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Review

# The battle against fungi: lessons in antifungal stewardship from COVID 19 times☆

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ABSTRACT

The COVID-19 pandemic has highlighted the detrimental effect of secondary pathogens in patients with a primary viral insult. In addition to superinfections with bacterial pathogens, invasive fungal infections were increasingly reported. The diagnosis of pulmonary fungal infections has always been challenging; however, it became even more problematic in the setting of COVID-19, particularly regarding the interpretation of radiological findings and mycology test results in patients with these infections. Moreover, prolonged hospitalization in ICU, coupled with underlying host factors. such as preexisting immunosuppression, use of immunomodulatory agents, and pulmonary compromise, caused additional vulnerability to fungal infections in this patient population. In addition, the heavy workload, redeployment of untrained staff, and inconsistent supply of gloves, gowns, and masks during the COVID-19 outbreak made it harder for healthcare workers to strictly adhere to preventive measures for infection control. Taken together, these factors favored patient-to-patient spread of fungal infections, such as those caused by *Candida auris*, or environment-to-patient transmission, including nosocomial aspergillosis. As fungal infections were associated with increased morbidity and mortality, empirical treatment was overly used and abused in COVID-19-infected patients, potentially contributing to increased resistance in fungal pathogens. The aim of this paper was to focus on essential elements of antifungal stewardship in COVID-19 for three fungal

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infections, COVID-19-associated candidemia (CAC), -pulmonary aspergillosis (CAPA), and -mucormycosis (CAM).



## 1. Introduction

The coronavirus disease-2019 (COVID-19) pandemic has gained the attention of healthcare workers (HCWs) around the world. Within this, the pandemic of opportunistic and multidrug-resistant organisms (MDROs) associated with COVID-19 must not be underestimated. Co-infections in COVID-19 patients have been reported [1,2], including infections with *Staphylococcus aureus* and *Klebsiella pneumoniae*, and many invasive fungal infections (IFIs), resulting in poorer outcomes [3,4]. Globally, the most commonly reported IFIs are candidemia and aspergillosis, and the prevalence of mucormycosis shows regional variation [5]. In a retrospective, multicenter, observational, cohort study from France, the mortality rate for critically ill COVID-19 patients with IFIs was 50.6%, compared with 22.6% for COVID-19 patients with no evidence of IFI [6]. Marked variation in the diagnostic capabilities of mycology laboratories in middle- and high-income countries further complicates reliable data capture [7,8]. The absence of a systematic approach to fungal diagnostics has led to over- or under-reporting of the problem [9].

It is difficult to diagnose IFIs in COVID-19 patients in the absence of pathognomonic clinical and radiographic findings on the background of lung injury secondary to the virus, coupled with limited sensitivity and specificity of diagnostic mycological tests. Distinguishing *Aspergillus* colonization from invasive disease is challenging. Contamination and clinically irrelevant colonization of the upper respiratory tract with fungi (mainly *Aspergillus*) was found in 17.2% of the COVID-19 patients admitted to five independent intensive care units (ICUs) from a single center [10]. Diagnostic uncertainty often leads to over-prescribing of antifungal agents, putting patients at risk for drug toxicity and drug interactions, and burdening institutions with high cost [11–14]. Overuse of antimicrobial agents has been correlated with emerging resistance, and antifungal agents are no exception. This has been one of the most alarming examples of collateral damage resulting from the COVID-19 pandemic [15,16]. Antifungal-resistant IFIs may be devastating for hospitalized COVID-19 patients [17], with infections including echinocandin-resistant *Candida glabrata* [18,19], MDR *Candida auris* [17] and triazole-resistant *Aspergillus fumigatus* [20] bringing antifungal stewardship (AFS) into sharp focus.

Strategies for implementation of AFS are yet to be fully integrated into hospital protocols. The Mycoses Study Group Education and Research Consortium (MSGERC) recently addressed the application of the core elements of antimicrobial stewardship (AMS) to AFS, providing specific recommendations for developing interventions to measure and improve the appropriate use of antifungal agents [21].

This review focuses on AFS relevant to COVID-19. Although AFS practices that are applicable to the COVID-19 pandemic could be applicable to influenza pandemics, there are major differences in the presentation and outcome of some mold infections, such as aspergillosis, following the two viral infections. In addition, mucormycosis has not been widely reported following influenza. This paper presents the predominant fungal pathogens affecting COVID-19 patients, and discusses the role of screening, the timely diagnosis of infections, and the principles of optimal antifungal use along with tailored treatment strategies and patient monitoring. Also discussed is the prevention of IFIs as a core strategy of AFS. As the trauma of the COVID-19 pandemic gradually fades from public memory, and the political discourse shifts to other areas of healthcare, it is important that the wisdom acquired in relation to IFIs is used to improve diagnostic and therapeutic interventions, and infection control protocols.

