Distribution and Diagnostics of Invasive Candidiasis

Subjects: Infectious Diseases

Contributor: Ben Y. Parslow , Christopher R. Thornton

Invasive candidiasis (IC) is a systemic life-threatening infection of immunocompromised humans, but remains a relatively neglected disease among public health authorities. Ongoing assessments of disease epidemiology are needed to identify and map trends of importance that may necessitate improvements in disease management and patient care. Well-established incidence increases, largely due to expanding populations of patients with predisposing risk factors, has led to increased clinical use and pressures on antifungal drugs. This has been exacerbated by a lack of fast, accurate diagnostics that have led treatment guidelines to often recommend preventative strategies in the absence of proven infection, resulting in unnecessary antifungal use in many instances. The consequences of this are multifactorial, but a contribution to emerging drug resistance is of primary concern, with high levels of antifungal use heavily implicated in global shifts to more resistant *Candida* strains.

Candida invasive candidiasis candidemia epidemiology antifungal diagnostics

1. Introduction

Until relatively recently, fungi were a rare cause of life-threatening human disease. Since the early 1980s, invasive fungal diseases (IFDs) have been an increasing occurrence in healthcare environments due to an ever-expanding population susceptible to infection [1][2]. This has largely been driven by the advent of more aggressive interventions and treatments in modern healthcare, placing patients in prolonged states of severe immunosuppression [3][4].

Invasive candidiasis (IC), caused by yeast species in the fungal genus *Candida*, is one of the main systemic, opportunistic fungal diseases of immunocompromised patients. It is associated with significant global burden, with an estimated 750,000 cases occurring annually [5] and with unacceptably high mortality rates of up to 30% [6][7]. More than 15 *Candida* species have now been described as etiologic agents of IC, but >90% of cases are attributed to just five: *C. albicans, C. glabrata, C. parapsilosis, C. tropicalis and C. krusei.* Of these, *C. albicans* is predominant [1][8]. The term invasive candidiasis is used to describe two distinct disease entities: candidemia bloodstream infection (BSI) and deep-seated tissue candidiasis (**Figure 1**), which may occur independently or concomitantly [9].

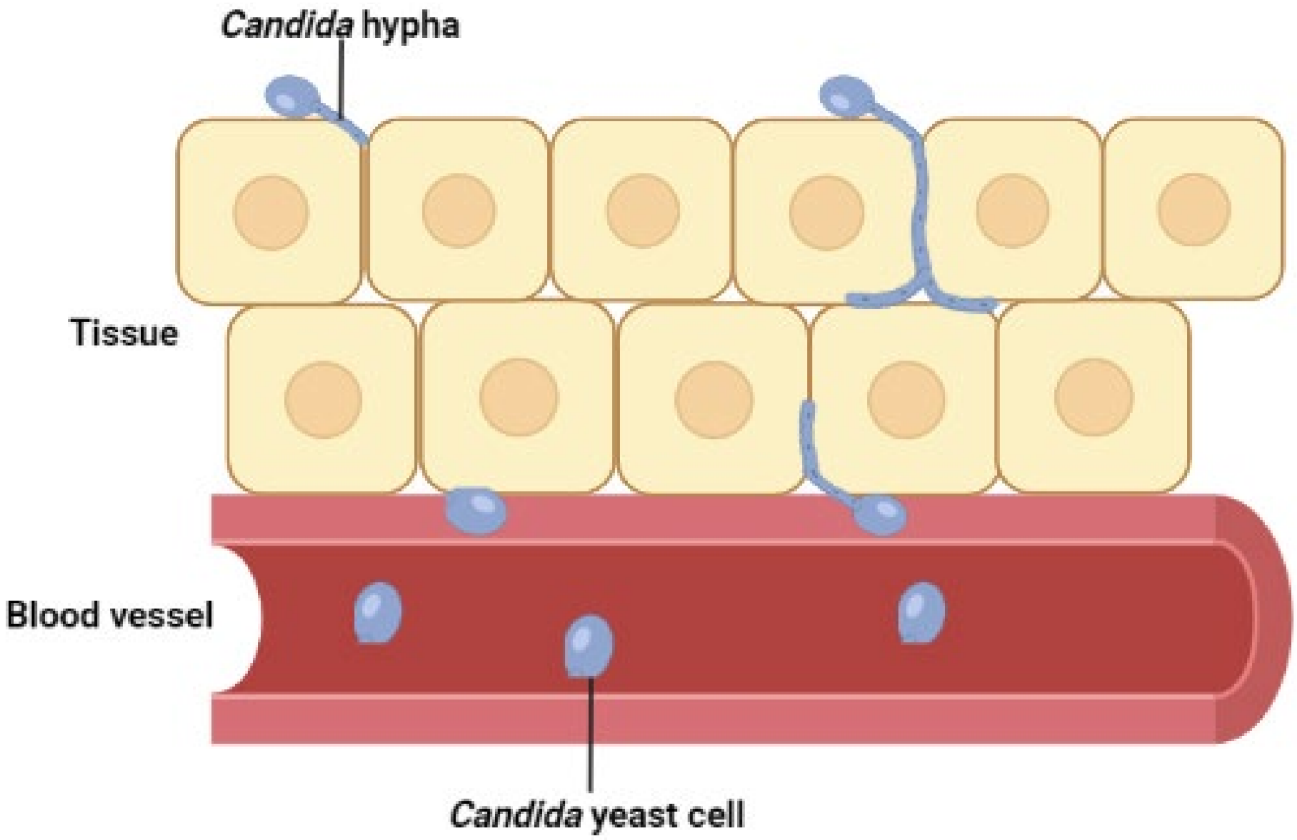

Figure 1. Invasive candidiasis involves rapid dissemination of *Candida* yeast cells in the bloodstream (candidemia BSI) and/or tissue penetration by invasive hypha (deep-seated candidiasis). Hematogenous seeding of *Candida* yeast from blood-borne candidemia is often a key source of tissue candidiasis and *vice versa* [9]. Although hyphal extension is a well-described mechanism of *C. albicans* tissue invasion, its role is less clear for other clinically important *Candida* species such as *C. glabrata* where other mechanisms of invasion may be involved.

Despite being an increasing cause of morbidity and mortality in healthcare settings, IC is still a somewhat neglected topic among public health authorities. Consequently, improvements in disease management and patient care are urgently needed [1][5]. Of particular importance is a lack of fast, accurate diagnostics, with clinicians continuing to rely on suggestive clinical findings and the use of culture-based diagnostics with sub-optimal sensitivity to inform decision making [10]. It is suggested that up to 50% of disease episodes may go undiagnosed by these conventional methods, resulting in delayed treatment initiation and markedly worse patient outcomes [9][10][11]. To mitigate this, current treatment guidelines recommend that prophylactic or empirical preventative strategies be initiated in high-risk populations in the absence of proven infection [12][13]. Whilst some patients will benefit from these measures, non-specific implementation leads to unnecessary use of precious antifungals in many instances. This has led many to raise concerns about the risks of widespread drug resistance among *Candida* spp., particularly given the already limited availability of front-line antifungals [14][15].

Overall, IC represents a major global public health concern. A robust understanding of ongoing disease epidemiology is therefore of importance to identify concerning trends that may inform policy decisions and necessitate the need for improvements in disease management and patient care. In this research, a critical

appraisal of the current IC epidemiologic landscape is made, focusing on prospective surveillance studies that assess patient pre-disposing risk factors, incidence, *Candida* spp. distribution and antifungal susceptibility patterns both spatially and temporally. Particular attention is given to the interplay between these factors. Antifungal treatment and diagnostics are outlined as two key components of IC management, with the influence of current practices on disease epidemiology considered. Realistic improvements in the implementation of these clinical activities are then proposed, offering the potential for a new era in disease management and patient care through improved antifungal stewardship and availability.

