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Bacterial co-infections and secondary infections in COVID-19: An integrative review of the clinical features, pathogens, risk factors and implications on the rational use of antimicrobials

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Abstract

Co-infections and secondary bacterial infections in COVID-19 are clinical complications associated with high mortality, which require immediate pharmacological treatment with antibiotics, in addition to the prevention and containment measures to prevent the spread of bacterial pathogens among those infected with SARS-CoV-2, mainly in hospitals and intensive care units. However, due to the emerging nature of COVID-19, little is known about co-infections and secondary infections in COVID-19. Therefore, this literature review gathered information on the forms of clinical presentation of bacterial co-infections and secondary infections in COVID-19 bacterial co-infection/secondary infections, as well as laboratory tools that can support clinical decision-making and guide the rational use of antibiotics, since the non-rational use of this pharmacological class has serious consequences for public health concerning the promotion of bacterial resistance.

Keywords: Co-Infection, secondary infection, SARS-CoV2, bacterial pathogens

Introduction

The success in the clinical management of infectious diseases and their complications depends on the basis that allows for the correct choice of treatment with selection of the appropriate antimicrobial drug, considering a variety of factors that play a part in the selection of the appropriate antimicrobial drug such as scientific evidence on safety and effectiveness, a correctly prescribed prescription, availability, and economic accessibility for the patient, and finally, adequate conditions at the time of dispensing along with suitable information to promote the correct use [1-3]. Moreover, the correct diagnosis and identification of risk factors are critical for making clinical decisions relevant to therapeutic effectiveness and prevention activities [4-6].

In this context, co-infection is a term that designates the simultaneous occurrence of two or more infections by different pathogens in an individual, while the term secondary infection describes a condition where a different infection occurs along with a previous one in the same individual [7-8]. Constituting both cases a significant clinical challenge in the scope of the diagnosis and choice of pharmacological treatments, also representing a challenge for the surveillance services in detecting sources of contamination/infection and application of control/prevention measures in the community and hospital environments [9].

Regarding the COVID-19 (infection by the SARS-CoV-2 virus), an emerging disease that humanity experiences for the first time, information on cases of co-infections and secondary infections, concerning their clinical and epidemiological features, are scarce [10-13]. Therefore, this study reports the main clinical presentations on bacterial co-infections/secondary infections in COVID-19, and the pathogens described in the literature. After gathering pieces of information relevant for the identification of these complications in COVID-19, it will better guide clinical decision making.

SARS-CoV-2 pathogenesis and clinical manifestations

COVID-19 pathology is highly transmissible and unpredictable concerning its clinical evolution that can range from mild symptoms to severe respiratory distress. Therefore, beyond measures to reduce the transmissibility, research for a greater understanding of

aggravations related to chronic comorbidities and diseases as well as co-infections/secondary infections is required. This will improve the health systems and service activities in fighting this viral disease of pandemic magnitude and emerging character [14-16].

In the pathology caused by the SARS-CoV-2, the most common symptoms are fever, nonproductive cough, myalgia, fatigue with abnormal chest findings on computed tomography, and loss/decrease of the senses of smell and taste. Less frequent symptoms include productive cough with or without blood, headaches, and diarrhea [15-17]. However, It must be highlighted that there are asymptomatic cases of COVID-19 [18], as well as inter-individual variability in symptom manifestation of COVID-19 [19], which tends to be more severe in cases of old age, presence

of chronic diseases such as diabetes, cardiorespiratory disorders, cancer, obesity, other comorbidities, and smoke. These risk factors and chronic diseases may increase the risk of developing acute respiratory syndrome which can lead to death [20, 21].

In this sense, COVID-19 is an acute respiratory syndrome (Figure1) that results from the replication of the SARS-CoV2 virus in the type II pneumocytes, which are cells responsible for the production and secretion of surfactant. [22]. When these cells are injured or killed, they release damage-signaling molecules with pro-inflammatory activity that accentuates the inflammation in the lungs, causing pulmonary edema that critically compromises the hematosis process, which could further lead to emergency and admission to an intensive care unit [23, 24].

