Clinical Trials of Antifungal Prophylaxis in Surgical Critically Ill Patients
Ed Horn, Sandra M Swoboda, and Pamela A Lipsett

Preemptive Antifungal Therapy in Critically Ill Surgical Patients
Frédéric Grenouillet, Laurence Millon, Gilles Blasco, and Renaud Piarroux

Diagnostic and Therapeutic Approaches to Fungal Infections in Critical Care Settings: Different Options but the Same Strategy
Rafael Zaragoza and Javier Pemán

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Foreword

Dear Colleagues,

Welcome to the second issue of the CME/CPE-accredited journal, *The Journal of Invasive Fungal Infections*.  

As in the first issue, this issue contains review articles from leading specialists in the field. These have been peer-reviewed for quality and CME/CPE-accredited to provide an ongoing educational resource. Three such leading articles are included, and all discuss antifungal therapeutic strategies in critically ill patients.

Professor Pamela Lipsett and colleagues (Johns Hopkins University School of Medicine and Nursing, Baltimore, MD, USA) provide an excellent overview of all clinical trials conducted to date on antifungal prophylaxis in surgical critically ill patients. They also discuss meta-analyses of clinical trials of antifungal prophylaxis, and discuss some of the concerns surrounding this therapeutic strategy in patients in intensive care. Comprehensive tables summarizing the clinical trials and meta-analyses are included.

Following this, Dr Frédéric Grenouillet and colleagues (University Hospital, Besançon, France) review preemptive antifungal therapy, again in surgical critically ill patients. Firstly, they discuss the issues regarding the definition of “preemptive” therapy, and the use of Candida colonization status of the patient in this classification. Focusing on invasive candidiasis, they discuss its pathophysiology and risk factors, and consider studies that have aimed to define criteria that predict which patients are at high risk of infection. Lastly, they discuss a management flowchart for fungal infection risk, in use at their unit since 2004.

The third and final leading article of this issue, from Drs Rafael Zaragoza and Javier Pemán (Hospital Universitario Peset and Hospital Universitario La Fe, Valencia, Spain), addresses the diagnostic and therapeutic approaches to fungal infections in critically ill patients. Preemptive and prophylactic therapeutic strategies are reviewed. In addition, newer diagnostic tests, such as the detection of (1,3)-β-D-glucan, which may guide the therapeutic strategy in critically ill patients are discussed. The choice of antifungal agent and the potential for combination therapy in these patients are also reviewed.

As in the first issue, Dr Zeina Kanafani (Duke University Medical Center, Durham, NC, USA) has provided a thorough analysis of recent papers in our Clinical Reviews section. This is followed by a report from the 48th Annual Meeting and Exposition of the American Society of Hematology from Dr Ana Berceanu and Professor Raoul Herbrecht (Hôpitaux Universitaires de Strasbourg, Strasbourg, France), in which the presentations describing invasive fungal infections, primarily aspergillosis, in patients with hematological malignancies or hematopoietic stem cell transplantation are reviewed.

We hope you find this issue of *The Journal of Invasive Fungal Infections* an educational and valuable tool. We welcome your feedback regarding the material presented as well as your suggestions for future topics to be covered.

John R Perfect
Editor-in-Chief

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Contents

Leading Articles

Clinical Trials of Antifungal Prophylaxis in Surgically Critically Ill Patients

*Ed Horn, Sandra M Swoboda, and Pamela A Lipsett* 34

Preemptive Antifungal Therapy in Critically Ill Surgical Patients

*Frédéric Grenouillet, Laurence Millon, Gilles Blasco, and Renaud Piarroux* 42

Diagnostic and Therapeutic Approaches to Fungal Infections in Critical Care Settings: Different Options but the Same Strategy

*Rafael Zaragoza and Javier Pemán* 50

Clinical Reviews

Aspergillosis

*59*

Coccidioidomycosis

*61*

Candidiasis

*63*

Cryptococcosis

*65*

Other Mycoses

*66*

Therapeutics

*67*

Meeting Report

The American Society of Hematology

48th Annual Meeting and Exposition

Orlando, FL, USA, December 9–12, 2006

*69*

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Editorial Policy

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Aims and Scope

*The Journal of Invasive Fungal Infections* is designed to bring a critical analysis of the world fungal infection literature, written by clinicians, for clinicians, to an international, multidisciplinary audience. Our mission is to promote better understanding of fungal infections across the global healthcare system by providing an active forum for the discussion of clinical and healthcare policy issues.

Leading Articles – These major review articles are chosen to reflect topical clinical and healthcare policy issues in invasive fungal infections. All contributions undergo a strict editorial review process.

Clinical Reviews – The most important papers from the best of the international literature on fungal infections are systematically selected by the Editor-in-Chief. The Editors then prepare concise and critical analyses of each paper, and, most importantly, place the findings into clinical context.

Meeting Reports – *The Journal of Invasive Fungal Infections* also provides incisive reportage from the most important international congresses.

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Clinical Trials of Antifungal Prophylaxis in Surgical Critically Ill Patients

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Fungal infections represent a difficult group of nosocomial infections with a growing incidence in the critically ill surgical patient. Multiple strategies aimed at preventing fungal infections utilizing a myriad of antifungal agents have been evaluated. In clinical trials on fungal prophylaxis, as well as systematic reviews, antifungal agents have been shown to prevent invasive fungal disease in high-risk patient populations, without affecting overall mortality rates. Fungal prophylaxis is an option in patients at high-risk of developing fungal infections, but should be utilized with caution. Resistant pathogens present the greatest concern with regard to widespread prophylaxis. More data are needed to measure any possible reduction in mortality rate that may occur with antifungal prophylaxis, as well as the impact on drug resistance. J Invasive Fungal Infect 2007;1(2):34–41.

Norocomial infections are an important source of morbidity and mortality in hospitalized patients. In the intensive care unit (ICU), infections from Candida spp. are increasingly common; indeed, candidemia is now the fourth leading cause of bloodstream infection in the surgical ICU [1–4]. As many as 50% of invasive candidiasis cases remain undiagnosed until autopsy [1]. Risk factors that are associated with fungal infection in surgical ICU patients include the following [2,3]:

- Severity of illness.
- Invasive devices or procedures.
- Broad-spectrum antibiotics.
- Parenteral nutrition.
- Immunosuppression.
- Length of stay in ICU.
- Fungal colonization.

Defining the surgical ICU patient who will benefit from antifungal prophylaxis is difficult. First, consensus on the definition of prophylaxis versus preemptive treatment must be reached. Prophylaxis is defined as the use of an agent to prevent infection prior to known colonization, whereas preemptive therapy is the introduction of an agent to patients with well-established risk factors, including a known degree of colonization with Candida spp. [4]. These subtle differences in definitions contribute to the ongoing confusion and controversy in this area. In some institutions, antifungal prophylaxis is performed without generalized consensus regarding the evidence from randomized clinical trials of prophylaxis [5].

When considering a prophylaxis regimen, several criteria must be considered. The overall incidence and severity of fungal disease must be high and/or fungal infections must cause a substantial and measurable increase in morbidity and mortality rates in the patient population. The prophylactic regimen must have high tolerability, be cost-effective, and be confined to use in the appropriate high-risk patients. Several published clinical trials have evaluated the use of antifungal agents for prophylaxis (azoles, amphotericins, and echinocandins) in selected critically ill and surgical patients (Table 1) [6–16]. This paper will review the use of the individual agents for prophylaxis in the critically ill adult surgical patient, focusing on recently published randomized, placebo-controlled trials and classic papers in this patient population.

Amphotericin B

Amphotericin B has been utilized for the prevention of fungal infections in several clinical trials. In surgical patients, recent trials have focused on the liver transplant population. The use of targeted amphotericin B lipid emulsion at three different doses was prospectively studied in 30 consecutive high-risk liver transplant patients (with a stepwise reduction in dose at 10-patient intervals) [6]. Targeted patients were those who required mechanical ventilation or renal support...
through continuous hemofiltration for ≥5 days. All patients received oral nystatin prophylaxis per standard protocol, and patients with identifiable pretransplant risk factors for invasive fungal infection (fulminant hepatic failure, retransplantation, or treatment pre-ICU) received intravenous or oral fluconazole prophylaxis. Singhal et al. concluded that amphotericin B prophylaxis in high-risk patients after liver transplantation is well tolerated and may prevent invasive fungal infection [6].

Another study of liver transplant patients examined the use of low-dose amphotericin B preparations for the prevention of invasive infection [7]. High-risk individuals were identified, and patients received either intravenous conventional amphotericin B or liposomal amphotericin B until discharge from the ICU, death, or the need for treatment of suspected or confirmed infection. Eighty-three patients met the inclusion criteria. The incidence of invasive fungal infection was low in both treatment arms – three in the lipid group and two in the conventional group. Candida spp. were isolated from the five subjects. The only significant difference between the two study groups was that patients who received lipid amphotericin B were more likely to survive ICU discharge (79.6% vs. 59.5%; p=0.038), but this difference could not be specifically attributed to fungal infections. Thus, in these studies, there were no specific benefits of amphotericin B.

Nystatin

The use of oral nystatin versus placebo as antifungal prophylaxis for prevention of Candida spp. colonization was studied in a clinical trial of 98 medical/surgical/trauma ICU patients who were ventilated for >48 h [8]. In this trial, oral nystatin prevented Candida spp. colonization in patients at low risk of developing invasive disease; however, there were no convincing data regarding the use of nystatin for prevention of fungal infections.

Azoles

Ketoconazole

Savino et al. prospectively randomized 292 surgical and trauma patients with an ICU stay of >48 h to one of four groups – placebo, clotrimazole, ketoconazole, or nystatin – to determine whether these regimens prevented colonization, fungal sepsis, or mortality. There were no differences between the groups in terms of these factors; thus, prophylaxis did not provide a benefit [9]. Fungal infection in this population was low (3%), and the study was not powered to determine a difference between the four groups in terms of this parameter. In another study of ketoconazole, Slotman et al. performed a placebo-controlled trial in 57 surgical ICU patients with clinical risk factors for infection with Candida spp. Routine surveillance was performed, and the incidence of Candida spp. colonization was significantly lower with ketoconazole, with no fungal sepsis occurring in this group [10].

Itraconazole

Itraconazole is an azole available in both oral and intravenous formulations. The spectrum of activity of itraconazole includes both Candida and Aspergillus species. The spectrum of activity and oral availability of itraconazole make it an attractive potential choice for antifungal prophylaxis. However, oral absorption may be limited under certain conditions (increased gastric pH and gastrointestinal motility) and the intravenous formulation should be used cautiously in patients with renal insufficiency. In a randomized, placebo-controlled study, Sharpe et al. evaluated the use of itraconazole (preoperative loading dose of 5 mg/kg followed by 2.5 mg/kg daily) [11]. Nine of 38 patients in the placebo group versus one of 33 patients in the itraconazole group (24% vs. 4%; p=0.04) acquired a fungal infection (either deep or suspected). However, there was no difference in mortality rate between the two groups. Thus, oral itraconazole is an acceptable prophylactic agent for the prevention of fungal infections in liver transplant patients.

Fluconazole

To date, the agent with the most data on the potential benefits of antifungal prophylaxis in surgical ICU patients is fluconazole. Winston et al. examined the prophylactic use of fluconazole versus placebo in liver transplant recipients [12]. Patients were randomized intraoperatively and treatment continued for 10 weeks post-transplant. Proven fungal infections of any type occurred less often in the fluconazole group compared with the placebo group (9% vs. 43%; p<0.001), with Kaplan–Meier estimates showing similar results. The incidence of invasive fungal infections was lower in the fluconazole group than the placebo group (6% vs. 23%; p<0.001). However, fluconazole had no effect on overall survival compared with placebo (11% vs. 14%), although death related to fungal infection was lower in the fluconazole group (2% vs. 13%; p=0.003). Furthermore, colonization with non-albicans strains was not increased in patients treated with prophylactic fluconazole.

