Drugs 2008; 68 (14): 1941-1962
0012-6667/08/0014-1941/$53.45/0

Patients at High Risk of Invasive Fungal Infections

When and How to Treat

Maria J.G.T. Rüping,[1] *Jörg J. Vehreschild*[1] and *Oliver A. Cornely*[1,2]

1 Department I of Internal Medicine, Clinical Trials Unit Infectious Diseases II, Hospital of the University of Cologne, Cologne, Germany
2 Clinical Trials Center Cologne, Hospital of the University of Cologne, Cologne, Germany

Contents

Abstract

When and how to treat invasive fungal infections (IFIs) is discussed in this review, with a focus on the two most prevalent non-endemic IFIs, namely invasive aspergillosis and invasive candidiasis. Early treatment initiation in patients with IFIs has a profound impact on mortality rates, but reliable diagnostic measures are lacking. This situation has led to the parallel use of different treatment strategies, e.g. prophylaxis, empirical and pre-emptive treatment, as well as targeted treatment in response to a definite diagnosis of IFI. Identifying high-risk patients is the first step in reducing IFI-related mortality. Patients at risk of invasive aspergillosis

comprise (i) those with acute myelogenous leukaemia (AML) or myelodysplastic syndrome (MDS) during remission induction chemotherapy; (ii) patients undergoing allogeneic haematopoietic stem cell transplantation (HSCT); (iii) recipients of solid organ transplants; and (iv) those with other conditions of severe and prolonged immunosuppression. Patients at high risk of invasive candidiasis are less well defined. Risk factors are diverse and include haematological malignancy, neutropenia, age <1 month or >65 years, and recent abdominal surgery. The individual risk further depends on the presence of a variety of other risk factors, including central venous catheters, use of broad spectrum antibacterials, prolonged intensive care unit (ICU) stay, total parenteral nutrition, mucosal *Candida* spp. colonization and renal failure.

Extensive research has been conducted to facilitate the best possible treatment strategies for these severe infections. Optimal timing and choice of antifungal agents largely remain a matter of controversy. After having reviewed the major clinical trials, we conclude that comparisons between different treatment strategies cannot be made, neither at present nor in the near future. The complexity of the clinical problem leads to an eclectic treatment approach to reduce morbidity and mortality from IFIs without compromising tolerability. We recommend prophylaxis with posaconazole for allogeneic HSCT recipients, patients receiving induction chemotherapy for AML or MDS, and those undergoing immunosuppressive therapy for graft-versus-host disease after allogeneic HSCT. For the empirical treatment of persistently febrile neutropenia, caspofungin is our first- and liposomal amphotericin B deoxycholate (LAmB) our second-line choice. Once a diagnosis of invasive aspergillosis has been established, voriconazole should be the preferred treatment option, with LAmB being an alternative. Fluconazole prophylaxis for invasive candidiasis should remain restricted to high-risk ICU patients. Once a diagnosis has been established, the drug of choice for adequate treatment depends largely on neutrophil count and haemodynamic stability. In non-neutropenic patients, an echinocandin should be considered the first-line treatment option, while patients with susceptible *Candida* spp. may be switched to fluconazole. In neutropenic patients, caspofungin or micafungin might be preferred to anidulafungin as first-line treatment. LAmB is a second-line treatment option in both settings.

Early diagnosis of IFIs is imperative to facilitate treatment success. In all patients at risk for IFIs, blood cultures, galactomannan antigen and diagnostic imaging should be rigorously enforced.

1. Invasive Fungal Infections

1.1 Scope of Invasive Fungal Infections in Clinical Practice

Patients with inadequately treated invasive fungal infections (IFIs) have a poor prognosis. Intensively pretreated patients with multiple organ dysfunctions, as well as severely or long-term immunosuppressed patients, are particularly at risk. IFI in otherwise healthy patients are extraordinarily rare. In this sense, all IFIs can be regarded as opportunistic diseases.

Two fungal pathogens are of particular interest, i.e. *Aspergillus* spp. and *Candida* spp. They probably account for over 95% of all IFIs.[1-3] The remaining infections are due to a variety of fungal pathogens, with *Pneumocystis jiroveci*, Zygomycetes and *Fusarium* spp. leading the field of the so-called 'rare' fungal infections, followed by *Scedosporium* spp., *Penicillium* spp. and numerous others.[4,5] The epidemiology of these species is

largely unknown, but dramatic local and regional differences have been reported, rendering some of them important differential diagnoses in different parts of the world. Adequate coverage of these regional variations is, however, beyond the scope of this article. We aim to identify treatment strategies, risk groups and diagnostic criteria, before presenting the available evidence from clinical trials, currently serving as the basis for our treatment recommendations.

