibility of AB, especially in some developing countries with low AB control procedures and poor availability of medical tolls. This suggested cause was confirmed by Ruiz J et al. in their study in Peru.[2]

Another suggested cause was that during April 2020, the COVID-19 pandemic overstressed intensive care units relaxed stewardship, perhaps enhancing AR as revealed by Livermore DM in his probable scenarios.[12] Rawson TM et al. stated that approximately 72% of hospitalised COVID-19 patients were treated by AB but only 8% of them had a true bacterial infection which reflects poor stewardship. Rawson TM et al. published similar findings.[13] As a consequence of raising AR as a result of AB abuse of six treatment society guidelines concerning AB treatment for coinfection in COVID-19, only two of them recommends the use of AB.[6] This increment in AR to gram-positive bacteria simultaneously accompanies the increment in AR to gram-negative bacteria as approved by Tizkam HH et al. in several Iraqi hospitals in Baghdad city.[14]

The COVID-19 patients in intensive care units (ICU) are commonly intubated and encounter the risk of pneumonia associated with ventilators. The COVID-19 patients that are under ventilation often receive multiple AB courses; as ICU capacity increased antibiotic use increased. This overuse of AB leads to concern that AR may propagate in medical institutes as a result of pandemic pressures, although with scant evidence that it has actually done so. Resistance drivers in the population potentially may increase also. This suggestion agreed with Abelenda-Alonso G et al. regarding multiple antibiotic uses for ICU patients.[15]

The AB used by all publications for different indications cannot be completely eliminated or metabolised in the body, and approximately 30-90% of which are excreted unchanged in urine into the waste system. The waste-water treatment by traditional processes can only remove 20-80% of the chemical and their metabolites. Therefore, either directly or indirectly, these AB will be present eventually in environments.[16] According to that, AB and disinfectants were detected frequently in surface and ground waters, soils, sediments and wetlands, with amounts up to 1 mg/L, which can promote persistently bacterial evolution toward AR.[17]

Disruptions of medical services during COVID-19 are the cause of interruptions of treatments, e.g., human immunodeficiency virus and tuberculosis (TB), which also can result in selection for AR. Similarly, disruption of vaccination programmes can raise the possibility of infection, potentially resulting in the overuse of AB. This problem presented by Getahun H et al.[1] agreed with the fact of elevated TB cases in Iraq as it is considered to be a middle-burden country with TB, and occupies a rank of 7 in the eastern Mediterranean region and 108 in the world among countries with TB burden size.[18]

Gentamycin has no activity against *Staphylococcus aureus* in COVID-19 samples, but it has 40% activity in non-COVID samples; these results may be caused by the fact that the COVID-19 patients take the resistant strains of *Staphylococcus aureus* that contain enzymes have the ability to inactivate gentamycin action against *Staphylococcus aureus*. This finding agreed with Dowding

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JE et al.[19] Number of isolates showed lower resistance to AB tested in COVID than non-COVID samples which may be due to the evidence that there was concomitant use of other AB during pandemic infections for each patient which reduce the resistance of these isolates compared to the isolates taken before pandemic which was taken from patients treated by single AB.

Azithromycin and levofloxacin were not commonly used as self-prescribed AB by the population in Iraq, this result agreed with Hasan AJ et al.,[20] who reported that third-generation cephalosporins were the most commonly prescribed AB in Iraq.

Meropenem was not used commonly by the population because it was under restricted regulations for description and dispensing by the Ministry of Health in Iraq resulted in restricted supply to hospitals and its high cost out of these hospitals compared to other ABs which is come in accordance with Hussin N et al.[21] Vancomycin was not used routinely because of its high nephrotoxicity which is agreed with the article reviewed by Zamoner W et al.[22] The absence of resistance in case of some isolates is due to seldom use of these AB either because of its restricted market availability and high cost, e.g., meropenem, or because of its high toxicity which restricts its use, e.g., vancomycin.

Improper use of AB by the general public was introduced as a probable cause of increasing AR by Zavala-Flores E et al., where they revealed in their research that 68.9% of COVID-19 cases documented the use of AB, namely azithromycin and ceftriaxone, before hospital admission with a rate of self-medication of 33.0%.[23] However, another study revealed that using macrolides did not improve the outcome in COVID-19 cases with the mentioned bacterial co-infections.[24] Some medical institutions initially used hydroxychloroquine along with azithromycin against COVID-19 itself, although any benefits, and their mechanism, are disputed and the therapy has become disfavoured.[13]

Conclusion

Amoxicillin-clavulanate, ceftriaxone and gentamycin were highly resisted by *Staphylococcus aureus*, *Streptococcus pneumonia*, *B-hemolytic streptococci* therefore, they have no clinical benefit in treating most of the infections during and after the pandemic.

Azithromycin, levofloxacin and vancomycin were less resisted than amoxicillin-clavulanate, ceftriaxone, gentamycin by gram-positive infection in COVID-19 patients.

Finally, meropenem represents a good AB in treating infection during the pandemic attack.

Recommendations

The fast characterisation of co-infection and avoidance of exaggerated administration of broad-spectrum AB in COVID-19 cases are important to decrease AR during the pandemic.

Multiplex PCR panels are essential for early and definitive diagnosis of associated co-infections and to find a wide range of potential microorganisms. They have a higher sensitivity for viral microbes, a shorter turnaround time of 1-2 hours, and help in the detection of a broad panel of virus and co-infections.

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Conflict of Interest

The authors declare that they have no conflict of interest.

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