



COVID-19-associated opportunistic infections: a snapshot on the current reports

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Received: 14 June 2021 / Accepted: 30 July 2021 / Published online: 23 August 2021
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Abstract

Treatment of the novel Coronavirus Disease 2019 (COVID-19) remains a complicated challenge, especially among patients with severe disease. In recent studies, immunosuppressive therapy has shown promising results for control of the cytokine storm syndrome (CSS) in severe cases of COVID-19. However, it is well documented that immunosuppressive agents (*e.g.*, corticosteroids and cytokine blockers) increase the risk of opportunistic infections. On the other hand, several opportunistic infections were reported in COVID-19 patients, including *Aspergillus* spp., *Candida* spp., *Cryptococcus neoformans*, *Pneumocystis jirovecii* (*carinii*), mucormycosis, *Cytomegalovirus* (CMV), *Herpes simplex virus* (HSV), *Strongyloides stercoralis*, *Mycobacterium tuberculosis*, and *Toxoplasma gondii*. This review is a snapshot about the main opportunistic infections that reported among COVID-19 patients. As such, we summarized information about the main immunosuppressive agents that were used in recent clinical trials for COVID-19 patients and the risk of opportunistic infections following these treatments. We also discussed about the main challenges regarding diagnosis and treatment of COVID-19-associated opportunistic infections (CAOIs).

Keywords COVID-19 · SARS-CoV-2 · Opportunistic infection · Cytokine storm syndrome · Immunosuppressive therapy · Aspergillosis · Candidiasis · Mucormycosis · Cryptococcosis · *Pneumocystis jirovecii* pneumonia · Tuberculosis · Cytomegalovirus · Herpes simplex virus · Toxoplasmosis · Strongyloidiasis · Helminth infections

Abbreviations

COVID-19	Coronavirus Disease 2019	IL	Interleukin
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2	IFN γ	Gamma interferon
CAOIs	COVID-19-associated opportunistic infections	TNF- α	Tumor necrosis factor- α
CSS	Cytokine storm syndrome	JAKs	Janus kinases
ARDS	Acute respiratory distress syndrome	GM-CSF	Granulocyte–macrophage colony-stimulating factor
VOC	Variants of concern	PCP	<i>Pneumocystis jirovecii</i> (<i>carinii</i>) Pneumonia
VOI	Variants of interest	CMV	<i>Cytomegalovirus</i>
VOHC	Variant of high consequence	HSV	Herpes simplex virus
		IBD	Inflammatory bowel disease
		SLE	Systemic lupus erythematosus
		RA	Rheumatoid arthritis
		DM	Diabetes mellitus
		TB	Tuberculosis
		CAPA	COVID-19-associated pulmonary aspergillosis
		ICU	Intensive care unit
		IPA	Invasive pulmonary aspergillosis
		BALF	Bronchoalveolar fluid
		GM	Galactomannan
		BDG	β -D-Glucan
		CAC	COVID-19-associated candidiasis

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CAM	COVID-19-associated mucormycosis
TMP/SMX	Trimethoprim/sulfamethoxazole
ALC	Absolute lymphocyte count
ETA	Endotracheal aspirate
IFM	Immunofluorescence microscopy
MRSA	Methicillin-resistant <i>Staphylococcus aureus</i>
NTDs	Neglected tropical diseases

Introduction

The Coronavirus Disease 2019 (COVID-19) was emerged in Wuhan, China, in late 2019 and immediately spread to become pandemic [1, 2]. The disease is caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and has diverse sequels in all ages [3, 4]. However, older individuals (> 60 years old), males, and patients who have comorbidities or coinfections, such as pulmonary diseases, chronic kidney disease, diabetes, hypertension, and cardiovascular diseases, have a higher risk of severe infection [1, 2, 5, 6]. Close contact and respiratory droplets are the main route of COVID-19 transmission through breathing, sneezing, coughing, and even normal speech [7–9].

Pulmonary system is the most commonly affected organ, and therefore, the main clinical manifestations of COVID-19 are respiratory signs, including cough, dyspnea, sore throat, and fever [10]. In the severe COVID-19 state, development of pneumonia with acute respiratory distress syndrome (ARDS), hypoxic respiratory failure, and/or death have been occurred. On the other hand, extrapulmonary organ involvement (*e.g.*, cardiac, neurologic, endocrine, gastrointestinal, hepatic, renal, ocular, and dermatologic) associated with loss of smell or taste has significant health threat [10, 11].

Mutations of SARS-CoV-2 virus and new classification

Mutations have been occurred in all viruses, including SARS-CoV-2 over time. While most mutations have scant or no influence on the viruses' properties, some mutations may influence on the virus's properties, such as speed of spread, disease severity, performance of vaccines, diagnostic tools, therapeutic medicines, or other public health measures (<https://www.who.int/en/activities/tracking-SARS-CoV-2-variants/>). Accordingly, three classes of SARS-CoV-2 variants were developed, including variants of concern (VOC) (B.1.1.7 (Alpha), B.1.351 (Beta), B.1.617.2 (Delta), and P.1 (Gamma)), variants of interest (VOI) (B.1.525 (Eta), B.1.526 (Iota), B.1.617.1 (Kappa) and C.37 (Lambda)), and variant of high consequence (VOHC)). VOC has increase transmissibility, severity of disease, reduced effectiveness of

diagnosis, treatment, and vaccination. VOI has an increased prevalence rate. There is no VOHC till now. Evidence suggests that VOHC has the following properties, including failure diagnostics, significant reduction in vaccine effectiveness, reduced susceptibility to approved therapeutics, and more severe clinical disease and hospitalization rate (<https://www.cdc.gov/coronavirus/2019-ncov/variants/variant-info.html#Consequence>). There are some differences between the symptoms of the new variants of SARS-CoV-2 with the typical symptoms of COVID-19. For instance, the symptoms of the Delta variant in the UK were akin to a heavy cold; instead, the typical symptoms of the COVID-19, such as loss of taste and smell and shortness of breath, were less prevalent [12].

