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Invasive Candidiasis in Critical Care: Challenges and Future Directions

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ABSTRACT

Invasive candidiasis is the most common critical care-associated fungal infection with a crude mortality of ~40-55%. Important factors contributing to risk of invasive candidiasis in ICU include use of broad-spectrum antimicrobials, immunosuppressive drugs, and total parenteral nutrition alongside iatrogenic interventions which breach natural barriers to infection (vascular catheters, renal replacement therapy, Extra Corporeal Membrane Oxygenation (ECMO), surgery). This review discusses three key challenges in this field. The first is the shift in *Candida* epidemiology across the globe to more resistant non-*albicans* species, in particular, the emergence of multi-resistant *Candida glabrata* and *Candida auris,* which pose significant treatment and infection control challenges in critical care. The second challenge lies in timely and appropriate initiation and discontinuation of antifungal therapy. Early antifungal strategies (prophylaxis, empirical and pre-emptive) using tools such as the *Candida* colonisation index, clinical prediction rules and fungal non-culture-based tests have been developed: we review the evidence on implementation of these tools in critical care to aid clinical decision-making around the prescribing and cessation of antifungal therapy. The third challenge is selection of the most appropriate antifungal to use in critical care patients. While guidelines exist to aid choice, this heterogenous and complex patient group require a more tailored approach, particularly in cases of acute kidney injury, liver impairment and for patients supported by Extra Corporeal Membrane Oxygenation. We highlight key research priorities to overcome these challenges in the future.

Keywords

critical care; candidiasis; fungal; biomarkers; antifungal

Declarations

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Conflicts of interest

IML is a section-editor for Intensive Care Medicine and has received speaking and advisory board fees from Merck and Gilead Sciences. TB has received speaking fees from Pfizer and speaking, advisory board fees and research support from Gilead Sciences. CL has received research support from Gilead Sciences.

Authors' Contributions

CL, TB and IML conceived the idea, CL performed the literature search and drafted the manuscript, which was critically reviewed and revised by IML and TB.

Take home message: Epidemiological shifts towards multi-resistant *Candida* requires enhanced surveillance and rigorous infection control to detect and prevent resistance emergence. The evidence around deployment of risk-scores and fungal non-culture-based tests in decision-making around starting and stopping antifungals in the ICU is lacking: adequately powered multi-site studies using a combination of tests linked to clinical and cost effectiveness outcomes are needed. Antifungal prescribing in special ICU populations, particularly acute kidney injury, liver impairment and ECMO requires a tailored approach and further PK evaluation.

Tweet: Key ICU Candidiasis Challenges: Resistance Emergence, Biomarker-driven antifungal prescribing (start & stop), Tailoring therapy in ICU hosts

Introduction

'Invasive candidiasis' (IC) is an umbrella term for three clinical conditions; candidemia; deep-seated candidiasis; and deep-seated candidiasis with associated candidemia[1]. Cases are often hospital-acquired, and critically ill patients are particularly vulnerable[2], with approximately one-third of all candidemia occurring in this setting[3]. Despite expanded access to fungicidal agents, IC-related outcomes remain poor, with a crude mortality of ~40-55% in Intensive Care Unit (ICU)-focused studies over the past decade[4–7].

The incidence of deep-seated candidiasis without concomitant candidaemia in ICU is less certain due to challenges in obtaining specimens for microbiological confirmation. Intra-abdominal candidiasis (IAC) accounts for most deep-seated cases, with ~30% occurring in critical care[8]. Perforation, anastomotic leaks, repeat laparotomies, necrotizing pancreatitis and abdominal organ transplants increase risk, therefore incidence is higher in surgical ICUs[8]. Other forms of deep-seated candidiasis include haematogenously disseminated disease (hepatosplenic, ocular, cardiac, central nervous system, bone and renal), seen more frequently with prolonged candidemia, and in immunosuppressed and neutropenic patients[9, 10]. Host genetics also influence IC susceptibility, with various single-nucleotide polymorphisms (SNPs) identified as increasing candidaemia risk[11].