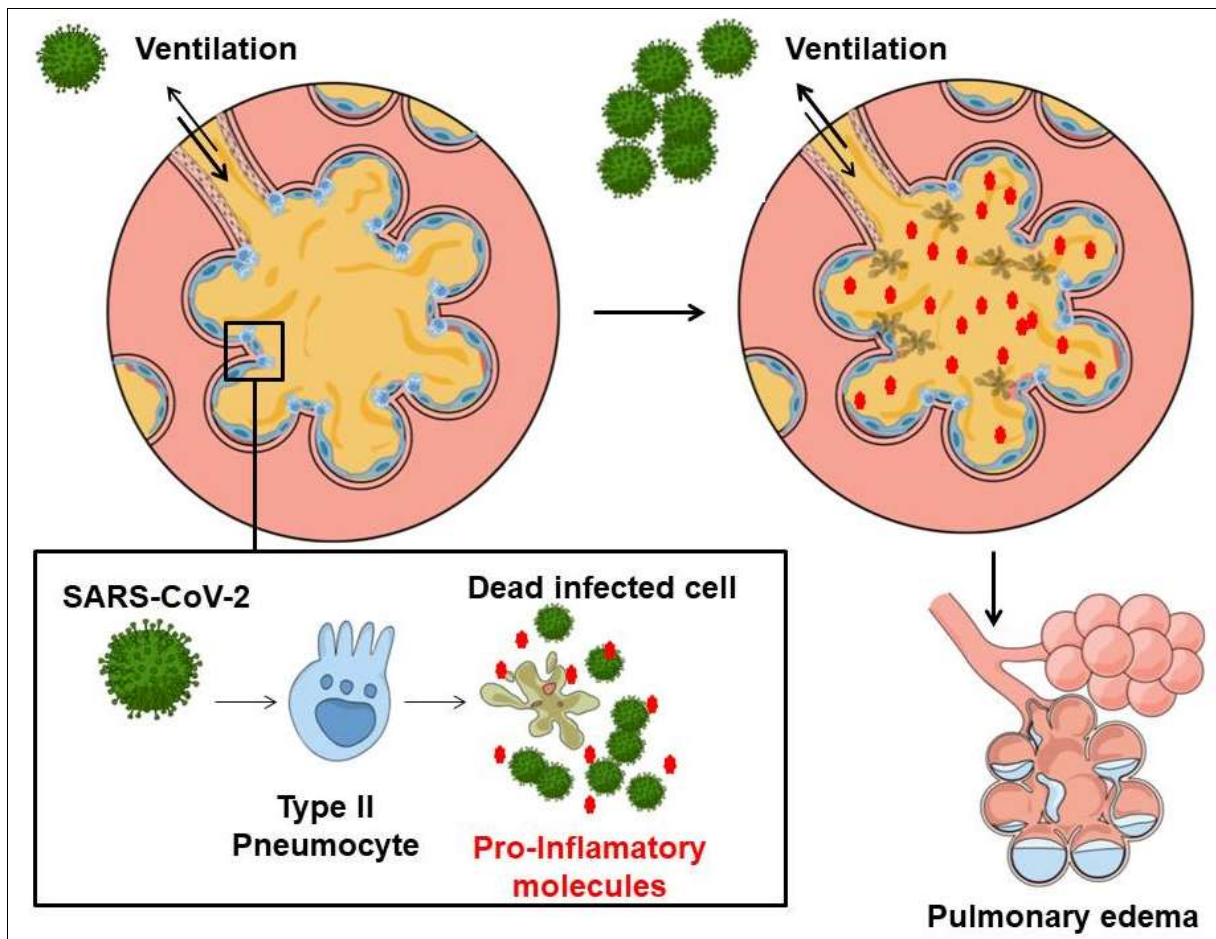


Fig 1: Severe acute respiratory syndrome pathogenesis. The SARS-CoV-2 virus infect type II pneumocytes that die and release pro-inflammatory molecules, increasing inflammation and causing pulmonary edema (fluid accumulation in the lungs), which leads to several complications due impaired gas exchanges

It has been noted the SARS-CoV-2 infection affects the immunological and respiratory system, also producing systemic effects on the kidneys, the liver, the blood, the cardiovascular system, and the nervous system, resulting in several health complaints that endure months after the resolution of the infection [25-30].

In addition, there are cases of reinfection by the SARS-CoV-2 with symptoms of higher intensity [31, 32], indicating gaps in the comprehension of the evolution and biological diversity in the strains of SARS-CoV-2, as well as the features of the host-pathogen interaction concerning the cellular pathways involved in the development of immunological memory after infection.

Clinical presentation and features of bacterial co-infections/secondary infections in COVID-19

Co-infections and secondary bacterial infections in SARS-CoV-2 can be asymptomatic or have symptoms distinct from isolated SARS-CoV-2 infection, involving several variations that hinder both the diagnosis of COVID-19 and bacterial co-infection/secondary infection [12, 33-34]. In cases in which the patient has advanced age, admission to the ICU with mechanical ventilation, use of venous or urinary catheters, treatment with corticosteroids, as well as chronic comorbidities such as diabetes, high blood pressure, heart disease, and infection by the HBV and/or HIV viruses can

all be associated with severe clinical states and high mortality [11, 35-42].

