Chapter 2

Candidemia

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Abstract

The invasive fungal infections are commonly in the bloodstream and mainly are caused by \textit{Candida} genus yeast, which are significant opportunistic pathogens [1,2]. Although \textit{C. albicans} remains the species more frequent, factors not yet fully understood, it has led to emergence of other species as \textit{C. parapsilosis} and \textit{C. tropicalis} and other uncommon species causing candidemia [3].

This unfavorable clinical condition has been increasingly growing all over the world and what is more aggravating; the mortality rates remain higher especially in critically ill patients [4]. Studies suggest that the incidence of candidaemia in the United States and Europe ≥40% [5], in country Latin America as the Brazil the rate greater than 50% [6]. In this scenario, it is clear that management is still a challenge [2,3,7]. Furthermore the risk factors related include, severe comorbidities and other conditions as prolonged stay hospital more than 72 hours, multiple
invasive medical procedures, chemotherapy, immunosuppressive therapy, catheter use, neutropenia and other conditions [8,9]. In the status of the candidaemia, neutropenia is an important condition, developing the neutrophils key role of phagocytes which inhibiting the germination of Candida yeasts into hyphae and are capable it killer [10].

Certainly for the emergence and the fatal clinical course of candidemia in addition to the risk factors of individuals, yeast strain virulence conditions are strongly connected as, the capacity growth at 37°C, adhesion, biofilm formation, enzymes production and other factors [11].

Thus the results therefore lead to need for more knowledge, and measured for better control and treatment of candidaemia. Generally is considered important in the treatment, the removing the catheter and, antifungal prophylaxis [12,13]. However, it is possible that the etiological agents involved in cases of candidemia, develop resistance to antifungal used for prophylaxis. Thus, clinical monitoring is essential, to avoid complications followed of death [2,14,15].

Although, the isolation of Candida in the blood of patients with candidemia, has sensitivity low, it is not routinely recognized the need of treatment to the yeast until to be identified in culture [8]. The antifungal agents used in the prophylaxis and treatment vary depending on the country. However, fluconazole is commonly used both in the prophylaxis and treatment. Still, in the treatment are used itraconazole, voriconazole, posaconazole, caspofungin, anidulafungin, micafungin, posaconazole flucytosine and amphotericin B. These antifungals feature differences in their mechanisms of action, antifungal properties, antifungal spectra and route of administration [16]. Considering that treatment with antifungal drugs have not shown a complete success, occurring only is partial improvement perhaps a otherwise might be to explore the immunotherapy strategy, it commonly it has not been performed [17].

Epidemiology and Distribution of Candida Species causing Candidemia

Candidemia is generally diagnosed using blood cultures, however many Candida infections are not detected in blood cultures [18]. Given these limitations, the true epidemiology and incidence of invasive candidiasis is imprecise. The incidence of candidemia expressed as cases per 100,000 inhabitants has been reported to range from 1 to 8 cases [19] with attributable mortality of 15–35% for adults and 10–15% for neonates, and the hospitalization cost for each episode is approximately US $40 000 [20].

Differences in the epidemiology of candidemia between is detected different countries, underscoring the need for continuous surveillance to monitor trends in the incidence, species distribution, and antifungal drug susceptibility profiles [21].
The distribution of *Candida* species causing candidemia is variable and notable differences are observed in different hospital units. The frequency of *Candida* species causing candidemia dependent on the predisposing conditions of the patients infected, the antifungal agents they receive, and the local hospital-related factors [22].

The list of *Candida* species causing candidemia is long and continues to expand as a consequence of more precise identification. Though only five species (*C. albicans*, *C. glabrata*, *C. tropicalis*, *C. parapsilosis*, and *C. krusei*) are accounted for 92% of cases of candidemia. *C. albicans* is the most common cause of candidemia worldwide, accounting for 62% of cases [23].

Over the past years, some studies have reported a shift in the etiology of candidemia. *C. albicans* is considered the most common species involved in candidemia cases, however episodes caused by *C. tropicalis*, *C. parapsilosis* species complex, *C. glabrata*, and *C. krusei* have been increasingly reported worldwide [24].

The reasons for the emergence of non-*albicans* *Candida* species are not completely understood, but some medical conditions may consistently impact the risk of developing candidemia due to non-*albicans* *Candida* species. *C. parapsilosis* complex fungemia has been associated with vascular catheters and parenteral nutrition, *C. tropicalis* candidemia is associated with cancer and neutropenia, and *C. krusei* and *C. glabrata* fungemias are associated with previous exposure to azoles [25].

