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Review Article

Bacterial Infections in Coronavirus Disease 2019

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Abstract

Infections caused by bacteria, viruses, and fungi have been reported in COVID-19 patients, but data on these infections is limited. These infections are classified as either community-acquired or hospital-acquired and coinfection or secondary/superinfection. The most common hospital-acquired superinfections are ventilator-associated pneumonia, hospital-acquired pneumonia, and bacteremia. The prevalence of community-acquired bacterial pneumonia in patients with COVID-19 infection is uncommon. Co-infection with COVID-19 and tuberculosis (TB) has also been reported. Empiric antibiotics may not be required in the majority of COVID-19 patients, especially those not severely ill. Superinfections by antibiotic-resistant bacteria have also been reported among critically ill patients with COVID-19 infection.

Keywords: Bacteria; Coronavirus Disease 2019; Community-acquired Infections; Hospital-acquired Infections

Introduction

Generally, infections caused by bacterial, viral, and fungal pathogens are categorized as either community or hospital-acquired infections. They are also may be described as co-infections or secondary/superinfection. According to the widely accepted US Centers for Disease Control and Prevention (CDC) 1988 guidelines, infections identified in samples taken more than 48 hours after admission and before discharge should be classified as hospital-acquired, while those taken before or within 48 hours of admission should be classified as community-acquired [1,2]. While some studies used the CDC definition to describe coronavirus disease 2019 (COVID-19) community and hospital-acquired infections [3,4], another study defined community-acquired coinfection as an infection detected within the first 24 hours of a patient's hospitalization [5].

Coinfection is an infection that occurs concurrently with the initial infection, whereas superinfection is defined as an infection that occurs after a previous infection, particularly when caused by microorganisms that are resistant or have become resistant to the antibiotics used previously [6]. The distinction is temporal: "coinfection occurs concurrently, whereas secondary/superinfection develops after the initial infection" [6]. Secondary infection is established if patients have clinical symptoms or signs of infection and are associated with a positive culture of new pathogens from the lower respiratory tract or blood samples collected ≥ 48 hours following admission [1,5,7].

Bacterial, viral, and fungal infections have been reported in COVID-19 patients [3,5,8,9] and may be associated with severe disease and worse outcomes [3,5]. The proportion of these infections in COVID-19 patients varied widely across studies [5,8,9].

This review explored the current literature on bacterial infections in COVID-19 patients. A review of viral and fungal infections in COVID-19 patients is beyond the scope of this review.

Prevalence of community and hospital-acquired infections

The prevalence of community-acquired coinfections by bacterial, viral, and fungal pathogens is low in COVID-19 patients [3,5]. However, patients with community-acquired co-infections required intensive care unit (ICU) admission more frequently than those who did not have an infection [5]. Hospital-acquired infections, especially bacterial or fungal infections, were frequently complicating the course of ICU patients [3,8]. In a Switzerland study of 162 COVID-19 patients, community-acquired coinfections were reported in only 3.7% (6/162) of patients [3]. Hospital-acquired infections, on the other hand, were reported in 10.5% (17/162) of patients and were more common in ICU patients (36.6%, 15/41) than in non-ICU patients (1.7%, 2/121) [3]. Furthermore, COVID-19 patients with coinfections had a prolonged length of hospital stay and an increased risk of death [4,5,10]. A retrospective study of 254 patients from England showed that patients with coinfection/co-colonization were more likely to die in ICU (with coinfection/co-colonization, n = 34 versus without coinfection/co-colonization, n = 48, crude OR 1.78, 95% CI 1.03-3.08, P = 0.04) and had a longer hospital stay (measured from admission to hospital to the end of ICU admission, sub hazards ratio (likelihood of discharge from ICU) = 0.53, 95% CI 0.39-0.71, P < 0.001) [4]. Similarly, a systematic review and meta-analysis of 30 studies, including 3,834 patients with COVID-19 found that COVID-19 patients with co-infection were more likely to die than patients who did not have co-infection (pooled crude odds ratio (OR) 582, % CI 34 - 99, n = 733, 4 studies, I 2 = 854%) [10]. In a Spanish study of 989 COVID-19 patients, the overall mortality rate was 9.8% (97/989) [5].

