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CANDIDEMIA POR *Candida glabrata*: REVISÃO DE LITERATURA

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RESUMO

Candidemia descreve a presença de espécies de *Candida* na corrente sanguínea. É a manifestação mais comum de candidíase invasiva e é uma das principais causas de morbimortalidade. Sua incidência vem aumentando devido à crescente complexidade dos pacientes, decorrentes de procedimentos como transplantes, cirurgias de grande porte, imunossuprimidos, uso de antibióticos de amplo espectro e tratamento com imunossuppressores. As infecções causadas por espécies de *Candida* são um problema de alto impacto na saúde pública devido à sua ou alta incidência em pacientes hospitalizados, acarretando aumento de custo e tempo de internação. Embora *Candida albicans* continue a ser a espécie mais frequentemente isolada, diferenças geográficas estão surgindo na epidemiologia entre diferentes países, demonstrando uma mudança para espécies não-*albicans*, incluindo *Candida glabrata*. Esta levedura apresenta característica de elevada resistência aos azólicos, frequentemente utilizados na profilaxia e tratamento de infecções de corrente sanguínea. Este artigo é uma revisão de literatura dos últimos 20 anos sobre candidemia causada por *Candida glabrata*.

Palavras-chave: Candidemia, *Candida glabrata*, *Candida* spp., Resistência aos antifúngicos.

ABSTRACT

Candidemia describes the presence of *Candida* species in the bloodstream. It is the most common manifestation of invasive candidiasis and is a major cause of morbidity and mortality. Its incidence has been increasing due to the increasing complexity of patients, resulting from procedures such as transplants, major surgeries, immunosuppressed, use of broad spectrum antibiotics and treatment with immunosuppressants. Infections caused by *Candida* species are a problem of high impact on public health due to their or high incidence in hospitalized patients, resulting in increased costs and length of stay. Although *Candida albicans* remains the most frequently isolated species, geographical differences are emerging in epidemiology between different countries, demonstrating a shift to non-albicans species, including *Candida glabrata*. This yeast has a characteristic of high resistance to azoles, frequently used in the prophylaxis and treatment of bloodstream infections. This article is a literature review of the past 20 years on candidemia caused by *Candida glabrata*.

Keywords: Candidemia, *Candida glabrata*, *Candida* species, Antifungal resistance.

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1 INTRODUÇÃO

A primeira documentação de leveduras do gênero *Candida* spp. como patógeno é atribuída a Langenbeck, que em 1839 observou e isolou, da cavidade oral de um paciente com afta bucal, um microrganismo, que atualmente é a mais importante levedura patogênica do homem, a *Candida albicans* [1]. O gênero *Candida* é o principal entre as leveduras patogênicas, compreendendo aproximadamente 200 espécies [2]

Candida spp é um microrganismo amplamente distribuído no ambiente [3], que na presença de fatores predisponentes para o desenvolvimento de doença, tais como: desnutrição, obesidade, diabetes, gravidez, antibioticoterapia, quimioterapia e uso de corticosteroides, tratamento intravenoso inadequado, neoplasias e outras doenças debilitantes pode se manifestar de forma grave [4].

É um microrganismo comensal, que habita primariamente o trato gastrointestinal, fazendo parte também da microbiota vaginal, da uretra e dos pulmões. A incidência é muito variável, desde porcentagens baixas nos indivíduos considerados normais, até índices superiores a 50%, dependendo do estado de saúde do paciente, alimentação e meio socioeconômico em que vive [5, 6].

Entretanto, essas mesmas leveduras podem se tornar patogênicas, caso ocorra um desequilíbrio em sua relação com o hospedeiro, por isso são consideradas oportunistas. Essa transformação pode ser devido ao comprometimento dos mecanismos de defesa do hospedeiro (extremos de idade, doença de base, imunossupressão) ou rompimento das barreiras anatômicas, como queimaduras, cateteres ou cirurgias invasivas [7].

Muitas das infecções fúngicas são de origem endógena e outras podem ser adquiridas por fonte exógena, além de apresentarem um alto custo hospitalar por prolongar o tempo de internação do paciente [8].

O gênero *Candida* produz diversos fatores de virulência, como proteinases, lipases, formação de biofilmes que contribuem para invasão do hospedeiro. As infecções são provavelmente iniciadas por modificações de defesas do hospedeiro que alteram a relação com o fungo [9].

