Bacterial infection in coronavirus disease 2019 patients: co-infection, super-infection and how it impacts on antimicrobial use

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Purpose of review
Since the beginning of the severe acute respiratory syndrome coronavirus 2 pandemic, there has been a large increase in the consumption of antimicrobials, both as a form of treatment for viral pneumonia, which has been shown to be ineffective, and in the treatment of secondary infections that arise over the course of the severe presentation of coronavirus disease 2019 (COVID-19). This increase in consumption, often empirical, ends up causing an increase in the incidence of colonization and secondary infections by multi and pan-resistant germs.

Recent findings
The presence of a hyperinflammatory condition induced by the primary infection, associated with the structural damage caused by viral pneumonia and by the greater colonization by bacteria, generally multiresistant, are important risk factors for the acquisition of secondary infections in COVID-19. Consequently, there is an increased prevalence of secondary infections, associated with a higher consumption of antimicrobials and a significant increase in the incidence of infections by multi and pan-resistant bacteria.

Summary
Antimicrobial stewardship and improvement in diagnostic techniques, improving the accuracy of bacterial infection diagnosis, may impact the antibiotic consumption and the incidence of infections by resistant pathogens.

Keywords
coronavirus disease 2019, multidrug-resistant pathogens, nosocomial infection, pan-resistant pathogens, stewardship

INTRODUCTION

Bacterial co-infections and secondary infections identified in severe respiratory viral infections are associated with increased morbidity and mortality [1▪▪]. A relevant issue during the course of the coronavirus disease 2019 (COVID-19) pandemic is the real importance of co-infection in the presentation of the viral disease, since this circumstance can lead to an excessive use of antibiotics. Also, risk for bacterial superinfection during prolonged ICU and hospital stay in these patients also is associated with an increase in antimicrobial use in healthcare. In addition, use of antibiotics in the first wave (including azythromicin) as ''specific'' therapy, as well as an overestimation of risk for bacterial co-infection at hospital admission contribute to potential excessive use of antimicrobial in this setting. In this review, we discuss some of the studies assessing co-infection, superinfection and antimicrobial consumption during the pandemic period and its impact on outcomes.

Pathophysiological aspects

Severe COVID-19 infection is associated, as well as others viral infections, with inflammatory response.

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KEY POINTS

- Despite the low incidence of bacterial co-infection in severely-ill coronavirus disease 2019 (COVID-19) disease, the antimicrobial consumption is high in this population.
- Secondary bacterial infections are a major concern in severe forms of COVID-19, with a potential impact on prognosis of this population.
- Ventilator-associated pneumonia and bloodstream infections occur later in disease, and differentiating between a secondary bacterial infection and colonization by pathogens constitutes an important assessment in these patients.
- Stewardship principles are essential to the maintenance of correct use of antimicrobials and prevent multidrug-resistant organisms' development.

Pulmonary lesions in COVID-19 show pathological changes, degeneration, infiltration, and hyperplasia consistent with inflammatory response throughout the course of the disease [2]. A decrease in lymphocytes is characteristic of severe COVID-19, and this may be the major feature of COVID-19-induced immunosuppression [3]. On the other hand, the elevated level of inflammatory cytokines observed among patients with COVID-19 indicates an hyperinflammation state; and this paradoxical immunity status may complicate COVID-19 recovery [2,3]. The immune pathogenesis associated with an aberrant immune response result in lung damage, functional impairment, reduced pulmonary capacity and eventually death.

As a vital part of the adaptative immune system, lymphocytes play an important role in clearance of the invading virus and provide effective protection of human health under the virus threat [3]. Studies have shown that lymphopenia is a common feature in patients with COVID-19, with decreasing counts of CD4+ T cells, CD8+ T cells, and B cells [2–5]. The most significant decrease in these cell counts is associated with increased mortality in COVID-19 patients, with greater reductions in cell counts in severe COVID-19 patients [3]. Moreover, COVID-19 is associated with a diminished T-cell response [6] that are known to further slowdown viral clearance, thus leading to a cytokine-driven vicious cycle [4].

