Antibiotics Prescribing during COVID-19 Pandemic

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It is axiomatic that hospital admissions increase risks of healthcare-associated infections (HCAIs), leading to a noticeable increase in antibiotic consumption. A recent study conducted on ICU patients in 88 countries highlighted that 70% of hospitalized patients receive at least one antibiotic during acute admission; of this cohort 54% developed a secondary bacterial infection that necessitated antibiotic therapy. In patients with severe disease, the WHO recommends the provision of antimicrobial therapy to prevent furthers infection complications, leading to severe acute respiratory distress syndrome (ARDS) and multi-organ failure.

Keywords: COVID-19 ; SARS-CoV-2 ; antibiotic ; antibiotic prescription ; ICU ; bacterial co-infections

1. Introduction

In December 2019, an outbreak of novel coronavirus was first detected in Wuhan City, the capital of Hubei province in Central China. The virus spread rapidly to other parts of the world, and by 11 March 2020, COVID-19, as it is commonly known, was declared a pandemic by the World Health Organization (WHO) [1]. Statistics from the WHO indicate that as of May 2021, more than 165 million persons were infected with COVID-19, and more than 3 million patients died [2]. The ambiguity of this serious disease over the first wave swept worldwide, posing considerable challenges, including diagnosis, management, provision of resources, and ethical consideration to all global healthcare institutions. Therefore, the catastrophic situation resulted in many patients with a wide range of clinical manifestations ranging from asymptomatic to fatal diseases that required critical care, including ICU admission [3]. Furthermore, in critical care settings, research indicates that COVID-19 is associated with increased mortality of up to 50% with pre-existing comorbidities, such as diabetes, hypertension, and renal and cardiovascular complications, in critical care settings [4].

It is axiomatic that hospital admissions increase risks of healthcare-associated infections (HCAIs), leading to a noticeable increase in antibiotic consumption [5]. A recent study conducted on ICU patients in 88 countries highlighted that 70% of hospitalized patients receive at least one antibiotic during acute admission; of this cohort 54% developed a secondary bacterial infection that necessitated antibiotic therapy [6]. In patients with severe disease, the WHO recommends the provision of antimicrobial therapy to prevent furthers infection complications, leading to severe acute respiratory distress syndrome (ARDS) and multi-organ failure [7]. Despite that, scientific literature still has many gaps and uncertainties regarding the impact of antimicrobial therapy during the pandemic, particularly in critical care settings, which needs to be assessed and evaluated for the sake of global health as well as humanity. Therefore, this review aims to determine the prevalence of COVID-19 patients admitted to the ICUs that have been exposed to antimicrobial therapy correlated against isolated pathogens, comorbidities, and clinical outcomes.

2. Current Insights

The unprecedented recorded numbers of patients infected with SARS-CoV-2 continues to escalate worldwide. As observed from the early stages of the pandemic, the extensive practice of prescribing antimicrobials for the treatment of COVID-19 infected patients might lead to the increased adverse events and long-term consequences such as antimicrobial resistance [8]. Several studies confirm that most hospitalized patients with COVID-19 are managed with broad-spectrum antimicrobials with unproven efficacy [9]. Cong et al. (2021) highlighted that the percentage of antibiotic prescriptions for patients with both severe/critical disease nearly equaled the percentage for patients with mild/moderate disease, even though more critically ill patients are at greater risk of developing secondary bacterial infections [3]. These unnecessary antimicrobials and excessive prescribing for mild and moderate COVID-19 will probably increase risks for adverse events and selective development of multidrug-resistant bacterial pathogens at local healthcare and regional levels.

To our knowledge, the presented study is the first systematic review to evaluate the prevalence of antibiotic prescribing for patients admitted to ICU settings with confirmed SARS-CoV-2 infection. Our review involved 16 different countries,

including major countries, where the plight of the pandemic was evident: China, USA, Italy, and France. The demographic data of this review demonstrate that 2715 ICU patients with ages ranging from 1 day to 92 years and a mean age of 62.7 were exposed to antibiotic therapy. Analogous to our findings, many previous studies concluded that old age patients are more susceptible to severe and critical illness leading to ICU admission. In addition to the clear age-related morbidity and mortality, older patients are more prone to an increase of long-term complications [10][11]. It is relevant to mention that our results were similar to those of Peckham H. et al. (2020) [12], who found that the proportion of male admission to ICUs was significantly higher when compared to females. These highlighted numbers can play an important role in risk stratifications and implications for the clinical management of COVID-19 [12].

