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CANDIDEMIA ASSOCIATED WITH COVID-19: RISK FACTORS AND PREDISPOSITION IN CRITICAL PATIENTS

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ABSTRACT

Introduction: Coronavirus diasease 19 (COVID-19) is an infection caused by the new coronavirus - SARS-CoV-2 in 2019. The infection quickly spread throughout the world, establishing itself like a pandemic. Reports on secondary fungal co-infections in critically ill patients COVID-19 are still scarce and their dynamics are poorly understood. Candidemia is defined as the presence of *Candida* species in one or more blood cultures, being one of the most reported opportunistic fungal infections in intensive care units (ICU).

Methods: Three databases were used for the literary search: Pubmed, Science Direct, and Scopus, including articles published between 2020 and 2021.

Results: The incidence of candidemia in COVID-19 patients ranged up to 12% of COVID-19 reported cases. *Candida albicans* was the most prevalent species, followed by non-*albicans* species. The use of broad-spectrum antimicrobials, corticosteroids, central venous catheters, mechanical ventilation, parenteral nutrition, immunosuppressants such as tocilizumab and prolonged hospital stay were predisposing factors for the candidemia in COVID-19 patients.

Conclusion: There are strongly established risk factors that influence the establishment of candidemia in critically ill COVID-19 patients, which contributes to increased mortality in these patients. Finally, active surveillance by the medical team should be maintained for previous signs of fungal co-infection associated with SARS-CoV-2 contamination.

Keywords: *COVID-19, candidemia, fungal co-infection, SARS-CoV-2, risk factors*

INTRODUCTION

Coronavirus disease 19 (COVID-19) is an infection caused by a new coronavirus, SARS-CoV-2, which present rapid transmission and contagion between humans. The first reports of the infection appeared in Wuhan, China, in late 2019. Consequently, COVID-19 has quickly been declared a pandemic by the World Health Organization (WHO)[1]. Currently, Brazil ranks third in the world in the total number of cases of infection and the second in several deaths. Reports on secondary infections in patients with an initial diagnosis of contamination by SARS-CoV-2 are still very limited[2,3]. The establishment of a secondary infection associated with COVID-19 can aggravate the inflammatory process in these patients, contributing to the increase of the pathogenicity and influencing a poor prognosis.[4]

Candidemia, defined as the presence of *Candida* spp. in one or more blood cultures, is one of the most common opportunistic fungal infections in intensive care units (ICU). Despite the diversity of species that the genus presents, cases of infection are primarily attributed to five species: *C. albicans*, *C. glabrata*, *C. tropicalis*, *C. parapsilosis*, and *C. krusei*[5,6]. External infections in medical devices, such as catheters and probes, can be the primary source of cases of candidemia. However, endogenous sources can also cause infection[7-9].

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In most cases of candidemia, antifungal therapy is not responsive. Thus, infection is associated with increased length of stay, a high cost to the health system and high mortality, between 40-60% of cases[10-12]. The most common risk factors for the establishment of candidemia include critical illness and prolonged ICU stay. Other risk factors, such as the presence of medical devices, exposure to corticoids and antibiotics, surgery, malignant tumors, acute necrotizing pancreatitis, organ transplants, and parenteral nutrition, can also contribute to the infection development[13,14].

From the exposure scenario, COVID-19 patients admitted to intensive care units (ICU) are more likely to the establishment of secondary fungal infections, such as candidemia. Thus, it is important to identify and address modifiable risk factors in an attempt to prevent and reduce the occurrence of candidemia in COVID-19 patients. Thus, this study evaluated to address risk factors in critically ill COVID-19 patients in establishing *Candida* spp. causing a secondary infection, in addition to providing a basis for a better understanding of this problem.

METHODOLOGY

For this study, the articles published in the area of interest were identified in three different databases: Pubmed, Science Direct, and Scopus. As inclusion criteria, english articles published between 2020 and 2021 and using the following keywords, alone or in combination: candidemia, covid 19, invasive candidiasis, coronavirus were selected. The studies were critically reviewed, excluding those that do not correspond to the theme delimitation and duplicate articles. In a total, 17 studies were selected and analyzed (Figure 1).