The delayed type I interferon (IFN) response in coronavirus infections is known to be associated with more severe forms of the disease resulting in rapid viral multiplication and paradoxical hyperinflammation induced by type I interferons. Further activation of the type I IFN signaling pathways leads to a significant influx of neutrophils, inflammatory monocytes-macrophages, dendritic cells and natural killer (NK) cells into the lungs, potentiating lung damage [2,4]. Such cytokine liberation is associated with early acute respiratory distress syndrome (ARDS). Reduced levels of type 1 IFNs are associated with increased susceptibility to secondary bacterial infections [4]. Severe COVID-19 patients have higher cytokine levels (interleukin [IL]-6, IL-8, IL-2R, tumor necrosis factor alpha [TNF-α]) when compared with mild-to-moderate COVID-19 patients [2]. The hyperinflammatory state eventually leads to a significant damage to the lung microvasculature and alveolar epithelium causing vascular leakage and alveolar edema resulting in life-threatening ARDS. These cytokines and chemokines have also been linked to extrapulmonary complications of COVID-19 including multiple-organ dysfunction syndrome.

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) may enhance colonization and attachment of bacteria to host tissue, and the combined infections may result in increased tissue destruction. Airway dysfunction, cytopathology and tissue destruction induced by SARS-CoV-2 infection or during bacterial co-infection may facilitate systemic dissemination of the virus and/or bacterial co-pathogens, dramatically increasing the risk of bloodstream infections and sepsis [4]. Changes in the bacterial composition of lower respiratory tract from patients with severe COVID-19, with a different bacterial diversity, composed multidrug-resistant bacteria such as Pseudomonas and Acinetobacter may be also a trigger for secondary infections [7].

ARDS per se is a trigger for immune impairment, which is associated with structural changes due to tissue damage and impaired mucociliary function, becoming a nidus for overlapping infections. Patients with ARDS typically demonstrate impaired immune response, including phagocytic function of alveolar neutrophils and prolonged suppression of immune function of macrophages and dendritic cells, and these variables may potentially reinforce immune dysfunction intrinsic to viral damage [8]. Figure 1 summarizes the main pathophysiological pathways that impair immune response in COVID-19 infection.

Is co-infection really an issue?

In another severe viral pneumonias, like influenza, bacterial co-pathogens are commonly identified in respiratory samples, and is associated with a greater severity of illness and increased risk of death [9]. In COVID-19, however, the spectrum is quite different. Despite the massive use of empirical antimicrobials on presentation, assuming a possible bacterial co-infection, the prevalence of this phenomenon is

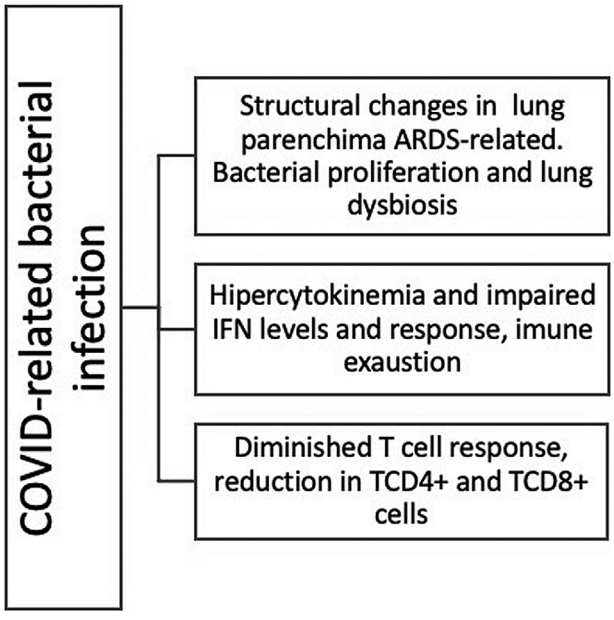

FIGURE 1. Pathophysiological pathways for COVID-19-induced immunological impairment.

relatively low, including severe COVID-19 presentations. Langford *et al.* [9], in a systematic review and meta-analysis of bacterial infection in severe COVID-19 patients, found a low prevalence (3.5%, 95% confidence interval [CI] 0.4–6.7%) of co-infection, most commonly *Mycoplasma*, *Haemophyllus* and *Pseudomonas* species. These findings were reinforced by a subsequent European multicenter study, analyzing early bacterial identification among intubated patients, the prevalence of bacterial identification was significantly lower in patients with SARS-CoV-2 pneumonia compared with patients with influenza pneumonia (9.7 versus 33.6%, adjusted odds ratio 0.23; 95% CI 0.16–0.33) [10▪], suggesting that a relatively frequent phenomenon in severe forms of influenza is not reflected in the same way in COVID-19. Despite that, antibiotic prescription at ICU admission is extremely frequent, between 88% and 94% in multicenter cohorts [10▪,11].

