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Bacterial, viral, and fungal infections among patients with coronavirus disease 2019: A mini-review

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Abstract

Infections with bacteria, viruses, and fungi have been reported in coronavirus disease (COVID-19) patients, however, data on these infections are still scarce. These infections are categorized as either community or hospital-acquired infections and may be described as coinfections or secondary/superinfection. The proportion of these infections varied widely across studies. Hospital-acquired infections, especially bacterial or fungal infections, are frequently complicating the course of intensive care unit (ICU) patients and associated with increased morbidity and mortality. The most common hospital-acquired superinfections are ventilator-associated pneumonia, hospital-acquired pneumonia, and bacteremia. The coprevalence of community-acquired secondary bacterial pneumonia and COVID-19 infection is unusual. Co-infection with COVID-19 and tuberculosis (TB) has also been reported. COVID-19 and TB patients frequently experience coughing, fever, and shortness of breath. This can lead to diagnostic confusion as well as worsening stigmatization of TB patients, especially in low- and middle-income countries (LMICs). Empiric antibiotics may not be required in the majority of COVID-19 patients, particularly those not severely ill. Superinfections by antibiotic-resistant bacteria have also been reported among critically ill patients with COVID-19 infection. The most prevalent identified viruses among COVID-19 patients are influenza type A, influenza type B, and respiratory syncytial virus. Patients with severe COVID-19 infection are also at risk for fungal infections such as Aspergillus, Candida, Pneumocystis, or other fungal species, which has been linked to increased morbidity and mortality such as Mucormycosis.

Introduction

An outbreak of severe pneumonia of unknown etiology first emerged in Wuhan, Hubei,China, in December 2019 and was reported to the World Health Organization (WHO) [1]. The etiology of this disease was linked to a novel virus that belongs to the coronavirus (CoV) family. The new virus was initially called 2019-nCoV by WHO [2] Subsequently, the WHO declared coronavirus disease (COVID-19) as a new name for this disease [3]. As regards the virus itself, the International Committee on Virus Taxonomy (ICTV) has renamed the 2019-nCoV as severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) [4].

Infections with bacteria, viruses, and fungi have been reported in COVID-19 patients [5–8] and may be associated with severe diseases and worse outcomes [6,8]. Because the disease is still spreading globally, data on these infections in COVID-19 are limited.

The proportion of bacterial, fungal, or non-SARS-CoV-2 viral infections in COVID-19 patients varied widely across studies [5–7]. Overall, viral and fungal infections are less common than bacterial infections [5,6,8–10]. In two studies involving 989 and 257 COVID-19 patients from Spain and China, respectively, and other microbiologically confirmed infections were reported in 7.2% and 94.2% of patients, respectively with 88 pathogens including 74 bacteria, seven viruses, and seven fungi in the first study [6] and 24 respiratory pathogens including 11 bacteria, 9 viruses, and 4 fungi in the second study [5]. Similarly, another study of 162 COVID-19 patients from Switzerland reported 31 infections, with the majority being bacterial infections (24), five viral infections, and three fungal infections [8]. Some of these pathogens were known antibiotic resistance, which may make the treatment of COVID-19 patients more difficult [5].

This brief review explored the current literature on bacterial, viral, and fungal infections in COVID-19 patients.

Overview of bacterial, viral, and fungal infections in COVID-19

Generally, infections 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 [11,12]. While some studies used the CDC definition to describe COVID-19 community and hospital-acquired infections [8,13], another study defined community-acquired coinfection as an infection detected within the first 24 hours of a patient's hospitalization [6].

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 [14]. The distinction is temporal: "coinfection occurs

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concurrently, whereas secondary/superinfection develops after the initial infection" [14]. 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 [6,11,15].

To identify bacterial or fungal, or non-SARS-CoV-2 viral pneumonia and to decide on the use of antibiotics, some tests are recommended [9]. 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 [9]. In the previous Spanish study, bacterial respiratory co-infections 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 [6]. Specific rapid real-time PCR testing was used for influenza A and B viruses, as well as respiratory syncytial virus diagnosis. Multiplex PCR testing was also used for influenza viruses A, B, and C; parainfluenza 1, 2, 3, and 4; and metapneumovirus diagnosis [6]. Because of concerns regarding SARS-CoV-2 virus aerosolization during diagnostic procedures or specimen preparation, Gram stain, culture, or another testing of respiratory specimens is often unavailable [16].

