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Epidemiology of candidemia in intensive care units

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Abstract

The incidence of candidemia in the overall population ranges from 1.7 to 10 episodes per 100,000 inhabitants and *Candida* is one of the ten leading causes of bloodstream infections in developed countries. An estimated 33–55% of all episodes of candidemia occur in intensive care units (ICU) and are associated with mortality rates ranging from 5% to 71%. *Candida* fungemia may have an endogenous or an exogenous origin, and in recent years a growing proportion of episodes of candidemia have been caused by *Candida* species other than albicans. The most important independent conditions predisposing to candidemia in ICU patients include prior abdominal surgery, intravascular catheters, acute renal failure, parenteral nutrition, broad-spectrum antibiotics, a prolonged ICU stay, the use of corticosteroids and mucosal colonization with *Candida*. In recent years, several studies have shown that ICU patients with mucosal *Candida* colonization, particularly if multifocal, are at a higher risk for invasive candidiasis, and that colonization selects a population amenable to antifungal prophylaxis or empirical therapy. Candidemia in ICUs is associated with a considerable increase in hospital costs and length of hospital stay.

Keywords: Candidemia; Invasive candidiasis; Invasive fungal infections; Intensive care units

1. Evolution of candidemia in the population in general

Of all bloodstream infections (BSI), yeasts belonging to the genus *Candida* are among the 10 most common microorganisms. In the USA, *Candida* is the fourth most common cause of BSI, and in European studies, *Candida* is the fifth to tenth most common causative pathogen [1–6]. *Candida* caused 2.3% of all episodes of BSI in 93 French hospitals [6]. Data with a population-based denominator are more scarce, but figures available mainly from the USA and Europe [7–12] report an incidence of candidemia ranging from 1.7 to 10 episodes per 100,000 inhabitants. Figure 1 shows the evolution of candidemia over a period of more than 20 years in a single institution in Madrid, and reflects the progressive increase of this condition, both in absolute figures and in the rates per 1000 admitted patients [11].

The main reason for this evolution is the change in the population at risk, with increased survival in patients with severe diseases; more aggressive use of surgery, invasive procedures, and immunosuppression; and also the increased use of broad-spectrum antibacterial agents.

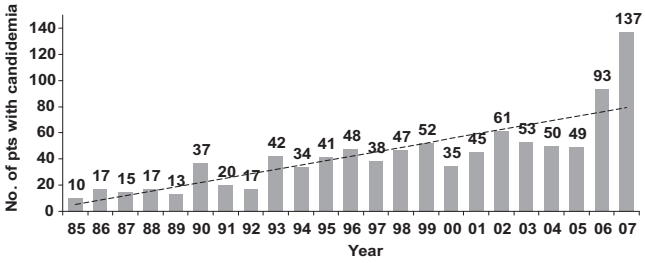

Fig. 1. Evolution of the episodes of candidemia at Hospital Gregorio Marañón, Madrid, 1985–2007.

2. Incidence of candidemia in intensive care units

Candidemia is a serious problem in adult and neonatal intensive care units (ICUs), and an estimated 33–55% of all episodes occur in ICUs [2,8,12–15]. Candidemia occurred in 5.4% of all admitted patients in an ICU in Greece [16] and the mean incidence of candidemia in 24 French ICUs was 6.7/1000 admissions [17].

The mean interval between ICU admission and candidemia was 19.0±2.9 days in a French study [17], and *Candida* BSI have an associated mortality estimated to be 5–71% and attributable mortality of 30–62% [13,17,18]. Figure 2 shows the distribution of candidemia in the various ICUs of our institution over a recent 20-year period.

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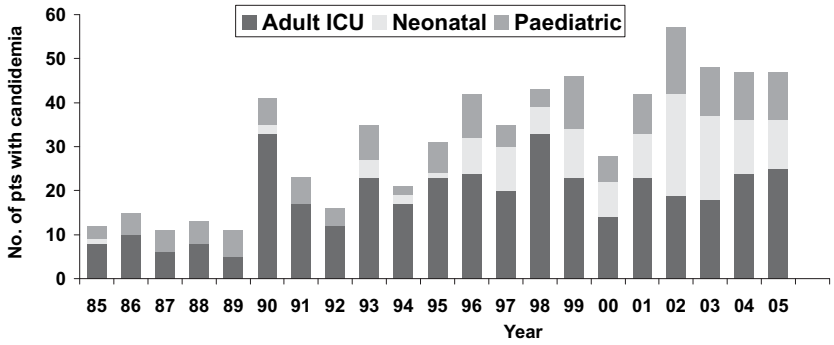

Fig. 2. Distribution of candidemia fungemia over different ICUs at Hospital Gregorio Marañón, Madrid, 1985–2005.