Risk for secondary infections/healthcare-associated infection

Secondary infections are the most important link between severe COVID-19 and bacterial infections. Virus pneumonia and secondary infection act as mutually reinforcing factors to promote the progression of COVID-19 [5]. These are the infectious complications most responsible for the increase in antimicrobial consumption in this population, frequently with the use of more than one antimicrobial class at the same time [1▪▪].

The incidence of ventilator-associated pneumonia (VAP) is substantially higher in late phases of COVID-19 disease, due to the high rate of patients in ICU requiring invasive mechanical ventilation (MV), the long period of MV that these patients require, the need for prolonged infusions of sedative and neuromuscular blockers in this population [11,12] and the higher incidence of ARDS in this population, a well known risk factor for VAP [13]. VAP range from 21% to 64% of patients requiring invasive MV, with a density ranging from 18 to 45 episodes per 1000 ventilator-days [14]. In a recent meta-analysis, a high proportion of COVID-19 patients treated with MV had VAP (45%), with a high mortality (42%) and a high mean ICU length of stay: 28 days (95% CI 21–35) [15▪]. COVID-19 patients are significantly more likely to develop VAP than patients without COVID (hazard ratio 1.7–2.0) [12,13], with a higher incidence density when compared mechanically-ventilated patients without COVID-19 [12], and even when compared those with severe influenza infection [13].

The incidence of bloodstream infection (BSI) is high (10.3 BSI per 1000 patient-days), with a significant proportion of patients developing this complication, majorly during ICU stay [16], and more frequently of unknown source [17]. BSIs are also more frequent in COVID-19 patients than non-COVID patients [17]. Major risk factors for BSI are higher SAPS II, longer time from hospital to ICU admission, intubation during period at risk for BSI, renal replacement therapy, antibiotic use prior to BSI [16] and immunosuppressive drugs [17]. Patients with BSI have worse outcomes than patients without BSI, with longer ICU and hospital length of stay and higher mortality rate [16,17].

Bacterial infections in coronavirus disease 2019 patients

The most frequent pathogens isolated in different samples of COVID-19 co-infected patients are coagulase-negative *Staphylococcus* (CNS) species (60–70% of samples) [18] and *S. aureus* (25–45% of samples) [19,20].

In large multicentric studies, *S. aureus* frequently is the most frequently identified in sputum and among deep respiratory samples, causing lower respiratory co-infections [21], and the early bacterial identification in critically-ill COVID-19 patients is due to Gram-positive cocci (58,2%), mostly *S. aureus* and *S. pneumoniae* [22,23].

Among hospitalized patients with positive blood cultures, COVID-19 patients had a significantly higher proportion of cultures that likely represented contamination with normal skin microbiota than

non-COVID-19 patients. In this context, coagulase-negative *Staphylococcus* species accounted for 59.7% of all positive cultures among COVID-19 patients in contrast to 32.0% among patients that tested negative for SARS-CoV-2. The great challenge, in this context, is to differentiate contaminating pathogens in blood culture from those that are truly pathogenic to the host, and this is very clearly reflected in patients with COVID-19. When potential contaminants were excluded, the rate of bacteremia for COVID-19 patients decreased to 1.6%, which was significantly lower than the rate of bacteremia, excluding contaminants, among COVID-19-negative patients [18].