Moreover, large patient flows between different hospitals are also reported as possible risk factors for bacterial co-infections / secondary infections in COVID-19 [43].

Concerning clinical findings of diagnostic value for bacterial co-infections/secondary infections in COVID-19, Neutrophilic leukocytosis is considered a hematological marker since, in isolated COVID-19, there are typically no changes in neutrophil counts [44, 45]. Furthermore, beyond microbiological culture, laboratory tests such as the quantification of interleukin 6, interleukin 1 β , calcitonin, tumor necrosis factor α , and ferritin levels can also be useful in the detection of bacterial co-infections/secondary infections in COVID-19, when they present abnormally high values [42, 44].

Moreover, some typical laboratory tests for the diagnosis of bacterial infections, such as the anti-streptolysin O test, pro-calcitonin and the speed of blood sedimentation can present inconclusive results [44, 46]. Therefore, a set of laboratory tests must be selected instead of a single one to avoid the non-detection of the complication in COVID-19.

Regarding imaging exams, in most cases on radiographs, the typical pattern of COVID-19 with bacterial respiratory infection presents opacity in the lobar or segmental space in the lungs, whereas, in computed tomography exams, the observation of segmental or focal dense consolidation with or without frosted glass opacity is common [12, 46-48].

However, bacterial co-infections/secondary infections in COVID-19 are not restricted to the respiratory tract, existing records of bacterial infections affecting the nervous system [49-51], the urinary system [36, 38, 52, 53], the gastrointestinal system [36, 54, 55], soft tissue [53], the bloodstream [36, 39, 53, 56], cellulite and endocarditis [57], caused by a wide variety of bacterial pathogens (Table 1).

Therefore, high attention to suspicious cases of co-infection/secondary infections with the employment of a set of clinical and laboratory exams can better guide clinical decisions regarding treatment and prevention strategies to avoid the spread of bacterial pathogens among those infected by the SARS-CoV-2 virus.

Bacterial pathogens reported in co-infections/secondary infections in COVID-19 and its implications over antibiotic therapy

A large proportion of patients with COVID-19 may require hospitalization, in which antimicrobials are used empirically, indiscriminately, and excessively (especially azithromycin), imposing an unpredictable negative impact on bacterial resistance to antibiotics, both in the hospital and in the community [58].

Consequently, recognizing the identity of the bacterial agents and the clinical characteristics of co-infection/secondary infection cases in COVID-19 is important when choosing therapy [59, 60] because the pharmacodynamics of antibiotics can be impaired by factors such as the intrinsic resistance of the etiologic agent due to the absence of a molecular target in the bacterial cell, or the presence of resistance acquired by horizontal gene transfer mechanisms. The effect of the antibiotics can be decreased by phenotypic attributes originating from social mechanisms

dependent on population density, as well as structural, metabolic and physiological features with influence over the bacterial metabolic and growth rates [61-67].

There are several factors that can interfere in the pharmacokinetic and efficacy/safety attributes of treatment with antimicrobials. Physical-chemical drug properties, vascularization of the infection site [68-70], patient age, metabolism, drug excretion profiles, as well as drug interaction between antimicrobials and drugs used for managing comorbidities and chronic diseases all play a part in antimicrobial treatment choice [71, 72]. Patient past experience could impose potentially negative effects on drug adherence to the treatment if a patient has had prior adverse drug reactions due to drug toxicity [73, 74].

In this context, a literary survey in the PubMed database with the Boolean operators COVID-19 'and' Bacterial co-infection 'and' secondary infection resulted in the selection of 70 studies, which made it possible to identify the involvement of 22 bacterial families, 23 genus, 39 species and 2 specific phenotypes of bacterial involved in co-infection/secondary infections in COVID-19 cases (Table 1), thus reinforcing the importance of requesting laboratory tests to confirm the identity of the pathogen and its profile of susceptibility to antibiotics in medical practice, which will further guide the selection of the treatment considering the clinical peculiarities of the patient that may affect the outcome of the pharmacological treatment, as well as the spectrum of activity of the antimicrobial drug.

