Epidemiology of invasive candidiasis

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Purpose of review

This review covers candidaemia in numbers, susceptibility issues, host groups, risk factors and outcome.

Recent findings

The incidence of candidaemia has increased over the last decades. *Candida glabrata* is particularly common in the northern hemisphere and with increasing age whilst the opposite is true for *C. parapsilosis*, *C. glabrata, C. krusei* and a number of emerging species are not fully susceptible to azoles. *C. parapsilosis* and *C. guilliermondii* are not fully susceptible to echinocandins. Increasing rates of *C. parapsilosis* have been observed at centres with a high use of echinocandins, and outcome for this species is not superior comparing echinocandins with fluconazole. Acquired azole resistance has recently been described in as many as a third of 19% resistant isolates and echinocandin resistance has emerged and been detected as early as day 12 of echinocandin therapy. ICU stay and abdominal surgery are among the most important risk factors. Outcome is dependent on species involved, timing, dosing and choice of therapy and management of the primary focus of infection. However, host factors are dominating predictors of mortality in recent studies of ICU candidiasis.

Summary

The changing epidemiology highlights the need for close monitoring of local incidence, species distribution and susceptibility in order to optimize therapy and outcome.

Keywords

candidaemia, epidemiology, ICU, invasive candidiasis, susceptibility

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Introduction

Candida is part of our normal microbial flora on mucosal surfaces, from where it may cause local infections like thrush in the oral cavity and candida vaginitis. However, in patients with various underlying diseases or host factors *Candida* may cause invasive disease (invasive candidiasis or candidosis), most often as bloodstream infection (candidaemia) with or without secondary dissemination to the eyes, liver, spleen, bones, heart valves, central nervous system and so on or as deep-seated candidiasis, such as peritonitis after gastrointestinal surgery. The overall mortality (day 30) associated with candidaemia is around 30–40% and depends on the severity of underlying disease, the *Candida* species involved, and timing and choice of antifungal treatment. The mean additional costs are significant and estimates range from 8000 € in ICU patients colonised with *Candida* to £8252 to 44 000 US$ per patient in various studies [1–3].

The epidemiology of invasive candidiasis has changed over the last decades. An increasing proportion of cases especially in adult and elderly patients involve species that are not fully susceptible to fluconazole [4]. Also, *C. parapsilosis*, which is less susceptible to the echinocandins, has emerged, particularly at centres using agents of this drug class [5•,6]. These changes have important consequences for our therapeutic strategies and hence, understanding and close monitoring of the local pattern of invasive candidiasis is of outmost importance. The aim of this review is to provide an updated overview of the current epidemiology of invasive candidiasis in general and which trends are of significance to treating ICU physicians and serving microbiologists.

Candidaemia in numbers

Epidemiology of candidaemia has been the subject of numerous studies and rates as different as 1.2–25 cases per 100 000 population or 0.19–2.5 per 1000 admissions have been reported, illustrating the complexity of this topic [7–11]. These differences are in part related to the nature of the different surveys. Studies carried out as single-centre or multi-centre studies or including only a selected group of patients will naturally reflect a priori risk for candidaemia specific for the surveyed population, which may be specific for the local area. Consequently,

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such studies are informative, but not necessarily easily comparable or translated into other settings. On the contrary, population-based surveys being either national or covering all inhabitants in a defined geographical area allow comparison of rates of candidaemia between regions and countries and reveal true differences between different parts of the world. Among the Nordic countries, Norway, Finland and Sweden report incidences of candidaemia around 3/100 000 population whereas Denmark reports 11/100 000 population in a seminational survey [12–18]. In the middle and southern parts of Europe population-based surveys in Switzerland, UK, Scotland, Spain and Italy have reported 1.2–6.4 per 100 000 population [10,19–23]. Finally, in the US surveys conducted in Iowa, San Francisco, Atlanta and Connecticut rates of 6–14 have been reported with the exception of the Baltimore area reporting 25/100 000 [4,8,9,24,25]. In general, the highest incidences are observed at the extremes of age. Thus, compared to the overall incidence, the incidence is up to 10 and 5 times higher in patients younger than 1 year of age and older than 65 years of age, respectively [7,8,13,21].

The candidaemia rate has remained stable or even decreased over time in some settings (e.g. in Switzerland and the ICU setting at some institutions [19,26]) presumably owing to an increased use of antifungal prophylaxis in high-risk groups; however, in most population-based surveys the overall rate of invasive candidiasis has increased. Thus, Norway, Finland, Iceland and Denmark document increasing rates, though at different magnitudes, and so do recent 3–12-year surveys in Ireland, Slovakia, Australia and Canada [7,12–15,17,18,27–30,31•,32]. The most likely explanation for this increase is that the number of patients susceptible to invasive candidiasis has grown owing to increased survival of patients with severe diseases or extreme low-birth weight, more aggressive use of surgery and transplantations and increased use of invasive procedures and devices, of immunosuppressive therapy and of broad spectrum antibiotics.