Similarly, the prevalence of Gram-negative germs are quite variable in the literature. Series that include nosocomial infection in their analysis, as well as non-respiratory foci (urinary, abdominal), have a higher prevalence of Gram-negative pathogens. Co-infection in early stages of disease is infrequent, but there is an increase in incidence at late stages [24,25]. The most commonly pathogen identified is *Enterobacterales*, but nonfermenting Gram-negative bacilli were also very frequent [25]. Gram-negative is a common cause of secondary lower respiratory tract infections, and, in a large cohort, the most prevalent pathogens are *E. coli, K. pneumoniae* and *P. aeruginosa*, that is the most frequently isolated in those with chronic lung disease [21]. These pathogens are highly prevalent in other cohort [23], both in hospital-acquired pneumonia as well as ventilator-associated pneumonia. In series with high incidence of secondary infections due to *Klebsiella*, *Acinetobacter* and *Stenotrophomonas* species, there is an increase in rates of multidrug antimicrobial resistance, especially in carbapenem-resistant samples [25].

An ancillary analysis of the COVID-19-ICU study found first episode of BSI occurred after a median [IQR] of 9 [5–9,10▪,12,13] days after hospital admission, and after adjusting for potential confounders using Cox model multivariable analysis, BSI occurring during hospital stay remained associated with day-90 mortality (hazard ratio [HR] 1.28, 95% CI 1.05–1.56) [26]. The incidence of bloodstream infections rises during the hospital stay; and there is a shift towards a higher prevalence of Gram-negatives and yeasts at this time [27], despite the major predominance of Gram-positives, particularly CNS, in distinct series [24]. The vast majority of blood samples become positive within 1–2 days of incubation, and among COVID-19 patients, 97.3% of positive cultures signaled positive within 3 days of incubation [18].

Hospital-acquired infections (HAIs) are common in critically-ill COVID-19 patients, and the first episode commonly occurs in later stages of disease, in a median of 12 days according to one cohort study [28]. Ventilator-associated pneumonia is frequently the most common infection, followed by bloodstream infections. The majority of VAP episodes were caused by Gram-negative bacteria, and HAIs secondary to multidrug-resistant bacteria, both Gram-positive (methicillin-resistant *S. aureus*) and Gram-negative (extended-spectrum beta-lactamase and carbapenemases). HAIs prolong mechanical ventilation and hospitalization, and HAIs complicated by septic shock showed an almost doubled mortality rate [28]. Descriptive findings in the most relevant cohorts are summarized in Table 1.

Impact on antimicrobial consumption and stewardship policies

COVID-19 pandemic brought to light the discussion about the use of distinct antiinfective agents against viral infection. This discussion was based on some issues: the use of antimicrobials with in vitro activity against SARS-Cov-2, without evidence of in vivo activity [29–33], a difficulty in clinically differentiating bacterial and viral infection, and the presence of viral plus bacterial co-infection.

The advance of the pandemic resulted in overwhelmed health services globally and boosted the research for the magic bullet, which would help in the treatment of COVID-19. The lack of technical information for the management of patients affected by SARS-CoV-2 impacted the use and consumption of many drugs, mainly on antiinfective agents, with no scientific support based on evidence [33,34▪].

Azithromycin, hydroxychloroquine and ivermectin showed in vitro activity against the SARS-CoV-2, and their widespread use generated an increase in the consumption of these drugs [34▪]. Some clinical trials, such as RECOVERY and PETAL, were designed to assess the clinical benefit of hydroxychloroquine with or without azithromycin in hospitalized patients [35,36]. The results of these studies did not identify evidence of clinical benefit of hydroxychloroquine and/or azithromycin when compared to the usual standard of care, therefore, their use to treat COVID-19 is not recommended [35,36]. Ivermectin is another drug with in vitro activity that has been used against SARS-CoV-2. Although there are some clinical studies evaluating the use of ivermectin for the treatment of COVID-19, to date there are no adequate studies demonstrating clinical efficacy in this use.

Further issues which impacted antibiotics use were difficulties with viral and bacterial etiology differential diagnosis and the possibility of co-infection [37]. As previously mentioned in this review, there are many similarities between viral and bacterial infection signs. This fact justifies an initial antibiotic use, but when the pathogen

