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Update on the management of SARS-CoV-2 infection

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COVID-19: Impact on prescribing and antimicrobial resistance

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ABSTRACT

The onset of the COVID-19 pandemic challenged healthcare systems focusing their activity on patients infected with SARS-CoV-2. Previous experience with co-infections and superinfections in patients infected with other coronaviruses (SARS-CoV and MERS), the influenza patients admitted to hospitals and prevention of the unknown led to the increased empirical use of broad-spectrum antibiotics in hospitals. The breakdown of antimicrobial stewardship and infection control programs determine an increase in infections due to multidrug-resistant bacteria, particularly in intensive care units. Most of these infections are related to high-risk carbapenemase-producing clones and occasionally with resistance to new β-lactam-β-lactamase inhibitor combinations. On the contrary, in the primary care, there has been a decrease in the use of antimicrobials during the first wave, although it would not have had a significant impact on pathogens associated with community-acquired infections. The accumulated experience reaffirms the need to maintain antimicrobial stewardship and infection control programs in future health crises.

Key words: COVID-19; antimicrobial resistance; antimicrobial prescription; co-infections; superinfections.

INTRODUCTION

The impact that the COVID-19 pandemic has had on antimicrobial prescription and antimicrobial resistance has been a widely debated topic. From a general perspective, arguments against the rise of antimicrobial resistance and antimicrobial use during the pandemics are based mainly on the reinforcement of hygiene and infection control measures, as well as deep changes in social behavior [1]. In healthcare facilities, improved adherence to hand hygiene, infection control precautions and surfaces cleaning, should decrease the spread of multidrug-resistant (MDR) bacteria circulating in these settings. In parallel, healthcare-associated infections (HAIs) or superinfections, especially those caused by MDR bacteria, will decrease and therefore there should not be an increase in antibiotic consumption for the treatment of these infections. On the other hand, social distancing in the community prevents contact between people, hindering the transmission of SARS-CoV-2 but potentially also of community bacterial pathogens such us *Streptococcus pneumoniae* or extended-spectrum beta-lactamase (ESBL)-producing *Escherichia coli*. For this reason, it could also reduce the antimicrobial consumption in the community setting.

On the contrary, there are also arguments in favor of a possible increase in antimicrobial resistance and antimicrobial use, especially in healthcare facilities [2]. The pandemic has disrupted healthcare services in many countries due to overload of health care centers caused by COVID-19 patients. This situation may have interrupted infection control and antimicrobial stewardship activities, facilitating the spread of MDR bacteria and the inadequate use of antibiotics. Moreover, the lack of prevalence data on bacterial co-infection at the early stages of the pandemic and the potential development of superinfections by the presence of multiple risk factors and long hospital stays, especially in critical ill patients, could significantly increase antibiotic consumption in COVID-19 patients. Finally, the Microbiology laboratories have also directed their efforts to the diagnosis of SARS-CoV-2 infection, which may have had a negative impact on the development of other activities related to diagnosis of bacterial infections, screening and surveillance for MDR bacteria. So that, the combination of all of these factors may contribute to exacerbate the problem of antimicrobial resistance [2].

Based on the current evidence, in this review we will discuss the impact of the COVID-19 pandemic on antimicrobial

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prescription and antimicrobial resistance, emphasizing the role that co-infections and superinfections might have played in this impact.

CO-INFECTIONS AND SUPERINFECTIONS

It is important to distinguish between co-infections and secondary bacterial infections or superinfection. Co-infections are those that are present on admission while secondary infections are HAIs resulting from patient care during hospitalization.

It is well known that bacterial co-infections are a frequent complication of viral respiratory tract infection such as influenza. It has been reported that during the 2009 H1N1 influenza pandemic between 18-30% of patients requiring intensive care unit (ICU) admission had bacterial co-infection, resulting in a worse prognosis and greater use of healthcare resources [3]. With other coronavirus-originated infections such as SARS-CoV-1 and MERS-CoV, the prevalence of bacterial co-infections is not well defined, especially due to the lower number of recorded cases. The largest SARS-CoV-1 series estimated that 11% of patients have co-infections, predominantly secondary infections [4] and a multicenter study conducted in Saudi Arabia found that 19% of patients with MERS-CoV infection admitted to the ICU had bacterial co-infections. Thus, taking into account this experience, bacterial co-infection in COVID-19 patients was estimated to play an important role during the first wave of the pandemic.

