ANTIBIOTIC USE IN PATIENTS WITH COVID-19: PRESENT AND FUTURE PERSPECTIVES

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ABSTRACT

The COVID-19 pandemic, caused by the SARS-CoV-2 virus has become a public health emergency with more than 120 million confirmed cases and 2 million deaths worldwide, as of 18 March 2021. Several studies report that the pandemic has led to a further increase and inappropriate use of antibiotics, which might have a long-term impact on public health due to antibiotic bacterial resistance (AMR). The present study aims to: i) provide updated information on antibiotic prescriptions in patients with COVID-19, ii) discuss issues related to irrational use of antibiotics and, iii) provide guidelines to face the growing threat of antibiotic-resistant bacteria. This is a summary review on issues and scientific aspects related to the current state of knowledge in the field, as a result of the selection of publications until March 2021. The rationale for antibiotic treatment in COVID-19 patients seems to be related to the previous experience on bacterial superinfection in influenza, where the rate of co-infection/secondary bacterial pneumonia was 11-35% in hospitalized patients. On the other hand, the currently limited evidence suggests that in COVID-19 this incidence is much lower. Several studies report a high prevalence (more than 70%) of broad-spectrum antibiotic use in patients with COVID-19. In fact, the most prescribed antibiotics were fluoroquinolones, third-generation cephalosporins, piperacillin/tazobactam and carbapenems. Moreover, empirical antibiotic prescriptions seem to be based on clinical symptoms, rather than on laboratory markers of inflammation or radiology findings. High rates of empiric prescriptions of broad-spectrum antibiotics were reported during the COVID-19 pandemic, which suggests that more guidance on the use of antibiotics is needed. Guidelines need to be repurposed and promoted even in these difficult times where there is a massive pressure on all healthcare workers. A close and continuous surveillance of the

antibiotic use, along with national recommendations and continuous education, might contribute to the improvement of the appropriate use of antibiotics and mitigate the consequences due to AMR. Further investigations through larger and prospective studies are required to help and guide stewardship practices.
***Keywords*:** COVID-19; antibiotics; AMR; SARS-CoV-2; antimicrobial stewardship

1. INTRODUCTION

COVID-19 is an infectious disease caused by the recently discovered virus, known as SARS-CoV-2 (Severe Acute Respiratory Syndrome-Related Coronavirus 2) (WHO, 2020).

The COVID-19 pandemic has become a public health emergency with more than 120 million confirmed cases and 2 million deaths worldwide, as of March 18th, 2021 (WHO, 2021). However, as many people are most likely asymptomatic and tests and/or surveillance is limited, the real number of infected or dead persons may be underestimated.

Data indicate that this pandemic is the most severe of the three coronavirus-induced pandemics in the past two decades after SARS-CoV-induced respiratory viral disease in 2002–2003 and MERS-CoV respiratory syndrome in 2012 (da Costa *et al.*, 2020).

A substantial portion of SARS-CoV-2–infected individuals report a few, if any, symptoms and recover completely (80%). However, approximately 20% of the patients develop a severe disease requiring hospitalization and oxygen support, 5% of whom are admitted to Intensive Care Units (ICU) (Matheson *et al.*, 2020).

The deadly nature of SARS-CoV-2 might be partially related to bacterial co-infections. In fact, many colonizing bacteria, such as *Streptococcus pneumoniae* or *Staphylococcus aureus*, might take advantage of the compromised immunological status of patients with underlying viral infection, to cause secondary bacterial pneumonias (Ginsburg *et al.*, 2020). For instance, during the pandemic there has been an increase in the number of hospitalized patients fulfilling the criteria for community-acquired pneumonia (CAP). The diagnosis of bacterial co-infection in patients positive for SARS-CoV-2 remains a major challenge because fever, cough and lung infiltrates are common symptoms of both diseases (Sieswerda *et al.*, 2021).

Despite the viral nature of the disease, several studies report that the pandemic has led to a further increase and inappropriate use of antibiotics mainly due to suspected bacterial co-infection or to prevent secondary infection during hospitalization such as hospital-acquired pneumonia (HAP), ventilator-associated pneumonia (VAP) and so on (Rawson *et al.*, 2020; Lansbury *et al.*, 2020; Langford *et al.*, 2020). These trends could have a long-

term impact on public health due to the emerging antimicrobial resistance (AMR).

The increased and irrational use of antibiotics is not new since antibiotics are among the most widely used drugs worldwide. Between the years 2000-2015, the consumption of antibiotics increased by 39% (CDDEP, 2019).

