REVIEW ARTICLE
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Bacterial infections in COVID-19 patients: a review

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INTRODUCTION

The COVID-19 pandemic is the most severe transmissible event to affect the global population in more than a hundred years[1]. Along with the direct social and health-related consequences, the infection brought several indirect effects, that is, one of those is the increasing occurrence of bacterial resistance[2-4]. This effect was not only a direct consequence of the increase of antimicrobial consumption, mainly related to the real occurrence of bacterial infections, but also as a consequence of uncertainties due to the severity of COVID-19 infections and the difficulties in establishing a correct diagnosis of a concomitant or secondary bacterial infection. Additionally, adding up to these uncertainties and the increased prescription of antimicrobials, bacterial infections may worsen COVID-19 prognosis and viral infections are commonly perceived as risk factors for concomitant or subsequent bacterial infections.

There are two types of bacterial infections associated with COVID-19 or other viral infections[5]: (a) coinfections are the result of impaired immune systems, increased nasopharyngeal colonization, and damage of the respiratory tract mucosa, occurring at the same time or shortly after the appearance of COVID-19 or other viral symptoms, and (b) superinfections, which are usually healthcare-associated infections (HAIs), with clinical manifestation and diagnostic criteria resembling other HAIs and usually occurring in patients with severe COVID-19 submitted to invasive procedures during hospitalization.

Frequently, the clinical diagnosis of COVID-19-associated bacterial infections does not meet the criteria of coinfections or superinfections and is usually guided by clinical severity status or by previous experience, non-evidence-based. Such a situation leads to antibiotic misuse, ecological pressure, and previsible increase in bacterial resistance[6,7].

The objective of this study was to review the different aspects of the association of bacterial infections and COVID-19, namely, the impact of COVID-19 in antimicrobial use, incidence and etiology of bacterial infections associated with COVID-19, diagnostic strategies for bacterial infections in COVID-19, and antimicrobial stewardship strategies in COVID-19 patients.

COVID-19, VIRAL SEPSIS, AND ANTIMICROBIAL USE

COVID-19 is not only a respiratory infection but also a systemic infection[8]. After reaching the circulatory system, the severe acute respiratory syndrome *coronavirus 2 (*SARS-CoV-2) disseminates to several organs, using the angiotensin-converting enzyme-2 receptor (ACE-2) to enter the cell[9]. It infects not only the lungs but also several other cells such as enterocytes, renal cells, hepatic cells, and many others[10]. In severe cases, COVID-19 is associated with a cytokine storm, a hyperinflammatory syndrome that resembles bacterial sepsis, with multiorgan failure and an increase of inflammatory biomarkers[11,12]. This syndrome is related to viral subtypes, clinical predisposing factors, and host expression of variant immune proteins, such as toll-like receptors, human leukocyte antigen (HLA)[13], and ABO system[14].

The clinical manifestations of this syndrome are fever, dyspnea, hypotension, tachycardia, confusion, cough, oliguria, and other signs that are commonly seen in bacterial sepsis[8]. Under these circumstances, it is expected that the clinical differentiation between bacterial and viral sepsis is challenging.

The clinical use of antibiotics in COVID-19 is reportedly elevated[15], with an increase in the prescriptions of antibacterials and antifungals, potentially targeting secondary infections. Of note, the increased use of azithromycin as a potential

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antiviral drug has been reported, despite evidence against its use in these situations[16].

Langford et al.[15] performed a systematic review of antibiotic use in COVID-19 patients and found that 74.6% received an antibacterial agent. This proportion of patients receiving is substantially higher than in surgical or medical wards, whereas Charani et al. found the rates of 55 and 45%, respectively[17]. These rates vary according to the country, hospital, and characteristics of the patients. Antibiotic consumption is directly associated with the elevation of resistance rates[7].

There is a concern about the increase in antibiotic resistance as a consequence of the elevated rates of antibiotic prescriptions during the COVID-19 pandemic[18], as well as the reports of the occurrence of infections that may be associated with antibiotic use, such as *Clostridioides difficile*[19] or fungal infections[20,21].

INCIDENCE OF ASSOCIATED BACTERIAL INFECTIONS IN COVID-19

Contrasting with high antibiotic consumption, systematic studies show a low incidence of bacterial coinfections and superinfections in COVID-19 patients[22], with lower rates than the ones reported with influenza[23].