Different studies have analyzed the occurrence, risk factors and aetiology of bacterial co-infections in COVID-19 patients. A recent meta-analysis described that the percentage of patients with bacterial co-infections at the time of admission was as low as 3.5% (95% CI 0.4-6.7%), so it can be considered an infrequent complication in these patients [4]. However, the percentage of co-infections is higher among patients requiring admission to the ICU and can reach values of 30% [5]. Some of the risk factors that have been associated with co-infections are advanced age and comorbidities, such as chronic kidney disease, diabetes, and chronic heart disease [5]. Regarding the aetiology of community-onset bacterial co-infection, the microorganisms most frequently isolated from respiratory and blood samples are *Staphylococcus aureus* followed by *Streptococcus pneumoniae* and *Haemophilus influenzae* [5]. On the other hand, pathogens such as *Mycoplasma pneumoniae*, *Chlamydia pneumoniae* or *Legionella pneumophila* causing the so-called atypical pneumonias are rarely detected in these patients [3,5].

Most importantly, COVID-19 patients are at risk of acquiring secondary infections during hospitalization and this risk increases especially with the severity of COVID-19 disease and length of stay. It has been described that the prevalence of secondary infections varies between 4-22% and this prevalence can be higher than 45% among patients admitted to the ICU [5]. The average time to develop a secondary infection is between 1 and 2 weeks, with pneumonia and bloodstream infections (BSIs) being the most frequent [5]. The predominant pathogens have been gram-negative bacteria, especially *Klebsiella pneumoniae*, following by *Pseudomonas aeruginosa*. These pathogens have been associated mainly with hospital and ventilator-acquired pneumonia, particularly in the ICU cohorts. Among the gram-positive bacteria, coagulase-negative staphylococci as well as *Enterococcus faecalis* and *Enterococcus faecium,* following by *S. aureus* are the most common and mainly caused of BSIs [5-7].

ANTIBIOTIC PRESCRIPCION DURING THE COVID-19 PANDEMIC

Hospital setting. Despite the low prevalence of co-infections and secondary infections in patients with COVID-19, a high percentage of them have received antimicrobial treatment. In a recently published meta-analysis performed by Langford et al. of 3.338 hospitalized and critical COVID-19 patients across 24 studies reported an antibiotic prescription prevalence of 74% (95% CI 68.3-80.0%), with fluoroquinolones, macrolides, cephalosporins and β-lactam-β-lactamase inhibitor combinations being the most commonly used antimicrobial families [4]. Prescriptions were higher among elderly patients and those admitted to ICU. Moreover, in this study the estimated co-infection rate was 8%, so that antibiotic prescription was much higher than the rate of co-infections, suggesting that a high number of prescriptions were unnecessary [4]. Along with these data, a recently published multicenter study in Spain on the use of antimicrobials in a cohort of 13.932 COVID-19 patients showed that in 34% of these patients, antibiotic prescription was inadequate [8].

Different studies that have analyzed antibiotic consumption prospectively during the first wave of COVID-19 pandemic describe different trends over time. In the first months of the pandemic, they describe an increase in the consumption of amoxicillin-clavulanate, ceftriaxone or azithromycin, while over the months the consumption of broad-spectrum antibiotics such as carbapenems, daptomycin, linezolid, ceftaroline and even novel cephalosporin-β-lactamase inhibitor combinations increases, especially in ICU [9,10]. This biphasic trend in antibiotic prescribing is associated with the evolution of COVID-19 cases in hospitals. The early stages corresponded to high hospital admission rate and the antibiotic empirical coverage of all cases of COVID-19 pneumonia in the absence of real data on bacterial co-infection in these patients. In addition, it was recommended that azithromycin be included in the treatment of patients with severe or mild-moderate COVID-19 disease because of its immunomodulatory properties. In Spain, data on antibiotic use in hospitals reported on the website of the National Plan to Combat Antimicrobial Resistance (PRAN) (https://resistenciaantibioticos.es/es/profesionales/vigilancia/mapas-de-consumo/consumos-antibioticos-en-hospitales) showed a significant increase in the use of azithromycin during the first 6 months of 2020 (Figure 1). However, randomized trials have not demonstrated a clinical benefit from the use of azithromycin, while it may increase the risk of side effects such

as prolongation of QT interval [11]. The second phase, characterized by an intensive consumption of broad-spectrum antibiotics corresponds to a phase of accumulation of patients in the ICU with severe disease and suspected or confirmed superinfections caused by nosocomial pathogens, including MDR.

In order to avoid overuse of antibiotics, the current WHO guidelines for the clinical management of COVID-19, do not recommend the use of empirical antibiotic therapy in patients with suspected or confirmed mild-moderate COVID-19 unless there is clinical suspicion of a bacterial infection [12]. In this scenario, it is important the role of antimicrobial stewardship programs on supporting the optimal selection of empirical therapies and the rapid de-escalation of treatment once SARS-CoV-2 infection is confirmed.