Ables et al. conducted a small trial on the effects of fluconazole prophylaxis on mortality and infectious outcomes [13]. Trauma and surgical ICU patients with an expected length of ICU stay of ≥48 h and the presence of more than one risk factor were randomized to fluconazole prophylaxis (intravenous loading dose followed by a daily dose) or placebo [13]. Infection was classified as documented candidiasis (presence of positive cultures),
<table>
<thead>
<tr>
<th>Authors</th>
<th>Patient population</th>
<th>Sample size</th>
<th>Intervention (prophylaxis vs. preemptive)</th>
<th>Primary outcomes</th>
<th>Infection definitions</th>
<th>Results (infection)</th>
<th>Results (mortality)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Singhal et al. [6]</td>
<td>Liver transplant requiring ICU care for &gt;5 days</td>
<td>30</td>
<td>Prophylaxis; ABLC 1–5 mg/kg IV daily until ICU discharge</td>
<td>Prevention of IFI</td>
<td>IFI: histological evidence of tissue invasion; isolation of Candida spp. from more than three normally non-sterile sites (throat, rectum, urine, sputum)</td>
<td>No patients had evidence of fungal infection</td>
<td>Overall: 20%. None related to IFI</td>
</tr>
<tr>
<td>Shah et al. [7]</td>
<td>Liver transplant requiring ICU care for &gt;5 days</td>
<td>92 episodes, 83 patients</td>
<td>Prophylaxis; AmB 15 mg IV daily or LipAmB 50 mg IV daily until ICU discharge</td>
<td>Prevention of IFI</td>
<td>IFI: histological evidence of tissue invasion; isolation of Candida spp. from more than three normally non-sterile sites (throat, rectum, urine, sputum)</td>
<td>AmB: two episodes LipAmB: three episodes</td>
<td>3-month survival: AmB 54.8% vs. LipAmB 69.4%; p=0.108</td>
</tr>
<tr>
<td>Normand et al. [8]</td>
<td>Medical/surgical ICU (low risk)</td>
<td>98</td>
<td>Prophylaxis; nystatin 3 million units/day</td>
<td>Reduction of Candida spp. colonization</td>
<td>Presence of Candida spp. in trachea, stomach, urine, rectum, groin, and blood</td>
<td>Placebo 25% vs. nystatin 0%</td>
<td>Not reported</td>
</tr>
<tr>
<td>Savino et al. [9]</td>
<td>Surgical/trauma ICU (non-burn, non-transplant)</td>
<td>292</td>
<td>Prophylaxis; clotrimazole 10 mg PO TID or ketoconazole 200 mg PO daily or nystatin 2 million units every 6 h</td>
<td>Prevention of yeast sepsis</td>
<td>Positive culture of sterile site specimen or more than two other sites</td>
<td>Placebo 3% vs. clotrimazole 1% vs. ketoconazole 2% vs. nystatin 7%; p=NS</td>
<td>Mortality: Placebo 15% vs. clotrimazole 14% vs. ketoconazole 6% vs. nystatin 20%; p=NS</td>
</tr>
<tr>
<td>Slotman et al. [10]</td>
<td>Surgical ICU</td>
<td>57</td>
<td>Prophylaxis; ketoconazole 200 mg PO daily until ICU discharge (maximum 21 days)</td>
<td>Prevention of yeast invasion</td>
<td>Positive culture of sterile site</td>
<td>Yeast invasion: placebo 17% vs. ketoconazole 0%; p=NS</td>
<td>Mortality: 60% of those with fungal sepsis died</td>
</tr>
<tr>
<td>Sharpe et al. [11]</td>
<td>Liver transplant</td>
<td>71</td>
<td>Prophylaxis; itraconazole 5 mg/kg preoperatively, then 2.5 mg/kg PO BID for a total 56 days</td>
<td>Incidence of DFI</td>
<td>Proven DFI: positive histological evidence; one positive blood culture; clinical/radiological signs of Aspergillus spp. infection + isolating hyphae in BAL SFI: clinical signs/symptoms with fever unresponsive to broad-spectrum antibiotics; highly suggestive radiological findings without mycological/histological evidence; clinical signs/symptoms in the presence of fungal colonization</td>
<td>DFI: placebo 16% vs. itraconazole 4%; p=0.225 SFI: placebo 8% vs. itraconazole 0%; p=0.141</td>
<td>Mortality: placebo 15.7% vs. itraconazole 3%; p=NS</td>
</tr>
<tr>
<td>Winston et al. [12]</td>
<td>Liver transplant</td>
<td>212</td>
<td>Prophylaxis; fluconazole 400 mg IV/PO daily for 10 weeks</td>
<td>Proven IFI; SFI</td>
<td>SFI: positive skin, oropharynx, vagina, GI tract, wound or urine culture with signs of inflammation, ulceration, plaque IFI: positive blood, pulmonary tissue, secretions, sinuses or peritoneal cavity cultures; other organs with signs/symptoms of infection not otherwise explained</td>
<td>Proven IFI: placebo 43% vs. fluconazole 9%; p&lt;0.001 IFI: placebo 23% vs. fluconazole 6%; p&lt;0.001</td>
<td>Overall: placebo 11% vs. fluconazole 14%; p&gt;0.2 IFI related: placebo 13% vs. fluconazole 2%</td>
</tr>
<tr>
<td>Study</td>
<td>Setting</td>
<td>Prophylaxis</td>
<td>Length of Study</td>
<td>Outcome</td>
<td>Placebo vs. Fluconazole</td>
<td></td>
<td></td>
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<tr>
<td>Ables et al. [13]</td>
<td>Trauma, intra-abdominal, or intra-thoracic surgery; expected ICU LOS &gt;48h; &gt;1 risk factor</td>
<td>Prophylaxis; fluconazole 800 mg IV x1, then 400 mg IV/PO daily until ICU discharge (maximum 6 weeks)</td>
<td>25</td>
<td>Documented candidiasis</td>
<td>Placebo 20% vs. fluconazole 13%</td>
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<td></td>
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<td>Documented candidiasis: positive culture from respiratory, mucosal, or peritoneal specimens</td>
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<td>Suspected IFI: compatible clinical illness (including SIRS) but no evidence of bacterial/viral cause</td>
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<td></td>
<td></td>
<td>Superficial FI: fungal UTI, thrush, skin lesions</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Eggimann et al. [14]</td>
<td>Surgical patients with recurrent GI perforations or anastomotic leakage</td>
<td>Prophylaxis; fluconazole 400 mg IV daily until complete resolution of abdominal disease (median 15–17 days)</td>
<td>49</td>
<td>Frequency and time to intra-abdominal Candida infections</td>
<td>Candida peritonitis: placebo 35% vs. fluconazole 4%; p=0.02</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Intra-abdominal abscess/peritonitis caused by Candida spp.; one or more blood cultures positive for Candida spp.; urine culture positive for &gt;100 000 CFU</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>Candida spp.; clinical evidence of tissue infection with Candida spp. isolated from biopsy</td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Garbino et al. [15]</td>
<td>Medical/surgical patients ventilated for 48 h with anticipated duration of &gt;72 h</td>
<td>Prophylaxis; fluconazole 100 mg IV daily + SDD until withdrawn from mechanical ventilation</td>
<td>220</td>
<td>Development of severe Candida infection</td>
<td>SFIs: placebo 9.9% vs. fluconazole 3.8%; p value not reported</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Candidemia: more than one positive blood culture + histologically documented IFI or Candida endophthalmitis; more than two positive blood cultures from two distinct sites</td>
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<td></td>
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<td>Severe candidemia: SIRS plus candidemia</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pelz et al. [16]</td>
<td>Surgical ICU patients with an expected LOS of &gt;72 h</td>
<td>Prophylaxis; fluconazole 800 mg enterally x1, then 400 mg enterally daily until ICU discharge</td>
<td>260</td>
<td>Time to occurrence of fungal infection during ICU stay</td>
<td>Proven IFI: placebo 15.3% vs. fluconazole 8.5%; p&lt;0.01</td>
<td></td>
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<td>Time to proven infection: Kaplan-Meier curve favors fluconazole over placebo; p&lt;0.01</td>
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<td>Definite: histological/microbiological evidence from two separate sterile sites (not bladder and urine)</td>
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<td>Presumed: positive blood culture or single sterile site (not indwelling drains or catheters); catheter with &gt;15 CFU, as per CDC guidelines; deep surgical site infection requiring debridement; two positive urine cultures after urinary catheter change</td>
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<td></td>
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<td>Proven IFI: definite or presumed</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Piarroux et al. [19]</td>
<td>Surgical ICU</td>
<td>Preemptive; fluconazole IV 800 mg x1, then 400 mg daily for 2 weeks</td>
<td>933</td>
<td>Prevention of proven candidiasis</td>
<td>Proven infections as per EORTC/MSG (European Organization for Research and Treatment of Cancer/Mycoses Study Group)</td>
<td></td>
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<tr>
<td></td>
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<td>Proven candidiasis: control 7%; preemptive: 3.8%; p=0.03</td>
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ABLC: amphotericin B lipid complex; AmB: amphotericin B; BAL: bronchoalveolar lavage; BID: twice daily; CDC: Centers for Disease Control and Prevention; CFU: colony-forming units; CI: confidence interval; DFI: deep fungal infection; GI: gastrointestinal; ICU: intensive care unit; IV: intravenous; IFI: invasive fungal infection; LipAmB: liposomal amphotericin B; LOS: length of stay; NS: not significant; PO: orally; RR: relative risk; SDD: selective digestive decontamination; SIRS: systemic inflammatory response syndrome; SFI: superficial fungal infection; TID: three times daily; UTI: urinary tract infection.
suspected infection (inflammatory response but no clear evidence of infection), or superficial signs of infection. While there was a trend towards a decreased incidence of infection with fluconazole (13% vs. 19%; relative risk [RR] 0.66, 95% confidence interval [CI] 0.29–1.49), there was no effect on overall mortality. Furthermore, the inclusion of patients with an inflammatory response but no clear signs of fungal infection makes this study difficult to interpret.

Eggimann et al. randomized 49 high-risk recurrent gastrointestinal surgery patients to intravenous fluconazole or placebo [14]. Primary outcomes included frequency of, and time to, intra-abdominal candidiasis, as well as the emergence and persistence of colonization. There was a significantly lower incidence of *Candida* peritonitis in the fluconazole group compared with the placebo group (4% vs. 35%; p=0.02), and time to infection analysis revealed that fluconazole prophylaxis was associated with a longer disease-free interval (p=0.04). Overall fungal infection rates were 8.7% in the fluconazole group and 35% in the placebo group (RR 0.25, 95% CI 0.06–1.06; p=0.06). There were no significant differences in mortality rate and length of stay in hospital between fluconazole and placebo groups. However, this well-conducted trial shows that, in highly selective surgical patients, fluconazole prophylaxis is effective and should be considered for prevention of candidal peritonitis.

In a larger randomized, placebo-controlled trial, Garbino et al. added fluconazole to a selective digestive decontamination (SDD) regimen in critically ill medical and surgical patients to assess the effect on candidal infections [15]. Mechanically ventilated patients were randomized during or after the third day of their ICU stay to either 100 mg of intravenous fluconazole daily (n=103) or placebo (n=101). *Candida* infections occurred less frequently in patients treated with fluconazole prophylaxis compared with those who received placebo (6.8% vs. 16%, RR 0.35, 95% CI 0.11–0.94). Ninety percent (9/10) of the cases of candidemia occurred in the placebo group. In addition, there was a decrease in both the frequency and intensity of colonization in the fluconazole arm. Crude mortality was not different between placebo (41%) and fluconazole (39%) patients.

In one of the largest single-center, randomized, double-blind, placebo-controlled trials of antifungal prophylaxis, enteral fluconazole (800 mg loading dose followed by 400 mg/day) or placebo was administered in 260 critically ill surgical ICU patients with an anticipated surgical ICU stay of ≥3 days [16]. Therapy was continued until ICU discharge, and the mean length of stay was 5 days. Infection definitions were consistent with both European and National Institutes of Health consensus groups [16]. The intent-to-treat analysis showed that enteral fluconazole prophylaxis reduced the incidence of proven fungal infections from 15.4% to 8.5% (p<0.01) – a 7% absolute risk reduction that translates into a number needed to treat (NNT) to prevent one fungal infection of 15 patients. Of the 11 patients in the fluconazole group with a proven fungal infection, four were infected prior to randomization but were included in the analysis to take the most conservative approach to the analysis. Taking this into consideration, fluconazole reduced the incidence of fungal infections by a factor of 2- to 3-fold [17]. A time-to-event analysis showed that fluconazole had a significant advantage in delaying the time to fungal infection (p<0.01). A multivariate Cox regression model showed that the following factors significantly increased the risk of fungal infection:

- Acute Physiology and Chronic Health Evaluation III (APACHE III) score.
- Days to first dose of study drug.
- Fungal colonization at enrollment.
- Parenteral nutrition prior to enrollment.

Thus, when considering antifungal prophylaxis, delaying therapy could decrease its effectiveness. The study was not powered to assess the effect on mortality. This was the only trial to exclusively use enteral fluconazole for prophylaxis. A follow-up study published by the same investigators showed that enteral fluconazole is well absorbed in critically ill surgical patients [18]. Serum concentrations of fluconazole were above the highest minimum inhibitory concentrations (MIC) for *C. albicans* and *C. parapsilosis* isolates in all but 4% of patients, but were below the median MIC obtained from strains of *C. glabrata*.

The issue of preemptive therapy was assessed in a study by Pierraux and colleagues [19], which utilized a retrospective control group. During the prospective period, patients who developed a corrected colonization index of ≥0.4 were placed on fluconazole (intravenous 800 mg loading dose followed by 400 mg/day for 2 weeks). When compared with the retrospective control group, patients given preemptive fluconazole had a lower rate of proven candidiasis (7% vs. 3.8%; p=0.03). No emergence of azole-resistant *Candida* spp. was noted in the treatment group.

**Posaconazole**

Posaconazole is a newer, extended-spectrum, orally bioavailable azole that shows good activity against several pathogenic fungi, including species of *Candida* that are less susceptible to fluconazole. A recent randomized, double-blind trial involving 600 patients with graft-versus-host disease assessed the efficacy of posaconazole for prophylaxis against invasive fungal infections [20]. This agent was found to be as effective as fluconazole in preventing invasive
fungal infections (p=0.07), and the rate of proven or probable invasive aspergillosis was lower in the posaconazole-treated group compared with that in the fluconazole group (2.3% vs. 7.0%; p=0.006). However, at present, the paucity of an intravenous formulation of posaconazole limits its potential as a therapeutic option in invasive fungal infections in critically ill patients.

Newer agents
As a class of agents, the echinocandins are increasingly utilized in the treatment of critically ill patients with proven or suspected fungal infections. A decision analysis was recently conducted based on considerations of likely pathogens, incidence of fungal infections, and signs of a clinical infection that has not responded to antibacterial therapy [21]. The results suggested that caspofungin is the most effective agent but is too costly for a base case analysis. On closer inspection of the specific details, it would appear that, while very useful in conceptualizing different agents and balancing issues of incidence and resistance, the clinical use proposed in this analysis is not prophylaxis. Another echinocandin, micafungin, has been studied as an agent for prophylaxis in neutropenic patients and is approved in the US for this indication [22].

Meta-analyses on fungal prophylaxis in the critically ill
There have been four published meta-analyses and one Cochrane review examining clinical trials of antifungal prophylaxis in the critically ill patient population (Table 2) [23–26]. Many of these studies show some effect on the reduction of fungal infections in critically ill patients by fungal prophylaxis with an azole antifungal. Meta-analysis is difficult in this group of clinical trials because patient characteristics and dosing regimens vary greatly depending on the population studied (ICU versus ward, medical versus surgical, severity of illness). In the majority of the trials, ketoconazole (in early trials) and fluconazole were studied. Definitions for outcomes vary between trials and could over- or underestimate treatment effects.

The first analysis, by Cruciani et al., examined nine clinical trials of 1226 patients in both surgical and trauma ICUs [23]. The dose and antifungal agent used for prophylaxis varied between studies, with some using ketoconazole (200 mg administered enterally) and others using fluconazole (100–400 mg administered either enterally or intravenously). Only two of the trials utilized a loading dose for fluconazole (800 mg). Some of the studies examining the effect of ketoconazole excluded patients with hepatic dysfunction or encephalopathy. There was significant heterogeneity in the definitions of fungal infections and outcome measures. The overall risk of candidemia was significantly reduced by azole antifungal prophylaxis (RR 0.30, 95% CI 0.11–0.83; p=0.02). Overall mortality was significantly reduced in this analysis (RR 0.61, 95% CI 0.45–0.82; p=0.001), as was mortality attributable to fungal infections (RR 0.25, 95% CI 0.08–0.80; p=0.019). According to this meta-analysis, the NNT to prevent one episode of candidemia was 27.9 patients (95% CI 24.0–44.6). Overall mortality and mortality attributable to fungal infections also had low NNTs (11.5 [95% CI 7.5–25.0] and 35.2 [95% CI 30.6–71.2], respectively).
In 2005, Shorr and colleagues re-examined the clinical trials on the use of fluconazole for prophylaxis [24]. In this meta-analysis, only the efficacy of fluconazole in critically ill surgical patient populations was examined. This included four trials (previously reviewed) with 626 patients in total [13–16]. Again, doses and routes of fluconazole administration varied from 100–400 mg/day (either intravenously or enterally), with two trials utilizing loading doses of 800 mg on the day of enrollment. The primary focus of these studies was the impact of fluconazole on candidal infections and mortality. Fluconazole was shown to significantly reduce the incidence of fungal infections (odds ratio [OR] 0.77, 95% CI 0.56–1.07). No heterogeneity was noted in reporting this outcome. When the four trials that examined ketoconazole were included, there was a significant reduction in mortality of almost 25% (RR 0.76, 95% CI 0.59–0.97). Invasive fungal infections (reported in 10 of the trials) were significantly reduced by fluconazole (RR 0.47, 95% CI 0.32–0.71) but not by ketoconazole (RR 0.30, 95% CI 0.07–1.31). Overall risk reduction was almost 50% (RR 0.46, 95% CI 0.31–0.68). Other analyses of outcomes showed that pooled adverse events were not different in patients treated with either fluconazole (RR 0.73, 95% CI 0.20–2.64) or ketoconazole (RR 1.24, 95% CI 0.17–8.74). The authors of this analysis suggest that antifungal prophylaxis with fluconazole should be considered in patients at increased risk of invasive fungal infections.

