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Review Article

# COVID-19-associated candidiasis and the emerging concern of *Candida auris* infections

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**Abstract** The incidence of COVID-19-associated candidiasis (CAC) is increasing, resulting in a grave outcome among hospitalized patients with COVID-19. The most alarming condition is the increasing incidence of multi-drug resistant *Candida auris* infections among patients with COVID-19 worldwide. The therapeutic strategy towards CAC caused by common *Candida* species, such as *Candida albicans*, *Candida tropicalis*, and *Candida glabrata*, is similar to the pre-

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pandemic era. For non-critically ill patients or those with a low risk of azole resistance, fluconazole remains the drug of choice for candidemia. For critically ill patients, those with a history of recent azole exposure or with a high risk of fluconazole resistance, echinocandins are recommended as the first-line therapy. Several novel therapeutic agents alone or in combination with traditional antifungal agents for candidiasis are potential options in the future. However, for multidrug-resistant *C. auris* infection, only echinocandins are effective. Infection prevention and control policies, including strict isolation of the patients carrying *C. auris* and regular screening of non-affected patients, are suggested to prevent the spread of *C. auris* among patients with COVID-19. Whole-genome sequencing may be used to understand the epidemiology of healthcare-associated candidiasis and to better control and prevent these infections.


## Introduction

Severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), a new RNA virus of the family Coronaviridae and the cause of coronavirus disease 2019 (COVID-19) infection, resulted in the global pandemic.[1—4] The clinical characteristics of COVID-19 ranged from asymptomatic infection, mild disease, to severe hypoxia, respiratory or multi-organ failure, and even death.[2,5] Following the Alpha, Beta, Gamma, and Delta variants of concerns (VOCs) of SARS-CoV-2, the Omicron variant has been raging throughout the world since November 2021 and remains the current global threat.[6] SARS-CoV-2 is expected to be a persistent threat in the near coming years.

Secondary bacterial and fungal infections, especially nosocomial pathogens, were associated with a high mortality rate among those with COVID-19.[7—10] Invasive candidiasis is one of the important healthcare-associated infections caused by *Candida* species and associated with substantial morbidity and mortality. COVID-19-associated candidiasis (CAC) has been reported among critically patients with COVID-19 in many publications.[11,12] However, there was no consensus in the temporary relationship of "concurrent" COVID-19 and candidiasis. In the present review, CAC is arbitrarily defined as secondary infection or super-infection of candidiasis occurring after the event of COVID-19. Compared with non-COVID-19 patients, the incidence of candidemia was higher among critically ill COVID-19 patients with mechanical ventilation, indwelling central venous catheter and receipt of corticosteroids and immunosuppressants.[11,12] Moreover, among hospitalized patients with COVID-19 in Taiwan, the major respiratory pathogen resulting in rapid progression to death was *Candida* species (77.8%).[13] Furthermore, multidrug-resistant *Candida* species, such as *Candida auris*, had been reported during the treatment course of COVID-19 infection.[14] Inadequate personal protective equipment (PPE), PPE shortage, poor hand hygiene adherence, and a high level of antibiotic use, were the commonly potentially modifiable factors contributing to candidiasis.[15] The aim of this review is to summarize the risk factors and clinical impact of CAC, the emerging threat of *C. auris*, and the diagnosis and management of CAC, including novel therapeutic options.

## Candidiasis is not uncommon among COVID-19 patients

During the COVID-19 pandemic, clinically significant candidiasis has been reported.[7,16,17] In India, *Candida* species was the third common pathogens (4.1%) of secondary bloodstream infections among patients with COVID-19, following *Klebsiella pneumoniae* (10.9%) and *Acinetobacter baumannii* (8.8%).[7] Moreover, another study in central India found that the incidence of secondary infections caused by *Candida* species (24.3%) was the same as that due to *A. baumannii* complex.[16] In Korea, *Candida albicans* was one of the common pathogens among patients with COVID-19.[17] In a meta-analysis of multidrug-resistant organisms encountered during COVID-19, *C. auris* was also recognized.[14] Based on the current evidence, candidiasis especially due to multidrug-resistant *C. auris*, is not uncommonly associated with COVID-19 during the pandemic and such a scenario warrants clinical attention.