Figure 1. illustrates key factors contributing to development of IC in ICU. IC risk factors have fluctuated with advances in intensive care medicine; while there is increased use of renal replacement therapy, Extra Corporeal Membrane Oxygenation (ECMO), and immunosuppression treatments, there has been improved vascular catheter management, more judicious use of total parenteral nutrition (TPN) and greater emphasis on antimicrobial stewardship[12–14]. The collective impact of this on IC incidence is unclear. Large multi-centre studies examining IC incidence in ICU have been conducted over the past decade[4–7, 15–18]. Rates of candidaemia reported vary significantly between 3.5 – 16.5 per 1000 admissions[4, 6, 7, 16–18]. However, due to inter-centre variability, the fact most studies focused on candidaemia only, and some encompassed cases likely to represent colonization rather than IC, evaluation of IC incidence trends in ICU over time is challenging.

In this narrative review, we sought to summarise key epidemiological, diagnostic and treatment challenges of managing IC in ICU and highlight future directions in this field. To ensure broad coverage of relevant literature, we undertook a MEDLINE search for English language articles published before 1 July 2020, using the terms "candidiasis", "candidaemia", "critical care",

“resistance”, “biomarkers” and “antifungal”, including further relevant studies from reference lists of articles identified.

Challenge 1: Changing Epidemiology and Emergence of Antifungal Resistance

Epidemiological shifts

There is significant geographic and demographic variation in IC[19]. *C. albicans* remains the dominant species in Europe[5–7]; in a pan-European ICU cohort study (2015-16)[6], *C. albicans* represented 57% of cases, followed by *C. glabrata* and *C. parapsilosis*. Across India, *C. tropicalis* was the most common cause of ICU-acquired candidaemia[20], whereas *C. albicans* and *C. parapsilosis* predominate in Latin America[21]. The USA sees a higher proportion of non-*albicans* cases (approximately two-thirds), with increasing *C. glabrata* incidence[22]. Echinocandin-resistant *C. glabrata* is reported; while European prevalence appears low (<1%)[23], US studies report a prevalence of 6-12%[24–26], with azole cross-resistance in up to one-third of isolates[27]. This is concerning given echinocandins are recommended first-line treatment in IC, and azoles the most widely used antifungals globally. Moreover, the emergent multi-drug resistant *C. auris* has caused outbreaks on ICUs worldwide[28]. It is the 3rd most common cause of candidaemia in South Africa, with 88% of cases associated with ICU stays[29]. *C.auris* is usually fluconazole-resistant, with variable amphotericin and echinocandin susceptibility, and pan-fungal resistance to all three classes reported[30].

Reservoirs of resistance in ICU: the patient and environment

The patient and the environment can be reservoirs of fungal resistance in ICU. Antibiotic use disrupts the skin and gut microbiome, increasing *Candida* colonization and risk of IC[31]. Antifungal exposure selects for less susceptible *Candida* species such as *C. parapsilosis, C. krusei* and *C. glabrata*[32] and fosters resistance; in a US study, echinocandin-resistant *C. glabrata* was associated with prior echinocandin exposure, fluconazole resistance, and prolonged hospitalization[26]. In Denmark, post-treatment (≥7 days) mouth swabs in candidaemic patients demonstrated acquired resistance to fluconazole and echinocandins in 29% and 22% of *C.glabrata* isolates respectively[33]. Specifically, reduced echinocandin penetration into the gut may select for the emergence of echinocandin-resistant species[33, 34].

Resistant isolates spread between patients, and within the ICU environment, with reports of genotype-linked clusters of azole-resistant *C. parapsilosis*[35], and inter-hospital spread of azole-resistant *C. glabrata*[36] in ICU. *C. auris* studies have described widespread contamination of environmental surfaces and equipment persisting for months, with patient acquisition of *C. auris* occurring after as little as 4-hours of contact[37]. The limited efficacy of commonly used environmental disinfectants and absence of effective skin decolonization regimens for *C. auris*,

have made transmission difficult to interrupt[38]. A UK ICU *C.auris* outbreak was only stemmed when reusable temperature probes were removed from circulation[39]. For *C. auris*, infection control measures including screening, isolation, cohorting and environmental disinfection are advised in Public Health guidance[40, 41]. ICU interventions for tackling fungal resistance are summarized in Figure 2.