Two meta-analyses were performed on the incidence of bacterial infections in COVID-19 patients (Table 1). Langford et al.[24] analyzed 24 studies from 1,308 publications reviewed. The pooled bacterial infection incidence was 6.9% (95%CI 4.3–9.5), with a higher incidence in severely ill patients. They found 5.9% (95%CI 3.8–8.0) coinfected among all hospitalized patients and 8.1% in critically ill patients (95%CI 2.3–13.8). Coinfection was present in 3.5% (95%CI 0.4–6.7)[24] of COVID-19 patients at the time of initial clinical presentation, while superinfections were detected in 14.3% (95%CI 9.6–18.9)[24]. The latter were probably HAIs related to the use of antibiotics, invasive devices, and severity, and their incidence varied according to the characteristics of the hospital and patients[25]. Ventilator-associated pneumonia (VAP) was reported as the most frequent superinfection.

Table 1. Incidence of bacterial infections in COVID-19 patients.

Study	Infection	Incidence (%)	95%CI
Langford et al.[24]	Pooled rate	6.9	4.3–9.5
	Hospitalized patients	5.9	3.8–8.0
	ICU patients	8.1	2.3–13.8
	Coinfection	3.5	0.4–6.7
	Superinfection	14.3	9.6–18.9
Lansbury et al.[26]	Coinfection	7	3–12
	ICU patients	14	5–26
	Mixed hospital–ICU patients	4	1–9

CI: confidence interval; ICU: intensive care unit.

Lansbury et al.[26] analyzed 3,834 patients from 30 studies and considered only the laboratory-confirmed coinfections at the time of presentation. They found coinfection in 7% of patients (95%CI 3–12), and the subgroup analysis disclosed 14% (95%CI 5–26) in intensive care unit (ICU) and 4% (95%CI 1–9) in mixed hospital–ICU patients.

There is heterogeneity in the diagnostic criteria of the studies included in both meta-analyses. Nevertheless, both show low rates of coinfections and superinfections. The incidence of bacterial infections remains low even in studies of the autopsy findings including the most severe cases, where coinfections and superinfections could be expectedly higher. Clancy et al.[27] performed a systematic review including 621 patients from 75 studies focusing on histopathological criteria. Bacterial infections, including both coinfections or superinfections, were observed in 200 (32%) patients. The most common infection observed was pneumonia (95%), followed by abscesses or empyema (3.5%) and septic emboli (1.5%).

ETIOLOGY OF ASSOCIATED BACTERIAL INFECTIONS IN COVID-19

The etiology of coinfections and superinfections is also variable, depending on the clinical scenario. Studying coinfections, Lansbury et al.[26] showed that *Mycoplasma pneumoniae* was the most common agent and surprisingly *Streptococcus pneumoniae* was not identified in any patient, which probably indicates a selection or sample bias. Another bias in this study was the overexpression of *Pseudomonas aeruginosa* as a causative agent of community-acquired infections. This microorganism, frequently associated with healthcare-related infections, was more frequently isolated than the common causative agents of community-acquired infections, such as *S. pneumoniae* or *Haemophilus influenzae*. This finding probably indicates a selection bias, difficulties in discrimination between community- or healthcare-acquired infections, or selective use of diagnostic tools, such as bronchoscopy, in the more critically ill patients. This finding needs to be further clarified.

Singh et al.[28] used real-time polymerase chain reaction (PCR) in 50,419 individual samples for identifying the presence of SARS-CoV-2 and other bacterial and viral respiratory pathogens, as an effort to evaluate coinfections in COVID-19 patients. From 4,259 SARS-CoV-2-positive patients, bacterial

agents were detected in 33%, with *S. pneumoniae* (8.66%), *H. influenzae* (9.27%), and *Staphylococcus aureus* (13.17%) being the most frequently identified.

Sharov et al.[29] studied bacterial coinfections during the initial epidemic. They analyzed 3,382 samples and similarly identified *S. pneumoniae*, *S. aureus*, and *H. influenzae* as the most common agents associated with bacterial pneumonia.

No studies have evaluated the agents associated with HAIs, especially VAP, in COVID-19 patients; it should, however, be noted that the etiology of such superinfections is highly dependent on local epidemiology. Nevertheless, the increased incidence of *Acinetobacter baumannii* and the fungal infections has been reported[27], which has not been detected in all locations and may reflect local characteristics.

