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FUNGAL PATHOGENESIS (S DIEZMANN, SECTION EDITOR)

When to Initiate Antifungal Treatment in COVID-19 Patients with Secondary Fungal Co-infection

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Abstract

Purpose of Review Severe-acute respiratory coronavirus 2 (SARS-CoV-2) has been driving the health care delivery system for over 2 years. With time, many issues related to co-infections in COVID-19 patients are constantly surfacing. There have been numerous reports about various fungal co-infections in patients with COVID-19. The extent of severity of fungal pathogens has been recognized as a substantial cause of morbidity and mortality in this population. Awareness, understanding, and a systematic approach to managing fungal co-infections in COVID-19 patients are important. No guidelines have enumerated the stepwise approach to managing the fungal infections co-occurring with COVID-19. This review is intended to present an overview of the fungal co-infections in COVID-19 patients and their stepwise screening and management.

Recent Findings The most common fungal infections that have been reported to co-exist with COVID-19 are Candidemia, Aspergillosis, and Mucormycosis. Prevalence of co-infections in COVID-19 patients has been reported to be much higher in hospitalized COVID-19 patients, especially those in intensive care units. While clear pathogenetic mechanisms have not been delineated, COVID-19 patients are at a high risk of invasive fungal infections.

Summary As secondary fungal infections have been challenging to treat in COVID-19 patients, as they tend to affect the critically ill or immunocompromised patients, a delay in diagnosis and treatment may be fatal. Antifungal drugs should be initiated with caution after carefully assessing the immune status of the patients, drug interactions, and adverse effects. The crucial factors in successfully treating fungal infections in COVID-19 patients are optimal diagnostic approach, routine screening, and timely initiation of antifungal therapy.

Keywords COVID-19 · Candidemia · Mucormycosis · Pulmonary aspergillosis · Opportunistic fungal pathogen

Introduction

While the medical world was still battling the coronavirus pandemic, the incidence of co-infections with bacterial, fungal, or other viral infections started becoming prominent in people already infected with the novel coronavirus. In the second wave of the Coronavirus Disease of 2019 (COVID-19) pandemic, another infectious disease of epidemic proportions threatened the morbidity and mortality rate of the COVID-19-affected individuals. The co-infections of severe acute respiratory syndrome coronavirus-2 (SARS CoV-2) with other bacterial, fungal, and respiratory viral pathogens have frequently been occurring. Musuuza J. S. et al., in a meta-analysis published in May 2021, reported that 19% of patients with COVID-19 have co-infections and 24% have superinfections. The presence of both co-infection or superinfection is associated with poor outcomes and a higher incidence of mortality [1•]. Many fungal infections have been reported with COVID-19, especially in severely ill or immunocompromised patients [2]. The most common fungal infections reported in 2020 were Aspergillosis and Candida. However, the second surge of COVID-19 has witnessed a high incidence of mucormycosis cases in India [3•]. In fact, it has been reported that the country contributed to 81% of the cases of COVID-19-associated fungal disease, rhino-orbital-cerebral mucormycosis (ROCM) [4•].

The SARS-CoV-2 infection leads to an infection of the lower respiratory tract. COVID-19 disease is marked by

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diffuse alveolar damage and an immunosuppressed state with a reduction in CD4 + T cells and CD8 + T cells [4•]. The cell wall components such as β-glucans and α-mannans and the lipid molecules of fungal pathogens are known to stimulate the immune response. For instance, in critical COVID-19 cases, the Toll-like receptors or TLR-4 (activated by fungal pathogen-associated molecular patterns (PAMPs)) synergize with TLR-7 (virus activated), and TLR-2 (fungus activated) synergize with NLR family pyrin domain-containing proteins NLRP-3 (viral activated). COVID-19 and fungal co-infection leads to a dramatic increase in the cytokine level and generate a cytokine storm. This cytokine storm or hyperinflammation generally inhibits viral propagation and causes excessive cell death, which might cause respiratory distress and, in due course, multiorgan failure [4•]. The occurrence of invasive fungal infections becomes very probable in patients with aggressive features of COVID-19, specifically the ones with a high primary pulmonary entry and an airborne route of infections such as invasive pulmonary Aspergillosis and mucormycosis [5]. Critically ill patients, especially those admitted to intensive care units, requiring mechanical ventilation, or having a longer duration of hospital stay, even up to 50 days, had higher chances of developing fungal co-infections [6]. It can be observed that the chances of developing fungal co-infections in COVID-19 patients become more prominent in the middle and later phases of the disease, particularly affecting the patients affected with severe disease [5].