Many hospital laboratories do not identify yeasts in non-sterile specimens to species level; as a result, changes in ecology and resistance may go undetected. Misidentification of *C. auris* for other species, particularly C*. haemulonii*, when using common diagnostic platforms is recognized[42]. Matrix-assisted laser desorption/ionization time-of-flight (MALDI-TOF) allows quick, accurate identification but is not universally available. Improving laboratory capacity for *Candida* speciation, particularly *C.auris*, and fungal susceptibility testing is important for surveillance and early detection of resistance emergence in ICU.

Challenge 2: When to Start and When to Stop Antifungal Therapy?

Timely delivery of effective AFT in proven IC is crucial, as delays are associated with increased mortality[43]. Conversely, over-prescription may be detrimental, exposing patients to drug toxicities and driving resistance emergence. A cross-sectional study of French and Belgian ICUs demonstrated that while 7.5% of patients were prescribed systemic AFT, two-thirds subsequently had no evidence of IFI[44], emphasising the challenge of achieving a balance between targeted, timely AFT whilst avoiding excessive and unnecessary use.

Earlier antifungal strategies have thus been developed (prophylactic, empiric, pre-emptive), (Table 1) although the optimal strategy in ICU remains controversial. To aid decision-making about stopping and starting antifungals, three key tools, for use alone or in combination, have been proposed: *Candida* colonisation assessment, clinical prediction rules, and fungal non-culture-based tests (NCBT) (Table 2). Table 3 summaries key studies using these tools to initiate or discontinue AFT, however their impact on clinical practice remains hotly debated.

Role of candida colonization and clinical prediction rules

Candida colonization is considered a pre-requisite for the development of IC (Fig.1)[62]; those with a higher Candida Colonization Index (CCI) are at greater risk[45]. However, although the proportion of ICU patients colonized with *Candida* increases over time (~50-80%), only 5-30% will develop IC[63]. While studies have proposed colonization can be used to guide prophylaxis and reduce IC[64–66], they have not shown a mortality benefit. A study found colonization-triggered caspofungin or azole use changed the ICU fungal ecology (increased *C. glabrata)*, without reducing IC-associated mortality or incidence[67]. Hence, the moderate positive predictive value (PPV) of this approach (~66% for CCI[45]) could lead to excessive antifungal use that is neither appropriate or cost-effective.

To improve the PPV, clinical prediction rules, incorporating host factors with or without *Candida* colonization, have been established. The UK FIRE Study reviewed ~60,000 ICU admissions and evaluated risk models for predicting IC. However, IC incidence was lower than expected (0.6%), and analysis suggested a strategy of no risk-assessment or AFT prophylaxis was the most cost-effective [68].

RCTs have evaluated the impact of clinical prediction rules triggering early AFT on IC incidence and mortality in ICU. The MSG-01 trial[57] (n=219) randomized to caspofungin prophylaxis or placebo based on the Ostrosky-Zeichner Clinical Prediction Rule, demonstrating a non-significant

reduction in IC (9.8% vs 16.7%, p=0.14) and no difference in all-cause mortality (16.7% vs 14.3%, p=0.78).

The similarly-sized INTENSE trial[58] (n=241) randomized ICU patients with intra-abdominal infection requiring emergency surgery to 'pre-emptive' micafungin or placebo. Given prescribing was not based on NCBTs or radiology, current definitions would consider this an antifungal prophylaxis trial. There was no reduction in IC incidence (micafungin 11.1% vs placebo 8.9%). AFT was possibly initiated too late (max. 120-hours post-surgery) given many developed IC early in their admission. No details around source control were presented (e.g. drainage of collections/second laparotomies), which may play a more significant role than early AFT in patients with a surgical abdominal focus.

Both trials suggest early AFT based on risk factors alone does not reduce IC incidence or impact mortality. However, they also illustrate the challenges of powering studies adequately: in the MSG-01 trial, IC incidence in the control group was lower than expected, and the INTENSE trial highlighted the importance of selecting the right at-risk group and timepoint for intervention.

