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Best practice in managing fungal infections

Invasive candidiasis: Every milligram of antifungal counts! Think Aspergillus!

Invasive fungal infections (IFIs) are a major cause of morbidity and mortality in critically ill patients. Almost 80% of IFIs are due to Candida spp., which are the third most common isolated microorganisms in the intensive care unit (ICU) (Kett et al. 2011; Bassetti et al. 2017). Although the incidence of invasive candidiasis (IC) varies considerably according to different reports and geographic locations, it ranges from 1 to 10 per 1000 ICU admissions. Candidaemia is the most common form of IC, followed by intra-abdominal candidiasis. Both are characterised by a high crude mortality, ranging from 25 to 60%, although strongly affected by underlying conditions and presence of sepsis and septic shock (Cortegiani et al. 2017b). The recently completed Epidemiological study on incidence of candidemia in European ICUs (EUCANDICU), conducted by the European Society of Clinical Microbiology and Infectious Diseases Study Group for Infections in Critically Ill Patients (ESCMID ESGCIP), will soon provide more homogenous and updated data about ICU-related incidence of IC in Europe.

Aspergillus is the second most common cause of IFI in ICU. It is difficult to assess the exact incidence of invasive pulmonary aspergillosis (IA) in non-neutropaenic critically ill patients, due to difficulties in risk stratification and diagnosis. However, it is increasing and it is probably higher than previously thought (Taccone et al. 2015).

Recent data have changed our understanding of and view about the management of both IC and IA in non-neutropaenic patients. The aim of this report is to discuss best practice in management of IFIs in the ICU, according to recent evidence.

Early discontinuation of empirical antifungal treatment in high-risk patients, using serial measurement of biomarkers...may be safe and cost-effective

Invasive candidiasis

“Dilemmas” from the evidence

The gold standard for the diagnosis of IC remains blood culture, which may miss more than 50% of cases in bloodstream infections and up to 80% in deep-seated candidiasis (Clancy and Nguyen 2018). Moreover, the average turnaround time for identification is 3–5 days, with additional time needed for susceptibility testing. Several retrospective and prospective observational studies found a strict correlation between timing of antifungal treatment initiation and patients’ survival, especially in case of sepsis and septic shock. Of note, this association has been found in patients with both candidaemia and intra-abdominal candidiasis (Puig-Asensio et al. 2014; Bassetti et al. 2015). These findings led to a widespread use of antifungals according to “untargeted” treatment strategies, such as prophylaxis (based on risk factors or scores), pre-emptive (based on “surrogate markers”) or empiric (signs and symptoms of infections) (Cortegiani et al. 2017b). In a recent cross-sectional 1-day multicentre study in France, 7.5% of all ICU patients received antifungals without proof of IFI in two-thirds of these cases (Azoulay et al. 2012).

At least two negative consequences on fungal ecology may be correlated to the increased use of antifungals. The first is the increasing rate of antifungal resistance, especially in non-albicans Candida spp (e.g. C. glabrata). Although not homogenous worldwide, reports from North America demonstrated a worrisome trend of bloodstream infections by echinocandin-resistant C. glabrata (to around 13%) with a hot-spot mutations in FKS genes, which encode glucan-synthase enzyme (target of echinocandins) (Cortegiani et al. 2018a). Of note, fluconazole and amphotericin B resistance are frequently associated with these mutations. Another issue is the very fast spread worldwide of Candida auris, a nosocomial pathogen which frequently presented multidrug or even extended or pan-drug resistance with a crude mortality rate up to 72% (Cortegiani et al. 2018b).

Four major multicentre randomised controlled trials (RCTs) failed to demonstrate a benefit in terms of mortality when comparing azoles or echinocandins versus...
placebo in a wide range of non-neutropenic critically ill patients (i.e. general non-neutropenic ICU patients at low or high risk of IFI, emergency abdominal surgery patients, and septic patients with multi-site Candida colonisation) (Schuster et al. 2008; Ostrosky-Zeichner et al. 2014; Knitsch et al. 2015; Timsit et al. 2016; Cortegiani et al. 2017b). However, in two trials enrolling high-risk patients and septic patients with Candida colonisation, there was a significant reduction of proven or probable IFI in patients receiving antifungals (Ostrosky-Zeichner et al. 2014; Timsit et al. 2016).