Table 1. Summary of main findings in bacterial infection in COVID-19 patients

Study, year	Country	Number of patients	Prevalence of bacterial infection (%)	Site of infection	Main pathogens isolated	Severity score
Nori, 2020	USA	4267	3.6%	2.1% respiratory 1.9% BSI	*S. aureus* 44%, *P. aeruginosa* 16%, *Klebsiella* spp. 10%	Charlson Comorbidity Index 2
Li, 2020	China	1495	6.8%	86% respiratory	*A. baumannii* 35%, *K. pneumoniae* 30%, *S. maltophilia* 6%	Not reported
Grasselli, 2021	Italy	774	46% - HAI	Respiratory 50%, BSI 34%	Gram-negative: 64%	SOFA score 4, SAPS II 37
Massart, 2021	France, Switzerland and Belgium	4010	19%		Enterobacteriaceae 14%, MSSA 9%, MRSA 3%	SOFA score 7, SAPS II 40
Sepulveda, 2020	USA	28011	3.8%		*E. coli* 16%, *S. aureus* 13%, *Klebsiella* 10%	Not reported
Ripa, 2021	Italy	731	7.9% (BSI) and 3% (LRTI)	BSI and respiratory	CNS 69%, 42% LRTI	Not reported
Garcia-Vidal, 2021	Spain	989	7.2%	BSI, respiratory and urinary	*S. pneumoniae* 16%, *S. aureus* 16%, *P. aeruginosa* 13%	Not reported
Scott, 2021	USA	1398	8%	Respiratory	*S. aureus* 25%, *K. pneumoniae* 14%, *P. aeruginosa* 12%.	Charlson Comorbidity Index (mean) 0

BSI, bloodstream infection; LRTI, lower respiratory tract infection; SAPS, Simplified Acute Physiology Score; SOFA, Sequential Organ Failure Assessment.

causing the infection is identified, the antibiotic adjustment,
de-escalation or interruption is mandatory, as advocated by rational antimicrobial use policies. Data about co-infection has demonstrated a low frequency of this event in noncritical inpatients, being unnecessary an antimicrobial coverage [9]. On the other hand, critical patients showed higher rates of bacterial and fungal co-infections, and the administration of broad-spectrum antimicrobial therapy is recommended in severe infections [38].

Despite a lack of evidence for antimicrobial use, its prescription was abundant against COVID-19 suspected or confirmed [34▪,39], resulting in increased consumption of several classes of antibiotics such as aminoglycosides, macrolides, carbapenems, cephalosporins, glycopeptides, beta-lactam plus beta-lactamase inhibitors and macrolides, with exception of prophylaxis cephalosporins (cefazolin/cefoxitin) [39]. A recent systematic review by Abu-Rub *et al.* [40] has evaluated the use of antibiotics for patients with confirmed SARS-CoV-2 infection admitted to ICU settings. That review showed that most of the studies (69.2%) had a lack of bacterial co-infection although antibiotics have been prescribed for patients [40]. In another study, Silva *et al.* [34▪] compared antimicrobial consumption in COVID-19 and non-COVID-19 dedicated clusters (ICU, emergency department, and clinical ward). All COVID-19 clusters showed higher rates of antimicrobial use than non-COVID-19. Patients admitted in ICU usually receive antimicrobials, but in the COVID-19 scenario an overuse has been observed in some studies [34▪,41, 42]. Of note, data about antimicrobial consumption are predominantly from the beginning of the pandemic.

In this turbulent period, antimicrobial stewardship practices and organization were greatly impacted. Infectious diseases physicians were moved to the front line of care, leaving their roles in Stewardship uncovered, corroborating for antibiotics misuse [43]. Nowadays, there is an impact of the high use of antimicrobials on bacterial resistance, due to the misuse of antimicrobials in the pandemic period and the high number of multidrug-resistant infections in this population [44].

So far, studies reinforce the lack of effectiveness of antibiotics to treat COVID-19 infection. Furthermore, Stewardship principles must be applied to the maintenance of correct use of antimicrobials and prevent multidrug-resistant organisms' development [44].

CONCLUSION

Despite concerns regarding risk of co-infection in COVID-19 patients, secondary infections are the most important link between severe COVID-19 and bacterial infections. These HAIs impact on outcomes such as mechanical ventilation and hospitalization duration, risk for complications such as shock and organ dysfunction and mortality. Unnecessary increased consumption of antimicrobial agents during pandemic, particularly at admission, might have impact on multidrug resistant pathogens emergence and difficult to treat healthcare associated infections.

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Conflicts of interest

There are no conflicts of interest.

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- ■ of special interest
- ■■ of outstanding interest

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