Furthermore, the evolution of AMR represents nowadays a serious threat to the public health worldwide as well as a catastrophic economic impact. Thus, AMR is considered another global pandemic. Millions of infections and approximately 700,000 deaths occur each year due to antibiotic-resistant infections. At this rate, it is estimated that by 2050 mortalities will reach 10 million per year (O'Neill, 2014). For these reasons there is a great worldwide concern that the increase in antibiotic prescriptions during the COVID-19 pandemic could further exacerbate the existing problem of AMR.

The present study aims to: i) provide updated information on antibiotic prescriptions in patients with COVID-19, ii) discuss issues related to the irrational use of antibiotics and, iii) provide guidelines regarding the growing threat of antibiotic-resistant bacteria.

2. MATERIALS AND METHODS

This study is a literature review on issues and scientific aspects related to the current knowledge in the field regarding antibiotic prescription practices during the COVID-19 pandemic. Consequently, databases such as Pubmed and Hinari for published eligible and reliable studies on human subjects in English up to March 2021 were used. Studies were included if they evaluated patients with confirmed COVID-19 and/or reported the prevalence of bacterial co-infections.

3. RESULTS

Several studies in different countries have indicated high rates of antibiotic prescriptions in COVID-19 patients, raising concerns about the irrational use of antibiotics and the pandemic's potential impact on AMR.

These trends occur both in the community and in the hospital sector. The results of a behavioral research conducted by the World Health Organization (WHO), in nine countries and areas of Europe, showed that 79-96% of the community that was using antibiotics reported no infection with COVID-19, but that antibiotics were used to "prevent infection'' (Di Guardo, 2021). This problem was even more complicated in the hospital sector where the anxiety/uncertainty during the pandemic, the difficulty in excluding the risk of co-infection upon admission, the possibility of secondary infections during

hospitalization and the increased workload of the healthcare workers could contribute to a further increase in the use of antibiotics (Lucien *et al.*, 2021).

Rate of co-infection

The rationale for antibiotic treatment in COVID-19 patients seems to be related to the experience with bacterial superinfection in influenza, where the rate of co-infection/secondary bacterial pneumonia was 11-35% in hospitalized patients (Chien *et al*., 2009; Sheng *et al*., 2011). In fact, due to the increase in mortality linked to bacterial superinfection, several guidelines advocated the initiation of empirical antibiotic use in patients with severe COVID-19 (Alhazzani *et al*., 2020; WHO 2020). On the other hand, the current although limited evidence suggests that this incidence is much lower for COVID-19. One rapid systematic review, considering 3506 patients, estimated that bacterial co-infection was present in 3.5% of patients and bacterial secondary infection was identified in 14.3% of patients. When stratified by patient population (an estimate of COVID-19 illness severity), bacterial infection ranged from 5.9% in all hospitalized patients to 8.1% in critically ill patients (Langford *et al*., 2020). In another systematic review and meta-analysis, 7% of hospitalized COVID-19 patients had a bacterial co-infection, with the highest prevalence observed in ICU wards (14%) (Lansbury *et al*., 2020). Moreover, other studies conducted in the United Kingdom showed that bacterial co-infections seem to be uncommon among Covid-19 patients. For example, a review study conducted in the United Kingdom showed that 8% patients (62/806) experienced bacterial/fungal co-infection during hospitalization (Rawson *et al*., 2020). Another study in the Whiston hospital (Prescot, UK) estimated that only 4% of the patients had pneumococcal co-infection (Adler *et al*., 2020). These results are consistent with other studies, such as those conducted by the Dutch Working Party on Antibiotic Policy (SWAB), where bacterial co-infection upon admission was reported in 3.5% of COVID-19 patients, while bacterial secondary infections during hospitalization occurred in around 15% of the patients (Sieswerda *et al.*, 2021). Even more lower rates are reported in another study that evaluated the data of patients admitted in 5 hospitals in the Johns Hopkins Health System, were the prevalence of bacterial co-infection was 1.2% (Karaba *et al*., 2020). Same rates are also reported from hospitals in Netherland (Karami *et. al*., 2021).

The data on pathogens causing bacterial superinfections in COVID-19 seem to be scarce and yet unknown. The systematic review and meta-analysis of Langford *et al*., (2020) concluded that the most frequent microorganisms reported were *Mycoplasma* species, *Haemophilus influenzae* and *Pseudomonas aeruginosa*. However, bacterial co-pathogens were reported only in 45.8 % of the cases, representing less than 14% of the patients with

reported infections. In other studies, the most frequent pathogens were *Staphylococcus aureus*, *Haemophilus influenzae* and *Streptococcus pneumoniae* (Sieswerda *et al*., 2021). When physicians were consulted, most of them declared that the need to start empirical therapy was due to the coverage of atypical pathogens, followed by *Staphylococcus aureus* and *Pseudomonas aeruginosa*. On the other hand, Methicillin-Resistant *Staphylococcus Aureus* (MRSA) was recognised as non-critical (Beović *et al*., 2020).