The proportion of community and hospital-acquired infections

The proportion of community-acquired coinfections is low in COVID-19 patients [6,8]. However, patients with community-acquired co-infections required intensive care unit (ICU) admission more frequently than those who did not have an infection [6]. Hospital-acquired infections, especially bacterial or fungal infections, were frequently complicating the course of ICU patients [5,8]. In the Switzerland study, community-acquired co-infections were reported in only 3.7% (6/162) of patients. 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) [8]. Furthermore, COVID-19 patients with coinfections had a prolonged length of hospital stay and an increased risk of death [6,13,17]. A retrospective study of 254 patients from England showed that patients with co-infection/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) [13]. 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 %) [17]. In the Spanish study, the overall mortality rate was 9.8 % (97/989) [6].

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%) [18]. 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) [10]. 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 [9]. According to a recent 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 [19]. 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 [20].

Hospital-acquired bacterial superinfections

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) [13]. 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%) [10]. 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 [21]. 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 [21]. 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 [6]. Of these 3.8% superinfections, 56.8% occurred in patients admitted to the ICU [6]. Some studies have shown that Gram-negative bacteria were more common than Gram-positive organisms [13,19,20]. In the England study, the proportion of Gram-negative bacteria, especially Klebsiella pneumoniae and Escherichia coli, increased with the length of the ICU stay [13].

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) [6]. In a previous retrospective study of 918 patients from China, the incidence of VAP was 32.3% [20]. A recent 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) [22].

Community-acquired bacterial co-infections

Based on limited data, the coprevalence of community-acquired secondary bacterial pneumonia and COVID-19 infection is uncommon and may be more common with influenza [16]. 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%) [10].

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 [16]. In the Spanish study, community-acquired bacterial coinfections, mainly caused by Streptococcus pneumoniae and Staphylococcus aureus, reported only in 2.5% (25/989) of COVID-19 patients [6]. Similarly, in the England study, the commonest pathogens within 48 hours of hospital admission (community-acquired infection) were Staphylococcus aureus and Streptococcus pneumonia [13]. 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 co-infection 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%) [23].

Common bacteria involved in COVID-19 co-infections/ 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 [10]. 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 [10]. Approximately, 34 bacterial co-pathogens were identified [10]. The most common bacteria were Mycoplasma species (32.4%), followed by Haemophilus influenzae and Pseudomonas aeruginosa (14.7%, each) [10]. 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%) [10].

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 [24,25]. 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%) [24]. Forty-two (85.7%) patients had active TB and seven (14.3%) had post-TB treatment sequelae [24].

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 [26]. 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 [26]. 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 [26]. 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 [24]. 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) [24]. 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 [27]. Furthermore, the time to death was shorter and the time to recovery was longer in patients with TB than in patients without TB [27]. 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 [28]. HIV increased the risk of COVID-19 mortality by approximately two-fold, irrespective of viral suppression [28]. Current and previous TB also increased COVID-19 mortality by approximately two-fold and one-fold, respectively [28].

COVID -19 and TB coinfection rates have been reported to be higher in males and migrants [24,29], however, the mortality rate was lower in migrants most likely due to their younger age and lower number of comorbidities [24,30]. 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 [30].

Cough, fever, and shortness of breath are common symptoms in COVID-19 and TB patients [25,26,31]. This can result in diagnostic confusion as well as worsening stigmatization of TB patients, particularly in low- and middle-income countries (LMICs) [31]. 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 [29]. Bilateral ground-glass opacities were more frequent in patients with COVID 19 infection, and cavitary lesions were more frequent in patients with TB [29].

Of note, the clinical features of TB and COVID-19 vary in some aspects [26]. TB has a longer incubation period and a slow onset [26]. In TB, coughing is productive of sputum and even blood, while in uncomplicated COVID-19, dry cough is more common [26]. 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 [26]. 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 [26].

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 [31]. 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 [26]. A careful history of TB exposure, or a previous episode of TB in the same patient or family, may help to make a diagnosis [26]. Sputum, along with a variety of other biological specimens, can be used to diagnose TB using culture or molecular techniques [26]. Chest radiography or imaging may aid in distinguishing TB from other pathologies [26]. Although health systems are being strained by the COVID-19 pandemic, routine and testing services for TB should be prioritized [27].