Empirical antifungal therapy in ICU

Given signs and symptoms of IC are non-specific, overlapping with many other infectious and non-infectious aetiologies, empirical AFT to cover the possibility of fungal infection in the septic ICU patient is common practice. A major factor driving empirical therapy are limitations of conventional culture-based methods. Although gold-standard for diagnosing IC, blood culture (BC) sensitivity is suboptimal (~75% in bloodstream infection, ~5-20% in abdominal candidiasis)[1, 69], sterile site sampling (e.g. abdominal pus) often difficult, and time-to-culture-positivity prolonged (2-3 days)[1].

No survival benefit of early AFT in non-neutropenic ICU patients was demonstrated in a 2016 meta-analysis (>2300 patients from 22 RCTs)[70], although criteria triggering antifungal prescribing in the analyzed studies were very heterogenous. Subsequently, the EMPIRICUS trial[59] (n=261) randomized ventilated patients with evidence of ICU-acquired sepsis, *Candida* colonization, and multi-organ failure to empirical micafungin or placebo. No improvement in 28-day fungal-free survival was demonstrated (68% vs 60.2%, p=0.18), despite significant reduction in proven IC in the micafungin arm (3% vs 12%, p=0.008). Subgroup analysis suggested a trend towards better survival in those with SOFA score >8 (HR, 1.69 [95% CI, 0.96-2.94], p=0.07); Demonstrating survival benefit in ICU patient groups, often with multiple co-morbidities and high

baseline mortality, requires much larger trials to achieve adequate power. Identifying the subset of ICU patients who could benefit from early AFT remains a key challenge.

Guidelines do not address de-escalation or discontinuation of empirical therapy for suspected infection in the absence of microbiological confirmation. In a post-hoc analysis (n=647) of the observational ARMCAND2 study including patients with suspected(57%) or proven IC(43%), de-escalation (defined as *either* switch to azole *or* antifungal discontinuation by day 5) only occurred in 22% (n=142; 96 switched; 48 stopped), of which half had no microbiological evidence of IC[71]. De-escalation was associated with shorter total AFT duration, with no negative impact on mortality or length of ICU stay despite similar illness severity scores between those who did and did not de-escalate. A smaller observational study had similar findings[72]. Nevertheless, the low proportion switched or stopped highlights barriers to de-escalation in practice. This includes reluctance to modify empirical treatment in unstable patients with uncertain diagnoses, alongside a desire to use a fungicidal, well-tolerated agent to cover the possibility of azole-resistant Candida. Yet, for patients on empirical therapy where the clinical picture suggests low IC-risk and BC are negative, discontinuing AFT appears a reasonable option and could be beneficial in preventing resistance emergence. For those where likelihood of IC is deemed moderate-to-high, non-culture-based diagnostics may have a role in informing decisions.

Role of non-culture-based tests

Non-culture-based tests (NCBTs) have been developed in attempt to overcome the shortfalls of culture-based fungal diagnostics, given their quick turn-around-time, the potential for earlier IC detection and given they may remain positive for longer while on AFT[1]. They include 1,3-β-d-glucan (BDG), T2 magnetic resonance Candida assay (T2Candida), Multiplex candida real-time PCR, and the detection of mannan antigen (MAg) and anti-mannan IgG antibodies (Anti-Mn) (Table 2). Potential roles for NCBTs include aiding clinical decision-making to guide; 1) the *initiation* of pre-emptive AFT; 2) the *discontinuation or withholding* of empirical AFT; 3) monitoring clinical improvement in patients with IC.

NCBTs have been described as “Bayesian”[69]; i.e. they do not deliver a definitive result, but assess the likelihood of infection. IC prevalence varies between ICUs due to differences in case-mix and interventions. With variation in the pre-test likelihood, the negative predictive value (NPV) and PPV of NCBTs changes; in higher-risk patients and settings (e.g. surgical ICU) the PPV will rise and the NPV will decrease, and vice-versa[69]. Hence, as recently outlined in Mycoses Study Group recommendations, NCBTs must be requested and interpreted in the context of the pre-test

likelihood of IC[73]; they suggest that the clinical value of NCBTs is limited when this figure is less than 10%.