Rate of antibiotic use

Although data on antibiotic prescriptions given to patients with SARS-CoV-2 infection are scarce, current studies report a high prevalence (more than 70%) of antibiotic use, especially broad-spectrum antibiotics. A large systematic review conducted in Canada showed that the prevalence of antibiotic prescriptions was 74.6%. The most common antibiotic classes prescribed were fluoroquinolones (20.0%), macrolides (18.9%), □-lactam/□-lactamase inhibitors (15.0%) and cephalosporins (15.0%) (Langford *et al*, 2020).

Moreover, the results of an international web-based survey, addressed to physicians from 23 countries, estimated that 71.8% of the patients were receiving antibiotics. Although the piperacillin/tazobactam was the most used antibiotic, different trends were seen in different countries. In Italy, the most prescribed antibiotics were carbapenems in combination with fluoroquinolones, whereas in North America, anti-MRSA antibiotics were mainly used and in Turkey, fluoroquinolones. The decision on antibiotic use is based on clinical symptoms and on laboratory markers or radiology. An interesting result of this study is that, although 61.8% of the participants followed the local guidelines for the use of antibiotics in patients with COVID-19, 82.9% of these cases were following local CAP guidelines. The duration of the antibiotic therapy also differs by country, ranging from 5 days in the UK and North America, to 7 or even 8 days in Italy (Beović *et al*., 2020).

During the New York City pandemic, out of 5,853 COVID-19 patients admitted to the hospital in a 7-week period, 71% were receiving at least one antibiotic such as doxycycline, azithromycin, levofloxacin, ciprofloxacin, ceftriaxone, cefepime, intravenous vancomycin, and piperacillin/tazobactam. Furthermore, 79% of the patients were exposed to antibiotic therapy in the 30 days that preceded positive bacterial diagnosis. The duration of the therapy rather empirical or targeted was high (approximately 8.5 days) (Nori *et. al*, 2020). High rates of antibiotic use are also reported from other studies conducted in the United States. For example, a single-center retrospective analysis conducted in a medical center in Philadelphia, estimated that 67% of

patients received antibiotic therapy, yet 72% did not have an obvious source of bacterial infection. The most common antibiotics used were cefepime (45%), ceftriaxone (54%), vancomycin (48%), and azithromycin (47%) (Goncalves Mendes Neto *et. al*, 2021).

These data are also consistent with several studies reported from China. Chen *et al*. reported that 71% of the patients received antibiotic treatment, 25% of whom were treated with a single antibiotic and 45% with a combined therapy. The most prescribed antibiotics were cephalosporins, quinolones, carbapenems, tigecycline (against MRSA) and linezolid. Antibacterial therapy by moxifloxacin (64%), ceftriaxone (25%) and azithromycin (18%) is very common in Chinese hospitals (Chen *et al*. 2020; Wang *et al.*, 2020).

On the other hand, surprisingly very lower rates are seen only in a Point Prevalence Survey study conducted in Singapore, with a prevalence of antibiotic use approximately 6.2%. Although authors stated that ‘’Despite low prevalence of antibiotic use among confirmed and suspected COVID-19 patients, there was significant proportion of inappropriate antibiotics use where bacterial infections were unlikely (Tan *et.al*, 2021).

Incidence of antibiotic resistance

Studies on the possible impact of the pandemic on antibiotic resistance are very scarce and fragmentary. However, available data show an increase in multidrug resistant bacteria (MDR). A retrospective study in the Wuhan Union Hospital concluded that among 159 strains isolated from COVID-19 patients with bacterial secondary infections, 85.5% were Gram-negative, mainly *A.baumannii*, *K. pneumoniae* and *S. maltophilia*. At the same time, the carbapenem resistance rate of *A. baumannii* and *K. pneumoniae* was 91.2% and 75.5%, respectively (Li *et al*, 2020).

Another retrospective study in Italy estimated that there was an increase in the incidence of Carbapenem-Resistant *Enterobacteriaceae* (CRE) from 6.7% in 2019 to 50% in March–April 2020 (Tiri *et al*, 2020).

One study in the New York City hospital showed that there was a significant decline (>10%) in the susceptibility of multiple species (*K. pneumoniae, P. aeruginosa, and E. cloacae*) to one antibiotic at least (Nori *et al*., 2020).

4. DISCUSSION

The COVID-19 pandemic has become a public health emergency worldwide. Our review shows that antibiotic prescriptions for COVID-19 patients, especially broad-spectrum antibiotics, are very common compared to other therapeutic agents (more than 70%). Although the amount and type of prescriptions may vary in the different countries, there is a consistently high

prevalence of antibiotic consumption in the healthcare settings. Therefore, it becomes very important to highlight the major long-term impact that these trends could have on the emergence of antimicrobial resistance.