As for the occurrence of resistant bacteria, they were reportedly low in coinfections, which is at least partly explained by the absence of previous antibiotic exposure or hospital contact in many COVID-19 patients. This lack of risk exposure may lead to a lower risk of nasopharyngeal colonization by drug-resistant bacteria such as *P. aeruginosa* and methicillin-resistant *Staphylococcus aureus* (MRSA). Finally, the current data do not support the empirical use of broad-spectrum agents in the treatment of coinfections, particularly in patients without risk factors for antibiotic resistance.

DIAGNOSIS OF BACTERIAL INFECTIONS IN COVID-19

While the diagnosis of VAP or HAI may follow previously established criteria, the diagnosis of coinfections is particularly difficult, once severe COVID-19 may present as sepsis, resembling many aspects of a bacterial etiology. There is no unique clinical sign or laboratory test sufficiently specific to discriminate between viral and bacterial etiology in COVID-19 patients with sepsis.

Since severe COVID-19 may be considered a viral sepsis, many clinical features such as high fever and signs of organ failure may be present[8,30-32], making differentiation between single-agent infection and coinfection a difficult task. New-onset and high fever may be an indication of the development of a coinfection[33] but may also reflect the worsening of clinical status and cytokine storm. An important aspect is that cough in COVID-19 cases is more frequently nonproductive, and bacterial coinfection may commonly present with productive cough and purulent sputum.

Radiologic features are not either completely specific. Both bacterial and viral pneumonia may generate consolidative foci. COVID-19 consolidations in images usually develop in late disease phases and are characterized by multiple peripheral consolidations, while bacterial pneumonia tends to be single and accompanied by air bronchograms[34].

Laboratory tests and biomarkers have been proposed as an important laboratory aid to clinical diagnosis. Neutrophilia, lymphopenia, increased neutrophil-to-lymphocyte rate, thrombocytopenia, elevated transaminases, and lactic dehydrogenase may be useful for the establishment of prognosis but do not discriminate between bacterial and viral infections[35-37].

C-reactive protein (CRP) and procalcitonin have been proposed as the indicators of a bacterial coinfection, but both CRP and procalcitonin do not reach an acceptable specificity to be useful confirmatory tests of bacterial infections[38]. In fact, both biomarkers may be elevated during cytokine storm[37,39-41], blurring their positive predictive values. Dolci et al.[42] studied the value of biomarkers in 83 COVID-19 patients and 33 of those with bacterial secondary infections. Procalcitonin and CRP had a low accuracy (area under receiver-operating characteristic curve [AUC]: 0.757 and 0.874, respectively) and also a weak positive predictive value (0.650 and 0.654, respectively). These findings led to the deduction that the use of both biomarkers without more discriminant, associated clinical data may lead to the unnecessary prescription of antibiotics. However, they are specific enough to help rule out bacterial infections, in conjunction with other clinical and radiological findings[43].

ANTIMICROBIAL STEWARDSHIP STRATEGIES IN COVID-19

Improving antimicrobial prescriptions in a COVID-19 scenario may focus not only on reducing the consumption of broad-spectrum antibiotics or the duration of antibiotic therapy but also on the development of more specific diagnostic criteria for bacterial infections, which may reflect in the general amount of antibacterial prescriptions[44].

A combination of clinical and subsidiary data may be more useful for the diagnosis of bacterial infection than using a single biomarker alone. Some studies[45] suggested that a clinical score alone or combination of data including biomarkers may reduce antimicrobial consumption. This combination may consider the worsening of the clinical status; appearance of a new, high-degree fever and purulent sputum; image with central consolidations or air bronchogram; worsening of lymphopenia; and increased biomarkers such as CRP, procalcitonin, or interleukin-6[33]. Peters et al.[45] proposed a clinical pathway, which may be useful as a guide for specialists and nonspecialists to drive into a better antibiotic prescription (Figure 1). A combination of clinical history and physical examination and procalcitonin may probably be more accurate than a single marker for indicating antibiotic therapy, and clinical reasoning is an important tool in antimicrobial stewardship.