## 2. Antifungal Stewardship diagnostics

Various fungal infections may occur in COVID-19 patients and an active diagnostic strategy should be pursued [22]. Blood culture remains the cornerstone for the diagnosis of yeast bloodstream infection (BSI), but the yield of blood culture remains suboptimal; (1,3)-$\beta$-D-glucan (BDG) detection may enhance the diagnosis of BSI [23–25]. COVID-19-associated pulmonary aspergillosis (CAPA) is often diagnosed based on biomarker test and culture results from respiratory tract samples, as radiological findings are commonly non-specific. Also, serum galactomannan (GM) is positive in a minority (typically less than 15%) of patients [23,26,27]. The diagnosis of CAPA has proven difficult due to the frequency of positive cultures from the upper respiratory tract (e.g., sputum and tracheal aspirates), which may reflect colonization rather than invasive disease. Lung biopsy provides definitive diagnosis but is not normally undertaken due to associated risks. Bronchoscopy and lavage are widely used as diagnostic interventions, with the associated risk of aerosol generation. The European Confederation of Medical Mycology and the International Society for Human and Animal Mycology support the use of polymerase chain reaction (PCR) assay to estimate the contagiousness of severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2). The PCR assay results may be used to guide the appropriateness of bronchoscopy without putting HCWs and other patients at risk of viral transmission. In centers with limited facilities for bronchoscopy, tracheal aspirates can reveal a mold, but it may not be indicative of pulmonary tissue infection. The usefulness of sputum culture is even more limited. Thus, sampling of lower respiratory tract by bronchoscopy is generally recommended to diagnose CAPA. A positive bronchoalveolar lavage (BAL) culture and/or positive BAL-biomarkers, such as *Aspergillus* GM or BDG, do not confirm the presence of invasive disease [28], but the diagnosis of CAPA must be considered.

BDG is a cell wall component present in many fungi. Basidiomycetes, the Mucorales, and *Blastomyces* species lack or have low quantities of BDG. BDG has a high negative predictive value (NPV) for diagnosis of aspergillosis and candidiasis and its absence excludes an IFI in a setting with low clinical suspicion. In practice, BDG is mostly used for the diagnosis of invasive candidiasis (IC), as there are specific tests, such as GM, available for diagnosing invasive aspergillosis (IA). Additional mycological tests are required to identify pathogens with certainty.

The use of BDG to detect IFI may be an attractive concept, but the proportion of CAPA patients with positive serum biomarkers is relatively low [23,29]. Therefore, fever and clinical or respiratory deterioration are the triggers for fungal diagnostic work-up [22,28]. There is overlap in the timing of various secondary IFIs, although the median time to CAPA and COVID-19-associated mucormycosis (CAM) and that of COVID-19-associated candidemia (CAC) is 7 and 15 days (interquartile range, 8–21) post ICU admission, respectively [5,30,31].

Computed tomography scan of the chest seldom shows specific lesions [28]. However, when multiple pulmonary nodules or lung cavitation are present, a diagnostic work-up for fungal pneumonia is recommended, as these appearances are rarely associated with

SARS-CoV-2 infection [28]. In a case series of 12 patients with pulmonary CAM, a reversed halo sign was observed in 1 patient, consolidation in 10 patients, including cavitation in 4, and pulmonary nodules in 1 [32]. Given the lack of specific radiological images, the diagnosis of secondary pulmonary mold infections relies on bronchoscopy and BAL [22,28].

Invasive *Aspergillus* tracheobronchitis may be present in up to 47% of COVID-19 ICU patients with CAPA; therefore, bronchoscopic inspection of trachea and bronchi is required [27]. In patients with endotracheal plaques, a mucosal biopsy is recommended to demonstrate the presence of tissue invasion by *Aspergillus* [22]. If invasive procedures are precluded due to thrombocytopenia, the use of a brush can be considered. Positive BAL culture, GM, or *Aspergillus* PCR in the clinically deteriorating, critically ill COVID-19 patient are considered sufficient evidence to initiate antifungal therapy. Presence of serum GM is a marker of angioinvasion, indicating advanced disease [33]. One study showed 86% mortality in serum GM-positive CAPA patients and 90% morality in serum BDG-positive patients, compared with 38% in those who remained biomarker negative [29]. In other studies, high BAL-GM, positive serum GM, and multiple positive markers in BAL (i.e., microscopy, BAL-GM and *Aspergillus* PCR), were associated with increased mortality [29,34,35].

The *Aspergillus* Lateral Flow Assay (LFA) has several advantages, including ease of use, single sample testing, rapid availability of results, and good concordance with GM. The LFA showed good diagnostic performance for CAPA diagnosis using respiratory samples at the 1.0 cutoff in a retrospective multicenter study. Sensitivity of LFA for CAPA was 52%, 80% and 81%, and specificity was 98%, 88% and 67%, for BAL fluid, nondirected BAL, and tracheal aspiration, respectively. There was an increased sensitivity of 72%, 90% and 100%, but a reduced specificity of 79%, 83% and 44%, respectively, at a 0.5 cutoff. The sensitivity of serum LFA is limited (20% and 9% at the 0.5 cutoff and 1.0 cutoff, respectively), and is probably linked to weak invasiveness during CAPA [36]. Processing of potentially infectious respiratory samples, including those for LFA testing, should take place in appropriate facilities (ideally in a category 2/3 safety cabinet) as per good laboratory practice, to protect staff and patients from infection, and the sample from contamination.

Fig. 1 provides an integrated approach to therapy, triangulating the clinical, radiological, and laboratory findings of CAPA.

