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Epidemiology of candidaemia and invasive candidiasis. A changing face

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ABSTRACT

Invasive candidiasis is a leading cause of mortality. Candidaemia is the most common clinical presentation of invasive candidiasis but more that 30% of these infections do not yield positive blood cultures. *Candida albicans* remains the predominant aetiology, accounting for 50% of all cases. However, there has been an epidemiological shift in the last decades. Some species of *Candida* different to *C. albicans* have emerged as an important cause of severe candidaemia as they can exhibit resistance to fluconazole and other antifungal agents. Moreover, there is a different distribution of non *C. albicans Candida* species in relationship to patients' and hospital characteristics. Thus, *Candida parapsilosis* has been associated to candidaemia in neonates and young adults. This species usually has an exogenously origin and contaminates medical devices, causing central venous catheter-associated candidaemias. *Candida glabrata*, *Candida tropicalis* and *Candida krusei* are isolated in blood cultures from older patients (>65 years) with important risk factors, such as major abdominal surgery, solid tumours and haematologic malignancies, transplants, and/or prolonged treatment with corticoids. Moreover, important geographical differences in the distribution of the *Candida* species different to *C. albicans* causing invasive candidiasis have been reported: *C. parapsilosis* predominates in Australia, Latin America and Mediterranean countries of Africa, Asia and Europe. In contrast, *C. glabrata* has an important aetiological role in USA and Central and Northern Europe. Finally, an important and worrying issue is that mortality due to invasive candidiasis remains unacceptably high.

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Epidemiología de la candidemia y la candidiasis invasiva. Un rostro en continuo cambio

Palabras clave:
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RESUMEN

La candidiasis invasiva es una causa destacada de mortalidad. Su presentación más habitual es la candidemia peroen más de un 30% de las candidiasis invasivas, los hemocultivos son negativos. *Candida albicans* continúa siendo el patógeno etiológico más frecuente de las candidiasis invasivas y alrededor del 50% de todos los aislamientos de hemocultivos corresponden a esta especie. Sin embargo, en las últimas décadas, se está observando un cambio epidemiológico, con un incremento notable de especies de *Candida* diferentes de *C. albicans*. Además, las candidemias causadas por esta última especie pueden ser más graves porque muchas de ellas son resistentes a fluconazol y otros fármacos antimicóticos. La distribución de las candidemias causadas por especies de *Candida* diferentes de *C. albicans* difiere según la población de pacientes estudiados y las características del hospital. Así, *Candida parapsilosis* causa candidemias en recién nacidos y adultos jóvenes. Esta especie suele tener un origen exógeno y contamina instrumental y diferentes dispositivos médicos, por lo que induce candidemia asociada a catéteres. *Candida glabrata*, *Candida tropicalis* y *Candida krusei* se aíslan de hemocultivos de pacientes de mayor edad (>65 años) con importantes factores de riesgo subyacentes, como cirugía abdominal, tumores sólidos y neoplasias hematológicas, trasplantes o tratamientos prolongados con corticoesteroides. También se han descrito diferencias geográficas importantes en la distribución de las especies de *Candida* diferentes de *C. albicans* causantes de candidiasis invasiva: *C. parapsilosis* predomina en Australia, América Latina y los

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países de la cuenca mediterránea de África, Asia y Europa. Por el contrario, *C. glabrata* desempeña un sustancial papel etiológico en los Estados Unidos y en los países nórdicos y de Europa central. Por último, un aspecto muy importante y preocupante es que la mortalidad atribuida a la candidiasis invasiva sigue siendo inaceptablemente alta.

Este manuscrito forma parte de la serie de artículos presentados en el «V International Workshop: Molecular genetic approaches to the study of human pathogenic fungi» (Oaxaca, México, 2012).

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Invasive candidiasis is a severe infection that causes high morbidity and mortality. Candidaemia is the commonest presentation of invasive candidiasis, but it represents less than 75% of all invasive candidiasis. These invasive mycoses are mainly hospital-acquired infections and approximately two-thirds of them have their origin in different hospital wards. In recent years, community invasive candidiasis is raising in association to an increase of at home healthcare.[21,66] Hajjeh et al.[29] observed in a population-based study that 36% of candidaemia occurred in the Intensive Care Unit (ICU), and a third of them were of community onset. Wenzel and Edmond[65] estimated that 5% of the patients admitted to tertiary hospitals will be affected by a nosocomial infection; a 10% of them will suffer from bloodstream infections (BSI), being 8–10% of these BSI caused by *Candida*. Since the 1980s, *Candida* is the fourth most common cause of BSI in USA and Europe, accounting for >85% of all fungaemias.[56,61]

