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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.

This manuscript is part of the series of works presented at the "V International Workshop: Molecular genetic approaches to the study of human pathogenic fungi" (Oaxaca, Mexico, 2012).

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

Palabras clave:
Candidemia
Candidiasis invasive
Epidemiología
Candida albicans
Candida parapsilosis
Candida tropicalis
Candida krusei

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).

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]

Table 1
Selected population-based epidemiological studies on candidaemia and invasive candidiasis.

Location	Year	Incidence (no. of cases/100,000 inhabitants/year)			References
		Total	Children <1 year old	Patients ≥65 years old	
America					
Canada	1999–2004	2.9	20	21.3	33
USA	1992–1993	8	70 (Black: 165 vs. white 41)	26 (Black: 40 vs. white 10)	30
USA	1998–2001	6			22
USA	1998–2000	10 (7–24)	Black: 157 vs. white: 33	Black (92) vs. white (30)	29
Europe					
Denmark	2004–2006	10.4	16.3	36.9	6
Denmark	2004–2009	8.6	11.3	27.7	4
Finland	1995–1999	1.9	9.4	5.2	54
Finland	2004–2007	2.86	6.9	12.2	53
Iceland	1980–1989	1.4		12.7	7
Iceland	1990–1999	4.9	11.3	19.3	7
Iceland	2000–2011	5.7	20.7	18.1	8
Norway	1991–2003	2.4	10.3	7	59
Spain	2002–2003	4.3	38.8	12	3
Spain	2010–2011	8.14	96.4	25	1
Scotland (UK)	2005–2006	4.8		55.9	46
Oceania					
Australia	2001–2004	1.8	24.8	13.7	13

C. parapsilosis is acquired from an exogenous source and is primarily isolated from cancer patients, and young adults and neonates in ICUs, usually in association to colonisation of central venous catheters and parenteral nutrition. This species predominates in candidaemias reported from Australia, Latin America and the Mediterranean countries of Africa, Asia and Europe. *C. parapsilosis* is usually susceptible to most antifungal agents, but there are reports of clinical isolates with decreased susceptibility to azoles and echinocandins.[1–3,10–16,23–26,38,40,43–48,52,60]

C. glabrata and *C. krusei* are associated with recent major abdominal surgery, solid tumours, old patients (>65 years), neutropaenic neonates, transplant recipients, and patients treated with corticoids.[1,10,45,48,60] *C. glabrata* predominates as second cause of candidaemia in USA and the countries of the North and Centre of Europe.[4–8,20,55] The proportion of *C. glabrata* has remained constant worldwide at 9–12% but *C. glabrata* is more common in USA (21.1%) than in the rest of the world (7.6–12.6%).[15,47–49] Some authors have linked institutional or individual fluconazole use to the selection of *C. glabrata*, especially in cancer centres.[28,35,51,56,57] In a recent SENTRY study, including 79 medical centres and a total of 1752 *Candida* isolates, *C. glabrata* was the only species in which resistance to azoles and echinocandins was reported.[50] Of interest, candidaemia due to *C. glabrata* and *C. krusei* is relatively low in Latin America, and the fluconazole resistance rates of clinical isolates of *C. glabrata* are lower (10–13%) than in USA (18–20%).[44,45] However, in Brazil a significant increase of *C. glabrata* blood isolates from the 1995–2003 period to the 2005–2007 period was observed, mainly in hospitals with higher use of fluconazole in the treatment of invasive candidiasis.[15] In Northern European countries, *C. dubliniensis*, a species close-related to *C. albicans*, can exceed 2–3%

Table 2
Selected epidemiological studies on candidaemia and invasive candidiasis.