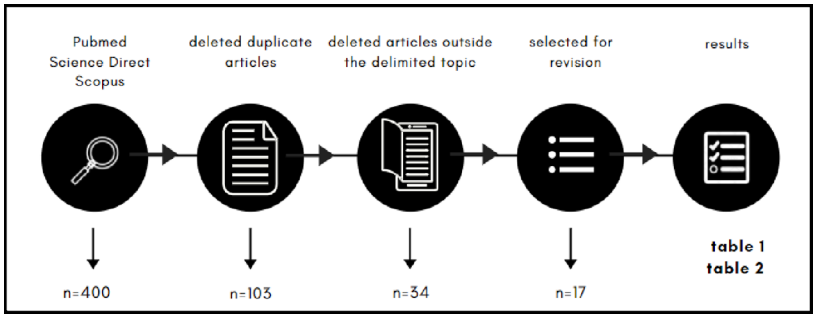

Figure 1: Scheme sequence of the methodology used to select the analyzed articles.

IMMUNE RESPONSE EXPRESSION ASSOCIATED WITH CANDIDEMIA IN COVID-19 PATIENTS

Candida spp. is present in a commensal manner of the mucosal microbiota of approximately 50-70% of immunocompetent individuals under normal conditions. Changes in the individual's immune response due to external factors or the imbalance of intestinal barriers, such as in surgeries involving the gastrointestinal tract (GIT), can spread through the abdominal cavity, developing an opportunistic infection, such as candidemia[9,11].

Neutrophils play an important role in the innate immune response to fungal pathogens, as they are the first cells to be recruited through pro-inflammatory cytokines[9,15,16]. Thus, neutropenia is an established risk factor for both dissemination candidemia and patient mortality[11]. Monocytes and macrophages also perform another principal function, as they can phagocytose and eliminate yeast, secreting cytokines and inflammatory factors that contribute to the host's immune respons. A study by Ngo[17] showed that mice who are deficient in phagocytic cells had more proliferation and lethality by *C. albicans* than the control group[17,18] NK cells also represent a major component of the innate immune system. Studies demonstrate the ability of these cells to control fungal infection[19,20], despite that their participation in the individual's immune response against fungi is still poorly understood.

SARS-CoV-2 infection promotes an innate immune response that induces an excessive inflammatory process, known as "cytokine storm". The *Candida* genus has specific virulence factors that allow the establishment of opportunistic infection when the individual is in a picture of immunosuppression, observed in patients with associated risk factors. The disruption of the enterocyte epithelial barrier, caused by SARS-CoV-2, can facilitate the translocation of *Candida* species from the intestinal lumen to the bloodstream alteration in the host's defense mechanisms caused by the virus allows the colonization and installation of secondary infection by *Candida* spp[21,22]. Although the immune system is compromised in COVID-19 patients, the immune cells, responsible for the innate immune response to *Candida* spp., are still present. Thus, it is possible that the risk factors related to the patient's clinic are crucial and determine substances for the development and installation of candidemia cases[23].

Tocilizumab is a recombinant monoclonal antibody that binds to the membrane of interleukin-6 [IL-6], preventing binding to the enzyme receptor and inhibiting the activation of the inflammatory cascade[24]. The use of tocilizumab is based on the hypothesis that it supposedly decreases the rate of mortality caused by SARS-CoV-2 is still being studied, as there are conflicting results among several clinical trials reported[24-26]. In this sense, the use of this drug may be associated with an increase in invasive fungal infections, as it is an immunosuppressant and its adverse effect is neutropenia, a known risk factor for candidemia[27].

