Bacterial Infections Associated with COVID-19 and the Effect of Many Common Antibiotics in the Treatment of These Infections

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ABSTRACT

Background and Aim: Undetected coinfections in COVID-19 patients may have serious clinical consequences, including increased hospitalization and mortality. The current study was conducted on 455 patients diagnosed with the new epidemic coronavirus disease who were admitted to quarantine halls in Diwaniyah in Iraq for one month, from February 2021 to March 2021. The aim of the study was to investigate secondary bacterial infections associated with the virus and the effect of using some commonly used antibiotics such as azithromycin, Beta-lactam, ciprofloxacin, and ceftriaxone.

Materials and Methods: Sputum samples were collected from all patients who tested positive for COVID-19 (Real-Time PCR) seven days after confirming the infection with the virus. The samples were streaked on a group of culture media, then transferred to pure cultures and diagnosed, and their sensitivity to antibiotics was determined using the Vitek -2 compact system technique.

Results: According to the findings, the two strains of methicillin-resistant and *Staphylococcus aureus* sensitive were the most common isolated species with a percentage of 85%, followed by *Pseudomonas aeruginosa* 78%, in addition to *Streptococcus pneumonia* 60%, *Acinetobacter baumannii* 64%, and *Legionella pneumophila* 60%. Also, many fungi were observed. Most isolated strains were resistant to antibiotics used in the study.

Conclusion: The study concluded that these antibiotics have no role in treating the infection. Still, it may contribute to the emergence of new, multi-drug resistant MDR species, resulting in increased mortality rates. Also, excessive use of antibiotics may lead to increased mortality.

Keywords: Azithromycin, Ciprofloxacin, COVID-19, Coinfection, *Staphylococcus aureus,* Vitek 2 compact system

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1 Introduction

Coronavirus disease 2019 (COVID-19) has spread around the whole world. A total of 896,450 laboratory-confirmed cases had been reported till April 2020, with a very high mortality rate of 24,000 weakly worldwide according to World Health Organization information in April 2020 **(1)**. Coinfection in patients with COVID-19 (secondary bacterial and/or fungal infections) is one of the remarkable aspects that might result in death. Although coinfections have a significant impact on mortality, they have received insufficient attention. Bacterial and fungal infections are considered the typical consequences of viral pneumonia, particularly in severely ill patients **(2, 3)**.

They result in a higher demand for intensive care and a higher mortality rate. When it comes to influenza, bacterial coinfection affects about 0.5% of healthy people at young ages and 2.5% of older people **(4)**. In the 2009 H1N1 season, one out of every four H1N1 cases died due to bacterial or fungal infections.

Information about the bacterial or fungal infection caused by Coronaviruses is limited **(5)**. According to a cohort report by Zhong Nanshan *et al.*, 20 of 90 severe acute respiratory syndrome (SARS) patients experienced subsequent lower respiratory tract infections **(6)**. In 2003, 70.6% of the critical SARS

patients were born in the United States and were subjected to an intrusive procedure **(7)**. The most prevalent microorganisms that caused secondary infections in SARS cases were *Bacillus* and *Aspergillus niger*, while *Candida* was also prevalent **(8)**. So far, bacterial and fungal infections in COVID-19 patients have been understudied and insufficiently reported. Only some of the hundreds of published articles with clinical data have recorded secondary infection, and pathogens have not been identified in most cases **(9)**. Even in cases where secondary infection data were available, and antibiotics were accessible, the utilization rate (94%-100%) was substantially greater.(Even in cases that involve diagnosing secondary infections and administering antibiotics to the patient).

Secondary infection is more common (10%-15%) than previously thought **(10)**. In addition, the risk of bacterial or fungal infection has increased. Most published papers do not include a prognostic analysis. Most synchronous infection control procedures try to inhibit SARS-CoV-2 transmission and cross infection without considering the prevention of subsequent bacterial or fungal infections. Secondary infection was discovered in 50% of non-survivor patients with COVID-19. Many diagnostic and preventative measures for the problems of COVID-19 patients have been detailed in clinical guidelines in China **(11)**. Until now, there have been no reliable estimates of the prevalence of bacterial coinfections in COVID-19 patients, and no clinical trials have investigated the usage of antibiotics. However, more clinical trials are required to assess the situation thoroughly and evaluate the outcomes **(12)**.

