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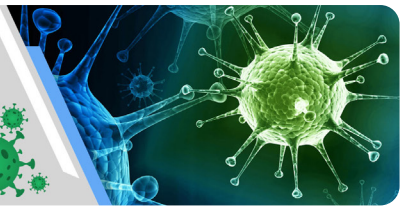

Antibiotic Use: A Modifiable Factor to Avoid Candidemia in Critically Ill Patients with COVID-19

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Abstract

Background and Purpose: Secondary fungal infections, such as Candidemia, are often identified as a severe complication of COVID-19 in Intensive Care Units (ICUs), leading probably to a worst prognosis. Therefore, the objective of this study was to identify the risk factors of candidemia in critical ill COVID-19 patients hospitalized in ICU.

Materials and Methods: A retrospective and case control of patients with severe COVID-19 hospitalized in ICUs was performed at two hospitals in Curitiba, from March 2020 to January 2022. The case group consisted of patients with severe COVID-19 and positive blood culture for any *Candida* during their hospitalization in ICU. The control group consisted of patients also with severe COVID-19 hospitalized in ICU but without candidemia and any positive microbiological culture. Epidemiological data, signs and symptoms related to COVID-19, comorbidities, risk factors for Candidemia, microbiological cultures, laboratorial and radiologic exams were extracted from electronic medical records.

Results: A total of 81 patients with severe COVID-19, 27 were cases and 54 controls were enrolled. Independent risk factors for candidemia were time of hospitalization at ICU (OR = 1.31; IC 95% 1.08 - 1.60; p = 0.006) and number of antibiotics used (increased in almost 80% this risk - OR = 1.78; IC 95% 1.06 - 3.0; p = 0.02). *Candida albicans* (44%) was the most frequent causative agent.

Conclusion: Among the independent risk factors related to candidemia in this study, the control over the use of antibiotics is the only modifiable factor, consequently, it can be an important tool for preventing candidemia.

Keywords: Candidemia, Antimicrobials, COVID-19, Intensive Care Unit

Introduction

The initial phase of COVID-19 pandemic, before vaccination became available for SARS-COV2, was responsible for a high number of deaths, especially in high-risk group patients. In this period, almost a quarter of the patients with COVID-19 hospitalized needed intensive care unit (ICU) admission [1] due to mostly acute respiratory distress syndrome (ARDS). An extended length of stay in ICU associated with prolonged use of invasive devices (mechanical ventilation and central venous catheter) and dialysis have been associated as risk factors for secondary infections, although robust data are limited, mainly for invasive fungal disease, such as candidemia [2,3,4]. Bloodstream infections for *Candida* have been associated with high rate mortality in patients even before the emergence of COVID-19 [4,5,6].

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In pandemic context, those rates can be worse [3,4,7,8]. Therefore, aiming for reduction of morbidity and mortality by opportunists´ invasive fungal disease, as candidemia, a general awareness about fungal co-infection is crucial to an early diagnosis and treatment [9].

But it is still imprecise whether COVID-19 corresponds to a significant risk factor to the patient and a predisposition to a posterior fungal infection [10]. It is also not clear if the risk factors to acquire candidemia without COVID-19 are similar to COVID-19 [2,11,12], and beyond that it is important to identify the modifiable risk factors and learn how to mitigate this infection [13], which has received less attention from scientific society. Thus, this research is justified due to the actual relevance and scarcity of studies about the topic. It aims to broaden the comprehension of the clinical characteristics of candidemia for an early diagnosis and treatment and mainly prevention of this disease. Therefore, the objective of this study was to identify the risk factors of candidemia in severe COVID-19 patients hospitalized in ICU.

Materials and Methods

Study Design and Setting

A multicenter, retrospective and case control study was conducted, in ICUs of two hospitals in Curitiba, Brazil: Hospital Santa Casa de Curitiba (philanthropic hospital, reference in chest pain, kidney and heart transplant, with 249 beds - of which 48 are ICU beds) and Instituto de Medicina (private hospital, reopened by the town hall as a field hospital for COVID-19 patients, with 100 beds - of which 60 are ICU beds) from March 2020 to January 2022.

Case group consisted of patients with severe COVID-19 and positive blood culture for any *Candida* during their hospitalization in ICU. These patients were paired with a second group (control group) also with severe COVID-19 hospitalized in ICU but without candidemia and any microbiological culture positive. Controls were randomly selected from the same period of admission as cases in a 2:1 ratio. The COVID-19 infection was confirmed by positive Real-Time reverse transcriptase Polymerase Chain Reaction (RT-PCR) for SARS-CoV-2 via a nasopharyngeal swab. Patients were considered to have severe or critical COVID-19 if the oxygen saturation was (SpO2) ≤94% on room air, or requiring supplemental oxygen, or requiring mechanical ventilation, or requiring extracorporeal membrane oxygenation [14].