Several risk factors, including lung injury, immunosuppression, the need for oxygen therapy, monoclonal antibodies, and steroid therapy, predispose the cases of COVID-19 to fungal infections.[11,18,19] COVID-19 patients showed an impaired immune response, including decreased upregulation of monocyte CD80, and impaired release of interleukin (IL)-6, tumor necrosis factor (TNF), IL-1$\alpha$, and IL-1$\beta$ toward *C. albicans* infection.[19] Salivary histatin-5 production, a potent inhibitor against opportunistic oral *C. albicans*, was compromised due to salivary gland damage mediated by SARS-CoV-2 virus.[20] *Candida* species has been recovered in 69% of bronchoalveolar lavage specimens from immunosuppressed patients with COVID-19, and *Candida* colonization in respiratory tract was regarded as having no impact on the severity of COVID-19.[21] However, recent studies demonstrated dysbiosis of lung and gut microbiota characterized by a shift to *Candida* colonization and a decrease of fungal diversity was correlated to the development of acute respiratory distress syndrome among patients with COVID-19.[22—24] Therefore, impaired immunity, use of antiviral or immunosuppressant drugs, direct SARS-CoV-2 damage, and microbiota dysbiosis may lead to the emergence of pathogenic *Candida* species among patients with COVID-19.

## Clinical impact of CAC in hospitalized patients with COVID-19

To evaluate the clinical impact of COVID-19-associated candidemia, literature review on PubMed® for relevant studies published before May 2022 was performed with key words "(COVID-19 or SARS-CoV-2) AND (*Candida* or candidemia or candidiasis)". Only five studies comparing candidemic patients in intensive care units (ICUs) with or without COVID-19 were included. Two studies showed that there was a significantly higher mortality rate of COVID-19 patients with candidemia than non-COVID-19 patients with candidemia (Table 1).[12,25–28] The risk factors for mortality among CAC patients with candidemia included longer ICU stay, the use of mechanical ventilator (MV), central venous catheter (CVC), steroid, or immunosuppressants, older age, presence of sepsis, or a higher sequential organ failure assessment (SOFA) score.[12,25–28] Thus, candidemia poses a significant impact on the outcome of COVID-19 patients, especially those with critically ill condition.

Another challenging clinical setting is the presence of fungal or bacterial co-infection of respiratory tract in hospitalized patients with COVID-19.[8,29,30] In Iran, nearly one fifth of ICU patients with COVID-19, especially those with diabetes mellitus and pneumonia, had fungal and/or bacterial secondary infection,[31] and *C. albicans* was the most frequent pathogen of fungal secondary infection.[29] For COVID-19 patients superinfected by bacterium, fungus, or virus, the cytokine storm could result in a dynamic and highly complex infectious and inflammatory process, which precipitates acute lung injury, severe hypoxemia, and even death. The risk of mortality increased when bacterial (odds ratio [OR] 11.3) or fungal (OR 6.0) infection was present, and further increased if COVID-19 patients had certain comorbidities, such as cardiovascular disease (OR: 11.5), diabetes mellitus (OR: 6.0), or obesity (OR: 5.6). The need to aggressively investigate the etiology of secondary infections or superinfections in the cases of COVID-19 should be constantly reminded.[31] Early diagnosis of secondary fungal infections among COVID-19 patients is essential to provide optimal therapeutic interventions to ameliorate the unfavorable outcomes among those with underlying chronic illness.[32]