In most cases, TB treatment does not differ between patients infected with COVID-19 and those who do not [26]. Experience with comanagement of COVID-19 infection and TB is still limited [26]. Suspension of TB treatment in COVID-19 patients, on the other hand, should be considered exceptional [26]. 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 [26]. 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 [24]. In a previous review of 80 patients with TB and COVID 19 coinfections, most patients with TB were treated with multidrug regimen antitubercular therapy [29].

Superinfections by multidrug-resistant bacteria

Super-infections by multidrug-resistant (MDR) bacteria have also been reported among critically ill patients with COVID-19 infection [6,8,32,33]. 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 [19]. 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 [19]. The Switzerland study reported the identification of Acinetobacter baumannii producing the carbapenemase OXA-23 from 2.9% (1/34) of patients with VAP [8]. Another study reported the detection of a highly resistant Acinetobacter baumannii from 1% (1/99) of critically ill patients [32]. Klebsiella pneumoniae and Aspergillus flavus fungi were also detected in the same patient [32]. In another study, carbapenem-resistant Klebsiella pneumoniae was detected in 2% (1/52) of critically ill patients [33]. 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) [6]. MRSA was detected in two patients [6]. 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 [13]. Overall, the rate of MDR infection was low, probably due to the effect of COVID-19 isolation measures that prevented horizontal transmission between patients [6].

Bacterial coinfections/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 [34]. VAP occurred in ten 31% (10/32) of patients requiring invasive mechanical ventilation [34]. 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) [19]. 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 [19]. 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%) [35]. Potential bacterial superinfections included pneumonia (95%, 191/200), abscesses or empyema (3.5%, 7/200), and septic emboli (1.5%, 3/200) [35]. In 73 percent of cases, the pneumonia was focal rather than diffuse [35]. The most common histopathologic findings were intra-alveolar neutrophilic infiltrations, which differed from those seen with COVID-19-associated diffuse alveolar damage [35]. The pathogens of infection according to their sequential order 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 [35].

Viral coinfections

Viral coinfection was defined as the detection of another viral respiratory pathogen concurrent with the diagnosis of SARS-CoV-2 [8]. A previous Chinese study found that 31.5 % (81/257) of patients had viral coinfection [5]. In the Spanish study, 0.7% (7/989) of patients had viral community-acquired coinfections; four cases of influenza A virus coinfection, one of influenza B virus coinfection, one of respiratory syncytial virus coinfection, and one of herpetic disease. Unfortunately, two (28.6%) of these seven patients died as a result of influenza A and influenza B virus coinfection [6]. Similarly, another study found that influenza A virus coinfection was one of the most common coinfections among COVID-19 patients, and two of the reported patients had false-negative SARS-CoV-2 rRT-PCR results [7]. Thus, false-negative SARS-CoV-2 rRT-PCR results can occur in COVID-19 patients coinfected with influenza A virus [7]. In the previous systematic review and meta-analysis, the pooled prevalence of viral coinfection was 3% (95% CI 1-6, n=1014/3834, I2=62·3%) [17]. The most prevalent respiratory virus was a respiratory syncytial virus (16·9%), followed by influenza A (15·5%) [17]. In another meta-analysis based on 118 studies, the pooled prevalence of viral co-infections was 10% (95% CI: 6%-14%) and viral superinfection was 4% (95% CI: 0%-10%) [18]. The most prevalent identified viruses were influenza type A (22.3%), influenza type B (3.8%), and respiratory syncytial virus (3.8%) [18]. COVID-19 patients with new respiratory symptoms, with or without fever or respiratory distress, and having no clear diagnosis should be evaluated for the possibility of nosocomial influenza [16].

Fungal hospital-acquired superinfections

It has been reported that patients with severe COVID-19 infection are at risk for fungal infections such as Aspergillus, Candida, Pneumocystis, or other fungal species, which has been linked to increased morbidity and mortality [6,13,36]. A Spanish study found that the proportion of patients with fungal hospital-acquired superinfection were 0.7% (7/989); three cases were caused by Aspergillus fumigatus and four by Candida albicans [5]. In a meta-analysis based on 118 studies, the pooled prevalence of fungal co-infections was 4% (95% CI: 2%- 7%) and fungal superinfection was 8% (95% CI: 4%-13%) [18]. Aspergillus was the most commonly identified among those co-infected [18]. One study showed that 4% (4/99) of COVID-19 patients had fungal infections, including Aspergillus flavus and Aspergillus fumigatus, which were detected in respiratory tract secretions, with each pathogen found in one patient [33]. In the Switzerland study, two cases of hospital-acquired infections were caused by invasive Aspergillus fumigatus; in one case, Aspergillus fumigatus was identified in the tracheal aspirate culture on day 13, whereas the galactomannan antigen test in blood was negative [8]. However, multiorgan invasive aspergillosis was confirmed by autopsy [8]. In a second case, Aspergillus fumigatus was identified in tracheal aspirate culture at day 20 and confirmed by an Aspergillus-specific PCR (bronchial secrete) [8]. Patients with tracheobronchitis caused by Aspergillus fumigatus

