Secondary bacterial infections in patients with COVID-19

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ABSTRACT

Coronavirus Disease 2019 (COVID-19) has been classified as a global threat, affecting millions of people and killing thousands. It is caused by the SARS-CoV-2 virus, which emerged at the end of 2019 in Wuhan, China, quickly spreading worldwide. Patients' clinical features vary, and secondary infections represent a constant risk of increased mortality among those who need hospitalization. Damaged respiratory epithelium and dysregulation of the immune response are the main pathophysiological mechanisms of increased microbial adhesion to the airway epithelial cells and the development of secondary infections. However, the exact incidence of secondary infections in COVID-19 patients is not thoroughly known (3.2%–80%) due to limited and heterogeneous studies that lead to conflicting or non-comparable results. Infection-risk stratification in critically ill patients includes early ICU admission (within 48 hours from hospitalization), age, comorbidity, immunosuppressive drugs administration, and disease severity indexes (oxygenation, inflammation, and cytolysis score). In treating secondary infections, the local epidemiology (which usually includes multidrug-resistant strains) and the modification of any antibiotic regimen according to the cultures' results are critical. Prompt and appropriate antimicrobial agents represent the cornerstone in secondary infection treatment for COVID-19 hospitalized patients.

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INTRODUCTION

During the period December 2019–December 2020, the SARS-CoV-2 has infected more than 70 million people and caused far more than 1.6 million deaths worldwide[1]. SARS-CoV-2 contains monoclonal RNA, has a spherical structure with characteristic corona-like glycoprotein projections, hence the name Corona Virus (CoV), and causes the disease COVID-19 (Corona Virus Disease-19)[2-4]. SARS-CoV-1, another coronavirus, was responsible for the outbreak of Severe Acute Respiratory Syndrome (SARS) in 2003 and the Middle East Respiratory Syndrome (MERS) in 2007[5]. Although mostly asymptomatic, COVID-19 sometimes presents with mild symptoms, myalgias, taste and smell changes in some cases, or moderate pneumonia. Less commonly, COVID-19 manifests as severe pneumonia and Acute Respiratory Distress Syndrome (ARDS), mainly affecting older patients and people with previous comorbidities and inducing high mortality[6]. Specific treatment for COVID-19 is currently not available, and its management mainly consists of preventing transmission by avoiding exposure to the virus. The WHO (World Health Organization) recommends adopting hygiene measures, such as frequent and thorough handwashing with soap and water, antiseptics use, smoking cessation, social distancing, and application of face-nose masks[7]. The recommended treatment for non-critically ill patients includes oxygen, dexamethasone, and remdesivir administration. Dexamethasone appears to increase patients' survival requiring oxygen therapy or invasive mechanical ventilation, while remdesivir may reduce their hospital stay[8,9]. Newer antiviral drugs and monoclonal antibodies are under evaluation. In ICU patients with COVID-19 additional hemodynamic and organ support is often necessary[5]. In intubated and non-intubated patients, the prone position appears useful, while extracorporeal oxygenation (ECMO) benefits selected patients. During their hospitalization, patients with COVID-19 develop secondary bacterial infections. The present article attempts to provide a comprehensive review of the currently available literature on secondary bacterial infections in COVID-19 patients.

REVIEW

Secondary infections in patients with COVID-19

Data on the frequency and characteristics of secondary infections in patients with COVID-19 are limited and conflicting. Initially, studies in China, the United States, and the United Kingdom identified bacterial infections in this group of patients as minor[10-13]. A retrospective study from the UK included 836 patients with confirmed SARS-CoV-2 infection and a control group of flu patients of the same period (2019–2020). In the first five days of hospitalization of patients with COVID-19, the rate of bacterial infections was 3.2%. This percentage amounted to 6.1% throughout their hospitalization, without reported fungal infections. The results were similar to those of the control group[14].

