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Invasive candidiasis: current clinical challenges and unmet needs in adult populations

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Invasive candidiasis (IC) is a serious infection caused by several *Candida* species, and the most common fungal disease in hospitals in high-income countries. Despite overall improvements in health systems and ICU care in the last few decades, as well as the development of different antifungals and microbiological techniques, mortality rates in IC have not substantially improved. The aim of this review is to summarize the main issues underlying the management of adults affected by IC, focusing on specific forms of the infection: IC developed by ICU patients, IC observed in haematological patients, breakthrough candidaemia, sanctuary site candidiasis, intra-abdominal infections and other challenging infections.

Several key challenges need to be tackled to improve the clinical management and outcomes of IC patients. These include the lack of global epidemiological data for IC, the limitations of the diagnostic tests and risk scoring tools currently available, the absence of standardized effectiveness outcomes and long-term data for IC, the timing for the initiation of antifungal therapy and the limited recommendations on the optimal step-down therapy from echinocandins to azoles or the total duration of therapy.

The availability of new compounds may overcome some of the challenges identified and increase the existing options for management of chronic *Candida* infections and ambulant patient treatments. However, early identification of patients that require antifungal therapy and treatment of sanctuary site infections remain a challenge and will require further innovations.

Introduction

Invasive candidiasis (IC) is a serious infection caused by several *Candida* species (spp.) and the most common fungal disease in hospitals in high-income countries, with a worldwide prevalence ranging from 250 000 to approximately 700 000 people per year, an incidence rate of 2–14 cases per 100 000 persons and mortality rates ranging between 40% and 55%.[1–3] IC includes both candidaemia (i.e. bloodstream infections) and deep-seated tissue candidiasis, which arises from dissemination of *Candida* spp. to a sterile body site (e.g. abdomen, peritoneum or bone).[4–6] Most IC infections are caused by five pathogens: *C. albicans*, *Nakaseomyces glabrata* (previously known as *C. glabrata*), *C. tropicalis*, *C. parapsilosis* and *Pichia kudriavzevii* (previously known as *C. krusei*). *C. albicans* is the most common species, but non-*albicans* species are increasing, being responsible for more than 50% of cases in some series.[7] However, this trend appears limited to specific continents (e.g. Europe, mainly due to the rise of *N. glabrata*) and a high heterogeneity is observed between studies, overall but also in subgroups by continents.[8] *C. auris* is a novel pathogen that has emerged in 2009, triggering global outbreaks.[9]

Candida spp. are commensal organisms present in the gut and skin of 50%–70% of healthy individuals in low numbers due to competition within the microbiome (i.e. the gut mycobiome represents only around 0.1% of the total gut microbes[10]). Several factors can lead to overgrowth of *Candida* spp., in particular exposure to antibiotic treatment, immunosuppression and corticosteroid treatment.[11] Moreover, *Candida* translocation from the gut into the bloodstream can be facilitated by increased permeability of the gut epithelia (for example, due to mucositis in onco-haematological patients or patients with inflammatory bowel disease),[12–15] or breaches in the intestinal barrier following abdominal surgery,[16] all of which significantly increase the risk of candidaemia. Additionally, the ability of *Candida* spp. to form biofilms on inert surfaces makes the presence of prosthetic material a risk factor for developing IC.[17] Once candidaemia has developed, it can disseminate and generate deep-seated secondary

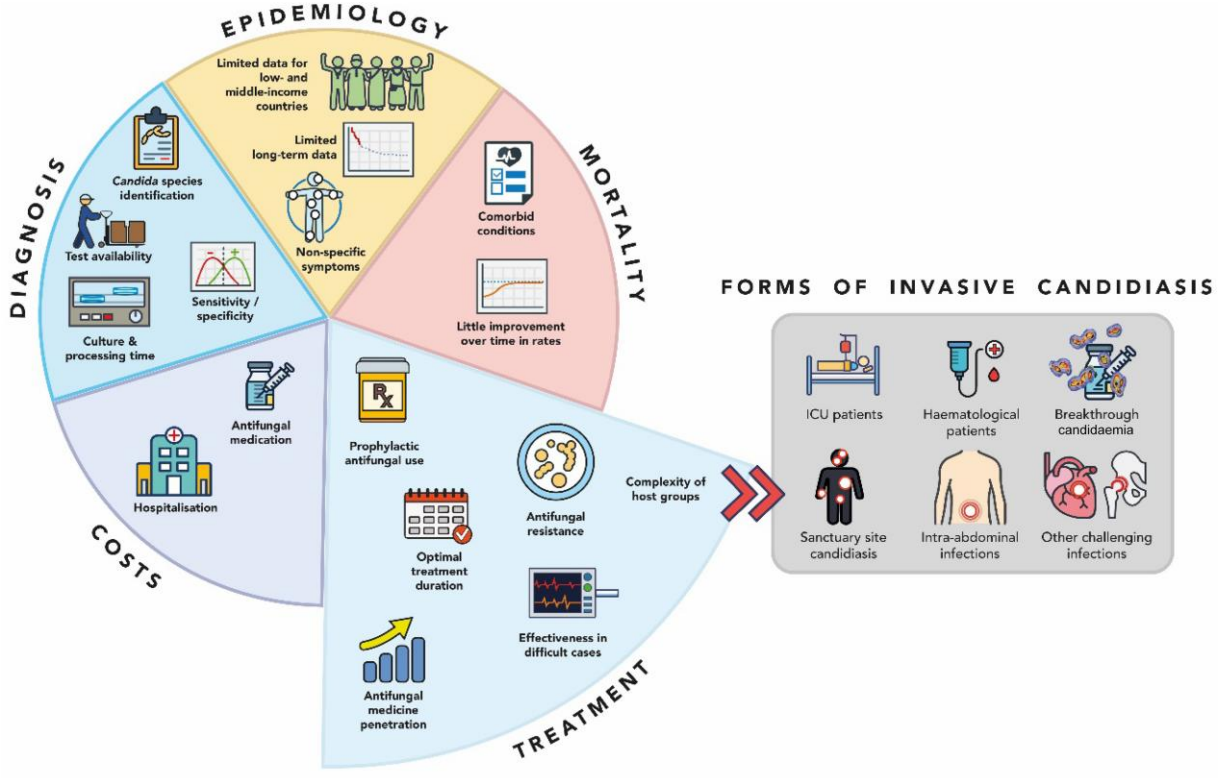

Figure 1. Current clinical challenges of IC.

infections in organs such as the lungs, liver, heart, eye, brain and bones.[1]

Despite overall improvements in health systems and ICU care in the last few decades, as well as the development of different antifungals and microbiological techniques, mortality rates in IC have not substantially improved.[18] Several challenges hinder the clinical management of patients with IC (Figure 1). Firstly, early diagnosis of candidaemia and deep-seated candidiasis remain a challenge due to the prolonged time to positivity of blood cultures, which can take up to 5 days to become positive, and due to the low yield of culture diagnostic tests for deep-seated candidiasis (~50%).[19] Biomarkers [e.g. (1–3)-β-D-glucan (BDG), mannan (Mn)/anti-Mn antibodies] could aid earlier diagnosis; however, their role has not yet been clearly defined.[19] Second, a worldwide shift to multidrug-resistant species (including *C. auris*, *N. glabrata* and *P. kudriavzevii*) has been observed.[20] While guidelines exist to guide the choice of antifungal therapy, patients affected by IC may require a tailored approach due to heterogenous host factors and significant geographical variation in species distribution and antifungal drugs resistance rates.[21–23] Moreover, the value of different treatment strategies remains to be clarified.