Bacterial coinfections

The exact proportion of bacterial infections in COVID-19 patients remains unknown. In a meta-analysis based on 118 studies, the pooled prevalence of bacterial coinfections was 8% (95% CI: 5%-11%) and bacterial superinfection was 20% (95% CI: 13%-28%) [11]. In another meta-analysis and systematic review of 24 studies, including 3,338 patients with COVID-19, bacterial infections were reported in 5.9% of all hospitalized patients (95%CI 3.8-8.0%) and 8.1% of critically ill patients (95%CI 2.3-13.8) [12]. According to the National Institute for Health and Care Excellence (NICE), evidence as of March 2021 indicates that bacterial infections occur in less than 8% of COVID-19 patients, and could be as low as 0.1% in hospitalized patients with COVID-19 [13]. According to a study from Pakistan, the severity of COVID-19, as well as the use of steroids, were risk factors for bacterial infection in COVID-19 patients and both increased the bacterial infections by about four-fold [14]. In another retrospective study of 918 COVID-19 patients from China, the significant predictors of nosocomial infection were invasive devices, diabetes, and antibiotic combinations, which increased the risk of nosocomial infection by approximately four-fold, three-fold, and one-fold respectively [15].

Hospital-acquired bacterial superinfection

The England study showed that the rate of co-infection/co-colonization >48 hours after admission was 27.0 per 1000 person days (95% CI 21.3-34.1) [4]. In a meta-analysis, a secondary bacterial infection that developed during the disease course or hospital stay was 14.3% of patients (95%CI 9.6-18.9%) [12]. In a large multicenter retrospective study from the United States, where 141,621 patients were tested for SARS-CoV-2 (17,003 [12.0%] positive) and 449,339 patients were not tested, bacteria were responsible for approximately 80% of pathogens in all three groups, with Gram-negative bacteria, primarily Enterobacterales accounting for the majority of pathogens in all three groups [16]. Specific pathogen rates were generally comparable across the three groups, although the rates of some bacteria, including *Pseudomonas aeruginosa*, were significantly higher in SARS-CoV-2-positive patients compared to negative or untested patients [16]. According to the Spanish study, hospital-acquired bacterial superinfections, mostly caused by *Pseudomonas aeruginosa* and *Escherichia coli*, were diagnosed in 38 patients (3.8%), with a mean (SD) time from hospital admission to superinfection diagnosis of 10.6 (6.6) days [5]. Of these 3.8% superinfections, 56.8% occurred in patients admitted to the ICU [5]. Some studies have shown that Gram-negative bacteria were more common than Gram-positive organisms [4,14,15]. In the England study, the proportion of Gram-negative bacteria, especially *Klebsiella pneumoniae* and *Escherichia coli*, increased with the length of the ICU stay [4].

The most common hospital-acquired superinfections were ventilator-associated pneumonia (VAP) 25% (11/44), hospital-acquired pneumonia (HAP) 9% (4/44), and bacteremia 36.3% (16/44) [5]. In a previous retrospective study of 918 patients from China, the incidence of VAP was 32.3% [15]. Another study from Cambridge, United Kingdom, compared the incidence of VAP and bacterial lung microbiome composition in 81 ventilated COVID-19 and 144 non-COVID-19 patients and found that patients with COVID-19 developed VAP at a rate of 28/1000 ventilator days, while those without COVID-19 developed VAP at a rate of 13/1000 ventilator days (p = 0.009) [17].

Community-acquired bacterial coinfections

Community-acquired bacterial pneumonia has also been reported in patients with COVID-19 infection but it is uncommon, with a prevalence that ranges from 0% to 6% [18]. In the previous meta-analysis of 24 studies, bacterial coinfection (estimated on presentation) was identified in 3.5% of patients (95%CI 0.4-6.7%) [12].

The most common bacterial causes of community-acquired pneumonia with severe influenza are *Staphylococcus aureus* (methicillin-resistant, *Staphylococcus aureus* [MRSA], and methicillin-susceptible *Staphylococcus aureus* [MSSA]), *Streptococcus pneumoniae,* and group A Streptococcus [18]. In the Spanish study, community-acquired bacterial coinfections, mainly caused by *Streptococcus pneumoniae* and *Staphylococcus aureus*, were reported only in 2.5% (25/989) of COVID-19 patients [5]. Similarly, in the England study, the commonest pathogens within 48 hours of hospital admission (community-acquired infection) were *Staphylococcus aureus* and *Streptococcus pneumonia* [4]. In a retrospective study from France, bacterial coinfection was found in 28% (26/92) of critically ill COVID-19 patients at ICU admission. When the 30 patients who had been hospitalized for more than 48 hours prior to ICU admission were excluded, 29% (18/62) of the patients were considered to have a bacterial coinfection upon ICU admission, mostly with *Staphylococcus aureus* (n = 5/18, 28%), Haemophilus influenzae (n = 4/18, 22%), *Streptococcus pneumoniae* (n = 3/18, 17%), *Enterobacteriaceae* (n = 3/18, 17%), *Pseudomonas aeruginosa* (n = 2/18, 11%) and *Acinetobacter baumannii* (n = 1/18, 6%) [19].