2. Species Distribution and Antifungal Susceptibilities

Globally, more than 15 *Candida* spp. are known etiologic agents of IC [16][17], but the majority (>90%) of infections are attributed to just five: *C. albicans, C. glabrata, C. parapsilosis, C. tropicalis and C. krusei* [2][6][18][19][20][21]. As such, they will be the focus here. *Candida albicans* has long been and remains the predominant species present as clinical isolates from infected patients [1], but an ongoing global shift towards non-*albicans Candida* (NAC) species that exhibit decreased antifungal susceptibility is well-established [2][22][23]. Emerging multi-drug-resistant species such as *C. auris*, first described in 2009, represent a serious public health threat and highlight further the concerning global divergence of *Candida* spp. implicated in IC to more resistant strains [24].

As with incidence, when assessing IC species distributions and antifungal susceptibilities, limitations in data must be considered. First is the sub-optimal sensitivity of blood culture, meaning data represent only the testing of isolates from disease events that were culture-positive [25], a partial spectrum of the total IC disease events. Furthermore, although undefined, inevitably not all culture positive cases will undergo species identification and antifungal susceptibility testing. However, as testing is common and even compulsory in some countries and healthcare settings [6][20], the volume of testing may be considered adequate and representative of the species distribution and antifungal susceptibility landscape. Comparisons are also challenged by factors that are not standardised across healthcare settings, with the use of different blood culture systems notable. For example, *C. glabrata* positivity rates have been shown to be higher where the BacT/Alert culture system is used [26][27]. Although this is clinically significant, quantification of differences between culture systems shows inconsistencies and will be impacted by other currently contested confounding factors [27][28]. As such, acceptable concordance will be assumed between blood culture systems in the isolation rates of *Candida* spp.

Here, an assessment of *Candida* spp. distribution and antifungal susceptibility will focus on spatial and temporal data shifts at the continental level. Additionally, specific consideration will be given to the role of patient pre-disposing risk factors in species distribution as well as the interaction between increased use of antifungals and shifts towards strains with less susceptibility [29].

2.1. Influence of Pre-Disposing Risk Factors

Pre-disposing risks for IC, both host and healthcare related factors, can influence the *Candida* spp. implicated in infection [6][29][30]. Increasing patient age, transplant procedures and prior fluconazole exposure are well-

documented factors for increased isolation of *C. glabrata* [29][31][32][33][34]. The latter may point towards an applied selection pressure from fluconazole use, driving *C. glabrata*-implicated infection with greater drug resistance [35]. *C. parapsilosis* is renowned for its high prevalence among pre-term and low-birthweight infants [36][37][38][39]. This may be due to an elevated ability to form biofilms on indwelling devices, which are commonly used in this patient group [40][41]. Another key driver of *C. parapsilosis* infection is its ability for nosocomial spread, notably by hand carriage, leading to hospital outbreaks and persistence [39][42]. With the advent of at-home CVC management, *C. parapsilosis* may therefore also be responsible for the rise in community-acquired IC [8][43]. *C. tropicalis* and *C. krusei* have a heightened presence among severely neutropenic patients on oncology wards [44][45][46]. Oncology-specific *C. tropicalis* incidence now appears to be declining in certain settings, with widespread fluconazole prophylaxis and improved management of central venous catheters (CVCs) likely determinants in these observations [18][29]. Conversely, as with *C. glabrata*, fluconazole exposure is cited as a selection pressure that has acted in the emergence of resistant *C. krusei*, particularly among the oncology patient population [29]. However, reported increases in *C. krusei* prevalence pre-date widespread prophylaxis regimens [47], suggesting other factors have also influenced its emergence. These may include oncology-specific risk factors such as the long-term use of subcutaneous portacaths and CVCs as well as administration of certain chemotherapy agents [48].

2.2. Geographical Trends

Species distribution and antifungal susceptibility shows considerable geographical variation between individual countries, but trends can generally be elucidated at the continental level, such as the Americas and Europe (**Figure 2**). Across some continents (Asia, Africa and Oceania), few distinctive trends are observed and are not well-defined due to limited and contrasting data from mostly single-institution studies [49][50][51][52][53][54]. As a result, data from Asia will be assessed briefly and Africa and Oceania will be excluded from this research.

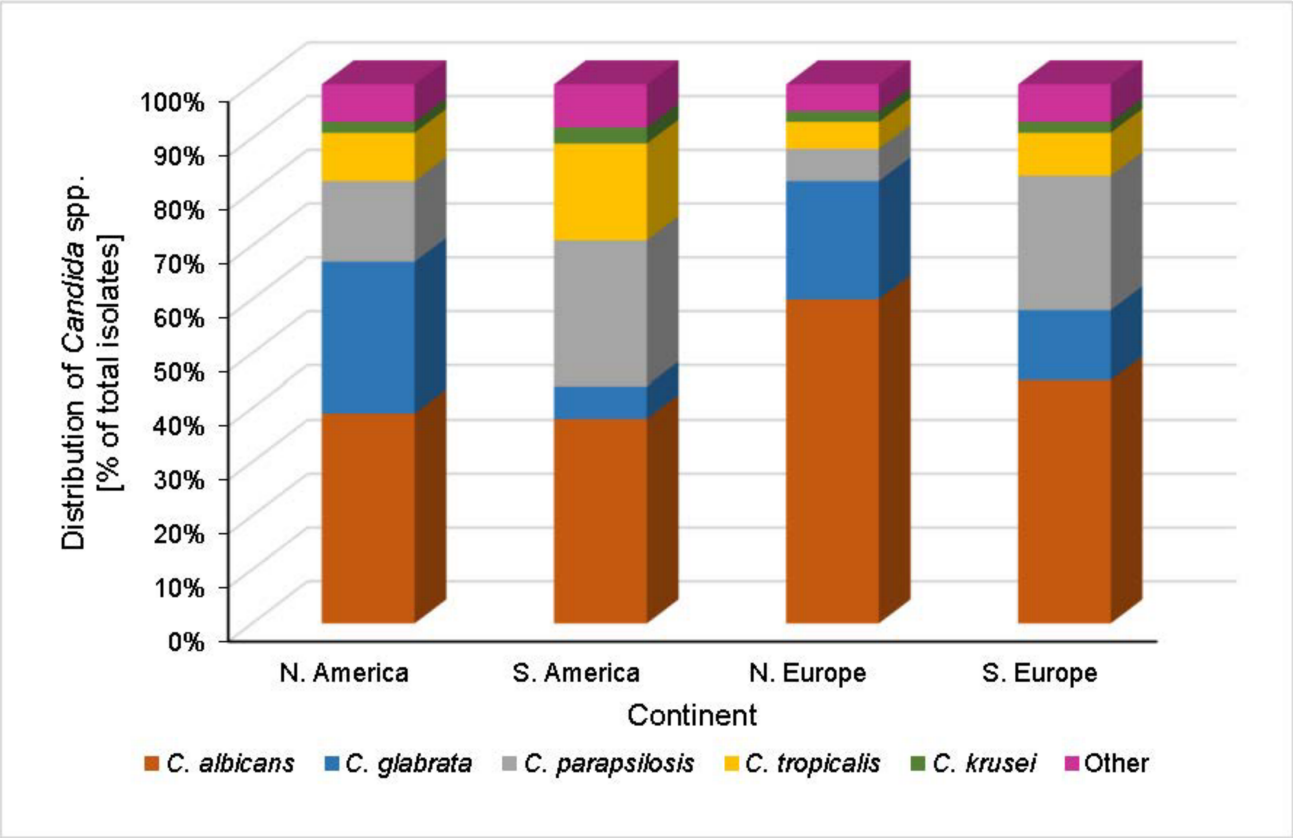

Figure 2. Distributions of *Candida* spp. as a percentage of total IC case counts across North America, South America, North Europe and South Europe [6][55][56][57][58]. In North America, *C. albicans* is the most prevalent *Candida* species, accounting for ~39% of IC episodes. The most common NAC species, representing just under 30% of cases, is *C. glabrata* with sequentially lower case contributions from *C. parapsilosis, C. tropicalis and C. krusei.* European IC species distribution shows two clear trends, split broadly between the north and south of the continent. Northern Europe typically exhibits a similar species distribution to North America, although a greater contribution from *C. albicans* is seen, accounting for 60% of cases. In contrast, the species landscape in southern Europe is more akin to that in South America, where *C. parapsilosis* is the most common NAC species. Across these four regions, <10% of total cases are attributed to species outside of the five described.