Taramasso et al. evaluated the administration of tocilizumab in critically ill COVID-19 patients[28]. The group of patients who received the drug and developed secondary infections showed no significant changes in laboratory parameters, only reduced C-Reactive Protein (CRP) parameters when compared to patients who did not receive the drug, which is commonly observed when using treatment with immunosuppressants. Because of this, when there is suspicion of secondary infections in patients who used tocilizumab, the medical approach should not be based only on examinations of inflammatory signs, as these may not be completely reliable for the patient's condition. The study also mentions that the drug did not change manifestation of infection symptoms, such as fever, hypothermia, and hypotension. According to y Al-Baadani et al., among the group of patients who used tocilizumab (n=62), 10 patients developed secondary infections: 5/10 hospital pneumonia associated with mechanical ventilation and another five patients, bloodstream infections, with candidemia being reported in 4/5 of the cases[26] (Table 1).

According to Antinori et al., the use of tocilizumab was considered a risk factor for the development of candidemia[25]. All patients received a dose of 8mg/kg of the drug and had a mean time of 13 days between the last administration and the development of infection (Table 1). Seeing the immune response may be altered after using the drug, the presence of an inflammatory response associated with symptoms of fever and high serum levels of CRP, which are characteristic of clinical suspicion of infections, may be minimized. Therefore, medical professionals must be on active surveillance for the risk of candidemia in these patients.

NOTIFICATION OF CANDIDEMIA CASES IN COVID-19 PATIENTS

COVID-19-associated candidiasis (CAC) has been registered and reported in several countries, with different incidences between different continents, ranging from 0.7 - 12%. The difference between the pandemic management protocols between each country, and the difficulty in diagnosing secondary infections, means that the manifestation of fungal infections remains under-reported[29].

In this study, countries from all continents were not included, which can explain due to some factors: inadequate studies or insufficient data for analysis, different managements during the pandemic between governments, contact isolation protocol making it difficult to diagnose underlying infections for later notifications and the urgency to face the seriousness of the social and economic effects caused by the health crisis. Thus, what is available from the report and published studies are a sample of cases. However, some factors make it impossible to have a panoramic and global view of the problem associated with the COVID-19 pandemic (Figure 2).

Figure 2: Geolocation of candidemia case studies in COVID-19 patients presented in Table 1 (United States, Greece, India, Oman, Brazil, Italy, United Kingdom, Spain, Turkey, Iran).

CANDIDEMIA EPIDEMIOLOGY IN COVID-19 PATIENTS

Among the fungal infections acquired in hospital environments, the *Candida* genus is the most prevalent and is among the major pathogens involved in bloodstream infections in ICU'S[30,31]. Worldwide, *C. albicans* is the most prevalent species in blood cultures, accounting for approximately 40 to 60% of cases, although the rates of candidemia caused by *Candida* non-albicans have increased due to the high mortality rates in standard patients[32,33]. Following this pattern, in most of the countries included, *C. albicans* was the most prevalent species in COVID-19 patients who developed candidemia, followed by non-albicans species, varying by continental region. Of these, *C. krusei* and *C. dubliniensis* were mentioned less prevalently (Table 1).

C. albicans is the most prevalent species United States of America (USA) ICU, followed by *C. glabrata* and *C. parapsilosis*[34]. This is in agreement with Macauley et al.[35] and Seagle et al[36]. studies, that related to the incidence of patients who developed CAC[35,36]. In Spain, *C. albicans* was the most prevalent species in COVID-19 patients with candidemia, followed by *C. parapsilosis* and *C. glabrata* (Table 1) and are in accord with the epidemiology of the genus in patients with candidemia in the country[5]. The difference in the epidemiological pattern of species between continents may be related to the variation of important factors such as climate, antifungal treatment, and protocols related to the use of central venous catheters in patients.

In Latin America, *C. albicans* also remained the most prevalent species, *C. tropicalis* and *C. glabrata* ranged between the second and third most common isolate. The emerging incidence of non-albicans in recent years poses a problem since they have low susceptibility to fluconazole[37]. In Brazil, in a group of COVID-19 patients who developed candidemia, *C. glabrata* was the most prevalent species among non-*albicans Candida,* followed by *C. tropicalis*. *C. auris* was reported by Chowdhary et al.[38] and Magnasco et al.[39] and related to nosocomial infection that culminated in local outbreaks of candidemia in COVID-19 patients[38,39]. This may be related to the ease of transmission in hospital environments. The standard of care and the need for intensive care in severe cases of COVID-19 make these patients more susceptible to the colonization of this yeast. This situation is alarming, as it has high rates of resistance to available clinical treatment, such as fluconazole and other antifungals[38].

