Review Article

COVID-19 Cytokine Storm, Co-Infections, and Secondary Infections: Recent Information and Clinical Implications

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Abstract | Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is a novel respiratory infection that has caused the most recent epidemic of coronavirus disease 2019 (COVID-19). Although COVID-19 has a wide range of clinical manifestations, affecting many vital organs, the virus enters via the respiratory system, and the lungs are the leading site of the infection. The virus spreads primarily by respiratory droplets generated by coughing, sneezing, spitting, talking, singing, or breathing of infected people. COVID-19 infection has been linked to an intense cytokine storm (CS) and the immune-inflammatory mechanism that exacerbates disease symptoms and complications. Up to 20% of the infected people need hospitalization on account of the severity of the infection, while the rest of the patients are asymptomatic or have minor symptoms. In addition, many COVID-19 patients have co-infection or secondary infection, which exacerbate the disease. In general, it is believed that viral infections predispose patients to superinfections that have much worse consequences than the infection alone. Notably, the latest reports of high mucormycosis mortality and disease severity in India raise global concerns. Several studies have been reported that describe different levels of superinfections and disease severity in COVID-19 patients. Perhaps, there is just not enough data to distinguish between the worst outcomes of COVID-19 alone and coinfections, particularly when it comes to CS. Current clinical use of immunosuppressive therapies, including cytokine blockade, JAK, and IL-6 inhibition in severely ill COVID-19 patients, is associated with increased secondary infections. Therefore, the current review aims to collect literature on the incidence of COVID-19 co-infections and immune-inflammatory responses to such infections. A better understanding of immune-inflammatory markers of COVID-19-associated coinfections is vital to advance COVID-19 treatment and management protocols.

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Introduction

Human coronaviruses account for 10–30% of all common cold infections annually (Paules *et al.*, 2020). Coronaviruses, which live in the upper respiratory tract, cause mild to moderate flu-like illnesses. However, more deadly and violent coronaviruses have ascended with the potential to

invade the lungs and cause severe pneumonia. In Asia in 2003, severe acute respiratory syndrome coronavirus (SARS-CoV) affected over 8,000 people and induced mortality in 10% of the infected population. In 2012, the Middle East respiratory syndrome coronavirus (MERS-CoV) spread throughout the Middle East, infecting 2,468 people with a mortality rate of more than 30% (Ramaswamy *et al.*, 2021). The emerging SARS-CoV-2 pandemic, on the other hand, has worldwide implications, affecting all countries and territories and creating a situation unlike any other in recent history.

Severe COVID-19 cases are characterized by acute respiratory distress syndrome (ARDS) and a powerful cytokines storm (CS). The virus attaches to target cells using spike protein, which is primed by transmembrane protease, serine 2 (TMPRSS2) (Torres Acosta and Singer, 2020). The co-expression of ACE2 and TMPRSS2 is necessary for virus infection to begin in respiratory track cells. After infecting the nasal mucosa and eliciting a weak innate immune response, the virus spreads to the lower respiratory tract.

Viral infections damage the pulmonary tract by impairing acquired and innate immune responses and provide an atmosphere conducive to commensal pathogens adherence, growth, and invasion. Commensal pathogens colonize mucosal cavities asymptomatically and survive indefinitely until the conditions are right for their propagation and infection. The chances of bacterial coinfection or secondary infection among patients infected with respiratory viruses vary between 11 and 35% (Klein *et al.*, 2016). Influenza is the best illustration of viral-bacterial coinfections. MacIntyre *et al.* (2018) suggest that bacterial superinfections can worsen influenza infections, raising inflammatory markers and increasing the risk of death. During the 1918 influenza pandemic, bacterial co-infections accounted for most fatal cases (Morens *et al.*, 2008). Similarly, bacterial pneumonia exacerbated the 2009 H1N1 pandemic, affecting 4-33% of hospitalized patients (Crotty *et al.*, 2015). Respiratory fungal infections, on the other hand, are less common despite the fact that they are challenging to treat and may result in life-threatening infections. Opportunistic pathogens such as Aspergillus, Candida, Cryptococcus, and Pneumocystis can cause clinical severe illnesses in patients with compromised immune systems (Li *et al.*, 2019).