1.2 Treatment Strategies

When treating patients at risk for invasive aspergillosis or invasive candidiasis, clinicians must decide when and how to intervene. Timing and circumstances of treatment initiation are defined by the terms prophylactic, empirical, pre-emptive and targeted treatment (figure 1). Prophylactic treatment refers to the preventive administration of an antifungal agent to patients at risk of an IFI without attributable signs and symptoms. Empirical treatment is defined as the initiation of antifungal treatment in patients at high risk of an IFI and established clinical signs and symptoms, but without pathogen identification. In former definitions of treatment strategies, radiographic signs used to be allocated to the empirical treatment situation.[6-8] This concept has changed. Today, radiographic signs and/or laboratory tests that yield a result suspect of a IFI in a high-risk host, without definitive verification by histopathology and/or culture of the causal pathogen, are considered surrogate markers for the initiation of pre-emptive treatment. This definition also includes nonspecific infiltrates on chest CT scans. If diagnostic criteria allowing pathogen identification – i.e. culture from a physiologically sterile site or histopathological evidence of an IFI – have been fulfilled, targeted therapy is initiated.

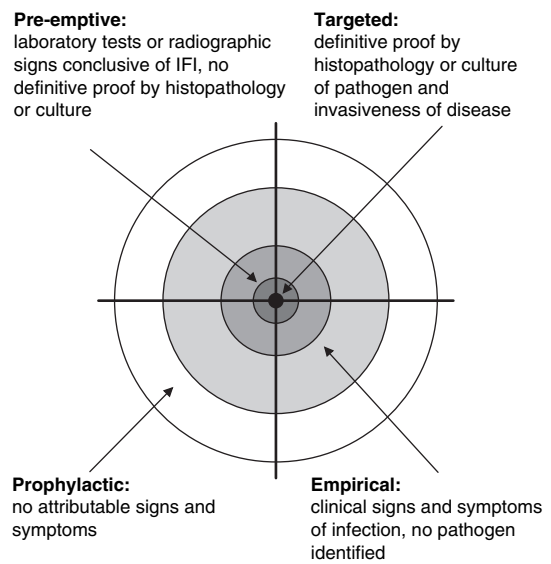

Fig. 1. Antifungal strategies for patients at high risk of invasive fungal infection (IFI).

Many readers may be wondering whether such a multitude of treatment strategies is really necessary. Why not just use voriconazole for aspergillosis[9] and caspofungin for candidiasis?[10] The evidence base for these choices is adequate but a generalized approach is not justified for several reasons. To begin with, only a minority of all IFIs can be proven *ante mortem*. Diagnostic measures with a high sensitivity often show a lower specificity, allowing diagnosis of only probable or possible IFI.[11,12] Considering the poor performance of diagnostic markers, combined with the reduced chances of a successful outcome associated with delays in the administration of antifungal treatment, the increasing popularity of prophylactic strategies comes as no surprise. However, they narrow therapeutic options and mean overtreating patients who would not have developed a IFI.[13] Until reliable diagnostics become available, we need to analyse epidemiological data to identify patient-related and external risk factors, and set up risk stratification systems. The aim of such systems is to identify high-risk patients who may benefit from prophylactic, empirical or pre-emptive treatment strategies, the efficacy of which can then be assessed in clinical trials.[11]

1.3 Risk Groups

1.3.1 Invasive Aspergillosis

Three major groups are at high risk for invasive aspergillosis: (i) patients with haematological malignancy; (ii) recipients of solid organ transplants; and (iii) a heterogeneous group of otherwise immunosuppressed patients.

Prolonged and profound neutropenia, i.e. >10 consecutive days with neutrophil cell counts

<500/μL, is the single most important risk factor for invasive aspergillosis, thus concerning mainly patients with acute leukaemia or myelodysplastic syndrome (MDS) during remission induction chemotherapy and patients undergoing allogeneic haematopoietic stem cell transplantation (HSCT). The risk of invasive aspergillosis reaches 24%[1,14,15] in the former and 10%[15-19] in the latter group. Following the chronology of the individual patient with acute leukaemia or MDS, the first period of substantial risk of acquiring an IFI is the time until first remission. In patients who are not responding to chemotherapy or who are at a high risk of relapse from leukaemia, allogeneic HSCT is pursued, if suitable, and a donor is found. For these patients, the next high-risk period follows with the conditioning chemotherapy regimen and subsequent neutropenia. Additional immunosuppressants, such as ciclosporin, tacrolimus, corticosteroids and antithymocyte globulin, further impair the patient's host defence mechanisms. Once neutropenia is overcome, graft-versus-host disease (GvHD) may require further escalation of immunosuppressive treatment.

If left untreated, the mortality rate of invasive aspergillosis approaches 100% in this population. Even with antifungal treatment, overall mortality rates range between 30% and 40% for acute myelogenous leukaemia (AML) patients and reach 60% in recipients of allogeneic HSCT.[14,20-22]

Solid organ transplant recipients are another group at high risk of invasive aspergillosis. Because of the intensified use of immunosuppressive agents, graft survival rates have improved substantially, leading to a constant expansion of this population. Improvements of graft survival have been paralleled by a decline of mortality from infectious complications. Nevertheless, the rate of infectious complications, including invasive aspergillosis, now represents one of the major limiting factors to disease-free survival in these patients.[23-26]

Invasive aspergillosis incidence rates are highest among heart-lung and small bowel transplant recipients, ranging between 11% and 14%.[19,27] In lung transplant recipients, the common form of invasive pulmonary aspergillosis constitutes only one-third of all invasive aspergilloses. A unique form of ulcerative tracheobronchitis accounts for 37% and invasive aspergillosis of the area of bronchial anastomosis for another 20%.[28] In liver transplant recipients, incidence rates approaching 8% have been reported,[29-32] while rates <1% have been reported from recipients of renal transplants.[19,27]