COVID-19 THERAPY AS A RISK FACTOR FOR THE CANDIDEMIA ESTABLISHMENT

The corticosteroids use is described as a risk factor for the fungal infection establishment of fungal, as it can promote exacerbated fungal growth, is associated with an increased risk of establishing systemic infections, such as candidemia[40]. Corticosteroids are used to treat a variety of symptoms and diseases, including in the COVID-19 treatment. Dexamethasone, for example, is used in combination therapy with antimicrobials because it exerts an important inhibitory effect on inflammatory factors, being about 25 times more active than other drugs in the same group. The main effect of dexamethasone is the inhibition of a pro-inflammatory gene that encodes chemokines, cytokines, and adhesion molecules to the acute inflammatory response, mainly affecting two aspects: chemotaxis and vasodilation[41-43].

Studies associating corticosteroids with antifungal therapy have shown changes in the patient's response after the introduction of corticosteroids, with a deleterious effect on treatment[44-46]. Corticosteroids are a therapeutic alternative for pneumonia caused by SARS-CoV-2, but it is important to determine protocols for treatment and the right time to start these interventions. High doses of corticosteroids may be related to the increased frequency of candidemia in COVID-19 patients. Medical professionals should be aware of the potential for establishing systemic infections in critically ill patients[40].

The use of broad-spectrum antimicrobials in hospitalized patients, both in targeted treatments and in empirical treatment, can alter the normal microbiota, promoting the overgrowth of opportunistic fungi[6]. Since the beginning of the pandemic, several studies have shown an increase in prescriptions of antimicrobials. During the first global wave of COVID-19, the use of broad-spectrum antibiotics was observed in more than 70% of cases, even with literature data showing that bacterial co-infection occurs in less than 10% of cases[47]. The indiscriminate use of antimicrobials in the absence of a well-established protocol may be contributing to the increase in cases of candidemia observed in COVID-19 patients[48]. The selection of bacterial and fungal isolates resistant to antimicrobial therapy has become a problem worldwide, justifying the emergence of programs for the rational use of medicines and the establishment of infection control measures[39].

Seeing that some intestinal bacteria regulate the growth of pathogenic microorganisms and also the proliferation of yeasts, the indiscriminate and undirected use of broad-spectrum antimicrobials favors the opportunistic growth of *Candida* spp. As can be seen in the studies described (Table 1), the use of broad-spectrum antibiotics and the use of corticosteroids in the therapeutic protocol of COVID-19 patients is extremely prevalent and related to an important risk factor in the development of candidemia.

RISK FACTORS FOR THE ESTABLISHMENT OF CANDIDEMIA IN CRITICAL ICU PATIENTS

Approximately 5 to 30% of patients diagnosed positive for SARS-CoV-2 require admission to the ICU. Widely known risk factors for the development of candidemia are present in these patients, such as mechanical ventilation, parenteral nutrition, and the use of a central venous catheter[49]. In our study, these widely known risk factors for invasive *Candida* infection were cited in the absolute majority of the studies analyzed.

Catheter-related disseminated infections can originate from various pathways, such as through the patient's skin microbiota, exogenous contamination in the handling of healthcare professionals, or contamination from infusions[50]. *Candida* spp. it is the third most prevalent etiologic agent in central venous catheter-related infections[51]. These devices are highly associated with the development of candidemia, as the *Candida* genus is a colonizer of this type of access, as it provides an adhesion surface for yeast colonization in these sites forming biofilms[31,52].

An epidemiological study by Fram carried out by a university hospital in São Paulo during the pandemic revealed that candidemia was the most prevalent bloodstream infection associated with central venous catheters in ICU's in 2020, with approximately 29.1% of the reported infections cases[53]. *Candida* spp. it is among the most commonly isolated pathogens from the biofilm formed in the endotracheal tube and tracheal secretions in patients with ventilator-associated pneumonia[54]. Central venous catheters should be removed in patients with candidemia if this situation is clinically feasible. When removal is not possible, therapy with echinocandin or amphotericin B should preferably be performed, as they are effective against biofilms[55].