## *Increasing incidence of* Candida auris *infections among patients with COVID-19*

Analyzing invasive fungal isolates collected from 2018 to 2020 in 48 hospitals worldwide, the common *Candida* species were *C. albicans, Candida glabrata, Candida parapsilosis*, and *Candida tropicalis* in before and in the era of COVID-19. In detail, the incidence of *C. tropicalis* (10.8%—11.0%), *Candida dubliniensis* (2.7%—3.0%), and *Candida krusei* (2.6%—3.6%) increased, whereas *C. parapsilosis* (14.7%—12.8%) and *Candida lusitaniae* (2.6%—1.4%) decreased during the COVID19 pandemic.[33] In a systematic review, the prevalence of *C. auris* infections increased to 14% in COVID-19 patients, particularly in those with diabetes mellitus (42.7%), hypertension (32.9%), and obesity (14.6%); and those with central venous catheter insertion (76.8%), stay in the intensive care unit (ICU) (75.6%), and broad-spectrum antibiotic usage (74.3%).[34] Risk factors associated with *C. auris* candidemia in hospitalized adult and pediatric patients with COVID-19 include a longer hospital stay before the onset of candidemia (20 days *vs.* 9 days), prior isolation of multidrug-resistant bacteria (100% *vs.* 50%), prior colonization with *Candida* (50% *vs.* 14%), and a lower beta-D-glucan levels (48.73 pg/ml *vs.* 138.146 pg/ml).[35] However, the critical conditions contributing to the acquisition of *C. auris* colonization or infection among those with COVID-19, rather than COVID-19 itself, may be the major factor resulting in a grave clinical outcome. Nevertheless, early detection and appropriate therapy is generally believed to be critical to improve the outcome of *C. auris* infections in the era of COVID-19.

## Antifungal drugs susceptibility of clinical candida isolates

By searching on PubMed® with the keywords of (COVID-19 or SARS-CoV-2) AND (candida or candidemia or candidiasis)", English literature published before May 2022 was reviewed, but the studies conducted before the COVID-19 pandemic were excluded. Eighteen articles, including case reports, case series and clinical research providing minimal inhibitory concentration (MIC) results, were included for

**Table 1** Summary of the English literature for the rates and risk factors of mortality related to candidemia among the patients with and without COVID-19 in intensive care units (ICUs).

| Country | Case numbers[a] | Risk factors of mortality | Mortality rates[a] | *P* value | References |
|---|---|---|---|---|---|
| USA | 64/187 | ICU care, mechanical ventilation, central venous catheter, steroid, immunosuppressant | 62.5%/32.1% | <0.001 | 12 |
| Italy | 21/51 | ICU stay, steroid | 57.1%/58.8% | 0.895 | 26 |
| Brazil | 9/32 | Mechanical ventilation | 66.7%/56.3% | Not available | 27 |
| Turkey | 105/131 | Steroid, old age, presence of sepsis | 92.5%/79.4% | 0.005 | 29 |
| USA | 12/38 | Lower Sequential Organ Failure Assessment score at ICU admission, longer ICU stay, central venous catheter | 75.0%/61.0% | 0.50 | 30 |

[a] COVID-19/non-COVID-19.

further evaluation. With the same method to yield MIC results, the data from different studies have been combined and the overall antifungal susceptibility to *Candida* isolates from COVID-19 patients was shown in Table 2.[36—53] The susceptible rate of commonly used antifungal agents, such as fluconazole, voriconazole, echinocandins, or amphotericin B, was higher than 80% for *C. albicans* and *C. tropicalis*. The susceptible rate of voriconazole (100%), itraconazole (100%), posaconazole (100%), amphotericin B (100%) among *C. glabrata* was high, and that of echinocandins, such as micafungin (86%), anidulafungin (70%), or caspofungin (40%), was lower. Against all *C. krusei* and *C. parapsilosis* isolates tested, voriconazole, itraconazole, posaconazole, micafungin, anidulafungin, amphotericin-B, and flucytosine were active. The *in vitro* antifungal susceptibility among the three common *Candida* species *(i.e., C. albicans*, *C. tropicalis*, and *C. glabrata*) obtained before and during the era of COVID-19 did not change significantly.

In a 5-year, laboratory-based surveillance of *C. auris* in Colombia prior to the COVID-19 pandemic, between 2016 and 2020, including 393 (23%) colonized isolates and 1327 (77%) clinical isolates, 35% were resistant to fluconazole, 33% to amphotericin B, 0.3% to anidulafungin, and 12% were multidrug-resistant.[54] During the COVID-19 pandemic, only echinocandins were active against ≥90% of clinical *C. auris* isolates, and other antifungal drugs, such as fluconazole, voriconazole, or amphotericin B, were less active against *C. auris* (Table 2). The high level of antifungal resistance in *C. auris* isolates is troublesome among patients with COVID-19. Timely and appropriate administration o f anti-fungal drugs, namely echinocandins, is important when *C. auris* infection is suspected or detected to improve outcome.