In this context, actions, such as clinical and epidemiological surveillance of agents in co-infections / secondary infections, identification of risk factors and population groups most likely to develop co-infections / secondary bacterial infections along with control and prevention measures such as quarantine, social distancing, hand washing, use of sanitizers and personal protective equipment, are important to provide support in clinical decisions considering the rational use of medicines and prevention of new cases of the disease [58, 75-77].

Moreover, epidemiological information is also important for the different stages of pharmaceutical assistance (selection, programming, acquisition, storage, distribution, and dispensing) by preventing the waste of medicines, which are an important resource and of considerable cost for health systems, thus enabling the allocation of health resources to better meet the needs of the population, assuring the availability of necessary pharmaceutical products in adequate quantity and quality to meet the demands of prescribed treatments [78-80].

However, it is important to highlight that several factors hinder the development and implementation of strategies that can improve infection protection and prevention services, especially concerning the diagnosis of co-infections and secondary infections. It is important to emphasize the development of new sensitive and accurate diagnostic tools, whose results may be obtained quickly, and therefore contributing to the choice of the most appropriate treatment [77], while also providing support for their availability to the population through the management and clinical pharmaceutical services provided to other health professionals, as well as patients in conditions of conducting the pharmacological treatments on their own [81].

Table 1: Bacterial pathogens and type of infection reported in cases of co-infection and secondary infection in COVID-19

Reported pathogen	Infection	Reference
Alcaligenaceae family		
<i>Achromobacter</i> spp	INA	[82]
<i>Bordetella bronchiseptica</i>	Respiratory infection	[83]
<i>Bordetella pertussis</i>	Bacteremia and respiratory infection in children	[34, 84-86]
Actinomycetaceae family		
<i>Actinomyces</i> spp	INA	[44]
Bacteriodaceae family		
<i>Bacteroides</i> spp	INA	[53]
Burkholderiaceae family		
<i>Burkholderia cepacia</i>	Bacteremia	[36]
<i>Lautropia</i> sp	INA	[59]
Brucellaceae family		
<i>Brucella</i> spp	Bacteremia	[87]
Chlamydiaceae family		
<i>Chlamydia</i> spp	Bacteremia and respiratory infection	[84]
<i>Chlamydia pneumoniae</i>	Bacteremia and respiratory infection	[11, 34, 88-90]
Clostridiaceae family		
<i>Clostridioides difficile</i>	Gastrointestinal infection	[54, 55]
Enterobacteriaceae family		
<i>Citrobacter koseri</i>	Urinary tract infection in a newborn	[52]
<i>Escherichia coli</i>	Bacteremia and respiratory infection	[34-37, 39, 42, 44, 56, 57, 82, 89, 91-96]
<i>Enterobacter</i> spp	Bacteremia and respiratory infection	[11, 35, 36, 95]
<i>Enterobacter aerogenes</i>	Respiratory infection	[56]
<i>Enterobacter cloacae</i>	Bacteremia, respiratory and soft tissue infection	[37, 39, 42, 53, 59, 91, 97]
<i>Halfnia</i> spp	INA	[35, 91]
<i>Halfnia alvei</i>	Bacteremia	[37]
<i>Klebsiella</i> spp	Bacteremia and respiratory infection	[84, 95]
<i>Klebsiella aerogenes</i>	Bacteremia and respiratory infection	[39, 44, 57]
<i>Klebsiella oxytoca</i>	Respiratory infection	[57, 85, 96]
<i>Klebsiella pneumoniae</i>	Bacteremia, respiratory and soft tissue infection	[11, 34-37, 39, 42-44, 53, 56, 59, 82, 91, 92, 94, 97-99]
<i>Klebsiella variicola</i>	INA	[96]
<i>Morganella</i> spp	INA	[91]
<i>Proteus mirabilis</i>	Bacteremia	[36, 100]
<i>Providencia</i> spp	INA	[91]
<i>Serratia</i> spp	INA	[35]
<i>Serratia marcescens</i>	Bacteremia	[53, 56]
Enterococcaceae family		
<i>Enterococcus</i> spp	Respiratory infection	[35, 36, 44, 56, 91]
<i>Enterococcus casseliflavus</i>	INA	[39]
<i>Enterococcus faecium</i>	Bacteremia, respiratory and urinary infection	[11, 39, 43, 53, 93, 94, 96]
<i>Enterococcus faecalis</i>	Bacteremia, cellulitis, respiratory and urinary tract infection	[36, 39, 42, 53, 57, 91]
Legionellaceae family		
<i>Legionella</i> spp	Bacteremia and respiratory infection	[84]
<i>Legionella pneumophila</i>	Bacteremia and respiratory infection	[59, 84, 89, 96-98, 101, 102]
Moraxellaceae family		
<i>Acinetobacter</i> spp	Bacteremia	[36]
<i>Acinetobacter baumannii</i>	Bacteremia, respiratory and urinary infection	[11, 37, 40, 42, 44, 53, 56, 59, 93, 94, 97, 101]
<i>Moraxella catarrhalis</i>	INA	[34, 35, 37, 85, 92, 99]
Mycobacteriaceae family		
<i>Mycobacterium abscessus</i>	Respiratory infection	[103]
<i>Mycobacterium bovis</i>	Respiratory infection and extrapulmonary tuberculosis	[104, 105]
<i>Mycobacterium leprae</i>	Skin and peripheral nervous system infection	[51]
<i>Mycobacterium tuberculosis</i>	Respiratory infection and central nervous system infection	[50, 105-108]
Mycoplasmataceae family		
<i>Mycoplasma</i> sp	Bacteremia	[84]
<i>Mycoplasma pneumoniae</i>	Bacteremia and respiratory infection	[11, 18, 34, 41, 59, 85, 88-90, 101, 119-123]
Neisseriaceae family		
<i>Neisseria meningitidis</i>	Infection of the central nervous system	[49, 85]
Pasteurallaceae family		
<i>Haemophilus</i> spp	INA	[59]
<i>Haemophilus influenzae</i>	Respiratory infection	[11, 35, 37, 44, 82, 85, 89, 92, 119]
<i>Haemophilus parainfluenza</i>	Respiratory infection	[82, 84]
Propionibacteriaceae family		
<i>Cutibacterium</i> spp	INA	[44]