Parenteral nutrition (PN) is commonly identified as a risk factor for the development of candidemia. PN causes important changes in the patient, such as the alteration of the normal intestinal microbiota from gram-positive bacteria to a predominance of gram-negative bacteria, alters the barrier function of epithelial cells, and causes inflammation. These factors turn the intestine into a favorable environment for colonization by *Candida* spp.[12] Another hypothesis is related to the development of hyperglycemia due to the high concentration of dextrose caused by continuous infusion, which can impair and reduce the immune response of critical patients, leading to secondary infections[50].

The prolonged length of stay in the ICU's is also considered a risk factor for the establishment of opportunistic infections. According to Bishburg et al.[34], COVID-19 patients without candidemia were hospitalized for an average of 10 days[34]. On the other hand, in the group of patients with CAC, the average hospital stay was 40 days. This behavior was also observed by Macauley et al.[35], since patients in the CAC group remained hospitalized significantly longer until the development of candidemia on average 19 days[35].

Table 1: Outcome of studies approach cases of candidemia in COVID-19 patients published between 2020 - 2021.

Authors/Country	Isolated	Main results	Risk factors
Arastehfar, 2021[56] (Iran)	*C. albicans* *C. glabrata*	In the period analyzed (November/2020 to January/2021), 1988 patients were diagnosed with COVID-19 and admitted to the hospitals. Seven patients developed fungemia (0.03%), of which 6/7 had candidemia. All patients with CAC died despite treatment with antifungal agents. This led to an extremely high mortality rate in COVID-19 patients when compared to patients without candidemia (452/1988).	Central venous catheter Broad spectrum antibiotics ICUs Parenteral nutrition Mechanical ventilation
Macauley & Epelbaum, 2021[35] (United States)	*C. albicans* *C. glabrata* *C. parapsilosis* *C. tropicalis* *C. krusei*	Fifty patients with candidemia were identified, with an incidence rate of approximately 13/1000 admissions. In the non-COVID group, 38 patients with candidemia and 12 in the COVID group were identified. The corresponding incidence (CI) rates were 11/1000 admissions in non-COVID and 51/1000 admissions in the COVID group. The mortality rate in the non-COVID group was 61%, while in the COVID group this rate reached 75% of cases.	Mechanical ventilation Central venous Catheter broad spectrum Corticosteroid therapy Days in ICU Hemodialysis

Continues...

Table 1: Continuation.

Authors/Country	Isolated	Main results	Risk factors
Kayaaslan, 2021[57] (Turkey)	*C. albicans* *C. glabrata* *C. parapsilosis* *C. tropicalis*	The incidence of candidemia in the COVID-19 group was 2.16%. The time for the development of fungal infection was shorter (approximately two weeks), the mortality rate was higher (92.5%) when compared to the non-COVID group, which had a CI of 1.06% and a mortality rate of 79.4 %.	Broad spectrum antibiotics Corticosteroid therapy CCentral venous catheter Mechanical ventilation Hemodialysis Surgery
Riche, 2020[40] (Brazil)	*C. albicans* *C. glabrata* *C. tropicalis*	During the study period, the incidence of candidemia was 1.43 (hospital 1) and 1.15 (hospital 2) in non-COVID-19 patients per 1000 patients/day. When compared to the previous year (pre-pandemic), these incidences remained unchanged. On the other hand, in the COVID-19 group of patients, the incidence was 11.83 (hospital 1) and 10.23 (hospital 2) per 1000 patients/day and during the same period analyzed. The mortality rate of patients with candidemia in the covid-19 group was 72.7% (8/11).	Corticosteroids Central venous catheter Broad spectrum antibiotics
Nucci. 2021[22] (Brazil)	*C. albicans* *C. glabrata* *C. tropicalis*	During the study period, 41 episodes of candidemia were observed Hospital days: 16 in period 1 (pre-pandemic) and 25 in period 2 Mechanical ventilation (during the pandemic). Of this total, nine cases in COVID-19 Central venous catheter patients. In period 2, the incidence of candidemia per 1000 admissions was 4.76 in patients without COVID-19 and 2.68 when considering cases of candidemia occurring in COVID-19 patients. The hospital average at an incidence of 1.3 per 1000 admissions over the years.	Hospital days Central venous catheter Mechanical ventilation
Abdullah, 2020[58] (Oman)	*C. albicans,* *C. glabrata,* *C. tropicalis*	Five cases of candidemia were reported in the adult ICU. All five patients had CVC and received broad-spectrum antibiotics. Persistent candidemia occurred in one patient even after removal of the CVC and administration of antifungal therapy. Despite appropriate management, 3/5 patients died.	Hospital days Central venous catheter Surgery Broad spectrum antibiotics Mechanical ventilation
Mastrangelo, 2020[59] (Italy)	*C. albicans*	In 21 patients belonging to the COVID group and 51 patients to the control group, the incidence rate of candidemia per 10,000 cases was significantly higher in the first group (10.97 versus 1.48.)	Days in ICU Immunosuppressants
Giacobbe, 2020[60] (Italy)	*C. albicans* *C. glabrata* *C. parapsilosis*	Seventy-eight critically-ill patients were included in the study 45 episodes of bloodstream infections were observed in 31 patients, with an incidence rate of 47 episodes per 1000 patient-days. Of these, 3/45 episodes were candidemia, representing 6.67% of cases.	-----