Uma série de fatores têm sido implicados no aumento da ocorrência de doenças fúngicas, mas é geralmente aceito que o uso aumentado e generalizado de certas práticas médicas, como terapias imunossupressoras, procedimentos cirúrgicos invasivos e uso de antibióticos de amplo espectro tem papel significativo [10].

A candidíase invasiva está relacionada a diversos fatores que comprometem as condições do paciente, como neutropenia, transplantes de órgãos, colonização prévia por espécies de *Candida*, uso prolongado de antibióticos, presença de cateteres para alimentação nasogástrica, uso de sondas urinárias ou parenterais para hemodiálise ou ventilação mecânica, neoplasia, doenças imunossupressoras, drogas e cirurgias gastrointestinais [8].

O termo candidemia descreve a presença de espécies de *Candida* no sangue. Candidemia é a manifestação mais comum de candidíase invasiva. *Candida* em uma hemocultura nunca deve ser vista como um contaminante e deve sempre levar a uma busca pela fonte de infecção da corrente sanguínea [11].

Embora *C. albicans* continue a ser a espécie mais frequentemente isolada, diferenças geográficas estão influenciando na distribuição epidemiológica das diferentes espécies entre os países, demonstrando uma mudança na prevalência para espécies não-*albicans*, entre elas, *C. glabrata* [12].

As infecções por *Candida* spp são um problema de alto impacto na saúde pública devido a sua ampla incidência em pacientes hospitalizados. Um estudo demonstrou que *C. glabrata* foi responsável por 6,4% do total de infecções causadas por *Candida* spp em pacientes hospitalizados [8].

O uso intensivo de antifúngicos em ambiente hospitalar desencadeou um aumento nas infecções fúngicas que ocorrem em pacientes hospitalizados. Sabe-se que, especificamente no caso de *C. glabrata*, a exposição prévia a azólicos é decisiva para a proliferação desta espécie [13].

C. glabrata aumentou significativamente como agente de infecções em seres humanos, chegando a ser o segundo ou terceiro patógeno em casos de candidíases, principalmente em ambientes hospitalares. Comparando-se a mortalidade entre outras espécies de *Candida* não-*albicans*, a da *C. glabrata* é relativamente alta. Mais especificamente a mortalidade é em torno de 50% em pacientes com câncer e 100% quando em complicações de transplante de medula óssea [14].

O interesse por *C. glabrata* reside no fato de ser considerada um patógeno emergente, com a particularidade de que um número considerável de cepas pode ser resistente *in vitro* aos antifúngicos triazólicos [15]. Além disso, mostrou estar associada a internações hospitalares mais longas com custos mais elevados do que *C. albicans* [6, 16].

Dada a importância do tema, este trabalho apresenta uma revisão sobre candidemia por *Candida glabrata*.

1.1 OBJETIVOS

1.1.1 Objetivo geral

Uma revisão bibliográfica acerca de candidemia por *Candida glabrata*.

1.1.2 Objetivo específico

Elucidar os principais aspectos a respeito de candidemia causadas por *Candida glabrata*, tais como aspectos epidemiológicos, patogenicidade, fatores de virulência e fatores de risco.

2 ARTIGO CIENTÍFICO

CANDIDEMIA BY *Candida glabrata*: LITERATURE REVIEW

ABSTRACT

Candidemia is a bloodstream infection caused by yeasts of the genus *Candida* spp. Candidemia is the most common manifestation of invasive candidiasis and is a major cause of morbidity and mortality, and its incidence has been increasing due to the increasing complexity of patients, mainly immunocompromised. Although *Candida albicans* remains the most frequently isolated species, geographical differences are emerging in epidemiology between different countries, demonstrating a shift to non-*albicans* species, including *Candida glabrata*. The high resistance to traditional antifungal therapies results in a low therapeutic response and several recurrent candidiasis, mainly due to the capacity of biofilm formation. The interest in this yeast lies in the fact that it is considered an emerging pathogen, with the particularity that a considerable number of strains can be resistant *in vitro* to triazole antifungals. This article reviews candidemia and invasive candidiasis by *Candida glabrata*.