Species distribution and intrinsic susceptibility pattern

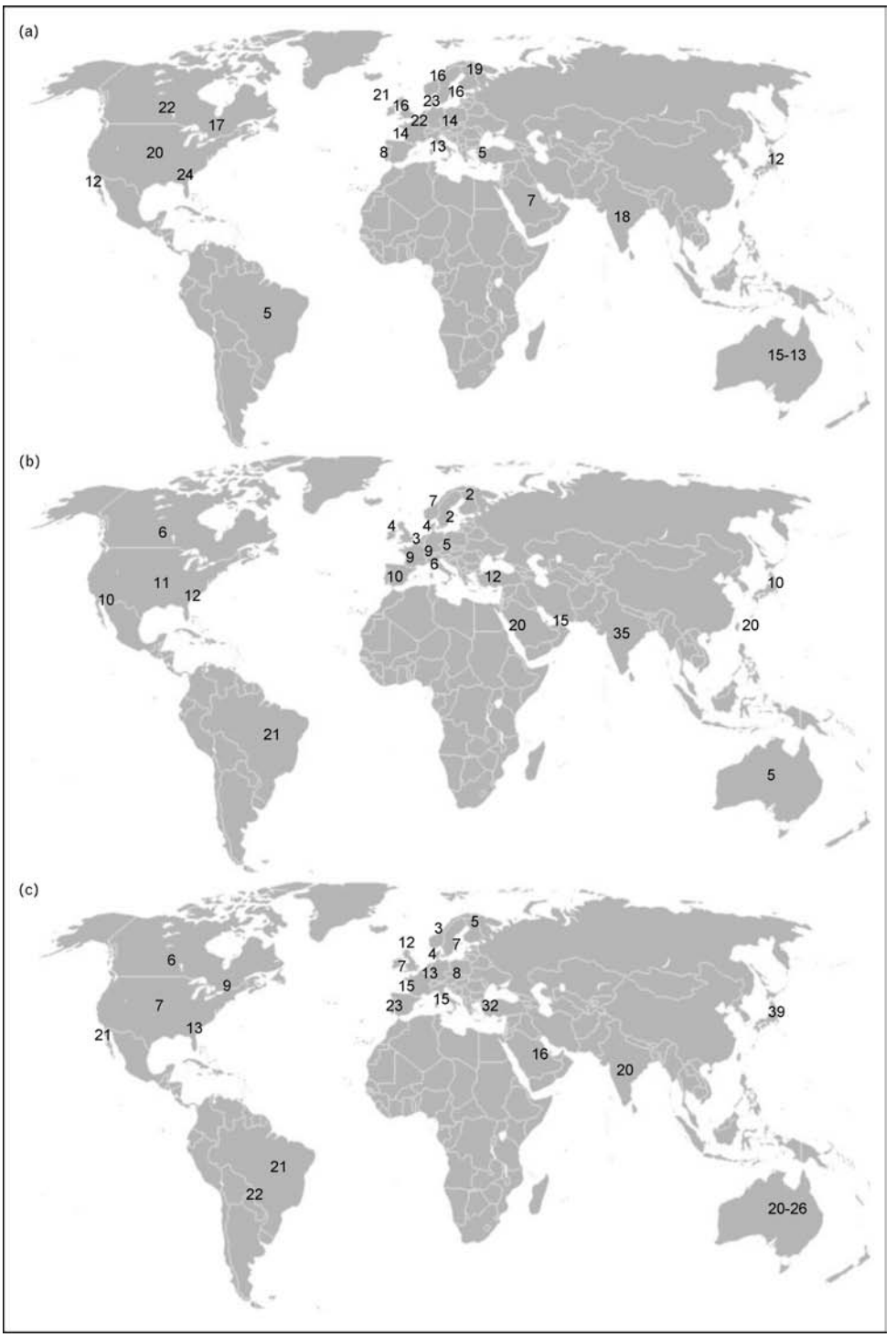
Globally, *C. albicans* is still the major pathogen, causing 50–70% of the cases. This is, however, significantly lower than a few decades ago. In most countries the proportion of other species, and of *C. glabrata* or *C. parapsilosis* in particular, has increased with notable geographical differences in species distribution as displayed in Fig. 1 [7,8,10,11,13,15,16,18,20,21,24,25,28,31•,32–40]. Moreover, species distribution varies by age; thus, the proportion of candidaemia cases involving *C. glabrata* increases by age, whereas the opposite is true for *C. parapsilosis* [8,12]. The susceptibility pattern is closely linked to the species and therefore it is important to understand and monitor local species epidemiology (Table 1). *C. glabrata* and *C. krusei* are the most frequent species with reduced susceptibility to one or several azoles and *C. parapsilosis* the most common one with decreased susceptibility to echinocandins. However, an increasing number of rarer species with intrinsically reduced susceptibility to one or several antifungal compounds have been described over the recent years including, but not limited to the following that are not fully susceptible to one or several azoles: *C. cifferrii*, *C. guillermondii*, *C. inconspicua*, *C. humicula*, *C. lambica*, *C. lipolytica*, *C. norvegensis*, *C. palmioleophila*, *C. rugosa* and *C. valida* and the following two that are not fully susceptible to the echinocandins: *C. fermentati* and *C. guilliermondii* [41,42••,43]. Finally, *C. lusitaniae* is less susceptible to amphotericin B owing to higher mutational rate and the drug being less cidal against this species, and therefore other drug classes should be preferred for infections owing to *C. lusitania* [44].

Several factors have been identified that predisposes to infection with species other than *C. albicans*. Triazole therapy, gastrointestinal tract surgery in 30 days before onset of candidaemia and age more than 65 years were independent predictors of fluconazole resistant candidaemia (predominantly *C. glabrata* and *C. krusei*) in patients with cancer in a recent study [45]. In contrast, Magill *et al.* [46] documented a decrease in ICU-acquired invasive candidiasis 3 years after introduction of fluconazole prophylaxis to patients with expected ICU stay more than 3 days and no concomitant increase in the *C. glabrata* proportion. Probably, these contradictory findings may be related to differences in length of fluconazole exposure as long-term prophylaxis and treatment is more common in cancer patients than in the ICU setting thus leading to a more pronounced azole selection pressure in the first setting. Also time at risk and certain antibiotics, including vancomycin and linezolide have been associated with increased risk of *C. glabrata or C. krusei* with elevated MICs (minimal inhibitory concentrations) illustrating the multifactorial genesis [47–49]. Finally, younger age, central venous lines, echinocandin use and poor infection control practices have been associated with *C. parapsilosis* [5•,6,50•,51] whereas *C. tropicalis* is particularly common in neutropenic patients with underlying haematological disease [5•,31•].

Acquired resistance in *Candida*, is it a problem?

Echinocandins include anidulafungin, caspofungin and micafungin and have played an increasing role in the management of invasive candidiasis since the millennium and is regarded first line treatment for candidaemia [52]. Acquired resistance has been associated with mutations in hot spot regions of the two subunits of

Figure 1 Geographical differences in proportion of candidaemia cases



Geographical differences in proportion of candidaemia cases involving *Candida glabrata* (a), *C. tropicalis* (b) and *C. parapsilosis* (c), respectively, compiled from the following publications [7,8,10,11,13,15,16,18,20,21,24,25,31•,32–35,37–41].