COVID-19 and the cytokine storm syndrome

Hyperinflammation and cytokine storm syndrome (CSS) are among the major causes of acute respiratory distress syndrome (ARDS), multiorgan failure, and death due to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection [13–15]. An unexpected increase in the circulating levels of proinflammatory cytokines, especially interleukin-1 (IL-1), IL-6, gamma interferon (IFN γ) and tumor necrosis factor- α (TNF- α), leads to hyperinflammation and the CSS [16]. When CSS occurs, different immune cells (*e.g.*, neutrophils, macrophages, and T cells) infiltrate into the site of infection, and consequently, a cascade of damage of the vascular barrier, diffuse alveolar damage and lung injury, multiorgan failure, and ultimately death occurs [17]. ARDS is one of the major consequences of CSS that directly link to severe sequel and mortality in acute COVID-19 patients [13, 16]. Therefore, therapeutic strategies to mitigate the risk of CSS and ARDS are essential.

Immunosuppressive therapy as a treatment option for COVID-19

Immunosuppressive therapy has been used to mitigate hyperinflammation and cytokine storm syndrome (CSS) in COVID-19 patients [18]. Administration of dexamethasone among hospitalized patients with COVID-19 resulted in lower 28-day mortality in patients who received oxygen or invasive mechanical ventilation [19]. The results of a recent meta-analysis revealed that administration of systemic corticosteroids (*e.g.*, dexamethasone, hydrocortisone, and methylprednisolone) was associated with lower 28-day all-cause mortality compared with usual care or placebo [20]. Other studies reported the usefulness of Janus kinase (JAKs) inhibitors and inflammatory cytokine blockers, including IL-6, IL-1, TNF α , and

granulocyte–macrophage colony-stimulating factor (GM-CSF) for CSS in COVID-19 patients (Table 1). Taken together, immunosuppressive therapy has shown to have an important therapeutic option for patients with severe COVID-19.

Immunosuppressive therapy as a risk factor for opportunistic infection

Immunosuppressive therapy has been used for a number of autoimmune diseases to alter their immune status (Supplementary Table 1). However, it is an important risk factor for opportunistic infection [21, 22]. Previous studies among patients with Inflammatory Bowel Disease (IBD) revealed that the use of corticosteroids, infliximab, and azathioprine/6-mercaptopurine was significantly increased the odds of opportunistic infection (OR = 3.4, OR = 4.4, and OR = 3.1, respectively) [22]. As reviewed elsewhere, a number of opportunistic pathogens (e.g., *Aspergillus* spp., *Candida* spp., *Cryptococcus neoformans*, *Pneumocystis jirovecii* (*carinii*), mucormycosis, *Cytomegalovirus* (CMV), *Herpes simplex virus* (HSV), *Strongyloides stercoralis*, *Mycobacterium tuberculosis*, and *Toxoplasma gondii*) have been reported from patients who received immunosuppressive therapy for their underlying diseases, such as IBD, systemic lupus erythematosus (SLE), and rheumatoid arthritis (RA) [21] (Table 2).

Table 1 A snapshot on immunosuppressive agents that were used for “cytokine storm syndrome” in severe cases of COVID-19

Agents	Drug names
Corticosteroids [20]	Dexamethasone [19, 184] Hydrocortisone [20] Methylprednisolone [20]
JAKs inhibitors [200]	Ruxolitinib [195–197] Baricitinib [198, 199] Tofacitinib [200]
IL-6 blockers	Tocilizumab [185, 186, 213]
IL-1 blockers	Anakinra [203, 204] Canakinumab [205, 206]
TNF- α blockers	Infliximab [201, 202]
GM-CSF blockers	Mavrilimumab [207]

JAKs: Janus kinases, IL: Interleukin, TNF- α : tumor necrosis factor- α , GM-CSF: granulocyte–macrophage colony-stimulating factor

COVID-19-associated opportunistic infections

The increased case reports of opportunistic infections in COVID-19 patients raise an important concern, especially for patients with underlying diseases and who received immunosuppressive therapy. Among the opportunistic infections, fungal infections account for the most case reports in COVID-19 patients. Other reported pathogens were related to viral, bacterial, protozoa, and helminth infections (Fig. 1). This narrative review is a snapshot about the main opportunistic infection among COVID-19 patients.

Fungal infections

Fungal infections are among the major infections among immunocompromised patients [23]. A sharp increase in the incidence and mortality rates of fungal infections has been reported among COVID-19 patients, especially those who received immunosuppressive therapies or who have underlying conditions [24–28].

Aspergillosis

Aspergillosis is caused by a common mold, *Aspergillus* spp., that lives indoors and outdoors. Most people are exposed to *Aspergillus* spores and breathe them every day without getting sick; however, individuals with compromised immune systems or lung diseases have a higher risk of developing active infection [23, 29, 30]. Until the emergence of COVID-19, a number of cases with COVID-19-associated pulmonary aspergillosis (CAPA) have been reported worldwide [31–36]. Invasive pulmonary aspergillosis (IPA) is associated with high mortality rates among COVID-19 patients [37, 38]. The results of a multicentric retrospective cohort in France revealed that the overall mortality rate among COVID-19 patients with and without IPI was 71.4% versus 36.8%, $p < 0.01$. Treatment with azithromycin as well as with high-dose dexamethasone (which both of them have immunomodulatory properties) increased susceptibility to IPA among COVID-19 patients [39]. According to a recent review [31], data from 186 cases of CAPA were gathered worldwide. The data revealed that 97.8% (182) of the patients with CAPA were admitted to the intensive care unit (ICU), for ARDS (180; 96.8%) or mechanical ventilation (175; 94.1%). The overall mortality rate was 52.2% (97); which 33.0% of them were attributed to CAPA. The common underlying conditions included corticosteroid use (98; 52.7%), chronic cardiovascular disorders (94; 50.5%), renal disease (74; 39.8%), diabetes mellitus (64; 34.4%), obesity (47; 25.3%), chronic pulmonary disorders (40;