Early detection and timely diagnosis of co-infections with fungal pathogens are important to initiate appropriate early therapy, improve outcomes, and restrict the unwarranted use of antifungals. The presence of co-infection or superinfection may have a profound effect on diagnostic testing and therapeutic decision-making. However, currently, there are no standard guidelines delineating the evidence-based treatment approach to be adopted for the management of fungal co-infections in coronavirus disease 2019 (COVID-19) patients. To bridge this gap, I have reviewed the existing and available evidence on the incidence of fungal infections in COVID-19 patients to provide an overview of the presence, detection, diagnosis, and management of the fungal infections co-existing with COVID-19. Based on existing evidence and clinical experience, an algorithm for the treatment of fungal infections in COVID-19 patients is also proposed.

Methodology

The author reviewed published literature to study the incidence, predisposing factors, diagnostic criteria, and management approach of different fungal infections in COVID-19 patients. The relevant articles that met the following criteria were selected for the study.

I. Original articles, systematic reviews and meta-analyses, case series, and case reports published from January 2020 to June 23, 2022 that studied the fungal infections in COVID-19 patients
II. Articles published in the English language

Articles excluded from the analysis were.

I. Articles on secondary infections other than bacterial or viral
II. Posters/abstracts, studies on animal models.

The study aimed to review all the published literature in the last 2 years comprising original research, clinical trials, case reports, case series, systematic reviews and meta-analyses, and reports. A search of the computerized bibliographic database, Medline, PubMed, and Google Scholar, was performed. The Medical Subject Headings (MeSH) terms used in the search were ((Antifungal Treatment) AND (COVID-19) AND (SARS-CoV-2)), ((Fungal co-infection) AND (COVID-19), (Antifungal treatment) AND (COVID-19). In a backward chronological search, the bibliographies of other relevant articles were checked for citations that were not identified in the primary search. Titles and abstracts were screened, and full-text articles meeting the selection criteria were obtained.

Results and Discussion

Following the literature search, 54 articles were identified in the study, including case studies and systematic reviews, meta-analyses, and reports. Based on the case reports and systematic reviews on fungal co-infections in COVID-19 patients, the risk factors, diagnostic mechanisms, and management approach for Candidemia, Aspergillosis, and Mucormycosis are discussed in the following sections.

Fungal Infections

It has been suggested that fungal co-infections may occur in critically ill or post-recovery COVID-19 patients. The co-infections may result from certain practices during the intensive care treatment of these patients [7]. A recent meta-analysis published in July 2021 included 31,953 patients with laboratory-confirmed SARS-CoV-2 from 72 observational studies to assess the prevalence of co-infection with bacterial, fungal, and respiratory viral pathogens. In the study, it was shown that the overall laboratory-confirmed bacterial infection was 15.9% (955 CI 13.6–18.2, $n=1940$, 49 studies, $I^2=99\%$, $p<0.00001$); 3.7% (95% CI 2.6–4.8, $n=177$, 16 studies, $I^2=93\%$, $p<0.00001$) had fungal infections, and 6.6% (955 CI 5.5–7.6, $n=737$, 44 studies, $I^2=96\%$, $p<0.00001$) had other respiratory viruses. It was

also seen that the prevalence of co-infections was reportedly higher in hospitalized COVID-19 patients, particularly those in intensive care units (ICU) [8].

Despite the ambiguity in the mechanism, COVID-19 patients are at a high risk of invasive fungal infections [5]. It has been previously seen that fungal infections like Candida and pulmonary Aspergillosis commonly occur in patients with viral pneumonia, especially in critically ill patients [9]. In a meta-analysis, including data from China, USA, Spain, Thailand, and Singapore, four fungal pathogens in COVID-19 patients were reported to occur commonly: *Candida albicans*, *Candida glabrata*, *Aspergillus flavus*, and *Aspergillus fumigatus* [10]. Even though rare, several cases of mucormycosis have been reported leading up to a significant increase in incidence in the rise of the ongoing COVID-19 pandemic [11].