Our reviewed studies of ICU patients with COVID-19 revealed associated underlying conditions including hypertension; diabetes mellitus; obesity; malignancy; heart, cardiovascular, liver, respiratory, renal, and neurological diseases; cancer; and organ transplantation. From early observational studies during the pandemic, several studies reported increased incidence and severity of COVID-19 in patients with similar underlying premorbid conditions [13][14][15][16]. Conversely, recorded severity markers include acute kidney and liver injuries, demonstrating the potential contribution of antibiotics exposure in vulnerable populations [16][17][18][19].

The review demonstrated the significant global healthcare hospital prescribing of antimicrobials, which might be a temporary pattern associated with the serious pandemic. Since the first wave of this pandemic, multiple regional protocols included empirical antimicrobials such as ceftriaxone and azithromycin, leading to a substantial increase in antimicrobial consumption at various healthcare settings [20][21]. In accordance, based on our findings, third generation cephalosporin (36.8%) and azithromycin (34.2%) antibiotics were the most prevalent antimicrobial agents reported during the management of COVID-19 in patients admitted to ICUs (**Table 1**). Macrolide azithromycin and hydroxychloroquine intended for the management of COVID-19 during the pandemic were initially used as an adjuvant anti-inflammatory and antiviral therapy rather than for their antibacterial properties. Nevertheless, conflicting studies and reports delayed their removal from management protocols [22][23]. Although ambiguous, the doors remain open for an antimicrobial therapy for various stages of the mysterious disease. A recent study constructed a computational drug repurposing approach in an attempt to find existing drugs against COVID-19, advocating that cephalosporin, ceftaroline, fosamil have a remarkable effect in treating vascular complications in infected patients.

Table 1. Percentage of the prevalence of prescribed antibiotics amongst reviewed studies.

Antibiotic	Frequency Amongst Included Studies	Percentage Amongst Reporting Studies (*n* = 38) (%)
Cephalosporin		
Third generation cephalosporin	**14**	**36.8**
Fourth generation cephalosporin	**2**	**5.3**
Cephalosporin (unspecified)	**2**	**5.3**
Macrolides		
Azithromycin	**13**	**34.2**
Macrolide (unspecified)	**2**	**5.3**
Penicillin and Penicillin β-lactamase inhibitor combinations		
Piperacillin-tazobactam	**4**	**10.5**
Amoxicillin-clavulanate	**3**	**7.9**
Penicillin	**3**	**7.9**
Amoxicillin	**1**	**2.6**
Beta lactam-beta lactamase inhibitor	**1**	**2.6**
Carbapenems		
Meropenem	**4**	**10.5**
Imipenem	**1**	**2.6**

Antibiotic	Frequency Amongst Included Studies	Percentage Amongst Reporting Studies (*n* = 38) (%)
Carbapenems (unspecified)	**4**	**10.5**
Quinolones		
Fluoroquinolones	**3**	**7.9**
Quinolones	**2**	**5.3**
Moxifloxacin	**1**	**2.6**
Glycopeptide		
Vancomycin	**2**	**5.3**
Folate pathway inhibitors		
Trimethoprim-sulfonamide	**1**	**2.9**
Aminoglycosides		
Aminoglycosides	**1**	**2.9**
Lincosamides		
Clindamycin	**1**	**2.9**
Glycylcyclines		
Tigecycline	**1**	**2.9**
Lipopeptides		
Daptomycin	**1**	**2.9**
Others Antibiotic (unspecified)	**16**	**42.1**

Moreover, these antimicrobials act as antibacterial agents against MRSA, which is the most abundant observed bacterial infection reported in this review [22]. Of note, excessive use of these two antimicrobials probably contributed to some adverse outcome scenarios. They have been associated with cardiac toxicities, including arrhythmias and sudden death in susceptible patients with underlying cardiac diseases [23].

Consequently, the latest updates from the WHO's guidance on the clinical management of COVID-19 states that antibiotic overuse increases the risk of emergence and transmission of multidrug-resistant organisms (MDROs). Therefore, infection rates with MDROs are more challenging to treat, coupled with increased mortality of acute COVID-19 cases and increased management costs [24]. Worryingly, this review determines a moderate positive correlation (r = 0.393) between prescribing antibiotics and the percentage of ICU patient death, which is statistically significant (p = 0.029). This can be evaluated as an observation rather than causation since more antimicrobials were prescribed for patients with critical disease, which correlated with increased mortality. Nevertheless, more detailed evaluations are needed mainly for associated adverse events such as antimicrobial-induced acute kidney injuries in critical care settings [25]. Moreover, there is a difference in reporting mortality rates from previously reviewed studies covering a wide range between 0% and 100% of the ICU patients [26][27][28] (see Table S1). This mortality rate variation appeared to be affected by various clinical and social factors, such as age, comorbidities, regional COVID-19 pandemic situation, and timely access to optimal healthcare [29].