Primary care. In contrast to the hospital setting, the prescription of antimicrobials clearly decreased in the early stages of the pandemic. This fact has been pointed out in different publications, although the data collected are less when compared to those obtained in the hospital setting. The reasons for this decrease would have been the discontinuation of non-essential care in primary patients during the wave of the pandemics, the shift from in-person office care visits to telemedicine consultation, and the possible decrease in respiratory infections due to lock down and distancing [13]. A systematic review concludes that there was not yet evidence to conclude that remote consulting had a significant impact on antibiotic prescribing in primary care [14], although several publications and data from web sites alert of this situation

At least two studies have been published with data from the United States showing evidence of a dramatic reduction in antimicrobial consumption during the first wave of the pandemic. One of these studies estimated that between January and May 2020 there was a 33% decline in antimicrobial dispensing, with the months of greatest impact being April and May 2020 [13]. This reduction affected all groups of antimicrobials, although in the case of azithromycin, there was a 5% increase from February to March 2020 period, with a subsequent decrease in the next months (71%). Another study in this country confirmed these data without a subsequent increase during the months of May to July for azithromycin and the other antimicrobials [15].

In Australia, with a follow-up period until September 2020, an abrupt reduction in the dispensing of antimicrobials was also observed from March to May 2020, affecting to a greater extent those used in the treatment of respiratory infections. Subsequently, the dispensing of antimicrobials increased, although it did not reach pre-pandemic values with many of them [16].

In the United Kingdom, publications include data from specific health care geographic areas. One of these, conducted in northwest London, similarly showed an overall reduction in antimicrobial prescribing during the lock down (17). However, in some age groups there was an increase for some of the antimicrobials. In this regard, amoxicillin-clavulanic acid increased between February to April 2020 among patients above 50 years old, while declining in younger age groups during April. This study also showed that 31.5% of patients diagnosed with COVID-19 and not admitted in a hospital received antimicrobial treatment within the time window of 14 days before or after the diagnosis. The most prescribed antibiotics were amoxicillin (34.9%), doxycycline (27.4%), clarithromycin (9.3%), phenoxymethylpenicillin (5.7%) and amoxicillin-clavulanate (4.5%).

A Dutch study comparing follow-up data of prescriptions for outpatients also observed a decrease in pneumonia, mastoiditis, pyelonephritis and gastrointestinal infections, as well as in antimicrobial treatments [18].

In Spain, using data from the PIRASOA program in Andalusia a before and after cross-sectional study comparing antibiotic use in the community patients the first and second quarters of 2019 and the same quarters in 2020 also showed a significant decrease in antimicrobial prescribing, being 7.6% in defined daily doses per 1000 inhabitants per day (DID) [19]. This decrease occurred for all antimicrobials except azithromycin, which remained stable over the studied period. The Spanish Agency of Medicines and Health Products (AEMPS), in the section of its website dedicated to the National Plan to Combat Antimicrobial Resistance (PRAN), provides monthly data on antimicrobial consumption (https://resistenciaantibioticos.es/es/profesionales/vigilancia/mapas-de-consumo/consumo-antibioticos-humana). Unlike in the hospital setting, in the first wave of the pandemic in Spain (March to April 2020) there was a general decrease in the consumption of antimicrobials compared to the same period of the previous year, maintaining this decrease for the rest of the year (Figure 1).

IMPACT OF ANTIMICROBIAL CONSUMPTION ON ANTIMICROBIAL RESISTANCE DURING THE COVID-19 PANDEMIC

The impact of changing antimicrobial prescribing on antimicrobial resistance has been highlighted by several authors [7, 20-23]. The evidence so far has been clearest in the hospital setting where the relevant increase in prescribing of antimicrobials with wide-spectrum, the higher selection density, the difficulty to continue the adherence to epidemiological barrier measures and the discontinuation of antimicrobial stewardship programs may have been the cause of the increase of antimicrobial resistance.

There is a growing number of reports of superinfection caused by ESKAPE pathogens, especially carbapenemase-producing *Enterobacterales*, in patients with severe COVID-19 during hospitalization [7]. The local ecology, represented by the pool of resistance genes and circulating high-risk clones (HiRCs) plays an important role in the epidemiology of MDR bacteria in the hospital setting during the COVID-19 pandemic. Moreover, the selective pressure exerted by the heavy use of antimicrobials favors the selection and co-selection processes of these HiRCs and the breakdown of infection control measures facilitates their dissemination and transmission among patients [20].