In addition to increasing the risk of mortality, IC is associated with significant economic burden, mainly arising from the prolonged length of hospital stay, although the economic impact of IC is difficult to measure due to comorbidities.[24,25]

The aim of this review is to summarize the main issues underlying the management of adults affected by IC (Figure 1), focusing on specific forms of the infection: IC developed by ICU patients, IC observed in haematological patients, breakthrough candidaemia, sanctuary site candidiasis, intra-abdominal infections and other challenging infections. The impact of such issues on the clinical and economic burden of the disease is key to understanding the unmet needs of these patients. To maximize its reliability and quality, this narrative review followed the methodological recommendations from the Scale for the Assessment of Narrative Review Articles,[26] and eligible literature was identified through citation chasing of key references on IC and candidaemia and input from clinical experts (Supplementary Materials, available as Supplementary data at *JAC* Online).[27]

Global incidence, epidemiological shifts and economic burden of *Candida* species

Global data indicates that the incidence of IC and candidaemia is increasing, with large studies reporting an incidence rate of 3–5 per 100 000 persons in the general population, 1%–2% of all ICU admissions[28] and a global annual incidence estimated to be ~750 000 cases/year.[3] Within clinical settings, almost three-quarters of the cases were reported in the ICU (60%) and cancer and transplant units (13%).[3,29,30] *Candida* spp. are the aetiology of 17% of all ICU infections in culture-positive patients.[3,6,31,32] Pooled data for European countries reiterated the high ICU incidence rate, extrapolating that approximately 79 cases are diagnosed daily,[32] with a cumulative incidence of IC of 7.07 episodes

per 1000 ICU admissions and a crude mortality rate of 42%.[33] The current incidence rate may be higher due to emerging risk groups, such as patients with severe COVID-19.[32,34]

Intra-abdominal candidiasis may include *Candida* involvement of peritoneum or intra-abdominal abscess,[35,36] and is relatively common among specific high-risk groups with prevalence ranging between 5% and 30%.[19] A review on the global burden of IC reported data from 29 countries worldwide, estimating a global averaged incidence rate of 1.15 cases per 100 000 for *Candida* peritonitis or intra-abdominal candidiasis, being associated with approximately half of the total cases of IC in ICU patients.[3]

Patients with haematological malignancies are also prone to developing IC, due to their compromised immune system and chemotherapy-induced mucositis, which results in the translocation of *Candida* into the bloodstream.[6,15,37] A US prospective surveillance study of invasive fungal infections in haematopoietic stem cell transplant recipients conducted in 2001–2006 found *Candida* was responsible for 28% of invasive infections (mostly *N. glabrata*).[14] A study involving 11802 Italian patients with haematological malignancies identified 175 cases of candidaemia (1.5%),[13] whereas a Greek study on 27 864 candidaemia patients reported an incidence rate of 1.4 cases/1000 admissions among haematology patients (versus 0.83/1000 in non-haematology patients); candidaemia was caused predominantly by non-*albicans* species.[12]

Candida spp. distribution also differs geographically; *C. albicans* is the most prevalent species in most regions of the world, but in the past decade an increase in non-*albicans* diagnosis has been observed.[3,32,38] The second most prevalent species in the USA, north-western Europe and Canada is *N. glabrata*, particularly among elderly patients and solid organ transplant recipients. *C. parapsilosis* and *C. tropicalis* are more common in Southern Europe, South America, India and Pakistan, while *P. kudriavzevii*, the least common among the five main species, is more frequent in patients with severe immunodeficiency (e.g. haematological malignancies).[39,40] Other less frequent species usually present in specific hosts rather than geographically (e.g. *C. dubliniensis* is more common in HIV-infected patients[41]). It is important to note that current IC epidemiology is highly determined by antifungal selection pressure, which is influenced by both prophylaxis and treatment.[42] Widespread use of antifungals has driven the shift to non-*albicans* and more frequently resistant *Candida* spp. Additionally, *C. auris* has emerged as a global threat causing outbreaks in all continents. *C. auris*, known to survive on human skin and environmental surfaces for several weeks thereby facilitating its transmission,[9] is highly resistant to azole and polyene antifungals and can be resistant to some commonly used disinfectants.[43,44]

The collection and comparison of global data are hindered by specific challenges, including the lack of specific criteria for an incidence rate denominator.[20] Moreover, there are no available data for some low- and middle-income countries due to the absence of hospital infrastructures for blood culture analyses.[3] These differences between studies constrain to what extent global incidence rates can be established and comparisons across countries can be made, and point towards an underestimation of the burden of disease. Large longitudinal studies, alongside regional and local surveillance studies,[45] are required to understand epidemiological trends and shifts and to collect data to guide and support antifungal therapy.[46]

Systematic analysis of global evidence reported that costs associated with IC are mainly driven by bed day costs, incremental hospitalization and antifungal drug expenditure.[24,25] Survival and age influences costs, with both neonatal and older patients incurring higher costs, due to higher morbidity.[47]

Mortality rates over time and factors affecting mortality

Nosocomial candidiasis has the highest rate of mortality for hospital-acquired infections, with 30-day post-diagnosis mortality estimated to range between 40% and 55%.[1,2] Risk factors affecting mortality rates include older age, severity of the condition, use of immunosuppressive drugs, comorbidities, venous catheter retention and specific antifungal treatment.[1,33] A large retrospective study conducted in nine European countries extrapolated the 30-day mortality rate to be 29 patients out of the 79 cases diagnosed per day.[32] There have been limited changes to the mortality rate associated with IC in the past two decades (Figure 2), even though there are now several extended-spectrum triazole and echinocandin agents available for antifungal therapy, which have superior safety and potency than those antifungals agents available two decades ago.[18,45,48]

Diagnostics

Culture and nonculture diagnostics

Diagnostic tests for IC should be able to accurately detect the infection and differentiate between the presence of candidaemia, deep-seated candidiasis or a combination of both.[4,5,19] Identifying deep-seated candidiasis is important as patients may require longer therapy or surgical debridement.[5] An early diagnosis is paramount for a timely treatment, and any delays increase the odds of mortality and healthcare associated costs.[46,49]