The third meta-analysis, by Playford et al., included 12 trials (1606 patients) that utilized either ketoconazole (n=4) or fluconazole (n=8) for antifungal prophylaxis [25]. Both patient population and outcomes varied among these trials. Total mortality, reported in 11 trials, was not significantly reduced by fluconazole (RR 0.77, 95% CI 0.27–0.72) but not mortality (OR 0.87, 95% CI 0.59–1.28). The lack of effect on mortality could be multifactorial and attributed to small sample size. Based on this meta-analysis, fluconazole prophylaxis appears to be successful for the prevention of invasive fungal infections in critically ill surgical patients. However, the authors advise against the widespread use of fluconazole prophylaxis because of the possible emergence of resistance and non-\textit{albicans} species.

The most recent meta-analysis, published by Vardakas et al., examined six trials of azole prophylaxis in 847 critically ill surgical ICU patients [26]. Fluconazole was studied in five trials, and ketoconazole in one trial. A secondary analysis on mortality was conducted, which included the study by Jacobs et al. [27]. Antifungal prophylaxis was associated with significantly fewer overall fungal infections (OR 0.20, 95% CI 0.13–0.32). These results did not differ according to the type of fungal infection examined (invasive, candidemia, or superficial). The incidence of mortality was not significantly reduced by antifungal prophylaxis (OR 0.74, 95% CI 0.52–1.05). Analyses conducted in subsets of studies (fluconazole prophylaxis, studies that excluded transplant patients) revealed similar findings. In the secondary analysis, mortality was found to be significantly lower in the azole-treated patients (n=918; OR 0.68, 95% CI 0.49–0.95). Adverse events were not different between groups (n=499; OR 1.36, 95% CI 0.86–2.15). Hepatotoxicity was the reason for discontinuation of the study drug in only five patients in pooled trials. The authors’ conclusions echoed those of previous meta-analyses: fluconazole reduced the incidence of infection, but not all-cause mortality.

These four meta-analyses, all published recently, demonstrate the problems associated with both the topic of antifungal prophylaxis, and the use of meta-analysis to help define an important clinical issue. As noted previously, the definitions of an at-risk patient population and of what constitutes a fungal infection in non-neutropenic surgical patients have not been established. The trials are generally small, single-institution trials, primarily but not exclusively studying the use of azoles for prophylaxis. The endpoints of the clinical trials are not uniform. Thus, even if the use of prophylaxis is reasonable, the agent, route, and dose are not clearly established. The above meta-analyses demonstrate that the results of an analysis will greatly depend on which clinical trials are included and which are not.

In summary, these studies conclude that antifungal prophylaxis in the adult critically ill surgical patient is likely to reduce the incidence of fungal infections, but does not appear to affect mortality.

Potential problems associated with prophylaxis

There are several concerns surrounding routine prophylaxis with azole antifungal agents, including the emergence of resistance of previously susceptible strains (\textit{C albicans}), as well as an increase in non-\textit{albicans} species, if given to all patients (i.e. not selecting high-risk patients). In a surgical ICU, Swoboda et al. examined fungal isolates pre- and post-fluconazole prophylaxis in high-risk patients [28]. Prior to prophylaxis, \textit{C albicans} and \textit{C glabrata} were the predominant strains that caused infection (45% and 30%, respectively). In the time period after fluconazole prophylaxis implementation, based on the study by Pelz et al. [16], \textit{C glabrata} was the predominant strain causing candidemia (64%; p=0.05). \textit{C albicans} was also common, causing 21% of cases of candidemia. However, total non-\textit{albicans} species were 55% (38/69) in “pre” period and 79% (11/14) in the “post” period (p=0.12). This study shows that, while fluconazole prophylaxis clearly reduced the incidence of fungal infections, there was not a significant shift to non-\textit{albicans} species. One other
concern associated with azole prophylaxis is hepatotoxicity; however, the meta-analyses showed no significant increases. Thus, azole agents appear safe and well tolerated.

Conclusion
Surgical ICU patients are at increased risk of fungal infection as a result of a variety of risk factors. A review of the evidence suggests that antifungal prophylaxis in this population decreases fungal infection rates by almost 50%, depending on the baseline incidence. Antifungal prophylaxis should be reserved for the high-risk surgical patient, and its use limited to the ICU stay only. Current data suggest that, when prophylaxis is used only in high-risk surgical patients, that global shifts in Candida strains may not be seen. Further studies are needed to determine the impact of prophylaxis on mortality and resistance patterns, both on a local and national scale.

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References
Preemptive Antifungal Therapy in Critically Ill Surgical Patients

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The incidence of invasive candidiasis in critical care settings has increased exponentially over the past two decades. The crude mortality rates of these infections range from 35% to 60%. Most frequently, the source of invasive candidiasis is endogenous and the colonization stage plays a key role in the onset of the infection. Many studies have been performed to define the most pertinent risk factor criteria to help characterize patients who are at higher risk of candidiasis in the surgical intensive care unit (SICU). Thus, these patients could be given preventative treatment. Of these risk factors, isolation of Candida species from several body sites prior to infection seems to be one of the best predictors of infection. This review focuses on the use of colonization data in a strategy to prevent Candida infections in SICU patients, and on the preemptive approach, a concept that is midway between prophylaxis and curative treatment. J Invasive Fungal Infect 2007;1(2):42–9.
significant *Candida* colonization. Prophylaxis refers to the antifungal therapy prescribed for patients who are at high risk for *Candida* infection (e.g. organ-transplant recipients and immunocompromised patients with expected or current long-term neutropenia) but have no evidence of colonization [22]. Here, the definition of “preemptive” would be independent of the clinical status of the patient.

Ostrosky-Zeichner et al. define the term “preemptive” as early treatment of the infection based on clinical, laboratory, or radiological surrogate markers of disease in high-risk hosts, before clinical signs or symptoms of full-blown disease develop [23]. For these investigators, *Candida* colonization is not a surrogate marker indicative of early infection, but represents a risk factor at most. They favor the term “prophylaxis” or “targeted prophylaxis” for antifungal therapies given to patients highly colonized with *Candida* and who have several risk factors; they do not include *Candida* colonization data in their development of preventive strategies in SICUs [12,23].

We are in agreement with the definition of Eggimann et al. as it includes high *Candida* colonization, a prerequisite to the development of infection, and several other risk factors [21,22]. Thus, the term “targeted prophylaxis” can be included in this definition as well as the notion of “targeted empirical therapy”, because in each case, antifungal agents are implemented due to colonization by *Candida*. Preemptive therapies prevent the development of infection in patients who harbor a potential pathogen that is either at a not-yet-infecting stage, or patients in whom the infection is at an early stage. This approach to *Candida* infection closely resembles the preemptive approach used in lung transplant patients who have persistent *Aspergillus* airway colonization and are at a risk for aspergillosis [24].

Different terminologies used by our group to characterize antifungal therapies are shown in Fig. 1. Throughout this review, we will use the term “preemptive” for early, targeted antifungal therapy, based on *Candida* colonization data, regardless of the clinical status of the patient.

### Risk factors for invasive candidiasis

Many authors have extensively described the risk factors for invasive candidiasis. Table 1 reviews these, focusing on the independent factors in critically ill surgical patients as determined by multivariate analysis [2,3,12,13,18,20,25–31]. Most of these risks are common interventions or conditions that are seen in the intensive care setting. Unfortunately, data are often lacking to determine whether there is a causal relationship to the diseases or whether they are just associated markers indicating severity of illness and other predisposing conditions.

### Pathophysiology of invasive candidiasis

Most frequently, progressive colonization from the abdominal cavity to other body sites precedes candidiasis. The development of these infections from an exogenous source (via vascular accesses) is not frequent [14], with a proven endogenous source in 85–90% of candidemia [16,19]. The key role of the colonization stage in the development of invasive candidiasis has been demonstrated in several studies dealing with surveillance of at-risk patients using mycological...
culture of samples from multiple body sites [16,19,20,25]. In most cases, genotyping analyses have shown that the infecting strain is the actual strain or one of the strains that colonizes the gastrointestinal tract [16,18,19,32].

The first event in the colonization process is the ecological modification of the endogenous flora, which can be induced and/or amplified by diabetes, immunosuppression, broad-spectrum antibiotic therapy, or extended hospitalization [3,20]. All of these factors alter the balance of endogenous microorganisms, and thus may favor the proliferation of Candida microorganisms, and thus may favor the proliferation of [3,20]. All of these factors alter the balance of endogenous spectrum antibiotic therapy, or extended hospitalization and/or amplified by diabetes, immunosuppression, broad-modification of the endogenous florae, which can be induced colonizes the gastrointestinal tract [16,18,19,32].

For C albicans, filamentation and lytic enzyme secretion are often involved in the transition from the colonizing to the infecting stage. While filamentation facilitates tissue invasion, the two morphological forms, yeast and hyphae, are responsible for infection [34].

**Colonization as the main risk factor of candidiasis**

Pittet et al. studied the role of colonization as a predictive factor for invasive candidiasis in ICU patients [20]. Colonization was defined as the isolation of Candida from at least three samples from the same or different body sites during a period of at least 2 consecutive days. This study, conducted over a 6-month period, included 29 colonized patients of the 650 admitted to the ICU; 11/29 (38%) developed invasive candidiasis whereas 18/29 (62%) remained colonized without occurrence of any Candida infection.

A colonization index (CI) was calculated as the ratio of the number of Candida-positive samples to the total number of analyzed samples and the CI average was statistically higher in patients who developed candidal infection. The threshold of 0.5 was reached in a median number of 6 days (range 2–21 days) before the diagnosis of invasive candidiasis. The sensitivity, specificity, and positive and negative predictive values of this CI were 100%, 69%, 44%, and 100%, respectively. A corrected colonization index (CCI) was also defined as the ratio of highly positive samples to the total number of analyzed samples. The sensitivity, specificity, positive and negative predictive values of CCI were all 100% when using a threshold of 0.4. However, because the excellent predictive values of these two indices were not known at the time of the study, antifungal therapy was not implemented in patients before occurrence of proven infection.

Although the study of Pittet et al. is very well known, the role of colonization as the most important risk factor for infection is still under debate [20,23]. This is, in part, due to data from one multicenter study, which failed to identify colonization as a definite risk factor for candidiasis. The definition of colonization in this study was, however, based only on urine and rectal colonization without investigation of other body sites, and this may be partially responsible for the surprising result [3].

Other studies argue that colonization is a key point. During clinical trials that have shown the benefit of prophylaxis in ICU settings, there is often a decrease in Candida colonization in fluconazole-treated patients [29,35]. Another study underlined the high negative predictive values of number of colonized body sites and of CI, which strongly suggest that in the absence of fungal colonization, infection is unlikely [36].

It has been reported that CI determination in patients with several other risk factors can be of help in predicting

**Table 1. Risk factors for candidemia and invasive candidiasis.**

<table>
<thead>
<tr>
<th>Independent risk factors in critically ill surgical patients</th>
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<tr>
<td><em>Candida</em> colonization [20,25]</td>
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<tr>
<td>Broad-spectrum antibiotics [12,25,26]</td>
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<tr>
<td>(In particular, the number of antibiotics and duration of antibiotic therapy)</td>
</tr>
<tr>
<td>Central venous catheter [3,26]</td>
</tr>
<tr>
<td>Acute renal failure and hemodialysis [3,12,25,26]</td>
</tr>
<tr>
<td>Prior surgery [3,13]</td>
</tr>
<tr>
<td>Total parenteral nutrition (TPN) [3,13,27]</td>
</tr>
<tr>
<td>Severity of illness [18,28]</td>
</tr>
<tr>
<td>Other described risk factors* [2,29–31]</td>
</tr>
<tr>
<td>Length of stay in surgical intensive care unit</td>
</tr>
<tr>
<td>Diabetes</td>
</tr>
<tr>
<td>Mechanical ventilation</td>
</tr>
<tr>
<td>Multiple blood transfusions</td>
</tr>
<tr>
<td>Bladder catheter</td>
</tr>
<tr>
<td>Recurrent, persistent gastrointestinal perforation</td>
</tr>
<tr>
<td>High-risk gastrointestinal surgery</td>
</tr>
<tr>
<td>Severe acute pancreatitis</td>
</tr>
<tr>
<td>Solid organ transplantation (in particular liver, pancreatic, and small-bowel transplant)</td>
</tr>
<tr>
<td>Corticosteroids</td>
</tr>
<tr>
<td>Cancer, immunosuppressive drugs</td>
</tr>
<tr>
<td>Anti-histamine H₂ receptor blockers</td>
</tr>
<tr>
<td>Diarrhea</td>
</tr>
</tbody>
</table>

*Other risk factors include risks determined by univariate analysis and those described in non-critically ill surgical patients.
further candidiasis [37,38], although both the number of colonized body sites and the CI have low predictive positive values in patients with a lower risk of candidiasis [31,36,39]. In a recently published study, urinary, respiratory, and rectum/ostomy Candida colonizations were significantly associated with a higher risk of invasive candidiasis, whereas oropharyngeal and gastric colonizations were not [40]. These significant data need to be confirmed before reducing surveillance screenings to only urine, respiratory tract, and rectum/ostomy. The ranking position given to colonization data in care management clearly depends on the type of patients screened, on the exact risk level for candidiasis, and on body sites examined.

Prophylaxis or preemptive therapy to prevent candidiasis

For many clinicians, preventing the occurrence of candidiasis in SICU patients is very enticing. The effectiveness of antifungal prophylaxis has been proven in neutropenic and solid-organ transplant patients, and in selected subgroups of patients with cancer. The use of prophylaxis in ICU non-neutropenic patients is still under debate. The latest guidelines from the Infectious Diseases Society of America state that institutions in which high rates of invasive candidiasis in the adult or neonatal ICU persist despite standard infection-control procedures should consider fluconazole prophylaxis for carefully selected patients in these care areas [41].

Three recent meta-analyses focused on the use of antifungal prophylaxis in the ICUs [42–44]. As no multicenter, randomized studies of antifungal agents versus placebos exists, the authors of these analyses reviewed all monocenter studies dealing with this subject. The overall conclusions of the three meta-analyses were concordant. They all showed a significant decrease in the incidence of candidiasis, with an odds ratio of infection for patients with prophylaxis varying from 0.2 to 0.44, depending on the particular studies included in the meta-analyses and on the definition of infection. However, results concerning crude and attributable mortality rates were discordant; only Cruciani et al. showed a significant decrease in these mortality rates with prophylaxis [42]. All of these analyses also underlined the lack of data concerning the ecological consequences of prophylactic use of antifungals in the ICU. The potential ecological impact of azole prophylactic use has remained contentious since the first shifts toward azole-resistant isolates or species, such as C krusei or C glabrata, were demonstrated in several groups of patients who received fluconazole prophylaxis [45–47]. To reduce this risk, in addition to the exponential increase of antifungal ICU expenses, several authors have proposed a concept based on statistical modelization, where prophylaxis would be implemented only in patients with a risk of candidiasis of >10% [30].