Coinfections are not uncommon in COVID-19. In a meta-analysis of COVID-19 trials, Langford *et al.* (2020) discovered bacterial co-infection in 3.5% of the patients and secondary bacterial infection in 14.3%. Similarly, Lai *et al.* (2020) reviewed available literature on COVID-19 and secondary infections. The authors observed that COVID-19-associated co- and secondary infection prevalence ranged from 0.6% to 45.0% (Lai *et al.*, 2020). Secondary infections are particularly more common in hospitalized patients. Chong *et al.* (2021) reported that the prevalence of fungal infections (6.3%) is lower than bacterial infections (16%) in hospitalized COVID-19 patients. However, the second wave of COVID-19 delta variant in the Indian subcontinent has seen the high prevalence of secondary infection with mucormycosis. The fungal infection of the sinuses in patients recently treated for covid-19 is challenging to treat and mostly fatal (Dyer, 2021).

The immunodynamics of COVID-19 superinfections are poorly understood, resulting in a significant research gap. Furthermore, there is a scarcity of information on fungal superinfections, especially mucormycosis. This paper aims to review immune-inflammatory processes in COVID-19 patients who are co-infected with bacterial and fungal pathogens. The paper will also compare the disease complications caused by the bacterial and fungal pathogens identified.

COVID-19 infection

SARS-CoV-2 is an enveloped RNA beta-coronavirus that originated in Wuhan, China, in December 2019 and initiated the global COVID-19 pandemic. The exponential dissemination of SARS-CoV-2 has negatively affected the healthcare sector and undermined the global financial system. The virus is highly contagious with an R0 of 3, meaning that each case infects three other people on average. This starts a chain reaction with an infection doubling period of one week or less, resulting in communities of 60–80% infection rates if left unchecked. According to the World Health Organization, 14% of infected cases are severe that require hospitalization, 5% require intensive care admission and ventilation, and about 4% of the infected die (Organization, 2020). COVID-19 overtook tuberculosis as the leading cause of global mortality due to a single infectious pathogen in 2020 (Chakaya *et al.*, 2021).

Acute respiratory distress syndrome

SARS-CoV-2 not only triggers antiviral immune responses but can also induce unconstrained systemic hyperinflammation in critically ill patients, as evidenced by increased pro-inflammatory cytokine release. COVID-19 phasic progress begins with typified respiratory symptoms and fever that may evolve into critical complications such as hyperinflammation, ARDS, coagulopathy, and multi-organ failure. ARDS and cytokine storm (CS) are the hallmarks of critical COVID-19. According to preliminary estimates, CS promotes uncontrolled inflammation, which leads to ARDS and accounts for most COVID-19 fatalities (Jiang *et al.*, 2020). Yang *et al.* (2020) reported that up to 67% of critically ill COVID-19 patients suffered ARDS and organ failure. A more recent retrospective case study suggests that the incidence of ARDS in hospitalized patients was 32.5% and up to 89.9% in critical cases (Argenziano *et al.*, 2020).

Hypercytokinemia and excessive inflammatory response leads to ARDS, inducing broad endothelial-barrier breakdown and acute lung injury. SARS-CoV-2 infects the pulmonary mucosa and activates local and peripheral immunocytes. In a perfect physiological scenario, the immune response would be proportionate to defend against infection and maintain host survival. Activation of immunocytes and production of cytokines is a natural phenomenon that occurs as part of the host's innate and adaptive immune systems physiological response to infections. Inflammatory cytokines cause fever, cell death, and vascular damage that may lead to widespread collateral tissue damage and remote organ injury. Thus, beyond infection control, elevated levels of inflammatory cytokines promote immune-mediated tissue damage and worsen the disease state on the magnitude and kinetics of CS. After an acute infection, a CS develops locally and spreads through blood circulation (Fara *et al.*, 2020), inducing systemic inflammation and fever. Unorganized or partly neutralizing antibodies and responses from CD4+ and CD8+ T cells have been linked to COVID-19 ARDS.