Invasive aspergillosis in solid organ transplant recipients typically occurs at least 1 month post-transplant.[26,33] While survival rates among patients with invasive aspergillosis after liver transplantation have improved from 10% to 40% during the past decade,[34] mortality rates of 70% and 100% have been reported for lung and small bowel transplant recipients, respectively.[27]

Finally, there is a heterogeneous group of patients at high risk of contracting invasive aspergillosis whose state of immunosuppression is not related to a haematological malignancy or solid organ transplantation. In patients with AIDS, who are not receiving antiretroviral therapy, incidence rates of 12% have been observed.[15,35] Severe burns have been associated with incidence rates of up to 7%.[36-38] Nonmyeloablative chemotherapy with purine analogues is often used in the treatment of chronic lymphocytic leukaemia. In patients receiving a conditioning regimen with fludarabine, a significantly increased risk of IFI has been reported.[39,40] Data on the risk of IFI after therapy with other purine analogues, e.g. cladribine and pentostatin, are scarce and allow no valid conclusions on the associated risk of IFI. In contrast, after treatment of relapsed or refractory lymphoma with alemtuzumab – a CD52 antibody that causes profound T-cell suppression – invasive aspergillosis rates of 4–7% have been reported.[41,42] An incidence rate of 5.8% has been reported from a medical intensive care unit (ICU). In this population, invasive aspergillosis seems to occur mainly in patients with less obvious immunological derangements, such as malnutrition, chronic obstructive pulmonary disease, liver failure or corticosteroid use.[43,44] Under these circumstances, distinguishing between colonization and infection with *Aspergillus* spp. remains a major problem that probably leads to underestimation of the true incidence of invasive aspergillosis in the ICU. This is particularly troublesome, as mortality rates in these patients are as high as 80%.[44]

1.3.2 Invasive Candidiasis

Candida spp. are considered the single most important cause of opportunistic fungal infections worldwide[2] and the fourth most common cause of nosocomial bloodstream infections in the US, accounting for 8–10% of all isolates.[45] Population-based studies have revealed significant differences in local incidence rates of invasive candidiasis. While studies in Norway, Spain, Iceland, Canada and Finland documented incidence rates no higher than 5 infections per 100 000/year,[46-50] investigators from the US states of Iowa, Georgia, Connecticut and California, and Denmark reported between 6 and 11 infections per 100 000/year.[51-54] A study from Maryland showed an even higher rate of 24 infections per 100 000/year.[54] These data coincide with US national incidence rates. In the absence of significant differences in data collection and analysis between these studies, the pronounced variation in local incidence rates may reflect contrasting regional conditions in terms of demography and medical practice, in particular the use of intravascular catheters, as well as antibacterial and antifungal agents.[46,50,55] Mortality rates for invasive candidiasis average 0.4 deaths per 100 000/year.[2]

Typically, at least one of the following underlying conditions can be observed in patients with invasive candidiasis: (i) recent gastrointestinal surgery; (ii) age <1 month or >65 years; or (iii) haematological malignancy/neutropenia.[54,56-62] However, patients belonging to one of these groups may differ significantly in their individual risk for invasive candidiasis, depending on the presence of additional risk factors, such as a central venous catheter, use of broad spectrum antibacterials, prolonged ICU stay, total parenteral nutrition, mucosal colonization with *Candida* spp. and/or renal failure.[46,53,54,58,62-68] In this sense, the individual risk for invasive candidiasis must be regarded as a cumulative phenomenon. In order to adapt risk stratification to this concept, different authors have developed scoring systems for the identification of high-risk patients (table I).[66,69-72]

Such scoring systems will probably drive clinical trial design, as they allow a more accurate selection of patients at high risk of invasive candidiasis who might profit from prophylaxis or pre-emptive treatment.

Recently, changes in the epidemiology of invasive candidiasis have aroused considerable attention. According to Pfaller and Diekema,[2] 90% of all cases are caused by *C. albicans*, *C. glabrata*, *C. parapsilosis*, *C. tropicalis* or *C. krusei*. Even though *C. albicans* remains the leading pathogen, causing 62% of all invasive candidiases, *C. glabrata* has become an important emerging pathogen in the US, ranking second to *C. albicans* and with reported incidence rates of 20–24% of all *Candida* bloodstream infections.[2] In other countries, the incidence of *C. glabrata* has not increased to the same extent. A number of surveys conducted in Europe[49,50,73-75] and Asia[76,77] have shown incidence rates of 10–14%. Particularly low rates of 4–7% have been reported from Latin America.[78,79] *C. glabrata* displays an at best dose-dependent susceptibility to fluconazole as well as lower response rates to amphotericin B compared with *C. albicans*.[80,81] *C. glabrata* has been associated with particularly high mortality rates.[82]

C. krusei is reported with a far lower worldwide incidence rate than *C. glabrata*, but is inherently resistant to fluconazole.[83,84] Increasing use of fluconazole prophylaxis has been held responsible for this development. Other non-*albicans Candida* infections, especially *C. tropicalis* (4.6–7.5%) and *C. parapsilosis* (4.2–7.3%) have also increased between 1997 and 2003,[83] and during the past decade, many new *Candida* spp. have been isolated from clinical specimens, yielding a total of >500 currently known *Candida* spp.[85]

1.4 Diagnostic Criteria

The definition of diagnostic criteria is an important factor significantly influencing the timing and choice of treatment. The most commonly used criteria for the diagnosis of invasive aspergillosis and invasive candidiasis are briefly reviewed in this section.