Continues...

Table 1: Continuation.

Authors/Country	Isolated	Main results	Risk factors
Antinori, 2020[25] (Italy)	*C. albicans* *C. tropicalis* *C. parapsilosis*	During 11 days, 43 COVID-19 patients received drug therapy with tocilizumab in the ICU and wards. Of these, three patients (6.9%) developed candidemia. Patients received an 8 mg/kg dose of tocilizumab (maximum 800 mg/d) repeated within 12 h after the first administration. The median time since the last dose of tocilizumab and the diagnosis of candidemia was 13 days.	Tocilizumab Parenteral nutrition Broad spectrum antibiotics
White, 2020[61] (United Kingdom)	*C.albicans, C.parapsilosis*	A total of 135 adults were analyzed and included in the study. 12.6% (17 patients) had fungal yeast infections. Of this group, 14 cases were invasive *Candida* spp. All patients were on mechanical ventilation. Of these, 6/15 died within 30 days of diagnosis.	Mechanical ventilation Central venous catheter
Bishburg, 2020[34] (United States)	*C. albicans, C. tropicalis* *C. parapsilosis* *C. glabrata*	During the study period, 89 patients were included in the COVID-19 group. The incidence of candidemia was 8/89 (8.9%) and a mean ICU stay of 25 days. Compared to patients without candidemia, patients with candidemia remained in the ICU longer (10 vs. 40 days).	Central venous catheter Broad spectrum antibiotics Corticosteroids Tocilizumab Mechanical ventilation
Agrifoglio, 2020[62] (Spain)	*C. albicans, C. parapsilosis* *C. glabrata*	Among 139 patients admitted and analyzed in this study, 15 cases of candidemia were reported (10.8% of cases). This group had a mortality rate of 40%.	Mechanical ventilation Central venous catheter Vasoactive drugs Parenteral nutrition Use of broad spectrum antibiotics Corticosteroids
Kokkoris, 2021[3] (Greece)	*C. albicans, C. parapsilosis*	Among 50 patients included during the study period, 7/50 (14%) developed candidemia. Candidemia was more frequent in patients who had bacteremia.	Mechanical ventilation Use of broad spectrum antibiotics
Denny, 2021 (United Kingdom)	*C. albicans* *C. parapsilosis* *C. glabrata* *C.dubliniensis*	In the period analyzed, 11 cases of candidemia were identified. An average of 14.8 days was observed for the development of secondary infection after the diagnosis of COVID-19. Thus, the 30-day mortality rate was 54.4% (6/11).	Mechanical ventilation Use of broad spectrum antibiotics Hemofiltration Central venous catheter
Magnasco, 2021[39] (Italy)	*C. auris*	During the period analyzed by the study, 118 patients were admitted to the COVID-19 ICU. Of this group, in 6/118 - approximately 5.1% of the cases, the etiological agent was *C. auris*. Out of 4/6 patients developed candidemia. The average time from admission to the first case of candidemia was 38 days, with a mortality rate of 50% (n=2).	Use of broad spectrum antibiotics
Chowdhary, 2020[38] (India)	*C. auris* *C. albicans* *C. tropicalis* *C. krusei*	A total of 596 COVID-19 patients were admitted. Candidemia was detected in 15/596 patients (2.5% of cases). Among these, 8/15 (53%) died. The mortality rate for C. auris was 60%.	Central venous catheter Mechanical ventilation