Mangalmurti and Hunter (2020) elaborate dynamics of CS, suggesting super-replicative microorganisms and co-infected bacterially derived superantigens as potential stimulants for sustained elevated cytokines production. Increased levels of IFN-γ correlate with high viral load. IFN-γ and TNF-α, in combination with IL-6, are considered strong predictors of severe COVID-19 illness and ICU admission (Zheng *et al.*, 2020). The origin of IFN-γ has been a point of contention, but it is generally agreed that IFN-γ is produced by CD4 TH cells, which facilitates CD8 T cell differentiation and triggers their cytotoxic abilities. TNF-α induces hyaluronan-synthase-2 in fibroblasts, EpCAM+, and CD31+ lung alveolar tissue of COVID-19 patients and leads to ARDS (Shi *et al.*, 2020). In the case of CS, this may be considered a secondary side-effect of the pro-inflammatory cascade, which manifests crosstalk with the affected tissue to self-sustain amplify, resulting in CS enhancement at systemic level. Therefore, plasma concentrations of IL-1, IL-7, IL-8, IL-9, IFN-γ, and TNF-α are reported high in COVID-19 patients suffering from multiple bilateral lobular pneumonia (Huang *et al.*, 2020a). These cytokines are released from damaged alveolar tissue and are early immune drivers in ARDS patients of COVID-19.

SARS-CoV-2 immune response and cytokine storm

SARS-CoV-2 enters through the nasal cavity and aspirates into the lungs, where it begins rapid replication and is met with a robust innate immune response including immunocytes infiltration and cytokines production (Cyprian *et al.*, 2021b). The overproduction of cytokines is caused by the activation of the innate immune system via pattern recognition receptors (PRRs) and toll-like receptors (TLR-4), which recognize pathogen-associated molecular patterns (PAMPs) on infected epithelial and immune cells (Fung and Liu, 2019). Molecular interactions between PAMP and PRR induce phagocytosis and activate the intracellular signaling cascade, which enhances the production of cytokines and inhibits the propagation of the virus (Fung and Liu, 2019). Cytokines promote innate immune cell recruitment, including natural killer (NK) cells, dendritic cells (DC), polymorphonuclear cells, and monocytes, which further secrete chemokines (IP, MCP-1, and MIG) and activate more leukocytes in a positive feedback loop (Gustafsson *et al.*, 2008). Immunocytes are drawn to the site of infection, where they perform several antimicrobial functions and produce IL-1, IL-6, IL-12, and TNF in response to PAMPs and damage-associated molecular patterns (DAMPs). Although both innate and adaptive immune responses contribute to CS. An innate immune response dominated by neutrophils and monocytes to a bystander bacterial coinfection is sufficient to induce a CS that eschews the classic immune response kinetics (Shambat *et al.*,

2020). Activation of PAMPs and DAMPs promotes phagocytosis and the production of pro-inflammatory cytokines, which impede viral multiplication and activate lymphocytes. Other innate immune cells, such as NK cells, DC, and polymorphonuclear leukocytes, are recruited by inflammatory cytokines to release a variety of chemokines, including MIG, MCP-1, and IP-10 (Coveney *et al.*, 2020). The innate immune responses that contribute to CS are previously reviewed and briefly explained (Coveney *et al.*, 2020; Rodrigues *et al.*, 2020). Commencing with early COVID-19 interaction with ACE2, the machinery for pro-inflammatory cytokines production starts, including RNA synthesis, nuclear translocation, and transcription for pro-inflammatory cytokines (Coveney *et al.*, 2020; Rodrigues *et al.*, 2020).

Although the innate immune system is enough to develop an effective CS, the activation of T cells to produce large amounts of effector cytokines (IL-2, IL-6, IL-10, IFN, and TNF) is also essential in the development of CS. T cells specific for SARS-CoV-2 appear relatively early in COVID-19 patients and continue to grow over time (Weiskopf *et al.*, 2020). SARS-CoV-2 spike protein elicit the strongest T cell responses, producing T effector and T helper 1 (TH1), TH2, and TH17 cytokines (Weiskopf *et al.*, 2020). Huang *et al.* (2020) reported lymphopenia and CS in critically ill COVID-19 ARDS patients, although T-cell counts gradually recovered in survivors. In response to viral infection, the temporary rise in CD4+, CD8+, CD38+, and HLA-DR+ T cells is reported in non-severe, recovered COVID-19 patients after resolution of clinical symptoms (Thevarajan *et al.*, 2020; Xu *et al.*, 2020). Stimulating PBMCs from COVID-19 ARDS patients with SARS-CoV-2 MP and S antigens results in the production of IFN-γ, TNF-α, IL-2, IL-5, IL-13, IL-10, IL-9, IL-17A, IL-17F and IL-22 (Weiskopf *et al.*, 2020). Weiskopf *et al.* (2020) observed that SARS-CoV-2 S antigen stimulation elicited considerable cytokines production specifically from Th1 (IFN-γ, TNF-α and IL-2), Th2 (IL-5, IL-13, IL-9 and IL-10), and Th17 (IL-17A, IL-17F and IL-22). Luo *et al.* (2021) observed an increase in IL-6, IL-2, IL-10, and IL-17 cytokines and exhausted effector T cells in the lungs and peripheral blood.