Common bacteria involved in COVID-19 coinfections/ secondary infections

While some of the bacteria involved in the community and hospital-acquired COVID-19 superinfections were identified in previous sections, this section will summarize them based on the previous meta-analysis and a systematic review of 24 studies [12]. Bacterial infection was defined as an acute infection including either coinfection at the time of presentation, or secondary infection developing during disease or hospital stay [12]. Approximately, 34 bacterial co-pathogens were identified [12]. The most common bacteria were *Mycoplasma* species (32.4%), followed by Haemophilus influenzae and *Pseudomonas aeruginosa* (14.7%, each) [12]. Other pathogens identified included *Klebsiella* species (11.7%), *Enterobacter* species (11.7%), Serratia species (5.8%), *Staphylococcus aureus* (5.8%), *Acinetobacter baumannii* (2.9%) and *Enterococcus faecium* (2.9%) [12].

To identify bacterial pneumonia and to decide on the use of antibiotics, some tests are recommended [13]. These include a complete blood count, chest imaging (chest X-ray (CXR), computed tomography (CT), or ultrasound), respiratory and blood samples [for example, sputum or tracheal aspirate samples, blood cultures, urine samples for Legionella, pneumococcal antigen testing, throat samples for respiratory viral (and atypical pathogen) and polymerase chain reaction testing] [13]. In a Spanish study of 989 COVID-19 patients, bacterial respiratory coinfections were diagnosed in patients with one or more positive cultures of respiratory pathogens taken from blood, pleural fluid, qualified sputum (>25 polymorphonuclear leukocytes and < 25 epithelial cells) and bronchoalveolar lavage (BAL), and/or a positive urinary antigen test for *Streptococcus pneumoniae* antigen in urine that detected with a rapid Standard F S. pneumoniae Ag fluorescent immunoassay assay [5].

Because of concerns regarding SARS-CoV-2 aerosolization during diagnostic procedures or specimen preparation, Gram stain, culture, or another testing of respiratory specimens is often unavailable [18]

Tuberculosis and covid-19 coinfection

COVID-19 has been reported to occur irrespective of tuberculosis (TB) occurrence, whether before, simultaneously, or after an active TB diagnosis [20,21]. In the first cohort of 49

patients with current or former TB and with COVID-19 infection from eight different countries (Belgium, Brazil, France, Italy, Russia, Singapore, Spain, Switzerland), COVID-19 was diagnosed before TB in 14 patients (28.5%) and was diagnosed after TB in 26 patients (53.0%) whereas the diagnosis of both diseases was simultaneously or within the same week in 9 patients (18.3%) [20]. Forty-two (85.7%) patients had active TB and seven (14.3%) had post-TB treatment sequelae [20].

The risk factors of severe COVID-19 and the need for intensive care and mechanical ventilation include older age and certain comorbidities such as diabetes mellitus (DM) and chronic obstructive pulmonary disease (COPD), all of these also are a poor prognostic factor of TB [22]. The effect of COVID-19 on TB outcomes in patients with other risk factors like malnutrition, kidney failure, and liver disease is still being studied [22]. Although untreated human immunodeficiency virus (HIV) infection is a substantial risk factor for TB progression or poor outcomes in TB patients, its impact on the prognosis of COVID-19 patients is uncertain [22]. In the earlier cohort of 49 patients with current or former TB from eight different countries, 8/47 (17.0%) patients had COPD/asthma, 8/49 (16.3%) had diabetes, 7/49 (14.3%) had liver disease, 6/48 (12.5%) had HIV infection, and 5/49 (10.2%) had renal failure [20]. The case fatality rate was 12.3% (6/49) and was higher among elderly people (5/6 were >60 years old and all had at least one comorbidity) [20]. Another study from the Philippines, based on a matched sample of 530 COVID-19 patients with 106 cases with TB cases and 424 without, showed that COVID-19 patients with TB had a two-fold increased risk of death, and were less likely to recover [23]. Furthermore, the time to death was shorter and the time to recovery was longer in patients with TB than in patients without TB [23]. In another large cohort from South African with nearly 3.5 million patients (16% HIV positive), HIV, current TB, as well as a history of TB increased the risk of death in patients with COVID-19 infection [24]. HIV increased the risk of COVID-19 mortality by approximately two-fold, irrespective of viral suppression [24]. Current and previous TB also increased COVID-19 mortality by approximately two-fold and one-fold, respectively [24].