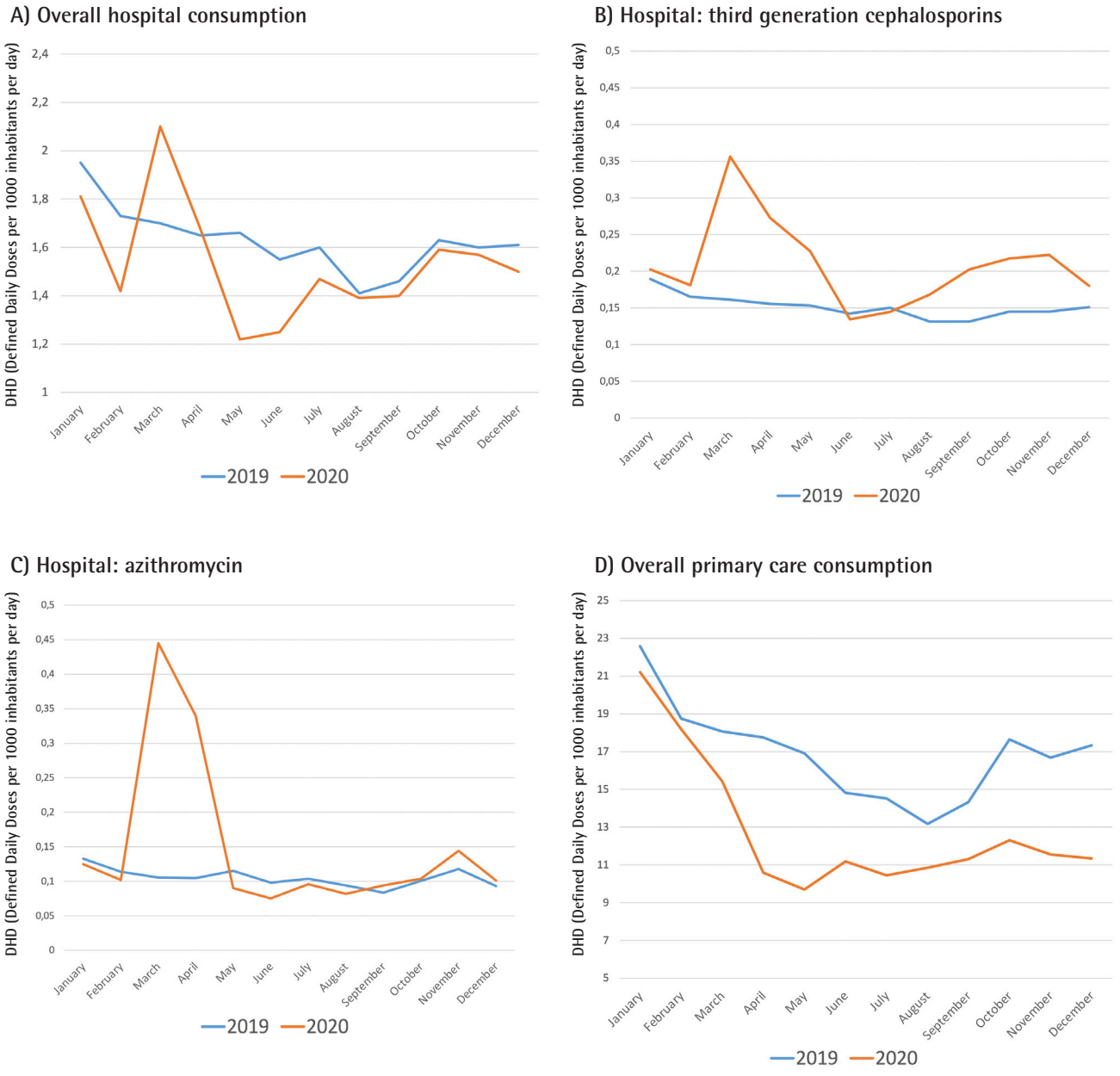

Figure 1 | **Comparative antimicrobial consumption in Spain in 2019 and 2020. Data obtained from the national consumption surveillance system of the Spanish National Plan against antimicrobial resistance (https://resistenciaantibioticos.es/es/profesionales/vigilancia/mapas-de-consumo): Overall antimicrobial consumption in the hospital setting (A), the corresponding to third generation cephalosporins (B) and azithromycin (C), and in the primary care (D)**