Another retrospective study of 918 patients with COVID-19 from Wuhan, China, found that only 7.1% developed a fungal or bacterial infection, such as pneumonia (32.3%), bacteremia (24.6%), and urinary tract infection (21.5%)[15]. Also, in 150 hospitalized patients with COVID-19 in Wuhan, China, the secondary bacterial infection incidence was 15%; however, among non-survivors, this rate rose to 50%[16]. In another study of 41 patients with COVID-19 from Wuhan, only four patients (10%) developed a secondary infection. However, only thirteen patients (32%) entered the ICU, of which six (15%) died[17]. In another study, the most common complications in 113 non-survivors with COVID-19 were sepsis due to *Acinetobacter baumannii* or *Klebsiella pneumoniae* and ARDS[10]. Respiratory tract infections were reported in 24 of 30 patients with COVID-19 (80%) in Qingdao, China, who developed IgM antibodies to influenza A virus (60%) and influenza B virus (53%), *Mycoplasma pneumoniae* (23.3%), and *Legionella pneumophila* (20%). Strikingly, the incidence of identical infections in patients with community-acquired pneumonia from the same geographical area was only 20.90%[18]. Also, elderly patients (>60 years) with COVID-19 often develop bacterial infections (42.8%)[19]. The rate of bloodstream infections in ICU reaches approximately 25% after the 15th day of hospitalization and 50% after the 30th day[20]. The incidence of COVID-19-associated pulmonary aspergillosis (COVID-Associated Pulmonary Aspergillosis – CAPA) varies from 4% to 35%, depending on the type of study (retrospective or prospective)[21]. Eventually, according to a recent meta-analysis, the prevalence of confirmed bacterial infections in ICU admitted patients with COVID-19 is approximately 14%, without being classified as early or late[22].

Pathophysiology of secondary infections in patients with COVID-19

Damage to the respiratory epithelium

The first line of defence of the respiratory system is the mucosal 'device' (cilia). The mucus covering the airway epithelium contains mainly glycoproteins (mucins) that support innate immunity through their antiviral and anti-inflammatory properties and allow viruses to be trapped and cleared[23-25]. After the virus invades the airways, epithelial cells produce the classical interferons (INFs), especially INF-a and INF-b, limiting virus spread[26-28]. In the airways' epithelium, microorganisms' recognition by special receptors occurs, triggering immune reactions by detecting bacterial and viral components. Infection of the airway epithelium by viruses leads to increased expression of platelet-activating factor receptors (PDF-r) and intracellular adhesion molecule-1 (ICAM-1), causing the chemotaxis of macrophages, neutrophils, natural killer cells, and eosinophils from the bloodstream to the site of infection[29].

Dysregulation of the immune response

Viral infections interfere with mucosal clearance, resulting in increased adhesion of bacteria to the mucosa and bacterial colonies' formation. Excessive mucus concentration (as a reaction to viral infection) also inhibits the accumulation of immune cells and antibacterial molecules[30]. Besides, cell death impairs pathogenic microbes' mechanical clearance and promotes the emergence of new receptors for bacterial adhesion or leads to biofilm formation, mainly by Str. pneumoniae[31,32]. Increased bacterial adhesion, caused by increased surface receptor expression (e.g. by PAF-r involved in the penetration of Str. pneumoniae into the respiratory epithelium) and by desensitized Toll-Like Receptors (TLRs) of lung cells (due to the action of viruses), contributes to the development of secondary bacterial infection[33]. The TLR4 and TLR5 channels change in shape, resulting in decreased neutrophil chemotaxis and increased bacterial adhesion, such as Str. pneumoniae and Pseudomonas aeruginosa, in the airway epithelial cells[34,35]. Other bacteria such as S. aureus are incorporated into the respiratory epithelial cells and cause a further increased ICAM-1 expression[36].

On the other hand, activation of TLRs induces the synthesis of INFs, which enhance the inflammatory response. The interaction of viruses and host cells leads to the secretion of inflammatory cytokines (e.g. TNF-a), which despite their bactericidal activity, can be harmful, causing the appearance of a hyperinflammatory reaction (cytokine storm), characterized by increased mortality[26,35,37]. The risk of secondary infections is higher in patients with hypoxemic respiratory failure (with or without severe lymphopenia) who need ICU admission in the early stages of the disease (<48 hours) (Table 1). Advancing age, comorbidities, concomitant administration of immunosuppressive agents, or increased inflammatory markers (C reactive protein and ferritin) are not substantial risk factors for secondary infections[38].