Mucorales are fragile and easily damaged during standard respiratory sample processing. Also, they cannot be detected using GM and BDG tests. Invasive procedures are considered critical to diagnose mucormycosis [37]; however, targeted lung biopsies are generally not conducted in COVID-19 patients due to the frequent absence of specific lung lesions on imaging. In a retrospective study from France, Mucorales PCR assay of serum was positive in 14 of 17 (82%) CAM patients, indicating that PCR may be of value in this setting [32]. Unlike with aspergillosis, respiratory tract recovery of Mucorales is uncommon in ICU patients [38]. Detection of Mucorales in a respiratory sample should prompt a full diagnostic workup, even in patients with CAPA as dual infections have been reported [32,39].

## 3. Treatment strategies

### 3.1. Background and treatment of common IFIs

Azoles, echinocandins, and amphotericin B (AmB) are commonly used to treat IFI in COVID-19 patients [40]. Although patients with positive *Aspergillus* cultures or GM have survived without receiving antifungal therapy [23,26,28], ICU mortality associated with secondary fungal infections in severe COVID-19 is reported to be more than 50%, and this is an incentive to start antifungal therapy in patients with positive fungal cultures and/or biomarkers. As the diagnosis of IFI is challenging, empirical antifungal therapy based on suspicion of infection, without laboratory confirmation, is sometimes used, particularly in critically ill patients. The clinical scenarios would differ in the settings of CAC, aspergillosis and mucormycosis. The optimal management of secondary fungal infections in these settings depends on the risk profile of the COVID-19 ICU patients, the changing virulence of SARS-CoV-2, the use of antivirals and immunosuppressants, and the fungal resistance profile. Table 1 lists first-line and alternative recommendations to treat common IFIs.

**Table 1**
Selected drugs recommended to treat common fungal infections [24,25,37,41,42].

| Fungal infections | First-line drugs | Alternative drugs |
|---|---|---|
| Candidiasis | Echinocandins (anidulafungin, caspofungin, micafungin) | • Azoles (fluconazole or voriconazole)<br>• Lipid formulations of amphotericin B (or amphotericin B deoxycholate*) |
| Aspergillosis | Isavuconazole, voriconazole | • Echinocandins (particularly in combination)<br>• Lipid formulations of amphotericin B (or higher dose of amphotericin B deoxycholate*)<br>• Other azoles (posaconazole, itraconazole, super bioavailability itraconazole) |
| Mucormycosis | Lipid formulations of amphotericin B | • Amphotericin B deoxycholate<br>• Azoles (isavuconazole, posaconazole)<br>• Echinocandins (in combination with amphotericin B) |

* If lipid formulations are not available.

#### 3.1.1. Invasive Candidiasis

The most common causative species of fungal infections is *Candida albicans*, which is almost always susceptible to azoles and echinocandins. Resistance to echinocandins is mainly reported for *C. glabrata* in North America [43]. High rates of azole resistance in *C. glabrata* and intrinsic azole resistance in *Candida krusei* are well known [43–45]. *C. auris* has been reported in COVID-19 patients, including in centers that had never reported cases prior to the pandemic [46,47].

Echinocandins remain the drugs of choice for suspected IC. Fluconazole is an acceptable alternative initial therapy in regions with low resistance in patients who are not critically ill. AmB is an acceptable alternative in critically ill patients, in scenarios of known resistance to echinocandins, or in low- and middle-income countries where echinocandins are not readily available. It is also acceptable as a step-down therapy, taking into account the problems of toxicity and the need for monitoring. In some clinical syndromes (central nervous system [CNS] infection, candiduria, and endophthalmitis), azoles are preferred. AmB lipid (L-AmB) formulations are preferred over AmB deoxycholate as they enable higher doses to be administered without increasing nephrotoxicity [25].

Switching to azoles is driven by susceptibility pattern and clinical improvement [25]. In clinically stable patients, empirical therapy can be withheld and should be discontinued if alternative diagnoses are established.

#### 3.1.2. Pulmonary Aspergillosis

Resistance of *A. fumigatus* to azoles has been reported, with marked variation in prevalence between countries [48]. CAPA appears to follow the local epidemiology of IA where data are available. The lack of data is mainly due to avoidance of bronchoscopy