The diagnosis of invasive aspergillosis should be made in accordance with the recently published revised consensus criteria of the European Organisation for the Research and Treatment of Cancer and the Mycoses Study Group (EORTC/MSG),[11,86] requiring histopathological, cytopathological or direct microscopic examination of a specimen obtained by needle aspiration or biopsy in which hyphae or

Table I. Rules for identifying patients at an increased risk of infection with *Candida* spp.

Study (year)	Approach	Inclusion criteria	n	Best rule identified	% of IC cases identified	Sensitivity; specificity	PPV; NPV	NNT
Paphitou et al. [66] (2005)	Prophylaxis	Surgical ICU >4 days	1251 screened 327 included	No antifungal use during day −7 to 3 plus any combination of DM, receipt of TPN (day 7–0), new onset haemodialysis (day 7–3) or use of broad-spectrum antibacterial therapy	78–83	NA	NA	12-19
Ostrosky-Zeichner et al. [70] (2007)	Prophylaxis	Medical and/or surgical ICU >4 days; no systemic antifungal agents during day −7 to 3	2890 included	Any antibacterial use (day 1–3) or CVC (day 1–3) and at least two of the following: any major surgery (day −7 to 0); immunosuppressive use (day −7 to 0); pancreatitis (day −7 to 0); TPN (day 1–3); any dialysis (day 1–3); corticosteroid use (day −7 to 3)	34.1	34%; 90%	9.9%; 97%	NA
Pittet et al.[71] (1994)	Pre-Emptive	Colonization with *Candida* spp., defined as detection in three or more samples taken from the same or different body sites on at least two consecutive screening days	650 screened 29 included	*Candida* CI: no. of nonblood DBS colonized by *Candida* spp./total no. of DBS cultured	NA	100%; 69%	66%; 100%	NA
				Corrected CI: CI × no. of DBS showing heavy growth/total of DBS growing *Candida* spp.	NA	100; 100	100; 100	NA
Dupont et al.[72] (2003)	Empirical	ICU with peritonitis	221 retrospective cohort 57 prospective cohort	Risk categories A–D (A = zero or one RF, B = at least two RF, C = at least three RF, and D = four RF). Applicable RF: female sex, upper gastrointestinal tract origin of peritonitis, intraoperative cardiovascular failure, and previous antimicrobial therapy at least 48 h before onset of peritonitis	71	84%; 50% (category C)	67%; 72% (category C)	NA
Leon et al.[69] (2006)	Empirical	Medical and/or surgical ICU ≥7 days	1699	1 point: TPN, surgery, or multifocal *Candida* spp. colonization. 2 points: clinically severe sepsis. Cut-off value: 2.5	NA	81%; 74%	NA	NA

CI = colonization index; **DBS** = distinct body sites; **DM** = diabetes mellitus; **IC** = invasive candidiasis; **ICU** = intensive care unit; **NA** = not available or applicable; **NNT** = number needed to treat; **NPV** = negative predictive value; **PPV** = positive predictive value; **RF** = risk factor; **TPN** = total parenteral nutrition.

melanized yeast-like forms are seen accompanied by evidence of associated tissue damage. In the absence of these findings, pathogen isolation from a sterile body fluid or tissue obtained by an invasive procedure in the presence of compatible clinical symptoms may serve to establish the diagnosis. Most patients at risk for invasive aspergillosis present with thrombocytopenia after chemotherapy and a significantly reduced general condition. Under these circumstances, invasive procedures are often deemed too risky and replaced by an eclectic diagnostic approach involving host factors, clinical features and myocological evidence. While the diagnosis of 'probable' invasive aspergillosis requires the presence of one criterion from each category, the diagnosis may be termed 'possible' invasive aspergillosis in the absence of myocological evidence.

Host factors have been defined as a recent history of neutopenia, HSCT, prolonged use of corticosteroids, treatment with T-cell immunosuppressants or purine analogues, as well as inherited severe immunodeficiencies. Microbiological criteria include direct detection of a mold by microscopy, cytology or positive culture of a sample obtained from bronchoalveolar lavage, sputum or sterile body fluids. Alternatively, indirect methods, such as the detection of β-D-glucan in serum, or of galactomannan in serum, plasma, bronchoalveolar lavage or cerebrospinal fluid are accepted. Clinical factors include a number of radiological findings, such as the halo sign, air crescent sign or cavitation in an area of consolidation on chest CT scans, focal lesions or meningeal enhancement on MRI or CT scans of the CNS, as well as any radiological finding indicative of sinusitis. EORTC/MSG criteria for the diagnosis of invasive aspergillosis have been subject to discussion and modification in the process of clinical trial design. We discuss these modifications in section 2.