Table 1 Intrinsic susceptibility pattern for selected human pathogenic *Candida* species

	Amb	Echino	Fluco	Itra	Vori	Posa
C. albicans	S	S	S	S	S	S
C. tropicalis	S	S	S	S	S	S
C. glabrata	S	S	I-R	I-R	I-R	I-R
C. krusei	S	S	R	I-R	S-I-R	S-I-R
C. guillermondii	S	I	I-R	I-R	S-I-R	S-I-R
C. parapsilosis	S	I	S	S	S	S
C. lusitaniae	S-I-R	S	S	S	S	S

Amb, amphotericin; C., candida; echino, echinocandins; fluco, fluconazole; itra, itraconazole; posa, posaconazole; vori, voriconazole. S: susceptible, I: intermediate (for fluconazole, itraconazole and voriconazole this group is named susceptible dose-dependent for susceptible dose dependent, indicating that higher doses or alternative treatment is recommended), R: resistant.

the *FKS* gene encoding the target enzyme for these drugs. The incidence may be underestimated because current breakpoints are too high to reliably identify all resistant isolates [53•,54•,55••,56•]. Breakthrough infections occur in up to 2.9% of patients and may be due to either clinical host factors or resistance in the pathogen. Echinocandin resistant strains have never been reported from echinocandin naïve patients, but have been documented as early as 12 days after initiation of treatment (mean duration time 24–33 days or 20 contiguous days) [57••,58••,59•]. *C. glabrata* appears to be the organism most often involved, which might at least in part be because this species is haploid and thus acquires full resistance after a single mutation [57••,58••,59•]. However, clinical cases involving *C. albicans*, *C. dubliniensis*, *C. krusei* and *C. tropicalis* have also been increasingly reported [56•,57••,59•,60,61].

Azoles act by inhibiting the fungal cytochrome P450-dependent enzyme lanosterol 14-α-demethylase, which is encoded by the gene *ERG11*. This enzyme converts lanosterol to ergosterol and its inhibition disrupts membrane synthesis in the fungal cell. Acquired resistance has been associated with mutations in the target gene leading to lower affinity of the azole compound to the enzyme, upregulation of the enzyme level or by active transport of the azole out of the cell mediated by efflux pumps [the major facilitators (encoded by *MDR* genes) or those of the adenosine-5'-triphosphate-binding cassette superfamily (encoded by *CDR* genes)]. Resistance may involve selected azoles or several azoles depending on the underlying mechanism and the various mechanisms may act alone or in concert [62,63••]. Although azole resistance has been described in invasive isolates, most resistant isolates have been detected after long-term treatment of mucosal infections. Overall, azole resistance in isolates belonging to normally susceptible species is still an infrequent event despite their use for several decades and nowadays for prophylaxis, empirical and preemptive therapy as well as for the management of proven disease [13,42••]. However, a recent study reported reduced fluconazole susceptibility in 19% of 243 candidaemia cases including in 8% *C. albicans*, 4% *C. tropicalis* and 4% *C. parapsilosis* [64•]. Reduced susceptibility in these three species composed 36% of the reduced-susceptibility group and 48% of the fully resistant group, suggesting that species identification alone may not be sufficiently predictive of fluconazole susceptibility [64•]. In multivariate analysis, independent factors associated with reduced fluconazole susceptibility included male sex, chronic lung disease, the presence of a central vascular catheter and prior exposure to antifungal agents [64•]. Attention to such factors that are associated with reduced fluconazole susceptibility may help clinicians choose adequate empirical anti-*Candida* therapy.

Patient groups and host factors

In population-based studies, the most important patient groups associated with invasive candidiasis are the following: neonates especially if being low-birth weight or preterm babies, critically ill patients especially if having severe disease and a long-term stay in ICU, patients undergoing abdominal surgery especially if complicated or repeated, patients with malignant disease or acute necrotizing pancreatitis and transplant recipients and burn patients especially if burns involve larger body surface area or full thickness area [8,21,31•,65–67,68•,69,70]. Moreover, a number of host factors predisposes to invasive candidiasis including *Candida* colonization especially if multifocal or heavy and exposure to broad spectrum antibiotics, central venous catheters, total parental nutrition, dialysis, steroids or to chemotherapy [68•,70,71,72•].

ICU-specific epidemiology

Not only is an ICU stay per se recognised as a risk for invasive candidiasis, ICU patients also often have a number of underlying diseases and host factors predisposing to invasive candidiasis and listed above. A recent prevalence study included 13 796 adult patients in 1265 ICUs in 75 countries. Fifty-one percent of the patients were infected, with *Candida* spp. ranking third as infection causing organisms (17% of infected patients) following *Staphylococcus aureus* 20.5% and *Pseudomonas* spp. (19.9%) [73••]. In fact, *Candida* spp. ranked second in Europe (18.5%) and North America (18.2%) and overall 16% of the patients received antifungal drugs illustrating

the magnitude and importance of *Candida* infections in the ICU setting globally [73••]. In agreement with this, candidaemia incidences in ICUs is typically 10 times higher than in non-ICU departments as illustrated in a recent survey in Queensland, Australia (4.89 vs. 0.44/10 000 patient days, $P < 0.0001$) [31•]. However, considerable differences in rate of candidaemia have been reported as illustrated by a recent survey comparing epidemiology of candidaemia in four ICUs in Belgium (2.8/1000 admissions), Australia (4.3/1000 admissions), Brazil (6.3/1000 admissions) and Greece (11.3/1000 admissions) [74]. Such differences probably reflect differences in case mix, in use of prophylaxis and of general hygiene procedures. In a recent intervention study (1999–2007), increasing incidence of candidaemia overall and, in particular, due to species other than *C. albicans* was observed during the years 1999–2002. In the same period, the use of fluconazole almost three doubled. In 2002, the prophylactic use of fluconazole was reduced and a year later, the number of candidaemia cases dropped significantly for all *Candida* spp. and remained low in the remaining study period 2003–2007 [75]. This is in contrast with the findings in other studies typically reporting a decrease in invasive candidiasis including candidaemia after introduction of systematic fluconazole prophylaxis [47,67,76]. The reason for these diverging observations is not clear, but factors other than antifungal prophylaxis per se may have been involved.

