Chapter

Invasive Candidiasis: Epidemiology and Risk Factors

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Abstract

Invasive candidiasis is a severe infection caused by the yeast of the genus *Candida*. This highly lethal infection can affect any organs, but it is usually identified by the growth of the yeast in bloodstream samples. Although *C. albicans* was the most frequently found species, there has been a global trend to the non-albicans isolates. The appearance of *C. auris,* a newly identified species around the world, is a cause of concern because of resistance to antifungals. In this chapter, the epidemiology and risk factors for the acquisition of candidemia and other forms of invasive candidiasis are reviewed, while showing the current knowledge of worldwide epidemiology.

Keywords: *Candida*, *Candida albicans*, invasive, candidiasis, fungemia, candidemia, intensive care units, surgery, immunosuppression, microbiota

1. Introduction

Candidiasis is the common name for diseases produced by the yeast of the genus *Candida*. This is the most frequently found yeast in human microbiome and is capable of causing disease at different sites of the human anatomy and with diverse severity [1]. Invasive candidiasis refers to severe fungal infections in which the yeast might be found in deep organs or blood [2]. Due to the difficulty of identifying *Candida* yeasts in tissues, since it requires a biopsy of the tissue compromised, invasive candidiasis in the literature has been primarily found as bloodstream infections, alone or with accompanying tissue compromise.

2. Microbiology and environment

Candida species are yeasts (i.e., they mainly have a unicellular form). They are small, with a size of 4–6 μm, with a thin wall and an ovoid aspect, named blastospores [3]. They reproduce by budding. Using the microscope, these yeasts can be seen in the form of pseudohyphae, budding cells that do not separate, or truly hyphae (multicellular organisms). *Candida* organisms belong to the class Ascomycetes, order Saccharomycetales, and family Saccharomycetes [4]. There are around 200 species of *Candida;* however, a limited number has a pathogenic effect on humans [4]. **Table 1** shows the most frequently found species. Due to their previous prevalence and pathogenic significance, they were usually classified as *albicans*

Species	Characteristic
C. albicans	Usually the most frequently found
C. parapsilosis complex	*C. parapsilosis, C. orthopsilosis, C. metapsilosis*
C. tropicalis	Related to cancer
C. glabrata	Usually resistant to azoles, seen more frequently in developed scenarios and older patients
C. guilliermondii	Less pathogenicity
C. lusitaniae	Potentially resistant to amphotericin
C. krusei	Intrinsically resistant to azoles
C. dubliniensis	Difficult to differentiate from *C. albicans*
C. auris	Responsible for a global outbreak

Table 1.
Most frequently found Candida *species in human disease.*

versus *non-albicans Candida* species. However, due to changes in epidemiology, this overall classification might not be useful any more.

They grow in agar as colonies with a smooth, creamy, white appearance. The formal identification can be made by use of biochemical physiological reactions, which can differentiate an important number of isolates. The metabolic reactions include carbohydrate fermentation, nitrate use, and urease production.

Candida yeasts might be seen with direct stains like KOH with 10–20% concentrations, but also with others like Gram, Giemsa, Wright para amino-salicylic (PAS) acid, and Papanicolaou. In direct stains, *Candida* might be seen as big aggregates of blastoconidiae, with short and large pseudohyphae. Usual growth media include Sabouraud agar, brain infusion, heart, and yeast extract. While *C. albicans* and *C. dubliniensis* grow in usual Sabouraud agar with antibiotics, some species might be inhibited by cycloheximide [4]. Usual growth time is 2–3 days at 28–37°C. Chromogenic agars were developed more than 20 years ago and are capable of identifying the most commonly found species, and speciation is desirable due to pathogenic and susceptibility differences among them. There are several commercial methods using chromogenic agars. The sensitivity for detection of *Candida* yeast is over 95%, usually with a low number or no false positive results [5]. The finding of a positive culture does not imply an invasive infection, and a special consideration has to be made for isolates from sterile sites.

Candida species differ in their susceptibility to different antifungals available in different countries. Most frequently found isolates of *C. albicans* and *C. parapsilosis* are susceptible to all antifungals available. *C. tropicalis* might have some resistance to fluconazole, while maintaining susceptibility to equinocandins and amphotericin B. *C. glabrata* tends to have higher minimal inhibitory concentrations (MICs) to azoles, while remaining susceptible to equinocandins and amphotericin B. *C. lusitaniae* isolates can be found to be resistant to amphotericin B. The recently found that *C. auris* is frequently found multidrug resistant.