Diagnosing invasive aspergillosis in ICU patients not meeting EORTC/MSG host criteria can be challenging. Radiological criteria, including the halo or air crescent sign, which are highly suggestive of invasive aspergillosis in the neutropenic and thrombocytopenic patient,[87] are found in only 5% of ICU patients with invasive aspergillosis. Even if present, they are not as specific in this population.[88] A positive culture from respiratory specimens is a frequent diagnostic clue,[89] but is found in only half of all patients with invasive aspergillosis.[90] Direct microscopic examination of respiratory samples may be helpful in distinguishing colonization from infection in these patients. Demonstration of septate hyphae is significantly higher in infected patients than in colonized patients.[91]

Serological testing based on the detection of circulating fungal cell wall components, such as galactomannan, have not been systematically studied for the diagnosis of invasive aspergillosis in the ICU, but may have a low sensitivity [44,92,93] and a high rate of false-positive results.[94]

The EORTC/MSG consensus criteria for the diagnosis of invasive aspergillosis are equally applicable to the diagnosis of invasive candidiasis. However, in clinical practice, most diagnoses of invasive candidiasis are established after isolation of yeasts from blood cultures. The presence of progressive retinal exudates on ophthalmological examination or small target-like abscesses (bull's eye lesions) in the liver or spleen within 2 weeks of an episode of candidaemia is highly suggestive of chronic disseminated candidaemia.

2. Evidence from Clinical Trials

2.1 Invasive Aspergillosis

2.1.1 Prophylaxis

Fluconazole and itraconazole are popular choices for antifungal prophylaxis in neutropenic patients, although few data support their efficacy.[12] In 2005, a meta-analysis revealed itraconazole might be more effective than fluconazole, probably due to its broader spectrum of activity.[95] Shortly afterwards, an open-label, randomized, parallel group, multicentre trial was published, comparing itraconazole oral solution 2.5 mg/kg twice daily (n = 248) with fluconazole oral solution or capsules 400 mg/day (n = 246) in patients with anticipated profound neutropenia. For the itraconazole and fluconazole arm, efficacy analysis yielded IFI rates of 1.6% and 2.0%, and mortality rates of 0.8% and 1.2%, respectively. There was no significant difference in the total number of adverse events between the two groups. The authors concluded that itraconazole and fluconazole were equivalent options in the prophy-

lactic treatment of neutropenic patients with haematological malignancies.[96]

With regard to the limited spectrum of early generation azole activity, and the unreliable bioavailability and inadequate tolerability of itraconazole, subsequent clinical trials evaluated posaconazole, an oral azole with *in vitro* activity against a wide spectrum of medically important fungi.

A randomized, multicentre trial compared antifungal prophylaxis with oral solutions/suspensions of posaconazole 200 mg three times daily (n = 304) versus itraconazole 200 mg twice daily (n = 58) or fluconazole 400 mg/day (n = 240) in patients receiving remission induction chemotherapy for AML or MDS. Prophylaxis was initiated with the first cycle of chemotherapy and was continued until complete remission of the underlying malignancy, or at the occurrence of an IFI or at 12 weeks, whichever event occurred first. If further induction chemotherapies were given, patients commenced the assigned prophylactic azole. The primary endpoint was defined as the incidence of proven or probable IFI during prophylaxis. The original EORTC/MSG criteria[11] were used for the diagnosis of invasive aspergillosis. Seven patients (2%) in the posaconazole arm and 25 patients (8%) in the fluconazole or itraconazole arm were diagnosed with proven or probable IFI ($p < 0.001$). Posaconazole fulfilled the predefined statistical criteria for superiority over the standard azole approach. Similarly, survival was significantly improved in the posaconazole group ($p = 0.04$). The overall number of serious adverse events was not significantly different between the groups.[97]

Subsequently, another trial on systemic antifungal prophylaxis with voriconazole in the same patient group was discontinued, as randomization against placebo seemed unethical regarding the reduced mortality by posaconazole prophylaxis. Although only 25 patients (10 with voriconazole and 15 with placebo) were recruited before termination, it showed an interesting (although not statistically significant) reduction in the incidence rates of pulmonary infiltrates (0% vs 33%) and hepatosplenic candidiasis (0% vs 26.7%) by administration of voriconazole prophylaxis.[98]

In an historical comparison among patients (n = 95) receiving induction chemotherapy for AML or MDS, infection rates prior to and following introduction of posaconazole prophylaxis were analysed. After the introduction of posaconazole prophylaxis, significant reductions in the incidence rates of lung infiltrates (65% vs 26%; $p < 0.001$), typical imaging findings of IFI (33% vs 8%; $p < 0.01$) and probable/proven IFI (18% vs 3%; $p = 0.04$) were observed.[99]

In patients undergoing allogeneic HSCT, landmark trials by Goodman et al.[100] and Slavin et al.[101] established oral fluconazole prophylaxis 400 mg/day for at least 75 days after transplantation by demonstrating a significant reduction in overall mortality. A recent multicentre, randomized, double-blind trial performed by Wingard et al.[102] compared oral fluconazole 400 mg/day with oral voriconazole 200 mg twice daily for the prophylaxis of IFIs in 600 standard-risk allogeneic HSCT patients receiving full-intensity conditioning regimens. Prophylactic treatment was administered for 100 days. If, at the end of this period, patients were still receiving prednisone at 1 mg/kg/day or had a CD4+ cell count <200/μL, treatment was continued until day 180. The primary endpoints were defined as absence of a IFI and fungal-free survival. There was no significant difference in the rates of proven, probable and presumptive IFI, and fungal-free and overall survival between the two groups. There was a trend towards fewer invasive aspergillosis in the voriconazole arm.