Candidemia

Candidemia is one of the most important opportunistic fungal infections occurring in intensive care unit patients and is associated with high mortality [7]. In New Delhi, India, a study reported that candidemia affected 15 critically ill COVID-19 patients admitted to the intensive care unit from April to July 2020. About two thirds of these cases were due to an infection from *Candida auris* [12]. The most common risk factors associated with the occurrence of candidemia co-infection include increased age, prolonged hospital stay, broad-spectrum antibiotics, central vascular catheters, parenteral nutrition, mechanical ventilation, antifungal prophylaxis, long-term antibiotic therapy, severe sepsis, long-term corticosteroid use, and even chemotherapy. Candidemia patients are also at an increased risk of mortality, including septic shock, depending on acute kidney injury and the amount of antibiotic exposure before candidemia [13].

The diagnosis is based on culture methods, including blood culture or other samples collected under sterile conditions. Non-culture diagnostic tests, including mannan and antimannan IgG tests, *C. albicans* germ tube antibody (CAGTA), 1,3-β-d-glucan (BDG), and PCR-based assays, are used as adjuncts to culture [14]. However, blood culture is associated with long duration and reduced sensitivity compared to PCR, with a much lower detection limit when *Candida* concentration is ≤ 1 CFU/mL. Hence, there are chances of failure to detect the infection if the infection is in low concentration or it has not entered the systemic circulation [15]. A combination of culture and non-culture diagnostic tests are recommended. In addition, a susceptibility test is also recommended for all systemic and clinically relevant *Candida* isolates, particularly *C. glabrata* or *C. parapsilosis* [2]. In a retrospective study conducted between January 2019 and December 2020 at Hospital General Universitario Gregorio Maranon in Madrid, Spain, it was observed that *C. albicans* was the most commonly found species (58%), followed by *C. parapsilosis* (15.2%), *C. glabrata* (11.4%), *C. tropicalis* (9.5%), *C. krusei* (5%), and *C. kefyr* (0.9%) [16].

A case report demonstrated a case of *Candida* colonization in a COVID-19 patient on antiviral therapy and broad-spectrum antibiotics. The patient did not survive after spending 4 days in the intensive care unit, mechanical ventilation, and parenteral feeding [5]. Another case reported co-infection with *Candida duobushaemulonii* fungemia following multiple courses of antibiotics and prolonged mechanical ventilation. The patient was treated with intravenous fluconazole and caspofungin. However, the patient's condition was complicated by pneumothorax which was followed by cardiac arrest and death [17]. A COVID-19 patient with diabetes and hypertension and on treatment with corticosteroids and tocilizumab was reported to develop *Candida albicans* infection. The diagnosis was confirmed through a blood culture. The patient was treated with voriconazole injection and fluconazole [18]. In another case series, 14 patients with *Candida auris* co-infection were reported from Lebanon. All the patients were administered broad-spectrum antibiotics, including piperacillin-tazobactam, carbapenems, and ceftolozane-tazobactam, while 12 out of 14 patients received steroids and 13 out of 14 received mechanical ventilation [19].

Early recognition of candidemia and initiation of treatment with appropriate antifungal therapy is of utmost importance in managing candidemia patients. The antifungal drugs which have shown some susceptibility towards different Candida species include flucytosine, voriconazole, amphotericin B, itraconazole, and casponfungin. However, optimum use of broad- or narrow-spectrum antibiotics is very important in preventing and controlling fungal co-infections [17]. There are no standard guidelines for the management of *Candida auris* infections; however, echinocandins are considered to be the first-line therapeutic agents. While *Candida* isolates show varying minimum inhibitory concentrations (MICs) to amphotericin B, a combination of voriconazole and micafungin has also been recommended for synergistic activity. Amphotericin B may be used in *Candida* isolates non-responsive to echinocandins [19]. In the case of *Candida glabrata* infections also, the first line of therapy is echinocandin; however, many patients have shown resistance, bringing in the need to initiate an aggressive therapy [20]. It is suggested that when amphotericin B and its liposomes are used, therapeutic drug monitoring for azoles should be used to optimize efficacy and control toxicity [2].