In order to select these patient subgroups, several studies were performed to define risk factor-based clinical prediction rules. Papitou et al. showed in a single center, retrospective study, that surgical/trauma intensive care patients with a SICU stay of at least 4 days, who had any combination of diabetes, new-onset hemodialysis, parenteral nutrition, and broad-spectrum antibiotics, had an invasive candidiasis rate of 16%, while the rate in other patients was 5% [12]. From a multicenter retrospective study, Ostrosky-Zeichner et al. created a prediction rule for candidiasis, which was a combination of two categories of risk factors for patients that stayed in the unit for >3 days and were expected to stay for an additional 2 days. This rule identified a subgroup of 10.6% of ICU patients, having a risk for candidiasis of approximately 10%; however, this rule was able to predict only one-third of the candidiasis [48]. These rules need to be prospectively validated. More recently, a multicenter, prospective, observational study defined the “Candida score”, which would guide implementation of early antifungal treatment in non-neutropenic ICU patients. This score included multifocal Candida colonization, prior surgery, parenteral nutrition (each factor with a value ≈1) and severe sepsis (value ≈2). According to these authors, patients with a “Candida score” of >2.5 should receive an early antifungal treatment (sensitivity 81%, specificity 74%). The “Candida score” is useful and applicable either for medical or surgical patients, and underlines the relative importance of fungal colonization in the pathogenesis of candidiasis [13,39].

A similar approach was previously developed by our group. In a “before and after” intervention study of 2-year prospective and 2-year historical control cohorts, Piarroux et al. assessed a preemptive strategy to prevent candidiasis in SICU patients with a SICU stay of ≥25 days and several risk factors [21]. This strategy, based on systematic mycological screening at admittance and weekly thereafter, led to implementation of an early preemptive antifungal therapy in patients with a CCI of ≥0.4. The incidence of SICU-acquired proven candidiasis significantly decreased from 2.2% to 0% (p<0.001; Fisher test). The main results of this study are presented in Table 2 and show that a targeted preemptive strategy can efficiently prevent acquisition of proven candidiasis in SICU patients.

This study underlines that CCI can be very useful for identifying subgroups of SICU patients exposed to several risk factors, in order that they can receive appropriate antifungal preemptive treatment [21]. This study also suggests that a CCI of <0.4 is probably an indication that no prophylactic or preemptive therapeutic intervention is necessary in clinically stable, low-risk patients, even when the CI is ≥0.5 [21].
confirms the poor positive predictive value of CI alone – a result with which other previous studies concur [36,50]. However, a CI value of ≥0.5 in a clinically unstable septic patient justifies implementation of an antifungal therapy. As underlined by others [51], the integration of colonization data into patient care management requires standardized processing of peripheral mycological samples in laboratories, especially for the accurate quantification of yeasts. A management flowchart for fungal risk in SICU patients, including colonization index data and other risk factors, was proposed in 2003 by Eggiman et al. [22]. Our approach is very similar; the care management procedures we have used since 2004 are shown in Fig. 2.

Preemptive strategy in SICUs: what remains to be done?
Several points need to be clarified before the preemptive approach can be widely used in SICUs. Firstly, more precise criteria are needed for identification of patients and units, in which systematic mycological surveillance and subsequent early antifungal treatment could be implemented. As pointed out by Ostrosky-Zeichner, the “before and after” intervention assessment of this strategy suffers from the geographical limitations imposed by a single unit with a defined baseline of disease, a specific patient base, and a particular epidemiological makeup [52]. Obviously, the more frequent the occurrence of systemic candidiasis in a given population and in a particular SICU, the more pertinent a preemptive strategy should be. In contrast, in subclasses of patients with a very low risk of systemic candidiasis, a systematic surveillance of colonization followed by treatment of highly colonized patients should be avoided, because it may be either inappropriate or not cost-effective [9,31,39,51]. Thus, because of the relatively rare occurrence of invasive candidiasis and the large

Table 2. Characteristics of patients included during the two periods of the “before and after” intervention study conducted by Piarroux et al. [21].

<table>
<thead>
<tr>
<th>Characteristics of patients</th>
<th>Retrospective cohort Without preemptive strategy (n=455)</th>
<th>Prospective cohort With preemptive strategy (n=478)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean years±SD</td>
<td>50.7±19.6</td>
<td>52.0±19.0</td>
<td>0.33</td>
</tr>
<tr>
<td>SAPS II score, mean points±SD</td>
<td>39.0±15.0</td>
<td>43.2±15.5</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>SICU stay, median day (inter-quartile range)</td>
<td>15 (9–23)</td>
<td>12 (7–21)</td>
<td>0.001</td>
</tr>
<tr>
<td>Male/female ratio</td>
<td>295/160</td>
<td>331/147</td>
<td>0.15</td>
</tr>
<tr>
<td>Number of antibiotics</td>
<td>2.8±2.2</td>
<td>2.8±2.0</td>
<td>0.82</td>
</tr>
<tr>
<td>Antibiotic therapy duration, mean days±SD</td>
<td>9.4±9.1</td>
<td>8.8±7.3</td>
<td>0.25</td>
</tr>
<tr>
<td>Receipt of anti-anaerobics/no receipt</td>
<td>259/196</td>
<td>385/93</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Bacteremia</td>
<td>55 (12.1%)</td>
<td>49 (10.3%)</td>
<td>0.37</td>
</tr>
<tr>
<td>Underlying disorders</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Abdominal surgery</td>
<td>94 (20.7%)</td>
<td>109 (22.8%)</td>
<td>0.63</td>
</tr>
<tr>
<td>Vascular surgery</td>
<td>19 (4.2%)</td>
<td>32 (6.7%)</td>
<td>0.09</td>
</tr>
<tr>
<td>Severe neurotrauma and trauma</td>
<td>197 (43.3%)</td>
<td>197 (41.2%)</td>
<td>0.52</td>
</tr>
<tr>
<td>Neurosurgery</td>
<td>120 (26.4%)</td>
<td>106 (22.2%)</td>
<td>0.13</td>
</tr>
<tr>
<td>Others</td>
<td>25 (5.5%)</td>
<td>34 (7.1%)</td>
<td>0.31</td>
</tr>
<tr>
<td>Overall SICU mortality</td>
<td>76 (16.7%)</td>
<td>73 (15.3%)</td>
<td>0.55</td>
</tr>
<tr>
<td>Non-septic conditions</td>
<td>47 (10.3%)</td>
<td>49 (10.3%)</td>
<td>0.96</td>
</tr>
<tr>
<td>Septic conditions*</td>
<td>29 (6.4%)</td>
<td>24 (5.0 %)</td>
<td>0.37</td>
</tr>
<tr>
<td>Bacterial infections</td>
<td>8 (1.8%)</td>
<td>6 (1.3%)</td>
<td>0.53</td>
</tr>
<tr>
<td>Candidiasis</td>
<td>7 (1.5 %)</td>
<td>2** (0.4%)</td>
<td>0.10</td>
</tr>
<tr>
<td>Aspergillosis</td>
<td>2 (0.4%)</td>
<td></td>
<td>0.49</td>
</tr>
<tr>
<td>Undocumented sepsis††</td>
<td>14 (3.1 %)</td>
<td>14 (2.9%)</td>
<td>0.89</td>
</tr>
<tr>
<td>Occurrence of proven candidiasis</td>
<td>32 (7%)</td>
<td>18 (3.8%)</td>
<td>0.03</td>
</tr>
<tr>
<td>Diagnosed at admittance (imported cases)</td>
<td>22 (4.8%)</td>
<td>18 (3.8%)</td>
<td>0.42</td>
</tr>
<tr>
<td>SICU-acquired**</td>
<td>10 (2.2 %)</td>
<td>0</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

SAPS: Simplified Acute Physiology Score; SD: standard deviation; SICU: surgical intensive care unit.
*Patients with sepsis, as defined by Bone et al. [49] at time of death; **Imported candidiasis cases; †No isolation of pathogen from blood culture or a naturally sterile body site despite clinical features evoking infection; ††Diagnosed in SICU or during the month after SICU discharge.
diversity of patient profiles in SICUs, only large multicenter studies are likely to provide the information needed for further progress. Conceptual basis for design of such trials were excellently described in two recent reviews [51,53], particularly patient selection, study endpoints, and definition of infections.

Secondly, one of the major conceptual drawbacks of the preemptive strategy concept is that it could result in an epidemiological shift in SICUs, due to a non-targeted overuse of antifungal agents. However, no emergence of azole-resistant Candida species (particularly C. glabrata, C. krusei) was noted during the prospective period of our study (the first 2 years of implementation of the preemptive strategy) [21]. Studies are still in progress in the SICU in our hospital in order to assess SICU fungal ecology. Data of >5 years of preemptive antifungal strategy are likely to help address this issue. Confirmation of these monocentric ecological data in a multicentric assessment will be needed to provide definitive conclusions.

Thirdly, the economic impact of preemptive strategy needs to be assessed. As stressed in our previous study, the
cost calculation of a care strategy is complex. The estimated cost of one case of proven candidiasis is close to €35 000 [7,8]. Candida colonization was associated with an additional €8000 in direct hospital costs for each SICU-colonized patient [54]. Pharmacoeconomic analyses on preemptive strategy should take into account costs induced by fungal cultures and by administration of antifungals to highly colonized patients, and should compare both of these with savings gained by infections that were prevented. No dramatic increase in antifungal SICU expenses was shown in the SICU when a preemptive strategy was applied [21,55].

For patients with sepsis, decisions concerning initiation of antifungal therapy can be modified because colonization data are available, and this might change the cost calculation. It could eliminate the administration of antifungal empirical treatment in septic patients when CI is <0.5. Precise data on individual yeast epidemiology could also favor the use of fluconazole instead of costly broad-spectrum antifungal agents such caspofungin, voriconazole, or lipid-associated amphotericin B.

Additional studies are required to answer the following questions: Is mycological monitoring of anatomical sites efficient enough to differentiate patients who are at high risk of developing invasive candidiasis? Which anatomical sites need to be investigated – only urine, respiratory tract, and rectum as suggested by Maggill et al. – or additional sites [40]? How should other risk factors be included to optimize preemptive strategy as suggested by Leon et al. [13]? While fluconazole is the drug of choice for preventative strategy [51,53], how can patients who are highly colonized by fluconazole-resistant strains be better managed? Do they require “only” stringent surveillance and implementation of early antifungal therapy when infection starts or should preemptive treatment be based on other antifungals, i.e. candins or recently developed azoles such as voriconazole and posaconazole, be implemented in these patients? Could serological markers, such as mannans or (1,3)-β-D-glucan, be used to improve the efficiency of a preemptive strategy based on colonization data [56,57]?

Conclusion

In summary, epidemiological and pathophysiological studies have demonstrated the role of colonization in the development of invasive candidiasis in SICU patients. Recent clinical trials argue in favor of early antifungal treatment of high-risk patients, if possible, even before the occurrence of signs of infection. However, before the preemptive approach can be widely used, further studies are needed to better define indications and settings for this promising therapeutic strategy. Thus, the classic rounds question “should ICU patients receive antifungal prophylaxis or preemptive therapy?” is still being asked [52]. We hope that the quest for this “holy grail” will be realized in the near future.

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Disclosures

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References

PREEMPTIVE ANTIFUNGAL THERAPY IN CRITICALLY ILL SURGICAL PATIENTS


Diagnostic and Therapeutic Approaches to Fungal Infections in Critical Care Settings: Different Options but the Same Strategy

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Invasive fungal infections, especially in the critical care setting, have become an excellent target for prophylactic, empiric, and preemptive therapy interventions due to their associated high morbidity, mortality rate, increased incidence, and healthcare costs. For these reasons, new studies and laboratory tests have been developed over the last few years in order to formulate an early therapeutic intervention strategy in an attempt to reduce the high mortality rate associated with these infections. In recent years, there have been important developments in antifungal pharmacotherapy. Evidence-based studies have shown the roles that the new antifungal drugs play in the treatment of invasive mycosis in seriously ill and complex patients, although data from critically ill patients are more limited and must be taken and extrapolated from studies based on the general hospital population. New antifungal agents have been analyzed in different clinical situations in critical care units, and the increasing number of non-Candida albicans species and the high mortality rates in these settings suggest that the application of an early broad spectrum antifungal therapy in critically ill patients with fungal infection should be recommended. J Invasive Fungal Infect 2007;1(2):50–8.

Epidemiology and etiology of invasive fungal infections

Critical care medicine has advanced greatly in the past few decades. Patients with complex medical and surgical disorders are surviving longer due to equally complex medical and surgical interventions. These often involve the “collateral damage” of circumventing normal body defense mechanisms.

Approximately 10.4% of the episodes of infection in an intensive care unit (ICU) are related to a Candida species, with the majority being nosocomial [1]. However, this rate could be underestimated due to the fact that at least 4% of critically ill patients who die in an ICU are found to have an unexpected fungal infection during postmortem examination [2]. Furthermore, ICU admission itself has become an independent risk factor for the development of a Candida spp. infection [3,4]. Although less frequent, aspergillosis (particularly in patients with chronic obstructive pulmonary disease [5–7]) and other emergent moulds and yeasts such as Trichosporon asahii [8], Saccharomyces cerevisiae [9,10], Hansenula anomala [11], Dipodascus capitatus [12], or Rhizopus microsporus [13] have been described in intensive care settings during the last few years, with an elevated morbidity and poor outcome from infection.

Mortality and associated risk factors

Candida infections are associated with a significant mortality rate, especially among critically ill patients [14]. The crude mortality rate of these infections is high (40–75%), and the mortality rate attributable to candidemia has been estimated to be 25–38% by several authors [3,15–17]. A recent review of matched cohort and case–control studies was undertaken in order to examine the mortality rate that could be linked to candidemia [18]. This analysis included studies that compared the mortality rate of patients with candidemia with that of matched patients who did not have candidemia. The data suggest that candidemia is indeed associated with a considerable mortality rate that can be attributed, at least to some degree, to the infection itself and not only to the presence of comorbidity.

In recent years, the species of Candida that result in candidemia have shifted from a predominance of Candida albicans to non-C albicans species (NCA). This increase has been attributed to the use of fluconazole prophylaxis [19]. Approximately half of the reported cases of candidemia are...
now caused by NCA [3,17,20], and several publications have indicated that infections with these species have a worse prognosis than those caused by *C. albicans* [21–23]. Other adverse outcome predictors described in candidemia episodes are the stay in the ICU itself, renal failure, thrombocytopenia, hematological malignancy, and the need for mechanical ventilation or inotropic support [17,22]. In a Spanish multicenter study involving patients in ICUs of 28 hospitals, an Acute Physiology and Chronic Health Evaluation II (APACHE II) score of >20 at the time of candidemia was associated with a higher mortality rate [16], whereas early treatment with antifungal medication and removal of central venous catheters were factors protective against death [16,17]. Furthermore, it is well known that invasive fungal infections can be associated with inadequate empirical antifungal treatment [24]. Two recent reports have demonstrated a strong association between a delay in the start of antifungal therapy and an increase in hospital mortality rates [25,26]; thus, it is necessary to recognize that time is of the utmost importance when considering the therapy of invasive fungal infections.

**Empirical, preemptive therapy, and prophylaxis**

The early identification of risk factors for the development of candidemia, such as peritonitis, abdominal surgery, previous administration of broad-spectrum antibiotics, parenteral nutrition, multiple lumen catheters, prior *Candida* spp. colonization, renal replacement therapy, and mechanical ventilation [15,27,28] has become the cornerstone of empirical treatment of fungal infections in ICU settings in order to reduce the high mortality rate associated with these infections [29,30].