COVID -19 and TB coinfection rates have been reported to be higher in males and migrants [20,25], however, the mortality rate was lower in migrants most likely due to their younger age and lower number of comorbidities [20,26]. Nonetheless, the mortality rate was higher in young people in settings where advanced forms of TB were common and caused by drug-resistant strains of Mycobacterium tuberculosis [26].

Cough, fever, and shortness of breath are common symptoms in COVID-19 and TB patients [21,22,27]. This can result in diagnostic confusion as well as worsening stigmatization of TB patients, particularly in low- and middle-income countries (LMICs) [27]. In a review of eight studies, including 80 patients with COVID -19 and TB coinfection reported from nine various countries with most cases from Italy, the majority of reported patients were symptomatic; the clinical presentation and imaging findings of these symptomatic COVID 19 and TB patients were indeed similar to those of patients without TB [25]. Bilateral ground-glass opacities were more frequent in patients with COVID 19 infection, and cavitary lesions were more frequent in patients with TB [25].

Of note, the clinical features of TB and COVID-19 vary in some aspects [22]. TB has a longer incubation period and a slow onset [22]. In TB, coughing is productive of sputum and even blood, while in uncomplicated COVID-19, dry cough is more common [22]. Furthermore, shortness of breath occurs early after the onset of COVID-19, whereas in TB, it occurs much later or as a long-term sequela [22]. COVID-19 outbreaks in the same household or congregate setting typically manifest within a week or two, whereas TB progression is rarely abrupt and can occur months later [22].

Importantly, being diagnosed with COVID-19 does not rule out the possibility of underlying TB, and in TB-endemic areas, this should be taken into account [27]. The possibility of TB in a COVID-19 patient should be considered if the course of the illness after the first week was suggestive of TB, such as progression to hemoptysis, persistent fever, night sweats, or weight loss [22]. A careful history of TB exposure, or a previous episode of TB in the same patient or family, may help to make a diagnosis [22]. Sputum, along with a variety of other biological specimens, can be used to diagnose TB using culture or molecular techniques [22]. Chest radiography or imaging may aid in distinguishing TB from other pathologies [22]. Although health systems are being strained by the COVID-19 pandemic, routine and testing services for TB should be prioritized [23].

In most cases, TB treatment does not differ between patients infected with COVID-19 and those who do not [22]. Experience with comanagement of COVID-19 infection and TB is still limited [22]. Suspension of TB treatment in COVID-19 patients, on the other hand, should be considered exceptional [22]. TB preventive treatment, as well as treatment for drug-susceptible or drug-resistant TB disease, should be continued uninterrupted to protect the patient's health [22]. In the prior cohort of 49 patients with current or former TB, the majority of patients (n = 37) had drug-susceptible TB or were treated with first-line drugs for new cases, while eight patients who had drug-resistant TB were treated with second-line drugs [20]. In a previous review of 80 patients with TB and COVID 19 coinfections, most patients with TB were treated with multidrug regimen antitubercular therapy [25].

Superinfection by multidrug-resistant bacteria

Super-infection by multidrug-resistant (MDR) bacteria have also been reported among critically ill patients with COVID-19 infection [3,5,28,29]. In a previous study from Pakistan, MDR Acinetobacter was isolated from blood in three out of ten patients, followed by ceftriaxone-resistant *Escherichia coli* in two patients, vancomycin-resistant Enterococcus in two patients, and ceftriaxone resistant Klebsiella pneumonia in one patient [14]. MDR Acinetobacter was the most common cause of hospital-acquired infections, while Methicillin-resistant *Staphylococcus aureus* (MRSA) was the main cause of coinfection in COVID-19 patients [14]. The Switzerland study reported the identification of *Acinetobacter baumannii* producing the carbapenemase OXA-23 from 2.9% (1/34) of patients with VAP [3]. Another study reported the detection of a highly resistant *Acinetobacter baumannii* from 1% (1/99) of critically ill patients [28]. *Klebsiella pneumoniae* and Aspergillus flavus fungi were also detected in the same patient [28]. In another study, carbapenem-resistant *Klebsiella pneumoniae* was detected in 2% (1/52) of critically ill patients [29]. The Spanish study showed the detection of MDR Gram-negative bacteria in seven patients, including MDR *Pseudomonas aeruginosa* infection (n = 3), extended-spectrum β-lactamase (ESBL) *Escherichia coli* (n = 2) and ESBL *Klebsiella pneumoniae* (n = 2) [5]. MRSA was detected in two patients [5]. MRSA was also isolated from BAL PCR/ culture of one patient in the England study. The same patient had also MRSA in pleural fluid culture after 48 hours of hospital admission [4]. Overall, the rate of MDR infection was low, probably due to the effect of COVID-19 isolation measures that prevented horizontal transmission between patients [5].