2.2.1. United States

Candida glabrata is of the highest concern in the US due to a combination of increasing incidence and high levels of resistance to front-line antifungals [6]. Up until the late 1990s, *C. albicans* accounted for ~50% of all *Candida* BSIs in the US [59], but its contribution has since decreased [6][18][60], with a concurrent increase in NAC incidence observed [1][6][18][59][60]. *C. glabrata* has emerged as the most frequent NAC species, making up 12% of isolates in 1999 [59] but now consistently accounting for just under 30% [6][18][60]. The significance of this trend is justified as *C. glabrata* exhibits high levels of triazole tolerance and emerging echinocandin resistance, albeit to a lesser extent [23][61]. Importantly, resistance shows considerable state variation perhaps due to differing patterns of population pre-disposing factors at a local level, outlining the importance of robust surveillance in local healthcare settings more widely. *C. glabrata* fluconazole resistance has been as high as 20% in selected US states (Georgia), but a

gradual decline to ~10% has been observed since the 1990s [6][18]. Echinocandin resistance has increased simultaneously, with around 4% of *C. glabrata* isolates now displaying elevated MIC_{90} values (minimum concentration of antifungal required to inhibit growth of 90% of *Candida* cells) from susceptibility testing [6]. Decreasing clinical use of fluconazole in place of echinocandin as a first-choice treatment option is thought to be driving this shift, as selection pressures resulting from the use of these two drug classes change [60]. *Candida* echinocandin resistance remains low in most settings, but careful monitoring is required as clinical use inevitably increases [62]. *Candida parapsilosis*, *C. tropicalis* and *C. krusei* are much less frequently isolated, with events largely concentrated in specialist neonatal and oncology units. However, these NAC species also exhibit higher levels of antifungal resistance [35], suggesting the rapid emergence of *C. glabrata* in the US was mediated by several confounding risk factors in addition to selection for antifungal tolerant strains as the predominant factor [59]. It is noteworthy that *C. krusei* consistently exhibits fluconazole MIC_{90} values >64 µg/mL worldwide, rendering this antifungal of little use in *C. krusei*-implicated infections [59][60]. A more comprehensive national surveillance is required to track species-specific incidence and antifungal resistance trends.

2.2.2. Europe

Candida species distribution varies across the European continent. Northern Europe experiences a high contribution from *C. albicans* [55], whilst in central Europe, *C. glabrata* is of increasing prominence [63][64]. Regions of southern Europe consistently report *C. parapsilosis* as the most prevalent NAC strain [43][56][57].

Across northern Europe, *C. albicans* accounts for up to 70% of total IC cases, and *C. glabrata* is the most prevalent NAC species, contributing 10–20% of episodes [20][26][55][65][66][67][68][69]. However, an expected shift towards increasing isolation of more resistant NAC species with increased widespread antifungal use, as seen in the US, has not occurred [65]. A lower disease incidence in the overall population and thus reduced clinical use of antifungals to treat patients with IC may be responsible, limiting the selection pressure posed by such drugs [20]. In Denmark, observations differ and are more akin to the US, where continuing shifts to *C. glabrata* at the expense of *C. albicans* are seen [20][55][70][71]. Data from 2018 show that these species now account for 32.1% and 42.1% of culture confirmed cases, respectively [20]. Higher and combination use of numerous antifungals, notably fluconazole and itraconazole, in Danish healthcare may have driven the observed species disparity with other Nordic countries [55][70][71].

It might be expected that Danish *Candida* isolates would exhibit greater resistance resulting from higher antifungal use and associated selection pressures across Denmark (**Figure 3**). In fact, the opposite is observed whereby neighbouring countries (e.g., Norway) with lower antifungal use report *Candida* isolates with greater resistance levels, most notably for *C. glabrata* [55]. Explanations for this observation are not available, but it may be due to data contributing to these findings representing a small number of isolates (23 *C. glabrata* isolates from Norway compared to 165 from Denmark); hence, resistance rates calculated from susceptibility testing may not be nationally representative [55][72].

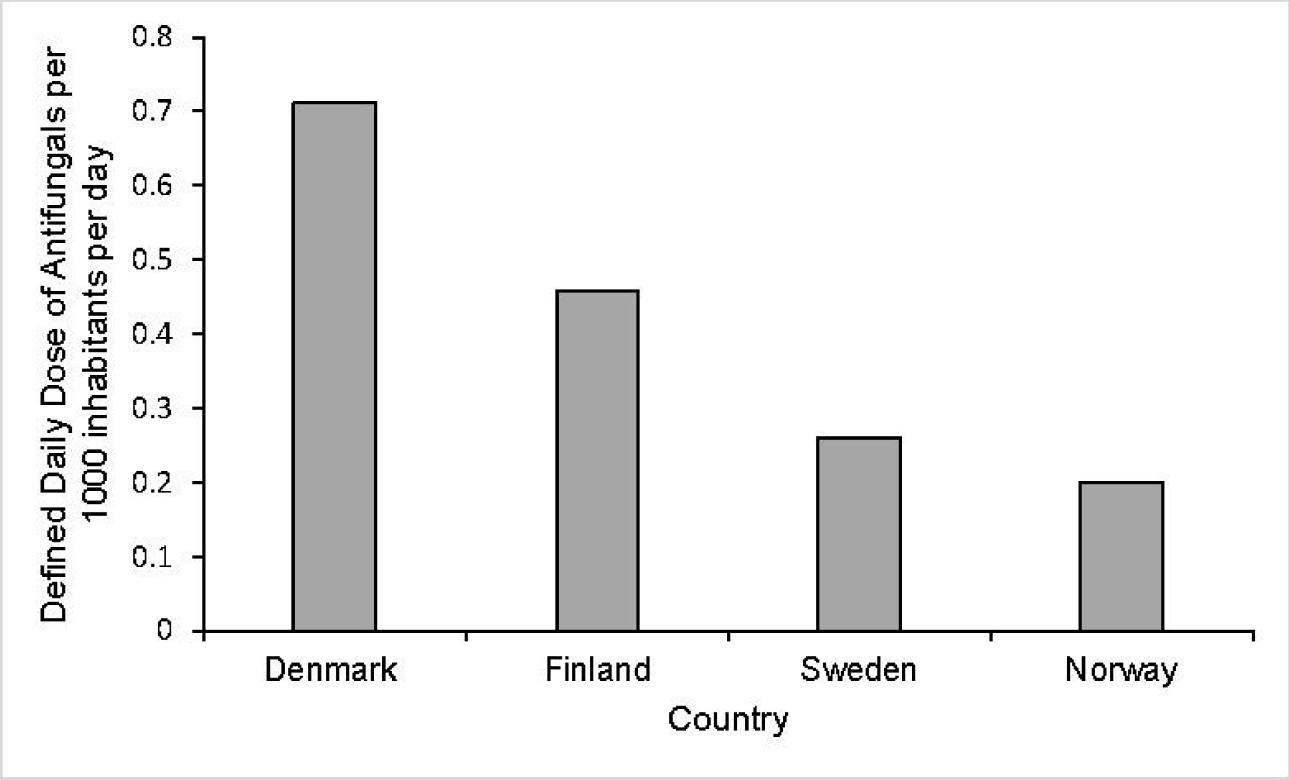

Figure 3. Defined daily dosage (DDD) of antifungal drugs for systemic use per 1000 inhabitants per day in 2011 in healthcare settings across Denmark, Finland, Sweden and Norway. The total use of systemic antifungal drugs is significantly higher across healthcare settings in Denmark than Norway, Sweden and Finland. In Denmark, the DDD per 1000 inhabitants per day was approximately 0.712 compared to 0.459, 0.26 and 0.2 for Finland, Sweden and Norway, respectively [55].