Susceptibility testing can be performed by different methods, including broth microdilution (recommended in the USA and Europe), but there are other different commercial methods available in hospitals. Two slightly different standards for susceptibility testing are currently available. One is suggested by the Clinical Laboratory Standards Institute (CLSI, in USA), while the other is proposed by the European Committee on Antimicrobial Susceptibility Testing (EUCAST), sponsored by the European Society of Clinical Microbiology and Infectious Diseases

(ESCMID). Basic differences between both methodologies include time and instrument to read the results. Different clinical breakpoints have been established for the most commonly found species, with the intention of differentiating the risk of clinical failure after treatment. The experience with fluconazole has allowed to develop better prediction models, in comparison with newer antifungals [6]. In summary, an isolate of *Candida* is exposed to different concentrations of the antifungal and the *in vitro* growth is observed. If there is no important growth, determined optically or by a spectrophotometer, a minimal inhibitory concentration (MIC) is established. As mentioned, data from clinical trials and observation cohorts with common species such as *C. albicans* and *C. glabrata* have allowed to identify clinically relevant breakpoints to differentiate isolates with low MICs (susceptible); intermediate MICs (also called susceptible dose dependent—SDD), in which an increase in the administered antifungal can control the infection; and high MICs, (resistant), for which a lower probability of success is expected. For some other uncommon species, only epidemiological breakpoints are available. These breakpoints are also MICs, but there is no clinical evidence of correlation with the clinical outcome after treatment. However, since MICs are higher than those in usual isolates, a worse outcome might be expected. These breakpoints are expected to identify isolates with natural or acquired mechanisms of antifungal resistance. The epidemiological breakpoints are based on the statistical distribution of MICs of the wild-type isolates (i.e., isolates without any previous resistant pressure). Commercial methods are modifications of the standard methods that use dyes to identify the growth (e.g., Alamar Blue) of the microorganisms. Examples include Sensititre™ and YeastOne™. Other methods are based on agar, in which a gradient of the antifungal is diffused in the solid growth media, which allows to directly read the MIC (e.g., Etest ™) [7].

Candida species are part of the human microbiota and they live in human mucosae and skin. *Candida* species can be found in the ground, animals, fruits and vegetables, and in the hospital environment. It is not considered a laboratory contaminant. It is considered an endogenous pathogen since around 60–75% of the people might have it in the mucosal epithelium, especially in the gastrointestinal and genital tracts [8]. In the hospital area, they have been found over inanimate surfaces, including percutaneous catheters and tubes. They might even be found in the hands of healthcare workers. Among patients in healthcare centers, the colonization of the mucosae has been related to antibiotic use and hospitalization time [9]. In patients in the intensive care unit (ICU), colonization might be found in different anatomical sites with ample variations [10, 11]. Pharyngeal colonization rate has been found to be between 34 and 65%, gastric colonization between 42 and 67%, rectal colonization between 21 and 40%, and colonization in other sites between 11 and 40% [10, 11]. These data show the possibility of colonization that has this microorganism in patients under stress conditions (in this case, severe disease). In the normal host, the colonization rate might reach over 50% in the mouth, 40% in the vaginal tissue in women, and 73% in any mucosa of the gastrointestinal or genital tracts [8].

3. Pathogenesis

Candida species have some characteristics that permit them to adapt to different environments and act as an opportunistic pathogen. These factors include adaptation to pH changes, permitting to survive in blood or some alkaline environments, as well as in the acidic environment of the vaginal tissue; these species have adhesins, mannoproteins with capacity to adhere to different cells and cell products.

These adherence proteins allow the isolates to survive in tissues, but also over inanimate surfaces that have been exposed to plasma or inflammatory host proteins like urinary or endotracheal catheters. *Candida* species have also important enzymes as virulence factors, since some of them have keratinolytic, peptidase, hemolysin, and other effects. One of the most frequently mentioned virulence factors include the possibility of a morphologic transition, which has been extensively studied. It refers to the possibility of morphologic changes of blastoconidia to pseudohyphae to real hyphae. These changes are stimulated by environmental conditions. The filamentous forms are related to active infection in the host, except for *C. glabrata*. Other factors related to pathogenicity or virulence also include a phenotyping change, the possibility of adopting different phenotypes in the cultures (color or aspect of the colonies), and biofilm formation. A biofilm is a large community of symbiotic microorganisms adhered to a surface. This conformation allows the microorganisms to have a highly defensive capacity, persistence, and a highly antimicrobial resistance.