A recent Cochrane systematic review included 22 RCTs for a total of 2,761 patients (Cortegiani et al. 2016a; 2017a). There was moderate quality evidence that antifungal agents administration before the definitive diagnosis of IC in non-neutropenic patients (“untargeted” treatment) did not reduce mortality (RR 0.93, 95% CI 0.79 to 1.09, p=0.36). However, there was low-grade evidence that untargeted strategies significantly reduce the incidence of proven IFI (RR 0.57, 95% CI 0.39 to 0.83, p=0.0001). Interestingly, a subsequent trial sequential analysis demonstrated that it is unlikely that further research would change these results (Cortegiani and Giarratano 2018). Lastly, guidelines from the Infectious Disease Society of America strongly recommended empiric antifungal treatment with an echinocandin in patients with risk factors of IC (e.g. abdominal surgery) and no other cause of fever (Pappas et al. 2016). The treatment should be initiated as soon as possible in case of septic shock. The guidelines also underlined the need to support this decision with other means, such as score, surrogate markers or cultures from non-sterile sites.

These results are difficult to interpret (Cortegiani et al. 2016b) and apply in clinics, but they may suggest that classic “untargeted” antifungal strategies should be replaced. However, new strategies for effective “early” antifungal strategies are urgently needed (Figure 1). Useful insights came from recent evidence about non-culture diagnostics.

Non-culture diagnostics: the solution for dilemmas?
1,3-β-D-glucan (BDG) is a fungal cellwall polysaccharide of several pathogenic fungi. Although not specific for Candida spp., it is the most studied and used marker. A recent meta-analysis demonstrated a pooled sensitivity of 78% and specificity of 81% for IFI diagnosis and a best cut-off value of 80 pg/ml (He et al. 2015). The diagnostic performance of BDG improved if positivity was confirmed by two tests. Although most studies tested BDG in candidaemia, its usefulness has been proven for intra-abdominal candidiasis (sensitivity 70%, specificity 78%) and to differentiate IC from colonisation (Tissot et al. 2013; Martin-Mazuelos et al. 2015). Moreover, its association with other biomarkers such as procalcitonin (<2.00 ng/mL), could help in early differential diagnosis between candidaemia and bacteraemia (Cortegiani et al. 2014; Giacобbe et al. 2017). However, it is still unclear if BDG can be an effective marker to start antifungal treatment. In a subanalysis of the Empirical Antifungal Treatment in ICUS (EMPIRICUS) trial, empiric treatment with micafungin in septic patients did not improve survival in comparison to placebo, regardless of BDG levels (Timsit et al. 2016). The ongoing multicentre (1,3)-β-D-glucan Based Diagnosis of Invasive Candida Infection in Sepsis (CandiSep) trial will shed light on the effectiveness of a BDG-based strategy to initiate early antifungal treatment in comparison to standard culture-based strategy in patients with sepsis and high risk for IC (Bloos et al. 2018).

Recent studies evaluated biomarker-based strategies for early discontinuation of antifungal treatment. In a multicentre cohort study enrolling 85 ICU high-risk patients receiving empiric antifungal treatment for suspected candidaemia, two consecutive negative BDG tests permitted stopping anidulafungin at day 4, without missing any recurrent episode of candidaemia until day 30 (very high negative predictive value) (Nucci et al. 2016). Rouzé et al. (2017) performed a single-centre unblinded RCT enrolling 110 patients receiving empirical treatment. They randomised patients to receive treatment according to a biomarker-based strategy guided by the results of BDG, mannan and anti-mannan serum assays at day 0 and 4 after randomisation, in comparison to standard empiric treatment according to guidelines. The cut-offs used were 80 pg/mL for BDG, 125 pg/mL for mannan and 20 UA/mL for anti-mannan. Empirical antifungal treatment was discontinued more frequently in the biomarker-based group than in the control group (54% vs
2%, p < 0.001) with a significantly shorter duration of therapy (median 6 vs 13 days, p < 0.0001). Early discontinuation had no impact on patient outcomes, including the incidence of subsequent proven IC. These data suggest that early discontinuation of empirical antifungal treatment in high-risk patients, using serial measurement of biomarkers (especially more than one), may be safe and cost-effective (Figure 1).