Most studies have reported a steady increase in the rate of invasive candidiasis until 1990 that was remarkably consistent until 2003 (from 8 to 10 cases per 100,000 inhabitants). The current incidence of invasive candidiasis has remained similar in the last years or even has decreased slightly in Australia, Canada, Europe and USA. However, incidence is continuously growing in Latin America and the rest of the world (Tables 1 and 2). The incidence of candidaemia in Australia, Canada, Europe, and Latin America is significantly lower than in the USA. Incidences of 6–10 per 100,000 inhabitants have been reported in most population-based studies in the USA.[21,22,30] In contrast, most European surveys show incidences of 1.4–5.7 per 100,000 inhabitants.[3,7,8,46,63] However, there are two notable exceptions: Denmark and, most recently, Spain, where the incidence of invasive candidiasis is higher than in other European countries.[1,4–6] Most Nordic countries have reported candidaemia in the range of 1.4–5.7 per 100,000 inhabitants, with more than 70% of them caused by *Candida albicans*.[7,8,53,54,59] Candidaemia rates in Australia (1.8 invasive candidiasis per 100,000) and Canada (2.9 per 100,000) are similar to European ones.[13,33]

Although the epidemiology of candidaemia in Latin America has not been studied so deeply, a recent prospective laboratory-based survey in 22 hospitals from 8 Latin American countries showed an incidence of 0.98 episodes per 1000 hospital admissions. In spite of being broad variations among countries (0.33 in Chile versus 1.96 episodes per 1000 hospital admissions in Argentina and Colombia), the mean incidence was higher than those reported in USA (0.28–0.96 episodes per 1000 hospital admissions) or Europe (0.2–0.38 episodes per 1000 hospital admissions).[44,45] There is not a clear reason of these higher rates of invasive candidiasis in Latin America, USA, Denmark or Spain, but the different rates of sampling, distribution of risk factors in the populations studied, the age distribution, or in the study methodologies, can contribute.[1,6,33]

Of interest, the highest incidences of invasive candidiasis occur in males (60%), at age extremes (infants <1 year and adults >65 years' old: circa 16 episodes and circa 36 episodes per 100,000 inhabitants, respectively), in cancer (71 episodes per 100,000), and diabetic patients (28 episodes per 100,000).[1–3,29,30] Cancer is a very frequent underlying disease in patients suffering from candidaemia but there are differences among cancer patients. In those patients with haematological malignancies, chemotherapy and the consequent neutropaenia, digestive tract mucositis and treatment with corticoids are added risk factors for invasive candidiasis. By comparison, in patients with solid tumours, candidaemia is associated to complications of surgery, ICU admission, mechanical ventilation, hyperalimentation and presence of central venous catheters.[10] These rates are particularly high in surgical, trauma and burn units, and neonatal ICUs. A recent SENTRY study reported a total of 1752 *Candida* isolates distributed nearly equal from invasive ICU and non-ICU settings. The frequency of ICU-associated candidaemia was also higher in Latin America (56.5%) compared with Europe (44.4%) and USA (39.6%).[50,56,66]

Role of different species of *Candida* in the aetiology of candidaemia

During the past decades, most hospitals have reported an important and progressive shift in the aetiology of invasive candidiasis in different groups of patients and distinct hospital settings. Nevertheless, *C. albicans* remains the predominant species in most studies, with incidences ranging from 11.5% in Turkey or 32% in Mexico and Taiwan to more than 60% in Austria and Sweden (Table 3). The reasons of this shift are not completely understood but several factors have been associated with candidaemia depending on the implicated species. In the 2008–2009 SENTRY study including *Candida* isolates from 79 medical centres, approximately 90–95% of isolates belonged to five species: *C. albicans*, *Candida glabrata*, *Candida parapsilosis*, *Candida tropicalis* and *Candida krusei*.[50] However, the distribution of *C. albicans* and non-*C. albicans* *Candida* species causing candidaemia vary enormously between hospitals and patients with a significant increase in those invasive candidiasis caused by *Candida* different to *C. albicans*.[15,16,28,36,37,63] An interesting feature of the latter is a patient-specificity and a particular geographical distribution (Fig. 1 and Table 3). Moreover, other important feature of some *Candida* different to *C. albicans*, such as *C. glabrata* and *C. krusei*, is their lower susceptibility to fluconazole and other antifungal agents.[3,4,36,41,42,49–52] These characteristics can complicate the therapeutic approach of candidaemia caused by these *Candida* species. The attributable mortality rate of candidaemia is estimated to be >30%, with a crude mortality rate of >50%. This mortality exceeds widely the one reported for most bacterial infections. Since 1989, a 50% reduction in mortality rates for invasive candidiasis has been reported, following a steady increase in mortality in the previous decades reaching 0.62 deaths per 100,000 persons. A similar decline in rates of death from invasive candidiasis associated with HIV infection occurred (0.04 per 100,000). The explanation for decreased mortality in both HIV infected and non-infected patients could be related to the increased awareness, earlier diagnosis, and the enhanced therapy of candidaemias. Furthermore, candidaemia not only increases patient mortality, but also extends the length of stay and increases the total cost of medical care. Patient outcomes appear to be worst for candidaemia due to *Candida* different to *C. albicans*, mainly caused by *C. glabrata* and *C. tropicalis*, and to a lesser extent *C. krusei*. However, infections due to *C. parapsilosis* tend to be associated with reduced lethality (23%).[1,41,42]

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