As mentioned before, *Candida* might be part of the human flora. The majority of infections are due to the interplay between the risk factors, that pose a risk to the individual, the interaction with other microorganisms present in the skin or mucosa and the total quantity of microorganisms present. This was demonstrated some years ago in an experiment [12]. An individual ingested directly from a *C. albicans* culture. After some hours, this immunocompetent individual began to have fever. After 12 hours, *Candida* isolates were found in the bloodstream and, after 16 hours, they were found in the urine. After 24 hours, *Candida* isolates were cleared from the body and the individual returned to the normal state. This experiment proved the importance of colonization. With posterior evidence, it has been demonstrated that the first step to have an infection is colonization by *Candida* especially in the gastrointestinal tract, but otherwise in contact with indwelling catheters, the skin, or wounds that may permit the entry of the yeast into the bloodstream. In another critical observation, patients in the ICU were followed with cultures. The colonization index (it is the proportion of positive cultures for the same *Candida* species taken from different anatomical places) increased over time and was correlated to the probability of developing an invasive candidiasis [9]. These studies suggest that in individuals with *Candida* colonization, those factors that promote the grow of the yeast, by eliminating the bacteria that can compete for the environment, that alter or facilitate the penetration of the yeast to the bloodstream (lesions in the gastrointestinal mucosa, indwelling catheters) will promote the entry of *Candida* yeast to the blood, while the net state of compromise of the immune system will affect the probability of fungal clearance and the possibility of seeding on specific organs.

4. Epidemiology

4.1 Risk factors

4.1.1 Candida infection in the intensive care unit

Patients in the ICU have the highest rate of *Candida* infections in the hospital. In comparison with patients in other wards, patients in the ICU have more frequent abdominal surgery, stay longer in the hospital, and are more severely ill [13]. They also have a worse prognosis in the long term, with increased mortality after one year of the event.

4.1.1.1 Vascular devices

Patients in the ICU have higher rates of *Candida* infection in comparison with patients in other wards. Critically ill patients often require multiple vascular and other indwelling devices for their management and candidemia has been related to catheter colonization in 20–80% of the cases [14, 15]. One study in Japan identified the presence of a solid tumor, the use of total parenteral nutrition, and the administration of anti-anaerobic agents as the main risk factors for the development of *Candida* infections [16]. As mentioned, *Candida* colonization of the catheter might provide a route for entering into the bloodstream without a heavy gastrointestinal colonization. Studies have shown that *Candida* catheter-related bloodstream infections have a shorter time to grow in comparison with those from other sources [14]. With a breakpoint of 30 hours, the time to grow in patients with *Candida* bloodstream infection might identify 100% of those catheter-related infection. Probably, patients with catheter-related infection have a higher inoculum, which would explain the faster time to grow and the fact that observational studies have shown a lower mortality when catheter is removed [17, 18]. On the other hand, patients with non-catheter-related candidemia were more seriously ill, had a higher mortality, and the removal of the catheter did not affect the outcome [17].

4.1.1.2 Parenteral nutrition

Another commonly identified risk factor is the use of parenteral nutrition or the length of its use [15, 19]. This group of patients shares several risk factors, but parenteral nutrition has been identified in multivariate analysis [20]. Usually, they have an abdominal procedure (see below) and they require parenteral nutrition for several days. Lack of appropriate measures to handle the nutrition, colonization of the catheter or the ports used to infuse it, and probably the availability of optimal growing conditions are conditions related to its use. But clearly, the use of parenteral nutrition leads to the development of mucosal atrophy and a loss of mucosal epithelial barrier function [21], which might affect the relationship between microorganisms in the gut and the possibility of gaining access to blood vessels. Total parenteral nutrition has also a profound effect in the gastrointestinal microbiome [22].

4.1.1.3 Surgical procedures

Several studies have shown the relationship between candidemia and a previous surgical procedure [19, 23], specially an abdominal surgery. There are several explanations to this observation, but gut manipulation, and the effect of resected sections over the gut microbiology, microbiota abundance, and epithelial function might contribute to the possibility of candidemia. Studies have shown that patients with high anastomotic leak, as well as those with recurrent gastrointestinal perforation, or acute necrotizing pancreatitis, have a higher risk of candidemia [15].