Table 2 A snapshot on most common opportunistic infections following immunosuppressive therapy

Agents	Opportunistic infections
Corticosteroids	Cryptococcosis: cutaneous infection [214, 215], meningitis [216, 217], disseminated infection [218], pneumonia [219] <i>Pneumocystis jiroveci (carinii)</i> pneumonia [220, 221] Aspergillosis [222–225] Candidiasis: oral candidiasis [226], esophageal candidiasis [227], disseminated [228] Mucormycosis: pulmonary [229, 230], disseminated [230], cutaneous [231, 232], gastric perforation [233], maxillary sinus [234] Strongyloidiasis: Severe [235–238], disseminated [239, 240], cerebral involvement [239], pulmonary strongyloidiasis [241], hyperinfection [242] Tuberculosis (pulmonary) [243] Cytomegalovirus (CMV) infection [244, 245] Toxoplasmosis: ocular toxoplasmosis [154–156], cerebral toxoplasmosis [157, 158]
JAKs inhibitors	Toxoplasmosis: cerebral toxoplasmosis [159], toxoplasmic retinitis [160] Cryptococcosis: pneumonia and pulmonary infection [246–248], meningoencephalitis [249], meningitis [250] Aspergillosis: retinal necrosis [251] Tuberculosis (pulmonary) [252–255] CMV retinitis [256]
IL-6 blockers	Cryptococcosis: disseminated [190], meningitis [191] Aspergillosis [192] Tuberculosis (pulmonary) [194] CMV pneumonitis [193]
IL-1 blockers	Aspergillosis [257]
TNF- α blockers	Toxoplasmosis: toxoplasmic retinochoroiditis [161, 162], cerebral toxoplasmosis [163] Cryptococcosis: pneumonia and pulmonary infection [258, 259], disseminated infection [260, 261], meningitis [262, 263], cutaneous infection [264] <i>Pneumocystis jiroveci (carinii)</i> pneumonia [265–268] Aspergillosis: allergic bronchopulmonary [269], pulmonary [270], sinus aspergillosis [271], central nervous system aspergillosis [272], disseminated [273] Candidiasis: systemic candidiasis [274], arthritis [275], oral candidiasis [276] Mucormycosis: cutaneous [277], gastric perforation [233], disseminated [278], sinusitis [279], pulmonary [280] Strongyloidiasis: hyperinfection [281] Tuberculosis (pulmonary) [282–284] CMV retinitis [285], disseminated CMV [286]
IL-17A blockers (Ixekizumab)	Toxoplasmosis: lymphadenopathy [164]

21.5%), and hematologic or oncologic disease (21; 11.3%) [31]. Collectively, the most important risk factors of CAPA were reported corticosteroid use and the presence of comorbidities [31, 38, 39]. Unfortunately, there is not an optimal diagnostic algorithm for diagnosing CAPA until now [38]. The most promising diagnostic modality for CAPA was included recovery of *Aspergillus* spp. on culture media of bronchoalveolar fluid (BALF) and tracheal aspirate and conventional Galactomannan (GM) testing from BALF [38]. Utilizing *Aspergillus* PCR and serologic biomarker testing are also useful and sensitive diagnostic tests for CAPA [38]. The first-line treatment of IPA is the approved drug voriconazole. Posaconazole is also approved for prophylaxis against invasive fungal infections [40]. Among the CAPA, patients who received voriconazole had a higher survival rate [35]. However, drug–drug interactions are the major challenge of voriconazole in the ICU setting [38, 41, 42]. Other treatments such as mold-active triazole and amphotericin B (AmB) have been used for CAPA as well [37].

Taken together, early diagnosis and treatment are the major challenges of aspergillosis among COVID-19 patients.

Candidiasis

Candida spp. is the second most numerous fungal infection worldwide [23]. The fungi are normally living on the skin, as well as inside the body, such as the throat, mouth, gut, and vagina. Oropharyngeal candidiasis is one of the most common infections in immunocompromised people, such as HIV/AIDS. Invasive candidiasis and candidemia are a serious and common infection in hospitalized patients (<https://www.cdc.gov/fungal/diseases/candidiasis/invasive/index.html>). *C. albicans* is the most common *Candida* species; however, the emerging species such as *C. auris* is a highly invasive and multidrug-resistant yeast causing complicated conditions [43, 44]. COVID-19-associated candidiasis (CAC) has been reported in a number of cases until now [43], and *C. auris* was the most