Non-culture-based tests to trigger antifungal initiation

The ideal NCBT for guiding early antifungal initiation needs a high sensitivity to identify IC, but reasonable specificity to avoid over-prescribing. The most widely used NCBT, BDG, has moderate specificity (~60-85%[48–50]), marred by false-positivity which may occur due to haemodialysis, blood product administration, high-burden *Candida* colonisation, and disturbed GI-mucosa; all common in ICU. This may result in antifungal overuse. Establishing diagnostic cut-off values which optimise test performance in ICU is crucial. BDG specificity improves with consecutive sampling and increasing the 'positive' cut-off value to ≥250 pg/ml (instead of 80 pg/ml[74]) which in one study increased specificity to 87% but reduced sensitivity to 52%[75]. NCBT combinations may also improve specificity; a positive BDG (≥80 pg/ml) alongside a negative PCT (<2 ng/ml) had a 96% PPV for candidaemia, when distinguishing IC from bacteraemia in one study[76]. Additionally, a highly-positive BDG (>259 pg/ml) alongside a positive CAGTA better distinguished IC from *candida* colonisation in patients with severe gastrointestinal conditions, compared to either used alone[75]. A prospective Danish study (n=126) in ICU patients at high-risk of IC (particularly IAC) found a combination of T2Candida and BC compared to MAg and BC, or BC alone had a the greatest specificity (64%/53%/29% respectively), and a sensitivity of >95%, for diagnosing proven/likely IC[77]. Additionally, a retrospective study assessing NCBTs performance for IAC (n=48) found the sensitivity/specificity for T2Candida was 33%/93% and BDG 83%/67%; however concordant positive results diagnosed IAC in 100% of cases, and concordant negative results excluded IAC in 90% of cases, suggesting combinations would be more useful clinically[78].

To date, few prospective studies have examined the impact of NCBT-driven pre-emptive AFT on outcomes[79]. A small pilot RCT (n=64) administered pre-emptive anidulafungin to ICU patients with a BDG ≥60 pg/ml[56] during twice-weekly surveillance; while it demonstrated feasibility, enrolment difficulties meant it was not powered to assess a difference in IC or survival. In a sub-group analysis of the EMPIRICUS study, fungal-free survival was not significantly different in those with an elevated BDG who received micafungin versus placebo (BDG >80 [HR 1.41, 95% CI 0.85-2.33], BDG >200 [HR 1.51, 95% CI 0.47-5.00]), but the trend was in the direction of the micafungin arm[59].

Current evidence is not robust enough to support the use of NCBTs alone to trigger AFT. The moderate specificity of BDG hinders its use, but combination with other NCBTs, optimising 'cut-off' values, and directing testing to 'high risk' patients using Candida risk scores, make it a more valuable tool. NCBT-driven pre-emptive therapy using NCBT combinations which maximise test performance (T2Candida plus BDG) alongside culture is the most promising early AFT strategy which needs to be examined robustly in randomised multi-centre clinical trials. Outcomes should include IC, mortality, AFT consumption and cost-effectiveness, so benefits and risks of such a strategy can be holistically assessed. We eagerly await the results of the CandiSep trial (NCT02734550) comparing clinical outcomes of a BDG-driven versus culture-driven approach to AFT prescribing in septic ICU patients.

Non-culture-based tests to aid antifungal discontinuation

NCBTs with a high NPV may be better used to guide discontinuation or preventing initiation of AFT. A trial (n=109) randomized patients with evidence of infection who fulfilled IC-risk criteria to 14-days' empirical AFT or a NCBT-driven strategy, whereby AFT was stopped if BDG, MAg, Anti-Mn, and BC were negative[61]. Unsurprisingly, given comparison was to a 14-day standard, AFT duration was shorter in the NCBT arm, but importantly there was no deleterious impact on mortality or development of IC. A further study (n=85) prescribed empirical AFT to patients with risk factors and signs of infection[60]; based on negative BC and serial negative BDGs, AFT was safely discontinued in 21/85 by day 4 and none developed candidaemia upon follow-up. Other retrospective studies demonstrated similar findings[80, 81]. An ICU study assessing utility of BDG for therapeutic decision-making found that although introduced to target patients 'high-risk' of IC, in practice only 26% of patients in whom it was used were in this category[82]. Results influenced AFT prescribing in over half of cases, deemed appropriate in three quarters and inappropriate in a quarter of cases (AFT continued/started with no subsequent evidence of IFI). Thus paradoxically, in real-world deployment of ICU BDG testing, any reductions in antifungal consumption gained through earlier stopping of inappropriate therapy based on the test's good NPV may be outweighed by an excess in prescribing due to the test's poor PPV when used in an unselected population. Studies so far have been too small to assess the safety and clinical effectiveness of NCBT-driven AFT discontinuation algorithms. Multi-site studies comprising a range of low-to-high IC prevalence settings are needed for results to be generalisable.