Continues...

Table 1: Continuation.

Authors/Country	Isolated	Main results	Risk factors
Seagle, 2021[36] (United States)	*C.albicans* *C. glabrata* *C.parapsilosis* *C. tropicalis* *C. lusitaniae* *C. dubliniensis*	Of 251 cases of candidemia included in the study, 64/251 were COVID-19 patients, with a median time of 15 days between positive diagnosis for COVID-19 and positive culture for *Candida* spp.	Central venous catheter Mechanical ventilation

ANTIFUNGAL THERAPY FOR CANDIDEMIA AND COVID-19 PATIENTS

The basis of antifungal treatment for candidemias is to use the class of azoles. However, the use often empirically has led to increased selection of resistant isolates, especially among non-albicans *Candida*. Fluconazole is the drug of choice and is widely used for the treatment of infections caused by *Candida* spp. However, *C. krusei* and *C. glabrata* are intrinsically resistant and, in this case, the echinocandins (anidulafungin, caspofungin, and micafungin) or amphotericin B are used. In particular, the treatment for *C. auris* must be done carefully, as there are reports of lack of susceptibility to azoles and amphotericin B, which hinders and limits available therapeutic options[52,56].

In a randomized study, anidulafungin was shown to be equivalent to fluconazole; later, in a second analysis, it showed a higher response rate to the treatment (fluconazole about 60%, anidulafungin 76%). Fluconazole should be administered at a high initial dose (800 mg/d), and may also be used for continuation of oral treatment after initial treatment with echinocandins. In most cases, voriconazole does not offer advantages when compared to fluconazole - except for *C. krusei* infections or in cases of suspected filamentous fungus infection[11,55,57,58]. Voriconazole is a second-generation triazole that has high efficacy in the treatment of disseminated fungal infections, with less toxicity compared to other antifungals such as amphotericin B (Figure 3)[59].

Despite treatment with antifungal agents, the mortality rate associated with candidemia is high. Echinocandin-resistant *C. glabrata* isolates and multidrug-resistant *C. auris* isolates can lead to therapeutic failure, in addition to the risk of causing outbreaks in critically ill patients, which makes the challenge in the appropriate therapeutic approach for these patients even greater[60,61]. The development of specific protocols for epidemiological surveillance, such as periodic screening for colonization for *Candida* spp. in hospital spaces; the assessment of risk factors associated with each patient; the introduction of protocols that enable early diagnosis; and limiting the initiation of empirical fungal treatment according to the patient's condition and local epidemiology may contribute to the reduction in the selection of fungal resistance[62].

According to the Brazilian guideline for the candidemia treatment, non-neutropenic patients can use echinocandins (caspofungin 70 mg initial dose, followed by 50 mg/day), micafungin 100 mg or anidulafungin 200 mg initial dose followed by 100 mg/day) and they are strongly recommended; fluconazole 800 mg (12 mg/kg) followed by 400 mg is also strongly recommended and amphotericin B (3–5 mg/kg/d) is strongly recommended[62]. For neutropenic patients, the same dose and treatment of non-neutropenic patients can be used, only fluconazole 800 mg (12 mg/kg), followed by 400 mg, is not recommended. Daily blood culture collections are recommended, candidemia should be treated for at least two weeks after negative blood cultures. Duration of treatment depends on patient follow-up and response to antifungal therapy[55]. In candidemia associated with COVID-19, fluconazole is the first therapeutic choice, followed by echinocandins and amphotericin B (Table 2). The therapeutic management chosen is adequate to proposee by literature for these cases (Figure 3).