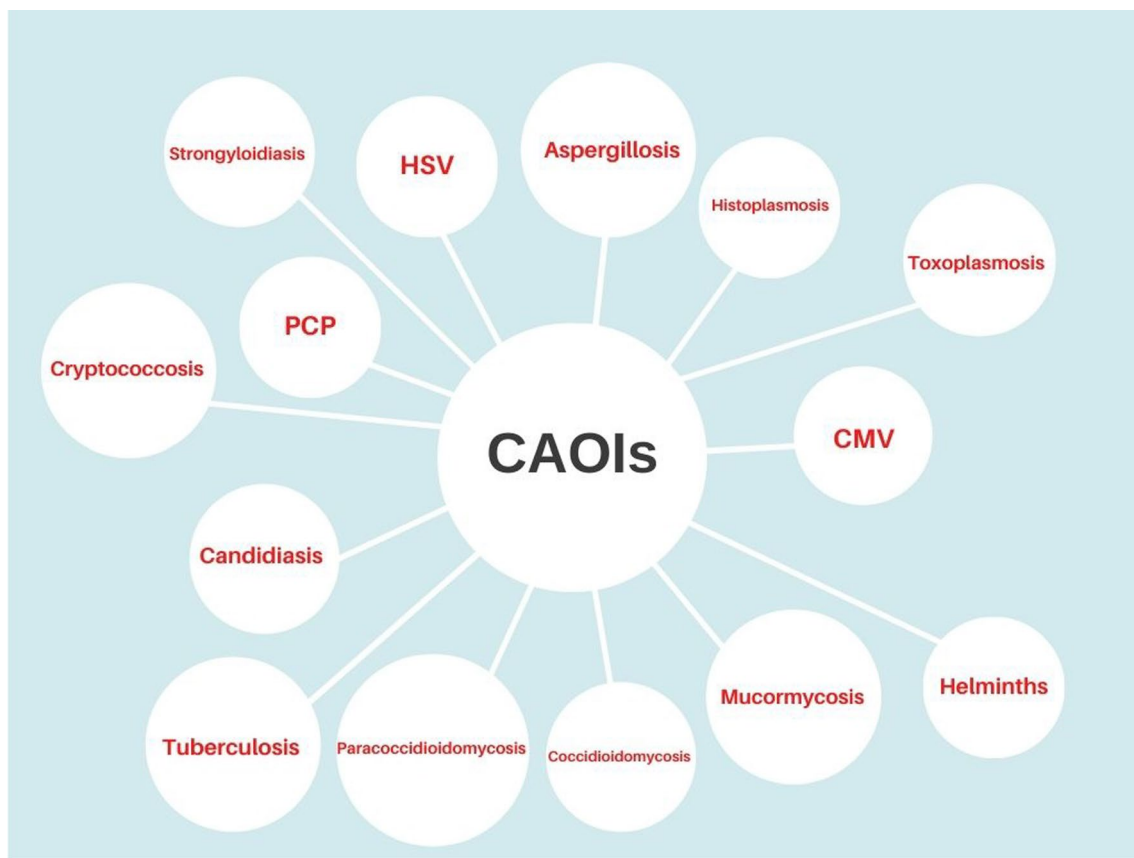


Fig. 1 A snapshot on the CAOIs. Created by <https://www.canva.com/>

reported species [43, 45–48]. Other reported *Candida* species were *C. albicans*, *C. tropicalis*, *C. parapsilosis*, *C. orthopsilosis*, and *C. glabrata* among COVID-19 patients [43, 49]. The coinfection of *C. auris* and COVID-19 in critically ill patients has been related to an above 50% mortality rate [50, 51]. Prolonged ICU stay, central venous catheters, and corticosteroid use were among the major risk factors for candidiasis in COVID-19 patients [43]. The diagnosis of invasive candidiasis remains challenging, mainly due to the low number of *Candida* in infected tissues or circulation [43]. Serologic tests with β -D-Glucan (BDG) and mannan antigen as well as molecular platforms are recommended tests for diagnosis of candidiasis [52–54]. In COVID-19 patients, the treatment of invasive candidiasis is similar to that of non-COVID-19 patients [43]. Echinocandins that are usually well tolerated are the choice drugs for invasive candidiasis, while voriconazole, fluconazole, liposomal amphotericin B, posaconazole, and isavuconazole are the second line of treatment [43]. Early diagnosis and treatment of CAC are important for management of the disease; however, multidrug-resistant species are a major challenge for CAC management.

Mucormycosis

Mucormycosis is an invasive fungal infection caused by species belonging to Mucorales. Classically, immunosuppressive conditions such as uncontrolled diabetes mellitus (DM), neutropenia, and corticosteroid therapy are the major risk factors for mucormycosis [55]. Inhalation of spores is the main route of infection that usually causes pulmonary infection; however, cutaneous and soft tissue invasion primarily occurs after skin disruption because of traumatic injuries, surgery, or burns [55]. Rhino-orbito-cerebral infection classically develops in patients with uncontrolled DM. Gastrointestinal mucormycosis is a rare manifestation of the infection, which is mostly reported in neonates [55]. The mortality rates of mucormycosis varied from 40 to 80%, depending on the site of infection and underlying conditions [55]. The global prevalence of mucormycosis is ranging from 0.005 to 1.7 per million, while its prevalence is about 0.14 per 1000 in India [56, 57]. Diabetes mellitus, ketoacidosis, hematological malignancies, glucocorticoid use, or broad-spectrum antibiotics, transplantation, prolonged neutropenia, trauma, iron overload, illicit intravenous drug use,

neonatal prematurity, and malnourishment are among the main predisposing factors of mucormycosis [58, 59]. Diagnosis of mucormycosis consists of clinical diagnosis, imaging modalities alongside with histopathology, cultures, and molecular techniques [59].

High-dose liposomal amphotericin B is the first-line treatment of mucormycosis, while isavuconazole (intravenous) and posaconazole (intravenous or delayed release tablets) are recommended with moderate strength [55].

COVID-19-associated mucormycoses (CAM) have been reported in a number of cases worldwide [60–63]. According to a recent systematic review, 101 cases (82 cases from India and 19 from the rest of the world) of CAM have been reported worldwide till now [60]. The infection was predominantly reported in males (78.9%) and in COVID-19 patients who had active (59.4%) or recovered (40.6%) infection. The most common clinical presentation of CAM was invasive infection in the nose and sinuses (88.9%), followed by rhino-orbital (56.7%) involvement. Preexisting DM was recorded in 80% of the cases, and corticosteroid therapy was seen in 76.3% of cases. The mortality rate was 30.7% of the cases [60]. The general management for mucormycosis included hyperglycemia control, early treatment with liposomal amphotericin B, and surgery [62], although treatment with amphotericin B and isavuconazole had only about 50% clinical improvement in CAM cases (reviewed in [58]). The major challenge of CAM is the late diagnosis of the disease and consequently treatment failure. Hence, early diagnosis of mucormycosis is of utmost importance in COVID-19 patients.