3. Portal of entry and origin of candidemia in ICUs

In most cases, Candidemia has an endogenous origin, being caused by yeasts belonging to the human microflora. In such cases, the intestinal tract is the main portal of entry. This is probably the most common cause in neutropenic patients [19]. In ICUs, the most common origin of candidemia is probably intravascular catheters [20] colonized by the microflora of the patient's own skin or from the skin of the hands of the healthcare workers [21,22].

The proportion of episodes of candidemia in ICUs due to horizontal transmission is still a matter of debate. In a study reported by Bliss et al. [23] mothers and low-birthweight neonates admitted to an ICU were surveyed, and the isolated organisms were compared using DNA fingerprinting techniques. Overall, 76 pairs of mothers and neonates were studied, and 66% of the mothers and 51% of the neonates proved to be colonized. In 11 of the 76 neonates, the strains isolated were identical to those isolated from their mothers.

In an unselected patient population, as many as one-third of all cases of candidemia may be attributable to nosocomial clusters, as demonstrated in a recently published study from Iceland [18]. The majority of those clusters affected patients in adult and neonatal intensive care units.

4. The shift of species

During the past two decades, most institutions have reported a progressive shift in the species of *Candida* that cause candidemia. Initially the vast majority of the isolates were *C. albicans*, but in recent years, close to 50% of all episodes of candidemia have been caused by non-*albicans* species [6,12,24–27].

Figure 3 shows the distribution of *Candida* species producing candidemia in a study reported by Almirante et al. from Barcelona, Spain [8]. In this study, 51% of the episodes were caused by *C. albicans,* 23% by *C. parapsilosis*, 10% by *C. tropicalis* and the remaining cases by species such as *C. glabrata* or *C. krusei*, in which fluconazole resistance is very common.

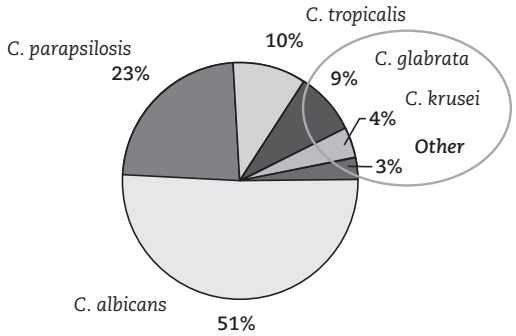

Fig. 3. Distribution of *Candida* species causing fungemia in a study reported by Almirante et al. from Barcelona, Spain [8].

When comparing candidemia caused by *C. albicans* (64.3%) with that caused by other species, candidemia caused by non-*albicans* species was independently associated with the administration of corticosteroids, central venous catheter placement, and pre-existing candiduria. Overall mortality was higher in patients with non-*albicans* species than in those with *C. albicans* bloodstream infections [16].

In other studies, simple clinical factors did not allow the clinician effectively to identify patients most likely to be infected with non-*albicans* pathogens or with possible fluconazole-resistant fungi [26,28]. The previous use of fluconazole is a risk factor for the presence of non-*albicans* fungemia [29].

C. glabrata is one of the main non-*albicans* isolates in ICUs. In a study carried out in Taiwan, *C. glabrata* was the second most common species and accounted for 45 of the 147 (30%) episodes of candidemia. The incidence of *C. glabrata* fungemia was 1.3/1000 ICU admissions and fluconazole resistance was found in 11% of *C. glabrata* isolates. The 30 day all-cause mortality rate was 58% [30].

5. Underlying conditions in ICU patients with candidemia

The most important independent conditions predisposing to invasive candidiasis and candidemia in ICU patients are prior abdominal surgery, intravascular catheters, acute renal

failure, parenteral nutrition, broad-spectrum antibiotics, a prolonged ICU stay, the use of corticosteroids, and mucosal colonization with *Candida* [22,31].