The WHO Clinical Progression Scale was used to measure the COVID-19 severity of each patient on the ICU admission: "0 (not infected); 1-3 (Ambulatorial Mild Disease); 4-5 Hospitalized Moderated Disease; 6 - 9 Severe Disease; 10 - Dead" [15]. Candidemia was defined as one or more positive blood cultures for *Candida spp,* which were performed using BACTEC FX (Becton, Dickinson and Co., Franklin Lakes, NJ) Blood Culture Systems. All isolates were then cultured on Chocolate Agar followed by Sabouraud dextrose agar for 24-48 h at 37 °C. Candida species were isolated and identified with Matrix-assisted laser desorption ionization–time of flight mass spectrometry (MALDI TOF-MS) as well as using automated VITEK 2 YST (BioMérieux, Lyon, France) panels according to the manufacturer's instructions.

Patient data was extracted from an electronic medical record and compiled into a data collection form:

- Epidemiological data: gender, age, weight, and body mass index (BMI);
- Signs and symptoms: cough, asthenia, fever, myalgia, coryza, dyspnoea, anosmia, nausea, vomiting, diarrhea, headache and chest pain.
- Comorbidities: systemic arterial hypertension, diabetes mellitus, obesity, dyslipidemia, HIV, cancer, hypothyroidism, neurological disease, chronic kidney injury, obstructive pulmonary disease, use of immunosuppressive or chemotherapy drug and transplant.
- Risk factors for invasive fungal disease: gastrointestinal surgery, length of ICU stay, use of invasive devices in the ICU (central venous catheter, mechanical ventilation, indwelling urinary catheter), length of fasting, vasoactive drug, neuromuscular blocker, antibiotics, tocilizumab, corticosteroids, parenteral nutrition and hemodialysis.
- Microbiological cultures (urine culture, blood culture, respiratory culture) during hospitalization at ICU.
- Laboratorial exams: total leukocyte count, number of lymphocytes, reactive C protein, creatinine, urea, total bilirubin at ICU admission and at candidemia diagnosis.
- Radiologic exams: chest X ray or computed tomography scan at ICU admission and at candidemia diagnosis.

The present study was approved by the ethics and research committee of Irmandade Santa Casa de Curitiba (Protocol: 5.134.404;CAAE: 53317521.2.0000.0020).

Data Analysis

It compared all severe COVID-19 patients with candidemia (cases) with the control group. The possible association of demographic and clinical variables with each dependent variable was initially tested in a bivariate analysis calculating the ratios of chance and the confidence interval of 95% for each variable. The variables potentially associated with the development of each dependent variable of the bivariate analysis ($p < 0,10$) were included in a multivariate logistic regression to determine the odds ratio (OR) adjusted. Statistical analyses were performed using EPI Info 7

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Software (version 7.2.4, Centers for Disease Control and Prevention, Atlanta, EUA). P-values <0.05 were considered to be statistically significant.

Results

We identified 81 patients with severe COVID-19, of whom 27 were cases "with hemoculture positive for *Candida"* and 54 controls. Among the analyzed data, complementary exams, clinical information and treatment measures implemented, the risk factors associated with the co-existence of candidemia and COVID-19, in the bivariate analysis were: time of use of urinary catheter; time of use of central venous catheter; time of use of vasoactive drug; time between the start of the symptoms and the hospital admission; time hospitalized in ICU; time of use of neuromuscular blocker; use of antibiotics; time of use of antibiotics; number

Table 1: Factors potentially associated with acquiring candidemia in patients with severe COVID-19 admitted to intensive care units of 2 hospitals (Curitiba, Brazil. March 2020-January 2022).