Across central and southern Europe, species and antifungal susceptibility data are comparatively scarce and rely on single/multi-centre studies rather than national programmes. Species distribution trends analogous to the US and Denmark have been reported from institutions across central Europe [63][64][73]. A multi-decade survey by the Fungal Infection Network of Switzerland emphasizes the role of antifungals in these observations, noting that increases in *C. glabrata* isolation and triazole use occurred concomitantly [64]. Studies by others in the region describe a potential reversal of epidemiologic trends, with a marked increase in *C. albicans* and simultaneous decrease in NAC species, driven mostly by reductions in *C. parapsilosis* and *C. tropicalis* prevalence [74][75]. Confirmatory data readouts are required, with important implications if these findings represent ongoing trends. Elsewhere, antifungal use has acted to increase incidence of more resistant NAC species, leading researchers to suggest that recent changes in antifungal practices that favour echinocandin use over triazoles may be implicated [76]. In southern Europe, *C. parapsilosis* is the most common NAC species [43][56][57], with fluconazole-resistant *C. parapsilosis* increasing in prevalence and responsible for a considerably higher neonatal candidemia incidence in the region [37][39][56]. Additionally, *C. parapsilosis* nosocomial transmission is common [42], and therefore outbreaks in an endemic situation cannot be ruled out and may contribute to its increasing isolation further [43]. Overall, given the increasing use of echinocandins in place of triazoles as first-line treatment for IC across Europe, potential changes in species distributions and associated echinocandin resistance should be monitored closely.

2.2.3. South America

In South America, *Candida* species distribution is characterised by high proportions of *C. parapsilosis, C. tropicalis and C. albicans*, contributing >80% of the total IC caseload [58]. *C. parapsilosis* is the predominant NAC species and accounts for ~26.5% of cases across the continent, comparable to observations from southern Europe [56][57][58]. In addition, data from certain countries (Colombia and Venezuela) suggest that *C. parapsilosis* might now be the most common species implicated in infection, surpassing *C. albicans* as the primary causative agent [58]. This may be explained as *C. parapsilosis* is isolated across all age strata whilst on other continents its frequency is heavily concentrated in infant candidiasis.

C. glabrata, of major concern in the US and Europe, accounts for just 6% of IC cases across the South American continent. Additionally, low levels of overall antifungal resistance are seen, and it is thought that lower antifungal use might be implicated in both these trends [58][77][78]. *C. glabrata* is of greater prominence in Brazil, increasing in prevalence and currently accounting for 10% of disease events. Interestingly, differences in antifungal (particularly fluconazole) use were found to be negligible in this increase, with defined daily doses (DDD) consistent with those in neighbouring countries. Therefore, it is suggested that an ageing Brazilian population might be the cause, with increasing age a pre-disposing risk for *C. glabrata* infection specifically [58]. This has important implications, because as other South American countries develop an ageing population in the future, they may expect to see increasing *C. glabrata* isolation with inherent resistance. In fact, more recent data from Peru support these claims with *C. glabrata* now approaching 10% of cases there also [77]. Of note, *C. guilliermondii* was found to have a higher incidence than both *C. glabrata* and *C. krusei*, driven by an exceptionally high prevalence in Honduras, accounting for 28% of candidemia cases. High prevalence of *C. parapsilosis* overall and *C. guilliermondii* in specific regions warrants important considerations for antifungal stewardship in South America, as these species contain naturally occurring polymorphisms that increase the likelihood of emerging echinocandin resistance [79][80].

At present, triazoles are still recommended as the first-line therapy for IC. With potential for future increasing isolation of *C. glabrata* and associated triazole resistance, as seen in Brazil, this may change. If this trend continues, treatment guidelines may increasingly recommend echinocandin use over triazoles. In this scenario, additional surveillance will be required to promptly identify trends that may arise in *C. parapsilosis* and *C. guilliermondii* echinocandin resistance specifically.

2.2.4. Asia

Across the Asian continent, few distinctive trends in current species distribution and antifungal susceptibility can be concluded due to limited, contrasting data from mostly single-institution retrospective surveillance studies. Generally, *C. tropicalis* might be the primary etiologic agent of IC across west Asia (e.g., Pakistan, India) whilst in east Asia (e.g., China), *C. albicans* remains the most prevalent species with widely varied contributions from NAC species [49][50][51][52][53][54]. This is unsurprising given that China covers a land area of 9.38 million km^2 and has a population of nearly 1.5 billion, which will inevitably show regional variations in pre-disposing population dynamics and risk factors that influence species distribution.

3. Diagnostics

Invasive candidiasis encompasses two distinct disease entities, candidemia BSI and deep-seated tissue candidiasis, with their distinction having important implications for diagnosis [9]. Blood culture representing the primary diagnostic choice to inform clinicians when IC infection is suspected [81][82]. Increasing development, availability and use of non-culture biomarker tests will likely complement rather than replace culture methods in the future, with combined use promising a new paradigm in patient care and disease management [10][82][83][84][85][86].

3.1. Culture-Based Diagnostics

Culture-based diagnostics, involving the detection and growth of viable *Candida* cells, typically from blood, has been the primary diagnostic tool for decades [81][82]. Culture accurately diagnoses the majority of active candidemia BSI cases, with non-culture diagnostics unlikely to offer significantly lower thresholds of detection [87]. However, ~50% of total IC infection episodes are thought to go undiagnosed by blood culture, reflecting insufficient or absent viable *Candida* cells in circulation for detection [10][25]. These missed diagnoses are largely due to low detection rates and false-negative results for deep-seated tissue candidiasis [9][85][88], resulting from intermittent release of cells from infected tissue sites into circulation or deep-seated candidiasis that is independent of blood-borne candidemia [9][10][85][89]. Sensitivity is also influenced by *Candida* spp., mode of infection and antifungal drugs with *C. glabrata*-implicated candidemia, infection stemming from extravascular sources and use of antifungals at the time of blood draw associated with lower burdens of the pathogen and decreased likelihood of positive culture [25][90][91]. In addition to sub-optimal sensitivity for deep-seated infection and non-active candidemia, blood cultures are associated with highly variable and slow turnaround times, taking up to 8 days until positive culture [25][89]. Sub-optimal sensitivity and slow turnaround times mean that blood culture has limited utility as a definitive diagnostic, with clinicians usually utilising culture for confirmatory purposes and often taking account of multiple suggestive clinical findings to inform clinical decision making instead.

3.2. CHROMagar for Species Identification

Widely used mediums for the isolation and growth of *Candida*, such as Sabouraud dextrose agar (SDA) and potato dextrose agar (PDA), are unable to differentiate between *Candida* spp. commonly implicated in IC [92][93]. CHROMagar *Candida* offers a solution, a selective and differential chromogenic isolation medium allowing for presumptive identification of some *Candida* strains of clinical importance through observations of contrasting colony morphology and colour [93][94][95][96]. Contrasting colony colours result from reactions of species-specific enzymes with a proprietary chromogenic substrate [93]. Studies indicate that *C. albicans, C. tropicalis, C. krusei* [94][97] and sometimes *C. glabrata* [94][98] can be differentiated based on these characteristics when grown on this chromogenic medium. Of note, *C. parapsilosis*, due to a wide range of colony colours and morphologies, cannot be distinguished using CHROMagar [99].

The use of CHROMagar medium to identify *Candida* strains implicated in infection, particularly NAC species, can assist clinicians in selecting appropriate antifungal drugs that will be effective and thus may yield significant patient

benefit. However, in settings where *C. parapsilosis* is the predominant NAC species, such as in South America and Southern Europe, the utility of CHROMagar will be more limited.