Location	Year	Incidence (no. of cases/1000 admissions/year)	References
America			
Argentina	2005–2008	1.15 (0.35–2.65)	38
Brazil	1997–2007	0.74 (0.41–1.21)	58
Brazil	2006–2010	0.54 (0.41–0.71)	16
International	2010	1.18 (0.33–1.96)	44
USA	1998–2000	0.15	29
Asia			
China	1998–2007	0.026	67
Taiwan	2000–2010	0.351	32
Europe			
Austria	2001–2006	0.27–0.77	55
Denmark	2004–2006	0.51	6
Denmark	2004–2009	0.41	4
England (UK)	2005–2008	0.11	20
Germany	1998–2008	0.47	64
Iceland	1980–1989	0.15	7
Iceland	1990–1999	0.55	7
International	1997–1999	0.20–0.38	62
Scotland (UK)	2005–2008	0.59	46
Spain	2002–2003	0.53	3
Spain	2008–2009	1.09	14
Spain	2010	0.92	47
Spain	2010–2011	0.90	1
Oceania			
Australia	2001–2004	0.21	13
Australia	1999–2008	0.45	52

Table 3
Distribution of the five most frequent species of *Candida* on selected epidemiological studies on candidaemia and invasive candidiasis.

Location	Year	No. of isolates	Species (%)					References
			CA	CP	CT	CG	CK	
Africa								
South Africa	1990	–	62	–	23	–	0.6	31
South Africa	2005–2007	–	46	25	–	23	0.6	31
America								
Argentina	2005–2008	683	41.3	24.3	19.9	6.3	0.6	38
Argentina	2007–2008	461	38.4	26	15.4	4.3	0.4	17
Brazil	1997–2007	151	44	22	15	9	6	58
Brazil	2006–2007	300	34	26	24	7	3	16
Brazil	2006–2010	313	44	14.4	21.7	11.2	3.5	43
Brazil[a]	2006–2010	117	31	23	23	6	3	10
Brazil[2]	2006–2010	248	41	15	20	12	3	10
Canada	1999–2004	209	51.1	6.2	5.7	21.5	4.8	33
Colombia	2001–2007	921	44.7	13.6	13.6	1.7	2.1	19
Mexico	2004–2007	398	31.9	37.9	14.8	8	2.7	26
International[c]	2010	303	37.6	26.1	14.2	3.3	3	60
International	2010	672	37.6	22.5	17.6	6.3	2.7	44
USA	1998–2000	1143	45	13	12	24	2	29
USA	2004–2007	108	47	12	6	29	0	21
USA	2001–2009	453	50	13	11	22	1	27
Asia								
China	1998–2007	102	57.8	10.8	12.8	10.8	0	67
Israel	2006–2007	444	44.4	16.6	17.1	15.3	3.1	9
Taiwan	2000–2010	2856	50	13.2	19.3	16.1	1.4	32
Taiwan	2001–2010	154	32	12	46	7	4	13
Thailand	2006–2009	147	39	6	28	22	–	11
Turkey	2010–2011	39	11.5	22.2	5.9	1.78	2.1	23
Europe								
Austria	2001–2006	283	70	8.1	4.9	13.8	0	55
Denmark	2004–2006	1133	59.8	4	4.6	20.5	4.1	6
Denmark	2004–2009	2820	57.1	3.7	4.8	21.1	4.1	4
England (UK)	2005–2008	106	43	20	3	31	2.5	20
Finland	1995–1999	479	70	5	3	9	7	54
Germany	1998–2008	35	45.7	17.1	5.7	14.3	0	64
Iceland	1980–1999	172	64.4	9.6	5.6	12.4	1	7
Iceland	2000–2011	222	56	9	13	16	1	8
Scotland (UK)	2005–2006	300	52	11.7	2	22.7	1	46
Spain	2002–2003	345	51	23	10	8	4	3
Spain	1990–2003	555	42.3	36.3	4.4	9.7	4	40
Spain	2008–2009	984	49.1	20.7	10.7	13.6	2.1	14
Spain	2009	1377	43	29	10	8.5	3	47
Spain	2009	752	46	26	8	11	3	1
Sweden	2005–2006	403	60.8	8.9	2	20.1	1.2	24
Oceania								
Australia	2001–2004	1068	47.3	19.9	5.1	15.4	4.3	13
Australia	1999–2008	1137	45.4	26.9	5.2	13.4	2.8	52

Candidaemia in patients with haematological malignancies[1] or solid tumours[2]. [3]Candidaemia in children from 8 Latin American countries. CA = *Candida albicans*, CP = *Candida parapsilosis*, CT = *Candida tropicalis*, CG = *Candida glabrata*, and CK = *Candida krusei*.