Ostrosky-Zeichner and colleagues created a prediction rule for invasive candidiasis in a retrospective, multicenter study setting (12 units in the USA and Brazil). The rule requires that a combination of one “major” and two “minor” criteria be met, with the criteria reflecting common risk factors for patients who stay in the ICU for >3 days and are expected to stay for an additional 2 days. This rule can be applied to approximately 10% of patients who stay in the ICU for ≥4 days, and, approximately 10% of patients to whom this rule is applied will develop proven or probable invasive candidiasis. Using a more broad definition of risk, patients with any combination of diabetes mellitus, new onset hemodialysis, use of total parenteral nutrition, or receipt of broad-spectrum antibiotics had an invasive candidiasis rate of 16.6% compared with a rate of 5.1% for patients who were lacking these characteristics (p=0.001). Fifty-two percent of patients staying ≥4 days in the ICU met this particular rule and the rule captured 78% of the patients who eventually developed invasive candidiasis [31,32]. Recently, a Spanish group reported the development of a bedside scoring system based on risk factors that allows early antifungal treatment when candidemia is suspected in non-neutropenic ICU patients. This “*Candida* score” was based on the predictive value of previously reported risk factors. Using a logistic regression analysis adjusting for possible confounding variables, the authors found that total parenteral nutrition, surgery, multifocal yeast colonization, and severe sepsis were independently associated with a greater risk for proven candidal infection. The scores for the individual factors were:

- Parenteral nutrition +0.908.
- Surgery +0.997.
- Multifocal colonization +1.112.
- Severe sepsis +2.038.

In this large cohort of critically ill patients, the authors concluded that a “*Candida* score” of >2.5 (sensitivity 81%, specificity 74%) could accurately select patients who would benefit from early antifungal treatment [33].

Poor outcomes are, in part, associated with the difficulty in establishing the microbiological diagnosis at an early stage of the infection. Blood culture results are positive in only 50% of invasive *Candida* and *Fusarium* infections and are very rarely positive in cases of invasive aspergillosis. Cultures of bronchoalveolar lavage fluid or brushing specimens are positive in <50% of subjects with invasive pulmonary aspergillosis. Finally, positive results of cultures of specimens from non-sterile body sites may be related to either colonization or disease, and distinguishing between these can be difficult. Non-culture-based diagnostic tests may provide a useful adjunct to these more traditional approaches. Of these, detection of circulating (1,3)-β-D-glucan (BG), galactomannan, or *C. albicans* germ tube antibodies (CAGTA) have appeared promising and could be useful as a preemptive therapy guide in these patients [34–37].

Recent multicenter clinical trial results have demonstrated that the BG assay can be used to measure serum BG in clinical specimens with a high specificity and positive predictive value for subjects with proven or probable invasive fungal infection compared with control subjects. This test appeared to be useful both as a single-point assay for patients hospitalized with suspicion of a fungal infection or as a part of a surveillance strategy in high-risk individuals. Serum BG cutoff values of 60 or 80 pg/mL seemed to be optimal for this test. The BG assay had a high positive predictive value for subjects infected with *Candida* (except *C. parapsilosis*), *Aspergillus*, or *Fusarium* species. Moreover, the performance of the assay did not seem to be significantly affected by antifungal therapy. However, the assay did not detect elevated levels of BG in subjects infected with *Mucor, Rhizopus*, or *Cryptococcus* species.
Furthermore, the results in patients undergoing hemodialysis must be considered with caution due to the false-positive results described in this patient population [36].

In 2006, the current authors’ group evaluated an immunofluorescence assay (IFA) for CAGTA detection (Candida albicans IFA immunoglobulin G; Vircell, Granada, Spain) in a selected population of critically ill patients (Fig. 1) [38]. Although there were no differences between CAGTA-positive and -negative patients in terms of age, sex, Sequential Organ Failure Assessment score, renal failure, and hepatic failure, the intra-ICU mortality rate was significantly lower in patients who tested positive for CAGTA (25% vs. 65.2% ; p=0.025). These results suggest that a strategy based on early determination of CAGTA expression may reduce the ICU mortality rate of patients with risk factors for the development of invasive candidiasis. However, more studies are necessary to validate this approach in critical care settings.

Piarroux et al. assessed the efficacy of a preemptive antifungal therapy in preventing proven candidiasis in critically ill surgical patients, using a corrected colonization index (ratio of highly positive samples to the total numbers of samples cultured) to measure the intensity of Candida mucosal colonization [39]. In patients with a corrected colonization index of ≥0.4, early preemptive antifungal therapy with fluconazole caused a reduction in the incidence of ICU-acquired proven candidiasis (from 2.2% to 0%). However, it is possible that the widespread use of this approach could be limited by the capacity of the microbiology laboratory to analyze multiple samples.

Although previously published data failed to show a reduction in mortality rates with fluconazole prophylaxis in surgical critical care patients [40,41], a recent meta-analysis of azole prophylaxis of Candida infections in a heterogeneous population of trauma and surgical intensive care patients did demonstrate reduced rates of candidemia, attributable mortality, and overall mortality rates [42]. Thus, data must be interpreted carefully in the context of local practices prior to the application of universal prophylaxis in this setting.

Available antifungal agents and therapy options

The past few years have brought exciting developments in antifungal pharmacotherapy. Evidence-based studies using the new antifungal agents are accumulating and these drugs are assuming important roles in the pharmacotherapy of invasive fungal infections in seriously ill and complex patients. However, data in these patients are more limited and must be recovered from general hospital population studies.

Voriconazole, the first available second-generation triazole, has been approved by the US Food and Drug Administration and by the European Medicines Agency for the treatment of invasive aspergillosis, serious infections caused by Fusarium and Scedosporium apiospermum fluconazole-resistant invasive Candida infections (such as C krusei and C glabrata), and candidemia in non-neutropenic patients.

A landmark trial showed that voriconazole had proven efficacy in the treatment of invasive aspergillosis [43], with the authors of the study concluding that treatment with this agent resulted in a better clinical response, improved survival rate, and fewer serious adverse reactions than treatment with amphotericin B. Moreover, voriconazole has been demonstrated to be an effective and well-tolerated treatment for refractory or less common invasive fungal infections [44].

In spite of these encouraging data on voriconazole, the best first-line treatment for candidemia remains controversial, especially in critically ill patients. Clinical studies have shown that amphotericin B, fluconazole, caspofungin, and voriconazole have similar efficacy in the treatment of Candida bloodstream infections [45–48]. In accordance with recent guidelines [49], many experts favor initial treatment with amphotericin B in severely ill or clinically unstable patients, but its renal toxicity could present a serious problem in these individuals, which may preclude its use as first-line therapy [50,51]. While the triazole, fluconazole, may be selected on the basis of its efficacy and safety [45,46], the increasing frequency of patients infected with Candida strains that are resistant to this drug highlight the need for initial treatment with a broader-spectrum agent – at least until the Candida species is identified – in order to avoid inadequate empirical treatment.
antifungal treatment and an associated increased mortality rate [52]. Thus, “de-escalation” therapy in these cases may be considered. De-escalation of antifungal therapy, according to the definition proposed by Marin Kollef, can be thought of as a strategy to balance the need to provide adequate initial antifungal treatment of high-risk patients with the avoidance of unnecessary antimicrobial utilization (which promotes resistance) using an early broad-spectrum antifungal agent and subsequent switching to a narrower-spectrum drug when mycological identification and susceptibility studies are provided [53].

Another triazole, itraconazole, has recently been developed as an intravenous formulation that has a wide spectrum of activity. However, the absence of clinical trials in Candida infections (particularly in ICU settings), issues of drug interactions, and the limited data regarding the use of cyclodextrin in its formulation are factors that may restrict its use as a first-line therapy in critically ill patients. In addition, 46–53% of C glabrata and 31% of C krusei isolates are resistant to itraconazole [49].

A novel class of antifungal compounds that target the glucan synthesis enzyme complex (echinocandins) has been developed in the last few years. Currently, three echinocandins are available: caspofungin, micafungin, and anidulafungin. Published reports suggest that caspofungin is equivalent to standard therapy (amphotericin B) in terms of efficacy in the treatment of invasive Candida infections [47].

Anidulafungin is the only antifungal compound that has been able to demonstrate superiority over a comparator (fluconazole) in a recent invasive candidiasis clinical trial, although these results must be considered with caution due to the fact that the study had been powered a priori for equivalency and has not yet been published. However, the efficacy and safety profile of anidulafungin indicate that it should be readily considered as a first-line option for the treatment of invasive candidiasis [54,55].

Micafungin has become the second available agent of the echinocandin class that is approved for use in clinical practice (currently, only in Japan and the US for treatment of esophageal candidiasis and prophylaxis in subjects with neutropenia). This agent shares an identical spectrum of in vitro activity against C albicans, non-albicans species of Candida, and Aspergillus species with caspofungin [56]. Although there are descriptions of the use of micafungin in candidemia [57,58], to date, these studies have not been published.

It should be noted that the administration of echinocandins could have several limitations in ICU settings. Factors that urge caution include the lack of data regarding the number of patients admitted in the ICU in the study of Mora-Duarte et al. [47], the potential hepatotoxic effect of caspofungin associated with cyclosporin, the high cost of these drugs, the difficulty of studying their action in vitro in a clinical laboratory (especially caspofungin), and the worrying number of breakthrough candidemias caused by C parapsilosis (in the caspofungin-treated group in the study of Mora Duarte et al. [47]). Furthermore, isolates from many of the echinocandin-treatment failures published in the literature had high minimum inhibitory concentrations, especially against C parapsilosis. Conversely, due to their safety profile and activity on biofilms, especially in renal dysfunction, all echinocandins have become first-line agents in patients with renal insufficiency admitted to an ICU or when artificial devices are related to the infection [59].

Successful therapy with compassionate use of voriconazole for the treatment of candidemia and invasive candidiasis in patients intolerant or refractory to other antifungal agents has been reported [60]. This study showed that voriconazole may be a suitable agent for the salvage treatment of invasive candidiasis, even in the setting of previousazole exposure and C krusei infection. These findings have been confirmed by two Spanish groups [61,62]. Another observational Spanish multicenter study has been performed to assess the clinical use and tolerability of voriconazole in daily practice in the ICU setting for the treatment of fungal infection in critically ill patients [63]. The key contribution of this study is the description of the scenario in which voriconazole is used in daily practice in the ICU. Notably, voriconazole was frequently used for the salvage treatment of invasive fungal infections in subjects with previousazole exposure. The typical patient was a middle-aged man with an underlying medical disease, in particular, active malignancy or chronic bronchitis, who had received treatment with antibiotics, corticosteroids, or chemotherapeutic drugs prior to admission to hospital, and with a high APACHE II score on admission to the ICU. The prescription of voriconazole was based on the presence of documented invasive fungal infection previously treated with other antifungal drugs. C albicans and Aspergillus fumigatus were the most common pathogens and the use of voriconazole was effective in 50% of cases. The drug was well tolerated and there were no treatment discontinuations due to adverse events.

Results from the first randomized, prospective, multicenter study in non-neutropenic patients with candidemia who were treated with voriconazole or amphotericin B deoxycholate followed by fluconazole demonstrated that the drugs were equivalent with regard to efficacy and mortality rates [48]. There was a high proportion of infection due to NCA species (55%), with a similar distribution of the species between the two treatment groups. Successful response rates were similar in the voriconazole and amphotericin B/fluconazole arms;
however, for *C. tropicalis* infections, the proportion of patients responding to treatment was substantially higher in the group treated with voriconazole. This is in spite of the fact that these strains were susceptible in vitro to amphotericin B. Although renal dysfunction was significantly lower in the voriconazole-treated group, the incidence of visual disturbances was slightly higher. These minor side effects are usually transient and resolve after the patient has become tolerant to the drug or treatment is discontinued. However, in critically ill patients, it is difficult to detect this complication because most are sedated and mechanically ventilated. The results of this study can be easily applied to critically ill patients as approximately half of the patients included were admitted to an ICU. The only limitation to the use of intravenous administration of voriconazole in these patients could be the accumulation and toxicity of cyclodextrin in severe renal dysfunction, although there are no data addressing this possibility in patients undergoing renal replacement therapy. There is no requirement for the adjustment of oral voriconazole in patients with renal dysfunction, although severe hepatic dysfunction could limit its use. Potential drug interactions should also be kept in mind, although to date, no dose-dependent relationship for voriconazole has been observed; however, a wide inter-patient variability exists with contrasting predictive intra-individual kinetics. Nevertheless, voriconazole must be discontinued in cases of interactions with rifampicin or sirolimus [64].

Encouraging clinical experience suggests that voriconazole may be a new therapeutic alternative in critically ill patients, not only as salvage treatment but also as an additional first-line option in suspected or proven *Candida*, and as a first choice in *Aspergillus* infection.

Posaconazole, a new extended-spectrum triazole, has *in vitro* activity against a variety of pathogenic fungi, including *Aspergillus*, *Candida*, *Cryptococcus*, and *Histoplasma*. This new agent has been studied extensively in a variety of animal models of mycoses and appears to be a useful oral agent in open trials for mycoses, including refractory fungal infections [65,66]. In patients undergoing chemotherapy for acute myelogenous leukemia or myelodysplastic syndrome, posaconazole prevented invasive fungal infections more effectively than either fluconazole or itraconazole and improved the overall survival rate [67]. However, due to the lack of availability of an intravenously administered formulation, it is very difficult to consider this drug as a therapeutic option in invasive candidiasis in critically ill patients at present.

The principal advantages and disadvantages of systemic antifungal agents in the ICU setting are summarized in Table 1.

**A similar and uniform strategy**

A recent publication shows a shift toward the use of antifungal drugs other than fluconazole due to the identification of an increasing number of NCA isolates [19]. Consequently, the application of an early tailored therapy in critically ill patients with fungal infection is recommended [68]. For this reason, voriconazole (due its broad spectrum of action and good safety profile in ICU settings), caspofungin, and anidulafungin (particularly in renal dysfunction) could be attractive options in the application of this strategy in critically ill patients. Finally, the antifungal drug selection must be based on the individual characteristics of the patient, and should particularly focus on the presence of renal or hepatic failure and possible interactions with other drugs. A strategy for de-escalation (tailoring) of antifungal drugs, and the diagnosis status–treatment protocol are proposed in Figs. 2 and 3.

**Combination therapy**

The availability of new antifungal agents with single mechanisms of action and improved tolerability has widened the possibilities for the use of combination antifungal therapy (combination of two antifungal drugs) for difficult-to-treat, opportunistic mycoses. Furthermore, additive *in vitro* interactions of voriconazole and echinocandins have been observed. Few randomized clinical trials have examined the role of this type of therapy for invasive mycoses, and no prospective, randomized trial of antifungal agent combinations has been completed for invasive mould infections. The results of *in vitro* studies and animal models suggest that combination therapy with azoles and echinocandins may have additive activity against *Aspergillus* species and suggest a great potential for combination therapy, confirming the need for further investigation [69]. However, the possible benefit of combination therapy with voriconazole for disseminated cryptococcosis and invasive candidiasis (or other emerging yeasts) needs to be elucidated. At present, a combination of amphotericin B plus flucytosine, and monotherapy with fluconazole, an echinocandin, voriconazole, or amphotericin B may be more desirable in these settings.