The use of antifungal agents has an impact on the distribution of *Candida* species [26]. Recent exposure to fluconazole promoting infection by *C. glabrata* and *C. krusei* and antifungal therapy with caspofungin affects the distribution of *C. parapsilosis*, *C. glabrata*, and *C. krusei* [27].

Species distribution is highly dependent on the patient’s underlying condition. *C. glabrata* is the most frequently detected species in stem cell recipients; *C. krusei* is also relevant in these patients, probably owing to the widespread use of azoles in this setting, which may promote infection by these two azole-resistant species. However, other patients, such as solid organ recipients, are infected mainly by *C. albicans* and *C. glabrata* [28,29]. *C. albicans* is more frequent in patients aged up to 18 years. Interestingly, the frequency of *C. parapsilosis* decreases with age, whereas *C. glabrata* is more common in the elderly [30].

Considerable differences are found in the proportion of cases caused by *C. glabrata* and *C. parapsilosis*. Studies from Northern Europe and the United States of America reported a high number of cases caused by *C. glabrata* and a low number of cases caused by *C. parapsilosis*. In contrast, reports from Spain and Brazil demonstrated a lower number of cases caused by *C. glabrata* and higher number of cases attributed to *C. parapsilosis*. The explanation
for this finding is unknown, although it may be a consequence of the impact of climate, antifungal policy, or central venous catheter care procedures. The kind of patient also has a considerable influence on the distribution and frequency of Candida spp., regardless of the geographic area [19,30].

In summary, the exposure to antifungals, the underlying disease of patients and geographic location are the main factors affecting the epidemiology of candidemia.

**Immunogenetics of Candidemia**

Systemic infections by Candida spp., especially C. albicans, occur when the host’s immune system is weakened. As discussed above, some factors associated with clinical patient can modify the risk of infection. However, some studies show that not all who are under clinical risk develop Candida infection [31]. Possible genetic variants associated with innate and adaptive mechanisms of host defense are potential targets for the development of preventive and therapeutic strategies.

Host cells presenting antigens, such as macrophages and neutrophils possess pathogen recognition receptors (PRRs), such as Toll-Like Receptors (TLRs), the most important family of these proteins. These receptors recognize several Molecular Patterns Associated Pathogens (PAMPs) such as phospholipomannans by TLR2 and O-linked mannans by TLR4. Another important family of receptors are C-type Lectins (CLRs), as Dectin-1, which recognizes beta-glucan [32,33,34].

This recognition process promotes the transduction of intracellular biochemical signals mediated by kinases which ultimately activate transcription of several genes of pro-inflammatory cytokines important in recruiting phagocytes at the site of infection and inhibiting the proliferation of the pathogen. After phagocytosis, processing and presentation of Candida-specific antigens induces adaptive immune responses Th1 and Th17, releasing IFN-gamma and IL-17, respectively. The activation of Th17 response is considered one of the key events to discriminate between Candida colonization and invasion of mucosal [35,36,37,38].

These and other factors involved in immunopathogenesis of Candida infection, are encoded by genes in the host cells. Genetic variants may be involved to a greater or lesser ability to recognize the pathogen, recruit effector cells produce cytokines and activate the adaptive response [37]. Evidence shows that three single nucleotide polymorphisms (SNPs) in TLR1 gene (4p14) are possibly associated with a decrease in IL-8 and IFN-gamma production and consequently increased susceptibility to candidemia [39].

In addition to TLRs, three new genetic risk factors have been identified in a study that evaluated approximately 200,000 SNPs at 186 loci from 217 cases and 11,920
healthy controls, all of Caucasian descent. Significant association was observed between candidemia and SNPs in the CD58 gene (1p13.1), LCE4A-C1orf68 (1q21.3) and TAGAP (6q25.3). The products of these genes act in major pathways of the immune response and presence of two or more risk alleles of these three genes potentially increases by 19-fold the susceptibility to candidemia [40].

Polymorphisms in some genes encoding inflammatory cytokines were investigated and a possible contribution of genetic variants of IL-10 (1q32.1) for invasive Candida infection was found in a study with 275 patients and 305 controls in China [41].

Further studies of genetic association of these risk factors for candidemia need to be developed independently to validate the results, especially in other populations. The main challenge is the recruitment of a sufficient number of patients to statistically validate the studies.

**Recommendations for the Diagnosis of Candidemia**

Diagnosis of candidemia can be achieved through various procedures, including conventional methods such as blood culture, serological assays for markers as 1-3-d-glucan and mannan, polymerase chain reaction and enzyme-linked immunosorbent assay to detect an antigen produced by Candida isolates.