Cultures from blood and sterile sites are currently the gold standard for diagnosis of IC.[50] Light microscopy using fluorescent brightener stains is also often used for the detection of *Candida* spp.,[6] and may provide additional diagnostic benefit.[51] It has been estimated that blood cultures have a sensitivity of between 63% and 83% for candidaemia in the absence of deep-seated candidiasis, and that their sensitivity is lower when deep-seated candidiasis is present,[46] ranging between 21% and 71%,[52] with an overall sensitivity of approximately 50%. Sensitivity can also vary according to the *Candida* spp., and the use of prior antifungals.[22] In addition, slow turnaround times, with a median time to positivity of 2–3 days, which may be even longer for *N. glabrata*,[53] may delay the start of the adequate antifungal therapy.[22,46,49] Diagnosing IC can be further constrained by the absence of a specific clinical presentation.[54]

These shortcomings may be complemented by nonculture diagnostic tests for *Candida*, such as mannan and anti-mannan antibody detection,[19,21,52] BDG detection,[19] *C. albicans* germ tube antibody (CAGTA) detection,[55] PCR detection of *Candida* DNA[56] and the T2 magnetic resonance (T2MR) *Candida* test.[4,49] The nonculture diagnostic tests have a varying degree of sensitivity and there have been recent calls for studies to further assess the role of combination testing.[19] For example, the mannan and

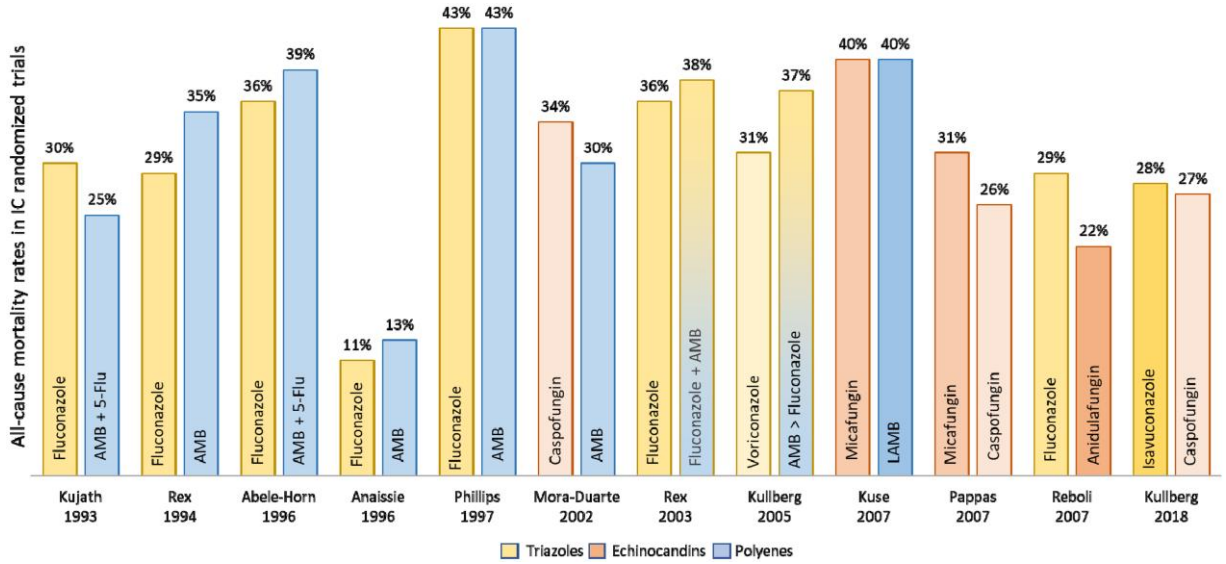

Figure 2. All-cause mortality rates in IC randomized trials (based on data reported by Demir).[18] The figure does not account for differences in study design, namely number of patients randomized, and only includes antifungals currently reimbursed. AMB, amphotericin B; 5-Flu, 5-fluorocytosine; LAMB, lipid formulation of amphotericin B.

anti-mannan assays combined were shown to achieve both sensitivity and specificity ≥80% for patients with *C. albicans*, *N. glabrata* or *C. tropicalis* infections.[19] It has also been suggested that the combined use of biomarkers could be used as a complementary decision-support tool for the diagnosis and management of IC.[19,52] For example, a combination of (1,3)-β-D-glucan, mannan and anti-mannan serum assays significantly shortened the duration of antifungal treatment in ICU patients with suspected IC, with no negative impact on outcome.[57] However, nonculture diagnostic tests also have limitations (Table 1) and ideally should be used as a complement to culture tests, while also taking into account patient characteristics, including the specific host group and severity of the clinical scenario to culture tests.[6,50,54,60]

Role of candidaemia risk scores

Due to the underlying limitations of diagnostic tests, prediction rules or scoring systems have been proposed as early diagnostic tools to assess the risk of IC early in patients admitted to ICU, such as the *Candida* Colonization Index (CCI)[61] and the Candida score.[62] There are concerns that scoring systems for IC have a high negative predictive value but a low positive predictive value, which means that they may be more useful to rule out patients who do not have or will not develop IC.[20,45,46,62,63] This is partially explained by the poor specificity of risk factors for developing IC, aligned with the low prevalence of IC in most clinical settings,[19] which would make many patients eligible for antifungal therapy even when their real risk is low,[64] thus increasing its use and consequently the risk of selecting resistant strains.[65] The use of the Candida score is largely debated, and not validated for all populations. While this risk score was showed to have sensitivity and specificity for invasive candidiasis of 81% and 74%, respectively, the population tested mostly included surgical ICU patients, with only 35% of admissions for medical reasons.[62] Thus, this tool may be less reliable for patients with nonsurgical reasons for ICU admission.

Other generic scoring systems that can be used to assess the risk of IC include the acute physiology and chronic health evaluation (APACHE II) score, which classifies disease severity and predict mortality in ICU patients,[46,66–68] and the simplified acute physiology score (SAPS II), also a prognostic model for hospital mortality at ICU admission.[69–71] However, the utility of these tests for IC is not clearly defined.