Treatment of secondary infections in patients with COVID-19

Patients with COVID-19 develop co-infections (bacterial infections that develop simultaneously with the viral infection) and superinfections (bacterial infections that develop during hospitalization). These infections overlap with COVID-19 disease in clinical and laboratory findings and imaging, requiring increased surveillance for their early diagnosis, frequent cultures, and measurement of biomarker levels (e.g. procalcitonin)[19,39]. Table 2 shows the algorithm proposed for the diagnostic approach of these infections.

About 15% of patients with influenza manifest bacterial co-infections, with the most identified bacteria being Str. pneumoniae, Staph. aureus and Haemophilus influenzae. Patients with COVID-19 are less likely to develop community-associated infections (approximately 8.4%), and the responsible bacteria's incidence is unknown. In patients with COVID-19 and co-infection, the treatment protocols of community-associated infections are applied, emphasizing Str. pneumoniae infections with the administration of a β-lactam in combination with a macrolide. In Greece, the

Table 1. Risk factors for secondary bacterial infections in patients with COVID-19 admitted in ICU

1. Hospitalization time before admission to ICU <48 hours
2. COVID-19 disease severity, number of lymphocytes ($<0.7\times10^9$/L)
3. Severity of respiratory failure (PaO_2/FiO_2)

resistance rate of Str. pneumoniae to penicillin is low (about 5.6%); however, macrolide is highly resistant (about 40–45%).

Inpatients with COVID-19 experience infections caused by nosocomial pathogens (Klebsiella pneumoniae, Pseudomonas aeruginosa, bacteria that produce broad-spectrum β-lactamases, Acinetobacter spp, E. coli, Enterococcus spp). Simultaneously, small studies from China reported polymicrobial infections caused by Candida albicans, Acinetobacter baumannii, Klebsiella pneumonia, and Aspergillus fumigatus[17,15,40,41]. The onset of secondary infections depends on patients' comorbidities, use of invasive techniques (e.g. central venous lines placement, hemodialysis techniques) leading to injury of the anatomical defensive barriers (e.g. skin), colonization of the patients, compliance with hand hygiene measures and nurse/patient ratio.

In patients with COVID-19, antimicrobial therapy can be empirical or targeted. The choice of empirical treatment should consider the local epidemiology and antimicrobial resistance profile. The early choice of an appropriate (right drug) and adequate (right dose) antibiotic treatment assumes the knowledge of the local epidemiology (data from the

Table 2. Proposed algorithm for diagnostic approach to secondary bacterial infections in patients with COVID-19 admitted in ICU

Patient with COVID-19
↓
Upon admission to the ICU
↓
Surveillance cultures Bronchial secretions, urine sample and rectum specimens → to know the flora with which the patient is colonized → appropriate empirical antimicrobial treatment awaiting cultures results or when the patient manifests signs of infection and the cultures are negative.
↓
After admitted to the ICU Signs and symptoms of infection (fever, leukocytosis, increased CRP and procalcitonin, worsening of CXR and respiratory function, hemodynamic instability needing fluids or vasoconstrictors, unexplained renal failure likely to indicate 'silent sepsis', increased lactic acid levels and unexplained metabolic acidosis).
↓
Blood cultures At least 1 pair of aerobics and anaerobic culture high fever → at least 2 pairs of cultures (endocarditis ?) positive cultures → RDT (BCID2 or T2MR) to quickly identify the pathogen (within 3 hours). Blood cultures require up to 2 days
Bronchoscopy and BAL Cultures for common bacteria as well as fungi (the incidence of CAPA ranging from 4–35%) Levels of galactomannan (increased in CAPA)
Computed Tomography Chest (respirator-related pneumonia or differential diagnosis of non-infectious causes of fever) Abdominal (ischemic damage due to hypercoagulability associated COVID-19) Brain (infarct by direct infection of the CNS by the virus or other lesions)
Fever persists and cultures are negative 1. TEE (endocarditis, vegetations) 2. Lower extremity ultrasound (septic thrombophlebitis) 3. Levels of 1 ,3-2-D-glucan (> 80 pg/mL → Candida spp infection → pre-emptive antifungal therapy 4. Ophthalmological examination (fungal endophthalmitis) 5. Lumbar puncture (CNS infection, rare in these patients) 6. Continuous obtaining of cultures 7. Check for HIV infection 8. Other infections (TBC, CMV, etc.) 9. Continuous measurement of ferritin levels → early diagnosis of hyper-inflammatory syndrome with cytokine storm (↑ IL-lb and IL-6) levels 10. Direct insult of CNS