3.3. Disease Management and Patient Care Impacts

Culture-based diagnostics have important implications for the patient care and management of IC in healthcare settings, resulting from their poor sensitivity and slow turnaround times that lead to limited clinical utility and gaps in people's understanding of the clinical disease spectrum [9][10][81]. Resulting delayed or missed diagnosis of these infections are therefore common and may negatively influence patient prognosis by hindering the initiation of treatment [11]. To mitigate this, current treatment guidelines recommend that early empirical and prophylactic therapy be initiated in high-risk individuals in the absence of an active infection or prior to culture diagnosis [12][13]. Although some individuals will benefit from this practice, its implementation across whole populations of high-risk patients leads to unnecessary use of precious antifungals in many instances, with important implications [12][100]. Of primary concern are the risks of emerging antifungal-resistant strains, as outlined previously, resulting from the high selection pressures caused by widespread high levels of antifungal use. This may decrease drug efficacy in an already limited number of licensed antifungal agents for IC treatment. Furthermore, the significant healthcare costs implicated in high antifungal use as well as severe side effects endured by recipients are also important [15][29][35]. Antifungal toxicities have both direct and indirect effects on patient health [15]. Indirect impacts may relate to patients' underlying conditions, with waning compliance to oral medication regimens due to antifungal-induced nausea and vomiting of particular concern among paediatrics [101].

Poor sensitivity of culture-based diagnostics for IC and slow turnaround times have ultimately meant that clinicians must balance the benefits of early empirical or prophylactic therapy in selected high-risk individuals with the risks posed by an increased propensity for emerging antifungal resistance, severe side effects and substantial healthcare costs.

References

1. Pappas, P.G.; Lionakis, M.S.; Arendrup, M.C.; Ostrosky-Zeichner, L.; Kullberg, B.J. Invasive candidiasis. Nat. Rev. Dis. Primers 2018, 11, 18026.
2. Pfaller, M.A.; Diekema, D.J. Epidemiology of invasive candidiasis: A persistent public health problem. Clin. Microbiol. Rev. 2007, 20, 133–163.
3. Fischer, M.C.; Gurr, S.J.; Cuomo, C.A.; Blehert, D.S.; Jin, H.; Stukenbrock, E.H.; Stajich, J.E.; Kahmann, R.; Boone, C.; Denning, D.W.; et al. Threats posed by the fungal kingdom to humans, wildlife and agriculture. mBio 2020, 11, e00449-20.
4. Yapar, N. Epidemiology and risk factors for invasive candidiasis. Ther. Clin. Risk Manag. 2014, 10, 95–105.

5. Bongomin, F.; Gago, S.; Oladele, R.O.; Denning, D.W. Global and multi-national prevalence of fungal diseases—Estimate precision. J. Fungi 2017, 3, 57.
6. Toda, M.; Williams, S.R.; Berkow, E.L.; Farley, M.M.; Harrison, L.H.; Bonner, L.; Marceaux, K.M.; Hollick, R.; Zhang, A.Y.; Schaffner, W.; et al. Population-based active surveillance for culture confirmed candidemia—Four sites, United States, 2012–2016. MMWR Surveill. Summ. 2019, 68, 1–15.
7. Saville, S.P.; Lazzell, A.L.; Monteagudo, C.; Lopez-Ribot, J. Engineered control of cell morphology in vivo reveals distinct roles for yeast and filamentous forms of Candida albicans during infection. Eukaryot. Cell 2003, 2, 1053–1060.
8. Pfaller, M.A.; Moet, G.J.; Messer, S.A.; Jones, R.N.; Castanheira, M. Candida bloodstream infections: Comparison of species distributions and antifungal resistance patterns in community-onset and nosocomial isolates in the SENTRY Antimicrobial Surveillance Program, 2008–2009. Antimicrob. Agents Chemother. 2011, 55, 561–566.
9. Clancy, C.J.; Nguyen, M.H. Finding the “missing 50%” of invasive candidiasis: How nonculture diagnostics will improve understanding of disease spectrum and transform patient care. Clin. Infect. Dis. 2013, 56, 1284–1292.
10. Clancy, C.J.; Nguyen, M.H. Diagnosing invasive candidiasis. J. Clin. Microbiol. 2018, 56, e01909-17.
11. Garey, K.W.; Rege, M.; Pai, M.P.; Mingo, D.E.; Suda, K.J.; Turpin, R.S.; Bearden, D.T. Time to initiation of fluconazole therapy impacts mortality in patients with candidemia: A multi-institutional study. Clin. Infect. Dis. 2006, 43, 25–31.
12. Pappas, P.G.; Kauffman, C.A.; Andes, D.R.; Clancy, C.J.; Marr, K.A.; Ostrosky-Zeichner, L.; Reboli, A.C.; Schuster, M.G.; Vazquez, J.A.; Walsh, T.J.; et al. Clinical practice guideline for the management of candidiasis: 2016 Update by the Infectious Diseases Society of America. Clin. Infect. Dis. 2016, 62, e1–e50.
13. Cornely, O.A.; Bassetti, M.; Calandra, T.; Garbino, J.; Kullberg, B.J.; Lortholary, O.; Meersseman, W.; Akova, M.; Arendrup, M.C.; Arikan-Akdagli, S.; et al. ESCMID Guideline for the diagnosis and management of Candida diseases 2012: Non-neutropenic adult patients. Clin. Microbiol. Infect. 2012, 7, 19–37.
14. Bassetti, M.; Righi, E.; Montravers, P.; Cornely, O.A. What has changed in the treatment of invasive candidiasis? A look at the past 10 years and ahead. J. Antimicrob. Chemother. 2018, 73, i14–i25.
15. Ostrosky-Zeichner, L.; Casadevall, A.; Galgiani, J.N.; Odds, F.C.; Rex, J.H. An insight into the antifungal pipeline: Selected new molecules and beyond. Nat. Rev. Drug Discov. 2010, 9, 719–727.

16. Hazen, K.C. New and emerging yeast pathogens. Clin. Microbiol. Rev. 1995, 8, 462–478.
17. Pfaller, M.A.; Diekema, D.J. Rare and emerging opportunistic fungal pathogens: Concern for resistance beyond Candida albicans and Aspergillus fumigatus. J. Clin. Microbiol. 2004, 42, 4419–4431.
18. Cleaveland, A.A.; Harrison, L.H.; Farley, M.M.; Hollick, R.; Stein, B.; Chiller, T.M.; Lockhart, S.R.; Park, B.J. Declining incidence of candidemia and the shifting epidemiology of Candida resistance in two US metropolitan areas, 2008—2013: Results from population-based surveillance. PLoS ONE 2015, 10, e0120452.
19. Magill, S.S.; Edwards, J.R.; Bamberg, W.; Beldavs, Z.G.; Dumyati, G.; Kainer, M.A.; Lynfield, R.; Maloney, M.; McAllister-Hollod, L.; Nadle, J.; et al. Multistate point-prevalence survey of healthcare associated infections. N. Engl. J. Med. 2014, 370, 1198–1208.
20. Risum, M.; Astvad, K.; Johansen, H.K.; Schonheyder, H.C.; Rosenvinge, F.; Knudsen, J.D.; Hare, R.; Datcu, R.; Roder, B.L.; Antsupova, V.S.; et al. Update 2016–2018 of the nationwide Danish Fungaemia Surveillance Study: Epidemiologic changes in a 15-year perspective. J. Fungi 2021, 7, 491.
21. Banerjee, S.N.; Emori, T.G.; Culver, D.H.; Gaynes, R.P.; Jarvis, W.R.; Horan, T.; Edwards, J.R.; Tolson, J.; Henderson, T.; Martone, W.J. Secular trends in nosocomial primary bloodstream infections in the United States, 1980–1989. Am. J. Med. 1991, 91, S86–S89.
22. Lass-Flörl, C. The changing face of epidemiology of invasive fungal disease in Europe. Mycoses 2009, 52, 197–205.
23. Pfaller, M.A.; Castanheira, M.; Messer, S.A.; Moet, G.J.; Jones, R.N. Echinocandin and triazole antifungal susceptibility profiles for Candida spp., Cryptococcus neoformans, and Aspergillus fumigatus: Application of new CLSI clinical breakpoints and epidemiologic cut-off values to characterise resistance in the SENTRY Antimicrobial Surveillance Program (2009). Diagn. Microbiol. Infect. Dis. 2011, 69, 45–50.
24. Satoh, K.; Makimura, K.; Hasumi, Y.; Nishiyama, Y.; Uchida, K.; Yamaguchi, H. Candida auris sp. nov., a novel ascomycetous yeast isolated from the external ear canal of an inpatient in a Japanese hospital. Microbiol. Immunol. 2009, 53, 41–44.
25. Pfeiffer, C.D.; Samsa, G.P.; Schell, W.A.; Reller, L.B.; Perfect, J.R.; Alexander, B.D. Quantification of Candida CFU in initial positive blood cultures. J. Clin. Microbiol. 2011, 49, 2878–2883.
26. Sandven, P.; Bevanger, L.; Digranes, A.; Haukland, H.H.; Mannsaker, T.; Gaustad, P. Candidemia in Norway (1991–2003): Results from a nationwide study. J. Clin. Microbiol. 2006, 44, 1977–1981.
27. Horvath, L.L.; George, B.J.; Murray, C.K.; Harrison, L.S.; Hospenthal, D.R. Direct comparison of the BACTEC 9240 and BacT/Alert 3D automated blood culture systems for Candida growth detection. J. Clin. Microbiol. 2004, 42, 115–118.