Keywords: Candidemia, *Candida glabrata*, *Candida* species, emergent fungal pathogen.

INTRODUCTION

The term candidemia describes the presence of *Candida* species in the blood. Candidemia is the most common manifestations of invasive candidiasis. *Candida* in a blood culture should never be viewed as a contaminant and should always prompt a search for the source of the bloodstream infection.¹

Infections by *Candida* species are a problem of high impact on public health due to their wide incidence in hospitalized patients.² Although *Candida albicans* remains the most frequently isolated species, geographical differences are emerging in epidemiology between different countries, demonstrating a shift to non-*albicans* species, among them, *Candida glabrata*.³

The interest in this yeast lies in the fact that it is considered a pathogen emerging, with the particularity that a considerable number of strains can be resistant *in vitro* to triazole antifungals.⁴

The increasing incidence of candidemia due to non-*albicans* species and emergence of antifungal resistance, necessitates the formulation of empirical therapy for treatment of patients suffering from candidemia and antifungal prophylaxis for patients at risk of developing the infection. Early and prompt diagnosis, proper treatment and prevention of candidemia pose a major challenge for microbiologists and clinicians worldwide.⁵

Studies conducted in Brazil revealed an increase in the incidence of candidemia due to *C. glabrata*, apparently related to a high level of fluconazole use in hospitals.⁶

The intensive use of antifungals in a hospital setting has triggered an increase in fungal infections that occur in hospitalized patients. It is known that, specifically in the case of *C. glabrata*, previous exposure to azoles is decisive for the proliferation of this species.⁷ Due to the importance of this topic, a review on candidemia and invasive candidiasis by *C. glabrata* is presented in this article.

METHODS

The aim of this review was to list important aspects regarding *Candida glabrata*.

This is a literature review of scientific articles with search at databases: PubMed, SciELO, LILACS and Web of Science, using the following descriptors: *Candida glabrata*, *Candida* species, candidiasis.

As an inclusion criterion, the use of full open access articles, published in Portuguese, Spanish and English was defined.

After selection, according to the inclusion and exclusion criteria, the articles were read and at the end of the review, a total of 41 articles were considered relevant to the study, besides books related to the subject.

Exclusion criteria were articles that were not available in full length and not in line with the study theme.

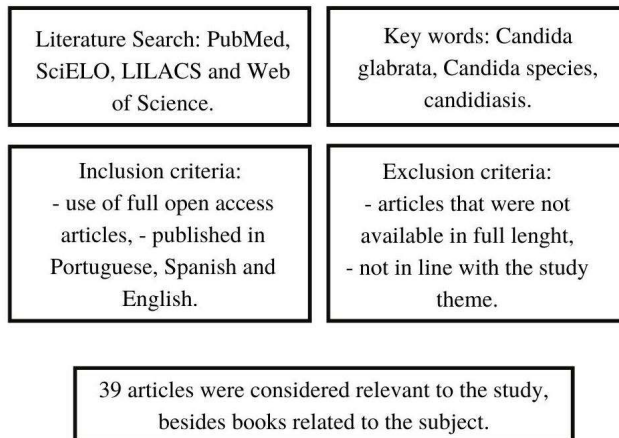


Figure 1. The literature search on *Candida glabrata*.

Epidemiological aspects

Historically, *C. albicans* accounted for 70 to 80% of the isolates recovered from infected patients. However, epidemiological data reveal a mycological shift from *C. albicans* to the non-*albicans* *Candida* spp. such as *C. glabrata*, *C. tropicalis*, *C. parapsilosis*, and *C. krusei*. *C. glabrata* has emerged as an important nosocomial pathogen, yet little is known about its epidemiology.^{8 - 10}

Although the list of *Candida* species cultured from patients with invasive candidiasis and candidemia is increasing, it has been clearly shown that only five species (*C. albicans*, *C. glabrata*, *C. tropicalis*, *C. parapsilosis* and *C. krusei*) account for more than 90% of the isolates.¹¹

C. glabrata has emerged as an important nosocomial pathogen, yet little is known about its epidemiology. Although *C. albicans* is the most common fungal species isolated from blood, *C. glabrata* currently ranks fourth among *Candida* species.⁸