After complete remission of symptoms, activated T and B cells and their products (antibodies and cytokines) remain in the blood for at least seven days, implying that substantial antiviral adaptive immune responses are essential (Thevarajan *et al.*, 2020). T and B cells play a role in the antiviral adaptive immune response that is essential for at least partial protection against COVID-19 and contribute to the innate immune responses that occur during CS.

IL-6 and TNF-α activate B cell-mediated immune response, including antibody production. Antibodies are directed toward viral surface proteins, primarily the S glycoprotein and nucleocapsid protein, neutralizing infection of cells and tissues expressing angiotensin-converting enzyme 2 (ACE2) (Tai *et al.*, 2020). The primary function of neutralizing antibodies is to bind to antigenic proteins and interact with Fc γ-receptors to modulate subsequent immune responses. Recent reports of primary humoral immunodeficiencies in COVID-19 suggest that antibodies do not play a significant role in the SARS-CoV-2 immune response (Quinti *et al.*, 2020; Soresina *et al.*, 2020). However, one observation that perplexes scientists is the correlation between ARDS symptoms and IgA, IgM, and IgG concentrations, which appear to be higher in patients with poor clinical outcomes (Okba *et al.*, 2020). Changes in circulating B cell subpopulations, including an increase in plasma blasts and a relative decrease in memory B cells, were also observed to correlate with the severity of inflammation in COVID-19 patients (De Biasi *et al.*, 2020). Woodruff *et al.* (2020) observed that extrafollicular B cell responses in COVID-19 were associated with IL-6, CXCL10, and CRP concentrations and morbidity. The precise role of IL-6 in the development of ARDS in COVID-19 is unspecified. Perhaps, it is suggested that IL-6 is involved in the activation, differentiation, and survival of both B and T cells and the production of cytokines and immunoglobulins from these cells. Furthermore, elevated IL-6 secretions trigger autoimmunity, chronic inflammation, and autoantibody hypergammaglobulinemia (Vatansever and Becer, 2020).

However, in early clinical trials, overexpression of IL-6 did not give a useful clinical indication for anti-IL-6 COVID-19 therapy. The COVID-19 clinical trial (COVACTA) of Tocilizumab, an anti-IL-6 receptor antagonist medication that excluded patients with other bacterial or fungal infections, found that it had no meaningful effect on clinical status or mortality (Rosas *et al.*, 2021). Although, in follow-up trials of hospitalized patients (Recovery) and ICU patients

(REMAP-CAP), Tocilizumab improved survival and other health outcomes (Anonymous, 2021a; b). Another potential candidate for COVID-19 treatment is an anti-human IL-1R7 antibody that inhibits IL-18-mediated inflammatory signaling (suppressing IFNγ and IL-6 production and NFκB activation) (Li *et al.*, 2021). IL-18 is a key cytokine in macrophage activation syndrome. Elevated blood concentrations of IL-18 correlate with other inflammatory markers and represent the severity of COVID-19. For these reasons, it's worth noting that many of the COVID-19-specific biomarkers have already been linked to other infections, including bacteria, yeast, other viruses, or even allergies (Seo and Webster, 2002; Rose-John *et al.*, 2017). To filter out specific cytokine release patterns, it is crucial to consider bacterial sepsis, viral coinfections, and allergies.