Cryptococcosis

Cryptococcus neoformans is an encapsulated yeast that causes subclinical infection in immunocompetent individuals. Humans can become infected by breathing fungal spores, and so, pulmonary infection is the major form of the disease. Corticosteroid or immunosuppressive therapy, DM, and malignancies are among the major risk factors of cryptococcosis [64]. Severe infections, cryptococemia, meningoencephalitis, and pulmonary cryptococcosis have been reported in immunocompromised patients [23, 64, 65]. Serologic methods based on antigen screening and advanced molecular methods are sensitive and specific tests for the diagnosis of cryptococcosis [66, 67]. Antifungal agents, including amphotericin B, fluconazole, and 5-flucytosine, are the current approved treatment of cryptococcosis [68]. Till now, some cases of *Cryptococcus* infection were reported in COVID-19 patients [65, 69, 70], which one of them was a 60-year-old man who received tocilizumab plus corticosteroids and diagnosed with candidemia and cryptococemia [65]. Despite antifungal therapy, the patient died within 10 days of cryptococemia [65]. Meningoencephalitis

due to *C. neoformans* was reported in a 73-year-old woman who received azithromycin and dexamethasone after COVID-19 infection [70]. Other cases were reported from COVID-19 patients with several underlying diseases who received immunosuppressive therapy (e.g., corticosteroids and tocilizumab) [24, 71–73]. Like other fungal infections, early detection and treatment can improve the outcome of infection in COVID-19 patients.

Pneumocystis pneumonia (PCP)

Pneumocystis jirovecii is another common respiratory opportunistic pathogen in individuals with immunocompromising conditions, which causes pneumocystis pneumonia (PCP). PCP spreads from person to person through the air. Some healthy adults have the fungus in their lungs asymptotically, and they can spread the infection to other individuals. The choice treatment for PCP is trimethoprim/sulfamethoxazole (TMP/SMX), which also known as cotrimoxazole (<https://www.cdc.gov/fungal/diseases/pneumocystis-pneumonia/index.html#symptoms>). Coinfection of PCP and COVID-19 has been reported in some patients with COVID-19 till now [74–87], in which some of them received immunosuppressive therapies, such as corticosteroids [76, 81, 88, 89] and tocilizumab [88]. The first confirmed case of PCP and COVID-19 coinfection was diagnosed by autopsy and real-time PCR in a 52-year-old male chronic smoker and drinker with severe dyspnea. The patient died 17 h postdiagnosis [90]. Chong et al. [85] reviewed 12 cases of COVID-19 and PCP coinfection. Accordingly, all PCP infections were reported in critically ill patients with COVID-19, which most of them were immunosuppressed with HIV (58.3%, 7/12) or long-term exposure to immunosuppressants (91.7%, 11/12), such as high-dose corticosteroids. In both HIV and non-HIV patients, severe lymphocytopenia (< 1000 cells/mm³) was encountered with absolute lymphocyte count (ALC) less than 900 and CD4⁺T cell count less than 200 cells/mm. Another laboratory finding among coinfecting patients was elevation of serum lactate dehydrogenase (LDH) and β -D-glucan. The diagnostic samples were lower respiratory tract (LRT) specimens, including sputum, BAL, and endotracheal aspirate (ETA). The diagnosis was made by microscopic staining, immunofluorescence microscopy (IFM), or molecular methods. Sulfamethoxazole–trimethoprim are the most used therapy of the patients. The mortality rate was 42.9% (3/7) in the HIV group and 40% in non-HIV group [85]. Diagnosis of COVID-19 and PCP coinfection is challenging because there are clinical and radiological similarities between the two diseases [90], while, in some cases, PCP was misdiagnosed as COVID-19 in patients with underlying diseases [89, 91–94]. In these cases, differential diagnosis by laboratory tests should be considered alongside with clinical and radiological findings.

Endemic fungal infections

To date, scarce information is available regarding the coinfection of endemic fungal infections with COVID-19. Histoplasmosis caused by *Histoplasma capsulatum* was reported in five cases of COVID-19 from Brazil [95–97] and Argentina [98, 99] in which three of them were HIV positive as well [96, 98, 99]. All cases had pulmonary infections and two of them developed disseminated histoplasmosis [98, 99]. All patients were successfully treated with the antifungal itraconazole.

Pulmonary coccidioidomycosis caused by *Coccidioides immitis* was reported in three cases of COVID-19 from the US. The infection was occurred in two Hispanic males (48 and 52 years) [100, 101] and a 48-year-old Hispanic female [102]. Two of them received dexamethasone before developing coccidioidomycosis [101, 102]. A 52-year-old male was died before receiving antifungals [101], while other two patients were treated with fluconazole that resulted in clinical improvement [100, 102].

Paracoccidioidomycosis coinfecting with COVID-19 was reported in a 19-year-old Brazilian male with abdominal distension, disseminated cutaneous lesions, and multiple cervical, axillary, and inguinal lymph node enlargements [103]. The patient was treated with Amphotericin B lipid complex, but later developed a bloodstream infection that empirically received piperacillin–tazobactam [103].

Bacterial infections

Bacterial coinfections are associated with increased morbidity and mortality rates among patients with respiratory viral infections, including influenza and COVID-19 [104–106]. To date, numerous studies have been reported the association of COVID-19 with bacterial infections; many of them are classified as nosocomial or hospital-acquired infections. In this regard, the results of a living rapid review and meta-analysis revealed that bacterial coinfection and secondary bacterial infection were detected in 3.5% (95%CI 0.4–6.7%) and 14.3% (95%CI 9.6–18.9%) of COVID-19 patients, respectively. Critically ill patients reported to have more bacterial infection (8.1%, 95%CI 2.3–13.8%) [107]. A prospective cohort study analyzed data from 48 902 COVID-19 inpatients from 260 hospitals in England, Scotland, and Wales. The results have shown that the most common pathogens causing respiratory coinfections were *Staphylococcus aureus* and *Haemophilus influenzae*, which diagnosed ≤ 2 days after admission. *S. aureus* and Enterobacteriaceae were also the most common secondary respiratory infections. As such, the most frequent bloodstream infections were caused by *Escherichia coli* and *S. aureus* [108]. A retrospective study among 257 laboratory-confirmed COVID-19 patients in

China (Jiangsu Province) revealed coinfection with 24 respiratory pathogens among the patients; *Streptococcus pneumoniae*, followed by *Klebsiella pneumoniae* and *H. influenzae*, was the most common bacterial coinfections [109]. A study among COVID-19 patients who admitted to ICU in Iran revealed that all patients had bacterial coinfections, including *Acinetobacter baumannii* (90%) and *S. aureus* (10%) strains. Antibiotics resistance was found in 17% of *A. baumannii* isolates. Methicillin-resistant *S. aureus* (MRSA) was detected in an isolate [110]. *Mycoplasma pneumoniae*, *Pseudomonas aeruginosa*, and *Legionella pneumophila* are other important bacterial pathogens that were detected among COVID-19 patients [104].