had prior lung disease [5]. They were also critically ill and received mechanical ventilation support and high doses of corticosteroids [5]. In contrast, three cases of invasive pulmonary aspergillosis (IPA) were identified among COVID-19-infected patients in a previous study from Cambridge, the United Kingdom, but none of these patients had received steroids before diagnosis [22]. COVID-19 associated invasive pulmonary aspergillosis (CAPA) is common in critically ill COVID-19 patients and is associated with a higher mortality rate [37,38]. The incidence of CAPA could range from 19.6% to 33.3% [37].

Patients hospitalized for COVID-19 are also at risk for Candida species superinfection, mainly related to parenteral nutrition and urinary catheters [6]. A previous retrospective study from the United States showed that the proportion of patients whose specimens tested positive for Candida species was nearly twice as high in SARS-CoV-2-positive patients (8.2%) compared to SARS-CoV-2-negative (4.6%) and untested (4.1%) patients [21]. In a study of 99 COVID-19 patients, Candida albicans was found in the urine culture of 2% patients [33]. COVID-19 hospitalized patients are also at risk for candidemia, or Candida-related bloodstream infections [36]. In patients with severe COVID-19, fungal infections resistant to antifungal therapy have also been reported [36].

Mucormycosis in patients with COVID-19 has also been reported. In a recent systematic review (In Press, Journal Pre-proof) of 101 cases with COVID-19 associated mucormycosis, with 82 cases from India and 19 from the rest of the world, mucormycosis was reported in both active (59.4%) and recovered (40.6%) COVID-19 patients [39]. The high prevalence of COVID infection and diabetes in India could explain the high number of reported cases of mucormycosis in this country [40]. In this systematic review, pre-existing DM was present in 80% of cases, while diabetic ketoacidosis (DKA) was present in 14.9% [39]. Corticosteroid use for COVID-19 treatment was recorded in 76.3% [39,41]. Mucormycosis of the nose and sinuses was the most common (88.9%), followed by rhino-orbital mucormycosis (56.7%). The mortality rate was 30.7% [39]. Similarly, in another systematic review of eight cases with COVID-19 associated mucormycosis, DM was the most common risk factor [41]. Other than concurrent Corticosteroid therapy, three patients had no risk factors for COVID-19 [41]. The majority of mucormycosis cases appeared 10–14 days after hospitalization, and all but one of the affected patients died [41].

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 [16]. 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 [16]. In the previous meta-analysis and systematic review, 72% of COVID-19 patients received empirical antibiotics (antibiotic use was reported in 14/24 studies) [10]. Antibiotic use was generally a broad spectrum, with fluoroquinolones and third-generation cephalosporins accounting for 74% of the antibiotics prescribed [10].

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 [10,17]. Additionally, antibiotics are not recommended for preventing or treating pneumonia caused by SARS-CoV-2, another virus, or a fungal infection [9]. They are also not recommended for preventing secondary bacterial pneumonia in COVID-19 patients [9]. Nevertheless, empiric broad-spectrum antimicrobial therapy is the standard of care for the treatment of shock [16]. Antibiotic stewardship is essential for avoiding reflexive or continued courses of antibiotics [16]. 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 [9]. 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 [42].

Conclusion

Bacterial, fungal, or non-SARS-CoV-2 viral infections have been reported in COVID-19 patients, but their proportion varied widely across studies.

Although the proportion of community-acquired coinfections is 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 infections, especially bacterial or fungal infections, are frequently complicating the course of ICU patients. The most common hospital-acquired superinfections are VAP, HAP, and bacteremia.

Co-infection 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.

The most prevalent identified viruses among COVID-19 patients are influenza type A, influenza type B, and respiratory syncytial virus. COVID-19 hospitalized patients are also at risk for CAPA, candidemia, or Candida-related bloodstream infections. Mucormycosis has also been reported in patients with COVID-19 and it is associated with high mortality.

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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