In summary, whilst NCBT results interpreted in context remain a useful adjunct in stewardship, to date there is insufficient evidence to support antifungal discontinuation based on negative NCBT[48, 83]. The A-STOP trial (ISRCTN43895480), a large multi-site (35 hospital) UK

diagnostic accuracy study prospectively assessing which NCBT (or combination thereof) can best rule-out IC and facilitate AFT discontinuation in ICU patients, holds promise of delivering on this.

Non-Culture-Based Tests for Monitoring

Clinical response markers for monitoring and prognostication in IC are lacking. BC clearance of fungi is often used as a proxy for treatment effectiveness, however this is less-than-ideal given their suboptimal sensitivity, particularly in deep-seated candidiasis.

Studies in ICU[77] and mixed ward/ICUs[84], found T2Candida remained detectable for longer than BC in candidaemia; in the latter study 7.5% (4/31) had a positive surveillance BC, yet 41.9% (13/31) had a positive surveillance T2Candida. Hence, time-to-negative result with T2Candida was significantly longer, perhaps unsurprising given T2Candida also detects non-viable *Candida* cells. To assess its clinical relevance, larger studies correlating persistent T2Candida positivity with clinical outcomes are needed. While studies have examined BDG kinetics for monitoring treatment response in IC[85–87], few have done so in an ICU-specific population[88, 89]. In heterogenous patient groups, serial BDG decline has been associated with successful therapy, with a slower decrease in patients with deep-seated candidiasis[85, 86], and persistently negative BDGs in candidaemic patients are associated with a lower 30-day mortality[90, 91]. However, in ICU patients with intra-abdominal candidiasis[88] and candididaemia[89] BDG was slow to clear from circulation and remained positive beyond clinical resolution of infection. Hence, while the trajectory of decline, or persistent negativity may have some monitoring use, there is little evidence to support that transition from a positive to negative BDG is valuable in assessing treatment response and currently no evidence that it can be used to guide AFT duration.

Challenge 3: Choosing the Optimal Antifungal Drug for the ICU Patient

The antifungal armamentarium is limited, with just four classes of drugs available for treatment of IC; azoles (fluconazole, voriconazole); echinocandins (caspofungin, anidulafungin, micafungin); polyenes (amphotericin B); and the pyrimidine analogue, flucytosine. Drug development is progressing, with several new agents undergoing trials (e.g. Ibrexafungerp, fosmanogepix, rezafungin)[92].

Several guidelines aid the appropriate selection of an antifungal[93, 94]. Echinocandins are recommended first-line treatment of proven[93, 94] and suspected[93] IC in non-neutropenic critically ill adults, due to their broader-spectrum compared to fluconazole, fungicidal activity, excellent tolerability and minimal drug interactions. In the only comparative RCT, anidulafungin was found to be non-inferior to fluconazole for the treatment of IC (global response 73.2% versus 61.1%, 95% CI, −1.1 to 25.3)[95]. A post-hoc subgroup analysis in ICU patients demonstrated significantly better response rates for those receiving an echinocandin (70.8% versus 54.1%, p=0.03), although this did not translate to a reduction in 28-day mortality (20.2% versus 24.3% *P* =0.57)[96]. Other observational studies comparing mortality between those initiated on fluconazole or echinocandins, showed either no difference[97–99], or favoured echinocandins[100, 101]. However, adjusting for the multiple confounders influencing outcome in ICU in non-randomised studies is difficult. A recent large RCT failed to demonstrate non-inferiority of the newest triazole, isavuconazole, when compared to caspofungin for IC (end-of-IV-therapy treatment response, 60.3% versus 70.1%, 95%CI -19.9– -1.8), consistent regardless of illness severity[102]. There is no evidence to suggest a difference in efficacy or mortality with Amphotericin B compared to azoles and echinocandins[103]. Given the higher cost and association with greater toxicity, amphotericin B in IC treatment is usually reserved for situations with no suitable alternatives eg. MDR *Candida,* for drug-penetration.