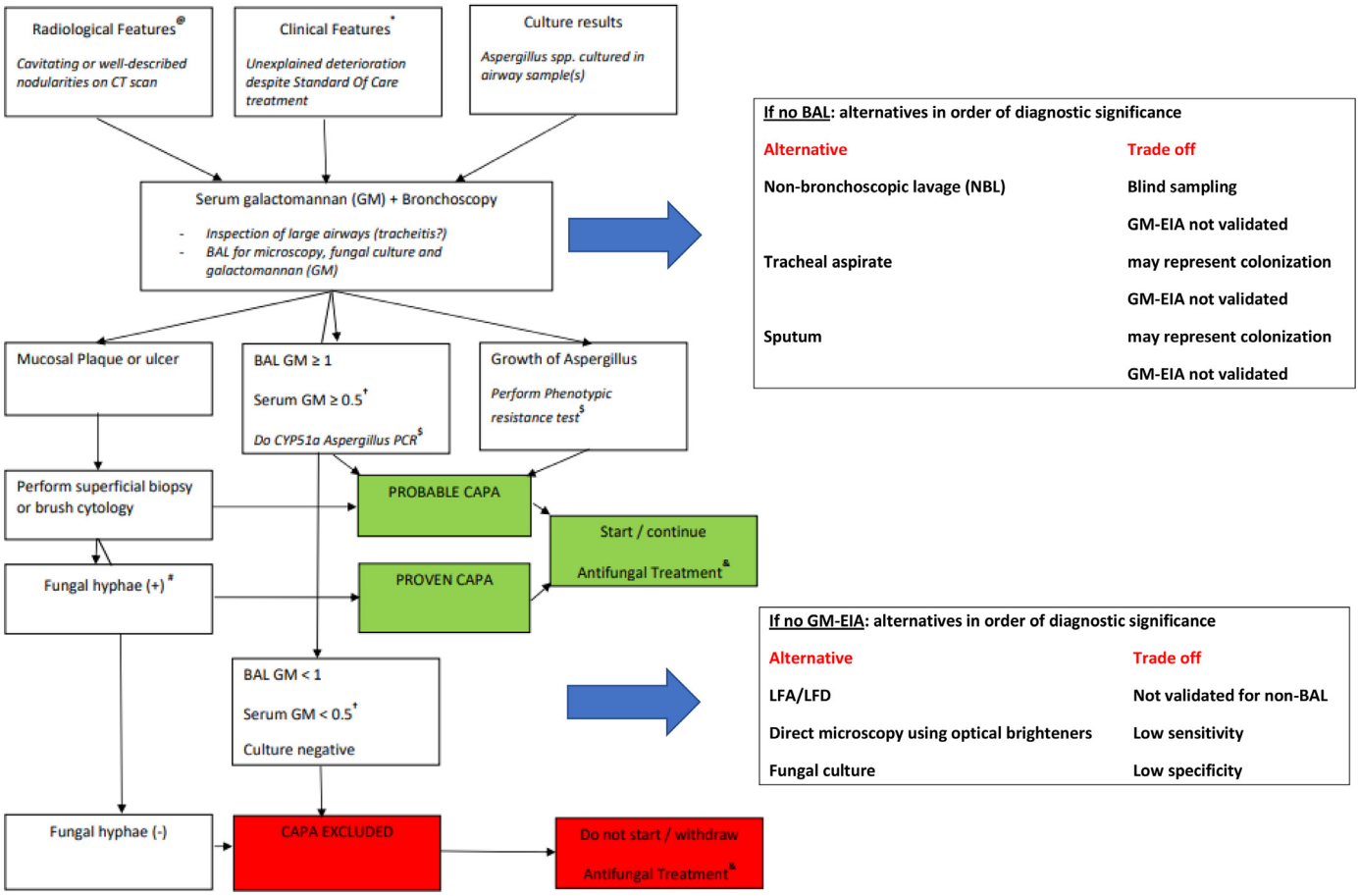


**Fig. 1.** An integrated approach to antifungal therapy in COVID-19
(@) This does not mean that a lung CT should be standard of care for all ICU patients with COVID-19. Instead, the flow diagram is meant to be used when a CT is done during routine patient care and shows cavitating or well-described nodular lung lesions.
(*) Standard of care. The SOC of COVID-19 is likely to change in the future but for now it includes thromboembolic prophylaxis, therapy with dexamethasone, and exclusion of pulmonary embolism with CT. Other causes of clinical respiratory deterioration may also need to have been excluded: pneumothorax, atelectasis, and progressive pulmonary fibrosis.
($) If there is growth of *Aspergillus*, phenotypic resistance testing can be used, e.g., with VIPcheck on site or at a mycology reference laboratory. In culture-negative but GM-positive BAL samples, the CYP51A *Aspergillus* PCR can be used to exclude the presence of the two most frequent resistance mutations that confer azole resistance ($TR_{34/TR46\ pattern}$).
(#) Formally, only when septate hyphae of 2.5–4.5 μm in diameter are seen AND the presence of *Aspergillus* DNA is documented, the infection is classified as proven CAPA. However, the presence of hyphae compatible with *Aspergillus* suffices to start antifungal therapy.
(†) Serum GM is generally negative, but increases the probability of CAPA if it is positive in combination with positive BAL GM.
(&) It is recommended to start antifungal therapy as early as possible. If BAL test results are available the same day, these can be awaited before antifungal therapy is started. If BAL test results are not immediately available, it is recommended to consider starting antifungal therapy pre-emptively while awaiting test results.

and other aerosol-generating procedures in the setting of COVID-19 [49–51]. In addition, testing for resistance is not routinely performed in many centers, so estimating the prevalence of azole resistance in CAPA is difficult.

Antifungal therapy is generally recommended in clinically deteriorating COVID-19 patients with evidence of *Aspergillus* in BAL [22]. The azoles are the most commonly used class, with voriconazole and isavuconazole being the azoles of choice, and posaconazole as an alternative [52]. Considering pharmacokinetic (PK) and pharmacodynamic (PD) issues, itraconazole should only be used in patients with less severe disease and when other azoles are not available [41].

AmB and L-AmB are alternatives for initial and salvage therapy when voriconazole or other azoles cannot be administered, or when the minimum inhibitory concentration (MIC) of voriconazole is >2 mg/L. Caspofungin or micafungin can be used when azoles and AmB are contraindicated [41,53], or as salvage therapy.