Invasive candidiasis manifests as either isolated candidaemia, invasive candidiasis without documented candidaemia or a combination of the two entities [77•]. As demonstrated in a multicentre study including 180 ICUs in France preceding surgery and solid tumour were significantly more common in patients with invasive candidiasis whilst prior antibiotics, neutropenia and haematological malignancy were significantly more common in candidaemic patients [77•]. Metastatic processes occur in a considerable proportion of candidaemic ICU patients. Among 185 ICU cases in a nationwide Australian 3-year survey 20 cases included such manifestations (11%) including six cases of eye involvement [among 48 undergoing ophthalmoscopy (13%)], nine cases of renal candidiasis, three of possible endocarditis and two autopsy proven cases of hepatosplenic candidiasis [78•]. These findings illustrate the importance of paying attention to possible secondary foci that may require specific diagnostic initiatives (e.g. ophthalmoscopy, imaging, echocardiography), prolongation of antifungal treatment or other interventions (surgery, drainage etc.).

Factors associated with outcome

In addition to correct management of the infectious focus when appropriate (e.g. removal of infected intravascular catheter and surgical drainage of an abscess), a triad of factors influence outcome: The susceptibility and virulence of the infecting organism, severity of the underlying illness and, finally, choice, timing and dosing of the antifungal treatment. The differences in intrinsic susceptibility pattern are summarised in Table 1. The most common *Candida* species can be divided into three groups with decreasing virulence: (1) *C. albicans* and *C. tropicalis*, (2) *C. glabrata*, *C. kefyr* and *C. lusitaniae* and (3) *C. parapsilosis*, *C. krusei* and *C. guilliermondii* [79]. In agreement with this, *C. albicans* and *C. glabrata* have been associated with a high and conversely *C. parapsilosis* with a low mortality in a number of reports [80–82].

The severity of the underlying disease is an important factor for mortality and overall mortality is consistently higher in candidaemic ICU patients than in candidaemic patients in general. In a recent study of determinants of mortality in non-neutropenic ICU patients, overall mortality was 52% with a median time to death of 7 days after candidaemia and host factors (older age, ICU admission diagnosis other than multitraumatised and mechanical ventilation at time of candidaemia) were independently associated with mortality in multivariate analysis [78•].

The impact of timing and choice of antifungal treatment on outcome has been investigated in several studies. In an Australian nationwide study, not receiving antifungal treatment was significantly associated with mortality in multivariate analysis. However, timing and choice of antifungal agent were not [78•]. This is somewhat surprising as timing [80,83,84] and treatment choice and dose (agent and exposure/MIC relationship) [85•,86–90] have been shown to be of significant importance in other studies including mixed ICU and non-ICU populations. However, in patient populations with severe illness, such as ICU patients, the potential benefits of optimal treatment may be masked as the underlying disease in a significant proportion of the patients may be the principal driver of mortality [91]. Moreover, patients receiving early treatment may include a higher proportion with multiple risk factors for candidaemia and death as such patients are more likely to be allocated to antifungal treatment early, before the blood culture flags positive. And such patients may have a higher fungal load leading to earlier blood culture positivity and thus treatment. In both scenarios timing outcome relationship may be confounded, as patients treated early tend to be the most severely ill or the most heavily infected, with the highest risk of death. Thus, it still seems reasonable to select the most efficacious agent for the fungus in question and in the appropriate dosages according to guidelines and clinical and animal studies. In this context, it is a bit worrying that therapeutic escalation was performed in only 16/34 (47%) of fluconazole nonsusceptible cases in a recent study including ICU patients only [77•].

Conclusion

In conclusion, invasive candidiasis remains a huge challenge owing to the associated morbidity, mortality and costs. Notably, differences in epidemiology are observed comparing various geographical regions, age groups and patient groups and changes in rate and species distribution and susceptibility have been observed over the recent decades. Outcome has in the majority of studies been linked to timing of therapy and of dosing and choice of antifungal agent with improved outcome related to newer treatment options although part of the ICU population may be out of therapeutic reach at the time of diagnosis. Thus, knowledge of local epidemiology is of crucial importance enabling prevention or early appropriate treatment of invasive candidiasis. For this purpose, continued research on diagnostics, predictive rules, epidemiology and resistance development is needed.

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References and recommended reading

Papers of particular interest, published within the annual period of review, have been highlighted as:

- • of special interest
- •• of outstanding interest

Additional references related to this topic can also be found in the Current World Literature section in this issue (pp. 517–518).

1 Olaechea] PM, Palomar M, Leon-Gil C, *et al.* Economic impact of *Candida* colonization and *Candida* infection in the critically ill patient. Eur J Clin Microbiol Infect Dis 2004; 23:323–330.

2 Hassan I, Powell G, Sidhu M, *et al.* Excess mortality, length of stay and cost attributable to candidaemia. J Infect 2009; 59:360–365.

3 Smith PB, Morgan J, Benjamin JD, *et al.* Excess costs of hospital care associated with neonatal candidemia. Pediatr Infect Dis J 2007; 26:197–200.

4 Pfaller MA, Diekema DJ. Epidemiology of invasive candidiasis: a persistent public health problem. Clin Microbiol Rev 2007; 20:133–163.

5 • Sipsas NV, Lewis RE, Tarrand J, *et al.* Candidemia in patients with hematologic malignancies in the era of new antifungal agents (2001–2007): stable incidence but changing epidemiology of a still frequently lethal infection. Cancer 2009; 115:4745–4752.

One of two recent papers reporting a link between echinocandin use and increasing proportion of candidaemia cases involving *C. parapsilosis*. Furthermore, a significant link between echinocandin use and breakthrough infections being *C. parapsilosis* was observed.

6 Forrest GN, Weekes E, Johnson JK. Increasing incidence of *Candida* parapsilosis candidemia with caspofungin usage. J Infect 2008; 56:126–129.