4.1.1.4 Antibiotic use

Almost all studies of candidemia have shown an extremely high use of antibiotics previous to the identification of bloodstream or tissue infection. The proportion of patients with antibiotic use is over 80% [24]. The number and spectrum of the antibiotics used might affect the risk of candidemia. Antimicrobials also have an

effect over gut microbiota, and some studies have shown some impact from antibiotics with anti-anaerobic effect, and those with higher gastrointestinal concentration [25]. They contribute to the observed increased colonization over time observed in patients in the ICU. With more antibiotic effect, there is a net decrease in the number of species in the gastrointestinal tract, an increase in the number of patients colonized, and the proportion of them being heavily colonized [26].

4.1.1.5 Other risk factors

Studies have identified several risk factors that alone, or in combination, might increase the probability of having candidemia. The presence of renal failure, the use of antihistaminic blockers, the severity of illness, and the length of stay in the ICU contribute to colonization and development of candidemia [24, 27]. All these factors contribute to the acquisition of *Candida*, its colonization, or failure in the gastrointestinal epithelial function, favoring the entry of the yeast to the bloodstream.

4.1.1.6 Scores based on risk factors

The identification of risk factors lead to the use of some scores based in the presence of such factors to identify patients with higher risk of *Candida* infection. The first and most simple of those scores was introduced in mid-1990s. Pittet et al. in a surgical ICU followed prospectively patients admitted in the ward with cultures of several anatomical sites [9]. They defined the colonization index as previously stated, establishing that with an index of 0.5 or more (50% of the sites with the same species), there was an increase in the risk of candidemia. With a lower colonization index, the risk in the original study was 0%. They defined a second index based on the density of colonization, in which patients overpassing some thresholds in the number of colonies isolated per site, being able to improve the identification of the patients at risk.

A second score to identify risk factors in patients was developed in Spain by León and his collaborators [20]. They identified colonization (with a different definition from that used by Pittet et al.), surgery at ICU admission, and use of total parenteral nutrition as risk factors independently associated with candidemia. They also identified sepsis as independently related, but this is clearly more a clinical syndrome than a risk factor. A third score was developed by a multicenter collaboration group, in which they again identified the same risk factors [28]: antibiotic use, having an intravascular catheter, in conjunction with at least two additional risk factors such as any surgery, immunosuppressive use, pancreatitis, total parenteral nutrition, dialysis, or steroid use.

Common to these scores has been the presence of the aforementioned risk factors. The problem, however, is that such scores identify a huge number of patients at risk with a final intermediate risk of developing candidemia, in a range from 7 to 30% [29, 30]. The great advantage of the diagnostic scores relies in their high negative predictive value. Patients with a negative score have a low probability of candidemia, below a 1% probability.

4.1.2 Hematological malignancy, solid organ transplantation, and other immunosuppressive states

These disorders share a common factor: immunosuppression. However, different types of immunocompromise entail different risks for the patients. The incidence of candidemia among patients with cancer is higher in comparison with other patients in the hospital. In a multicenter study in Greece, patients with

hematological disease had an incidence of candidemia of 1.4 cases per 1000 admissions, while other patients hospitalized had an incidence of 0.83 cases per 1000 admissions [31]. A multicenter European study found an incidence of 1.2% cases of candidemia among patients with bone marrow transplantation (BMT) and leukemia [32]. An Italian multicenter study from a surveillance network showed a diminishing trend for candidemia among patients with cancer, especially among those with acute myeloid leukemia [33]. Whether this trend can be inferred to other European countries or not is not known, and the most likely explanation for this decrease in the number of cases could be related to the use of prophylaxis among those patients with acute leukemia with posaconazole. In general, non-albicans *Candida* species are more frequently found among these groups of patients [31].

4.1.2.1 Neutropenia

Neutropenia, a count of leukocytes in peripheral blood below 500 cells per μl, is the common risk factor among patients with hematological disorders (i.e., leukemia, lymphoma, multiple myeloma among others) as well as those with bone marrow transplantation (BMT). Neutropenia might be a consequence of the activity of the hematological disease, an effect of chemotherapeutic strategies or side effect of multiple medications including antimicrobials. It also is a marker of the intensity of chemotherapy. Patients with chemotherapy-induced neutropenia accumulate various risk factors: they usually receive wide spectrum antibiotics for several days, they have serious gastrointestinal epithelial tissue dysfunction, usually with diarrhea and signs of mucosal damage, and the use of vascular catheters for the infusion of chemotherapeutic drugs and antibiotics [34]. Several studies have shown that isolates of *C. tropicalis* are more frequently found among patients with cancer [35]. A study that looked for risk factors identified underlying leukemia as one of the major risk factors, together with chronic lung disease [36].