It has also been suggested that biomarkers of fungal infection, such as BDG, could be superior to candidaemia risk scores to support the decision to initiate treatment earlier.[46,64,72] In one study including 95 patients with sepsis and >5 days in the ICU, a single negative BDG test at sepsis onset had a negative predictive value for candidaemia of 98.7%, and both negative and positive predictive values of such biomarkers were superior to the *Candida* score.[72] These encouraging study results require further confirmation in high-quality studies.[63] Advances in genetic polymorphisms identification in the host have shown promising results in the identification of patients with a genetic predisposition to develop IC, which would put them at higher risk and more likely to benefit from antifungal treatment.[73] Using data from a prospective observational cohort study of 89 high-risk surgical ICU patients, the authors showed how one single-nucleotide polymorphism increased the susceptibility to intra-abdominal candidiasis infection.[69] Albeit promising, these results need to be confirmed in larger studies.[74] Finally, the use of risk scores (e.g. *Candida* score) could be combined with diagnostic tests with short turnaround, such as BDG detection, for a more accurate and time-efficient prediction of IC.[75]

Critical factors for the management of IC

Treatment

The treatment of IC has evolved in the last three decades. Generally, treatment guidelines[21,76] are more relevant for patients with candidaemia, as available IC evidence mostly came

Table 1. Overview of key diagnostics

Test		Advantages	Limitations
Microscopy		Fast turnaround[46] High sensitivity when using fluorescent brightener staining[6,51]	Inability to identify species[6]
Blood culture		Species identification[19] Susceptibility pattern	Slow turnaround[21,53] Timing of blood collection, during the course of infection[19] Necessary to culture a large blood volume (40 mL) in aerobic flasks[53] When *Candida* density is low (<1 cfu/mL), blood cultures can result in false negatives Cultures may become negative after initiating antifungal therapy[5]
Sterile site cultures		Species identification Susceptibility pattern	May require invasive procedures[19] Cultures may become negative after initiating antifungal therapy[5] Long incubation required for optimal performance (3 days)[6] For intra-abdominal candidiasis, lack of specificity to differentiate infection from colonisation[35]
Mannan antigen/anti-mannan antibodies		Early detection[22,54] Useful to rule out infection[22]	Serial determinations required[22] Lower utility in immunosuppred hosts[52] May not distinguish between past and acute infections[19] Sensitivity varies regarding *Candida* species (better for *C. albicans*, *N. glabrata* and *C. tropicalis*)[54] Decreased specificity if *Candida* colonisation is present[54] Low positive predictive value, potentially leading to antifungals overuse Limited by low serum concentrations and rapid bloodstream clearance[19] Not species-specific, requiring further tests to identify the fungus[46] No data on susceptibility pattern Not approved by FDA[19] Not universally available
CAGTA		Fast turnaround and low cost[5] Could be used to detect whether candidaemia originated in a catheter or deep organs[55]	May not distinguish between past and acute infections[19] Limited by low serum concentrations and rapid bloodstream clearance[19] Sensitivity varies according to *Candida* species (lower for *C. tropicalis*)[5,19] Not species-specific, requiring further tests to identify the fungus[46] Low positive predictive value, potentially leading to antifungals overuse No data on susceptibility pattern Not approved by FDA[19] Not universally available
BDG		Early detection[22] Useful to rule out infection[22]	Serial determinations required[22] Lower utility in patients with haematological disease[22] and immunosuppred hosts[52] Sensitivity varies according to *Candida* species (lower for *C. parapsilosis*)[19] May not distinguish between past and acute infections[19] Not species-specific, requiring further tests to identify the fungus[45] Low positive predictive value, potentially leading to antifungal overuse No data on susceptibility pattern Not universally available
Nucleic acid amplification-based methods	PCR	Early detection[58] Monitoring of persistence or resolution of infection[4]	Mostly developed in-house or commercially[19] Frequently performed in reference laboratories limiting the advantage of short turnaround time[45] Data interpretation impaired by test heterogeneity[19] Not universally available
	T2Candida	Early detection[19,59] Automated molecular diagnosis[49,59] May detect candidaemia missed by cultures during	Costs associated with the test[46] Limited to some *Candida* species (*C. albicans*/*C. tropicalis*, *N. glabrata*/*P. kudriavzevii*, and *C. parapsilosis*, groupings that are based on typical antifungal susceptibility pattern)[49,59]

Continued

Table 1. *Continued*

Test	Advantages	Limitations
	empirical or pre-emptive AF therapy[4] Improved performance in neutropenic patients[4]	No data on susceptibility pattern[59] Not universally available

AF, antifungal; BDG, β-D-glucan; CAGTA, *C. albicans* germ tube antibody; cfu, colony forming units; FDA, Food and Drug Administration; PCR, polymerase chain reaction.

from trials enrolling patients with candidaemia, with fewer trials investigating deep-seated candidiasis.[21,77–82] The rarer forms of IC have seldom been studied in prospective studies; hence, treatment regimens for these forms are based on anecdotal experience and retrospective case series.

The antifungal drugs available for the treatment of IC belong to three classes: echinocandins (anidulafungin, caspofungin or micafungin), azoles (fluconazole, voriconazole, itraconazole, posaconazole, isavuconazole) and amphotericin B-based regimens.[23,76] The comparative effectiveness of these agents for the treatment of IC was recently reported by a network meta-analysis, which included data from 13 trials that randomized 3528 patients to one of the three antifungal classes.[18] Results showed that echinocandins were associated with best clinical outcomes (i.e. response to antifungal therapy) when compared with the other two groups of agents. Moreover, a combined analysis of clinical studies involving almost 2000 patients showed that initial therapy with an echinocandin is a significant predictor of survival.[83] Overall, these agents have shown efficacy in 70%–75% of patients in randomized clinical trials.[79–81,83–85] Accordingly, guidelines recommend echinocandins as a first-line treatment in most IC patients, without preference for a specific compound, mostly due to their broader spectrum of activity, higher fungicidal activity for most *Candida* species, low drug–drug interaction, rare acquired resistance and increased safety profile.[18,76]

Azoles are generally well tolerated, but they have been shown to be about 15% less effective than echinocandins on average.[86] They are used instead of echinocandins as first-line therapy in some forms of deep-seated candidiasis, such as brain, intraocular and urinary tract infections, where echinocandins have lower penetration. In terms of formulations, echinocandins are approved for once-daily intravenous administration, and azoles can be administered intravenously or orally. Amphotericin B deoxycholate formulations have been associated with severe adverse events, such as nephrotoxicity and infusion-related adverse effects; hence, lipid formulations have been developed that present fewer, but still frequent, toxicities.[78,87] These formulations are commonly used to treat patients who are intolerant or resistant to echinocandins and/or azoles, as well as in some deep-seated infections such as endocarditis, meningoencephalitis and endophthalmitis.[76]

Although the use of echinocandins as first-line therapy has increased and the major role for fluconazole in the current management of IC is for step-down therapy,[7,88] fluconazole is sometimes still used as first-line therapy, as shown by a retrospective chart review of diagnostic and treatment decisions in patients with candidaemia conducted in six German hospitals.[89] This contrasts with ESCMID guidelines, but is in line with the Infectious Diseases Society of America (IDSA) guidelines accepting fluconazole as alternative for those not critically ill and without prior azole exposure.[21] Further deviations from international guideline recommendations include the indication, dosage, route of administration and duration, with approximately half of the prescriptions being assessed as inappropriate.[90,91]