7 Chen S, Slavin M, Nguyen Q, *et al.* Active surveillance for candidemia, Australia. Emerg Infect Dis 2006; 12:1508–1516.

8 Hajjeh RA, Sofair AN, Harrison LH, *et al.* Incidence of bloodstream infections due to *Candida* species and in vitro susceptibilities of isolates collected from 1998 to 2000 in a population-based active surveillance program. J Clin Microbiol 2004; 42:1519–1527.

9 Ahlquist A, Farley MM, Harrison LH, *et al.* Epidemiology of candidemia in metropolitan Atlanta and Baltimore city and county: preliminary results of population-based active, laboratory surveillance – 2008–2009. In: 49th Interscience Conference on Antimicrobial Agents and Chemotherapy (ICAAC); 14 September 2009. Abstract M-1241.

10 Kibbler CC, Seaton S, Barnes RA, *et al.* Management and outcome of bloodstream infections due to *Candida* species in England and Wales. J Hosp Infect 2003; 54:18–24.

11 Colombo AL, Nucci M, Park BJ, *et al.* Epidemiology of candidemia in Brazil: a nationwide sentinel surveillance of candidemia in eleven medical centers. J Clin Microbiol 2006; 44:2816–2823.

12 Arendrup MC, Fuursted K, Gahrn-Hansen B, *et al.* Seminational surveillance of fungemia in Denmark: notably high rates of fungemia and numbers of isolates with reduced azole susceptibility. J Clin Microbiol 2005; 43:4434–4440.

13 Arendrup MC, Fuursted K, Gahrn-Hansen B, *et al.* Semi-national surveillance of fungaemia in Denmark 2004–2006: increasing incidence of fungaemia and numbers of isolates with reduced azole susceptibility. Clin Microbiol Infect 2008; 14:487–494.

14 Poikonen E, Lyytikainen O, Anttila VJ, Ruutu P. Candidemia in Finland, 1995–1999. Emerg Infect Dis 2003; 9:985–990.

15 Poikonen E, Lyytikainen O, Ruutu P. Candidaemia in Finland, 1995–1999 vs. 2004–2007. In: European Conference on Clinical Microbiology and Infectious Diseases (ECCMID); 16 April 2009. p. P1961.

16 Klingspor L, Tornqvist E, Johansson A, *et al.* A prospective epidemiological survey of candidaemia in Sweden. Scand J Infect Dis 2004; 36:52–55.

17 Sandven P, Bevanger L, Digranes A, *et al.* Candidemia in Norway (1991 to 2003): results from a nationwide study. J Clin Microbiol 2006; 44:1977–1981.

18 Nordøy I. Candidaemia in Norway. In: Trends in Medical Mycology (TIMM); 19 October 2009. Abstract M-105.

19 Marchetti O, Bille J, Fluckiger U, *et al.* Epidemiology of candidemia in Swiss tertiary care hospitals: secular trends, 1991–2000. Clin Infect Dis 2004; 38:311–320.

20 Odds FC, Hanson MF, Davidson AD, *et al.* One year prospective survey of *Candida* bloodstream infections in Scotland. J Med Microbiol 2007; 56:1066–1075.

21 Almirante B, Rodriguez D, Park BJ, *et al.* Epidemiology and predictors of mortality in cases of *Candida* bloodstream infection: results from population-based surveillance, Barcelona, Spain, from 2002 to 2003. J Clin Microbiol 2005; 43:1829–1835.

22 Tortorano AM, Peman J, Bernhardt H, *et al.* Epidemiology of candidaemia in Europe: results of 28-month European Confederation of Medical Mycology (ECMM) hospital-based surveillance study. Eur J Clin Microbiol Infect Dis 2004; 23:317–322.

23 Tortorano AM, Kibbler C, Peman J, *et al.* Candidaemia in Europe: epidemiology and resistance. Int J Antimicrob Agents 2006; 27:359–366.

24 Kao AS, Brandt ME, Pruitt WR, *et al.* The epidemiology of candidemia in two United States cities: results of a population-based active surveillance. Clin Infect Dis 1999; 29:1164–1170.

25 Diekema DJ, Messer SA, Brueggemann AB, *et al.* Epidemiology of candidemia: 3-year results from the emerging infections and the epidemiology of Iowa organisms study. J Clin Microbiol 2002; 40:1298–1302.

26 Trick WE, Fridkin SK, Edwards JR, *et al.* Secular trend of hospital-acquired candidemia among intensive care unit patients in the United States during 1989–1999. Clin Infect Dis 2002; 35:627–630.

27 Asmundsdottir LR, Erlendsdottir H, Gottfredsson M. Increasing incidence of candidemia: results from a 20-year nationwide study in Iceland. J Clin Microbiol 2002; 40:3489–3492.

28 Arendrup MC, Fuursted K, Schonheyder HC, *et al.* Ongoing semi-national surveillance of fungaemia in Denmark: have we cracked the curve? In: Trends In Medical Mycology (TIMM); 20 October 2009. Abstract O-4.6.

29 Boo TW, O'Reilly B, O'Leary J, Cryan B. Candidaemia in an Irish tertiary referral hospital: epidemiology and prognostic factors. Mycoses 2005; 48:251–259.

30 Krcmery V Jr, Kovacicova G. Longitudinal 10-year prospective survey of fungaemia in Slovak Republic: trends in etiology in 310 episodes. Slovak Fungaemia study group. Diagn Microbiol Infect Dis 2000; 36:7–11.

31 • Playford EG, Nimmo GR, Tilse M, Sorrell TC. Increasing incidence of candidaemia: long-term epidemiological trends, Queensland, Australia, 1999–2008. J Hosp Infect 2010 [Epub ahead of print].

This is the most recent and comprehensive nationwide epidemiological survey of candidaemia reporting a 3.5-fold increasing incidence of candidaemia in Australia in the 1999–2008 period. A changing species distribution was observed (*C. albicans* decreasing and *C. parapsilosis* increasing) and species distribution varied by clinical setting.