The use of other classes of drugs with antifungals – as a combination therapy – should also be considered. For instance, a human recombinant monoclonal antibody against heat shock protein 90, Mycograb® (NeuTec Pharma, Manchester, UK), has been shown to act synergistically with amphotericin B against a broad spectrum of *Candida* species *in vitro* [70]. Subsequently, a double-blind, randomized study was conducted to determine whether lipid-associated amphotericin B plus Mycograb was superior to lipid-associated amphotericin B plus placebo in patients with culture-confirmed invasive candidiasis [71]. Patients received a lipid-associated formulation of amphotericin B plus a 5-day course of Mycograb or placebo, having been stratified on the basis of *Candida* species (*C. albicans* versus NCA...
species). A favorable overall response, defined as a complete clinical and mycological response, with resolution of all signs and symptoms of candidiasis and culture-confirmed eradication of the pathogen, by day 10 was obtained for 29 of 61 (48%) patients in the amphotericin B alone group, compared with 47 of 56 (84%) patients in the Mycograb combination therapy group (odds ratio [OR] 5.8, 95% confidence interval [CI] 2.41–13.79; p<0.001). A greater proportion of the combination therapy group, compared with the amphotericin B alone group, met individual efficacy criteria including clinical response (86% vs. 52%, OR 5.4, 95% CI 2.21–13.39; p<0.001), mycological response (89%
vs. 54%, OR 7.1, 95% CI 2.64–18.94; p<0.001), Candida-attributable mortality rate (4% vs. 18%, OR 0.2, 95% CI 0.04–0.80; p=0.025), and rate of culture-confirmed clearance of the infection (hazard ratio 2.3, 95% CI 1.4–3.8; p=0.001). These results underscore the potential for the use of combination therapy in critically ill patients. Nevertheless, further clinical trials are required to clarify this issue in intensive care settings.

Concluding remarks
Invasive fungal infections, especially in the critical care setting, have become an excellent target for prophylactic,
empiric, and preemptive therapy interventions due to the high morbidity and mortality rate associated with these infections, their increased incidence, and their attendant healthcare costs. Early diagnosis and treatment are associated with a better prognosis in invasive candidiasis. Fluconazole, amphotericin B, echinocandins, and voriconazole are the antifungal agents currently available to treat invasive candidiasis in critically ill patients. The antifungal drug selection must be based on the individual characteristics of the patient. A tailored therapy (de-escalation) must also be considered in ICU settings.

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References
Clinical reviews were prepared by Zeina Kanafani

**ASPERGILLOSIS**

Treatment of invasive aspergillosis with posaconazole in patients who are refractory to or intolerant of conventional therapy: an externally controlled trial

Walsh TJ, Raad I, Patterson TF et al.


This study from Walsh and colleagues suggests that posaconazole is a viable option in the treatment of patients with invasive aspergillosis who are refractory to or intolerant of conventional therapy.

This was an open-label, prospective trial in which patients refractory to or intolerant of conventional therapy received posaconazole for the treatment of invasive aspergillosis. These subjects were compared with an external, retrospectively collected control group. The success rate at the end of therapy was 42% in the posaconazole group and 26% in the control group (p<0.006).

Additional data recently presented at the 46th Interscience Conference on Antimicrobial Agents and Chemotherapy (ICAAC) confirmed the efficacy of posaconazole in invasive aspergillosis. In a comparative retrospective cohort study, Raad et al. compared posaconazole to lipid formulations of amphotericin B as salvage therapy for invasive aspergillosis in patients with hematological malignancy [1]. A total of 51 patients received posaconazole and 49 patients received high-dose lipid formulations of amphotericin B (≥7.5 mg/kg/day). The response rate was significantly better with posaconazole than with lipid formulations of amphotericin B (39% vs. 8%; p≤0.001). In addition, the mortality rate attributable to aspergillosis was lower in the posaconazole group (39% vs. 63%; p=0.02). On multivariable analysis, posaconazole treatment was the only factor significantly associated with improved outcome (odds ratio 8.8; 95% confidence interval 2.6–29.4).

Furthermore, posaconazole appears to be useful in preventing invasive aspergillosis in high-risk patients. A recently published trial compared posaconazole with fluconazole prophylaxis in patients with graft-versus-host disease following allogeneic stem cell transplantation [2]. Posaconazole was superior to fluconazole in preventing aspergillosis (2.3% vs. 7.0%; p=0.006). Additionally, fewer breakthrough episodes were observed in the posaconazole arm (1.0% vs. 5.9%; p=0.001). In another trial, posaconazole improved survival (p=0.04) and was superior to both fluconazole and itraconazole in preventing invasive aspergillosis in patients with prolonged neutropenia (1% vs. 7%; p<0.001) [3].


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**Micafungin (FK463), alone or in combination with other systemic antifungal agents, for the treatment of acute invasive aspergillosis**

Denning DW, Marr KA, Lau WM et al.


This study was a prospective non-comparative trial that examined the efficacy of micafungin, alone or in combination with other antifungal agents, in the treatment of adult and pediatric patients with various underlying diseases and proven or probable invasive aspergillosis. Clinical response was achieved in 36% of patients in the overall population (50% of patients who received micafungin alone). Of the patients who completed the 6-week follow-up period, 32% were deemed to have a complete or partial response.

In this non-comparative, prospective trial the authors found that micafungin is efficacious as part of the therapeutic regimen of patients with invasive aspergillosis. The sole
other published trial on micafungin in the treatment of aspergillosis was conducted by Kohno and colleagues in Japan [1]. In that study, patients had a variety of underlying diseases and did not receive any other antifungal therapy while on micafungin. At the end of therapy, six of the 10 patients with invasive pulmonary aspergillosis had a favorable clinical response.

In addition, two studies recently presented at the 46th Interscience Conference on Antimicrobial Agents and Chemotherapy (ICAAC) evaluated the use of micafungin alone or in combination with other antifungal agents in the treatment of invasive aspergillosis. The first study was conducted in adult bone marrow transplant recipients (n=98). Eight patients were treated with micafungin alone while the remaining 90 patients received micafungin in combination with other antifungal therapy [2]. Twenty-two patients on combination therapy (24%) and three patients on micafungin alone (38%) had a partial or complete response to therapy. The second study was conducted in 58 pediatric patients with invasive aspergillosis [3]. Forty-seven patients received micafungin in combination with liposomal amphotericin B. Only two patients received micafungin alone. Nine patients exhibited complete response to therapy (16%) and another 17 patients had a partial response (29%). In both studies, micafungin was well tolerated.

Evidence from other clinical trials suggests that micafungin is also efficacious in the treatment of mucocutaneous and invasive candidiasis, as well as in the treatment of patients with hematological malignancies and febrile neutropenia.

The present authors conducted a prospective non-comparative trial that examined the efficacy of micafungin alone or in combination with other antifungal agents in the treatment of 225 adult and pediatric patients with various underlying diseases and proven or probable invasive aspergillosis. Clinical response was achieved in 36% of patients, half of whom had received micafungin alone. Nine patients exhibited complete response to therapy (16%) and another 17 patients had a partial response (29%). In both studies, micafungin was well tolerated.

Impact of the intensity of the pretransplantation conditioning regimen in patients with prior invasive aspergillosis undergoing allogeneic hematopoietic stem cell transplantation: a retrospective survey of the Infectious Diseases Working Party of the European Group for Blood and Marrow Transplantation


Patients with hematological malignancies who undergo chemotherapy are often referred for subsequent allogeneic hematopoietic stem cell transplantation (HSCT). However, invasive aspergillosis (IA) is a common complication of chemotherapy, and until recently was considered to be an absolute contraindication to allogeneic HSCT due to the potential for relapse of IA after transplantation, and an elevated nonrelapse mortality rate. Following advances in antifungal drugs and development of reduced-intensity chemotherapeutic conditioning regimens, successful outcomes of allogeneic HSCT have been reported in patients with prior IA.

The aims of this study were to determine outcomes in patients who had a recent history of proven or probable IA undergoing allogeneic HSCT with a conventional myeloablative or a reduced-intensity conditioning regimen, and to identify risk factors for progression of IA after allogeneic HSCT.

A total of 129 patients (median age 42 years) from 44 centers across 12 countries who received an allogeneic HSCT were studied. IA progressed in 27 patients (21%) after transplantation, and the incidence of progression was similar in patients receiving either conditioning regimen; however, there was a trend toward a higher IA-related mortality in the conventionally treated group. Patients in partial remission or complete remission from infection at transplantation were less likely to progress than those who were not (17% vs. 32%; p=0.012). Due to the wide range of antifungal regimens employed, it was not possible to identify significant differences between these in terms of IA progression in each the two conditioning groups, although voriconazole monotherapy as
second-line prophylaxis in the immediate post-HSCT phase showed a trend in reducing progression of IA (p=0.15).

In a multivariate analysis, early progression of IA (<30 days post-transplantation) was more common in patients who received a conventional conditioning regimen (15% vs. 7%; p=0.054). Late progression of IA (>30 days post-transplantation) was more common in those with cytomegalovirus, bone marrow or cord blood as a source of stem cells, and in those with grades II–IV acute graft-versus-host disease. Other variables that increased the risk of progression during the entire transplantation period were a longer duration of neutropenia (>20 days post-transplantation), advanced status of the underlying disease, and a short time-period between the start of antifungal therapy and the allogeneic HSCT (<6 weeks). From these data, the authors generated a risk model for progression of IA.

The authors conclude that a history of IA is not an absolute contraindication for allogeneic HSCT, particularly if the patients have a low-risk profile. Furthermore, they suggest that high-risk subjects could be prospectively assessed in studies that aim to reduce the high risk of progression of IA.

The authors of this literature review of postoperative aspergillosis report that successful treatment requires prompt diagnosis, and surgical excision of the affected tissue together with antifungal therapy. Regular maintenance of operating theater ventilation systems should be undertaken to minimize the risk of infection.

The authors of this review performed a literature search to investigate cases of surgical site infection with Aspergillus spp. in immunocompetent individuals. Keyword searches of Medline, LILACS (Latin American and Caribbean Health Science Literature Database), and EMBASE (Excerpta Medica Database) databases identified more than 500 cases. In their review, the authors discuss the presentations and treatment of infection following different types of surgery. Cardiac surgery was the procedure that was most commonly associated with infection (n=188), followed by dental surgery (>100), and ophthalmological surgery (>90).

Among those with infection following cardiac surgery, the mean time to diagnosis was 2.7 months, but this varied from <1 to >12 months, and the diagnosis was often made following autopsy. Indeed, only 43.5% of cases had a pre-autopsy diagnosis, and there was a very high overall mortality rate (92.7%) in these subjects. The authors suggest that this may be due to delayed diagnosis as a result of the infrequent isolation of the fungus from blood cultures – in most of the cases, surgical intervention was vital in obtaining a definitive diagnosis. Furthermore, Aspergillus aortitis can often go undetected by trans-thoracic and trans-esophageal echocardiography, but is more readily identified by computed tomography, magnetic resonance imaging, and angiography.

Although there have not been any studies of the optimal treatment for infection to date, the findings of this literature review suggest that the infected tissue should be excised and a systemic antifungal agent should be given, with results indicating that this should be continued for 3 months after the last evidence of active disease.

The authors conclude that the development of better diagnostic methods is essential if outcomes are to be improved. Moreover, given that in the majority of cases presented in this review the Aspergillus spores originated from the air in the operating theater, special attention should be paid to the maintenance of ventilation ducts in these areas.
There is strong evidence to suggest that diabetes mellitus is an important determinant of the manifestations and outcomes of various infectious processes, including fungal infections. In one study, oral colonization and infection with *Candida* occurred more frequently in 405 patients with insulin-dependent diabetes mellitus than in 268 non-diabetic controls (15.1% vs. 3.0%) [1]. Upon multivariate analysis, poor glycemic control (as evidenced by an elevated glycosylated hemoglobin level) was an independent predictor of *Candida* colonization and infection (odds ratio 1:9). In another similar study, fungal colonization in the vagina and rectum of pregnant women was more common in diabetic patients with poor glycemic control than non-diabetic women [2]. The majority of isolated fungal strains were *Candida* species (89.6%).

Other fungal infections that have been strongly associated with diabetes mellitus include zygomycosis. However, unlike the case with coccidioimycosis and *Candida* infections, glycemic control does not seem to be the principal factor predisposing to zygomycosis, as affected patients tend to have similar hemoglobin A1c levels to non-affected patients [3].

Of the other dimorphic fungi, *Blastomyces dermatitidis* can also act as an opportunistic pathogen in diabetic patients. In fact, 22% of all patients with blastomycosis have an underlying diagnosis of diabetes mellitus [4].

It has been suggested that the diminished cell-mediated immunity in pregnancy contributes to the establishment and dissemination of fungal infections. During pregnancy, there is decline of CD4+ T cell function and augmentation of suppressor T lymphocyte function. In addition, interleukin production by the placenta causes down-regulation of type 1 T helper cells and upregulation of type 2 T helper cells. The resulting immune modulation facilitates the dissemination of endemic fungal infections that are usually kept in check by the host’s cell-mediated immunity [1].

Infections with other dimorphic fungi have been rarely reported in pregnancy. Whitt et al. described three cases of disseminated histoplasmosis in pregnant women, two of which (one with diabetes mellitus and the second with HIV infection) resulted in a fatal outcome [2]. The patient who survived was previously healthy. Transplacental transmission of *Histoplasma capsulatum* was confirmed in one fetus.

Blastomycosis is slightly more frequently encountered in pregnancy than histoplasmosis. A review of the medical literature by Lemos et al. yielded 16 cases of pregnancy-associated blastomycosis [3]. The authors were able to identify three additional cases at the University of Mississippi Medical Center (Jackson, MI, USA). The majority of cases consisted of pulmonary blastomycosis (14 cases) and skin involvement was present in nine cases. Antifungal therapy was administered in 16 patients (amphotericin B in 13 cases). There were no fatalities and complete cure was achieved in 14 cases. Four additional women experienced good responses to treatment. Transplacental infection was documented in two cases resulting in the deaths of both fetuses.

The present report provides a comprehensive review of the literature on coccidioidomycosis in pregnancy. Although infections with dimorphic fungi are uncommon in pregnancy, they are associated with significant morbidity. In the 80 cases identified, there was a higher likelihood of dissemination of the infection during the third trimester (96%) compared with the first (50%) and second trimesters (62%), with an overall mortality rate of 36%. The authors report that early recognition of disease and treatment are associated with an improved outcome.

The authors of this report identified 80 cases of coccidioidomycosis in pregnant women in the literature. There was a higher likelihood of dissemination of the infection during the third trimester (96%) compared with the first (50%) and second trimesters (62%). The overall mortality rate was 36%. Early diagnosis and treatment were associated with improved maternal and fetal outcome.

Coccidioidomycosis in pregnancy: case report and review of the literature


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Biofilms are structured, three-dimensional microbial communities attached to a surface and encapsulated within a protective extracellular matrix. This unique environment is distinct from that of planktonic (free-floating) cells, and provides survival advantages to the microbe such as protection from host immune defenses and increased resistance to antimicrobial agents. A number of studies have shown dramatically reduced sensitivity of Candida biofilms to fluconazole and amphotericin B [1–3]. Novel antifungals such as caspofungin, a member of the echinocandins, look more promising as potent activity against C. albicans within the approved therapeutic range has been demonstrated [3].

Use of artificial materials in implanted medical devices allows microbes such as Candida to colonize and proliferate in the body, and the infection can, in many cases, only be eradicated by removing the device. This can be difficult or even impossible, resulting in a reservoir for persistent infections being established inside the patient. Biofilm formation often leads to infections associated with high rates of morbidity and mortality, and can also cause device malfunction. The problem is widespread as different types of catheters and endotracheal tubes are used in millions of patients every year, some of which carry a risk of Candida infection of up to 30%. Other common devices frequently affected by Candida biofilms include prosthetic joints, neurosurgical shunts, heart valves, voice prostheses, and dentures.