BAL: bronchoalveolar lavage. BCID2: blood cultured identification technique. CAPA: COVID associated pulmonary aspergillosis. CNS: central nervous system. RDT: rapid diagnostic technique. TEE: transesophageal echocardiography. T2MR: T2 magnetic resonance.

records of the Hospital Infection Committees) and PK/PDs of the selected antibiotics[10,15,42,43]. Subsequently, the physician can de-escalate or escalate the treatment according to the cultures' results and the antibiotics' susceptibility tests[42,43]. Targeted treatment choice should consider the cultures' results (bacterial species), the susceptibility tests, and Minimum Inhibitory Concentration (MIC) of each antibiotic. Procalcitonin levels distinguish between bacterial and viral infection and serve to discontinue or continue antibiotic treatment[41,43,44].

Often, the local epidemiology differs not only from country to country but also among the same geographical area's hospitals. For this reason, the treatment of secondary infections in patients with COVID-19 cannot follow specific treatment protocols. In China, cephalosporins, carbapenems, and quinolones have been the first-line antibiotics for the treatment of infections, along with the administration of antiviral agents[41]. However, in Greece, the treatment must be different because of the increased incidence of Multi-Drug Resistant (MDR) strains, emphasizing the National Treatment Guidelines for these infections. Besides, the adequate dose of an antibiotic (adequate treatment) depends on specific characteristics of the treated patient (e.g. increased body mass index, increased volume of distribution in septic shock due to capillary leakage, hypoalbuminemia, and renal dysfunction, leading to low concentrations of antibiotics at the site of infection), and the profile of antimicrobial resistance. The optimal dose of an antibiotic also depends on its pharmacokinetic/pharmacodynamic properties (PK/PDs) (antibiotic dose- or time-dependence, the volume of distribution, augmented creatinine clearance) (Figure 1), targeting in therapeutic concentration at the infection's site without concomitant toxicity. Therapeutic Drugs Monitoring (TDM) is the method to achieve therapeutic concentrations of an antibiotic by measuring its trough levels (minimum concentration before the next dose). The continuous infusion (within 24 hours) of the total daily dose of an antibiotic (mainly β-lactams) helps to steadily obtain adequate levels of antibiotic concentration (above MIC) at the site of infection (Figure 2)[45].

Figure 1. Main pharmacodynamic parameters of antibiotics. AUC (Area Under the Curve) = area enclosed between Cmax and MIC, indicating the concentration of antibiotic at the site of infection. Cmax (Concentration maximum) = maximum concentration achieved after a dose of antibiotic, MIC (Minimum Inhibitory Concentration) = minimum inhibitory concentration required to fight a bacterium, t (time) = the time at which an antibiotic displays concentrations above MIC