Some researchers have focused on the usage of macrolides in COVID-19 patients. For example, azithromycin and clarithromycin were not examined only for their antibacterial properties **(13)**, but they have also been studied for their antiviral properties. The anti-inflammatory and immunomodulatory properties could be especially beneficial in viral illnesses, such as COVID-19 **(14)**. Antibiotics can reduce the generation of cytokines as an inflammatory

reaction **(15)**. Moreover, azithromycin has been demonstrated to have antiviral properties that interact with the internalization of many other viruses, including Zika virus and H1N1 viruses **(16)**. On the other hand, some studies have mentioned that the overuse of these medications leads to the risk of antibiotic resistance **(17)**. The present study aimed to investigate the coinfection that might accompany COVID-19 and the role of using common antibiotics to inhibit these infections.

2.Materials and Methods

The current study was conducted in the laboratories of the Department of Biology at the College of the Science, University of Al-Qadisiyah, Iraq, in cooperation with the laboratories of Al-Diwaniyah Teaching Hospital and the isolation halls of the mentioned hospital. Sputum samples were obtained from 455 patients who tested positive by reverse transcription-polymerase chain reaction (RT-PCR) for SARS-CoV-2 and were admitted to the hospital during February 2021-March 2021. One week after the patient was quarantined, patient data, including age, gender, date of injury, and whether antibiotics were taken before admission to quarantine hall, were collected. The obtained samples were streaked on previously prepared blood and MacConkey agar media, and a diagnosis was made using the VITEK 2 compact test (BioMérieux Company, France). A sensitivity test was conducted for a group of antibiotics, namely azithromycin, beta-lactams, ciprofloxacin, and ceftriaxone.

3.Results

The results of the current study showed that 150 of 455 (32.9%) patients had secondary bacterial infections. Although the remaining 305 patients also had secondary bacterial infections, the isolated species did not show an apparent resistance to the antibiotics used in this study. Table 1 shows the number of patients, their ages, and those who had secondary bacterial infections.

Table 1. number of patients with COVID-19

Age group	Positive secondary infections	Negative secondary infection	Total number
30-40	38	90	128
41-50	37	78	115
51-60	41	71	112
61-70	34	66	100
Total number	150	305	455
percentage	32.96%	67%	

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Table 2 summarizes the bacterial types isolated and the number of patients from whom they were isolated.

Table 2. types of isolated bacteria

Bacterial species	No of positive patients	Percentage to all positive cases
S aureus	128	85%
P aeruginosa	117	78%
S .pneumonia	90	60%
A baumannii	96	64%
L pneumophila	84	56%
Other species	135	90%

It can be noted that *Staphylococcus aureus* was the most isolated species (85%), followed by *Pseudomonas aeruginosa* (78%), *Streptococcus pneumoniae* (63%), *Acinetobacter baumannii* (60%), and *Legionella pneumophila* (58%). Furthermore, many fungi were observed. Table 3 demonstrates the antimicrobial susceptibility results showing the most isolated species to be *S. aureus* in two groups that were methicillin-sensitive and -resistant (MSSA and MRSA).

Table 3. antibiotic sensitivity results depending on VITEK -2 results

Antibiotics	*S. aureus*		*P. aeruginosa*		*S. pneumonia*		*A. baumannii*		*L . pneumophila*	
	MIC	I	MIC	I	MIC	I	MIC	I	MIC	I
Ampicillin	NEG				≥4	S	4	S	≥4	R
Piperacillin\tazobactam	≥4	R							≥64	S
Erythromycin	≥8	R	≥128	R			16	R		
Beta-lactam	12	R								
Ciprofloxacin	≥4	R								
Ceftriaxone	16	S	≥16	S	64	R	4	*R		

MIC minimum inhibitory concentration, I: interpretation, NEG: negative

4.Discussion

The current study aimed to investigate the bacterial coinfections associated with the new coronavirus pandemic. The isolated bacteria were diagnosed, and an antibiotic sensitivity test was conducted on a group of 455 patients who entered the quarantine halls of Al-Diwaniyah Teaching Hospital, Iraq, during February 2021-March 2021. The samples were collected a week after admission to the hospital because microorganisms require time to colonize and infect the host.