If simultaneous mucormycosis infection is suspected, L-AmB, isavuconazole or posaconazole are preferred. Several studies have investigated alternative management strategies, including the use of nebulized or systemic antifungal prophylaxis and diagnostic driven strategies, but firm conclusions cannot be drawn at this stage [41,53]. Only six studies to date have looked into antifungal prophylaxis for CAPA [54–59]. Posaconazole, administered through a gastric tube or intravenously, and inhaled AmB have been investigated. Prophylaxis significantly reduced the incidence of CAPA in three of these investigations [54–56], but did not influence survival in the two studies [54,55] that reported survival data. There are currently insufficient data to recommend prophylaxis. Nonetheless, in hospitals where these infections are common (e.g., 15–30%), prophylaxis can be considered.

### 3.1.3. *Mucormycosis*

Mucoraceous molds are a broad group of fungi that are intrinsically resistant to voriconazole, the first-line treatment for IA, but are usually susceptible to posaconazole and isavuconazole. L-AmB is the treatment of choice. The therapeutic place for this drug is treatment of viral-associated mucormycosis, triazole-resistant aspergillosis, or if there is intolerance to triazoles or echinocandins.

For the management of non-pulmonary manifestations of CAM, treatment initiation with L-AmB and surgical debridement to clean margins is recommended. Isavuconazole or posaconazole can be used as step-down therapy [37].

### 3.2. Specific recommendations

#### 3.2.1. Combination therapy

Empirical use of combination therapy is discouraged. Attention should focus on compliance and other factors, as mentioned above, if adequate drug levels are not attained. Reversal of immunosuppressive status, whenever possible, should also be considered when managing difficult-to-treat IFIs. However, dexamethasone and interleukin-6 inhibitors (tocilizumab or sarilumab) should not be discontinued in COVID-19 patients without expert advice. Combination therapy may sometimes be required to treat MDR *Candida* spp. and *A. fumigatus*, infections of the CNS or endocarditis, in salvage therapy for IA (combination of echinocandins with voriconazole) or when treating rare mold infections [60]. For aspergillosis, combining voriconazole with an echinocandin may be considered for patients who are not responding to monotherapy, in serious presentations in critically ill patients, or when azole resistance is suspected. Concomitant therapy with azoles and AmB remains controversial as azoles may decrease AmB-binding sites. For mucormycosis, combination therapy (isavuconazole or posaconazole, with AmB) is not supported by clinical data, although it has been used in severely immunosuppressed patients with variable results [60].

#### 3.2.2. Therapeutic drug monitoring

Therapeutic drug monitoring (TDM) of antifungals is expensive, time consuming, and not fully supported by evidence. However, the costs of TDM should be weighed against the costs of diagnosis and treatment of IFI. Also, recent studies have shown that in critically ill patients, antifungal drug exposure is unpredictable due to altered PK and PD [61–64]. TDM for azoles has been shown to have potential clinical benefit but is not recommended for polyenes and echinocandins [65]. Fluconazole has linear PK and high oral bioavailability, therefore TDM is not indicated except when treating CNS infections, pathogens with high MIC, or in patients on renal replacement therapy [66]. On the other hand, itraconazole has non-linear PK and variable bioavailability, hence TDM is recommended [66]. Voriconazole has numerous drug-drug interactions and attains variable levels, necessitating TDM [67]. Plasma levels of 1–5.5 mg/L are considered adequate for most patients [52] and the trough concentration to minimize drug-related toxicity is $<4$ mg/L [66]. Higher trough levels (2–6 mg/L) are recommended in patients with severe infections (multifocal or disseminated disease, CNS infections, infection with pathogens with elevated MICs, i.e., $>2$ mg/L) [52,66].

TDM is recommended for posaconazole as it has many drug-drug interactions, and food-related factors affect oral absorption of the liquid formulation. A target concentration $>0.7$ mg/L for prophylaxis and $>1$ mg/L for treatment is recommended [68]. There are limited data to define a target therapeutic range or support the need for routine TDM for isavuconazole; however, TDM for isavuconazole may be indicated in patients who remain unresponsive, have unexpected toxicity, or have difficult-to-treat conditions (e.g, CNS infections). A plasma trough concentration of 2–3 mg/L is considered adequate after day 5 of exposure [52]. There is limited support for first-line use of isavuconazole [69].

Although there is no indication for TDM for AmB or L-AmB, patients should be carefully monitored (2–3 times weekly) for cell count, electrolytes, serum magnesium, and serum creatinine. Progressive steps to target TDM are displayed in Table 2.

**Table 2**
Progressive steps to perform when therapeutic drug monitoring is not available

1. Check compliance
2. Stop interacting drugs, if possible
3. Use more bioavailable formulations (e.g., switch to super bioavailability [SUBA] for itraconazole or switch to gastro-resistant tablet formulations for posaconazole instead of suspensions)
4. Stop histamine-2 inhibitors or proton-pump inhibitors
5. Use fat-rich food, such as ice cream, cheese, and other dairy products, when using posaconazole suspension
6. Switch to intravenous formulations, if possible
7. Escalate dose, change drug, or add another agent

**Table 3**
Suggested treatment duration for common fungal infections.

| Condition | Treatment duration |
|---|---|
| Uncomplicated invasive candidiasis | Two weeks after the first negative blood culture [70] |
| Complicated invasive candidiasis (e.g., sanctuary sites, endocarditis) | Three to 12 months, depending on clinical improvement and assessment of the local site (e.g., fundus examination, cerebrospinal fluid parameters in case of meningitis) and radiological images (magnetic resonance imaging or computed tomography etc.), if available [24,25,71] |
| Pulmonary aspergillosis | Six to 12 weeks, provided there is clinical and radiological improvement [72] |
| Disseminated aspergillosis | Up to 12 months, depending on the localization and possibilities of surgical removal [41,69] |
| Mucormycosis | Complete surgical debridement and at least 2 weeks of amphotericin B lipid formulation, followed by posaconazole or isavuconazole for 6–12 weeks [42,73] |

#### 3.2.3. Duration of treatment

Table 3 summarizes the duration of therapy for IFI in the setting of COVID-19.