of blood isolates.[4,8,46] Finally, *C. tropicalis* has been isolated from patients with solid tumours or haematologic diseases and it has been reported as the second etiological agent of invasive candidiasis in Asia and some parts of Latin America (Colombia and Brazil). The overrepresentation of *C. tropicalis* candidaemia in patients aged >70 years can be related to the increased frequency of solid tumours and haematologic malignancies in the elderly population.[32,34,43,67] Multi-fungal infections do not exceed 5% of candidaemias, being *C. albicans* the species most frequently isolated in combination with other yeasts, with *C. glabrata* and *C. tropicalis* accounting for the majority of episodes.[6]

Two of these emerging species, *C. parapsilosis* and *C. glabrata* are in fact complexes of species with special clinical and demographic characteristics.[12,18,40] *C. parapsilosis* includes 3 different species: *Candida parapsilosis sensu stricto*, *Candida metapsilosis* and *Candida orthopsilosis*, but the real importance of *C. orthopsilosis* and *C. metapsilosis* as human pathogens remains unknown. In a recent Spanish nationwide study, the incidence of episodes of candidaemia due to *C. parapsilosis* and *C. orthopsilosis* were 0.22 and 0.02 per 1000 admissions, respectively. *C. orthopsilosis* was the fifth most frequently isolated species, preceding *C. krusei* (0.018 episodes per 1000 admissions).[47,48] The prevalence of *C. orthopsilosis* is apparently higher in warmer Mediterranean countries than in the cooler countries of the Atlantic, Central and North Europe. A higher prevalence of *C. orthopsilosis* has also been reported in countries with hot and humid climates, such as Taiwan (8.5%), Brazil (9.1%) and Malaysia (24.4%). However, other factors could be responsible for local specificities, such as differences in hospital services (presence or absence of ICU or surgical wards) and the patient population (transplant recipients and other immunodeficient patients).[40] *C. glabrata* complex includes *C. glabrata sensu stricto* and two newly described species, *Candida bracarensis* and *Candida nivariensis*.[18,39] Lockhart et al.[37], in their analysis of 1598 *C. glabrata* isolates from 29 countries, observed that *C. bracarensis* and *C. nivariensis* isolates constituted a very small percentage (0.2%) of the *C. glabrata* clinical isolates. However, these cryptic species could be more prevalent in

Fig. 1. Distribution of most frequently species of *Candida* other than *Candida albicans* (in the case of *Candida dubliniensis* the areas represent those places reporting more than 2% of blood isolates corresponding to this species).

specific regions. Most reports have underlined the lower susceptibility of *C. bracarensis* and *C. nivariensis* to the most commonly used azoles.

Conclusions

Invasive candidiasis is a leading cause of mortality worldwide. *C. albicans* remains the predominant cause of candidaemia and invasive candidiasis, accounting for 50% of all cases. However, an evident shift has been reported in the epidemiology, as some *Candida* species different to *C. albicans* have emerged as cause of candidaemia and can exhibit resistance to fluconazole and other triazoles, echinocandins and/or amphotericin B. *C. parapsilosis* is associated to infections in neonates and young adults, usually related to the presence of central venous catheter and hyperalimentation. *C. glabrata*, *C. tropicalis* and *C. krusei* cause infections in older patients in association to recent major abdominal surgery, solid tumours, transplants, and/or prolonged treatment with corticoids. Moreover, there are some important geographical differences in the distribution of those *Candida* species different to *C. albicans* causing invasive candidiasis. *C. parapsilosis* is the first or second aetiology of candidaemia in Australia, Latin America and Mediterranean countries of Africa, Asia and Europe. Conversely, *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.

Conflict of interest

In the past 5 years, GQA has received grant support from Astellas Pharma, Gilead Sciences, Pfizer, Schering Plough and Merck Sharp and Dohme. He has been an advisor/consultant to Merck Sharp and Dohme, and has been paid for talks on behalf of Astellas Pharma, Esteve Hospital, Gilead Sciences, Merck Sharp and Dohme, Pfizer, and Schering Plough.

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