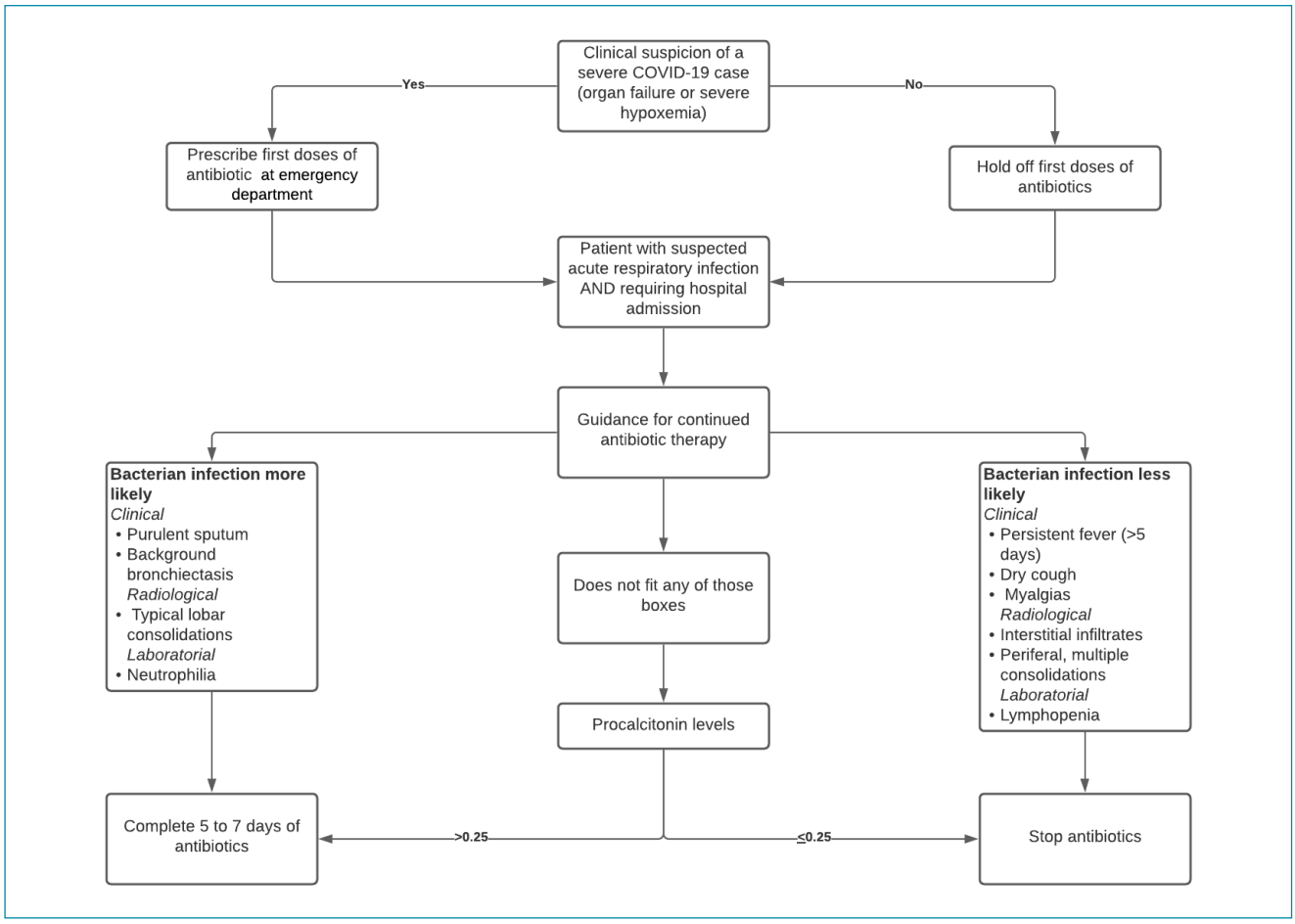

Figure 1. Clinical pathway to guide antibiotic therapy in COVID-19 patients. Adapted from Peters et al.[45].

CONCLUSIONS

Our review reinforces that bacterial coinfections are uncommon in COVID-19 settings, and there is not a single clinical finding, radiological, or laboratory biomarker that is sufficiently specific to guide diagnosis. A combination of signs and tests may be more discriminant than a single marker alone. These efforts could lead to a decrease in antibiotic prescription and consumption with potential improvement in resistance emergence and clinical outcomes. The development of more specific clinical criteria or score is a priority and may help improve clinical practice for COVID-19 or any other viral respiratory infection guidelines.

AUTHORS' CONTRIBUTION

RSG: Writing – original draft, Writing – review & editing.
CRVK: Writing – original draft, Writing – review & editing.

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