Improving patient outcomes

Early initiation of antifungal therapy has been shown to reduce hospital mortality but requires starting antifungal therapy within 24 hours of taking blood cultures.[92] As *Candida* spp. generally take longer than 24 hours to grow, the benefit from this time window is lost when relying on culture results. Most antifungal treatments are thus started empirically, when patients who are at high risk of developing IC are persistently febrile in the absence of microbiological evidence of infection.[76] Recent international guidelines for the management of sepsis and septic shock suggest that empirical antifungal therapy should be preferred for adults at high risk of fungal infection.[93] Empirical therapy has been associated with reduced overall mortality, although most evidence comes from uncontrolled studies.[76] Importantly, a Cochrane review reported that, on the basis of 19 studies that included 2374 non-neutropenic critically ill patients, empirical antifungal treatment reduced the risk of invasive fungal infection but did not reduce all-cause mortality.[94] Moreover, the broad use of empirical antifungals increases healthcare costs and is potentially linked with antifungal resistance.[1,91,95,96]

Prompt source control (i.e. the elimination of the focus of infection) is also key in the management of IC. This may consist of the removal of contaminated intravascular catheters, infected prosthetic devices (for example, cardiac pacemaker leads), prosthetic joints or other devices, as well as the adequate drainage of infected material (such as peritoneal fluid, pleural fluid and/or abscess material) and surgical correction of the underlying pathology (e.g. perforation or leak).[97,98] Source control is important due to the ability of *Candida* spp. to form biofilms on implanted medical devices representing a persistent nidus of infection.[99] In addition, biofilm formation is linked to the development of antifungal resistance due to decreased drug penetration and up-regulation of resistance mechanisms.[100,101] A recent systematic review analyzed data from 34 prospective and retrospective cohort and case-control studies, finding that a central venous

catheter was associated with a significantly increased risk of developing IC (odds ratio 4.7, 95% confidence interval 2.7 to 8.1).[64] Retrospective studies of adult patients diagnosed with candidaemia show how intravascular catheters were a risk factor for infection[5] and how catheter removal was associated with increased odds of survival.[89] Removal of indwelling intravascular catheters is therefore strongly recommended when candidaemia is present.[51,76] If removal is not possible then treatment with a lipid-base amphotericin B formulation or an echinocandin is suggested,[76] as these drugs have shown activity against *Candida* biofilms.[102] Catheter lock strategies, using high antifungal concentrations locally in the catheter lumen for hours or days, have also been performed. Lipid-based amphotericin B formulations and echinocandins are again the most commonly used antifungals, showing high efficacy to decrease biofilm formation but commonly failing to eradicate the *Candida* infection.[103] Novel strategies are being investigated including antifungal combination therapy, phototherapy, cationic peptides and even the use of plant-based therapies.[104,105]

Diagnosis-driven drug management

The duration of antifungal treatment is often guided by the extent of organ involvement.[76] For candidaemia, the ESCMID recommends for treatment to be continued for 14 days after the last negative blood culture, whereas organ involvement may be screened with transoesophageal echocardiography and fundoscopy.[76] Rapid diagnostic tests can support early discontinuation of empirical antifungal therapy, with retrospective data showing that results from T2Candida panel performed better than BDG, when combined with blood cultures, decreasing the number of days critically ill patients were on empiric echinocandin therapy.[106] The decision to de-escalate treatment from intravenous echinocandins to oral fluconazole should take into account not only diagnostics but also patient's stability, tolerance of the administration route and species susceptibility.[4,76,79,89,93,107]

The role of nonculture tests to guide treatment, including drug de-escalation, has also been explored. Evidence from a randomized trial of 234 critically ill non-immunocompromised patients admitted to ICU who were allocated to an echinocandin or placebo suggested that BDG monitoring could be used to decide when to de-escalate empirical therapy or when to withhold preemptive therapy,[60] whereas T2Candida has also been shown to improve management.[4,108]

Therapeutic drug monitoring

Therapeutic drug monitoring (TDM) is used to measure antifungal drug levels to prevent over or underdosing. The IDSA and ESCMID recommend TDM when treating IC with voriconazole; ESCMID also advise TDM when prescribing 5-fluorocytosine and posaconazole.[21,22]

Whenever antifungal absorption or excretion could be hindered [i.e. mucositis, administration via nasogastric tube or gastrostomy, or in critically ill patients undergoing continuous renal replacement therapy (CRRT)], TDM should also be considered.[109,110] Finally, TDM may also be helpful in those cases of treatment failure, breakthrough infections, serious toxicity or those *Candida* infections caused by species with high minimum inhibitory concentration (MIC).[111]

Drug resistance

Candida infections resistant to one or multiple types of antifungals are increasingly being diagnosed, with prior antifungal therapy found to be the main driver for resistance selection.[20,112,113] The widespread use of antifungals introduces a positive selection of *Candida* spp. that show some intrinsic or acquired resistance to treatment, including *N. glabrata* and *C. auris* (multidrug-resistant),[114,115] as well as *P. kudriavzevii* (azole resistant). Data gathered from population-based or multicentre studies showed that the rates of azole resistance vary considerably depending on the setting and the *Candida* spp., ranging from 3% to 21%.[20]

Acquired echinocandin resistance has also been reported, especially for *N. glabrata* and *C. tropicalis*. In the SENTRY antifungal surveillance programme, mutations in *FKS* gene hot spot regions were detected among echinocandin-resistant isolates, most of which were resistant to two or more echinocandins. Additionally, *C. parapsilosis* has an intrinsic polymorphism affecting also the *FKS1* gene, leading to decreased *in vitro* echinocandin susceptibility.[116] However, the clinical impact of such reduced susceptibility remains controversial. *C. auris* was initially detected in Japan in 2009 and shows some resistance to all major antifungal treatments, including multi-drug-resistant isolates, with higher resistance for fluconazole, followed by amphotericin B and echinocandins.[9,117] Hospital outbreaks of *C. auris* with rapid spread and high mortality have been since reported in Asia (India, Pakistan), Europe (the UK, Spain, Italy), Latin America (Colombia, Venezuela, Panama) and the USA.[117–119]

The rise in drug-resistant IC has highlighted a need for antifungal susceptibility testing, to achieve optimal treatment and to monitor the emergence of antifungal resistance. Several tests are currently available, including broth microdilution according to the CLSI[120] and the EUCAST,[121] which represent gold standards for antifungal susceptibility testing. Alternative tests include disc diffusion, epsilometer tests, colorimetric broth microdilution and automated spectrophotometric systems.[122] Generally, these methods can be time-consuming and/or technically complex, and the interpretation of results may be challenging.