Bacterial coinfection/secondary infections and associated mortality

Secondary infections had been diagnosed in 50% (27/54) of nonsurvivors and only 1% (1/137) of survivors in a study of 191 patients in China [30]. VAP occurred in ten 31% (10/32) of patients requiring invasive mechanical ventilation [30]. In the previous study from Pakistan, the mortality rate was 30% and it was higher in patients with COVID-19 having bacterial coinfection or secondary infections compared to controls (42% vs. 18%) OR = 3.29; 95% CI: 1.32-8.23 (p = 0.011) [14]. Among 18 of 21 COVID-19 patients who died from bacterial infections were infected with Gram-negative organisms, with Acinetobacter species (n = 9) and *Pseudomonas aeruginosa* (n = 7) being the most frequent pathogens [14]. In a comprehensive review of 621 patients dying with COVID-19, potential bacterial lung superinfections were evident at postmortem examination in 32% of patients (proven, 8%; possible, 24%) [31]. Potential bacterial superinfections included pneumonia (95%, 191/200), abscesses or empyema (3.5%, 7/200), and septic emboli (1.5%, 3/200) [31]. In 73 percent of cases, the pneumonia was focal rather than diffuse [31]. The most common histopathologic findings were intra-alveolar neutrophilic infiltrations, which differed from those seen with COVID-19-associated diffuse alveolar damage [31]. According to their sequential order, the pathogens of infection were *Acinetobacter baumannii*, *Staphylococcus aureus*, *Pseudomonas aeruginosa*, and *Klebsiella pneumoniae*. Lung superinfections were the cause of death in only 16% of potential cases and 3% of all COVID-19 patients [31].

Empiric antimicrobial agents in patients with COVID-19

Some clinicians routinely prescribe broad-spectrum antibiotics as empiric therapy for bacterial pneumonia to all patients with COVID-19 and moderate or severe hypoxemia [18]. Other clinicians only use antibiotics in particular cases, such as when a CXR shows a lobar infiltrate when a patient has leukocytosis, an elevated serum lactate level, microbiologic data, or shock [18]. In the previous meta-analysis and systematic review, 72% of COVID-19 patients received empirical antibiotics (antibiotic use was reported in 14/24 studies) [12]. Antibiotic use was generally a broad spectrum, with fluoroquinolones and third-generation cephalosporins accounting for 74% of the antibiotics prescribed [12].

Because the overall proportion of bacterial infections is low in COVID-19 patients, widespread empiric antibiotic use in the

majority of hospitalized patients is not recommended [10,12]. They are also not recommended for preventing secondary bacterial pneumonia in COVID-19 patients [13]. Nevertheless, empiric broad-spectrum antimicrobial therapy is the standard of care for the treatment of shock [18]. Antibiotic stewardship is essential for avoiding reflexive or continued courses of antibiotics [18]. Inappropriate antibiotic use may reduce their availability and may also result in *Clostridioides difficile* infection as well as antimicrobial resistance, especially when broad-spectrum antibiotics are used [13]. Prospective studies on superinfection are required, with clinical, microbiological, and epidemiological data that may be used to develop successful antimicrobial stewardship strategies, which can play a critical role in antimicrobial prescription [32].

Conclusion

Bacterial infections have been reported in COVID-19 patients, but their proportion varied widely across studies.

Although community-acquired coinfections are low in COVID-19 patients, ICU admission is more frequently required in those patients than in those who did not have an infection. Hospital-acquired bacterial infections are frequently complicating the course of ICU patients. The most common hospital-acquired superinfections are VAP, HAP, and bacteremia.

Coinfection with COVID-19 and TB has also been reported. Cough, fever, and shortness of breath are common symptoms in both infections, which can lead to diagnostic confusion as well as worsening stigmatization of TB patients, particularly in LMICs.

Empiric antibiotics may not be required in the majority of these patients, particularly those not severely ill. Moreover, superinfections by antibiotic-resistant bacteria have been reported among critically ill patients with COVID-19 infection.

Prospective studies on superinfection are required, with clinical, microbiological, and epidemiological data that may be used to develop successful antimicrobial stewardship strategies, which can play a critical role in antimicrobial prescription.

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