Provetellaceae family		
<i>Provetella</i> spp	INA	[124]
Pseudomonadaceae family		
<i>Pseudomonas</i> spp	Bacteremia	[35]
<i>Pseudomonas aeruginosa</i>	Bacteremia and respiratory infection	[11, 34–37, 39, 42–44, 53, 56, 57, 85, 89, 91–95, 101, 119]
<i>Pseudomonas putida</i>	INA	[37]
Staphylococcaceae family		
<i>Staphylococcus aureus</i>	Bacteremia, Cellulite, Endocarditis, Respiratory infection	[11, 34–37, 40, 42, 43, 53, 56, 57, 82, 85, 89, 91, 92, 95, 96, 98–101]
<i>Staphylococcus coagulase negative</i>	Bacteremia	[43, 53]
<i>Staphylococcus epidermidis</i>	Bacteremia	[36, 94, 96]
<i>Staphylococcus haemolyticus</i>	Bacteremia	[93, 94]
<i>Staphylococcus hominis</i>	Bacteremia	[94]
Streptococcaceae family		
<i>Streptococcus</i> spp	Bacteremia	[36, 44, 56]
<i>Streptococcus salivarius</i>	Bacteremia	[57]
<i>Streptococcus</i> group A	Bacteremia and respiratory infection	[125]
<i>Streptococcus pneumoniae</i>	Bacteremia and respiratory infection	[34, 35, 37, 42, 46, 59, 82, 85, 89, 92, 95, 96, 101, 126–128]
<i>Streptococcus pyogenes</i>	Bacteremia	[85]
Veillonellaceae family		
<i>Veillonella</i> spp	INA	[124]
Xanthomonadaceae family		
<i>Stenotrophomonas</i> spp	Bacteremia and respiratory infection	[36]
<i>Stenotrophomonas maltophilia</i>	Bacteremia and respiratory infection	[39, 53, 82, 91, 93, 94]

Final considerations

Co-infections and secondary bacterial infections in COVID-19 are clinical complications that require meticulous medical evaluation to be diagnosed and treated with the right drug. Emphasizing the diagnosis can be challenging due to the diversity of bacterial pathogens and the different anatomical sites that can be infected.

In this context, this work presents valuable insights that can contribute to the identification of co-infections and secondary bacterial infections in COVID-19. However, it also presents limitations concerning the diversity of studies analyzed, ranging from clinical cases to retrospective studies and literature reviews, which in some cases did not allow the extraction of pieces of information such as the type of infection to which some pathogens are linked. Nevertheless, the perspective presented on the phenomenon of bacterial co-infection/secondary in COVID-19 shows that diagnostic protocols for co-infections and secondary bacterial infections in COVID-19, antibiotic stewardship, as well as the development of faster diagnostic means, are necessary to improve clinical decision making to combat mortality involved in this problem.

Conflicts of interest

The authors declare that there are no conflicts of interest.

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