28. Horvath, L.L.; Hospenthal, D.R.; Murray, C.K.; Dooley, D.P. Detection of simulated candidemia by the BACTEC 9240 system with plus aerobic/F and anaerobic/F blood culture bottles. J. Clin. Microbiol. 2003, 41, 4714–4717.
29. Abi-Said, D.; Anaissie, E.; Uzun, O.; Raad, I.; Pinzcowski, H.; Vartivarian, S. The epidemiology of hematogenous candidiasis caused by different Candida species. Clin. Infect. Dis. 1997, 24, 1122–1128.
30. McCarty, T.P.; Pappas, P.G. Invasive candidiasis. Infect. Dis. Clin. North Am. 2016, 30, 103–124.
31. Alexander, B.D.; Schell, W.A.; Miller, J.L.; Long, G.D.; Perfect, J.R. Candida glabrata fungemia in transplant patient receiving voriconazole after fluconazole. Transplantation 2005, 80, 868–871.
32. Baran, J.; Muckatira, B.; Khatib, R. Candidemia before and during the fluconazole era: Prevalence, type of species and approach to treatment in a tertiary care community hospital. Scand. J. Infect. Dis. 2001, 33, 137–139.
33. Lin, M.Y.; Carmeli, Y.; Zumsteg, J.; Flores, E.L.; Tolentino, J.; Sreeramoju, P.; Weber, S.G. 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.
34. Blumberg, H.M.; Jarvis, W.R.; Soucie, J.M.; Edwards, J.E.; Patterson, J.E.; Pfaller, M.A.; Rangel-Frausto, M.S.; Rinaldi, M.G.; Saiman, L.; Wiblin, R.T.; et al. Risk factors for candidal bloodstream infections in surgical intensive care unit patients: The NEMIS prospective multicentre study. The National Epidemiology of Mycosis Survey. Clin. Infect. Dis. 2001, 33, 177–186.
35. White, M.H. The contribution of fluconazole to the changing epidemiology of invasive candidal infections. Clin. Infect. Dis. 1997, 24, 1129–1130.
36. Oeser, C.; Lamagni, T.; Heath, P.T.; Sharland, M.; Ladhani, S. The epidemiology of neonatal and pediatric candidemia in England and Wales, 2000–2009. Pediatr. Infect. Dis. J. 2013, 32, 23–26.
37. Oeser, C.; Vergnano, S.; Naidoo, R.; Anthony, M.; Chang, J.; Chow, P.; Clarke, P.; Embleton, N.; Kennea, N.; Pattnayak, S.; et al. Neonatal invasive fungal infection in England 2004–2010. Clin. Microbiol. Infect. 2014, 20, 936–941.
38. Levy, I.; Rubin, L.G.; Vasishtha, S.; Tucci, V.; Sood, S.K. Emergence of Candida parapsilosis as the predominant species causing candidemia in children. Clin. Infect. Dis. 1998, 26, 1086–1088.
39. Lupetti, A.; Tavanti, A.; Davini, P.; Ghelardi, E.; Corsini, V.; Merusi, I.; Boldrini, A.; Campa, M.; Senesi, S. Horizontal transmission of Candida parapsilosis candidemia in a neonatal intensive care unit. J. Clin. Microbiol. 2002, 40, 2363–2369.
40. Branchini, M.L.; Pfaller, M.A.; Rhine-Chalberg, J.; Frempong, T.; Isenberg, H.D. Genotypic variation and slime production among blood and catheter isolates of Candida parapsilosis. J. Clin. Microbiol. 1994, 32, 452–456.

41. Clark, T.A.; Slavinski, S.A.; Morgan, J.; Lott, T.; Arthington-Skaggs, B.A.; Brandt, M.E.; Webb, R.M.; Currier, M.; Flowers, R.H.; Fridkin, S.K.; et al. Epidemiologic and molecular characterization of an outbreak of Candida parapsilosis bloodstream infections in a community hospital. J. Clin. Microbiol. 2004, 42, 4468–4472.
42. Fridkin, S.K. The changing face of fungal infections in healthcare settings. Clin. Infect. Dis. 2005, 41, 1455–1460.
43. Almirante, B.; Rodriguez, D.; Cuenca-Estrella, M.; Almela, M.; Sanchez, F.; Ayats, J.; Alonso-Tarres, C.; Rodriquez-Tudela, J.L.; Pahissa, A. Epidemiology, risk factors, and prognosis of Candida parapsilosis bloodstream infections: Case-control population-based surveillance study of patients in Barcelona, Spain, from 2002–2003. J. Clin. Microbiol 2006, 44, 1681–1685.
44. Kontoyiannis, D.P.; Vaziri, I.; Hanna, H.A.; Boktour, M.; Thornby, J.; Hachem, R.; Bodey, G.P.; Raad, I.I. Risk factors for Candida tropicalis fungemia in patients with cancer. Clin. Infect. Dis. 2001, 33, 1676–1681.
45. Marr, K.A.; Seidel, K.; White, T.C.; Bowden, R.A. Candidemia in allogenic blood and marrow transplant recipients: Evolution of risk factors after the adoption of prophylactic fluconazole. J. Infect. Dis. 2000, 181, 309–316.
46. Castanheira, M.; Messer, S.A.; Rhomberg, P.R.; Pfaller, M.A. Antifungal susceptibility patterns of a global collection of fungal isolates: Results of the SENTRY Antifungal Surveillance Program (2013). Diagn. Microbiol. Infect. Dis. 2016, 85, 200–204.
47. Merz, W.G.; Karp, J.E.; Schron, D.; Saral, R. Increased incidence of fungemia caused by Candida krusei. J. Clin. Microbiol. 1986, 24, 581–584.
48. Teoh, F.; Pavelka, N. How chemotherapy increases the risk of systemic candidiasis in cancer patients: Current paradigm and future directions. Pathogens 2016, 5, 6.
49. Kaur, H.; Singh, S.; Rudramurthy, S.M.; Ghosh, A.K.; Jayashree, M.; Narayana, Y.; Ray, P.; Chakrabarti, A. Candidemia in a tertiary care centre of developing country: Monitoring possible change in spectrum of agents and antifungal susceptibility. Indian J. Med. Microbiol. 2020, 38, 110–116.
50. Zeng, Z.; Ding, Y.; Tian, G.; Yang, K.; Deng, J.; Li, G.; Liu, J. A seven-year surveillance study of the epidemiology, antifungal susceptibility, risk factors and mortality of candidemia among paediatric and adult inpatients in a tertiary teaching hospital in China. Antimicrob. Resist. Infect. Control 2020, 9, 133.
51. Zeng, Z.; Tiang, G.; Ding, Y.; Yang, K.; Liu, J.; Deng, J. Surveillance study of the prevalence, species distribution, antifungal susceptibility, risk factors and mortality of invasive candidiasis in a tertiary teaching hospital in Southwest China. BMC Infect. Dis. 2019, 19, 939.