With regard to the increased risk of invasive aspergillosis in patients receiving immunosuppressives for severe GvHD, a recent trial by Ullmann et al.[103] compared posaconazole 200 mg three times daily with fluconazole 400 mg/day for efficacy, safety and tolerability in the prevention of IFIs. A total of 600 patients receiving intense immunosuppressive therapy were included. At 112 days, posaconazole and fluconazole were found to be equally efficacious in preventing IFIs (incidence, 5.3% and 9.0%, respectively; $p = 0.07$), while posaconazole was superior in preventing invasive aspergillosis ($p = 0.006$) and improving attributable survival rates ($p = 0.046$).

2.1.2 Empirical Treatment

For empirical treatment of IFIs in patients with haematological malignancies undergoing chemotherapy, amphotericin B deoxycholate (D-AmB)

was long considered the gold standard. Walsh et al.[6-8] published three major randomized trials that challenged this concept. In all three trials, similar composite endpoints consisting of defervescence during neutropenia, survival, successful treatment of baseline fungal infections, prevention of breakthrough infection, and absence of early discontinuation due to adverse effects were used.[6-8]

The first of these trials was a randomized, double-blind, multicentre study comparing D-AmB (n = 344) and liposomal amphotericin B (L-AmB; n = 343). Treatment success and survival rates were similar in both groups, but breakthrough infections occurred in only 11 patients (3.2%) in the L-AmB group and in 27 patients in the D-AmB group ($p = 0.009$). Furthermore, only 19% of patients treated with L-AmB experienced nephrotoxic effects, compared with 34% of those treated with D-AmB ($p < 0.001$). In conclusion, L-AmB was found to be as effective as D-AmB, but was associated with a lower rate of breakthrough infections and a more favourable toxicity profile.[6]

In the subsequent open-label, randomized, multinational, multicentre trial, voriconazole (n = 415) was compared with the new gold standard L-AmB (n = 422). Overall success rates were 26% for voriconazole and 30.6% for L-AmB. Noninferiority criteria were not met. However, only eight patients (1.9%) in the voriconazole group had breakthrough infections, compared with 21 patients (5%) in the L-AmB group ($p = 0.02$), and infusion-related reactions and nephrotoxicity were reported with a significantly lower frequency compared with the voriconazole arm. On the other hand, patients receiving voriconazole also experienced more episodes of transient visual changes and hallucinations.[7] The question remains unanswered whether the trial design was unfavourable for voriconazole.[104,105]

The third trial was a double-blind, multinational, noninferiority trial on 1095 patients with haematological malignancies (94.2%), who were randomized to receive either caspofungin (n = 556) or L-AmB (n = 539). Overall success rates were 33.9% and 33.7%, respectively. Thus, caspofungin results fulfilled statistical criteria for noninferiority. Analysis of secondary endpoints revealed that caspofungin was associated with a higher success rate in baseline fungal infections, an improved overall survival, and with fewer premature treatment discontinuations due to adverse events.[8]

A randomized controlled trial comparing the empirical use of intravenous and oral itraconazole (n = 179) versus D-AmB (n = 181) in neutropenic cancer patients showed response rates of 47% and 38%, respectively. Interpretation of these results is difficult because of the high rate of non-evaluable patients, i.e. 24 (13%) in the itraconazole arm and 44 (24%) in the D-AmB arm.[106]

2.1.3 Pre-Emptive Treatment

Compared with the empirical treatment approach, only a few studies used a pre-emptive treatment approach. In general, these trials have generated only limited evidence. In a noncomparative trial assessing the feasibility of a pre-emptive approach, patients undergoing myeloablative allogeneic HSCT or chemotherapy for AML or MDS received fluconazole prophylaxis (400 mg/day) and daily serum galactomannan testing. Those patients with more than two consecutive galactomannan assays with an index of ≥0.5 or CT scan findings suggestive of invasive aspergillosis and supported by a compatible culture or microscopic evaluation, received intravenous L-AmB at 5 mg/kg/day. A total of 117 episodes of neutropenic fever were registered, with 41 (35%) being refractory to adequate broad spectrum antibacterials. They would therefore have been eligible for empirical therapy according to current guidelines.[107] Using the pre-emptive approach described here, only nine episodes were treated pre-emptively and the rate of antifungal use for these episodes was reduced from an estimated 35% to 8%. In addition, pre-emptive antifungal therapy was initiated in ten episodes that were clinically not typical of IFI, on the basis of seropositivity. One zygomycosis episode was missed. The authors concluded that pre-emptive therapy based on enzyme immunoassay and HRCT reduces unnecessary drug exposure and controls IFI effectively, whereas it fails to detect non-*Aspergillus* IFI.[108] However, interpretation is difficult because of lack of a control group and because antifungal prophylaxis was given to all patients in this trial.