Characteristics	Cases	Controls	Bivariate analysis	P*	Multivariate analysis	P*
	n=27	n=54	Odds Ratio		Odds Ratio	
			(95%CI)		(95%CI)	
Age, Years mean (SD)	62.2 (14,8)	63.0 (14,0)		0.81		
Gender - N (%)						
Female	13 (48)	25 (46)	0.92 (0.36 - 2.34)	0.87		
Male	14 (52)	29 (54)				
Hospital of admission - N (%)						
Santa Casa	7 (26)	14 (26)	1 (0.34 - 2.8)	1		
Instituto de Medicina	20 (74)	40 (74)				
Signs and symptoms on hospital admission – N (%)						
Cough	9 (33)	19 (35)	0.92 (0.34 - 2.4)	0.86		
Fatigue	7 (25)	8 (14)	2.01 (0.64 - 6.3)	0.23		
Fever ≥ 37,8ºC	5 (18)	10 (18)	1.00 (0.30 - 3.2)	1		
Myalgia	3 (11)	7 (12)	0.83 (0.19 - 3.5)	0.81		
Coryza	1 (3)	0 (0)	6.16 (0.24 - 156)	0.27		
Dyspnoea	14 (51)	30 (55)	0.86 (0.34 - 2.1)	0.75		
Anosmia	2 (7)	5 (9)	0.78 (0.14 - 4.3)	0.78		
Dysgeusia	3 (11)	2 (3)	3.25(0.50 - 20.7)	0.21		
Nausea or vomiting	0 (0)	2 (3)	0.38 (0.01 - 8.2)	0.53		
Diarrhea	2 (7)	1 (1)	4.24 (0.36 - 48.9)	0.24		
Headache	2 (7)	3 (5)	1.36 (0.21 - 8.6)	0.74		
Dermatological change	0 (0)	0 (0)	1.98 (0.03 - 102)	0.73		
Chest pain	0 (0)	1 (1)	0.64 (0.02 - 16.4)	0.79		
Comorbidities - N (%)						
Hypertension	18 (66)	29 (54)	1.72 (0.65 - 4.5)	0.26		
Diabetes	10 (37)	25 (46)	0.68 (0.26 - 1.7)	0.42		
Obesity	2 (7.4)	12 (22)	0.28 (0.05 - 1.3)	0.11		
Dyslipidemia	4 (15)	3 (5.5)	2.66 (0.55 - 12.9)	0.22		
HIV	1 (3.7)	2 (3.7)	1.0 (0.08 - 11.5)	1		
Cancer	2 (7.4)	2 (3.7)	2.08 (0.27 - 15.6)	0.47		
Hypothyroidism	1 (3.7)	8 (15)	0.25 (0.03 - 2.1)	0.21		
Neurological impairment	2 (7.4)	1 (1.8)	4.24 (0.36 - 48.9)	0.24		
Chronic kidney disease	1 (3.7)	1 (1.8)	2.03 (0.12 - 33.9)	0.61		

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Chronic obstructive lung disease	1 (3.7)	5 (9.2)	0.37 (0.04 - 3.3)	0.38		
Asthma	0 (0)	4 (7.4)	0.20 (0.01 - 3.9)	0.29		
Use of Immunosuppressant	1 (3.7)	1 (1.8)	2.03 (0.12 - 33.9)	0.61		
Use of Chemotherapy	0 (0)	0 (0)	1.98 (0.03 - 102)	0.73		
Prior Transplant	1 (3.7)	0 (0)	6.05 (0.23 - 153)	0.27		
Transplant in Hospitalization	0 (0)	0 (0)	1.98 (0.03 - 102)	0.73		
Treatment and outcomes						
Surgery N (%)	3 (11)	5 (9)	1.22 (0.27-5.5)	0.79		
IUC N (%)	27 (100)	45 (83)	4.90 (0.25-94.4)	0.29		
Days of IUC (Mean, SD)	9 (6.3)	6 (4.7)		0.018		
CVC N (%)	27 (100)	48 (89)	7.37 (0.39-135)	0.17		
Days of CVC (Mean, SD)	8 (6.3)	5 (4.2)		0.013		
MV N (%)	26 (96)	52 (96)	1.00 (0.08-11.5)	1		
Days of MV (Mean, SD)	8 (6.6)	7 (3.9)		0.39		
Fasting N (%)	4 (15)	10 (18)	0.76 (0.21-2.7)	0.67		
Days of fasting (Mean, SD)	1 (0.5)	1 (0.7)		1		
Use of vasoactive drug N (%)	27 (100)	50 (92)	4.90 (0.25-94.4)	0.29		
Days of vasoactive drug (Mean, SD)	7 (4.2)	5 (3.8)		0.035		
Use of NMB N (%)	25 (93)	46 (85)	2.17 (0.42- 11)	0.34		
Days of NMB (Mean, SD)	7.9 (6.8)	4.8 (2.8)		0.005		
Use of Antibiotics N (%)	26 (96)	43 (79)	6.6 (0.81 -54)	0.07		
Number of ATB (Mean,SD)	3.4 (1.8)	2.0 (1.5)		0.004	1.78(1.06-3.0)	0.02
Days of ATB (Mean,SD)	7 (4.3)	3.9 (3.6)		0.001		
Use of Tocilizumab - N (%)	0	0				
Use of CTC - N (%)	26 (96)	49 (91)	2.65 (0.29 - 23)	0.38		
Days of CTC (Mean,SD)	9.5 (5.7)	6.1 (3.2)		0.0009		
Use of parenteral nutrition	0	0				
Dialysis - N (%)	12 (44)	9 (17)	4 (1.40 - 11.35)	0.009		
Number of dialysis sections (Mean, SD)	2.75 (2.2)	3.1 (2.5)		0.52		
Days Between Admission and Hospitalization in ICU (Mean, SD)	0.88 (1.5)	0.54 (1.5)		0.34		
Days Hospitalization in ICU (Mean, SD)	17 (13.2)	7 (4.8)		< 0.0001	1.31(1.08-1.6)	0.006
WHO scale on admission – Mean (SD)	6.9 (1.5)	7.5 (1.4)		0.06		
Death -N (%)	25 (93%)	47 (87%)	1.86 (0.35- 9.6)	0.45		
Laboratory test results on admission to the ICU - Mean (SD)						
Lymphocytes	1,158 (982.4)	1,028 -652.5		0.48		
Platelets	245,370 (91886.3)	223,615 (96813.5)		0.42		
CRP	199.1 (126.4)	159.6 (107.2)		0.16		
Creatinine	1.8 (1.4)	1.98 (1.5)		0.65		
Urea	92.9 (64.0)	92 (75.7)		0.96		
Total Bilirubin	0.8 (0.6)	0.69 (0.5)		0.45		

