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Critical overview of clinical guidelines relating to invasive fungal infections

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Abstract

The incidence of invasive fungal infections (IFIs) has continued to grow in recent years. IFIs are associated with significant morbidity and mortality as well as costs. The diagnostic and therapeutic approaches to IFI have changed significantly in recent years, fostered by the introduction of new diagnostic methods and new antifungal products. There are also new therapeutic approaches such as de-escalation, pre-emptive antifungal treatment or combined treatment with antifungals. All of these aspects have been described in many trials, meta-analyses and reviews. There are also different clinical guidelines for IFIs with diagnostic and therapeutic recommendations. They are of unquestionable value and at the same time represent different perspectives on the problem. The lack of homogeneity when selecting and drafting the recommendations is a problem, and some of them are based more on personal opinion than on evidence. In this paper, we have put together a critical overview of the role of guidelines for IFIs, with emphasis on non-neutropenic critical patients.

Keywords: Clinical guidelines; Invasive fungal infection; Critical overview

1. Introduction

The incidence of community-acquired and nosocomial invasive fungal infections (IFIs) has increased greatly in recent years, with infections caused by *Candida* spp. being the most common overall (70–87%); however, *Aspergillus* spp. are being increasingly reported and identified as 'new emerging fungi' [1,2]. Intensive Care Unit (ICU) patients represent 25–50% of a hospital's cases of candidaemia [1–3]. Recent ICU studies show that IFIs caused by *Candida* spp. are responsible for >14% of all microbiologically documented infections [1–4]. The incidence of non-*albicans Candida* spp. has also increased in the ICU, together with strains of *Candida* resistant to fluconazole (FLZ) and other antifungals [2,3]. There is considerable variability in the worldwide distribution of these species (Table 1).

In hospitals, the ICU is the epicentre for many IFIs such as invasive candidiasis (IC), the incidence of which is ten times higher in the ICU than on medical or surgical wards [1–4]. The greatest risk factors for IFI are present in the ICU: prolonged hospitalisation; use of antimicrobial products (quantity and spectrum); parenteral nutrition; central lines; surgery; older patients with multiple underlying conditions; and immunosuppressed patients [1–6].

Table 1
Distribution of *Candida* spp. in different regions/countries (%)

Species	USA	Canada	Latin America	Europe
C. albicans	55	60	45	58
C. glabrata	21	12	6	10
C. parapsilosis	11	16	25	19
C. tropicalis	9	6	16	7
C. krusei	2	2	1	1
Candida spp.	2	4	7	5

The presence of IC presents a high raw mortality rate of 35–60%, with an attributable rate of 22–38%. Another very important aspect is the high cost of patients developing candidaemia, as an episode is estimated to cost approximately US$40 000 [1,3].

For some years, recommendations and guidelines have been drawn up in an attempt to facilitate the diagnostic and therapeutic management of patients with IFIs, particularly non-neutropenic critical patients (NNCPs), as well as other more specific guidelines for immunosuppression such as in transplant recipients and neutropenic patients.

2. Principles of the use of antifungal agents in non-neutropenic critical patients

In recent years, the concepts used in antibiotic treatment against bacterial infections have been incorporated into

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clinical practice in empirical antifungal therapy (EAT) [1, 5–8]. Early application is crucial and many studies have shown the impact of this on reducing mortality [3–5]. In a retrospective study of candidaemia, Morrel et al. [9] found that a delay of >12 h in initiating EAT was related to higher hospital mortality rates. A Spanish multicentre study showed a significant association between early EAT and greater survival and central line removal [10]. The presence of IFI is an independent factor for receiving inappropriate EAT in NNCPs with severe sepsis [11].

Factors influencing the choice of antifungal agents in NNCPs are: co-morbidities; spectrum and intrinsic activity; pharmacokinetic and pharmacodynamic parameters; focus and severity of the infection; local epidemiology and the incidence of non-*albicans Candida* and resistance; possible drug interactions; and undesirable effects [1,5–8].