A Spanish study showed that *C. glabrata* was responsible for 9.1% of invasive candidiasis,¹² while a study in Saudi Arabia showed that the most common *Candida* species during the study period was *C. glabrata* (30.1%).¹³

In Brazilian hospitals, *C. albicans* is the most common cause of candidemia, but there has been increased isolation of non-*albicans* *Candida* in recent years, among the most

prominent have been *C. glabrata* and this is important because some *C. glabrata* isolates are resistant to azoles.¹⁴

One study from the environment and health practitioners, a total positivity of 19.65% of *Candida* spp. The most recurring non-*albicans Candida* was *C. glabrata* (37.62%), generally considered a species of low virulence, but with a higher mortality rate than *C. albicans*.¹⁵

C. glabrata has a high incidence in Latin America, when compared to the Northern Hemisphere, reaching 10% in some countries (Brazil) and 2.4% (Venezuela), presenting a wide variety among hospitals, related to the use of prophylaxis with azoles in the institution.¹⁶

In a prospective, multicenter surveillance study showed a low incidence of candidemia in Chile, with high 30-day survival, a large proportion of elderly patients, *C. glabrata* as the third most commonly identified strain, a 6.6% resistance to antifungal agents and a frequent use of echinocandins.¹⁷

One study showed that in Brazil there are substantial differences in candidemia treated in medical centers with different mechanisms of funding, and that *C. glabrata* is an emerging pathogen in private institutions.¹⁸

Another study showed a clear association between increased fluconazole use and an increased incidence of candidemia due to *C. glabrata*, where a relatively higher rate of consumption of fluconazole also exhibited a greater incidence of candidemia due to *C. glabrata*, mainly for use as prophylaxis in transplant patients. Inadequate care of central venous catheters may play an important role for a higher incidence of candidemia.⁶

An epidemiology and microbiologic characterization of nosocomial candidemia from a Brazilian National Surveillance Program showed non-*albicans Candida* accounted for 65.7% of the 137 yeast isolates. *C. albicans* (34.3%), *C. parapsilosis* (24.1%), *C. tropicalis* (15.3%) and *C. glabrata* (10.2%) were the most prevalent species. Data from Colombo *et al* (1999, 2006, 2007, 2012, 2013) has demonstrated the prevalence of *C. glabrata* in Brazil in recent years (Table 1):^{19; 20}

Table 1- Prevalence of *Candida glabrata* in different regions of Brazil.

Variables	Colombo et al, 1999	Colombo et al, 2006	Colombo et al, 2007	Colombo et al, 2012	Colombo (ECMID-2013)
Period	1995-1996	2003-2004	2002-2003	2006-2007	2009-2010
Sites/cases	4/145	11/N=712	4/N=282	9/N=300	9/N=436
<i>C. albicans</i>	37%	41%	38%	34%	39%
<i>C. parapsilosis</i>	25%	20%	23%	33%	22%
<i>C. tropicalis</i>	24%	21%	17%	20%	20%
<i>C. glabrata</i>	4%	5%	3%	7 (13%)*	11%
<i>C. krusei</i>	1%	1%	1%	3%	4%

* Etiologic agent of candidemia in public and private hospitals.

Pathogenicity

C. glabrata has been considered a relatively nonpathogenic saprophyte of the normal flora of healthy individuals, rarely causing serious infection in humans. However, this view has changed, since this specie is now considered an emerging fungal pathogen along with other non-*albicans* *Candida*. The change in the prevalence of specie *albicans*, in addition to the impact on patients' health, since *C. glabrata* is considered the most lethal *Candida* spp. in hosts ever immunocompromised persons, like immunosuppressive therapy for the treatment of cancer, diabetes mellitus has also brought economic impacts on public health.^{8; 21} Higher mortality rates were observed in cases of candidemia due to *C. albicans* (61.1%) and *C. glabrata* (100%) in a tertiary hospital in Northeast Brazil.²²

Candida yeasts are pathogens highlighted mainly in immunocompromised patients, including those undergoing organ transplantations. However, other species such as *C. glabrata*, *C. parapsilosis*, *C. tropicalis* and *C. krusei* have been described as causative agents of candidiasis, some of which are resistant to antifungal agents.²³

The intensive use of antifungals in a hospital setting has triggered an increase in fungal infections that occur in hospitalized patients. It is known that, specifically in the case of *C. glabrata*, previous exposure to azoles is decisive for the proliferation of this species.⁷

