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Antifungal stewardship in invasive *Candida* infections

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Abstract

Bloodstream and other invasive infections due to *Candida* species (invasive fungal diseases = IFD) are a major cause of morbidity and mortality in hospitalized adults and children in many countries worldwide. The high infection-related morbidity and mortality associated with invasive *Candida* infection/candidaemia (IC/C), combined with suboptimal diagnostic tools, have driven the overuse of antifungal drugs. Antifungal stewardship (AFS) may be regarded as subentity of the more general term Anti-infective or Antimicrobial Stewardship Program (AIS/AMS). The high costs and high contribution of antifungal agents to the management of IFDs along with their recognized toxicities have been addressed as the principal justification for antifungal stewardship. AFS programmes should be organized by an interdisciplinary team of clinicians, pharmacists, microbiologists and infection control experts with the lead of an infectious disease specialist preferably in each large hospital/institution dealing with high-risk patients for invasive fungal infections. These programmes should consider various aspects of IC/C including (i) the local fungal epidemiology, (ii) information on antifungal resistance rates, (iii) establishing and application of therapeutic guidelines, (iv) implementation of treatment strategies for empirical, pre-emptive therapy including PK/PD data for antifungal drugs, de-escalation and 'switch and step-down strategies' (from intravenous to oral medication) in defined patient populations, (v) catheter management together with the application of routine diagnostic procedures such as ophthalmological and cardiac evaluations and (vi) the best available diagnostic tests for diagnosing IC and candidaemia.

Keywords: Antifungal stewardship, antifungal therapy, Candida, candidosis, invasive fungal infection, resistance
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Introduction

Infection-related mortality due to IC/C remains high, in particular in severely ill patients in the ICU and when antifungal therapy is delayed. The high infection-related morbidity and mortality associated with IC, combined with suboptimal diagnostic tools, have driven the overuse of antifungal drugs in therapy and prophylaxis of IC/C. The concept of anti-infective stewardship may be defined as an ongoing effort by a healthcare institution to optimize antimicrobial use in order to improve patient outcomes, ensure cost-effective therapy and reduce adverse sequelae [1–4]. This includes the appropriate use of antimicrobials by selecting the proper drug, dosage, duration and route of administration. Antimicrobial resistance—a consequence of the use and misuse of antimicrobial medicines—occurs when a micro-organism becomes resistant to an antimicrobial drug to which it was previously sensitive. Primary and acquired (or secondary) resistance to antifungal drugs is known for several pathogenic fungi (e.g. yeasts such as *Candida* spp., and moulds such as *Aspergillus* spp. or *Mucorales*) [5,6]. Resistance mechanisms have been extensively described, in particular for *Candida albicans* against fluconazole with potential cross-resistance to other azole antifungals [6]. Current issues related to treatment for invasive *Candida* infections include aspects such as choice of the optimal

antifungal drug for candidaemia, balance between overuse (empirical therapy) and underuse (waiting until proven disease) of antifungal therapy in severely ill patients, step-down strategies, implementation of PK/PD in everyday practice, emergence of non-*Candida albicans* infections, the role of noncultural diagnostic tests and pharmacoeconomics (see Table 1).

Antifungal Stewardship for IC/C

According to the Policy Statement on Antimicrobial Stewardship by the Society for Healthcare Epidemiology of America (SHEA), the Infectious Diseases Society of America (IDSA) and the Pediatric Infectious Diseases Society (PIDS), antimicrobial stewardship (AMS) is defined as a programme with coordinated interventions designed to improve and measure the appropriate use of antimicrobial agents by promoting the selection of the optimal antimicrobial drug regimen including dosing, duration of therapy and route of administration [7] (see Table 2). Antifungal stewardship (AFS) refers to a programme or series of interventions to monitor and direct antifungal use at a healthcare institution. According to Tamma and Cosgrove, the most effective antimicrobial stewardship programmes simultaneously incorporate multiple strategies after collaborating with the various specialties within a given healthcare facility, although interventions on a smaller scale to improve antimicrobial use are also valuable in some settings [8]. An understanding of the pharmacokinetics and pharmacodynamics (PK/PD) of these drugs has been demonstrated as important to optimize drug choice and dosing regimen [9]. Optimizing the use of currently available antifungal agents is not only influenced by antifungal drug properties (spectrum of activity, PK/PD, mode of action, route of application) but by their high cost and drug-related toxicities as well. However, reduction in healthcare costs should be regarded only as a secondary goal of AFS.