In patients with prolonged neutropenia, a condition called hepatosplenic candidiasis might be seen. In it, seeding of yeasts occurs during the neutropenic phase which might be not clinically evident until neutropenia recovery. In these patients, fever persists and lesions can be seen in the liver, usually known as bull-eye lesions [37] (**Figure 1**).

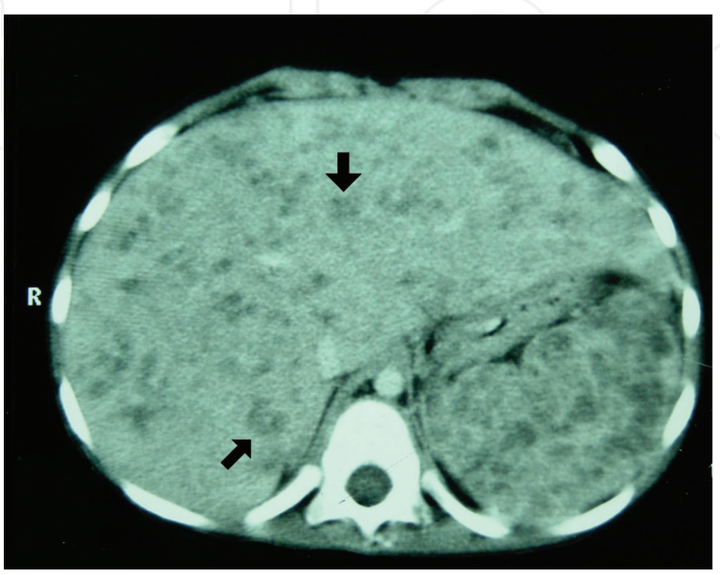

Figure 1.
Tomographic image of liver and spleen showing abscesses (bull's eye, arrows) and hypodense lesions in a patient with chronic disseminated candidiasis. Reproduced with permission from Cortés et al. [37].

4.1.2.2 Concurrent conditions in patients with cancer

In patients with cancer and candidemia, several factors were identified in comparison with those with cancer and bacterial infections [38]. Total parenteral nutrition over 5 days, urinary catheter for more than 2 days, distant metastasis of cancer, and gastrointestinal cancer were independent risk factors. Patients with solid tumors might accumulate factors as patients in critical care, since they have abdominal surgery (gastrointestinal neoplasm), require vascular catheters for extended periods of time (for chemotherapy or antibiotics), total parenteral nutrition and received antibiotics frequently [39]. A study to identify factors predicting catheter-related infections with *Candida* identified solid tumors and the use of anti-anaerobic antibiotics as risk factors [16].

Among patients with leukemia and BMT, the risk factors for occurrence of candidemia included bone marrow or cord blood stem cell source, T-cell depletion, use of total body irradiation, and acute graft versus host disease [32]. These data were derived from a huge multicenter registry of patients with cancer and transplantation, which allowed to identify more precisely the risk factors.

4.1.3 Neonates

Newborns have no gastrointestinal flora at birth and have to be colonized by enterobacteria and other microorganisms, which is made via maternal breast feeding. Any alteration in the normal process can lead to colonization by pathogenic microorganisms, including yeasts [40]. Neonates in the intensive care unit usually have limited breastfeeding, indwelling vascular catheters, total parenteral nutrition, and antibiotics [41]. Such combination of risk factors put. this group of patients at a higer risk of infection, reaching over 10% of patients in units with extreme prematures and low weight at birth (the group that requires more invasive interventions) [42]. Some studies have illustrated this relationship with proportion of candidemia between 3 and 10% among those with a weight of less than 1000 g while showing an incidence of less than 1% for those weighting over 2500 g [43]. In this scenario, disseminated candidemia can be found and near 10% of those with invasive disease can compromise the central nervous system. Another important risk factor includes the time that the patient has been in the unit [44]; clearly, patients with low weight, lower gestational age, and more comorbidity tend to spend more time in the neonatal ICU and to accumulate other risk factors (surgery, indwelling catheter, antibiotics, etc.) [45]. There are some high-risk units, in which the incidence of candidemia traditionally has been high, usually over 10% of the admitted cases. In this scenario, prophylaxis has been suggested for the prevention of infection [46].