The apparent increased non-*albicans Candida* emergence of these human pathogens can be attributed to improved identification methods and also associated with the degree of diseases of the patients, the interventions that they were subjected and the drugs used.¹⁰

From the cutaneous integument, they are more frequently isolated other *Candida* spp. than *C. albicans*. In the vaginal microbiota there is normally found *C. albicans* and *C. glabrata*. The incidence is very variable, from low percentages in individuals considered normal, up to higher rates to 50%, depending on the patient's health status, food and socio-economic environment in which he lives.²⁴

Clinical presentation

Candidiasis or candidosis is a primary or secondary opportunistic mycosis, endogenous or exogenous, where the lesions can vary from superficial to deep; mild, acute or chronic; involving different sites, such as mouth, throat, tongue, skin, scalp, genitalia, fingers, nails and sometimes internal organs.²⁵

Candida infections account for 80% of all fungal infections in the hospital environment, including bloodstream, urinary tract and surgical site infections. Bloodstream infections are now a major challenge for tertiary hospitals worldwide due to their high prevalence and mortality rates in Latin America, data generated from case series documented until 2005 show that the isolation of *C. glabrata* candidemia accounted for no more than 5–8% of all episodes of fungemia in public hospitals.²⁰

Among the genus *Candida*, *C. glabrata* stands out as an agent of invasive fungal infections, especially in elderly patients with cancer admitted to intensive care units and those with previous exposure to fluconazole. For cancer patients, candidemia is associated with a high mortality rate (30%–50%) that results in substantial healthcare costs and prolonged hospital stays.²⁷

A retrospective study conducted in Brazil revealed an increase in the incidence of candidemia due to *C. glabrata*, apparently related to a high level of fluconazole use in hospitals.⁶

The mortality rate due to candidemia is extremely high, ranging from 36% to 63%, depending on the patient population considered. The elderly population, which is increasing worldwide, is particularly vulnerable to *Candida* infections.³

C. glabrata is increasingly isolated from samples clinics as an agent of severe systemic mycoses and candidemia in critically ill patients, immunosuppressed and with hematological or solid neoplasms.²⁸

Virulence factors

C. glabrata displays several virulence factors (adherence, biofilm formation, and secretion of hydrolytic enzymes), swelling their persistence within the host, triggering host cell damage, and, finally, resulting in clinical and microbiological failure.²⁹ These many virulence factors that contribute to its extreme aggressiveness and result in a low therapeutic response and serious recurrent candidiasis, particularly biofilm formation ability.³⁰ For their extraordinary organization, especially regarding the complex structure of the matrix, biofilms are very resistant to antifungal treatments. Thus, new approaches to the treatment of *C. glabrata* biofilms are emerging.³¹

C. glabrata uses a combination of immune evasion and persistence to invade and colonize its host.³² *C. glabrata* is the only species of *Candida* that presents itself only in the blastoconid, and its emergence is associated with survival strategies such as the mechanism of induced phagocytosis. Biofilms, on the other hand, play an important role in emergence of non-*albicans Candida* since these structures, due to their extracellular matrix, have a high resistance to the penetration of drugs.³³ These biofilms can be formed on the host mucosa and/or on surfaces of medical devices and are composed by yeast cells embedded in a complex polymeric structure, which makes them much more resistant to treatments than original planktonic cells.³⁴

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The lack of invasive hyphal forms, secreted proteolytic activity and invasins, and limited nutrient plasticity including non-utilization of haemoglobin as an iron source are likely to contribute to the low pathogenicity of *C. glabrata*.³⁶

Risk factors

A number of factors have been implicated in this increased occurrence of fungal disease, but it is generally accepted that the increased and widespread use of certain medical practices, such as immunosuppressive therapies, invasive surgical procedures and use of broad-spectrum antibiotics are significant.¹⁰ Invasive candidiasis is related to several factors that compromise

patient conditions, such as neutropenia, organ transplantations, previous colonization by *Candida* species, prolonged use of antibiotics, presence of catheters for nasogastric feeding, use of urinary or parenteral probes for hemodialysis or mechanical ventilation, neoplasia, immunosuppressive diseases, drugs, and gastrointestinal surgeries.²