The use of antifungals cannot be 'generalised' to patients with severe sepsis, septic shock or *Candida* spp. colonisation, and patients must be carefully selected to avoid their indiscriminate use [1,5,7,8], which would only lead to complications (toxicity, pharmacological interactions, possibility of developing resistance and increased costs). The use of antifungals in NNCPs can currently be divided into 'conventional' indications (empirical and directed prophylaxis) or the more recent concept of 'pre-emptive treatment' [1,4–8,12]. Other therapeutic perspectives such as combined antifungal treatment are considered as possible alternatives in special cases [1,5,6,12].

However, before considering the type of treatment we must ensure an accurate and rapid diagnosis (cultures continue to take time and serology tests are not specific or sensitive enough when it comes to considering antifungal therapy) in order to reduce empirical antibiotic treatment and increase the proportion of pre-emptive therapy [3,5,7,8, 12–15].

EAT is based on starting antifungal treatment in patients with signs and symptoms suggestive of IFI for whom microbiological, histological or serological information confirming IC is not available. The use of EAT is widespread in ICUs and is the most frequent reason for the use of antifungals [5,12–15].

3. The role of guidelines

The number and type of published guidelines has proliferated in the last few years. From 1993 to 2005, for instance, 17 guidelines on community-acquired pneumonia were published, and another 7 relating to IC were published between 2000 and 2007.

There are unquestionable advantages relating to the provision of diagnostic and therapeutic guidelines: greater specialisation; simplification, making recommendations more 'understandable'; ability to generalise knowledge in fields that are often little studied; greater speed of preparation and publication; unification of the results obtained in different trials with varying levels of evidence (clinical applications often obtain better results); and support of scientific societies.

There are, however, also disadvantages and reasonable 'doubts' related to their use, such as: aetiological variability according to the geographic area or type of hospital; variability over time; the use of a guideline for a certain population could interfere with other types of infection; for some infections there are more guidelines than clinical trials; considerable variability in microbial 'sensitivity'; and different quality parameters applied to diagnostic and therapeutic guidelines. Guidelines are also rarely dynamic enough to make required changes deriving from the enormous quantity of scientific information currently generated on a daily basis.

4. Current NNCP guidelines

The Conference for the Development of a Consensus on the Management and Prevention of Severe Candidal Infections published in 1997 described the indications for empirical/pre-emptive use in surgical patients: candiduria in a high-risk patient with clinical deterioration; a single positive blood culture and/or endophthalmitis; isolation of *Candida* in a sterile source; or histological evidence of a yeast [16]. It also identified the patients who should receive FLZ as 'preventive' treatment: complicated abdominal surgery; severe pancreatitis; recurring perforation; suture failure or dehiscence; an Acute Physiology and Chronic Health Evaluation (APACHE) II score of >20; central line catheters; parenteral nutrition; prolonged therapy with broad-spectrum antibiotics; and multifocal isolation (two or more foci) of *Candida* spp. [16].

The need to review therapeutic guidelines is unquestionable and the Infectious Diseases Society of America (IDSA) recommends that they should be re-evaluated every 2 years. For instance, the 2000 IDSA guidelines published by Rex et al. [17] recommended amphotericin B deoxycholate (ABD) or FLZ, with or without the addition of 5-fluorocytosine, in IC, including candidaemia. Four years later, Pappas et al. [18] compiled the new IDSA guidelines that, in addition to ABD and FLZ alone or in combination, also recommended caspofungin (CSP), mentioning that voriconazole (VCZ) could be indicated. However, it was only approved for this type of patient in the USA in December 2004, therefore it was not included in the guidelines. The 2004 IDSA guidelines contain an interesting analysis of IC and the indications for antifungal plus other therapeutic approaches indicated in each case. One problem is the small amount of available evidence related to these therapies, mainly drainage and/or surgery, for which there are few well designed studies [18].