SARS-CoV-2 co-infections and secondary infections

Bacterial, fungal, and viral co-infections and secondary infections have been observed in COVID-19. Several systematic reviews and meta-analyses have been conducted to determine the prevalence rate of these infections. The outcomes of these reviews are summarized below to show the percentages of co-infections, secondary infections, antibiotic usage, and commonly discovered pathogens. The most reported bacterial and fungal pathogens in COVID-19 patients are *Staphylococcus aureus*, *Pseudomonas, Acinetobacter, Klebsiella, Aspergillus*, and *Candida* spp. (Musuuza *et al.*, 2021; Westblade *et al.*, 2021). Two reviews were also conducted to observe HIV and HBV co-infections and disease severity in COVID-19 patients (Ssentongo *et al.*, 2021; Zhu and Peltekian, 2021). Despite the low occurrence of bacterial co-infections, patients were nonetheless given empirical antibiotic therapy in most of the studies. For example, Musuuza *et al.* (2021) reviewed 118 COVID-19 studies reporting 19% (14-25%) co-infection and 24% (19-30%) secondary infection. Antibiotic use was recorded in 70% (83/118) of these studies, with 98% (81/83) reporting antibiotic administration. In a review of 49 observational and case series studies, Chong *et al.* (2021) report 60-100% antibiotic use despite low secondary bacterial and fungal infection rates of 16% and 6.3%, respectively.

Table 1: *Summary of published meta-analysis and systemic reviews describing co-infections and secondary infections.*

Reference	Co-infection	Secondary infection	Study design	Common pathogens	Antibiotic usage*
Rawson *et al.* (2020)	5.6%	13.7%	Cohort: 1/9 Case series: 8/9	*Acinetobacter baumannii, Klebsiella pneumoniae, Aspergillus*, and *Candida* spp.	72%
Langford *et al.* (2020)	3.5% (0.4-6.7%)	14.3% (9.6-18.9%)	Cohort: 24/24	*Mycoplasma spp.*, Haemophilus influenzae, and *P. aeruginosa*	71.8%
Lansbury *et al.* (2020)	7% (3-12%)		Trial: 1/30 Cohort: 7/30 Case series: 22/30	Mycoplasma pneumonia, P. aeruginosa, and H. influenzae	>90%
Chong *et al.* (2021)		Bacteria: 16% (4.8–42.8%) Fungi: 6.3% (0.9–33.3%)	Observational: 28/49, Case series: 21/49	*P. aeruginosa, Staphylococcus aureus, K. pneumoniae,* Aspergillus *spp.*,	60-100%
Westblade *et al.* (2021)	2.88%	0.07%	Cohort: 8/10 Case series: 2/10	*S. aureus,* *Streptococcus pneumoniae* *Enterococcis* spp., and *P. aeruginosa*	35-100%
Ssentongo *et al.* (2021)	1.22% (0.26-4.17%)		Case series: 22/22	Human immunodeficiency virus	NR
Zhu *et al.* (2021)	7.3%		Cohort: 6/6	Hepatitis B virus	NR
Musuuza *et al.* (2021)	19% (14-25%)	24% (19-30%)	Trial: 1/118 Case control: 2/118 Cohort: 71/118 Case series: 44/118	*S. aureus* (7.7/2.7)[$], *Acinetobacter* spp. (4.1/22.3), Influenza A (22.3/0), *Candida* spp. (1/18.8), and *Aspergillus* (6.7/13.5)	98%

**NA antibiotic usage not reported in the study. [$]Percentage of co-infection/secondary infections combined.*

Bacterial infections

Bacterial co-infections aggravate viral respiratory infections and are common causes of immune dysfunction and mortality. Respiratory viral infections damage the pulmonary mucosa, allowing commensal pathogens to invade and multiply, resulting in secondary infection. The treatment concept of COVID-19 CS has been met with skepticism because the premise of suppressing the immune system in an infectious disease goes against basic medicine practicing principles. Particularly when the source of the CS is a coinfection or secondary bacterial infection, which can result in a poor prognosis. While hypercytokinemia may be needed for antiviral clearance in COVID-19 patients, literature shows that IL-6 levels are also significantly elevated in ARDS and bacterial sepsis alone (Leisman *et al.*, 2020). Leisman *et al.* (2020) reported that, on average IL-6 concentrations were approximately 100 times higher in patients with cytokine release syndrome, 27 times higher in patients with sepsis, and 12 times higher in patients with ARDS unrelated to COVID-19. This suggests that dysregulated cytokine response can aid in the subsequent development of bacterial infections that further overamplify hypercytokinemia.