32 Laupland KB, Gregson DB, Church DL, *et al.* Invasive *Candida* species infections: a 5 year population-based assessment. J Antimicrob Chemother 2005; 56:532–537.

33 Swinne D, Watelle M, Suetens C, *et al.* A one-year survey of candidemia in Belgium in 2002. Epidemiol Infect 2004; 132:1175–1180.

34 Sendid B, Cotteau A, Francois N, *et al.* Candidaemia and antifungal therapy in a French University Hospital: rough trends over a decade and possible links. BMC Infect Dis 2006; 6:80.

35 Bakir M, Cerikcioglu N, Barton R, Yagci A. Epidemiology of candidemia in a Turkish tertiary care hospital. APMIS 2006; 114:601–610.

36 Al-Tawfiq JA. Distribution and epidemiology of *Candida* species causing fungemia at a Saudi Arabian hospital, 1996–2004. Int J Infect Dis 2007; 11:239–244.

37 Godoy P, Tiraboschi IN, Severo LC, *et al.* Species distribution and antifungal susceptibility profile of *Candida* spp. bloodstream isolates from Latin American hospitals. Mem Inst Oswaldo Cruz 2003; 98:401–405.

38 Nakamura T, Takahashi H. Epidemiological study of *Candida* infections in blood: susceptibilities of *Candida* spp. to antifungal agents, and clinical features associated with the candidemia. J Infect Chemother 2006; 12:132–138.

39 St-Germain G, Laverdiere M, Pelletier R, *et al.* Epidemiology and antifungal susceptibility of bloodstream *Candida* isolates in Quebec: report on 453 cases between 2003 and 2005. Can J Infect Dis Med Microbiol 2008; 19:55–62.

40 Presterl E, Daxbock F, Graninger W, Willinger B. Changing pattern of candidaemia 2001–2006 and use of antifungal therapy at the University Hospital of Vienna, Austria. Clin Microbiol Infect 2007; 13:1072–1076.

41 Chen SC, Marriott D, Playford EG, *et al.* Candidaemia with uncommon *Candida* species: predisposing factors, outcome, antifungal susceptibility, and implications for management. Clin Microbiol Infect 2009; 15:662–669.

42 •• Pfaller MA, Diekema DJ, Gibbs DL, *et al.* Results from the ARTEMIS DISK Global Antifungal Surveillance Study, 1997 to 2007: a 10.5-year analysis of susceptibilities of *Candida* species to fluconazole and voriconazole as determined by CLSI standardized disk diffusion. J Clin Microbiol 2010; 48:1366–1377.

Most comprehensive collection of fluconazole and voriconazole susceptibility data including 31 *Candida* spp. and almost 200.000 isolates from medical centres in the Asia-Pacific region, Latin America, Europe, the Africa/Middle East region and North America. Data also illustrate the emergence of rarer fluconazole resistant species.

43 Lockhart SR, Messer SA, Pfaller MA, Diekema DJ. Identification and susceptibility profile of *Candida* fermentati from a worldwide collection of *Candida* guilliermondii clinical isolates. J Clin Microbiol 2009; 47:242–244.

44 Atkinson BJ, Lewis RE, Kontoyiannis DP. *Candida* lusitaniae fungemia in cancer patients: risk factors for amphotericin B failure and outcome. Med Mycol 2008; 46:541–546.

45 Slavin MA, Sorrell TC, Marriott D, *et al.* Candidaemia in adult cancer patients: risks for fluconazole-resistant isolates and death. J Antimicrob Chemother 2010; 65:1042–1051.

46 Magill SS, Swoboda SM, Shields CE, *et al.* The epidemiology of *Candida* colonization and invasive candidiasis in a surgical intensive care unit where fluconazole prophylaxis is utilized: follow-up to a randomized clinical trial. Ann Surg 2009; 249:657–665.

47 Lee I, Fishman NO, Zaoutis TE, *et al.* Risk factors for fluconazole-resistant *Candida* glabrata bloodstream infections. Arch Intern Med 2009; 169:379–383.

48 Lin MY, Carmeli Y, Zumsteg J, *et al.* Prior antimicrobial therapy and risk for hospital-acquired *Candida* glabrata and *Candida* krusei fungemia: a case-case-control study. Antimicrob Agents Chemother 2005; 49: 4555–4560.

49 Lee I, Zaoutis TE, Fishman NO *et al.* Risk factors for fluconazole resistance in patients with *Candida* glabrata bloodstream infection: potential impact of control group selection on characterizing the association between previous fluconazole use and fluconazole resistance. Am J Infect Control 2010; 38:456–460.

50 • Dizbay M, Fidan I, Kalkanci A, *et al.* High incidence of *Candida* parapsilosis candidaemia in nonneutropenic critically ill patients: Epidemiology and antifungal susceptibility. Scand J Infect Dis 2010; 42:114–120.

This is a report from a Greek ICU with a remarkably high candidaemia rate and particularly of candidaemia owing to *C. parapsilosis.*

51 Brillowska-Dabrowska A, Schon T, Pannanusorn S, *et al.* A nosocomial outbreak of *Candida* parapsilosis in southern Sweden verified by genotyping. Scand J Infect Dis 2009; 41:135–142.

52 Pappas PG, Kauffman CA, Andes D, *et al.* Clinical practice guidelines for the management of candidiasis: 2009 update by the Infectious Diseases Society of America. Clin Infect Dis 2009; 48:503–535.

53 • Arendrup MC, Garcia-Effron G, Lass-Florl C, *et al.* Echinocandin susceptibility testing of *Candida* species: comparison of EUCAST EDef 7.1, CLSI M27-A3, Etest, disk diffusion, and agar dilution methods with RPMI and isosensitest media. Antimicrob Agents Chemother 2010; 54:426–439.

This is the most comprehensive simultaneous comparison of susceptibility methods for echinocandin MIC testing involving a high number of echinocandin resistant isolates with well characterised *FKS* mutations. The study demonstrated that the majority of resistant isolates is misclassified as susceptible using CLSI M28-A3 and current breakpoints (approximately 60% for caspofungin and 90% for anidulafungin and micafungin).