## Diagnosis and management of CAC

One of the key challenges to the management of CAC is early recognition of invasive candidiasis among COVID-19 patients. Invasive candidiasis should be suspected in patients with known risk factors, fever with unspecified etiologies, and poor response to antibacterial therapy.[55,56] Although previous studies demonstrated that critically ill patients with *Candida* colonization in multiple sites, *i.e.*, a high *Candida* score, may benefit from early antifungal treatment,[57,58] the *Candida* score may not be beneficial in early detection of CAC. Clinical diagnosis of *Candida* infections among COVID-19 patients remains to be problematic and relies on maintaining high alertness to symptoms and signs of healthcare-associated infections among high-risk patients.

Although the incidence of candidemia in patients with COVID-19 is significantly higher than in those without COVID-19, a genotyping study showed that the increase was not related to uncontrolled intra-hospital transmission.[59] An inter-hospital candidemia outbreak in Brazil caused by fluconazole-resistant *C. parapsilosis* was reported in the COVID-19 era,[60] and moreover the application of whole genome sequencing for genetic typing suggested that the spread of multidrug-resistant *C. auris* in Italy may be facilitated by the COVID-19 pandemic.[47] To prevent the spread of *C. auris* among patients with COVID-19, infection prevention and control policies, including contact

**Table 2** Antifungal susceptibility of *Candida* isolates from patients with COVID-19-associated candidasis[36—53??]

| *Candida* species | FLU | VOR | ITR | POS | MIC | CAS | ANI | AmB | 5-FU |
|---|---|---|---|---|---|---|---|---|---|
| *C. auris* | 8/75 (10.7) | 32/45 (71.1) | | | 54/55 (98.2) | 54/60 (90.0) | 70/72 (97.2) | 28/65 (43.1) | 36/36 (100) |
| *C. albicans* | 30/32 (93.8) | 24/25 (96.0) | 17/20 (85.0) | 9/12 (75.0) | 26/26 (100) | 10/12 (83.3) | 17/19 (89.5) | 23/23 (100) | 15/17 (88.2) |
| *C. glabrata* | 0/11 (0) | 10/10 (100) | 10/10 (100) | 7/7 (100) | 6/7 (85.7) | 2/5 (40) | 7/10 (70.0) | 10/10 (100) | 5/5 (100) |
| *C. tropicalis* | 5/5 (100) | 5/5 (100) | 4/4 (100) | 1/1 (100) | 5/5 (100) | 0/1 (0) | 19/19 (100) | 19/19 (100) | 19/19 (100) |
| *C. krusei* | | 2/2 (100) | 1/1 (100) | 2/2 (100) | 2/2 (100) | 0/1 (0) | 2/2 (100) | 2/2 (100) | 2/2 (100) |
| *C. parapsilosis* | 2/3 (66.7) | 3/3 (100) | 3/3 (100) | 3/3 (100) | 3/3 (100) | | 1/1 (100) | 1/1 (100) | 1/1 (100) |

Data are expressed as the numbers of susceptible isolates/total tested isolates (%).
Note: FLU, fluconazole; VOR, voriconazole; ITR, itraconazole; POS, posaconazole; MIC, micafungin; CAS, caspofungin; ANI, anidulafungin; AmB, amphotericin B; 5-FU, flucytosine.

precaution and regular surveillance,[61] require regular audit and emphasis. Whole genome sequencing could provide a new tool to disclose the epidemiology of healthcare-associated infection and to better control and prevent these infections.[47,62,63]

The management of CAC are based on the existing knowledge and conventional approach prior to the COVID-19 pandemic. For non-critically ill patients or those with a low risk of azole-resistant candidiasis, fluconazole remains the drug of choice for candidemia. For critically ill patients, those with a history of recent azole exposure, or with a high risk of the acquisition of fluconazole-resistant *Candida* species, echinocandins are recommended as the first-line therapy.[55,64]

Likewise, the management of CAC other than candidemia is based on the existing knowledge prior to the COVID-19 pandemic. In the previous guideline endorsed by the Infectious Diseases Society of Taiwan, surgical intervention is recommended in adults with fungus balls or casts in the pyelum or urinary bladder.[64] However, in view of the potential risk of SARS-CoV2 transmission, surgical intervention may be deferred, and antifungal agents prescribed as the initial treatment strategy.