Because there is a paucity of literature on COVID-19 patients in terms of well-defined pathophysiology of bacterial infections, this section will review information from previous viral-bacterial co-infections. Following a viral infection, physical and immunological factors might weaken the respiratory tract resistance to bacterial pathogens. Poor mucociliary clearance during a viral infection allows bacteria to attach to mucins more efficiently and enhances bacterial colonization (Hendaus and Jomha, 2020). In order to aid bacterial adhesion, viral infections can increase the production of binding proteins while decreasing the production of antimicrobial peptides in alveolar cells. (Avadhanula *et al.*, 2006). Bacterial adhesion, growth, and microbial dysbiosis, are facilitated by viral-induced dysregulation of proinflammatory cytokines (Cyprian *et al.*, 2021b). Robinson *et al.* (2015) observed that antimicrobial peptides, including CAMP, lipocalin2, REG3B, S100A8, and S100A9, were downregulated during influenza infection, promoting bacterial pneumonia. Similarly, infections with the respiratory syncytial virus (RSV) and adenovirus (ADV) stimulate the release of the surface glycoprotein adhesion molecule-1 (ICAM-1), which promotes *H. influenzae* infection. RSV infections also increase *S. pneumoniae* adherence to nasopharyngeal and pneumocyte type II cells, resulting in bacterial overgrowth and secondary infection (Nguyen *et al.*, 2015).

COVID-19 patients hospitalized for an extended period are more likely to develop secondary bacterial infections, with the most common pathogens being *S. aureus*, *Pseudomonas aeruginosa*, and *Klebsiella pneumonia* (Westblade *et al.*, 2021). Falcone *et al.* (2020) reported 109 episodes of superinfections in 69 (21.9%) patients over 19 days (range 11–29.75) of hospitalization. *Enterobacterales* (44.9%), polymicrobial (18.3%), Gram-negative bacilli (15.6%), Gram-positive bacteria (15.6%), and fungi (5.5%) were the most common pathogen for superinfection. Garcia-Vidal *et al.* (2021) found that compared with the nosocomial superinfections, community-acquired co-infections in COVID-19 patients were uncommon and were primarily caused by *S. pneumoniae* and *S. aureus*. Hospital-acquired bacterial superinfections, mostly caused by *P. aeruginosa* and *Escherichia coli*, were more common and lethal with worse outcomes (Garcia-Vidal *et al.*, 2021).

Antibiotic therapy is often used in COVID-19 patients, regardless of bacterial secondary or co-infections. The World Health Organization (WHO) does not advise using antibiotics in suspected, mild, or moderate COVID-19 infections, particularly broad-spectrum antibiotics on the watch and reserve list. Chedid *et al.* (2021) reviewed COVID-19 clinical studies revealing that the average rate of antibiotic treatment in disease management is 74.0%, while only 17.6% of patients have secondary infections. Similarly, Garcia-Vidal *et al.* (2021) found that only 7.2% of COVID-19 patients had co-infection, while 87.1% had at least one antibiotic treatment. The disparities between co-infected COVID-19 patients and the antibiotics treatment suggest that antibiotic prescriptions are being misused among COVID-19 patients. Another epidemic hazard hiding behind the COVID-19 pandemic is antimicrobial resistance, which has the potential to become a double-edged sword due to antibiotic overuse. Antibiotic overuse in COVID-19 patients could lead to widespread antimicrobial resistance, making resistant infections more likely to arise and spread. Table 1 reviews antibiotic usage in COVID-19 papers, as reviewed in clinical trials, case series, and cohort studies.