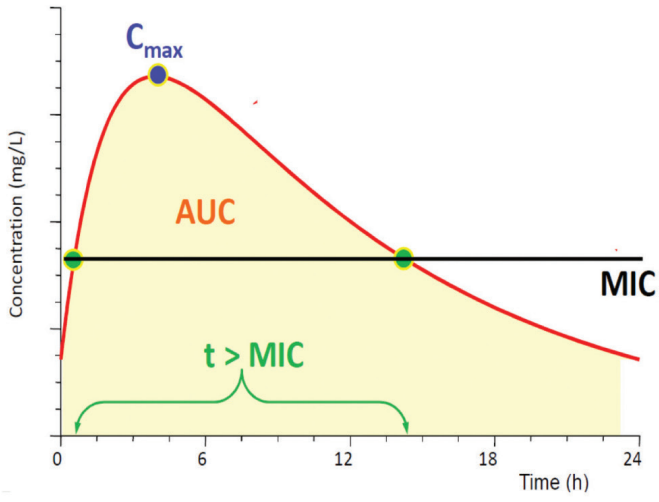

Figure 2. Intermittent, prolonged and continuous administration of antibiotics. (A) Intermittent administration of antibiotics. In susceptible pathogens (*f.i.* MIC 0.25 mg/L), the concentration of antibiotic at the site of infection (AUC_1), and the time of concentration above MIC [*f*T > $MIC_{(0.25mg/L)}$] are adequate. When the same pathogen is resistant (*f.i.* MIC 8 mg/L), the same parameters [AUC_2, *f*T > $MIC_{(8mg/L)}$] are reduced. (B) Prolonged (blue line) and continuous (red line) administration of antibiotics. AUC_3 and *f*T > $MIC_{(8mg/L)}$ are increased in relation to intermittent administration. Continuous administration shows continuously increased values of the same parameters[45]

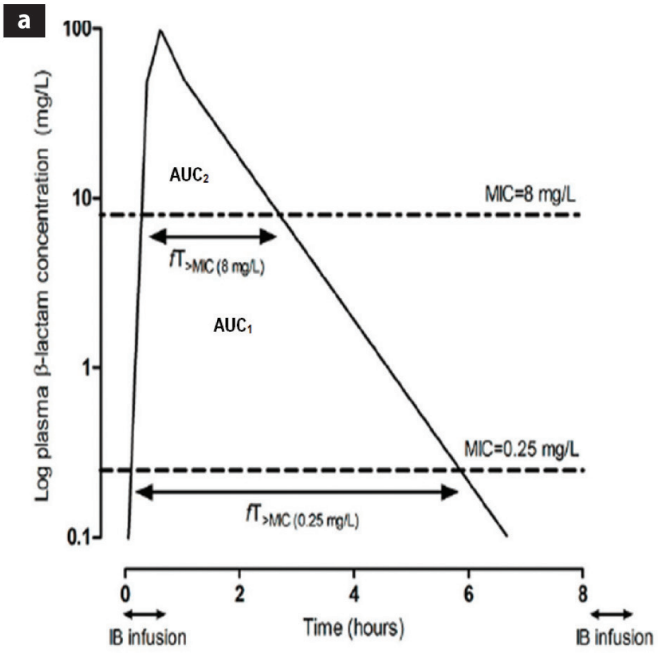

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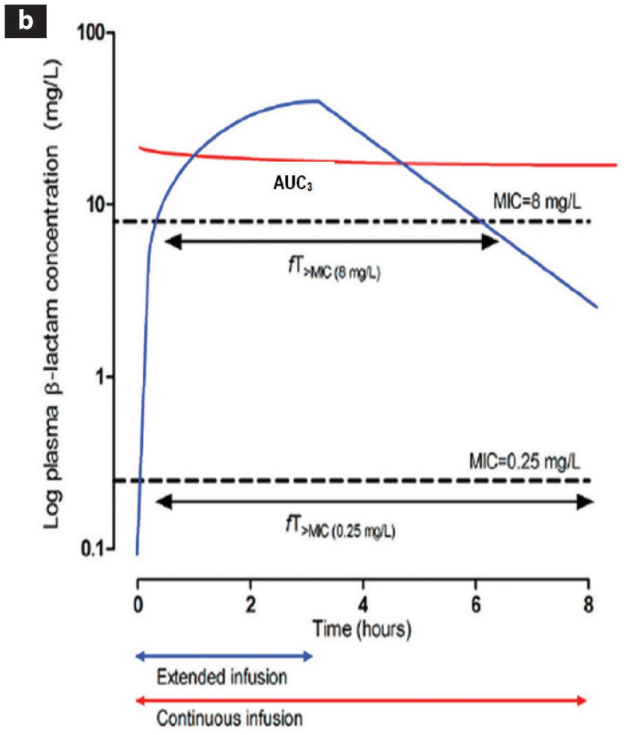
Figure 2. Continued