Invasive Aspergillosis

COVID-19 is associated with a high risk of invasive pulmonary Aspergillosis as highlighted in several reports from COVID-19 patients in intensive care. Invasive pulmonary Aspergillosis was first reported with H1N1 influenza, which

is a frequent and early-onset complication in critically ill patients with influenza (20–30% incidence), causing severe illness and mortality in 40–60% of cases [21]. In a systematic review published in July 2021, the percentage incidence of COVID-19-associated pulmonary Aspergillosis was reported to be 13.5% (total of 1421 patients) with a high mortality rate of 48.4% despite the prevalent use of antifungal drugs for treatment. However, the lack of standardized diagnostic criteria makes it difficult to accurately assess the incidence of pulmonary Aspergillosis in COVID patients [22]. Another systematic review also demonstrated that pulmonary Aspergillosis in COVID-19 patients is associated with high chances of mortality, and early diagnosis with promptly initiated therapy is important for the appropriate management of patients with aspergillosis secondary infection [23].

Infections caused by the Aspergillus genus are attributed to many predisposing factors, including prolonged treatment with corticosteroids and lung epithelial damage. The dysfunctional immune response and diffuse lung damage lead to the early onset of secondary infections like Aspergillosis [24]. Invasive pulmonary Aspergillosis has also been reported in an immunocompetent patient with COVID-19 disease after treatment with tocilizumab. This case underlines the importance of opportunistic infections in patients treated with immune-modulating therapy such as tocilizumab [25]. Pulmonary Aspergillosis includes a wide range of clinical syndromes mainly caused by *Aspergillus fumigatus*, based on the host response and existing condition of the pulmonary structure [26]. Some of the clinical characteristics seen in pulmonary aspergillosis patients include early symptom onset after ICU admission, absence of the European Organization for Research and Treatment of Cancer and the Mycoses Study Group Education and Research Consortium (EORTC/MSGERC) host factors, and high ICU mortality [27].

Microbiologic and histopathologic evidence is required to diagnose invasive Aspergillosis. However, the diagnostic tests are challenging considering the difficulty in collecting specimens as biopsy may be contraindicated in patients with coagulation diseases or severe respiratory failure [28]. While histopathological findings usually rely on detecting special fungal stains on lung fluid or tissue when a fungal infection is suspected, it is difficult to differentiate between infection from *Aspergillus* spp. From other filamentous fungi such as *Fusarium* spp. and *Scedosporium* spp. [29], a definitive diagnosis can be achieved by the use of a culture or non-culture technique, including direct microscopic examination, culture on fungal-specific media, molecular assays targeting rDNA sequences [30], and serum and broncho-alveolar lavage fluid–galactomannan (BALF-GM) testing [31].

In a case of *Aspergillosis niger* co-infection in a COVID-19 patient with ventilator-associated pneumonia (VAP)-related pulmonary Aspergillosis, the patient did not survive despite rapid administration of antifungal therapy [26]. In another case of co-infection of COVID-19 patients with *Aspergillus* section *Fumigati* showed an improvement in respiratory function following proper antifungal treatment with oral voriconazole [32]. Pulmonary Aspergillosis has also been reported in an acute myeloid leukemia patient co-infected with SARS-CoV-2 with acute respiratory distress syndrome-related complications. The patient was treated with intravenous liposomal amphotericin B; however, despite antifungal and antibacterial therapy, the patient did not survive due to respiratory and hemodynamic instability [32]. Another case of *Aspergillus fumigatus* was reported in a COVID-19 patient with diabetes and hypertension as comorbidity. The patient was treated with voriconazole. After the treatment, the patient showed relief in symptoms of chest tightness and shortness of breath and the symptoms of cough and expectoration showed improvement [34]. Another case of Aspergillosis highlighted the importance of early assessment of patients with COVID-19-related pneumonia to detect the secondary co-infection of *Aspergillus* [35].

Previously existing literature and guidelines have recommended the duration of treatment from 3 to > 50 weeks [36], while 2016 IDSA guidelines suggested a minimum of 6–12 weeks of treatment [30]. A quick diagnosis may provide support in the development of an accurate therapeutic plan and clinical remission in the case of a patient without comorbidities or extensive pulmonary damage [26]. Studies have demonstrated that diagnostic work-up should be initiated as early as possible, including fungal cultures, galactomannan detection, and Aspergillus PCR on tracheal aspirates or broncho-alveolar lavage fluid. Empiric antifungal therapy is also recommended in certain cases where the results of the diagnostic tests are not yet known [37]. While a delay in diagnosis poses a major challenge in the timely treatment of COVID-19-associated aspergillosis, the emergence of azole-resistant *Aspergillus* species underlines further challenges faced in the management of these patients [38].