Tuberculosis

Tuberculosis (TB) remains as a significant public health problem worldwide. According to the estimations, a quarter of the world's human population has latent TB infection [111]. Like COVID-19, TB can spread through the air from an infected person to others. The primary site of TB infection is the lungs; however, extrapulmonary infection is common, especially among immunocompromised patients [112]. Coinfection of TB with COVID-19 has been reported in a number of studies [113–117]. There are some similarities between the clinical symptoms of TB and COVID-19; hence, misdiagnosis of both infections has been reported [118]. However, studies have shown that TB infection can worsen outcome of the COVID-19 disease, leading to increased severity and mortality [114]. According to a recent meta-analysis, coinfection of *M. tuberculosis* with SARS-CoV-2 infection resulted in two times increased risk of mortality among COVID-19 patients (RR = 2.10; 95% CI, 1.75–2.51; I² = 0%) [119]. Hence, strategies for prevention, screening, and treatment of TB should be considered in patients who suspected to COVID-19 infection.

Viral infections

Respiratory viral pathogens, including Influenza, Parainfluenza, Metapneumovirus, and Rhinovirus, were reported among COVID-19 patients in different studies [120–122]. However, some infections such as CMV and HSV are opportunistic pathogens that could reactivate after immunosuppression.

Cytomegalovirus (CMV)

CMV is a latent infection in immunocompetent individuals. The seroprevalence rate of CMV accounts about 80% in the elderly. CMV has been shown to manipulate the immune system by affecting T cell proliferation, decreasing in naïve

T cell diversity, and increasing inflammatory cytokines (e.g., IL-6), leading to aging of the immune system (also called immunosenescence) [123, 124]. CMV infection has several sequels, mainly retinitis, pneumonitis, encephalitis/myelitis, neuropsychiatric disorder, and intrauterine infection [125–127]. Ganciclovir is an effective treatment option for CMV infection, especially for immunosuppressed individuals [128, 129]. To date, disseminated CMV infection [130], CMV myocarditis [131], CMV proctitis [132], pneumonitis [133, 134] as well as CMV viremia [135, 136] were reported among COVID-19 patients, in which some of them received corticosteroids [130, 132–136] or tocilizumab [135]. While CMV is latent in most individuals, reactivation of latent infection can lead to severe infections with fatal outcomes following immunosuppression in COVID-19 patients. Therefore, differential diagnosis and treatment should be considered in these patients.

Herpes simplex virus (HSV)

HSV is a contagious virus that categorizes into two types, including HSV-1 or oral herpes and HSV-2 or genital herpes. HSV-1 is generally responsible for cold sores and fever blisters around the mouth and lips; it can also cause genital herpes in some cases. HSV-2 is primarily causing sores around the genitals or rectum. HSV can be transmitted by direct contact. HSV-1 is transmitted through contact with oral secretions or sores on the skin and HSV-2 during sexual intercourse [137]. Sensory neurons are the main targets of HSV. Both HSV-1 and HSV-2 establish latent infections, and reactivation occurs after stress or immunosuppression [137]. Aciclovir is the standard therapy for HSV infections, which helps symptom control, but it could not eliminate the latent infection [137]. Reactivation of latent HSV and CMV infections has been reported among COVID-19 patients [138]. Seeßle et al. [139] found a high rate of HSV-1 reactivation (83.3%, 15 out of 18 patients) in invasively ventilated COVID-19 patients. Encephalitis due to HSV-1 was reported in a 73-year-old woman who suspected to prior COVID-19 infection [140]. Conjunctivitis was also reported in a 69-year-old male with COVID-19 infection [141]. Five cases of HSV-1 keratitis were reported in COVID-19 patients in Slovakia [142]. Fatal cases of acute liver failure due to HSV-1 infection were reported in two COVID-19 patients following tocilizumab and methylprednisolone prescriptions [143]. Coinfection of HSV and HIV infection [144] as well as with HSV and varicella zoster virus (VZV) infections [145] was reported in critically ill patients with COVID-19. Varicella-like exanthem was reported among 22 patients with COVID-19 in Italy [146]. While HSV has diverse symptoms and sequels, differential diagnosis and management of the infection could mitigate the outcome of COVID-19 patients.

Protozoa infections

Parasitic protozoa are a large group of unicellular pathogens, including blood and tissue protozoa (e.g., malaria, *Leishmania*, *Toxoplasma*, *Trypanosoma*, etc.) and intestinal and luminal protozoa (e.g., *Entamoeba*, *Giardia*, *Cryptosporidium*, *Cyclospora*, *Blastocystis*, *Trichomonas vaginalis*, etc.) [147]. However, intestinal protozoa and toxoplasmosis are an important opportunistic infections because their infections are usually latent or asymptomatic in healthy individuals, but severe infections could occur in immunocompromised patients [148, 149]. Reactivation of latent toxoplasmosis causes severe sequel in HIV/AIDS and immunocompromised patients (see the next subtitle) [149]. Intestinal protozoa can modulate immune responses through their direct interaction with host cells or by changing the gut microbiome composition [147]. To date, scarce information is available regarding the interaction of intestinal protozoa and COVID-19. Hence, there is an opportunity for researchers to investigate about the interaction of intestinal protozoa and COVID-19 in the clinical setting and experimental models. Nevertheless, opportunistic protozoa infection should not be neglected among COVID-19 patients, especially in endemic regions and in tropical and subtropical areas.