A study carried out in an Italian ICU during the first COVID-19 wave reported a significant increase in the incidence of carbapenemase resistant *K. pneumoniae* (CR-Kpn) acquisition (from 6.7% in 2019 to 50% in March-April 2020), despite infection control measures and performing surveillance cultures to identify CR-Kpn carriers. Among the factors proposed by the authors that may be related to the transmission of CR-Kpn in the ICU are the high intensity of care, the prolonged contact of healthcare workers (HCWs) with the patient or the presence of a large number new HCWs from other departments and without work experience in the ICU setting [24]. A high colonization pressure by MDR bacteria, as reported in this article, significantly increases the risk of transmission and at the patient level is also an important risk factor for the subsequent

development of infections. One hospital in New York City reported 13 patients with severe COVID-19 who subsequently developed superinfections with carbapenemase-producing *Enterobacterales*, including KPC-producing *K. pneumoniae* and NDM-producing *Enterobacter cloacae* [25]. All but one of these patients were under mechanical ventilation at the time of infection and 5 of the 13 patients died. Genomic sequencing identified that the majority of *K. pneumoniae* isolates belonged to multiple lineages of the HiRCs-ST258 harbouring bla_{KPC-2} and that these lineages were linked to isolates recovered in the hospital between 2011 and 2016, highlighting the importance of local clonal pool. Another noteworthy fact of this outbreak is the emergence of resistance to ceftazidime-avibactam in the one ST258-bla_{KPC-2} isolate of *K. pneumoniae* in patient with ventilator associated pneumonia [25]. The circulation of HiCRs, especially of KPC-producing *K. pneumoniae* in the ICU, has resulted in the use of intense broad-spectrum antimicrobials including new antibiotics such as ceftazidime-avibactam or meropenem-varbobactam increasing the risk of selection of strains resistant to the new antimicrobials as the case described above [25,26].

The situation in primary care would have been different than that depicted in the nosocomial setting. Antimicrobial consumption was drastically reduced in the former and the ecological impact on resistance could have been the reverse of that observed in the latter. However, the behaviour in the extra-hospitalary setting may not be so evident. It is well known that a high increase in antimicrobial consumption leads to a rapid increase in resistance, although a decrease in consumption does not translate into a rapid decrease in resistance.

So far, no studies have been published showing that the decrease in antimicrobial consumption during the COVID-19 pandemic in primary care, at least in the first wave, has had a positive effect on resistance in pathogens from the respiratory tract such as *S. pneumoniae* or *H. influenzae* or from the urinary tract such as *E. coli*. This could be due to a lower selection density in the extra-hospitalary environment, to the adaptation of previously selected resistant bacteria and their non-clearance over time and to the possible co-selection effect exerted by different antimicrobials, even if consumption had been low. It would also due to the fact that the decline in the antimicrobial use was not too long to have an ecological impact. However, the interconnection of different health care compartments might have also impact on the antimicrobial situation. In fact, the tremendous increment of the azithromycin use might have had a role on resistance, at least in *S. pneumoniae* and *H. influenzae*, and wide-spectrum antimicrobials on *E coli*. Further studies are needed to demonstrate these hypotheses, including the impact on the microbiome and resistome.

CONCLUSIONS

Although co-infection plays an important role in other viral infections such as influenza, studies in patients with COVID-19 have described that the prevalence of bacterial co-infection at admission is low. In the early stages of the pandemic, experience from the management of influenza and the lack of real data about the prevalence of bacterial co-infection in COVID-19 patients led to an increase in the prescription of antimicrobials traditionally used in the treatment of community-acquired pneumonia such as cefotaxime, ceftriaxone or amoxicillin-clavulanic acid. Throughout the evolution of the pandemic, an increase in superinfections has been observed, particularly in patients with severe COVID-19 disease who required prolonged ICU admissions. These infections have often been caused by MDR microorganisms and have required broad-spectrum antimicrobial treatment, including new antibiotics such as ceftazidime-avibactam. The overcrowding of hospitals and especially ICUs has led to a breakdown in infection control measures and antimicrobial stewardship activities. This may have led to outbreaks caused mainly by pre-exiting HiRCs circulating in hospitals, which are subject to intense selection and co-selection processes due to the use of broad-spectrum antimicrobials.

The data published so far in the extra-hospitalary setting are scarce, although the decrease in antimicrobial consumption may have been limited to the first wave, so the effect on resistance may have been of little relevance.

In any case, the COVID-19 pandemic and its consequences on antimicrobial resistance has demonstrated the necessity to maintain the antimicrobial stewardship and infection control programs. Moreover, to learn about the gaps during this period to avoid breakdown of these activities in futures similar situations.

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CONFLICTS OF INTEREST

The authors declare that they have no conflicts of interest.

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