52. Xiao, Z.; Wang, Q.; Zhu, F.; An, Y. Epidemiology, species distribution, antifungal susceptibility and mortality risk factors of candidemia among critically ill patients: A retrospective study from 2011–2017 in a teaching hospital in China. Antimicrob. Resist. Infect. Control 2019, 8, 89.

53. Boonslip, S.; Homkaew, A.; Phumisantiphong, U.; Nutalai, D.; Wongsuk, T. Species distribution, antifungal susceptibility and molecular epidemiology of candida species causing candidemia in a tertiary care hospital in Bangkok, Thailand. J. Fungi 2021, 7, 577.

54. Yamin, D.; Husin, A.; Harun, A. Distribution of candidemia in a Malaysian tertiary care hospital revealed predominance of Candida parapsilosis. Trop. Biomed. 2020, 37, 903–910.

55. Hesstvedt, L.; Arendrup, M.C.; Poikonen, E.; Klingpor, L.; Friman, V.; Nordoy, I. Differences in epidemiology of candidemia in the Nordic countries—What is to blame? Mycoses 2017, 60, 11–19.

56. Puig-Asensio, M.; Padilla, B.; Garnacho-Montero, J.; Zaragoza, O.; Aguado, J.M.; Zaragoza, R.; Montejo, M.; Munoz, P.; Ruiz-Camps, I.; Cuenca-Estrella, M.; et al. Epidemiology and predictive factors for early and late mortality in Candida bloodstream infections: A population-based surveillance in Spain. Clin. Microbiol. Infect. 2014, 20, O245–O254.

57. Barchiesi, F.; Orsetti, E.; Gesuita, R.; Skrami, E.; Manso, E. Epidemiology, clinical characteristics, and outcome of candidemia in a tertiary referral center in Italy from 2010–2014. Infection 2016, 44, 205–213.

58. Nucci, M.; Queiroz-Telles, F.; Alvarado-Matute, T.; Tiraboschi, I.N.; Cortes, J.; Zurita, J.; Guzman-Blanco, M.; Santolaya, M.E.; Thompson, L.; Sifuentes-Osornio, J.; et al. Epidemiology of candidemia in Latin America: A laboratory-based survey. PLoS ONE 2013, 8, e59373.

59. Kao, A.S.; Brandt, M.E.; Pruitt, W.R.; Conn, L.A.; Perkins, B.A.; Stephens, D.S.; Baughman, W.S.; Reingold, A.L.; Rothrock, G.A.; Pfaller, M.A.; 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.

60. Cleaveland, A.A.; Farley, M.M.; Harrison, L.H.; Stein, B.; Hollick, R.; Lockhart, S.R.; Magill, S.S.; Derado, G.; Park, B.J.; Chiller, T.M. Changes in incidence and antifungal drug resistance in candidemia: Results from population-based laboratory surveillance in Atlanta and Baltimore, 2008-2011. Clin. Infect. Dis. 2012, 55, 1352–1361.

61. Hajjeh, R.A.; Sofair, A.N.; Harrison, L.H.; Lyon, G.M.; Arthington-Skaggs, B.A.; Mirza, S.A.; Phelan, M.; Morgan, J.; Lee-Yang, W.; Ciblak, M.A.; 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.

62. Perlin, D.S. Echinocandin resistance in Candida. Clin. Infect. Dis. 2015, 61, S612–S617.

63. Marchetti, O.; Bille, J.; Fluckiger, U.; Eggimann, P.; Ruef, C.; Garbino, J.; Calandra, T.; Glauser, M.; Tauber, M.G.; Pittet, D. Epidemiology of candidemia in Swiss tertiary care hospitals: Secular trends, 1991–2000. Clin. Infect. Dis. 2004, 38, 311–320.

64. Adam, K.; Osthoff, M.; Lamoth, F.; Conen, A.; Erard, V.; Boggian, K.; Schreiber, P.W.; Zimmerli, S.; Bochud, P.; Neofytos, D.; et al. Trends of the epidemiology of candidemia in Switzerland: A 15-year FUNGINOS survey. Open Forum Infect. Dis. 2021, 8, ofab471.

65. Asmundsdottir, L.R.; Erlendsdottir, H.; Gottfredsson, M. Nationwide study of candidemia, antifungal use, and antifungal drug resistance in Iceland, 2000 to 2011. J. Clin. Microbiol 2013, 51, 841–848.

66. Poikonen, E.; Lyytikäinen, O.; Anttila, V.J.; Koivula, I.; Lumio, J.; Kotilainen, P.; Syrjälä, H.; Ruutu, P. Secular trend in candidemia and the use of fluconazole in Finland, 2004–2007. BMC Infect. Dis. 2010, 10, 312.

67. Asmundsdottir, L.R.; Erlendsdottir, H.; Gottfredsson, M. Increasing incidence of candidemia: Results from a 20-year nationwide study in Iceland. J. Clin. Microbiol. 2002, 40, 3482–3492.

68. Poikonen, E.; Lyytikäinen, O.; Anttila, V.J.; Ruutu, P. Candidemia in Finland, 1995–1999. Emerg. Infect. Dis. 2003, 9, 985–990.

69. Ericsson, J.; Chryssanthou, E.; Klingspor, L.; Johansson, A.G.; Ljungman, P.; Svensson, E.; Sjölin, J. Candidemia in Sweden: A nationwide prospective observational study. Clin. Microbiol. Infect. 2013, 19, E218–E221.

70. Arendrup, M.C.; Bruun, B.; Christensen, J.J.; Fuursted, K.; Johansen, H.K.; Kjaeldgaard, P.; Knudsen, J.D.; Kristensen, L.; Moller, J.; Nielsen, L.; et al. National surveillance of fungemia in Denmark (2004–2009). J. Clin. Microbiol. 2010, 49, 325–334.

71. Arendrup, M.C.; Dzajic, E.; Jensen, R.H.; Johansen, H.K.; Kjaeldgaard, P.; Knudsen, J.D.; Kristensen, L.; Leitz, C.; Lemming, L.E.; Nielsen, L.; et al. Epidemiological changes with potential implication for antifungal prescription recommendations for fungaemia: Data from a nationwide fungaemia surveillance programme. Clin. Microbiol. Infect. 2013, 19, E343–E353.

72. Hesstvedt, L.; Gaustad, P.; Andersen, C.T.; Haarr, E.; Hannula, R.; Haukland, H.H.; Hermansen, N.-O.; Larssen, K.W.; Mylvaganam, H.; Ranheim, T.E.; et al. Twenty-two years of candidemia surveillance: Results from a Norwegian national study. Clin. Microbiol. Infect. 2015, 21, 938–945.

73. Chalmers, C.; Gaur, S.; Chew, J.; Wright, T.; Kumar, A.; Mathur, S.; Wan, W.Y.; Gould, I.M.; Leanord, A.; Bal, A.M. Epidemiology and management of candidemia—A retrospective, multicentre study in five hospitals in the UK. Mycoses 2011, 54, e795–e800.