Toxoplasmosis

Like the latent CMV infection, toxoplasmosis is a latent infection in immunocompetent individuals, but reactivation of latent toxoplasmosis or acquired toxoplasmosis among immunocompromised patients can cause severe infections with various sequels, such as toxoplasmic encephalitis, disseminated infections, and death [150–153]. Combination of pyrimethamine and sulfadiazine is the choice drug for toxoplasmosis treatment among nonpregnant women [149]. Reactivation of latent toxoplasmosis has been reported in a number of patients who received immunosuppressive therapy, such as corticosteroids [154–158], JAKs inhibitors [159, 160], TNF- α blockers [161–163] and IL-17A blockers [164], and the most common sequels were ocular [154–156, 160–162] and cerebral [157–159, 163] toxoplasmosis. In a case–control study among 100 COVID-19 patients in Egypt, a significantly higher prevalence of toxoplasmosis was detected among mild to moderate COVID-19 patients than the healthy control group [165]. Indeed, *T. gondii* seropositive cases exhibited a significant increase in lymphocytic expression of programmed death-1 (PD-1), which is a marker that correlates with proinflammatory status. Due to the high prevalence rates of latent toxoplasmosis in

humans, reactivation of latent infection should be considered following immunosuppressive therapy in COVID-19 patients [166].

Helminth infections

Helminths are among the major neglected tropical diseases (NTDs) worldwide. Most of the helminth infections are causing chronic infections with minor clinical symptoms [167, 168]. Nevertheless, helminth infections could alter the immune system toward type 2 immunity and anti-inflammatory conditions, leading to diminished the essential immune response against microbial pathogens and increased susceptibility and severity of infectious diseases [167–169]. Helminths can also cause malabsorption and compete for host nutrients [169]. Helminth infections can also mitigate vaccine efficacy by suppressing immune responses [169]. The outcome of COVID-19 patients may be worsened in individuals with helminth coinfections [169–171]. Further investigations are needed to demonstrate the interaction between helminths and SARS-CoV-2 infection.

Strongyloidiasis

Strongyloidiasis is a neglected tropical infection caused by the soil-transmitted helminth *Strongyloides stercoralis*. Strongyloidiasis is usually asymptomatic in immunocompetent individuals, while disseminating infection and hyperinfection syndrome are important sequels among immunocompromised patients [172, 173]. The infected stage of the parasite is the filariform larva, which can penetrate into the human skin when it contacts with contaminated soil; then, the larva migrates to the small intestine and transforms to the adult worm. Alternatively, consumption of raw vegetables contaminated with filariform larva could be a source of infection. Internal autoinfection is common, leading to hyperinfection syndrome. Disseminated strongyloidiasis usually occurs in patients with immunocompromising conditions leading to complicated conditions [172, 173]. Ivermectin is the choice drug for treatment of strongyloidiasis; also, it could be used as a preventive strategy for high-risk populations (e.g., HIV/AIDS and immunocompromised individuals) [174]. Disseminated strongyloidiasis is reported in two patients with COVID-19 up until now [175, 176], in which both of them received immunosuppressive agents (dexamethasone [176], methylprednisolone, and tocilizumab [175]). Therefore, patients who received immunosuppressive therapy are considered as a high-risk group and should be screened for *S. stercoralis*, especially in tropical areas in which the infection is high prevalence.

Discussion

Most of the opportunistic infections have no or at least minor clinical symptoms among immunocompetent individuals. Nevertheless, these infections have several sequels among immunocompromised patients, such as patients with cancer and malignancies [177–179], organ recipients' individuals [180], patients with autoimmunity who received immunosuppressive therapies [22] and HIV/AIDS patients with low CD⁴ T cell counts [21, 181]. The CSS and ARDS are among the major causes of multiorgan failure and death due to COVID-19 [182, 183]. Hence, immunosuppressive therapy with corticosteroids [19, 20, 184] and monoclonal antibodies has been used to mitigate the CSS in critically ill COVID-19 patients (Table 1). Administration of dexamethasone in hospitalized patients with COVID-19 resulted in a significant increase in the number of ventilator-free days [184] and a lower mortality rates [19] over 28 days. The results of a meta-analysis have shown that administration of systemic corticosteroids (e.g., dexamethasone, hydrocortisone, and methylprednisolone) in comparison with usual care or placebo was associated with in lower 28-day all-cause mortality [20]. Previous reports revealed that corticosteroid use increases the risk of different opportunistic infections (Table 2). A number of opportunistic infections have been reported among COVID-19 patients who received immunosuppressive therapies (Table 3). For instance, CAPA and CAM were associated with corticosteroid use in 52.7% [31] and 76.3% [60] of COVID-19 patients, respectively. Tocilizumab is an IL-6 blocker that is used in a number of trials for COVID-19 patients [185]. The results of two randomized, double-blind, placebo-controlled trials revealed that tocilizumab was associated with a reduced likelihood of mechanical ventilation or death in hospitalized patients with COVID-19 [186], but was not effective for prevention of intubation or death in moderately ill patients with COVID-19 [187]. The results of a meta-analysis demonstrated that administration of tocilizumab to standard therapy was associated with reduced need for mechanical ventilation and mortality rate in patients with severe COVID-19 [185]. IL-6 is produced in response to infections and tissue damage [188], although IL-6 inhibition was associated with an increased risk of secondary bacterial and fungal infections [189]. Likewise, disseminated cryptococcosis [190], meningitis [191], invasive aspergillosis [192], CMV pneumonitis [193], and tuberculosis [194] were reported in patients who received tocilizumab (Table 2). In COVID-19 patients, different cases with cryptococcosis [24, 65, 71–73], aspergillosis [88], strongyloidiasis [175], PCP [88], CMV [135], and HSV [143] infections were reported following tocilizumab use

Table 3 Opportunistic infections in COVID-19 patients who received immunosuppressive therapy

Agents	Opportunistic infections
Corticosteroids	Aspergillosis [31, 88] Candidiasis [43] Mucormycosis [60] Cryptococcosis [24, 65, 71–73] <i>Pneumocystis jiroveci (carinii)</i> pneumonia [76, 81, 88, 89] <i>Histoplasma capsulatum</i> [95, 96, 98] <i>Coccidioides immitis</i> [101, 102] Strongyloidiasis [175, 176] CMV [130, 132, 135, 136] HSV [143]
IL-6 blocker (Tocilizumab)	Cryptococcosis [24, 65, 71–73] <i>Pneumocystis jiroveci (carinii)</i> pneumonia [88] Aspergillosis [88] Strongyloidiasis: [175] CMV: [135] HSV: [143]

(Table 3). Inhibition of the JAKs pathway (ruxolitinib [195–197], baricitinib [198, 199], and tofacitinib [200]), TNF α (infliximab [201, 202]), IL-1 (Anakinra [203, 204] and Canakinumab [205, 206]), and GM-CSF (Mavrimumab [207]) was also used for mitigating the CSS in COVID-19 patients (Table 1). These immunomodulatory agents can also increase the risk of opportunistic infections (Table 2), although there are not reported in COVID-19 patients till now.