CONCLUSION

Data on the incidence and characteristics of secondary infections in patients with COVID-19 are currently limited. The risk of bacterial infections increases in patients with COVID-19 admitted to the ICU. The innate immunity of patients with SARS-CoV-2 is impaired, leading to the development of secondary bacterial infections. According to local epidemiology and the antimicrobial resistance pattern, a key issue is choosing an appropriate empirical treatment with broad-spectrum antibiotics. The early, appropriate, and adequate treatment reduces mortality, while of great importance is the de-escalation according to cultures' results and isolated pathogens' susceptibility.

CONFLICTS OF INTEREST

The authors have completed and submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest and none was reported.

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ETHICAL APPROVAL AND INFORMED CONSENT

Ethics approval and informed consent were not required for this study.

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ΠΕΡΙΛΗΨΗ

Δευτερογενείς βακτηριακές λοιμώξεις σε ασθενείς με COVID-19

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Η νόσος από τον ιό SARS-CoV-2 (Coronavirus Disease 2019 - COVID-19) έχει χαρακτηριστεί ως μια παγκόσμια απειλή που πλήττει εκατομμύρια ανθρώπους και έχει οδηγήσει στο θάνατο χιλιάδες από αυτούς. Ο ιός SARS-CoV-2 πρωτοεμφανίστηκε στα τέλη του 2019 στη Βουχάν της Κίνας και έκτοτε εξαπλώνεται γρήγορα σε όλο τον κόσμο. Η κλινική εικόνα του COVID-19 ποικίλλει, ενώ οι δευτερογενείς λοιμώξεις που εκδηλώνονται στους νοσηλευόμενους ασθενείς αποτελούν έναν σταθερό κίνδυνο αυξημένης θνητότητας. Η βλάβη του αναπνευστικού επιθηλίου και η απορρύθμιση της ανοσοαπόκρισης είναι οι κύριοι παθοφυσιολογικοί μηχανισμοί της αυξημένης μικροβιακής προσκόλλησης στα επιθηλιακά κύτταρα των αεραγωγών και της ανάπτυξης δευτερογενών λοιμώξεων. Ωστόσο, η ακριβής συχνότητα εμφάνισης των δευτερογενών λοιμώξεων σε ασθενείς με COVID-19 δεν είναι πλήρως γνωστή (3,2%-80%) λόγω περιορισμένων και ετερογενών μελετών με συγκρουόμενα ή μη συγκρίσιμα αποτελέσματα. Στους παράγοντες κινδύνου για εμφάνιση δευτερογενών λοιμώξεων σε ασθενείς που νοσηλεύονται στη ΜΕΘ περιλαμβάνονται η πρώιμη εισαγωγή στη ΜΕΘ (εντός 48 ωρών από την έναρξη της νοσηλείας), η ηλικία, οι συννοσηρότητες, η χορήγηση ανοσοκατασταλτικών φαρμάκων και οι δείκτες βαρύτητας της νόσου (οξυγόνωση, φλεγμονή και βαθμός κυτταρόλυσης). Για τη θεραπεία των δευτερογενών λοιμώξεων, κρίσιμες παράμετροι είναι η τοπική επιδημιολογία (που συνήθως περιλαμβάνει στελέχη ανθεκτικά σε πολλά φάρμακα) και η επιλογή αντιβιοτικού σχήματος σύμφωνα με τα αποτελέσματα των καλλιεργειών. Η έγκαιρη και κατάλληλη αντιμικροβιακή θεραπεία αποτελεί τον ακρογωνιαίο λίθο της θεραπείας των δευτερογενών λοιμώξεων σε ασθενείς με COVID-19 που νοσηλεύονται.

Λέξεις - Κλειδιά: COVID-19, νοσηλευόμενοι στη ΜΕΘ, δευτερογενείς λοιμώξεις

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