6. The predictive value of *Candida* colonization in the ICU

Candida is a microorganism present in small numbers in the microflora of the mucosal surfaces and skin of many healthy hosts. Microbiological demonstration of such colonization with routine microbiologic techniques probably requires the presence of higher numbers or overgrowth and the elimination, at least in part, of the bacterial microbiota.

In recent years, several studies have shown that ICU patients with mucosal *Candida* colonization, particularly if multifocal, are at a higher risk for invasive candidiasis, and that such colonization selects a population amenable to antifungal prophylaxis or anticipative therapy [32–37].

León et al. [36], in a group of 1699 patients admitted to ICUs for more than seven days, showed that 883 patients were colonized by *Candida* and 97 of them developed invasive candidiasis. An index score was constructed utilizing the following criteria: surgery during the current admission (one point), *Candida* colonization of more than one site (one point), total parenteral nutrition (one point), and severe sepsis (two points). Every patient with three or more points was at a very high risk of invasive candidiasis and would have benefited from empirical antifungal therapy. In another study, reported by Ostrosky-Zeichner et al. [38], in 2890 patients who were admitted for at least four days to nine hospitals in the USA and Brazil, the best predictive rule for *Candida* infection was as follows: any systemic antibiotic (day 1–3) or the presence of a central venous catheter (day 1–3) and at least two of the following: total parenteral nutrition (day 1–3), any dialysis (day 1–3), any major surgery (day −7 to day 0), pancreatitis (day −7 to day 0), any use of steroids (day −7 to day −3), or use of other immunosuppressive agents (day −7 to day 0). The rate of invasive candidiasis among patients meeting the rule was 9.9% and the rule captured 34% of cases in the units, with the following performance: relative risk 4.36, sensitivity 0.34, specificity 0.90, positive predictive value 0.01, and negative predictive value 0.97. The rule may identify patients at high risk of invasive candidiasis.

7. The problem in pediatric intensive care units

The incidence of candidemia in pediatric patients follows the same pattern of recent increase in incidence as reported in adults. Pediatric patients in a critical condition, particularly neonates with low birthweight, are especially vulnerable to invasive *Candida* infections. Central venous catheters and arterial lines, parenteral nutrition, mechanical ventilation, and the extended use of antimicrobials enhance the risk of invasive *Candida* infections. *C. albicans* continues to be the most prevalent isolate. However, non-*albicans* species are increasing in prevalence, particularly *C. parapsilosis* and *C. tropicalis*, which account for almost half of all episodes. The increased use of antifungals in immunocompromised patients, mainly for prophylactic reasons, is considered to be the strongest contributory factor to the changes in species distribution that have subsequently affected the mortality rate and choice of empirical treatment [39].

A study involving 130,523 patients admitted to 128 neonatal ICUs (NICUs) in the USA between 1995 and 2004 reported 1997 *Candida* spp. BSIs. Overall, 1472 occurred in the <1000 g birthweight group. *C. albicans* BSIs were most common, followed by *C. parapsilosis, C. tropicalis, C. lusitaniae, C. glabrata*, and only three *C. krusei*. Incidence among neonates <1000 g ranged from 3.51 to 2.68 episodes/1000 admissions. Episodes produced by species resistant to azoles were extremely rare [40]. Outbreaks of *C. parapsilosis* are frequently reported from NICUs [41,42].

In a population-based study carried out in Spain in 2002–2003, 24 cases of candidemia occurred in NICUs, resulting in an annual incidence of 32.6 cases per 100,000 live births and 1.1 cases per 100 NICU discharges. *C. parapsilosis* was the most frequent species isolated (67%) and all isolates were fluconazole-susceptible. Crude mortality was 21% [43].

In patients admitted to a pediatric ICU (PICU) with congenital heart diseases, candidemia occurred more frequently in younger patients, in those with a longer median PICU stay and in those previously colonized with *Candida*. The severity of the clinical condition, as measured by the Therapeutic Intervention Scoring System (TISS), one week after PICU admission was also associated with a higher risk for candidemia [44].

8. The economic burden of candidemia

The extra cost of an episode of candidemia in adults has been estimated as US$44,000 and € 16,000 by two studies [37,45], and candidemia was associated with a US$28,000 increase in the hospital cost of neonates [46].

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