## 4. Infection control

With multiple reports of fungal outbreaks during the COVID-19 pandemic, it is essential not to underestimate the role of infection control in healthcare settings [74]. Although the pathogenesis of these fungal infections in COVID-19 patients is not fully elucidated, a rigorous understanding of their spread helps to guide some important preventive measures. Standard precautions, such as those used for MDROs are recommended [75,76]. However, this is a minimum requirement, and HCWs should use a medical mask, long-sleeved gowns, and gloves to avoid auto-inoculation.

Most patients with severe COVID-19 require ICU admission and immunosuppressive therapy, central venous catheter, parenteral nutrition, and mechanical ventilation. These factors, along with advanced age and high Sequential Organ Failure Assessment score, have been linked to a higher risk of candidemia [77–80], which is challenging for the management of these patients, particularly in the setting of a pandemic [81]. Nevertheless, adherence to evidence-based central line-associated BSI prevention bundles can reduce candidemia, alongside the early removal of the catheter, whenever possible [82,83].

*C. auris* is a growing healthcare threat [17,84]. Hospitals should have guidelines for the rapid detection and prevention of *C. auris*, including screening and isolation on admission of all patients at risk [85], such as patients transferred from institutions with ongoing outbreaks. Fine tuning this strategy to only ICU patients may be needed, depending on local resources and epidemiology [86]. Axilla and groin are favored screening sites; however, institutions

may choose to rely on their standard screening protocols, including sites such as nose, mouth, rectum, open wounds, catheter sites, or urine [87]. To minimize time spent in isolation, initial screening may be done by PCR, if possible [88], followed by culture, for epidemiological investigation. *C. auris* may remain deep within the skin tissue compartment for a considerable period of time, even when the skin surface swabs are repeatedly negative [89]. Patients colonized or infected with *C. auris* should be isolated until discharge and flagged for at least one year after the first negative screening culture. Alcohol-based hand rubs have been shown to be effective against *C. auris* [76], and HCWs should be reminded of the importance of adequate hand hygiene, including appropriate use of medical gloves. Despite potent in vitro activity [90], chlorhexidine (CHG) bathing showed little effect in an ex vivo skin model [91], possibly explaining the clinical failure of earlier attempts to decolonize patients [92]. In contrast, a recent in vivo study demonstrated the protective effect of CHG against *C. auris* colonization of both skin surface and skin tissue in murine models. Whether these results are applicable to the use of CHG bathing to decolonize patients requires further evidence from clinical trials [89]. Rigorous environmental cleaning is essential. Chlorine-based products are favored [93], but other products such as iodinated povidone, hydrogen peroxide vapor, and Ultraviolet-C have been found to be effective at concentrations used in clinical practice [86,94].

Air room pressure is an essential part of controlling the spread of infectious diseases within hospitals and this became a hot topic during the COVID-19 pandemic. For patients on oxygen supplementation that generates aerosols, such as high-flow oxygen, continuous positive airway pressure or bilevel positive airway pressure, the Centers for Disease Control and Prevention recommends the use of negative pressure rooms (NPR) with an anteroom to ensure safety of other patients, visitors, and HCWs [95,96]. However, the risk of acquiring superimposed infections, such as IA has not been specifically addressed. Positive pressure rooms provide a 'protective environment' (PE) by pressing particles out of the room, without them circulating back in [97]. PE-rooms may be preferred in wards with large numbers of immunocompromised patients to protect them from *Aspergillus* spp. [98]. In a study conducted in 15 ICU rooms in France, NPR was shown to increase the risk of airborne mold infections. Air-cultures from NPR were positive for *Aspergillus* spp., and probable or proven pulmonary aspergillosis developed in six patients. After a switch to a slightly positive pressure ($1.2 \pm 1.5$ Pa), the number of *Aspergillus* colonies markedly diminished and ultimately became undetectable, thereby theoretically reducing the possibility of developing IA [99]. The incidence of CAPA is variable across centers, and more research is needed to determine how common these infections are among COVID-19 patients. This information will be useful for providing tailored infection control guidelines for this cohort of patients. In the meantime, exposure to airborne *Aspergillus* can be minimized by implementing recommendations on environmental controls, using well-sealed rooms, and controlling air quality. Air-filtration using mobile high efficiency particulate air (HEPA) filters could reduce the load of aerosols in rooms with COVID-19-infected patients. Whether these systems are effective in preventing colonization with *Aspergillus* needs to be examined [100,101].