The authors conclude that the current mortality rates associated with biofilm-related infections are unacceptably high, and that novel drugs and strategies are required to better control this problem.


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CANDIDIASIS

Over the past 10–15 years, an increased understanding of the significance of microbial biofilms has developed. The present minireview by Ramage et al. describes the unique characteristics of biofilms in general and the clinical impact of Candida biofilms on implanted medical devices in particular.

Candida biofilms on implanted biomaterials: a clinically significant problem
Ramage G, Martinez JP, Lopez-Ribot JL.

Uniform distribution of three Candida albicans microsatellite markers in two French ICU populations supports a lack of nosocomial cross-contamination
Eloy O, Marque S, Botterel F et al.
BMC Infect Dis 2006;6:162.

This small epidemiological study, based at two intensive care units in France, found no evidence to suggest that nosocomial transmission of Candida albicans occurs between patients.

Candida albicans accounts for 55% of all yeast bloodstream infections in intensive care units (ICUs) [1], most of which are nosocomial, and the organism represents a growing concern. Genotyping is one method of determining the route of contamination. Using three highly specific polymorphic microsatellite markers (PMMs), the authors performed a follow-up to a previous single-center study showing that cross-contamination between patients was unlikely [2], with the aim of extending their findings to a more generalized setting.

Data from the earlier study showed that, between November 1999 and October 2000, 43 of 94 patients (46%) had at least one positive culture for C. albicans, 36 of whom had positive samples after 72 h of hospitalization. In the second hospital ICU, between February 2000 and January 2002, 36 of 60 patients (60%) had at least one positive culture for C. albicans, all of which were positive after 72 h. Of these, 26 had a specific multilocus genotype, two had a common multilocus genotype, and eight had the most common genotype in the general population. Of the patients who had common genotypes, the time between their periods of stay in hospital differed by 13–78 days, making any direct cross-contamination unlikely. By comparing the three PMMs between the two ICUs the authors found no evidence of a difference between the rate of nosocomial C. albicans colonizations, despite some potentially important methodological differences.

Thus, these data support the findings of the earlier study that ICU patients tend to harbor their own C. albicans isolates and that cross-contamination is unlikely. They also extend the findings of the previous study to suggest that no genotype is specific to a particular hospital. The authors suggest that efforts should be focused on treating the risk factors for infection rather than preventing cross-contamination, as this rarely occurs.


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Caspofungin for invasive candidiasis at a tertiary care medical center

Caspofungin has been reported to be a successful therapy in patients who have invasive candidiasis infection but are resistant to existing treatments such as amphotericin B or azoles. In this article, the authors describe a single-center study of 99 patients with 104 episodes of caspofungin treatment, and recommend that caspofungin should be used as first-line therapy, particularly in non-albicans Candida infections.

Invasive candidiasis is one of the most common fungal infections and is usually treated with amphotericin B or with azole drugs. Non-albicans Candida spp. (e.g. C glabrata) are more likely to be resistant to existing treatments, and comprise >50% of the isolates that cause invasive candidiasis. However, a few study groups have reported in favor of caspofungin, a new antifungal agent, in patients who were not responding to amphotericin B or to fluconazole treatment. In order to study the effects of caspofungin for the treatment of invasive candidiasis, the authors assessed a single-center experience of 104 consecutive courses of caspofungin in 99 patients.

From the Duke University Medical Center pharmacy antimicrobial indications database, the authors identified 241 patients who were receiving caspofungin (319 courses in total) from 2001–2003. Of these, only 99 patients (104 courses of caspofungin) met the criteria for inclusion in the study. The most common sites of infection were the bloodstream and the abdomen (66% and 25%, respectively). Non-albicans Candida infections comprised the majority (77%) of infections treated with caspofungin, of which C glabrata was the most common isolate and C parapsilosis the least common.

Following a median follow-up of 84 days, 81 patients (82%) remained free of candidiasis. Eighty-three percent of bloodstream and 84% of abdominal infections were cured after caspofungin treatment. On the whole, C parapsilosis had the highest clinical cure success rate (100%) while C albicans had the lowest (77%). Of the 104 “episodes”, 20% were administered caspofungin as primary therapy (the overall success rate was 76%) and the remaining 80% received various other antifungal treatments prior to caspofungin therapy. Although the trend was not significant, there was a decrease in the use of other antifungal treatments prior to caspofungin therapy between years 2001–2003. Treatment with caspofungin resulted in a few rare adverse events, which included elevated liver function tests, wheezing, and infusion-related hypotension. The lack of adverse events, even in patients who were critically ill, is one of the reasons caspofungin is an attractive alternative treatment.

Overall, the authors conclude that caspofungin therapy is a successful treatment for invasive candidiasis (similar to previous clinical trials) and should, therefore, be considered by clinicians as a primary therapy, particularly for non-albicans species.


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Oral nystatin prophylaxis to prevent invasive candidiasis in neonatal intensive care unit

In this study, the authors investigate the usefulness of oral nystatin prophylaxis for the prevention of invasive fungal infections in infants admitted to the neonatal intensive care unit. They found that infants who received nystatin were less likely to develop invasive candidiasis than infants who did not receive such prophylaxis.

Invasive candidiasis in neonates is associated with significant morbidity and mortality rates. By 6 weeks of life, 62% of extremely low-birth weight infants (ELBW; <1000 g) are colonized with Candida species. In this study the authors investigate the value of oral nystatin in the prevention of invasive candidiasis in infants admitted to the neonatal intensive care unit. They conclude that oral nystatin was effective in preventing invasive candidiasis in ELBW and very low-birth weight infants.

Three trials have studied the use of oral antifungal prophylaxis in preterm infants, with inconsistent results. In the first study, miconazole oral gel was compared with placebo in a sample of 757 infants [1]. Although rectal colonization was significantly lower in the miconazole group compared with the placebo group (19.5% vs. 36.2%; p<0.0001), there was no reduction in the incidence of systemic fungal infection with miconazole prophylaxis (2.0% vs. 2.6%). The second trial compared the outcome of 33 preterm infants who received oral nystatin prophylaxis with that of a control group of 34 preterm infants [2]. Oral nystatin was successful in reducing fungal colonization, systemic fungal infection, and mortality rate in this cohort of patients. The third study compared oral nystatin with oral fluconazole and found no significant differences in mortality rate or systemic fungal infections [3].

Due to these conflicting data, additional outcome studies are required before oral fungal prophylaxis can be widely recommended in preterm infants.
In this in vitro study, anidulafungin was compared with caspofungin for activity against 18 isolates of *Candida glabrata*. These isolates included three with elevated caspofungin minimum inhibitory concentrations (MICs). Overall, anidulafungin MICs were at least two dilutions lower than those of caspofungin. All three isolates with reduced susceptibility to caspofungin were fully susceptible to anidulafungin.

In a previous randomized, double-blind, controlled trial, the activity of anidulafungin was compared with that of fluconazole in patients with endoscopically proven esophageal candidiasis [1]. A total of 300 patients were randomized to the anidulafungin arm and 301 to the fluconazole arm. Endoscopic response rates were 97% in the anidulafungin group and 99% in the fluconazole group. However, relapse rates at the 2-week follow-up were greater in patients receiving anidulafungin (36% vs. 10%).

Anidulafungin has also been shown to be effective in the treatment of oropharyngeal candidiasis in patients unresponsive to treatment with fluconazole [2]. A total of 18 patients with azole-refractory oropharyngeal candidiasis were enrolled in an open-label study, of whom 17 had AIDS. The response rate to anidulafungin was very encouraging (17 of 18 patients).

In addition, anidulafungin was evaluated in three different dose regimens (50, 75, and 100 mg/day) in patients with invasive candidiasis [3]. The evaluable population consisted of 68 patients. The success rates at 2 weeks of follow-up were 72%, 85%, and 83%, respectively. These results were confirmed in another study where anidulafungin was successful in eradicating 84% of *Candida* species from the bloodstream [4]. The highest eradication rate was for *C. glabrata* (95%). The results of double-blind, randomized, controlled trial of anidulafungin compared with fluconazole in patients with invasive candidiasis were recently presented [5]. The success rate at 6-weeks follow-up was 56% with anidulafungin and 44% with fluconazole.

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### CRYPTOCCOSIS

**Symptomatic relapse of HIV-associated cryptococcal meningitis after initial fluconazole monotherapy: the role of fluconazole resistance and immune reconstitution**


The authors of this study prospectively enrolled HIV patients with relapsed cryptococcal meningitis who had received initial fluconazole monotherapy. In 76% of relapses in which cerebrospinal fluid culture tested positive for *Cryptococcus*, the isolate had reduced susceptibility to fluconazole. In addition, more than one-third of the relapses were attributed to immune reconstitution inflammatory syndrome.

In this study, Bicanic and colleagues found that fluconazole resistance and immune reconstitution inflammatory syndrome predicted clinical relapses of cryptococcal meningitis in HIV patients who received initial fluconazole monotherapy.

To date, three clinical trials have investigated the efficacy of fluconazole alone or in combination with other antifungal agents as initial therapy in cryptococcal meningitis, although none had a randomized, controlled design.
The first of these trials was a small, open, non-comparative study of intravenous fluconazole followed by oral fluconazole in AIDS patients with acute cryptococcal meningitis [1]. Thirteen patients received fluconazole 400 mg/day intravenously for 12–16 days followed by fluconazole 400 mg/day orally to complete therapy. The fluconazole dose was decreased to 200 mg/day if follow-up cerebrospinal fluid (CSF) cultures were negative at 32 weeks. Treatment was successful in six patients (46%); one patient died secondary to cryptococcal meningitis.

In another trial, 14 AIDS patients with cryptococcal meningitis received fluconazole 800–1000 mg intravenously [2]. Clinical response at the end of therapy was achieved in eight of 11 (73%) patients. The time to first negative CSF culture was longer in patients with initial CSF cryptococcal antigen titer of ≥1:1024 and when the minimum inhibitory concentration of fluconazole was 4 μg/mL.

Finally, a more recent study evaluated the efficacy of different antifungal combinations for the treatment of HIV-associated cryptococcal meningitis [3]. A total of 64 patients were randomized to receive either amphotericin B at 0.7 mg/kg/day, amphotericin B plus flucytosine 100 mg/kg/day, amphotericin B plus fluconazole 400 mg/day, or triple therapy with amphotericin B, flucytosine, and fluconazole. Amphotericin B plus flucytosine was found to be the most rapidly fungicidal combination.


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OTHER MYCOSES

Scedosporium infection in a tertiary care cancer center: a review of 25 cases from 1989–2006

This paper presents a review of the clinical manifestations and outcome of 25 cancer patients with Scedosporium infections. The infection was associated with a high mortality rate.

Scedosporium is an opportunistic dematiaceous fungus that causes serious invasive infections in patients with altered immune defenses. In addition to patients with malignancies, Scedosporium apiospermum and Scedosporium prolificans have been increasingly reported in transplant recipients.

The authors of this report present a review of 25 cases of Scedosporium infections in patients admitted to the MD Anderson Cancer Center (Houston, TX, USA) between 1989 and 2006. Most infections (n=21) were caused by S apiospermum. Interestingly, cases of S prolificans were not identified until the year 2000. Sixteen patients had disseminated disease, of whom 12 had fungemia. The disease was associated with a high mortality rate (12/18 for S apiospermum and 4/4 for S prolificans).

In a recent review, Husain and colleagues identified 80 transplant patients with Scedosporium infections [1]. The comparator group consisted of 190 patients who were also diagnosed with Scedosporium infections but were not transplant recipients. In the transplant group, 23 patients (29%) were hematopoietic stem cell transplant (HSCT) recipients while the remaining 57 patients had received solid organ transplants (SOTs). S apiospermum was more prevalent than S prolificans (76% vs. 24%). Scedosporiosis developed most commonly within the first 6 months after transplantation (64%). The vast majority of patients (96%) were receiving corticosteroids at the time of infection. Just one-third were receiving antifungal prophylaxis. The disease frequently presented as a disseminated infection (54%), with fungemia occurring in 17% of cases. When comparing transplant with non-transplant recipients, patients with hematological malignancies were at highest risk of developing disseminated infection (86%), followed by HSCT recipients (69%), HIV patients (57%), and SOT recipients (55%). The same pattern was seen for fungemia (66% with hematological malignancies, 25% with HSCT, 23% with HIV, and 16% with SOT). The mortality rate in the transplant group was 58%. Disseminated infection, fungemia, central nervous system involvement, and renal failure were associated with higher mortality rates.

Taken together, these data demonstrate that Scedosporium infections in transplant patients or in those with hematological malignancies are associated with a high rate of dissemination, and a poor outcome.


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Catheter-associated fungemia due to *Exophiala oligosperma* in a leukemic child and review of fungemia cases caused by *Exophiala* species
Al-Obaid I, Ahmad S, Khan ZU et al.

In this report, the authors describe a case of catheter-associated *Exophiala oligosperma* fungemia and provide a review of the literature. A total of 29 cases of *Exophiala* infection were identified, 14 of which had a diagnosis of malignancy. Of 23 patients who had a catheter in place, its removal was required in 20 cases. Two cases proved to be fatal; in both of these, the catheter was retained.

*Exophiala* (*Wangiella*) is a black dematiaceous fungus of the phylum Ascomycota order Chaetothyriales and is among the fungi that cause phaeohyphomycosis [1]. In addition to subcutaneous infections or mycetoma, *Exophiala* can cause disseminated infections such as fungemia and endocarditis. The authors of the current report describe the case of a pediatric patient with leukemia who developed catheter-associated fungemia caused by the demateaceous fungus *Exophiala oligosperma*. Furthermore, they review the literature, identifying 29 cases of *Exophiala* infection. Fourteen of these patients had a diagnosis of malignancy. Catheter removal was required in 20 of 23 patients who had a catheter in place. In two cases that had a fatal outcome, the catheter was retained.

The vast majority of catheter-related fungemia episodes occurring in cancer patients are due to *Candida* species [2]. However, a variety of other less common fungi have also emerged as causes of bloodstream infections in cancer patients.

*Rhodotorula* is a yeast of the family Cryptococcaceae that has been strongly associated with catheter-related infections in patients with altered immune defenses, with *Rhodotorula mucilaginosa* being responsible for the majority of cases. In a recent review of the literature, 66 cases of *Rhodotorula* fungemia were identified [3]. The most common underlying disease was malignancy in 44 patients (67%). Catheter removal was required in 77% of cases and the mortality rate was 18%.

*Trichosporon* is another opportunistic yeast that causes bloodstream infection in susceptible populations [4]. Risk factors include leukemia, neutropenia, and high-dose corticosteroid use. Trichosporonosis carries a high mortality rate exceeding 50% in cancer patients. Several other fungi have been occasionally reported to cause fungemia in cancer patients, including *Saccharomyces, Acremonium, Phialemonium, Fusarium*, and *Scedosporium*.


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### THERAPEUTICS

Issues related to the design and interpretation of clinical trials of salvage therapy for invasive mold infection
Almyroudis NG, Kontoyiannis DP, Sepkowitz KA et al.