An increasing incidence of fungal infections with *Candida* spp. has been noted in immunocompromised patients, including those in intensive care, postsurgical units and suffering from cancer.²⁷ Immunocompromised patients, including those with serious diseases such as neoplasms, acquired immunodeficiency syndrome, as well as patients undergoing immunosuppressive therapy, whether or not related to organ or bone marrow transplantation, are highly susceptible to invasive fungal infections by *Candida* spp.³⁵

Candida infection affects mainly children and the elderly, at a frequency 5% of newborns, 5% of people with diseases cancer and 10% of healthy elderly patients precarious. Therefore, candidiasis is more frequent in people at the extremes of age.³⁷

In patients admitted to the ICU (intensive care unit) the use of broad-spectrum antimicrobials, intravenous and ureteral catheters, previous surgical procedures, renal failure and parenteral nutrition are the main risk factors for serious infections by *Candida* spp.³⁷

There was a clear association between increased fluconazole use and an increased incidence of candidemia due to *C. glabrata*. A prospective trial evaluating strategies for rational use of fluconazole and the subsequent impact of fluconazole consumption on the distribution of species causing candidemia would be of inestimable value in clarifying these issues.⁶

Despite advances in the medical support of critically ill patients, hematogenous candidiasis is still considered difficult to diagnose, leads to prolonged hospitalization, has a mortality rate of around 50% and is a financial burden to health care systems.¹⁴

Laboratory diagnosis

The traditional gold standard for the diagnosis of candidemia and IC are cultures of blood or other sterile fluids or the histopathological demonstration of invasive tissue disease. Laboratory diagnosis of candidiasis is carried out through blood culture (blood culture), a method that traditionally has low sensitivity for detecting microorganisms present in the circulatory stream.¹¹

Blood cultures are positive in most patients if samples are collected during active candidemia. Use of antibodies, BDG (D-Glucan), commercial multiplex PCR can provide species identification.⁴¹

Therapeutic options

Azole (fluconazole, voriconazole), echinocandins (micafungin) and amphotericin has been used as therapy for the various infections caused by *Candida* spp.^{20; 38}

In infections by *C. glabrata* it is preferable to use an echinocandin.³⁹ The interest in natural products has increased regardless of whether they are associated with other therapies. In addition, other promising strategies such as the use of nanoparticles, antibodies and, more recently, photodynamic inactivation for treating fungal infections have been studied extensively because of their promising therapeutic potential.⁴⁰

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3 CONCLUSÃO E PERSPECTIVAS

C. glabrata é considerada um patógeno importante em infecções de corrente sanguínea, especialmente pela sua elevada resistência aos azólicos.

O uso profilático de antifúngicos e como tratamento de infecções de corrente sanguínea proporcionou um aumento na incidência desta espécie por pressão seletiva.

Novos dados sobre o tratamento e os mecanismos de *C. glabrata* exercer sua patogenicidade devem ser considerados tanto para o desenvolvimento de diretrizes internacionais quanto para o desenvolvimento de normas internas ou adaptação de diretrizes.

Esta revisão evidencia a importância da identificação da espécie envolvida na infecção e a necessidade dos laboratórios desenvolver técnicas que forneçam resultados satisfatórios ao clínico e auxiliem o tratamento e conduta terapêutica frente a estas infecções.

Cabe salientar a importância do acompanhamento da epidemiologia local incluindo o perfil de suscetibilidade aos antifúngicos para monitoramento do perfil de infecções na instituição e condutas juntamente com o Controle de Infecção.

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ANEXO A – NORMAS DE PUBLICAÇÃO DA REVISTA THE BRAZILIAN JOURNAL OF INFECTIOUS DISEASES



THE BRAZILIAN JOURNAL OF INFECTIOUS DISEASES

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AUTHOR INFORMATION PACK

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DESCRIPTION

The Brazilian Journal of Infectious Diseases is the official publication of the Brazilian Society of Infectious Diseases (SBI). It aims to publish relevant articles in the broadest sense on all aspects of microbiology, infectious diseases and immune response to infectious agents.

The *BJID* is a bimonthly publication and one of the most influential journals in its field in Brazil and Latin America with a high impact factor, since its inception it has garnered a growing share of the publishing market.

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