This research focused on *S. aureus* and *A. baumannii,* which play a role in lower respiratory tract bacterial infection. In recent years, emerging strains of both species that have acquired additional genetic features have commonly been associated with hypervirulence and resistance to many types of antibiotics. According to the laboratory reports, these were accompanied by many other bacterial species, namely *E. coli, Enterobacter spp., K. pneumoniae, Citrobacter freundii,* and *Serratia marcescens*. These species are isolated from the Intensive Care Units (ICUs) for non-COVID-19 patients.

According to a study in Mysuru, India, in 2018, *A. baumannii* and *Klebsiella spp*. were the most frequently isolated organisms. In 2014, *Stenotrophomonas maltophilia, S. aureus*, *P. aeruginosa,* and *A. baumannii* were the most common isolates in an ICU in Shanghai, China. The incidence of secondary bacterial infection in our study was 30%. This result differs from many of the same recent studies that have been conducted in many countries. For example, in Iran, Sharifipour *et al.* in 2020 reported 100%, while in China, in the investigation by Fu *et al.*, the incidence was 13.9%. In another study in

the UK, the secondary bacterial infection incidence was 6.1%. The relationship between the new coronavirus and secondary infections is not fully understood. However, the occurrence of secondary bacterial infections in the lower respiratory tract simultaneous with viral infection could be attributed to weak host immunity due to viral infection as viruses consolidate the process of bacterial adhesion to the membranes of the respiratory tract.

Furthermore, the present study assessed the sensitivity of isolated bacteria to a group of commonly used antibiotics in Iraq, especially after the spread of SARS-CoV-2. The results showed that MRSA strains were the most common species usually involved in the severe complications of infections in the ICUs. The risk of contracting MRSA may rise (>2.5-4 times) in patients who stay in hospitals for more extended periods (i.e., more than one week). Different studies have also proven that infections in the respiratory tract caused by MRSA might be linked to a significant increase in mortality. *A. baumannii* isolated strains were resistant to all antibiotics used in the research among patients admitted to the hospital due to COVID-19 **(18)**. In hospitalized patients, resistant bacterial isolates, particularly *A. baumannii*, are frequent, and hospital-acquired infections have become a severe problem for health systems **(19)**. According to Wang *et al.*, *A. baumannii* isolates were resistant to piperacillin, imipenem, ceftriaxone, ciprofloxacin, and ceftazidime with variable ratios. They were classified as multi-drug resistant by many studies. Castilho *et al.* 2017 noted that bacterial ability to synthesize Metallo beta-lactamase (MBL) might be responsible for developing resistance to carbapenems and β-lactams 18. However, no MBL-producing *A. baumannii* strain has been discovered, and bacteria may employ alternative tactics. Study

Limitations

We could not perform molecular tests to identify the genes responsible for the emergence of antibiotic resistance in the isolated bacteria because of the potential risks of the virus. In addition, we could not determine the percentage of deaths caused by secondary injuries because there was no negative control group of patients admitted to the hospital without COVID-19 and died due to secondary bacterial infection.

Conclusion

This study is similar to many studies conducted in many countries to investigate the existence of superinfections in COVID-19 patients' lower respiratory tracts. Our findings highlight the importance of concerns about bacterial infections in patients with COVID-19. *S. aureus* and *A. baumannii* strains are resistant to antibiotics widely used to treat life-threatening bacterial infections, particularly in patients with bacterial infections that may arise as a result of the first infection during or after COVID-19. Since the interaction of viral and bacterial infections may increase the risk of death, it is crucial to take the necessary precautions to avoid secondary injuries and limit the spread of antibiotic-resistant strains by avoiding the indiscriminate use of antibiotics. Secondary bacterial infections associated with COVID-19 must be taken seriously in future studies and considered as one of the important causes that may lead to death.

Conflict of Interest

The authors declare that there is no conflict of interest regarding the publication of this article.

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