2.1.4 Targeted Treatment

Since most cases of IFI can never be proven, targeted treatment is usually initiated on the basis of

a probable diagnosis. Therefore, many clinical trials allow a diagnosis of either probable or proven IFI according to the original or slightly modified EORTC/MSG criteria as a starting point for treatment initiation.[11]

Herbrecht et al.[9] conducted a randomized, open-label trial, in which immunocompromised patients – mostly undergoing allogeneic HSCT, autologous HSCT or chemotherapy for acute leukaemia – with probable or proven invasive aspergillosis were randomized to receive either voriconazole or D-AmB. While the definition of proven invasive aspergillosis was identical to the EORTC/MSG criteria published after completion of the trial,[11] criteria for the diagnosis of probable invasive aspergillosis differed. The original EORTC/MSG criteria of probable invasive aspergillosis are based on the coexistence of three factors: (i) a host factor; (ii) a clinical factor; and (iii) a microbiological factor. In the criteria used by the investigators of the trial, recipients of allogeneic HSCT or chemotherapy for haematological malignancy could be diagnosed with probable invasive aspergillosis in the presence of halo or air crescent signs on chest CT scan, even in the absence of microbiological evidence. Using these criteria, 144 patients in the voriconazole arm and 133 patients in the D-AmB arm were eligible for efficacy analysis. A successful outcome was defined as complete or partial clinical and radiological response, and results were reported as 53% with voriconazole and 32% in the D-AmB group; survival rates at week 12 were 71% and 58%, respectively. Criteria for superiority of voriconazole over D-AmB were met. Moreover, voriconazole was associated with significantly fewer severe drug-related adverse events.

The second trial on the treatment of probable or proven invasive aspergillosis was a multinational, double-blind comparison of L-AmB 3 mg/kg/day or 10 mg/kg/day for 14 days, followed by 3 mg/kg/day.[20] For the definition of diagnosis, basically the modified criteria from the preceding trial by Herbrecht et al.[9] were used. However, patients qualifying for a possible invasive mould infection, based on EORTC/MSG criteria (host factor plus at least one clinical or microbiological criterion), could be randomized and start treatment. They were also obliged to complete requirements for a probable or proven diagnosis within 4 days ('up-grading') in order to continue treatment with the study drug. The primary endpoint was defined as favourable outcome, i.e. complete or partial response at the end of randomly allocated treatment. There was no significant difference in efficacy between the two groups, with favourable response rates of 50% and 46% reported from the 3 and 10 mg/kg/day groups, respectively. Patients in the high-dose group experienced significantly higher rates of nephrotoxicity and hypokalaemia.[20]

It has been discussed whether caspofungin 70 mg/day loading dose followed by 50 mg maintenance represents a potential alternative to voriconazole. Results from a recent clinical trial did not measure up to these expectations. The noncomparative design and the large number of severely ill patients enrolled into the study might be partly responsible for this unexpected outcome, thus complicating its interpretation.[109]

Trials on the use of itraconazole as targeted treatment of invasive aspergillosis were limited by their small patient numbers, as well as their monocentric, nonrandomized and/or retrospective design.[110-112]

Concerning the efficacy of combination antifungal therapy, a large, randomized, controlled clinical trial is lacking. The current basis of evidence on this matter has been reviewed recently elsewhere.[113]

2.2 Invasive Candidiasis

2.2.1 Prophylaxis

From the numerous trials on antifungal prophylaxis with fluconazole in the ICU, three major randomized clinical trials need to be addressed.[68,114,115]

In a placebo-controlled trial, Eggimann et al.[114] assessed fluconazole prophylaxis in 43 surgical ICU patients at two Swiss university hospitals. Abdominal candidiasis, the primary endpoint, was reached by 35% in the placebo and 4% in the fluconazole group. Furthermore, colonization was reduced from 62% to 15%, respectively.[114] The second trial compared placebo with fluconazole prophylaxis in 260 patients staying >3 days at a surgical ICU.[68] Prophylaxis reduced overall incidence rates of proven IFI from 15% to 9%. An open-label follow-up study showed a sustained benefit of fluconazole

prophylaxis, but did not detect any differences in mortality.[116] The third placebo-controlled trial examined fluconazole prophylaxis in 204 medical and surgical ICU patients. For inclusion, patients had to be mechanically ventilated for at least 48 hours, with an expectation to remain so for at least an additional 72 hours, and receiving selective decontamination of the digestive tract. Invasive candidiasis was diagnosed in 16% of the placebo recipients versus 6% of those taking fluconazole. Prophylaxis significantly reduced *Candida* spp. colonization, but crude inhospital mortality was similar in both groups.[115]

Two large meta-analyses by Cruciani et al.[117] and Playford et al.[118] compared the prophylactic use of ketoconazole or fluconazole versus placebo or no treatment in adult ICU patients. Cruciani et al. reported reduced rates of candidaemia (relative risk [RR] 0.30; 95% CI 0.10, 0.82), mortality attributable to *Candida* spp. infection (RR 0.25; 95% CI 0.08, 0.80) and overall mortality (RR 0.60; 95% CI 0.45, 0.81). Similarly, Playford et al. reported reduction of the IFI incidence rate by about 50% (RR 0.46; 95% CI 0.31, 0.68) and overall mortality by about 25% (RR 0.76; 95% CI 0.59, 0.97). While emergence of azole-resistant *Candida* spp. strains during treatment was not assessed by Cruciani et al., Playford et al. observed no significant increase.