Blood culture is the best method available for the diagnosis of candidemia; however, its sensitivity is variable and it is a lengthy procedure. This can contribute to increased morbidity and mortality [42]. Time to detection can be influenced by Candida spp and the type of medium used for culture. In the purpose to optimize this method factors as blood volume or size of the inoculum, time to incubation, number and type of cultures bottles and media used should be carefully considered [43,44]. After patients have a confirmed diagnosis of candidemia, Candida isolates should be identified at species level.

Microbiological identification should to observe macro- and micromorphology as colour, shape and topology of the colony. In addition, traditional taxonomy can be achieved by using biochemical tests (assimilation and fermentation of carbon), enzyme assay (urease) and induction of sexual reproduction structure and chlamydospores formation. The maximum temperature of growth also is determined according Barnett et al. [45]. This classical method are time-consuming and is impracticable to include in routine laboratory.

A number of blood culture systems are available, which vary in sensitivity. These include conventional (manual), automated, and lysis-centrifugation methods. The Latin America Invasive Mycosis Network recommends the use of aerobic bottles for the diagnosis of candidemia by automated blood culture systems, as the standard procedure
which should be carried out in every hospital. This is the best culture option for the diagnosis of fungemia due to *Candida* species [46].

**Recommendations summary for detecting hematogenous *Candida* infection**

(Adapted from Reference 46)

1. Blood culture is the gold-standard method for the diagnosis of invasive candidiasis.
2. Aerobic bottles and automated blood culture systems are recommended to achieve optimum sensitivity.
3. Following diagnosis, *Candida* isolates should be identified at species level.

**Recommendations summary for *Candida* species identification**

1. As the minimum requirement, colony micromorphology observation complemented by macromorphology using CHROMagar *Candida* medium.
2. For secondary hospitals, species identification may be determined using one or more of the following methods:
   (a) Colony micromorphology.
   (b) Colony macromorphology (CHROMagar *Candida* medium).
   (c) Biochemical tests.

I. *In-house conventional methods.*

II. *Manual commercial systems with a limited database*

3. For tertiary care hospitals that provide care for transplant patients or treat many hematological and immunocompromised patients, as minimum requirement:
   (a) Micromorphology observation complemented by biochemical tests (API 20C, API 32C, VITEK 2 or MicroScanYeast Identification Panel).
   (b) Molecular methods (PCR and MALDI-TOF MS) in specific situations as emerging pathogens and when investigating outbreaks.

Currently, microbiological diagnosis has been performed by a physic-chemical technique called Matrix Assisted Laser Desorption/Ionisation Time-of-Flight Mass Spectrometry (MALDI-TOF MS) for rapid and reliable yeasts identification. The spectrum generated is analysed as an individual proteomic profile with the molecular mass ranging from 2000 to 20000 Da, where important ribosomal proteins appear, which is an advantage because they can be readily employed as biomarkers. Moreover, MALDI-TOF MS is able to discriminate closely related species, such as *C. glabrata* from *C. bracarensis*, *C. albicans* from *C. dublinskiens*, *C. metapsilosis* and *C. orthopsilosis* from *C. parapsilosis*, *C. neorugosa* and *C. pararugosa* from *C. rugosa*, previously separated only by molecular methods [47].

**Therapeutic Management of Candidemia**

There are currently three main antifungal agents classes used for the treatment of candidemia: polyenes, triazoles and echinocandins. Historically, fluconazole and amphotericin B deoxycholate (D-Amb) have been considered first-line treatment approaches for candidemia [48]. Although, with the growing incidence of resistance among *Candida* non-*C. albicans* species and fluconazole-resistant *C. albicans*, a new drug class, echinocandins, have emerged and in some cases become the preferred first-line option for treatment of critically ill patients suf-
ferring of Candida hematogeneous infection [49].

The choice of the most appropriate antifungal treatment is not an easy process. Some factors have to be considered as the fungal specie suspected or identified, the patient’s risk factors (e.g., age, underlying disease, length and depth of neutropenia) and the expected side effects [50].

Among the polyenes, amphotericin B deoxycholate and amphotericin liposomal formulations have been administered intravenously for candidaemia therapy [51]. Several in vitro studies demonstrated that Candida resistance to this antifungal agent is considered rare [52,53]. Though, the use of D-AmB is related to some important side effects as nephrotoxicity, hypokalemia, and acute infusion-related problems. In order to reduce this nephrotoxicity, there are currently three lipid formulations available: liposomal (L -Amb or AmBisome), amphotericin B lipid complex (Abelcet or ABLC) and amphotericin B colloidal dispersion (ABCD or Amphotec) [54].