The use of antibiotics in medical practice began in the 1940s and their role has been revolutionary in the treatment of severe infections in patients who have undergone interventions, suffering from neoplasms, immunosuppressed and for the prevention or treatment of diseases in the veterinary field (Aminov, 2010). However, the discovery and development of new antibiotic classes were accompanied by the onset of resistance and nowadays all antimicrobials used in humans are affected by this phenomenon (Ukuhor, 2021). The onset of resistance is a natural evolutionary phenomenon of microorganisms, that is accelerated by the selective pressure due to irrational and overuse of antibacterial drugs (Prestinaci *et al*., 2015). Hospital conditions, where the consumption of antibiotics is high and where the spread of resistance is facilitated, constitute a particularly favorable environment for the emergence and spread of resistance against multiple antibiotics (Almagor *et al*., 2018).

On the other hand, the widespread empirical use of antibiotics is currently not supported by the evidence, as the overall rate of co-infections/secondary bacterial infections in SARS-CoV-2 positive patients is low. Higher rates are reported only in critically ill patients in the ICU wards. As such, it seems there is a huge gap between the prevalence of antibiotic prescriptions and the rate of co-infections, that suggests a potential irrational use of these therapeutic agents.

There are several reasons that lead physicians to this practice of prescriptions. First, this tendency seems to be related to the experience with previous epidemic and pandemic outbreaks, such as the H1N1 influenza A in 1918, where the incidence of reported bacterial superinfections, that complicated viral infections, was relatively high (approximately 23%) (Ginsburg *et al.*, 2020). Second, guidelines regarding the use of antibiotics in patients with suspected or confirmed COVID-19 vary by country and, in some cases, may be confusing, since they do not differentiate between CAP and COVID-19 (Beović *et al*., 2020; Huttner *et al*., 2020). Third, healthcare professionals involved in the treatment of COVID-19 patients have a high workload, high levels of pressure and are continuously aware of the high risk of infection and mortality surrounding the pandemic every day. All the above reasons may impact on their inability to strictly follow the local clinical practice guidelines. In fact, as mentioned in the results of our study, the decision on antibiotic use is based on clinical symptoms rather than laboratory data.

In this background, Antibiotic Stewardships (AS) are an essential key to guide the rational use of antibiotics. Several guidelines, such as those

published by WHO and the National Institute of Health (NIH), advocate the empirical use of antibiotics in critically ill patients (WHO, 2020; NIH, 2021; Alhazzani *et al*., 2020). Furthermore, the European Society of Clinical Microbiology and Infectious Diseases (ESCMID) has published some more detailed guidelines, encouraging microbiological tests before prescription, and therapy re-evaluation/de-escalation. These guidelines also advise not to exceed 5-day treatment in most cases (Huttner *et al*., 2020). As described in the Results section, many of the routine prescription practices used by physicians during the pandemic differ from these guidelines.

These findings suggest that ASs need to be re-proposed during the COVID-19 pandemic. Guideline design should be evidence-based, but at the same time easy and accessible, to facilitate and promote a more proper use of antibiotics.

The impact that antibiotic prescription practices during the pandemic will have on future AMR still remains unclear. Given the excessive use of broad-spectrum antibiotics worldwide, there are several reasons for concern, and emerging studies are already showing an increase in the incidence of MDR bacteria.

According to some studies "the impact on AMR will be uneven, varying between epicenters and non-epicenters, geographic regions, hospital-to-hospital within regions and within specific hospital units". The increase is estimated to be higher in countries that were simultaneously epicenters for COVID-19 and AMR, such as USA, Brazil, Russia, UK, Spain and Italy.

Moreover, the pressure against AMR is expected to be significant in hospitals with the largest number of COVID patients and even in facilities with specific wards that were converted in COVID units, even if the rest of the hospital experienced an overall reduction in antibiotic consumption (Cornelius *et al*., 2020).

Conversely, other authors found that the chances for an increase in AMR are poor, due to the improved good health practices, the greater prevention/disinfection, both in healthcare facilities and in the community, and due to the national/international travel restrictions. However, the same authors state that this decrease is likely to happen especially in developed and wealthier countries, whereas in areas with poor infrastructure and infection control measures, AMR will still remain a major concern (Collignon *et al*., 2020). Unfortunately, it can take many years for these questions to be answered.

The current situation highlights a major need for further research to better comprehend several critical points that could drive irrational antibiotic use and help in the design of guidelines during the pandemic. These include the exact incidence of co-infection/secondary infections in COVID-19 patients,

the identification of the main pathogens causing those infections and the role of biomarkers in diagnosis.

In conclusion, a close and continuous surveillance of the antibiotic use, along with international/national recommendations and continuous education, could contribute to improve the appropriate use of antibiotics and mitigate the consequences due to AMR.

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