ATB: antibiotic; CI: confidence interval; CRP: c reactive protein; CTC: corticosteroids; CVC: central venous catheter; HAI: healthcare-associated infections; ICU: intensive care unit; IUC: indwelling urinary catheter; MV: mechanical ventilation; N: number; NMB: neuromuscular blockade; OR: odds ratio; SD: standard deviation; SpO2: oxygen saturation; WHO: World Health Organization.

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of antibiotics used; dialysis; WHO Clinical Progression Scale (Table 1).

In the multivariate analysis, the variables that significantly increased the risk of candidemia in patients admitted due to COVID-19 were: time of hospitalization at ICU (OR = 1.31; IC 95% 1.08 - 1.60; p = 0.006) and number of antibiotics used (increased in almost 80% this risk - OR = 1.78; IC 95% 1.06 - 3.0; p = 0.02) In-hospital mortality was higher in the cases compared with the controls, but statistically non-significant (93% vs 87% OR = 1.86; IC 95% 0.35-9.6; p =0.45). *Candida albicans* was the most frequently fungus identified (44%; 12/27), followed by *Candida glabrata* (19%; 5/27), *Candida tropicalis* (15%, 4/27), *Candida kefyr* and *Candida parapsilosis* each one with 7% of the cases (2/27) and *Candida dubliniensis* and *Candida lusitaniae*, both with 4% of the cases (1/27). Infective endocarditis and endophthalmitis were not encountered.

Discussion

In the present control case study composed by 81 adult patients with severe COVID-19 hospitalized in ICU of 2 reference hospitals of Curitiba, the authors verified that the independent factors associated with candidemia were the number of antibiotics used and the time of hospitalization at ICU. These risk factors seem not to be different from patients with candidemia without COVID-19 [2,8,16], such as extended hospitalization in ICU, central venous catheters, wide spectrum antibiotics, immunosuppression and dialysis. It is still imprecise whether COVID-19 corresponds to a significant risk factor to the patient and a predisposition to a posterior fungal infection [10,17].

There, among these risk factors, the only changeable risk factor was the use of antimicrobials, which can be improved by strong antimicrobial stewardship, which can implement systems for the safe and proper prescribing and use of antimicrobials, since there were advances in the prevention, diagnosis and therapeutic tools for COVID-19 and, at this moment it is known that co-infection is low in these patients, ranging from 3.5 to 11% [18,19]. Especially on the first and second wave of COVID-19, the therapeutic options available were scarce and the physiopathology of this disease was not fully understood. Thus, due to the severity of patients specifically with moderate to severe ARDS, for most of them, above 75% [20], antimicrobials were prescribed. Many hospitals also had not dedicated professionals to antimicrobial control as a result of the scarcity of specialized professionals in this area or by displacement of these professionals to care for hospitalized patients [20,21,22].