The burden of Mucorales spores in the hospital and outdoor environment was evaluated in several Indian centers during the pandemic [102–104]. A multicenter research study showed a significant Mucorales spore count in the hospital air and air-conditioning ducts, with a significantly higher burden in the air of rooms with personalized air cooling (AC) compared with that in rooms with central AC with connected microfilters. Mucorales spore count was also used at one center to measure the effect of cleaning the AC filters of five window ACs, and showed that washing with soap and water reduced spore counts from a pre-cleaning value of 24.8 ± 10.5 to 1.7 ± 1.2 cfu/m$^3$ [104], with similar findings in a hematological ICU from a different center [102]. Moreover, rooms with HEPA-filtered air had significantly less contamination (2.1%) than rooms without HEPA filters (20.5%), but spores were not isolated from hospital equipment and surfaces [104]. A large proportion of patients acquired CAM during convalescence at home, prompting an environmental assessment for Mucorales in their domestic environment [103]. Based on these findings of Ghosh et al., it would seem prudent to advise patients with a high risk of acquiring mucormycosis, such as those in the COVID-19 convalescence phase, to wear an appropriate mask even at home during the risk period. Further studies are warranted to ascertain the duration for masking. Regular aeration of quarantine rooms and exposure to sunlight may also potentially help reduce spore dispersal [103]. Prompt glycemic control, management of ketoacidosis and hypoxia, attention to leucopenia, and judicious use of corticosteroids, immunomodulators, and antimicrobials are all important for decreasing mucormycosis occurrence [105]. Of note, in a case control study from India, prolonged use of cloth and surgical masks (more than 4 and 6 h, respectively) and repeated nasopharyngeal swab testing during the COVID-19 illness were both independent variables of developing CAM. N95 masks and zinc therapy were found to be protective [106].

## 5. Antifungal stewardship: Quality improvement

The aim of AMS is to reduce inappropriate antimicrobial prescribing, minimize toxicity, limit selection pressure, and reduce costs [107]. More recently, AFS has gained attention following the emergence of triazole-resistant *A. fumigatus* and outbreaks of *C. auris*.

In a survey of AFS initiatives across hospitals in England, only 5 (11%) responders had a dedicated AFS program, and 20 (43%) had AFS included as part of their AMS program. Perceived benefits of AFS included improvements in safety, outcome and costs, reduced side-effects, and collection of surveillance data [108]. However, the impact of these programs on patient outcome remains elusive. In a systematic review of 13 studies on the impact of AFS interventions in the United States, improvement in clinical outcomes was not detected; however, the results indicated that AFS interventions improved appropriate antifungal choice and time to therapy, and decreased antifungal consumption [109].

Although the principles of AMS apply to the management of fungal infections, there are additional factors to consider. For example, patient-to-patient transmission is rare and fungal infections are more often acquired from the environment, the patient's own flora, or devices such as catheters. In addition, toxicity and drug–drug interactions are more common, biomarkers have variable sensitivity and specificity, and diagnostic tools are less available and are difficult to interpret [108].

Performance assessment followed by tangible measures enable a formal review of intervention, allow benchmarking, and serve as a quality improvement (QI) tool. The classification of performance assessment into process, outcome, and structural measures improves the understanding of quality assurance. Process measures refer to the main diagnostic and therapeutic aspects of QI, such as streamlining the use of antifungal agents and appropriate utilization of diagnostic tools, whereas drug expenditure is an outcome measure. Structural measures are broad-based and conform to the overall strategy, e.g., adoption of antifungal policies by hospitals [110].

Eighty-two experts from 17 countries participated in a series of web-based questionnaires to assess the significance and feasibility of metrics in AFS using Delphi technique. The basic AFS indicators provide a foundation for developing QI programs targeted at improving IFI prevention, management, and patient-centered out-

comes by systematically assessing the quantity and quality of antifungal medication within hospitals [111]. The effectiveness of AFS programs must be tracked using simple-to-measure variables, such as the prevalence and mortality of nosocomial IFI, the rate of fluconazole resistance, and the use and cost of antifungal medications. The Collaborative Group on Mycoses conducted point prevalence audits on 100 consecutive patients receiving systemic antifungals, with each day of therapy being assessed in accordance with a pre-established score that enabled individualized evaluation of the key elements of drug usage (need for antifungal therapy, selection of the drug, dose and administration route, adjustment to microbiology results and duration of therapy). The group demonstrated that the AFS program resulted in a definite improvement through educational initiatives, local guidelines, adoption of novel diagnostic techniques, and professional clinical guidance and audits. To help clinicians feel secure when stopping empirical antifungal treatment and excessively prolonged therapy, the group suggested using a combination of biomarkers - BDG and *C. albicans* germ tube assay - performed on days 0, 3, and 5 of empirical antifungal therapy, which showed a very high NPV (97% for the general population and 100% in ICU patients) [112]. A systematic review showed that a reduction in antifungal consumption was the single most effective measure in relation to impact assessment of AFS [113]. A clinical pharmacist-led candidemia treatment bundle implemented in a tertiary care facility in India significantly increased the appropriateness of antifungal prescriptions from 30% to 65% in the post-implementation period, with a reduction in in-hospital mortality rate from 40% to 36% (P=0.26; not significant), demonstrating successful implementation of an AFS program in a low-middle income country setting [114]. In a study from Greece that assessed the impact of the implementation of a non-compulsory AFS program with educational intervention to increase the awareness on proper use of antifungals, statistical analysis revealed a large, immediate decline in improper prescriptions and total consumption following intervention, with a downward trend thereafter. When pre- and post-interventional periods were compared, there was a considerable reduction in acquisition costs but no difference in in-hospital mortality or mean in-hospital length-of-stay [115]. Reviewing prescriptions at least three times a week, particularly for more expensive agents, and pre-authorization for these agents are effective in rationalizing and reducing their use. A fully functional AFS team is crucial for the successful implementation of AFS programs but many hospitals do not have such a team. The incorporation of PK and PD modeling in AFS needs further research [116].