Clinical challenges related to specific forms of IC

IC in ICU patients

Approximately 50% of episodes of IC occur in ICU, where the administration of antibiotics and immunosuppressive drugs, combined with the use of invasive procedures (e.g. the installation of central vascular catheters), total parenteral nutrition[16] or intrabdominal surgery,[36,38] significantly increase the risk of *Candida* infection.[2,3,32] Length of ICU stay is consistently reported as increasing the risk of developing IC, although it is seldom possible to disentangle length of ICU stay from other confounding risk factors, as patients with longer ICU stays will have increased disease severity as well as more invasive therapies.[50,64] All-cause mortality associated with candidaemia seems to be 2-fold higher for patients hospitalized in the ICU when compared with patients

Table 2. Antifungal dose adaptations during CRRT

Antifungal agent	Mechanism of action	Route of administration	Adverse effect	Elimination by CRRT	Recommended dose during CRRT
Lipid formulation of amphotericin B	Interacts with ergosterol in the fungal cell membrane	IV	Hepatic, renal and cardiovascular toxicity	Unaffected by CRRT	5 mg/kg/d
Fluconazole	Interacts with 14-demethylase in the fungal cell membrane	IV or oral	Hepatic toxicity	High elimination by CRRT	600 mg/12 h
Voriconazole	Reduces ergosterol synthesis	IV or oral	AKI toxicity with IV use, hepatic toxicity	Poor elimination of IV form by CRRT — No adaptations for CRRT	Loading dose: 6 mg/kg/12 h Maintenance dose: 4 mg/kg/12 h
Anidulafungin	Inhibits (1,3)-β-D-glucan synthetase	IV	Hepatic toxicity	Significant adsorption by CRRT adsorptive membranes	Loading dose: 200 mg/d Maintenance dose: 150 mg/d
Caspofungin	Interacts with 14-lanosterol demethylase in the fungal cell membrane and reduces ergosterol synthesis	IV	Severe hepatic toxicity	Unaffected by CRRT	Loading dose: 70 mg/d When BMI is >40 higher doses can be used (up to 140 mg/d) Maintenance dose: 50 mg/d (if >80 kg, maintenance with 70 mg/d is recommended)

AKI, acute kidney injury; CRRT, continuous renal replacement therapy; d, day; IV, intravenous.

in other hospital settings, although these results vary for different *Candida* spp.[123]

In critically ill patients, severe comorbidities can alter the antifungal drugs' pharmacological profile. Drug distribution can be influenced by haemodynamic alterations, while hepatic and/or renal impairment can affect drug concentration in the bloodstream, metabolism and elimination. Additionally, hypoalbuminaemia can reduce the percentage of bound antifungal, increasing activity and potentially toxicity.[124]

Dosing and PK/PD are also crucial during CRRT and extracorporeal membrane oxygenation (ECMO), which affect different classes of antifungals. Fluconazole is the most complex to dose in ICU during CRRT (Table 2) due to the high extracorporeal removal of fluconazole, which exceeds the normal renal clearance and necessitates a higher daily maintenance dose.[125] In line with available data and as long as hepatic function remains stable, a dose of fluconazole of 500–600 mg every 12 h is recommended in critically ill patients under CRRT.[126]

The COVID-19 pandemic led to high ICU admissions and subsequently triggered an increase in the number of secondary invasive fungal diseases, including *Candida* and *Aspergillus*,[34] partially due to the high doses of corticosteroids given.[127] Aggregated data showed that by September 2020 the extent of candidiasis associated with COVID-19, both superficial and invasive, ranged between 0.7% and 23.5%.[128]

Intra-abdominal infections

Intra-abdominal candidiasis is the most common type of deep-seated candidiasis.[98] A prospective study with 176 non-neutropenic critically ill patients with severe abdominal conditions and a high prevalence of IC (18%) showed how BDG (cut-off value of 259 pg/mL) and CAGTA (positive versus negative) accurately discriminated between *Candida* spp. colonization and IC.[129] However, currently there are no tight criteria to distinguish abdominal *Candida* colonization from true *Candida* infection, and general criteria for sepsis and septic shock are often used to differentiate between abdominal colonization and infection.[130] This is an issue as most of the time sepsis and septic shock are due to causes other than true *Candida* infection, and thus many abdominal colonizations, especially in the post-operative period, are overtreated leading to more antifungal resistance. There is an urgent need to build an algorithm to differentiate abdominal *Candida* colonization from true infection.

The burden of intra-abdominal infections and its associated morbidity and mortality are higher in high-income countries, which may be partially explained by the widespread use of antibiotics and increased drug resistance.[131]

Clinical guidelines/expert consensus papers recommend prophylactic use of fluconazole for patients with abdominal surgery and recurrent gastrointestinal perforations or anastomotic leakages,[35,76] with echinocandins or lipid formulation of amphotericin B being recommended as first-line antifungal therapy for critically ill patients or patients with previous exposure to azoles.[35] However, prophylactic use of fluconazole may be associated with an increase in fluconazole-resistant species.[132]

The outstanding clinical challenges in intra-abdominal candidiasis thus include prophylactic use of fluconazole, need for source control and treatment selection and duration.

IC in patients with haematological malignancies

Owing to their compromised immune response, patients affected by haematological malignancies are prone to develop IC with high mortality risk, prolonged hospitalization and rising healthcare costs.[15,37] This is a consequence of host defences being affected by cancer treatments, such as cytotoxic chemotherapy, ablative radiotherapy and immunosuppressive therapies. Other risk factors mentioned previously also apply to haematological cancer patients.[12,37,133] Several studies have reported candidaemia-associated mortality rates in patients with haematological malignancies ranging between 29.5% and 45%.[12,13,15,133]

To counteract the high incidence of candidaemia and its associated mortality, the use of fluconazole prophylaxis was introduced in the early 1990s.[42] Clinical guidelines recommend anti-*Candida* prophylaxis for patients receiving allogeneic stem cell transplantation.[23] Prophylactic treatment with fluconazole has also been recommended for patients undergoing remission-induction[134] or salvage-induction[135] chemotherapy for acute myeloid leukaemia.