74. Vannini, M.; Emery, S.; Lieutier-Colas, F.; Legueult, K.; Mondain, V.; Retur, N.; Gastaud, L.; Pomares, C.; Hasseine, L. Epidemiology of candidemia in NICE area, France: A five-year study of antifungal susceptibility and mortality. J. Mycol. Med. 2022, 32, 101210.

75. Schroeder, M.; Weber, T.; Denker, T.; Winterland, S.; Wichmann, D.; Rohde, H.; Ozga, A.-K.; Fischer, M.; Kluge, S. Epidemiology, clinical characteristics, and outcome of candidemia in critically ill patients in Germany: A single-centre retrospective 10-year analysis. Ann. Intensive Care 2020, 10, 142.
76. Bassetti, M.; Ansaldi, F.; Nicolini, L.; Malfatto, E.; Molinari, M.P.; Mussap, M.; Rebesco, B.; Pallavicini, F.B.; Icardi, G.; Viscoli, C. Incidence of candidemia and relationship with fluconazole use in an intensive care unit. J. Antimicrob. Chemother. 2009, 64, 625–629.
77. Rodriguez, L.; Bustamante, B.; Huaroto, L.; Agurto, C.; Illescas, R.; Ramirez, R.; Diaz, A.; Hidalgo, J. A multi-centric study of Candida bloodstream infection in Lima-Callao, Peru: Species distribution, antifungal resistance and clinical outcomes. PLoS ONE 2017, 12, e0175172.
78. Rodrigues, D.K.B.; Bonfietti, L.X.; Garcia, R.A.; Araujo, M.R.; Rodrigues, J.S.; Gimenes, V.M.F.; Melhem, M.S.C. Antifungal susceptibility profile of Candida clinical isolates from 22 hospitals of Sao Paulo state, Brazil. Braz. J. Med. Biol. Res. 2021, 54, e10928.
79. Garcia-Effron, G.; Katiyar, S.K.; Park, S.; Edlind, T.D.; Perlin, D.S. A naturally occurring proline-to-alanine amino acid change in Fks1p in Candida parapsilosis, Candida orthopsilosis, and Candida metapsilosis accounts for reduced echinocandin susceptibility. Antimicrob. Agents Chemother. 2008, 52, 2305–2312.
80. Douglas, C.M.; D'Ippolito, J.A.; Shei, G.J.; Meinz, M.; Onishi, J.; Marrinan, J.A.; Li, W.; Abruzzo, G.K.; Flattery, A.; Bartizal, K.; et al. Identification of the FKS1 gene of candida albicans as the essential target of 1,3-beta-D-glucan synthase inhibitors. Antimicrob. Agents Chemother. 1997, 41, 2471–2479.
81. Jones, J.M. Laboratory diagnosis of invasive candidiasis. Clin. Microbiol. Rev. 1990, 3, 32–45.
82. Ellepola, A.; Morrison, C. Laboratory diagnosis of invasive candidiasis. J. Microbiol. 2005, 43, 65–84.
83. Leon, C.; Ruiz-Santana, S.; Saavedra, P.; Castro, C.; Loza, A.; Zakariya, I.; Ubeda, A.; Parra, M.; Macias, D.; Tomas, J.I.; et al. Contribution of Candida biomarkers and DNA detection for the diagnosis of invasive candidiasis in ICU patients with severe abdominal conditions. Crit. Care 2016, 20, 149.
84. Clancy, C.J.; Nguyen, M.H. Rapid diagnosis of invasive candidiasis: Ready for prime-time? Curr. Opin, Infect. Dis. 2019, 32, 546–552.
85. Clancy, C.J.; Nguyen, M.H. Non-culture diagnostics for invasive candidiasis: Promise and unintended consequences. J. Fungi 2018, 4, 27.
86. Clancy, C.J.; Shields, R.K.; Nguyen, M.H. Invasive candidiasis in various patient populations: Incorporating non-culture diagnostic tests into rational management strategies. J Fungi 2016, 2, 10.

87. Nguyen, M.H.; Wissel, M.C.; Shields, R.K.; Salomoni, M.A.; Hao, B.; Press, E.G.; Shields, R.M.; Cheng, S.; Mitsani, D.; Vadnerkar, A.; et al. Performance of Candida real-time polymerase chain reaction, β-D-glucan assay, and blood cultures in the diagnosis of invasive candidiasis. Clin. Infect. Dis. 2012, 54, 1240–1248.
88. Cuenca-Estrella, M.; Verweij, P.E.; Arendrup, M.C.; Arikan-Akdagli, S.; Bille, J.; Donnelly, J.P.; Jensen, H.E.; Lass-Flörl, C.; Richardson, M.D.; Akova, M.; et al. ESCMID guideline for the diagnosis of Candida diseases 2012: Diagnostic procedures. Clin. Microbiol. Infect. 2012, 18, 9–18.
89. Ness, M.J.; Vaughan, W.P.; Woods, G.L. Candida antigen latex test for detection of invasive candidiasis in immunocompromised patients. J. Infect. Dis. 1989, 159, 495–502.
90. Telenti, A.; Steckelberg, J.M.; Stockman, L.; Edson, R.S.; Roberts, G.D. Quantitative blood cultures in candidemia. Mayo Clin. Proc. 1991, 66, 1120–1123.
91. Beyda, N.D.; Amadio, J.; Rodriguez, J.R.; Malinowski, K.; Garey, K.W.; Wanger, A.; Ostrosky-Zeichner, L. In vitro evaluation of BacT/Alert FA blood culture bottles and T2 Candida assay for detection of Candida in the presence of antifungals. J. Clin. Microbiol. 2018, 56, e00471-18.
92. Odds, F.C. Sabouraud(’s) agar. J. Med. Vet. Mycol. 1991, 29, 355–359.
93. Odds, F.C.; Bernaerts, R. CHROMagar Candida, a new differential isolation medium for presumptive isolation of clinically important Candida species. J. Clin. Microbiol. 1994, 32, 1923–1929.
94. Horvath, L.L.; Hospenthal, D.R.; Murray, C.K.; Dooley, D.P. Direct isolation of Candida spp. from blood cultures on the chromogenic medium CHROMagar Candida. J. Clin. Microbiol. 2003, 41, 2629–2632.
95. Bernal, S.; Mazuelos, E.M.; Garcia, M.; Aller, A.I.; Martinez, M.A.; Gutierrez, M.J. Evaluation of CHROMagar Candida medium for the isolation and presumptive identification of species of Candida of clinical importance. Diagn. Microbiol. Infect. Dis. 1996, 24, 201–204.
96. Hospenthal, D.R.; Murray, C.K.; Beckius, M.L.; Green, J.A.; Dooley, D.P. Persistence of pigment production by yeast isolates grown on CHROMagar Candida medium. J. Clin. Microbiol. 2002, 40, 4768–4770.
97. Powell, H.L.; Sand, C.A.; Rennie, R.P. Evaluation of CHROMagar Candida for presumptive identification of clinically important Candida species. Diagn. Microbiol. Infect. Dis. 1998, 32, 201–204.
98. Pfaller, M.A.; Houston, A.; Coffmann, S. Application of CHROMagar Candida for rapid screening of clinical specimens for Candida albicans, Candida tropicalis, Candida krusei, and Candida (Torulopsis) glabrata. J. Clin. Microbiol. 1996, 34, 58–61.

99. Hospenthal, D.R.; Beckius, M.L.; Floyd, K.L.; Horvath, L.L.; Murray, C.K. Presumptive identification of Candida species other than C. albicans, C. krusei, and C. tropicalis with the chromogenic medium CHROMagar Candida. Ann. Clin. Microbiol. Antimicrob. 2006, 5, 1.
100. Clancy, C.J.; Nguyen, M.H. Undiagnosed invasive candidiasis: Incorporating non-culture diagnostics into rational prophylactic and pre-emptive antifungal strategies. Expert Rev. Anti Infect. Ther. 2014, 12, 731–734.
101. Matsui, D. Current issues in pediatric medication adherence. Paediatr. Drugs 2007, 9, 283–288.