4.1.4 Outbreaks

Candida yeast can survive in inanimate surfaces and in the hands of healthcare personnel, which confers the risk of outbreak and cross dissemination among high-risk units such as neonatal, intensive care, and surgical intensive care units [44, 47]. An interesting study in Iceland over a long period of time allowed to confirm the presence of clonal isolates of different *Candida* species among patients in the ICU and other wards [48]. The proportion of patients involved at one time with an outbreak of all patients with *Candida* isolates might be as high as 38%. Other study in Spain showed that clusters (of patients with candidemia) were possible with *C. albicans* and *C. parapsilosis*, and reached in a period as high as 40% of the isolates [49]. Besides, the use of chlorhexidine has been shown to diminish the number of

candidemia events in patients in the ICU, showing the importance of colonization and cross infection among high-risk patients and establishing this recommendation in the guidelines for the prevention of candidemia [50].

As shown, colonization is the preliminary step to infection. Besides, a number of interventions are common to immunosuppressed and critically ill patients including indwelling catheters (urinary and vascular), severity of illness, total parenteral nutrition, etc. These conditions predispose the patients to cross contamination. An outbreak among newborns was demonstrated to be due to poor practices of catheter ports disinfection [51].

A study in China in a cancer institute showed that 21 out of 36 episodes of candidemia were caused by two endemic genotypes [52]. In this study, gastrointestinal cancer and insertion of a nasogastric tube were related to infection. As mentioned before, cancer patients with solid and hematological tumors share several of the risk factors of colonization and infection.

4.2 Global epidemiology

Since 2013, the Leading International Fungal Education (LIFE) portal has facilitated an important effort to know the epidemiology and burden of fungal infections around the world and allowed a better understanding of their epidemiology in different countries [53]. The real incidence of candidemia is difficult to calculate due to differences in the approach. While studies based on hospitals might overestimate the importance of some groups of high-risk patients, they are difficult to compare. Data from population studies might reflect better the real situation, but this kind of information is scarce. Studies have shown ample differences in the incidence in some regions and at specific times [54].

4.2.1 Changing trend for non-albicans Candida

Traditionally, *C. albicans* had been the most frequently isolated species. However, a trend toward non-albicans species has been observed around the world in the last 15 years. In United States, *C. glabrata* has been identified as second in frequency, while *C. parapsilosis* or *C. tropicalis* dispute this place in other regions. **Table 2** shows the proportion of isolates in some studies around the world in the last 10 years [55–59].

Two studies deserve a detailed description. The first one is a multicenter study from the Southeast Asia region, including 25 hospitals from 6 countries: China, Hong Kong, India, Singapore, Taiwan, and Thailand [60]. They found differences between the countries that include the frequency of *C. tropicalis* isolation, being

Area and publication year	*C. albicans* (%)	*C. glabrata* (%)	*C. tropicalis*	*C. parapsilosis*	References
USA 2012	38	29	17	10	[49]
Latin America 2013	37.6	6.3	17.6	26.5	[48]
Spain 2014	45.4	13.4	7.7	24.9	[50]
Asia-Pacific region 2016	20–55	5–22	2–20	8–27	[51]
France 2014	56	18.6	9.3	11.5	[52]

Table 2.
Proportion of Candida *species in selected studies of candidemia around the world.*

more commonly found in hematology-oncology wards and in tropical areas. This study confirmed the observed trend for a lower frequency of *C. albicans* isolates. The other study is the Latin-American surveillance study [55]. It involved patients from 20 centers in 7 seven countries: Argentina, Brazil, Colombia, Chile, Honduras, Mexico, and Venezuela. Important differences were seen among institutions, reflecting difference in healthcare systems, access, population types, and risk factors. However, in these two studies, the incidence of candidemia is higher than in developed countries in Europe and North America. In Latin America, *C. parapsilosis* frequency is over 30% of the isolates while this place is occupied by *C. tropicalis* in the Asian countries.

4.2.2 Epidemiology in Europe and North America

There are data from some population surveillance surveys in Europe and United States. In general, the incidence might be lower than in some other areas of the world. **Table 3** shows the incidence from data from North America and European countries [61–77]. In Europe, the highest incidence has been observed in Hungary, while in North America the highest incidence has been seen in some cities in United States.