T2 magnetic resonance (T2MR) assay is an automated molecular technology which can detect five commonly isolated Candida spp., namely Candida albicans, glabrata, parapsilosis, tropicalis, krusei. Very interestingly, it works on whole blood specimens (without blood culture) and does not need prior isolation of Candida spp. Moreover, T2MR does not need extraction or purification of target molecules, contrary to standard polymerase chain reaction (PCR). The estimated turnaround time is less than 5 hours (Clancy and Nguyen 2018).

The limit of detection ranges from 1 to 3 colony-forming units (CFU)/mL compared to the 100-1000 CFU/mL limit of standard PCR. Recently, two large multicentre studies, Detecting Infections Rapidly and Easily for Candidemia Trial (DIRECT1 and DIRECT2), evaluated the clinical performance of T2MR for rapid diagnosis of candidaemia. The overall sensitivity and specificity were 91% and 99%. In patients receiving antifungal drugs, T2MR was able to identify candidaemia episodes missed by blood culture (Clancy et al. 2018). Moreover, the recently published Serial Therapeutic and Antifungal Monitoring Protocol (STAMP) multicentre trial, enrolling 31 patients with candidaemia on antifungal treatment, demonstrated that T2MR was superior to blood culture for monitoring clearance of candidaemia (Mylonakis et al. 2018). Although these are promising results, the limited availability and costs may limit T2MR use in clinical algorithms. Further studies should evaluate T2MR performance in IC without candidaemia, in mixed Candida infections, and how to clinically interpret results that are discordant with blood culture.

"Bayesian" approach to Candida infection in ICU

Although several “dilemmas” remain unsolved, clinicians should apply a “Bayesian” approach to the management of Candida infections (Clancy and Nguyen 2018). This means that efforts should be made to estimate (and maximise) the pre-test likelihood of infection, whichever tests are used. Tests should be selected based on which is the most probable form of Candida spp. infection in that critically ill patient (e.g. candidaemia, intra-abdominal candidiasis). For example, the prevalence of candidaemia ranges from <1% in general patients in whom blood culture is collected to more than 10% in ICU high-risk patients, such as those in septic shock receiving broad-spectrum antibiotics though central venous catheter and multi-site Candida colonisation. The same is true for intra-abdominal candidiasis, the prevalence of which may range from around 5% to more than 30% in patients with peritonitis for recurrent gastrointestinal anastomotic leaks. After the decision to start antifungal treatment and after performing the appropriate source control (e.g. abdominal surgery, removing catheters) clinicians should focus on how and when to stop the drugs (Figure 1).