54 • Andes D, Diekema DJ, Pfaller MA, *et al.* In vivo comparison of the pharmacodynamic targets for echinocandin drugs against *Candida* species. Antimicrob Agents Chemother 2010; 54:2497–2506.

PK/PD data in animal experiments suggesting species specific breakpoints should be considered for echinocandins.

55 •• Garcia-Effron G, Park S, Perlin DS. Correlating echinocandin MIC and kinetic inhibition of fks1 mutant glucan synthases for *Candida* albicans: implications for interpretive breakpoints. Antimicrob Agents Chemother 2009; 53:112–122.

This is a demonstration at the enzyme level that hot spot mutations confer decreased susceptibility to echinocandins and that a breakpoint of 2 μg/ml will not correctly identify anidulafungin and micafungin resistant isolates.

56 • Arendrup MC, Garcia-Effron G, Buzina W, *et al.* Breakthrough *Aspergillus* fumigatus and *Candida* albicans double infection during caspofungin treatment: laboratory characteristics and implication for susceptibility testing. Antimicrob Agents Chemother 2009; 53:1185–1193.

First report of an ICU abdominal surgery patient with breakthrough disseminated *Aspergillus* and *Candida* double infection after 40 days of caspofungin. The *Candida* isolate, but not the *Aspergillus* was found to possess a *FKS* mutation.

57 •• Pfeiffer CD, Garcia-Effron G, Zaas AK, *et al.* Breakthrough invasive candidiasis on micafungin. J Clin Microbiol 2010; 48:2373–2380.

This is the first paper describing breakthrough cases on micafungin. Twelve cases were identified of which 11 occurred in transplant recipients. *C. parapsilosis* or *C. glabrata* with *FKS* mutations were most often involved. The clinical context is described.

58 •• Hsin-Yun S, Nina S. Characterisation of breakthrough invasive mycoses in echinocandin recipients: an evidence-based review. Int J Antimicrob Agents 2010; 353:211–218.

This is a comprehensive review describing published reports on breakthrough invasive mycosis in echinocandin recipients. 2.4% of patients receiving echinocandin prophylaxis experience breakthrough infection in most cases owing to nonalbicans spp. The earliest hot spot mutant isolate was obtained after 2 weeks of exposure.

59 • Dannaoui E, Desnos-Ollivier M, Garcia-Hermoso D, *et al.* Infections due to *Candida* spp. with reduced susceptibility to caspofungin in France. Clin Microbiol Infect 2010; 16:S2–S77.

Survey in Paris detecting 14 cases of caspofungin resistant isolates (12 of which were invasive candidiasis cases).

60 Park S, Kelly R, Kahn JN, *et al.* Specific substitutions in the echinocandin target Fks1p account for reduced susceptibility of rare laboratory and clinical *Candida* sp. isolates. Antimicrob Agents Chemother 2005; 49:3264–3273.

61 Garcia-Effron G, Kontoyiannis DP, Lewis RE, Perlin DS. Caspofungin-resistant *Candida* tropicalis strains causing breakthrough fungemia in patients at high risk for hematologic malignancies. Antimicrob Agents Chemother 2008; 52:4181–4183.

62 Pfaller MA, Diekema DJ. Azole antifungal drug cross-resistance: mechanisms, epidemiology, and clinical significance. J Invasive Fungal Infect 2007; 1:74–92.

63 •• MacCallum DM, Coste A, Ischer F, *et al.* Genetic dissection of azole resistance mechanisms in *Candida* albicans and their validation in a mouse model of disseminated infection. Antimicrob Agents Chemother 2010; 54:1476–1483.

This is a characterization of azole resistance mechanisms through sequential genetic manipulations of a clinical isolate with dual resistance mechanisms. Demonstration of how the altered target enzyme and efflux pumps act in concert decreasing the susceptibility *in vitro* and *in vivo* in an animal model.

64 • Oxman DA, Chow JK, Frendl G, *et al.* Candidaemia associated with decreased in vitro fluconazole susceptibility: is *Candida* speciation predictive of the susceptibility pattern? J Antimicrob Chemother 2010; 65:1460–1465.

Typically, species identification is a reliable predictor of susceptibility pattern. But in this report decreased fluconazole susceptibility is detected in as many as 8% of *C. albicans* isolates and in 4% of *C. tropicalis* and *C. parapsilosis*. Overall 19% of 243 episodes involved isolates with decreased fluconazole susceptibility and notably a third of these were isolates belonging to species that are normally susceptible. The implication is that species identification and susceptibility testing should be performed in cases of invasive candidiasis in this setting.

65 Ha JF, Italiano CM, Heath CH, *et al.* Candidemia and invasive candidiasis: a review of the literature for the burns surgeon. Burns 2010 [Epub ahead of print].

66 Roilides E, Farmaki E, Evdoridou J, *et al.* Neonatal candidiasis: analysis of epidemiology, drug susceptibility, and molecular typing of causative isolates. Eur J Clin Microbiol Infect Dis 2004; 23:745–750.

67 Manzoni P, Leonessa M, Galletto P, *et al.* Routine use of fluconazole prophylaxis in a neonatal intensive care unit does not select natively fluconazole-resistant *Candida* subspecies. Pediatr Infect Dis J 2008; 27:731–737.

68 • Mahieu LMM, Van Gasse NM, Wildemeersch D, *et al.* Number of sites of perinatal *Candida* colonization and neutropenia are associated with nosocomial candidemia in the neonatal intensive care unit patient. Pediatr Crit Care Med 2010; 11:240–245.
Maternal vaginal candidiasis, low-birth weight and vaginal delivery were associated with *Candida* colonization in the newborn. Risk of neonatal candidiasis correlated to degree of colonization, to neonatal neutropenia and to severity of disease. The findings offer opportunities for prevention of *Candida* infection in neonatal intensive care unit patients.

69 Moore ECM, Padiglione AAM, Wasiak JM, *et al.* Candida in burns: risk factors and outcomes. J Burn Care Res 2010; 31:257–263.