However, while prophylactic use of fluconazole succeeded in lowering the frequency of bloodstream infections caused by azole-sensitive *C. albicans*, it caused an increase in azole-resistant species such as *N. glabrata* and *P. kudriavzevii*, which now account for most candidaemia episodes in many cancer centres.[136] Additional concerns include drug–drug interactions, tolerability and breakthrough fungal infections,[134] as well as the non-specificity of signs and symptoms of IC in patients who frequently present with fever and sepsis. In a pooled analysis of 1271 patients with haematologic malignancies and patients undergoing haematopoietic stem cell transplant, echinocandins seemed to be marginally more effective than triazoles for prophylactic treatment.[48]

Breakthrough candidaemia

Breakthrough candidaemia is defined as candidaemia that develops during systemic antifungal therapy administered as either prophylaxis, pre-emptive, empirical or targeted therapy.[21,135] It has been linked to the emergence of drug resistance and poor outcomes,[137–140] and several risk factors have been identified. A retrospective study conducted in Brazil from 2011 to 2016 identified 27 breakthrough episodes from 148 candidaemia episodes, with neutropenia and mucositis being independent risk factors and non-*albicans* species being more frequent among these patients.[141] Similarly, in a multicentre study of hospitalized adults with candidaemia, *P. kudriavzevii* was more frequent and fluconazole-resistance was independently associated with risk of breakthrough episodes.[142] Another study identified neutropenia, use of corticosteroids and heavy antibiotic exposure (previous use of two or more antibiotics for at least 14 days) as risk factors.[143] Additionally, a 3-year prospective study conducted in 567 consecutive cases of candidaemia recorded 37 cases of breakthrough candidaemia, 86% of which on fluconazole; breakthrough candidaemia was associated with gastrointestinal mucositis, graft-versus-host-disease, immunosuppression and parenteral nutrition, and non-*albicans Candida* were isolated in most breakthrough cases.[144] Overall, breakthrough candidiasis appears to be caused by drug-resistant, non-*albicans* species selected by the use of antifungals and impairments in the immune response.

Sanctuary site candidiasis

CNS candidiasis

Candida CNS infections, mostly caused by *C. albicans*,[145] are rare but severe. They can arise from haematogenous spread, mostly in neonates due to blood–brain barrier immaturity, or in the presence of ventricular drainage devices or following neurosurgical procedures.[146] Increased risk in adults has been described for the immunocompromised patients[145,147–149] and individuals who have a deficiency of the lectin receptor adaptor molecule CARD9.[150] Moreover, *Candida*-caused endocarditis are associated with CNS embolic complications in 12% to 22% of cases.[148,151,152]

The most common manifestation of brain infection is overt meningitis, while in rarer cases chronic meningitis, brain abscesses, vasculitis with cerebral infarctions, spinal infections, ventriculitis and mycotic aneurysms can be observed.[153] A recent nationwide retrospective study conducted in France and covering the period between 2005 and 2018 identified 24 adult patients with CNS candidiasis. Mortality attributed to CNS candidiasis was 42%.[154]

Treatment guidelines suggest the use of liposomal amphotericin B combined with flucytosine for CNS IC. Fluconazole may be used as a step-down therapy, while poor penetration of echinocandins limit their use in CNS. However, due to data scarcity, no strong recommendation is given.[76] A study reported the use of amphotericin B deoxycholate combined with flucytosine for >2 weeks in a series of HIV-infected patients, with four of five patients being treated successfully.[147] In two other series, 27 of 34 patients survived after similar treatments.[155,156] Published data on voriconazole use in CNS candidiasis are sparse; efficacy may be limited by the variability of its concentration in the CSF.[157]

Urinary candidiasis

Critically ill patients and those with urinary catheters are at high risk of developing candiduria.[73] In critically ill patients undergoing surgical procedures, the rates of concurrent candidaemia derived from a urinary source may reach up to 10%.[158] Additional risk factors for adult candiduria include advanced age, female gender, urinary tract anatomic abnormalities, abdominal surgery, multi-morbidity, broad-spectrum antibiotics therapies and diabetes mellitus.[158]

If asymptomatic, then treatment is not recommended for candiduria, except in pre-operative patients who may be given flucozonale.[76] If possible, the urinary catheter should be removed to clear the infection,[76] and early urologic drainage procedure is also associated with improved outcomes.[159] The prophylactic antifungal treatment of *Candida* colonization in the urinary tract is a common inappropriate use of antifungal agents.[45] Different combinations of antifungal agents are available for symptomatic candiduria, including fluconazole or amphotericin B deoxycholate, with or without flucytosine; if fungus balls or casts are detected then surgical intervention is required.[21,76] For the treatment of fluconazole-resistant strains, only amphotericin B and micafungin seem to reach adequate

urinary concentrations, although the clinical evidence is limited.[160,161]

Endophthalmitis and chorioretinitis

In rare cases, candidaemia can give rise to two types of ocular infection: *Candida* chorioretinitis, restricted to the chorioretinal layers, and *Candida* endophthalmitis, usually extending into the vitreous body. The latter is associated with poor visual outcomes.[162] Candidaemia-associated endophthalmitis and chorioretinitis can be treated with antifungals administered systemically or locally (i.e. via intravitreal injection). Systemic amphotericin B and echinocandins do not penetrate well in the vitreous humour, whereas fluconazole and voriconazole can reach therapeutic vitreous concentrations.[163–165]

A randomized multicentre trial that compared voriconazole with amphotericin B followed by fluconazole for the treatment of candidaemia reported that ocular involvement occurred in 16% of patients with candidaemia, mostly manifesting as chorioretinitis, whereas endophthalmitis was uncommon (1.6%); treatment with either voriconazole or amphotericin B followed by fluconazole was successful for ocular candidiasis in most (65%) cases.[166] According to clinical guidelines, fluconazole or voriconazole are recommended as the drugs of choice for susceptible isolates, whereas liposomal amphotericin B either alone or combined with flucytosine is recommended when the susceptibility of the isolate is unknown. In the case of endophthalmitis, vitrectomy and intravitreal injection of amphotericin B are recommended in addition to systemic therapy.[76]

Additional challenging infection sites

Candida endocarditis

Candida species cause <2% of all infective endocarditis cases and can arise on a native valve, a prosthetic valve or in the presence of pacemaker or other implanted material. *Candida* endocarditis might be considered a biofilm-related infection following earlier fungal bloodstream infection. Overall, prognosis is poor with 1-year mortality >50% and substantial relapse rates.[149,167,168] *Candida* vegetations are typically larger and more friable than bacterial ones, harbouring a higher risk for embolic events, ophthalmologic complications and cutaneous lesions. Due to this high mortality, early diagnosis and initiation of antifungals is vital.[167,168] Most cases are identified with transthoracic echocardiography, although transoesophageal echocardiography could help improve diagnosis. Although blood cultures are mostly positive in *Candida* endocarditis,[169] its yield can be lower in patients receiving prior antifungals and cultures can take several days to produce results. Hence, attempts should be made to get a tissue sample for diagnosis. Moreover, nonculture methods could have an important role in early diagnosis, such as BDG detection and PCR amplification, with a sensitivity of 89% and over 92% for fungal endocarditis, respectively, according to a recent systematic review.[169]

