Epidemiology of invasive candidiasis
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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 utmost 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.

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

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,
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 3/100000 population whereas Denmark reports 11/100000 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 100000 population [10,19–23]. Finally, in the US surveys conducted in Iowa, San Francisco, Atlanta and Connecticut 6–14 have been reported with the exception of the Baltimore area reporting 25/100000 [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*]. 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 [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 is 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. ciferrii, C. guillermontii, C. inopsicuta, C. humicola, C. lambica, C. lipolytica, C. norvegensis, C. palmisolephila, C. rugosa and C. valida and the following two that are not fully susceptible to the echinocandins: C. fermentati and C. guillermontdi [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. lusitaniae [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 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].
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 14α-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 theazole compound to the enzyme, upregulation of the enzyme level or by active transport of theazole 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 predispose 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...

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

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<td><em>C. guilliermondii</em></td>
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<td><em>C. lusitaniae</em></td>
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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 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 hematological 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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There are no conflicts of interest.

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).


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


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


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.

Oman DA, Chow JK, Frenel G, et al. Candidaemia associated with de- creased 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.


69 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.


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.


86 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.