Azoles consist in other therapeutic option for hematogeneous candidiasis. Actually, five azole compounds are available for the treatment of invasive fungal disease: itraconazole, fluconazole, voriconazole, posaconazole and ravuconazole. Candidemia therapy is more frequently made with fluconazole or voriconazole [51]. With a favorable side effect profile, both oral and parenteral preparations, and a wide distribution throughout body tissues, fluconazole has become a safe and easy to use option [55]. Randomized studies have reported that the use of prophylactic fluconazole reduced the incidence of invasive disease [56]. However, there is also concern that this procedure may increase the incidence of resistant strains, A reduced sensitivity to fluconazole (“susceptible dose dependent”) is frequently seen in Candida species such as C. glabrata and C. tropicalis [57].

Moreover, in addition to polyenes and azoles, another option for the treatment of invasive candidiasis is echinocandins (represented by micafungin, caspofungin and anidulafungin) that are associated with reduced side effects and mortality [49]. Due to the therapeutic profile and favorable levels of security, the use of echinocandins in critically ill patients has shown a rapid increase and there are guidelines for these drugs as primary treatment for invasive candidiasis, particularly for those patients with prior triazole exposure, and those infected with less susceptible Candida species such as C. glabrata and C. krusei [49]. However, this recent increase in the use of echinocandins has raised fears of the emergence of resistance, but until now this phenomenon remains rare. Studies show a lower susceptibility to these drugs by C. parapsilosis and C. guilliermondii [58,59].

When the Candida infection is probably associated with intravenous lines they should be removed at initiation of antifungal therapy whenever it is possible. If the central venous catheter is retained, the duration of can-
didemia increases (from 3 to 6 days) as does the mortality of patients. However, if the catheter has to be kept in place, patients should be treated with an echinocandin or L-AmB as these antifungal agents have a better minimal inhibitory concentration in biofilms [60].

**Challenges for Control and Prevention**

The published data discussing candidemia cases worldwide scenario are surprising and definitely suggest there has been no decrease in number of affected patients. According to Centers for Disease Control and Prevention (CDC) candidemia is related as a disease of medical progress and the elevated incidence may be justified to more patients living with complications for a longer time, being instrumented more frequently, and receiving more broad-spectrum antibiotics. Also the better reporting of cases cannot exclude that as a cause of the increase.

Based on Eggimann and cols [61] the epidemiology and pathogenesis of invasive candidiasis differ according to the patient’s immune status; the majority of cases in immunocompromised hosts are candidemia, whereas non-candidemic systemic candidiasis accounts for the majority of cases in critically ill patients.

In this context for a consistent discuss about the challenges, it is worth noting that there are three main routes to the occurrence of invasive candidiasis/candidemia: by gastrointestinal mucosa damages; contaminated central venous catheter and by a localized infection focus such as pyelonephritis or others. The infection via gastrointestinal mucosa is probably the most common origin of infection and for this reason some experts are not favorable to the removal of central venous catheter in all patients with candidemia. Thus the risk of candidemia is exceptionally high in patients undergoing recent abdominal surgery or other gastrointestinal events such as gastroduodenal perforation, fistulas, or necrotizing pancreatitis. Unfortunately, this invasive infection presents nonspecific symptoms, which makes it difficult to identify and begin the prophylaxis before the development of candidemia [61,62].

According do Pappas et al. [62] in all cases, candidemia requires treatment with an antifungal agent. Thus the removal of a catheter alone is not the only procedure to guarantee the adequate therapy for candidemia. Several studies have demonstrated that the high mortality rates associated with candidemia is highest in those patients who were not treated with antifungals [61,62,63].

The 2016 Infectious Diseases Society of America (IDSA) guidelines recommend that empiric antifungal therapy be considered in critically ill patients who are at risk for invasive candidiasis and who have persistent fevers and no other known cause of fever; the decision regarding empiric therapy should be based upon clinical assessment of risk factors, surrogate markers for invasive candidiasis (eg, beta-D-glucan) and/or culture data from nonsterile
Empiric therapy should be started as soon as possible in patients with risk factors for invasive candidiasis and signs of septic shock because of the high mortality in this group of patients [62,64].

New insights into risk-based strategies were emphasized by Eggimann et al. [61] as the early empirical treatment currently relies on the positive predictive value of risk assessment strategies, such as (1) colonization index, (2) *Candida* score and (3) predictive rules, which are still under discussion. However, these authors also discuss that the most recent guidelines still score these strategies supported by limited evidence. Nevertheless these strategies are widely used at bedside and have substantially decreased the incidence of invasive candidiasis specially candidemia.

Thus the knowledge of the *Candida* isolated species, sensitivity profile, relationship between the clinical species and characteristics and the average time between the collection and growth from *Candida* species are essential for proper antifungal therapy and institution of preventive measures to minimize the risks and consequences of candidemia.

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