A recent review of 140 cases of *Candida* endocarditis showed that surgery, effective antibiofilm treatment (defined in such study as antifungal treatment with liposomal amphotericin B or echinocandins) and chronic suppressive antifungal therapy were independently associated with improved prognosis.[170] Accordingly, international guidelines recommend surgery whenever feasible, as well as antifungal treatment with liposomal amphotericin B, which can be combined with flucytosine,[76] or high-dose echinocandins. Additionally, long-term suppressive therapy should be considered for those patients who cannot undergo valve replacement and in those cases of prosthetic valve endocarditis. Finally, risk factors for *Candida* endocarditis are unspecific and this entity should be considered in patients with relapsing or persistent candidaemia, especially in critically ill patients.[171]

Bone and joint candidiasis

These infections include osteomyelitis/spondylodiscitis, arthritis and prosthetic joint infection, commonly following haematogenous dissemination, although direct inoculation and contiguous spread are also possible. The spine is the most common site of osteomyelitis involvement.[172] Although fluconazole monotherapy has been classically recommended, it is plausible that a biofilm component exists. Thus, initial 'induction' treatment with an echinocandin or lipid-based amphotericin, followed by long-term fluconazole therapy (6–12 months), seems advisable.[21,173,174] For septic arthritis, surgery is mandatory and in cases of prosthetic joint infections, removal of the joint prosthesis is advised. If this is not possible, lifelong fluconazole therapy is commonly indicated.[76] If reimplantation of the prothesis is considered, guidelines recommend administering antifungal treatment for at least 12 weeks before and 6 weeks after prothesis implantation.[21] Again, biofilm-active antifungals are conceptually desirable, although their use is limited by the need for intravenous administrations. Moreover, the quality of evidence that supports these recommendations is very low, and this scenario is further complicated by the reported increase in non-*albicans* species with decreased azole susceptibility[173,175,176] and frequent bacterial co-infection.

Candida pneumonia

While *Candida* species are often isolated from the respiratory tract of ICU intubated patients or patients with tracheostomies, the existence of *Candida* pneumonia has been largely debated.[177] Indeed, the true incidence of *Candida* pneumonia ranges from 0.23% to 0.4%, with increased risk linked to genetic predisposition and severe immunodeficiency.[7,21,177] In this context, antifungal therapy should only be considered in immunocompromised patients on mechanical ventilation with biopsy-proven candidiasis and without an alternative aetiology.[177]

Conclusions and perspectives

Candida is still one of the main fungal pathogens responsible for serious fungal disease, and non-*albicans* species as well as multidrug-resistant *Candida* infections are increasingly detected in clinical settings. Several key challenges need to be tackled to improve the clinical management and outcomes of IC patients. First, collecting and comparing global epidemiological data for IC is hindered by the absence of specific criteria for an incidence denominator and inconsistently collected data. Large longitudinal studies, alongside regional and local surveillance studies, are required to understand epidemiological trends and shifts and

to collect data to guide and support empirical antifungal therapy. Another key challenge concerns the currently available diagnostic tests and risk scoring tools, which have a limited capacity to inform appropriate treatment and improve clinical outcomes in a very heterogeneous population of patients. Additionally, the lack of standardized effectiveness outcomes and long-term data for IC limits the ability to capture downstream consequences of treatment pathways, namely treatment failures.[178] Understanding which elements of care, like survival or length of stay, are most likely to be affected by treatment, and standardizing those outcomes and their reporting across trials, would promote comparability across treatments.

The timing for the initiation of antifungal therapy is also a key aspect to improve patient outcomes, hindered by the diagnostics limitations. Empirical antifungal therapy is recommended for adults who are at high risk of fungal infection, alongside prompt source control to eliminate the focus of the infection, when possible. Finally, treatment-wise, echinocandins have shown promising efficacy and safety results[18] and are recommended by guidelines as first-line treatment in most IC patients, but they carry higher costs of drug acquisition and administration compared with older-generation antifungal agents.[179,180] Furthermore, available cost-effectiveness data for echinocandins in treating IC are limited, both quantitatively and qualitatively,[178] and inconsistently reported. In addition, few studies are available to support recommendations on the optimal step-down therapy from echinocandins to azoles or the total duration of therapy. Strategy studies should prospectively identify optimal step-down protocols as well as explore further limitations of the total duration of antifungal treatment in selected patient groups.

Several new drugs have shown promising efficacy against IC in recent phase 2 and 3 clinical trials. Rezafungin is a novel echinocandin with an extended half-life and prolonged therapeutic drug concentrations in peripheral tissues, allowing weekly versus daily administration compared to existing echinocandins. These pharmacodynamics properties simplify treatment of outpatients requiring extended therapy and make rezafungin a viable alternative for IC prophylaxis in haematological patients. A phase 2 trial has demonstrated that the efficacy and safety of rezafungin are comparable to those of the other echinocandins,[82] while recently published results of the phase 3 trial ReSTORE have shown that rezafungin is non-inferior to caspofungin in patients with candidaemia or IC regarding day-14 global cure and 30-day all-cause mortality, with no differences in adverse events occurrence.[181] Ibrexafungerp is an oral glucan synthase inhibitor with broad activity against *Candida* spp., including azole resistant (e.g. *C. auris*), and it has a comparable efficacy and safety with standard of care, according to a small phase 2 trial.[182,183] An ongoing salvage study suggests it could be used for drug-resistant infections as an alternative to echinocandins (NCT03059992). Fosmanogepix is a guanosine monophosphate inhibitor with a broad activity against *Candida* species (except against *P. kudriavzevii*) and can be administered orally and parenterally twice daily.[184] A small phase 2 clinical trial has shown good efficacy and safety in fluconazole-resistant IC[185]; a similar study on *C. auris*-candidaemia has recently successfully met its clinical objectives (NCT04148287). ATI-2307 mitochondrial inhibitor was found to have *in vitro* and *in vivo* activity against most *Candida* species and has potential to be used for drug-resistant *Candida* infections.[186] However, no comparative clinical trials have been conducted so far.

In addition to new drug development, there is an increased interest in combination therapy to tackle the rising of drug resistance and the high mortality rates in IC. A recent systematic review found that, although the effect of combination treatments varied greatly across studies depending on *Candida* species, drug and methodology used, some combination regimens had a synergistic effect on difficult-to-treat species or had higher efficacy than monotherapy on the prevention/reduction of biofilms and the clearance of infected tissues.[187] However, these data are subject to substantial biases, and further data on combination therapy is needed.

The availability of new compounds and combination therapy overcome some of the challenges identified and increase our options for management of chronic *Candida* infections and ambulant patient treatments. However, early identification of patients that require antifungal therapy and treatment of sanctuary site infections remain a challenge and will require further innovations.

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Supplementary data

Available as Supplementary data at *JAC* Online.

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