One of the drawbacks of AFS is the limited epidemiological data in relation to antifungal resistance. In parallel, there is increasing use of antifungal agents in agriculture and farm animals, which predisposes fungi to become resistant even before they infect humans [117]. Together, the increase in fungal infections and rising level of resistance create a threat that can no longer be ignored. Indeed, mutations that define azole resistance are found in clinical and environmental *Aspergillus* [118] and in many *Candida* spp. [85]. Considering these facts, ideally all invasive yeasts and molds should be identified to the species level and subjected to susceptibility testing. However, the Infectious Diseases Society of America does not recommend routine MIC testing for *Aspergillus* spp. (only in case of treatment failure) and little is known of the usefulness of MIC testing of Mucorales [41]. Where local susceptibility testing is not possible, isolates should be referred to a regional reference laboratory. The value of routine screening of patients for *C. auris* is uncertain. When there is low background prevalence of *C. auris*, universal screening for this fungus is not recommended but can be targeted to high-risk groups [119,120].

Pre-authorization, post-authorization review, audit, promoting local guidelines, and early intravenous-to-oral switch form the basis of stewardship [121]. Whitney and colleagues found that as many as 25% of patients who received antifungal agents as part of 'targeted' therapy did not have proven, probable or possible IFI based on European Organisation for Research and Treatment of Cancer/MSGERC criteria, and a significant number of patients who received empirical antifungal therapy did not have fungal infection on retrospective analysis [122]. AFS needs to focus on this overuse. The COVID-19 pandemic led to an unprecedented interest in fungal infections [123]. Yet, research in mycotic diseases is underfunded in many countries, such as the UK, which has an allocation of only 2% of the budget for infectious diseases [124]. A One Health approach, using integrated data platforms, such as EpiCollect and EpiCollect plus, is the way forward [125].

QI is also applicable to environmental sampling. If an unexplained cluster of cases of nosocomial IA is detected, an environmental audit should be carried out to detect any linked cases within a stipulated time frame. Genotyping of clinical and environmental isolates may point to a common source, with some evidence showing a correlation between aerial fungal counts and occurrence of fungal infection [126].

**Table 4**
Minimum bundles for the management of prevalent fungal infections

***Candidiasis***

- Removal of an indwelling central line within 24 h of diagnosis
- Complete clinical examination to rule out infection of sanctuary sites
- Assessment of clinical efficacy 3–5 days after starting therapy and evaluating the need for alternative therapy based on culture identification and susceptibility results, once available [21]
- Avoid treatment of *Candida* isolated from urine or respiratory sample as they indicate colonization in most cases
- Use echinocandins and step down to azoles according to susceptibility
- Step down to oral fluconazole therapy in patients with a favorable clinical course and an isolate with documented susceptibility [21]
- Keep good infection control and antibiotic stewardship practices to prevent invasive candidiasis

***Aspergillosis***

- Keep a high index of clinical suspicion of pulmonary aspergillosis in ICU patients or in those in respiratory failure due to SARS-CoV-2 as clinical signs may be subtle
- According to the patient's condition, perform chest CT looking for changes possibly not related to SARS-Cov2 infection and perform bronchoalveolar lavage, if possible [51]
- Measure serum galactomannan in patients with a high index of suspicion of clinical infection and repeat the measure periodically (e.g., weekly) to assess response [21]
- Voriconazole remains the drug of choice, but drug-drug interactions and need for therapeutic drug monitoring is a major limiting factor in its usage
- Isavuconazole, amphotericin B and posaconazole are good alternatives
- Step down to oral triazole therapy in patients with a favorable clinical course

***Mucormycosis***

- Control of predisposing factors (e.g., glycemic control)
- Avoid excessive use of steroids, and enable early diagnosis of underlying diabetes and tight sugar control
- Prompt initiation of antifungal therapy and surgical debridement
- Check drug-drug interactions if posaconazole or isavuconazole are used

## 6. Conclusions

The COVID-19 pandemic has increased awareness of clinical manifestations associated with the broad spectrum of fungal pathogens. Fungal infections are over-suspected and underdiagnosed. Reports on the presence of fungal disease associated with COVID-19 have varied widely because of the difficulties in differentiating colonization from infection. Under both circumstances, and independent of the causative pathogen, the use of antifungal drugs has increased. The uncertainty of diagnosis has made clini-

cians err on the safe side and initiate antifungal therapy at an early stage. This has led to spiraling and indiscriminate use of antifungal agents. To curb overprescribing, adhering to the principles of AFS is vital. A multidisciplinary team that benefits from the expertise of the intensivist, pulmonologist, infection specialist, and clinical pharmacist is desirable for optimal delivery of AFS. AFS teams should incorporate experts in fungal infections and should regularly evaluate performance on relevant structural, process and outcome measures, and implement evidence-based strategies in a continuous quality of care improvement cycle. In this process, it is essential to not disregard the role of infection control to alleviate the burden of these infections. All these elements need to be integrated in a bundle approach (Table 4). It is imperative to remain alert and continue to fight against this developing global pandemic of drug-resistant fungi.

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