TABLE 1. Current issues related to treatment for invasive *Candida* infections

Which is the optimal antifungal drug treatment for candidaemia?
How to balance between overuse (empirical therapy) and underuse (waiting until proven disease) of antifungal therapy in severely ill patients
How long do handle central lines and do we need to treat in patients with catheter-related candidaemia vs. other forms of invasive *Candida* infections?
What is the importance of *Candida* non*albicans* infections for the choice of initial therapy?
What is the appropriate choice of drugs in patient groups/hospitals with high prevalence of azole resistance?
What is the role of noncultural tests (e.g. Ag/Ab, ß-D-Glucan, PCR)?
Should different patient populations be treated differently (e.g. granulocytopenic)?
How to treat patients with invasive *Candida* infection and organ failure (e.g. renal and/or liver), severe sepsis or septic shock?
When to apply step-down strategies (switch from i.v. to oral)?
When and how to implement PK/PD in everyday antifungal treatment?
Which antifungal therapy is most cost-effective (pharmacoeconomics)?

TABLE 2. Minimum requirements for developing an institutional programme to enhance Antifungal Stewardship (adapted from Policy Statement on Antimicrobial Stewardship by the Society for Healthcare Epidemiology of America (SHEA), the Infectious Diseases Society of America (IDSA) and the Pediatric Infectious Diseases Society (PIDS))

Creation of a multidisciplinary interprofessional antifungal stewardship team that is physician directed or supervised. Team members should include but are not limited to:
• a physician
• a pharmacist
• a clinical microbiologist
• an infection preventionist
Institutional guidelines for the management of invasive Candida infections/ candidaemia
Additional interventions to improve the use of antifungals, including those designed to detect and eliminate:
• Multidrug regimens with unnecessarily redundant antimicrobial spectra
• Antifungal therapy for the management of 'fever' syndromes (without detection of fungi in sterile specimen) or cultures that represent contamination or routine colonization
• Empiric regimens that are inadequately
• Regimens that do not adequately treat infections caused by culture-confirmed pathogens
Processes to measure and monitor antifungal use at the institutional level for internal benchmarking
Periodic distribution of facility-specific epidemiological data together with the rates of relevant *in vitro* susceptibilities to Candida pathogens

Challenges for the Implementation of AFS in *Candida* Infections

Implementation of an AFS programme using a comprehensive care bundle for the treatment for candidaemia has been shown to improve management of infected patients [10]. Key issues of the strategy in a study from Michigan/USA were as follows: (i) utilization appropriate antifungal drugs with appropriate duration of use, (ii) removal of intravenous catheters, (iii) adequate diagnostics with repeated blood cultures and (iv) performance of ophthalmologic examinations [10]. In a prospective study on AFS in IC/C from Thailand, interventions included education, introduction of an antifungal hepatic and/or renal dose adjustment tool, antifungal prescription forms and prescription-control strategies [11]. Accordingly, for the implementation of an effective AFS programme, various important aspects and questions need to be considered.

What is the adequate diagnosis of IC/C and the role of noncultural tests (e.g. Ag/Ab, ß-D-Glucan, PCR)?

Blood cultures (BC) are still the method of choice for the diagnosis of candidaemia. Two pairs of blood culture bottles (10 mL each) should be obtained for aerobic and anaerobic culture when candidaemia is suspected before the initiation of antifungal therapy [12]. Standard BC media detect most *Candida* species. It appears that the detection of *C. glabrata* is