4.2.3 Epidemiology in Central and South America and the Caribbean

This region has profound differences in healthcare systems, access to care, and medical technology development. With a transition toward a higher income, a growing number of institutions with capacity to attend cancer patients, and more

Country/region	Publication Year	Incidence (per 100.000 inhabitants)	References
Belgium	2015	5	[54]
Denmark	2008	10.4	[55]
Finland	2010	2.8	[56]
Germany	2015	4.6	[57]
Hungary	2015	11	[58]
Ireland	2015	7.3	[59]
Norway	2018	3.8	[60]
Portugal	2017	2.57	[61]
Romania	2018	6.8	[62]
Russia	2015	8.29	[63]
Serbia	2018	10	[64]
Spain	2015	8.1	[65]
Sweden	2013	4.2	[66]
Ukraine	2015	5.8	[67]
Canada	2017	2.91	[68]
México	2015	8.6	[69]
USA	2015	9.5–14.4	[70]

Table 3.
Estimated incidence of invasive candidiasis or candidemia in countries of the European or North American regions.

Country/region	Publication year	Incidence (per 100,000 inhabitants)	References
Argentina	2018	6.25	[71]
Brazil	2016	14.9	[72]
Chile	2017	5.8	[73]
Colombia	2018	14.7	[74]
Ecuador	2017	7.2	[75]
Guatemala	2017	6.4	[76]
Jamaica	2015	5.8	[77]
Perú	2017	5.8	[78]
Trinidad and Tobago	2015	5.8	[79]
Uruguay	2018	36.5	[80]

Table 4.
Estimated incidence of invasive candidiasis or candidemia in countries of Central and South America and the Caribbean.

complex medical needs, the number of candidemia cases seems to be higher than in developed countries.

Ample information exists about the problem in Brazil, where a number of studies have been carried out in high-complexity hospitals in the main cities of the country [78, 79]. These studies show a higher frequency of invasive candidiasis in comparison with developed countries, an increased isolation of *C. glabrata* for the last period and an important exposition to fluconazole (which might have increased the selection for non-albicans species) [79]. Country-wise estimates for incidence are shown in **Table 4** [80–89].

4.2.4 Epidemiology in Africa and Asia

A multicenter in Asia gathered information from various countries, including nine hospitals from China [60]. The incidence rate among patients hospitalized was 0.38 per 1000 admissions, which is lower than that observed in the Latin-American region with 1.08 cases per 1000 admissions [55]. The estimated incidence of candidemia in countries in Asia is shown in **Table 5** [90–100]. In Asia, the highest incidence has been observed in Pakistan, followed by Qatar and Israel. In China, geographic variations in the causative species and susceptibilities were noted, with increasing isolates resistant to fluconazole [101]. The numbers for the African countries are lacking and for some countries like Algeria, Burkina Faso, Cameroon, Egypt, Malawi, Mozambique, and Tanzania, the estimated incidence is 5.8 cases per 100,000 inhabitants, a standard calculation based on previously reported incidence in other countries [102–108].

4.2.5 Azole resistance epidemiology

Azole-resistant *Candida* isolates have had an increased frequency over the years. Susceptibility changes with the species, and fluconazole use has been related to an increase in the frequency of *C. glabrata* and *C. krusei,* and a low increase in the number of resistant *C. albicans* or *C. tropicalis*. A large multicenter study in French ICUs identified the age and the exposure to antifungals as independent risk factors for resistance [109]. Patients with isolates resistant to fluconazole tended to be older than 15 years and to have been exposed to this drug, while those with

Country/region	Publication year	Incidence (per 100,000 inhabitants)	References
Bangladesh	2017	5	[83]
Israel	2015	11	[84]
Jordan	2018	5.75	[85]
Kazakhstan	2018	4.3	[86]
Korea	2017	4.57	[87]
Malaysia	2018	5.8	[88]
Pakistan	2017	21	[89]
Philippines	2017	2.25	[90]
Qatar	2015	15.4	[91]
Thailand	2015	13.3	[92]
Uzbekistan	2017	5.93	[93]

Table 5.
Estimated incidence of invasive candidiasis or candidemia in countries of Africa and Asia.

equinocandin-resistant isolates were younger and found to have been exposed to equinocandin. In general, risk factors for resistance remain the same as in resistant bacteria: immunosuppression, previous use of antifungals [110, 111]. Other identified risk factors include chronic renal failure and anti-tuberculous treatment. This last one might be due to a medication interaction.

Among patients with cancer, not only are non-albicans *Candida* species more frequently found, but also resistance to azoles has increased. In a study in Greece, resistance to fluconazole among patients with cancer reached 27% [31]. Since azoles have been widely used in the prophylaxis against fungal infections among cancer patients [112, 113], this seems to be a natural consequence of their use. Among patients with cancer, isolates of *C. tropicalis*, *C. glabrata*, and *C. krusei* have increased resistant proportions [35].