Recent evidence on invasive aspergillosis

Prompt administration of an effective treatment for invasive aspergillosis (IA) is pivotal to reduce mortality, which ranges from 60 to 90%. Patient selection is important and should start with considering risk factors. Nowadays, many critically ill patients not belonging to groups with “classic” immunosuppression criteria (e.g. haematologic, HIV, transplant) may develop IA, with general incidence in ICU ranging from 0.5% to 19% (Bassetti et al. 2014). The diagnosis in ICU is challenging due to unspecific radiological findings, difficulty in obtaining histological specimens and the low applicability of standard European Organization for Research and Treatment of Cancer/Invasive Fungal Infections Cooperative Group and the National Institute of Allergy and Infectious Diseases Mycoses Study Group (EORTC/MSG) criteria in this setting. New guidelines specifically addressing IFI in ICU, including aspergillosis, are ongoing (Bassetti et al. 2018). Risk factors to be considered in the general ICU population are chronic heart failure, severe bacterial infection under broad-spectrum antibiotic treatment, surgery, malnutrition, sepsis, acute respiratory distress syndrome (ARDS) and, above the others, chronic obstructive pulmonary disease (COPD) and the cumulative dose of steroids. There is a correlation between the degree of immunocompromise due to the above-mentioned comorbidities and the risk of acquisition of IA. Very recently, a retrospective multicentre cohort study evaluated the association between influenza and IA in non-immunocompromised ICU patients (Schauwvlieghe et al. 2018). Influenza was found to be an independent risk factor for IA (adjusted odds ratio 5.19; 95% CI 2.63–10.26; p=0.0001). The group with both influenza and IA had significantly higher 90-day mortality than without influenza (51% vs 28%; p=0.0001). Moreover, a recent retrospective analysis of the Extracorporeal Life Support Organization registry (ELSO) registry suggested that mortality of patients in extracorporeal membrane oxygenation (ECMO) with Aspergillus involvement was significantly lower than the overall ELSO cohort (35.7% vs 48%) (Cavayas et al. 2018). Based on these data, influenza and severe respiratory failure (even in ECMO) should be considered major risk factors for IA in ICU patients.

Diagnosis of pulmonary IA should be based on clinical, radiological and microbiological (culture and non-culture) results. Galectomannan in broncho-alveolar (BAL) fluid lavage is actually the best non-culture assay for the diagnosis of pulmonary IA, since it is more sensitive than standard culture. The 2017 European Society of Clinical Microbiology and Infectious Diseases-European Confederation of Medical Mycology-European Respiratory Society (ESCMID-ECMM-ERS) guidelines recommend to consider an optical density index (ODI) of 0.5–1, although ODI >1 has higher predicted values (strong recommendation) (Ullmann et al. 2018). BDG may be helpful for specific detection of IA, but in association to BAL galectomannan. Thin-section chest computerised tomography (CT scan) is the imaging of choice, but classic signs are rare in ICU patients, who usually present unspecific radiological findings (Ullmann et al. 2018). Aspergillus PCR from blood and BAL may be of help, especially in combination with galectomannan.

It is still unclear if a prophylactic treat-
ment may be cost-effective in high-risk non-neutropenic ICU patients. A "diagnosis-driven" approach based on the clinical picture, respiratory culture and BAL galactomannan may be reasonable. Voriconazole is the treatment of choice, with amphotericin-B or echinocandins as suitable alternatives (Ullmann et al. 2018).

**Conclusion**

Management of IFIs in ICU still remain a matter of intense debate and a clinical challenge. Uncertainties in diagnostics, high mortality and resistance to antifungals are burning issues. However, “best practice” should include all available information, from simple risk factors analysis to non-cultural diagnostics. Early discontinuation is safe and should be applied. Two themes should guide our clinical approach: 1) in IC “Every milligram of antifungals counts!” 2) “Think Aspergillosis!”

**Conflict of interest**

Andrea Cortegiani declares that he has no conflict of interest. In the past five years Matteo Bassetti has participated in advisory boards and/or received speaker honoraria from Achaogen, Angelini, Astellas, AstraZeneca, Bayer, Basilea, Cidara, Gilead, Melinta, Menarini, MSD, Nabirva, Paratek, Pfizer, Roche, The Medicine Company, Shionogi, Tetraphase, VenatoRX, and Vifor.

**References**


Be Performed Based on Trial Sequential Analysis Results? Antimicrob Agents Chemother.


**Abbreviations**

CFU colony-forming unit
CT computerised tomography
IA invasive aspergillosis
IC invasive candidiasis
ICU intensive care unit
IFI invasive fungal infection
ODI optical density index
RCT randomised controlled trial
T2MR T2 magnetic resonance

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