It is suggested to screen for Aspergillosis in critically ill patients with COVID-19 [19], highlighting the significance of screening and early diagnosis [37]. EUCAST guidelines have shown that Aspergillus has susceptibility to voriconazole, isavuconazole, itraconazole, Posaconazole, and amphotericin B [39]. The ECMM expert guidelines have recommended voriconazole or isavuconazole as recommended first-line therapy for suspected and confirmed COVID-19-associated pulmonary Aspergillosis [40]. In a kidney transplant patient diagnosed with invasive pulmonary Aspergillosis, the patient showed recovery following treatment with isavuconazole and nebulized pulmonary amphotericin B combination and removal of immunosuppression [41]. Another case report of Aspergillosis in a post-COVID-19 patient suggested that pulmonary resection may be the last and most effective strategy

to manage the disease. Since the patient was azole-resistant, lobectomy was conducted to remove the infected lobe, and the patient was released from the hospital in good condition [42, 43]. Most patients can be given triazole drugs to treat invasive Aspergillosis; however, therapeutic drug monitoring is recommended, and interaction between azoles and other drugs should be monitored [2].

Mucormycosis

Singh A. K. et al. have reported that among all the reported cases of mucormycosis in people with COVID-19, the disease was predominantly seen in males (78.9%), either in people who had an active COVID-19 infection (59.4%) or recovered (40.6%) from COVID-19. The risk factors leading to the disease included pre-existing diabetes mellitus (80% of cases), diabetic ketoacidosis (14.9%), and in patients using corticosteroids (76.3% of cases). Mucormycosis with clinical manifestation in the nose and sinuses occurred frequently, followed by rhino-orbital disease. A high rate of mortality was also associated with mucormycosis [44]. In earlier studies, it has been established that predisposing factors toward causing mucormycosis are diabetes mellitus, neutropenia, severe trauma, and immunosuppression following bone marrow transplant. It was also suggested that host-specific conditions might raise the susceptibility to infection [45], as is seen in the case of COVID-19 patients. The use of corticosteroids in COVID-19 patients acts as a double-edged sword, predisposing patients to secondary fungal infections [46].

The onset of ROCM from the diagnosis of COVID-19 was reported to be 14.5 ± 10 days, with 56% of the patients developing within 14 days. The most common symptoms of ROCM were orbital/facial pain, orbital/facial edema, loss of vision, ptosis, and nasal block. Other symptoms include proptosis, nasal discharge, diplopia, headache, orbital and facial discoloration, toothache, loose teeth, epistaxis, and facial deviation. Nasal ulcer or eschar, diplopia or ocular movement restriction, periocular or facial discoloration, periocular hypesthesia, oral or palatal ulcer or eschar, facial palsy, and changed sensorium were some of the other signs seen in reported cases [3•].

The diagnostic tools for diagnosing COVID-19-associated ROCM included nasal endoscopy, deep nasal swab or sinus debridement for microbiological evidence, histopathology, CT scan, and MRI. Radiological tests revealed the clinical involvement of the PNS (diffuse and bilateral involvement), orbit (diffuse, medial, and orbital apex involvement), and CNS (cavernous and bilateral involvement) [3•]. The culture of specimens is recommended to identify the genus and species, also antifungal susceptibility testing.

Successful management is based on the timing of the treatment. It is recommended to conduct the biopsy and initiate treatment with intravenous antifungal treatment as soon as the disease is suspected [45]. It was seen that a delay of even 6 days in initiating treatment raises the 30-day mortality from 35 to 66%, emphasizing the significance of early diagnosis and treatment [47]. In this context, it is recommended that empirical treatment with antifungal medications should be initiated upon clinical or clinical-radiological correlation in a symptomatic COVID-19 patient, while the results of culture test and histopathology results are awaited [2].

A meta-analysis showed that in 52% of the cases, the primary initiation of treatment was done with amphotericin B. In 21% of the cases, primary functional endoscopic sinus surgery (FESS) or PNS debridement was performed. In about 9% of the cases, amphotericin B and FESS or PNS were concurrently used. The meta-analysis also reported the use of combination therapy with amphotericin B and Posaconazole or isavuconazolein in 23% of the cases. In some instances, multiple sessions of debridement are also needed [2]. The VITAL study demonstrated that isavuconazole was non-inferior to amphotericin B against mucormycosis, as primary treatment, in refractory cases and patients with toxicity to other antifungal agents [48, 49]. Another study from India has also demonstrated Posaconazole to be highly effective as salvage therapy for mucormycosis with life salvage with a 67% complete resolution in patients [50]. A report observed that 23% of the patients received combination therapy with Posaconazole as the second-line therapy added to amphotericin B [3•].