The authors of this article review the issues related to the design and interpretation of clinical trials of salvage antifungal treatments for invasive mold infections. Patients who are refractory to standard antifungal treatments usually have a worse prognosis than those who have become intolerant; thus, the authors propose that these two groups of patients should be analyzed separately in salvage therapy studies. Furthermore, the authors suggest a composite outcome assessment to define refractory infection. Other factors, such as heterogeneity of patients and pathogenic risk factors, and the initial antifungal treatment are also discussed.

Patients who are refractory to or have developed intolerance to standard antifungal therapy are generally considered for inclusion in trials of salvage antifungal therapy. The authors of this article review issues related to the design and interpretation of such studies.

One of the common problems of salvage study design is the inclusion of standard therapy-refractory and -intolerant patients in the same group. Frequently, those who experience toxicity to initial therapy are classed as “intolerant”, and often respond well to a subsequent agent. Those who are refractory to initial therapy have a poorer outcome; thus, the authors suggest that these two groups should be analysed separately. Following on from this, problems associated with variable definitions of refractory mold infections are discussed. The authors suggest that well-defined clinical, radiological, and laboratory criteria are employed, and that the definition of refractory disease could be limited to those with evidence of disease progression in
response to standard therapy. Furthermore, they propose a composite outcome assessment for refractory disease, in which there is a worsening at least two of three criteria (clinical, radiological, and mycological), with patients assessed for ≥7 days.

A prolonged neutropenia is the major risk factor for invasive mold infection; however, many other risk factors may exist, and patients with a range of diseases (e.g. recipients of allogeneic hematopoietic stem cell transplants, advanced AIDS patients) are at risk of infection. Thus, a heterogeneous group of patients is often included in salvage studies. The authors propose that randomized studies, with specified subgroup analyses should be undertaken. Such studies would also allow subgroup analysis on specific pathogens to be performed. However, randomized studies are generally thought to be impractical due to the requirement for a large number of patients for adequate subgroup analysis. Inclusion of a contemporaneous group of control subjects (rather than a historical comparator group) should be considered as a useful alternative.

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Amphotericin B nasal lavages: not a solution for patients with chronic rhinosinusitis

The authors conducted a randomized, double-blind, placebo-controlled trial to investigate the efficacy of amphotericin B nasal lavages in the treatment of chronic rhinosinusitis. They found that amphotericin B nasal lavage was not effective in the treatment of chronic rhinosinusitis with or without nasal polyps.

In this randomized, double-blind, placebo-controlled trial patients with chronic rhinosinusitis were randomized to receive 25 mL of amphotericin B (100 μg/mL) or placebo in each nostril twice daily for 3 months. At the end of the study, amphotericin B was not more effective than placebo in improving clinical signs and symptoms in this group of patients.

These results confirm findings in other studies. For instance, in a 3-month, prospective, open trial conducted in Switzerland, nasally applied amphotericin B spray was ineffective in controlling the growth of nasal polyps [1]. Another recent study described the effect of topical antifungal therapy on nasal cell activation markers (eosinophil cationic protein and tryptase) in chronic rhinosinusitis [2]. Nasal amphotericin B treatment did not have an effect on eosinophil cationic protein or tryptase levels. Furthermore, eradication of fungal colonization did not correlate with the levels of these activation markers of nasal inflammatory cells.

However, these emerging data contradict earlier studies showing that amphotericin B nasal irrigation may influence the inflammatory process of chronic rhinosinusitis by decreasing the production of interleukin-5 (IL-5) from nasal polyps compared with normal inferior turbinates [3]. Since high IL-5 levels have been linked to the eosinophilic inflammation that characterizes chronic rhinosinusitis with nasal polyps, there has been interest in investigating the effect of anti-IL-5 therapy on the growth of nasal polyps. In a recent randomized controlled trial, Gevaert and colleagues found that a single intravenous infusion of reslizumab (humanized anti-human IL-5 monoclonal antibody) was effective in reducing the size of nasal polyps in 50% of patients who received the drug [4].

It can be concluded that specific anti-IL-5 therapy could be more effective in treating chronic rhinosinusitis than the non-specific antifungal therapy with intranasal amphotericin B.


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Several presentations at the American Society of Hematology annual meeting held in December 9–12, 2006 in Orlando, FL, USA, were devoted to invasive fungal infections in patients with hematological malignancies or hematopoietic stem cell transplantation (HSCT). Here, the most relevant of these abstracts are reported, with a focus on aspergillosis. All abstracts appeared in *Blood* 2006;108(16).

**Host defense**

Neutrophils and monocytes are key cells in the host defense against *Aspergillus* infection. Their quantitative deficiency is one of the best-known risk factors for developing invasive filamentous fungal infection. It is also accepted that functional defects of phagocytic cells, such as in chronic granulomatous diseases or in alveolar proteinosis, also expose patients to opportunistic infection. Loeffler et al. demonstrate that the activation of neutrophil oxidative burst induced by *Aspergillus* is regulated by Toll-like receptor 2 (TLR2) signaling [1]. The blockade of TLR2 by an antibody leads to a significant reduction in oxygen intermediates released by neutrophils after induction through exposure to zymosan or to *Aspergillus*.

**Diagnostics**

Mycological confirmation of an invasive fungal infection is often lacking in neutropenic patients despite the availability of an *Aspergillus* galactomannan detection test in most centers and a recent update of diagnosis criteria. Detection of a 1,3-β-D-glucan antigen in serum has been used for many years in Japan, but few centers in Western countries have experience of using this test. 1,3-β-D-glucan is a cell wall component of most fungal pathogens, with the exception of *Cryptococcus* and *Zygomycetes*. Senn et al. monitored 1,3-β-D-glucan levels in 189 episodes of neutropenia following induction or consolidation chemotherapy for acute leukemia [2]. From a total of 320 febrile episodes, 31 invasive fungal infections were diagnosed according to the European Organization for Research and Treatment of Cancer/Mycoses Study Group (EORTC/MSG) criteria. A median of 15 samples was analyzed per episode of neutropenia. In patients with invasive candidiasis, the median time between onset of fever – as the first sign of invasive fungal infection – and 1,3-β-D-glucan positivity was 0 days (range –3 to +17 days); this contrasted with 16 days (range 0 to +51 days) until diagnosis of infection using conventional microbiological and imaging techniques. In patients with invasive aspergillosis, the median time to 1,3-β-D-glucan positivity was 3 days (range –9 to +14 days) compared with a diagnosis at a median of 7 days (range +1 to +21 days) using conventional methods. Overall, the sensitivity and specificity of the test were 76% and 89%, respectively, using a 5-pg/mL cut-off value for 1,3-β-D-glucan, and 38% and 99%, respectively, using a cut-off of 11 pg/mL. This study demonstrates, in a large number of patients at high risk for fungal infection, the clinical utility of a 1,3-β-D-glucan detection test as an additional diagnostic tool in febrile neutropenia episodes.

**Breakthrough fungal infections**

Trifilio et al. reported their experience with the prophylactic use of voriconazole in 71 allogeneic HSCT recipients [3]. The patients received voriconazole prophylaxis as they were at very high risk of invasive aspergillosis infection (history of a previous episode or steroid therapy due to graft-versus-host disease [GVHD]). The length of voriconazole therapy was 6–956 days (median 133) with a total number of patient-days on voriconazole of 13 805. A total of 10 breakthrough invasive fungal infections were observed. *Candida glabrata* was the most common pathogen (n=5) followed by *Rhizopus* spp. (n=2), *C krusei*, *Mucor* sp. and *Cunninghamella* sp. (one
of each). The 1-year probability of breakthrough invasive fungal infection was estimated to be 18%. No *Aspergillus* infections were observed. All patients who developed a *Candida* breakthrough infection had steady-state trough serum levels of voriconazole of <-2 μg/mL. The authors conclude that:

- Voriconazole shows excellent efficacy in the prevention of aspergillosis.
- Zygomyces and *C. Glabata* breakthrough infections are a concern in voriconazole-treated patients, although the incidence is low.
- Serum levels of voriconazole should be monitored in order to reduce the possibility of breakthrough infections with fungi that would otherwise be susceptible to voriconazole.

**Treatment strategies**

Empiric antifungal therapy is a well-accepted strategy in neutropenic patients who have persistent fever. Recent improvements in the diagnosis and treatment of invasive fungal infections suggest that preemptive therapy may be a more cost-effective strategy, with fewer patients receiving excessive treatment and no decrease in efficacy. Cordonnier et al. compared the two therapeutic strategies in patients at high risk for fungal infection [4]. A total of 293 adult patients with an expected prolonged severe neutropenia were randomized to receive empiric therapy (neutropenia and persistent fever) or preemptive therapy (onset of antifungal therapy only in the case of pneumonia, severe mucositis, septic shock, sinusitis, skin lesions suggesting filamentous fungal infection, *Aspergillus* colonization, or a positive galactomannan test). The primary endpoint of survival was not inferior in the preemptive therapy arm (136/143) compared with the empiric therapy arm (147/150). Although more fungal infections were diagnosed in the preemptive therapy arm (13/143 vs. 4/150; p<0.02) the fungal infection-related mortality rate was similar in both arms (three in the preemptive therapy arm and none in the empiric therapy arm). An economic analysis was performed in the same set of patients by Schwarzinger et al. [5]. Total medication costs were computed from individual patient records during their hospital stay. Overall, medication costs were not different in both arms. However, an analysis according to the type of chemotherapy (induction versus consolidation) showed a significant decrease in cost of preemptive therapy during consolidation chemotherapy (€1387 vs. €2610 for empiric therapy; p<0.02) but not during induction chemotherapy (€5714 vs. €4793; non significant). The difference could be explained by a higher invasive fungal infection rate during induction chemotherapy than during consolidation treatment in the preemptive therapy arm (16.4% and 1.4%, respectively) while the rates were similarly low in the empiric therapy arm (3.9% and 1.4%, respectively). Therefore, it can be concluded from these two presentations that there is no overall difference between both strategies in terms of survival rates, but also that, unexpectedly, there is no decrease in medication costs using the preemptive treatment strategy compared with the empiric strategy.

Recently published trial results demonstrated the superiority of posaconazole over fluconazole in the prophylaxis of proven or probable invasive aspergillosis in patients with GVHD, and in preventing invasive fungal infections and reducing overall mortality rate in high-risk neutropenic patients [6,7]. Thus, O’Sullivan et al. conducted a separate cost-effectiveness analysis of antifungal prophylaxis (from a US perspective) in high-risk neutropenic patients [8]. Posaconazole was found to be associated with slightly lower costs (US$4887 vs. US$5070) per patient compared with standard azole therapy over a lifetime perspective. Further sensitivity analyses demonstrated that there was a 75% probability of posaconazole being cost saving compared with standard azole therapy. The authors concluded that posaconazole is likely to be more cost-effective than standard azole therapy in the prophylaxis of invasive fungal infections in high-risk neutropenic patients.

Barron et al. retrospectively assessed compliance with published guidelines for prevention of fungal infection in 242 HSCT recipients hospitalized in 13 US hospitals [9]. Fifty-seven percent of the patients were classified as high risk for invasive fungal infection. Overall, 85% of the patients received antifungal prophylaxis, with no difference between the proportions of those at high risk and low risk of invasive fungal infections receiving prophylaxis (84% and 86%, respectively). The majority of patients received fluconazole (84%). Compliance with national guidelines for antifungal prophylaxis was low, at only 54%. Prophylaxis failed in 29% of the high-risk patients and in 6% of the low-risk patients. This study demonstrated a poor compliance with guidelines and the authors stated that prophylaxis was both under- and over-utilized. The reasons for poor adherence to guidelines were not identified in this study.

**Monitoring of plasma levels of antifungal agents**

Plasma levels of newer azoles may differ significantly between patients. Explanations for these differences include variability in oral bioavailability, genetic polymorphisms in cytochrome isoenzymes, and drug–drug interactions. Data on plasma levels of antifungals are scarce in clinical practice. Trifilio et al. monitored voriconazole levels in patients with...
hematological malignancies, mostly allogeneic HSCT recipients, receiving 400–800 mg/day (2.0–16.3 mg/kg) oral voriconazole [10]. Steady-state plasma levels of voriconazole were measured after ≥5 days of therapy. Median plasma levels were 1.2 μg/mL (range undetectable to 12.5 μg/mL). Fifteen percent of the patients had undetectable levels of voriconazole in plasma and an additional 12% had levels between 0.2 and 0.5 μg/mL. According to published data suggesting a higher efficacy in patients achieving plasma levels >0.5 μg/mL [11], 27% of the patients treated orally with voriconazole did not achieve optimal levels. Nonlinear pharmacokinetics does not allow prediction of plasma levels from the daily dose. In another presentation (discussed earlier), the same group related low plasma levels of voriconazole to breakthrough Candida infections [3]. Although there was no correlation between plasma levels and efficacy or adverse events in this presentation, this study strongly suggests that monitoring the plasma levels of voriconazole to avoid subtherapeutic levels in a substantial proportion of patients at high risk of severe invasive fungal infections be made.

Outcome

Woods et al. proposed the Aspergillus galactomannan detection test as a surrogate marker of outcome in invasive aspergillosis [12]. Thirty patients, mostly myeloma patients, with respiratory tract aspergillosis tested positive for the Aspergillus-specific polysaccharide galactomannan. Among 25 neutropenic patients, the persistence of a positive galactomannan test was associated with death (five deaths out of five cases), while a return to a negative value predicted survival (20 patients surviving out of 20 cases). Similarly, a correlation was found in non-neutropenic patients (one death with persistent positive galactomannan test and no deaths in four patients whose galactomannan test became negative). This study confirms the previously reported correlation between a persistent positive galactomannan and a poor outcome [13]; however, it does not address the issue of lack of sensitivity of galactomannan testing at baseline, and thus, it cannot be considered as a unique outcome assessment of invasive aspergillosis.

Nivoix et al. presented a multivariate analysis of pretreatment prognosis factors for survival in 303 oncohematological patients with possible, probable, or definite invasive aspergillosis [14]. Most patients had acute leukemia, HSCT, or hematological malignancy. Twenty-one patients had a non-malignant disease. Overall, the 12-week survival rate was 52.3%. Nine factors were found to be associated with a poor overall survival: allogeneic HSC or solid organ transplantation, progression of underlying cancer, prior noninfectious respiratory disease, steroid therapy (doses of ≥0.2 mg/kg), renal impairment, a low monocyte count, pleural effusion, dissemination of the aspergillosis, and probable or proven aspergillosis (compared with possible cases). This is the largest study on prognosis factors that has been performed in a nonselected patient population to date. It underscores the importance of some factors not previously associated with a poor outcome in invasive aspergillosis, such as steroid therapy, renal impairment, or the presence of noninfectious respiratory disease.

Disclosures

Professor Herbrecht has received grants/honoraria from Astellas, Gilead, Merck Sharp & Dohne, Pfizer, Schering-Plough, and Zeneus Pharma. Dr Berceau has no relevant financial interests to disclose.

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6. Ullmann AJ, Lipton JH, Vesole DH et al. Posaconazole or fluconazole for prophylaxis in noninfectious respiratory disease, steroid therapy (doses of ≥0.2 mg/kg), renal impairment, a low monocyte count, pleural effusion, dissemination of the aspergillosis, and probable or proven aspergillosis (compared with possible cases). This is the largest study on prognosis factors that has been performed in a nonselected patient population to date. It underscores the importance of some factors not previously associated with a poor outcome in invasive aspergillosis, such as steroid therapy, renal impairment, or the presence of noninfectious respiratory disease.

References

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References

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27–29
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9–13
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