Some opportunistic infections are associated with alterations of the immune system, such as CMV [123] and helminth infections [167, 169]; hence, coinfection with these pathogens could mitigate essential immune responses against SARS-CoV-2 and probably diminish the immune response following vaccination [169].

Early detection and differential diagnosis of opportunistic infections are an important point and challenging issue in COVID-19 patients. Early detection can lead to early treatment and consequently lower sequel and better outcome of COVID-19 patients. Differential diagnosis should be considered especially for opportunistic respiratory infections, such as PCP [89, 91–94]. These infections could be misdiagnosed with COVID-19 in some cases due to some clinical and paraclinical similarities. In the COVID-19 period, the diagnostic procedures are diverted to COVID-19. Although vigilance is needed in the diagnosis of COVID-19, the common disorders should not be negligible [208].

Reactivation of latent infection following immunosuppression is the major cause of severe infections in some opportunistic infections, such as HSV, CMV, TB, and toxoplasmosis [21, 149]. Prophylaxis with TMP-SMX can reduce the risk of some opportunistic infections, such as PCP, TB, toxoplasmosis, and different bacterial infections [21, 209, 210]. Hence, prophylactic strategies may

be useful for COVID-19 patients, especially for those who received immunosuppressive therapy or who have underlying diseases.

Drug–drug interaction is a challenge for treatment of opportunistic infections in COVID-19 patients, especially those who hospitalized in ICU [211]. For example, drug–drug interactions are the major challenge of voriconazole in the ICU setting [38, 41, 42]. Concentrations of itraconazole and clindamycin are increased by lopinavir/ritonavir, while voriconazole, posaconazole, and clarithromycin increase lopinavir/ritonavir concentration [212]. Hence, the possibility of drug–drug interaction should consider when prescribing new medications in COVID-19 patients.

Mutations of the SARS-CoV-2 virus are an emerging challenge that could be associated with reduced effectiveness of diagnosis, treatment, and vaccination as well as increased transmissibility and severity of the disease (<https://www.cdc.gov/coronavirus/2019-ncov/variants/variant-info.html#Consequence>). In these conditions, coinfection with opportunistic pathogens could be an additional challenge for the diagnosis, treatment, and management of COVID-19 patients.

To date, some clinical studies are registered in the clinicaltrials.gov regarding opportunistic infections and COVID-19. However, it seems that future studies are needed for standard diagnosis and new treatment options of these infections in COVID-19 patients (Table 4).

Table 4 Clinical studies that registered in the clinicaltrials.gov regarding opportunistic infections and COVID-19

Trial/phase	Title	Setting	Status	Estimated Primary Completion Date
NCT04818853	COVID-19 Associated Pulmonary Aspergillosis (CAPA) and Other Invasive Fungal Infections (IFI)	Observational: Cohort	Recruiting	March 1, 2023
NCT04240886 Phase 2	A Phase 2, Open-Label Study to Evaluate the Safety and Efficacy of APX001 in the Treatment of Patients with Invasive Mold Infections Caused by Aspergillus Species or Rare Molds	Interventional	Recruiting	July 2021
NCT04368221	Characterization of Fungal Infections in COVID-19 Infected and Mechanically Ventilated Patients in ICU	Observational: Cohort	Completed	February 23, 2021
NCT04707703 Phase 3	Isavuconazole for the Prevention of SARS-CoV-2-associated Invasive Aspergillosis in Critically-Ill Patients	Interventional	Recruiting	January 2022
NCT04935463	Mucormycosis in COVID-19	Observational: Cohort	Enrolling by invitation	June 1, 2022
NCT04813328	A Pilot Study of the Effects of Helminth Infection and SARS-CoV-2 Seropositivity on Immune Response and the Intestinal Microbiota in India	Observational	Not yet recruiting	April 2022

Limitations of the study

In this review, we summarized the main opportunistic infections among COVID-19 patients. However, one of the major limitations of this review is lots of case reports or case series with various settings, diagnosis, and treatment strategies. Hence, if there was a systematic review article regarding opportunistic infections, we selected these articles instead of each case report.

Conclusions and future perspectives

Taken together, the COVID-19 patients with underlying diseases or who received immunosuppressive therapy have an increased risk of CAOIs. Strategies for screening and early diagnosis, treatment, and prophylaxis could mitigate the risk of CAOIs in COVID-19 patients. Future investigations for generation of reliable algorithms and standardization of diagnostic procedures are highly needed for early and differential diagnosis of CAOIs in COVID-19 patients. As such, standard prophylactic strategies are needed in high-risk COVID-19 patients, such as those who received immunosuppressive therapy, patients with underlying diseases, patients who admitted to the ICU, and those who received invasive mechanical ventilation.

Supplementary Information The online version contains supplementary material available at <https://doi.org/10.1007/s10238-021-00751-7>.

Acknowledgements The authors would like to apologize from authors whose works have not cited in this article because of space limitations.

Authors' contributions AA conceived the article. AA, SF, and AK analyzed the references. AA, SF, and AK wrote the draft of manuscript. All authors revised the initial manuscript and approved its final version.

Funding None.

Declarations

Conflict of interest The authors declare that they have no competing interests.

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