An early complete surgical treatment for mucormycosis is recommended whenever possible, in addition to systemic antifungal treatment. Amphotericin B lipid complex, liposomal amphotericin B, and Posaconazole oral suspension are the first-line antifungal monotherapy. Prophylactic therapy with Posaconazole is recommended in neutropenic patients with graft versus host disease or high-risk factors [2].

Other Opportunistic Fungal Infections

Apart from *Aspergillus* and *Candida* species, the COVID-19 pandemic has also witnessed patients with secondary infection with other fungal pathogens like *Cryptococcus*, *Histoplasma*, and *Pneumocystis*. Cryptococcosis is an opportunistic fungal infection causing cryptococcosis. *Cryptococcus neoformans* is known for fatal meningoencephalitis in immunocompromised patients with multiple infections. Recently, cases of cryptococcal meningoencephalitis in patients with SARS-CoV-2 infection have been reported [51].

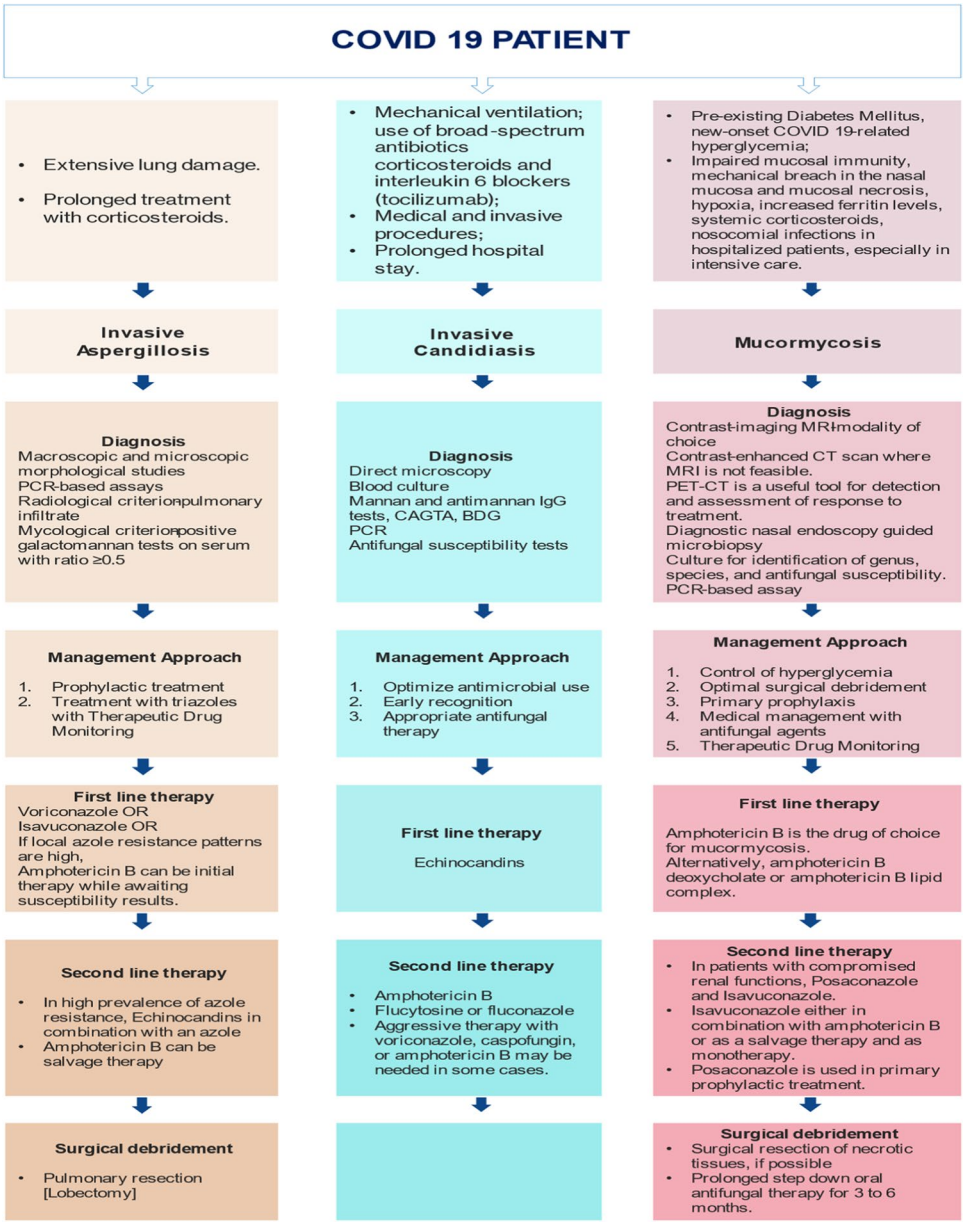

Fig. 1 Algorithm to diagnose and manage the fungal co-infections in COVID-19 patients

Heller et al. [52] reported cryptococcal meningoencephalitis in a young male who was HIV-positive. The study revealed that the CD4:CD8 T cell ratio tends to be preserved in patients with COVID-19-associated lymphopenia, while a drop in the quotient is observed in patients with advanced HIV infection. COVID-19 patients are more susceptible to fungal infections due to the decrease in CD4 and CD8 T lymphocytes and the use of corticosteroids and other immunosuppressant drugs. Cryptococcemia was reported in a COVID-19 patient with several comorbidities who received tocilizumab and corticosteroids [53]. Cryptococcus may affect the lungs or the central nervous system. Isavuconazole was found to be useful in cases of invasive fungal infection due to *Cryptococcus* and *Histoplasma*. Few cases with SARS-CoV-2 and *Pneumocystis jirovecii* co-infection have also been reported. In a recent study, it was noted that due to similar clinical features between *P. jirovecii* infection and Pneumocystis pneumonia, the diagnosis is challenging, thus outlining the need for additional diagnostic testing for *P. jirovecii*, especially in patients with high lactate dehydrogenase [54].

Treatment Approach

A meta-analysis showed that 98% of 83 studies included in the analysis administered antibiotics to COVID-19 patients. However, judicious use of antibiotics is warranted and only in the case of diagnosed bacterial co-infections [3•]. Besides, the use