70 Vardakas KZ, Michalopoulos A, Kiriakidou KG, *et al.* Candidaemia: incidence, risk factors, characteristics and outcomes in immunocompetent critically ill patients. Clin Microbiol Infect 2009; 15:289–292.

71 Leon CM, Ruiz-Santana SMP, Saavedra PP, *et al.* Usefulness of the ''*Candida* score'' for discriminating between *Candida* colonization and invasive candidiasis in nonneutropenic critically ill patients: a prospective multicenter study. Crit Care Med 2009; 37:1624–1633.

72 • Playford EG, Lipman J, Kabir M, *et al.* Assessment of clinical risk predictive rules for invasive candidiasis in a prospective multicentre cohort of ICU patients. Intensive Care Med 2009; 35:2141–2145.
Several reports have proposed prediction rules for invasive candidiasis and evaluated their performance subsequently. However, in this study, the performance of several of these prediction rules and of *Candida* colonization is evaluated outside the population used for establishing the rules. The performances are somewhat disappointing, but improve when combined with colonization index or corrected index.

73 •• Vincent JL, Rello J, Marshall J, *et al.* International study of the prevalence and outcomes of infection in intensive care units. JAMA 2009; 302:2323–2329.
This is a comprehensive global study of prevalence and outcome of almost 14 000 bacterial or fungal infections in the ICU setting.

74 Holley A, Dulhunty J, Blot S, *et al.* Temporal trends, risk factors and outcomes in albicans and nonalbicans candidaemia: an international epidemiological study in four multidisciplinary intensive care units. Int J Antimicrob Agents 2009; 33:554–557.

75 Bassetti M, Ansaldi F, Nicolini L, *et al.* Incidence of candidaemia and relationship with fluconazole use in an intensive care unit. J Antimicrob Chemother 2009; 64:625–629.

76 Swoboda SM, Merz WG, Lipsetta PA. Candidemia: the impact of antifungal prophylaxis in a surgical intensive care unit. Surg Infect (Larchmt) 2003; 4:345–354.

77 • Leroy O, Gangneux JP, Montravers P, *et al.* Epidemiology, management, and risk factors for death of invasive *Candida* infections in critical care: a multicenter, prospective, observational study in France (2005–2006). Crit Care Med 2009; 37:1612–1618.
This is a thorough study of 300 candidaemia or invasive candidiasis cases in French ICUs. Risk factors for invasive candidiasis vs. candidaemia are investigated as are species distribution, antifungal treatment choices before and after species identification and outcome.

78 • Marriott DJ, Playford EG, Chen S, *et al.* Determinants of mortality in nonneutropenic ICU patients with candidaemia. Crit Care 2009; 13: R115.
This is an interesting study on risk factors for mortality in a nationwide survey of candidaemia in Australia. Furthermore, data on metastatic infections are provided. The main predictor of mortality was host factors probably owing to the severe underlying illness in the majority of patients.

79 Arendrup M, Horn T, Frimodt-Moller N. In vivo pathogenicity of eight medically relevant *Candida* species in an animal model. Infection 2002; 30:286–291.

80 Garey KW, Rege M, Pai MP, *et al.* Time to initiation of fluconazole therapy impacts mortality in patients with candidemia: a multiinstitutional study. Clin Infect Dis 2006; 43:25–31.

81 Viscoli C, Girmenia C, Marinus A, *et al.* Candidemia in cancer patients: a prospective, multicenter surveillance study by the Invasive Fungal Infection Group (IFIG) of the European Organization for Research and Treatment of Cancer (EORTC). Clin Infect Dis 1999; 28:1071–1079.

82 Weinberger M, Leibovici L, Perez S, *et al.* Characteristics of candidaemia with *Candida-albicans* compared with nonalbicans *Candida* species and predictors of mortality. J Hosp Infect 2005; 61:146–154.

83 Morrell M, Fraser VJ, Kollef MH. Delaying the empiric treatment of candida bloodstream infection until positive blood culture results are obtained: a potential risk factor for hospital mortality. Antimicrob Agents Chemother 2005; 49:3640–3645.

84 Taur Y, Cohen N, Dubnow S, *et al.* Effect of antifungal therapy timing on mortality in cancer patients with candidemia. Antimicrob Agents Chemother 2010; 54:184–190.

85 • Ortega M, Marco F, Soriano A, *et al. Candida* spp. bloodstream infection: influence of antifungal treatment on outcome. J Antimicrob Chemother 2010; 65:562–568.
This is a retrospective comparison of outcome of candidaemia before and after introduction of echinocandin. The numbers treated with echinocandin are quite low, but still a significantly better outcome was observed in the echinocandin period though mortality was equal in the two periods, if comparing patients receiving azoles.

86 Pai MP, Turpin RS, Garey KW. Association of fluconazole area under the concentration-time curve/MIC and dose/MIC ratios with mortality in nonneutropenic patients with candidemia. Antimicrob Agents Chemother 2007; 51:35–39.

87 Baddley JW, Patel M, Bhavnani SM, *et al.* Association of fluconazole pharmacodynamics with mortality in patients with candidemia. Antimicrob Agents Chemother 2008; 52:3022–3028.

88 Clancy CJ, Yu VL, Morris AJ, *et al.* Fluconazole MIC and the fluconazole dose/MIC ratio correlate with therapeutic response among patients with candidemia. Antimicrob Agents Chemother 2005; 49:3171–3177.

89 Parkins MD, Sabuda DM, Elsayed S, Laupland KB. Adequacy of empirical antifungal therapy and effect on outcome among patients with invasive *Candida* species infections. J Antimicrob Chemother 2007; 60:613–618.

90 Reboli AC, Rotstein C, Pappas PG, *et al.* Anidulafungin versus fluconazole for invasive candidiasis. N Engl J Med 2007; 356:2472–2482.

91 Rex JH, Pappas PG, Karchmer AW, *et al.* A randomized and blinded multicenter trial of high-dose fluconazole plus placebo versus fluconazole plus amphotericin B as therapy for candidemia and its consequences in nonneutropenic subjects. Clin Infect Dis 2003; 36:1221–1228.