The clinical management of *C. auris* infections is challenging, since *C. auris* shows extensive resistance to antifungal agents and causes sporadic cases or outbreaks in many countries.[36,37,39–41,44,45,47,48,51] The extent of antifungal resistance related to *C. auris* was reported for 75 *C. auris* isolates from 6 retrospective clinical studies,[36,37,41,44,47,51] and the susceptibility data were summarized in Table 2. Meanwhile, there is an emerging threat of echinocandin-resistant or pan-resistant *C. auris*.[65] Based on currently published results, echinocandins are recommended as the first-line therapy for candidemia caused by *C. auris*. If there is no evidence of resistance to amphotericin B and there is persistent candidemia after echinocandin treatment, liposomal amphotericin B or amphotericin B deoxycholate can be considered.

## Novel therapeutic options for candidiasis in the COVID-19 pandemic

Nowadays, there are novel therapeutic options for candidiasis and several new antifungal agents are evaluated by the phase III trials. Previous studies have demonstrated the effectiveness of ibrexafungerp against candidiasis due to *Candida* species resistant to azoles and echinocandins.[66,67] Moreover, rezafungin, a novel long-acting echinocandin, can be administered once weekly with non-inferiority to other echinocandins against invasive candidiasis in a phase II trial.[68,69] Efungumab, a monoclonal antibody against heat shock protein 90 (Hsp90), shows fungicidal activity in combination with lipid-associated amphotericin B, although a prior study revealed such effect may be nonspecific.[70,71]

Furthermore, there are promising antifungal compounds under development or evaluated in the early phase trials. Oteseconazole, belonging to a new class of antifungal agent, tetrazole, shows effectiveness against acute vulvovaginal candidiasis and *in vitro* activity against azole-resistant *C. albicans*.[72,73] Fosmanogepix, an inhibitor of Gwt1 which involves acylation of inositol and cell growth of *Candida* and *Aspergillus* species, has been proved with a low potential for inducing resistance among *Candida* species.[74–76] Even old drugs commonly prescribed for the clinical indications other than fungal infection, such as colistin, cyclosporin A, and tacrolimus, are now under preclinical studies.[77,78]

To combat the multidrug-resistant *Candida* species in the era of COVID-19 infection, well-defined nanocomposite structures have recently been employed.[79] A synthesized Ag@Ag2O core—shell nanocomposites via chemical method was made for biosafe antimicrobial and anti-biofilm applications against candidiasis.[79] Some synthetic compounds had been designed and produced as inhibitors of ergosterol synthesis in yeasts.[80] Fibrate-based compounds and substituted pyrroles that inhibit the enzyme, 3-hydroxymethyl-glutaryl-CoA reductase, of *C. glabrata* (CgHMGR), was examined as an alternative therapeutic choice through decreasing yeast viability and ergosterol synthesis in animal models.[80]

Vaccines targeting *Candida* species had been designed, and multi-epitope vaccine candidates (MEVCs) had been developed with mapping protein-specific and proteome-wide immunogenic peptides (such as cytotoxic T lymphocytes, B cells, and helper T lymphocytes), and showed strong antigenic features against *Candida* species.[81] Although the novel therapeutic choices for candidiasis listed above are under-investigation, new therapeutic agents alone or in combination with traditional anti-fungal drugs, require further studies and will provide other treatment options in the future.

## Conclusion

CAC has been recognized during the COVID-19 pandemic, and the therapeutic strategies recommended for CAC due to *Candida* species, such as *C. albicans*, *C. tropicalis*, and *C. glabrata*, are similar to those before the era of COVID-19. Close surveillance for the incidence of multidrug-resistant *C. auris* infections among patients with COVID-19 is essential, since the treatment options are limited and inappropriate treatment may jeopardize the clinical outcome of affected individuals.

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