Antibiotic use can have several negative effects on the gut microbiota, including reduced species diversity, that favors the multiplication of yeast, due to elimination of native microbiota, which establishes an ecological control of candida species present in the digestive tract, preventing invasion or overgrowth of these fungus [6]. Our findings were similar to Kayaaslan et al (2021) and Nucci et al (2021). Beyond the use abusive of antimicrobials, is worth highlighting that the SARS-COV-2 infection can lead to the rupture of the intestinal mucosal barrier, facilitating the translocations of *Candida spp.* from the intestinal lumen to the bloodstream, which can be an additional risk factor to candidemia [4]. Although Sars-COV-2 leads to immunological dysfunction and hypercytokinemia there is no evidence of an essential defect in the immune cells that are intrinsically necessary to Candida immunity following this [2]. Another independent factor associated with candidemia was the length of stay in the ICU before the diagnosis of candidemia. Several studies point to the influence of prolonged ICU stay as one of the risk factors for the development of invasive candidiasis [23], which has also been related to severe ICU patients with COVID-19 [2,9,10,13,17,24,25].

Only a few studies have showed at the interval between ICU admission and diagnosis of COVID-19-associated candidemia [3,8,10,25,26,27,28]. It was observed that at 10, 20 and 30 days of ICU admission, the percentage of candidemia diagnosis in patients with COVID-19 was respectively 6%, 26% and 50%, with a mean of 12 days from ICU admission to diagnosis of candidemia [28]. Bishburg et al (2021) observed an mean of 26 days for the first yeast isolation. In the present study, the mean time between admission to the ICU and the diagnosis of candidemia was significantly longer in the group with candidemia compared to the control without candidemia (17 days vs 7 days), similar to the mean of 16 days for the first yeast isolation reported by Beştepe et al (2022). Macauley and Epelbaum (2021) noted an mean of 19 days in the ICU for the diagnosis of candidemia in a group with COVID-19, suggesting that a longer ICU stay before the development of candidemia may indicate a phenomenon later in the course of critical illness in patients with COVID-19. According to Kayaaslan et al (2021), when candidemia develops early, it may be due to premature and high use of corticoids in patients admitted to the wards before admission to the ICUs.

The correlation between length of ICU stay and candidemia can occur due to deteriorating immune system and a combination of factors associated with prolonged stays at ICU [12,29]. These patients have increased risk of medical interventions, such as mechanical ventilation, central intravenous catheters, indwelling bladder cateter and parenteral nutrition [10,29]. *Candida spp*. often forms biofilms on these devices, acting as physical barriers to protect them from fragile host immune defenses due to COVID-19 as well as antifungal therapy [29,30,31]. Lastly, evidence shows that severe COVID-19 and candidemia are complex infections and when associated can elevate the mortality rate [3,4,7,8]. It was observed in our study, that the

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case group had a higher mortality rate (92%) than the control group (87%), although it was not statistically significant, similar to the findings from Mina et al (2022), but in contrast to the findings of Dixit et al (2022), who found a statistical difference in mortality between patients with COVID-19 and without candidemia (68% vs 40%; $p < 0.01$). For these authors, it could have occurred because these patients with candidemia required ICU admission, tocilizumab, antibiotics, paralytic infusions, renal replacement therapy, and central lines more frequently prior to developing candidemia than patients without candidemia.

The strengths of this study are the multicenter design and originality in the theme, since the topic is scarce in the literature. Among the limitations of this research we have a small sample size despite the inclusion of all patients with severe covid-19 in the ICU for almost two years and its retrospective character due to imprecise or incomplete data from medical charts.

Conclusion

In this work, the independent factors associated with candidemia were the number of antibiotics used and the time of hospitalization at ICU. Among those risk factors the one that can be changed is the antibiotic control by an effective antimicrobial stewardship, which can decrease preventable infections, such as candidemia.

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Authors' Contributions

Viviane de Macedo - designed and reviewed the study

Ana Carolina do Rocio da Trindade Areco - designed the study, performed data collection, cured the data, writing and editing the manuscript.

Elizabeth Amann Simões - performed data collection,cured the data, writing and editing the manuscript.

Liete Antosz Lopes Maia - performed data collection,cured the data, writing and editing the manuscript.

Nayane Hiba Fuga - performed data collection,cured the data, writing and editing the manuscript.

Nicolle Gabriela de Oliveira - performed data collection,cured the data, writing and editing the manuscript.

All the authors read and approved the final version of the manuscript.

Conflict of interests

The authors declare that they have no conflicts of interest.

Financial Disclosure

No financial interests related to the material of this manuscript have been declared.

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