of corticosteroids and other comorbidities act as predisposing factors for acquiring fungal infection. Even though more experts are aware of fungal co-infections, the unavailability of standard guidelines to be followed in fungal co-infections in COVID-19 patients creates a challenging scenario in the management of the fungal infection. Early diagnostic work-up, early initiation of first-line therapy, salvage therapy, or surgical resection is described as the optimal strategy for the management of secondary fungal infections in COVID-19. In the case of mucormycosis, prolonged step-down therapy with oral antifungal agents is also required for 3 to 6 months. Figure 1 provides the diagnostic and management approach for fungal co-infections in COVID-19 patients.

Conclusion

Secondary fungal infections have been increasingly reported in COVID-19 patients, including candidemia, aspergillosis, and mucormycosis, with mucormycosis dominating the secondary fungal infection scene during the second COVID wave in India. Additionally, *Cryptococcus*, *Histoplasma*, and *Pneumocystis* infections have also been detected in COVID-19 patients. The severity of fungal co-infections was enhanced in COVID-19 patients with predisposing factors such as ARDS, diabetes, mechanical ventilation, organ transplant recipients, antibiotics, and immunosuppressive therapies. Secondary fungal infections have been challenging as they were more reported in critically ill or immunocompromised patients, delayed diagnosis, and initiation of therapy.

In the treatment of fungal infections in critically ill COVID-19 patients, antifungal drugs should be used with caution keeping in mind the immune status of the patients, drug interactions, adverse effects, costs, and ability to measure drug levels. Optimal diagnostic approach, routine screening of critically ill COVID-19 patients, especially those at high risk, and early initiation of antifungal therapy are the hallmarks of managing COVID-19 patients with fungal co-infection.

Glossary

Co-infection	Recovery of other respiratory pathogens in patients with SARS-CoV-2 infection at the time of a SARS-CoV-2 infection diagnosis
Superinfection	The subsequent recovery of other respiratory pathogens during care for SARS-CoV-2 infection

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Declarations

Conflict of Interest The author declares no competing interests.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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