Of note, a wide range of broad-spectrum antibiotics has been frequently prescribed for ICU patients, including piperacillin-tazobactam, meropenem, amoxicillin, beta lactam-beta lactamase inhibitor, imipenem, moxifloxacin, aminoglycosides, trimethoprim-sulfonamide, lincosamides, tigecycline, and daptomycin, highlighting potential further development of current or future AMR as most of them have been prescribed empirically or as prophylaxis to prevent secondary bacterial infection [30]. In support of this, our review revealed that most of the studies (69.2%) demonstrated the spectrum of prescribing antibiotics for patients admitted to ICUs with COVID-19 lacking any clear evidence of bacterial co-infection. Despite that, 15 different bacterial species were identified in 30.8% of the reviewed studies. Our findings support the results of a multi-hospital cohort study in the USA [30], which similarly showed widespread use of antibiotics. The prescription of early empiric antibacterial therapy treatment occurred in 56.6% of 1705 patients, in which only 3.5% of the cases were confirmed with bacterial infection [31].

The observed high rates of prescribing antimicrobial therapy to COVID-19 patients admitted to ICUs can be partially understandable, considering the complexity of the novel critical illness and challenges in excluding associated bacterial co-infections [32].

With limited accurate tests for pathogen identifications, Nag and Kaur, (2021) [33] reported that the incidence of superadded infection ranged between 13.5% and 44% for patients with COVID-19 admitted to the intensive care unit (ICU), usually ventilator-associated pneumonia (VAP) caused by bacterial or fungal causes [33]. Another group reviewed the earliest SARS-CoV-2 pandemic cases, and their study observed that overall, 14% of the hospitalized COVID-19 ICU patients had a bacterial co-infection [34]. In the same study, the authors compared influenza and COVID-19 pandemic patients and found that bacterial co-infections were more prevalent in influenza patients than in COVID-19 patients. This bacterial infection was associated with the high mortality rate of influenza A (H1N1) [35]. Commonly, the identification of co-infection bacteria is consistent with the types of pathogens usually associated with hospital-acquired pneumonia (HAP) or ICU-HAP as a complication of ICU and does not advocate a specific preference for bacterial co-infections in COVID-19 [35].

Intriguingly, for patients with COVID-19 admitted to ICUs, pathogen identification revealed the dominance of the Gram-positive *S. aureus* infection in 75% of studies as opposed to the usual culprits of Gram-negative bacteria (GNB). This observation emulates the previous noticeable scientific and clinical knowledge of secondary *S. aureus* pneumonia following influenza infection attributed to upregulation of specific *S. aureus* virulence factors [36].

A comparable result found in a study reported the rate of bacterial co-infection at ICU patients with SARS-CoV-2 pneumonia, which was about 28%; generally, it was associated with *S. aureus, H. influenzae, S. pneumoniae,* and Enterobacteriaceae [37]. Likewise, during the SARS-CoV-2 outbreak (2003), there was a notable increase in *S. aureus* superinfection [38]. Clinicians should be alert to the high percentage of *S. aureus* co-infection during COVID-19 pneumonia [39]. This significant analyzed outcome must be considered when deciding empirical antimicrobial therapy that ideally should include *S. aureus* cover as superior or equal to GNB.

Although there were limited data in the reviewed studies about the antimicrobial resistance patterns in the identified bacteria, a study in our review reported the detection of extended-spectrum beta-lactamase (ESBL) *E. coli* in ICU patients [40]. Furthermore, a retrospective report in France mentioned the detection of other MDR bacteria such as *Morganella morganii*, *Enterobacter cloacae*, *Stenotrophomonas maltophilia*, *Enterobacter cloacae*, *Klebsiella pneumoniae,* and *E. coli* [21]. Some studies also reported detection of methicillin-resistant *S. aureus* (MRSA) with different percentages: 1.9%, 5%, and 61.5% among ICU COVID-19 patients [41][39][42]. Compared with the SARS pandemic, the rate of isolating MRSA in the ICU patients' samples was 3.53% before the SARS pandemic; then, it increased to 25.3% during the SARS pandemic [43]. These findings emphasize secondary MDRO infections in patients due to *Acinetobacter baumannii* and *S. aureus* resistant to multiple commonly used antibiotics [41]. In developing countries, where there are well-known high rates of multidrug-resistant organisms in ICU settings, superinfections in COVID-19 patients can cause a huge challenge leading to an upsurge in mortality [32]. Correspondingly, there is a necessity to link empirical antibiotics therapy at ICU settings based on local antibiogram patterns in countries with a high burden of the disease [8]. Concomitantly, effective antibiotic stewardship should be applied in ICU settings, which has a critical role in preventing the inappropriate use of antimicrobials. Nevertheless, data related to antibiotic prescribing in the ICU for COVID-19 patients are limited but continue to emerge; hence, more studies should be focused on this crucial aspect of critical care management.

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