Critically ill COVID-19 patients have the concomitant presence of predisposing factors to the development of opportunistic co-infections, such as the use of broad-spectrum antimicrobials, corticosteroids, central venous catheters, mechanical ventilation, parenteral nutrition, use of immunosuppressants such as tocilizumab and time of prolonged hospital stay. The incidence and reporting of candidemia cases in COVID-19 patients varied up to 12% of the cases. Overall, the candidemia epidemiology in patients who developed CAC maintained *C. albicans* as the most prevalent species, followed by *C. glabrata*, *C. parapsilosis*, and *C. tropicalis*, varying according to the country. Infections by *C. auris* in critically ill COVID-19 patients were also observed, which is a worrying factor, as it has multi-resistance against currently available antifungal therapies. Fluconazole was used as the first choice in the CAC treatment, followed by echinocandins and amphotericin B. The development of candidemia in critically ill COVID-19 patients leads to increased mortality associated with the infection, even in patients who received antifungal treatment. Thus, we highlight the importance of the medical team in the active surveillance of hospital units, as these patients are at greater risk for the development of opportunistic fungal co-infections.

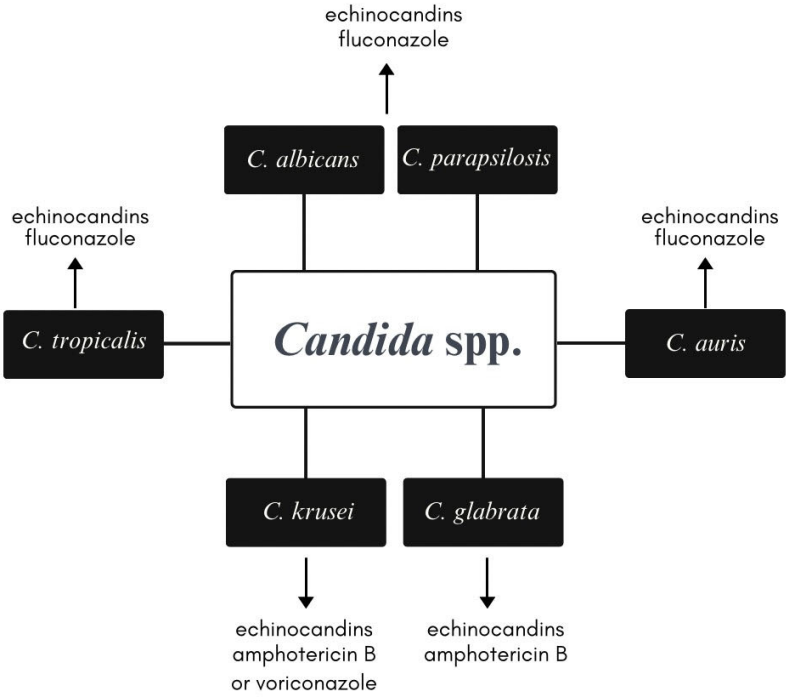

Figure 3: Suggestion treatment according to the species in the therapeutic management proposed by the Infectious Diseases Society of America from the isolation of *Candida* spp.

Table 2: Therapy administered in cases of candidemia.

Author/year	Treatment
Arastehfar (2021)	fluconazole, caspofungin
Riche (2020)	anidulafungin, fluconazole, amphotericin B, voriconazole.
Nucci (2021)	anidulafungin and fluconazole.
Abdullah (2020)	caspofungin, amphotericin B, voriconazole.
Antinori (2020)	caspofungin, fluconazole.
White (2020)	fluconazole, caspofungin, amphotericin B.
Bishburg (2020)	fluconazole, caspofungin.
Denny (2021)	fluconazole.
Magnasco (2021)	caspofungin, amphotericin B

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Conflict of interest

All authors declare to have no conflict of interest.

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