Fungal infections

Although we know that fungal superinfections increase disease severity and are associated with high mortality, whether COVID-19 increases the likelihood of secondary fungal infections is still up for debate. Aspergillus and Candida species are the most frequent invasive fungal pathogens linked to COVID-19 infection (Chiurlo *et al.*, 2021). The other less frequently reported fungal superinfections in COVID-19 patients are *Cryptococcus* spp., *Histoplasma* spp., *Mucormycetes*, and *Pneumocystis jirovecii* (Song *et al.*, 2020). Aspergillus infection has been linked to a high morbidity and mortality rate in COVID-19 patients, often complicating critically ill patients. Pulmonary Aspergillosis is a difficult infection to diagnose and treat, and it can have catastrophic consequences in patients undergoing tissue transplantation, neutropenia, immunodeficiencies, and immunosuppressive therapy (Baddley, 2011). Chiurlo *et al.* (2021) reviewed the incidence of invasive Aspergillosis (1.7% to 34.4%) in COVID-19 patients and found that the co-infected patients had a significant mortality rate. According to some studies, there is an overall mortality rate of 48-55% due to Aspergillosis in COVID-19 patients (Chong and Neu, 2021; Mitaka *et al.*, 2021). Zhu *et al.* (2020) described a large case series of 243 COVID-19 patients, 23.3% of whom were co-infected with Aspergillosis, depicting mild to acute symptoms. Pathogenesis of Aspergillosis and COVID-19 coinfection may involve IL-10 and IL-6 cytokines (Lai and Yu, 2021). Clemons *et al.* (2000) observed that IL-10 has deleterious effects during systemic Aspergillosis, resulting in increased Th2, decreased Th1 responses, and down-regulation of macrophage activity of which increase susceptibility to a fungal pathogen.

Candida albicans, a common human intestinal flora, a proclivity for infecting severely ill patients with compromised immune systems, resulting in high mortality. Compared to the controls, SARS-CoV-2-infected patients may be more susceptible to invasive candidiasis (Mastrangelo *et al.*, 2020). Several studies revealed that 0.03 to 10% of hospitalized COVID-19 patients had Candida coinfection (Table 1) (Chiurlo *et al.*, 2021). Falcone *et al.* (2021) observed that candidiasis develops late during the disease course (one-week post-hospitalization) and is associated with a prolonged hospital stay and a significantly high mortality rate (>50%). Lamers *et al.* (2020) observed that SARS-CoV-2 damages enterocytes and disrupts the integrity of the intestinal barrier, allowing commensal microorganisms to invade and coinfect. Therefore, COVID-19 patients are reported to have a higher prevalence of systemic translocation of gut pathogens, and the fungal microbiome is skewed toward an increased presence of *Candida* spp. (Zuo *et al.*, 2020; Cyprian *et al.*, 2021a).

Mucormycosis is an uncommon fungal infection caused by a genus of myocytes called Rhizopus. The most recent COVID-19 outbreak in India was accompanied by a second catastrophe in the shape of chronic mucormycosis, which was extremely difficult to treat and had a high mortality rate (Sahoo *et al.*, 2021). Mucormycosis, also known as black fungus, infected more than 30,000 patients in India recovering from severe COVID-19 infection (Vinay *et al.*, 2021). Fekkar *et al.* (2021) observed that 4.8% of COVID-19 patients admitted to ICUs were diagnosed with invasive pulmonary mucormycosis. Furthermore, according to a nationwide study in France, seventeen COVID-19 patients were co-infected with mucormycosis and suffered from diabetes, hematological malignancies, and organ transplantation (Danion *et al.*, 2021). Mucormycosis has long been linked to poorly managed diabetes and other immunosuppressive disorders or immunosuppressive therapy.

The possible causes of the co-occurrence of SARS-CoV-2 and fungal infections are currently being investigated. Perhaps, many risk factors for fungal infections, such as diabetes, immunosuppression, and old age, are substantially represented in the SARS-CoV-2 infected population (Richardson *et al.*, 2020). Furthermore, excessive use of immunosuppressants, such as IL-6 receptor antagonists, steroids, or antibiotics, might also promote the growth of opportunist pathogens and exacerbate disease outcomes.

Conclusions and Recommendations

In COVID-19 patients, secondary infections and coinfections are prevalent. COVID-19 disrupts the protective lining of the respiratory and digestive tracts and dysregulates the host immunological response, making patients vulnerable to secondary infections. The consequences of coinfections are exacerbated because of underlying disorders, healthcare-related risk factors, and COVID-19-related therapeutics. Excessive antibiotics, steroids, and immunosuppressive

drug administration have become a pandemic within a pandemic. Unsupervised medication lurked potentially hazardous infections with opportunistic pathogens. Although more information on the prevalence, etiology, and pathogenesis of bacterial and fungal coinfections in COVID-19 is becoming available, clinical trials and prospective studies are still needed to improve the treatment regime of complex infections.

Author's Contribution

All authors contributed equally.

Conflict of interest

The authors have declared no conflict of interest.

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