In candidaemia, de-escalation from echinocandins to fluconazole for azole-susceptible isolates, when repeat BCs are negative and the patient is clinically stable is recommended within 5-7 days in IDSA[93], and at 10-days in ESCMID guidelines[94]. A number of studies, (albeit not RCTs) have demonstrated the safety of this approach at day 5 in proven IC[71, 100, 104] with no impact on clinical outcomes. The ESGCIP taskforce recently recommended considering de-escalation at day 5, dependent upon clinical response[105].

Antifungal drugs in special ICU populations

Alongside guidelines, patient-specific factors need to be considered when choosing the most appropriate drug, dose and duration for different clinical scenarios[106], summarised in table 4.

Acute kidney injury (AKI) is common in ICU, sometimes requiring continuous renal replacement therapy (CRRT) which can significantly affect antifungal PK/PD. The kidneys excrete 60-80% of fluconazole unchanged[107]; dose reduction in AKI is thus required due to delayed elimination. Conversely, high elimination is seen with CRRT due to low protein-binding and high water solubility, therefore increased fluconazole doses are advised[107]. For voriconazole, no renal or CRRT dose adjustment is required but frequent TDM is needed. Given the voriconazole IV solvent vehicle can accumulate in moderate-to-severe renal impairment, oral over IV therapy is recommended[107]. Amphotericin B, particularly the deoxycholate formulation, can be associated with nephrotoxicity and should be avoided in renal impairment if suitable alternatives are available. CRRT dose adjustment is not required. Echinocandins are highly protein-bound with minimal renal excretion, therefore no dose adjustment is required in renal failure, and CRRT has no clinically significant effect on drug removal[108], making them an optimal choice.

Chronic and acute liver failure is frequently seen in ICU patients. Drug-induced liver injury (DILI) is a risk with all azoles, therefore caution is required in pre-existing moderate or severe liver disease and alternatives considered. No dose adjustment is required for amphotericin [109]. Anidulafungin is the only echinocandin eliminated through extrahepatic metabolism[110] and therefore often the preferred agent in hepatic impairment.

ECMO is increasingly used for cardiorespiratory support in ICU; altered antifungal PK/PD may occur due to drug sequestration, increased volume of distribution, and drug clearance changes while on the ECMO circuit, but data are scarce[111]. Micafungin extraction by ECMO was demonstrated in an ex-vivo study[112], however there are conflicting data with caspofungin[113, 114], the latter study demonstrating adequate levels at usual doses. Satisfactory liposomal amphotericin B levels at standard dosing on ECMO are reported[115], while others administering higher doses (10mg/kg/day) found a ~50% reduction in C_{max}[116]. Due to increased volume distribution, larger fluconazole loading doses were required in children, however adult data are lacking[111, 117]. Voriconazole sequestration is reported, although the degree of sequestration changes with time, possibly due to saturation of ECMO circuit binding sites[114]. Hence frequent azole TDM is crucial yet rarely available in real-time, highlighting a pressing need for development of point-of-care antifungal TDM in ICU patients. Given expanding ICU ECMO use and its

association with higher IFI risk, further antifungal PK/PD studies are needed as current data is insufficient to adequately inform antifungal ECMO guidelines.

CONCLUSION

The diagnosis and management of IC poses many challenges in critical care; numerous unanswered questions remain as research priorities (Table 5). Improved identification of at-risk patients and the widening spectrum of diagnostics and therapeutics available for IC are promising. Personalized approaches to drug dosing and monitoring treatment response are needed. The key knowledge gap remaining is how tools such as risk scores and NCBTs can best be implemented in ICU practice to optimise clinical outcomes whilst exercising antifungal stewardship.

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