4.2.6 Candida auris *global outbreak*

Up to 2009, there was no report on *C. auris*. In that year, a clinical case from Japan was published, and 2 years later three cases of candidemia were identified [114, 115]. During the following years, isolates of *C. auris* were responsible of outbreaks around the world, affecting hospitals in India, Pakistan, South Africa, England, and Venezuela [116–119]. It was detected in the USA in 2013 with growing frequency [120]. A worldwide alarm was raised in 2016 because of two problems related to this species. The first one was the difficulty in proper identification [121]. *C. auris* is most commonly identified as *C. haemulonii* and *Rhodotorula glutinis* by the commercial systems and sometimes as *C. famata*, *C. guilliermondii*, and *C. parapsilosis* [121]. The other problem is the higher frequency of resistance to multiple antifungals, including azoles and amphotericin [122]. Currently, *C. auris* has been isolated in several areas in the USA, continental Europe, and the Caribbean coast of South America, including the islands [123–125], and continue to extend to other areas, where reports are being published. A search for virulence factors in the isolates of *C. auris* has shown some different properties, specially the capacity for biofilm formation [126]. Molecular observations have diverse geographic dissemination caused by unique clades in each geographic region [127].

5. Outcomes

Patients with candidemia and cancer are considered to have higher mortality, but this issue has not been clearly assessed. Older studies showed an attributable mortality around 40%. Although mortality among patients with candidemia or invasive candidiasis is reported usually around 40–50%, they occur in patients with important comorbidity. A recent multicenter analysis showed a crude mortality for patients with candidemia of 53%, while those without candidemia had a mortality of 26% [128]. After adjusting in a propensity score analysis, the crude mortality was 51% for the candidemic patients and 37% for the others and the difference was not statistically significant. The study shows that an increase in mortality might exist for those patients with candidemia, but it is clear that patients with candidemia also have severe comorbidity and some of them can die with candidemia instead of because of it.

Risk factors for mortality among patients with candidemia include ascites, presence of septic shock, ICU admission, concomitant bacterial infection and catheter-related infections [129]. Studies with diverse population have shown that elderly patients have higher mortality [130]. In these patients, a combination of comorbidity, poor clinical situation, and more pathogenic species might contribute to their mortality [131]. A pooled analysis from patients included in randomized clinical trials comparing micafungin and amphotericin B showed differences among geographic regions, severity of disease (measured with Apache score for patients critically ill), and catheter removal [132]. In those with abdominal candidiasis, the lack of control of the source of infection has been related to increased risk of death [133]. Among patients with cancer, risk factor for mortality includes infection by a *C. tropicalis* isolate, a high Charlson index score, neutropenia, and septic shock [35, 134]. One multicenter study identified tachypnea as a risk factor for mortality [135], while others identified respiratory failure and use of non-antifungal medications [39]. Besides, antifungal prophylaxis and remission of the underlying cancer had a protective effect over mortality [135].

The impact of the antifungal treatment in the mortality of patients with candidemia is not entirely clear. There are several constrains to identify the benefits of the antifungal treatment: An important proportion of patients did not receive antifungal treatment despite the identification of a bloodstream infection; of those that receive the treatment, some of them can receive it as empirical treatment, based on the risk factors, clinical condition, while others have an antifungal started upon detection of candidemia. Besides, some of them are infected with a resistant isolate and some do poorly, and an additional antifungal must be started. Although meta-analysis with patient-level data has showed the benefit of equinocandin use (in contrast to azole treatment) [136], neither the cohort data [137], nor the randomized trials have confirmed this finding [138]. There is an additional complication in understanding this relationship; the laboratory breakpoints for identification of susceptible versus resistant isolates have changed over the time, especially for azoles [130]. Among those patients with septic shock, the delay in the administration of the antifungal treatment has been associated with increased mortality.

6. Conclusion

Candidemia is the most frequently found form of invasive candidiasis. The *Candida* species might be found as part of the flora and patients with previous colonization are at risk of developing an infection. They share some common factors

like antibiotic exposure, use of indwelling catheters, parenteral nutrition, and surgery. These factors affect the normal physiology of the gastrointestinal tract or provide access to the bloodstream to yeast in patients with some comorbidities, in critical care or with immunosuppressive states.

Conflict of interest

There is no conflict of interest to declare.

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