In conclusion, three randomized trials and two large meta-analyses showed a decrease of invasive candidiasis among ICU patients receiving fluconazole prophylaxis, and none of them reported emergence of fluconazole-resistant *Candida* spp. However, the validity of these findings is curtailed by the moderate size and mostly monocentric design of the trials. In addition, the broad inclusion criteria used did not adequately match the heterogeneity of risk patterns found among ICU patients. This is problematic insofar as average baseline invasive candidiasis incidence rates among unselected ICU patients are usually low, giving little room for further reduction of incidence rates through prophylaxis. To obtain statistical significance in such a sample, at least several hundreds of patients per treatment arm would have to be included in the analysis. Even if the trial managed to show a significant reduction of invasive candidiasis incidence rates, the number needed to treat might still be too high to justify the implementation of azole prophylaxis from a medical point of view.

In contrast, demonstrating the value of prophylaxis in a selected patient group with comparatively high incidence rates that leave a large margin for reduction requires smaller samples and yields lower numbers to treat.[119] Different authors have made an effort to identify these high-risk groups. DuPont et al.[72] conducted a retrospective cohort study including 221 patients with peritonitis hospitalized in a surgical ICU for the retrospective cohort and 57 patients in the prospective cohort. Four independent risk factors of yeast isolation in the peritoneal fluid were identified, i.e. female gender, upper gastrointestinal tract origin of peritonitis, intraoperative cardiovascular failure and previous antibacterial therapy at least 48 hours prior to the onset of peritonitis. Based on these findings, a predictive risk score was created. In the presence of three risk factors, sensitivity was 84% and specificity was 50%, positive and negative predictive values were 67% and 72%, respectively. Overall accuracy was 71%. Based on a retrospective study of 327 patients who stayed in a surgical ICU for ≥4 days, Paphitou et al.[66] showed that any combination of diabetes mellitus, new onset haemodialysis, use of total parenteral nutrition or receipt of broad spectrum antibacterials was associated with an invasive candidiasis rate of 17% versus 5% for patients lacking these characteristics ($p = 0.001$). Using this method, 78% of the patients who eventually developed invasive candidiasis were identified. Using Paphitou's rule, coupled with statistical observations by Rex and Sobel,[119] data from the meta-analysis by Playford et al.[118] were examined. It was shown that if the cumulative incidence of invasive candidiasis in a certain subpopulation of the ICU approached or exceeded 10%, between 9 (for a risk of 11%) and 17 patients (for a risk of 20%) would receive fluconazole prophylaxis to prevent one case of invasive candidiasis. To prevent one death, the number needed to treat ranges between 83 (for a mortality risk of 5%) and 9 (for a mortality risk of 50%) patients.

In spite of these encouraging calculations, prospective trials confirming the validity of such risk selection criteria are scarce. A notable attempt was made by Ostrosky-Zeichner et al.,[70] who created a

clinical prediction rule for invasive candidiasis in the ICU that was applied for high-risk patient selection in a randomized, placebo-controlled, multicentric trial, assessing the use of caspofungin prophylaxis in the ICU. The rule was obtained through analysis of a group of 2890 patients, in which incidence of invasive candidiasis was 3% (n = 88). Statistical modelling revealed a particularly high risk for patients under systemic antibacterial treatment (days 1–3) or with an indwelling central venous catheter (days 1–3) and at least two of the following factors: total parenteral nutrition (days 1–3); any dialysis (days 1–3); any major surgery (days −7 to 0); pancreatitis (days −7 to 0); any use of corticosteroids (days −7 to 3); or use of other immunosuppressive agents (days −7 to 0). The rule was associated with a sensitivity of 34% and a specificity of 90%. Its positive and negative predictive value was 9.9% and 97%, respectively.[70] Unfortunately, its highly restrictive character led to difficulties enrolling subjects, and the study had to be stopped prematurely. However, in the 38 patients enrolled, caspofungin prophylaxis appeared to be safe and effective.[120]

Solid organ transplant recipients are another special population among high-risk ICU patients who might experience a benefit from antifungal prophylaxis. Few randomized controlled trials have been conducted in this group, whereas most of them focused on liver transplant recipients. A meta-analysis of these trials by Cruciani et al.[121] concluded that antifungal prophylaxis in liver transplant recipients reduces the incidence of IFI and attributable mortality. However, overall mortality rates were not affected, and patients receiving fluconazole experienced a higher proportion of episodes of non-*albicans Candida* infection, in particular *C. glabrata*.

2.2.2 Empirical Treatment

Our search has revealed no literature on the empirical use of antifungal agents in febrile, high-risk ICU patients with negative microbial cultures. According to some authors, patients with blood cultures positive for *Candida* spp., but with information on species and susceptibility pending, are also classified as potential recipients of empirical treatment.[122] We discuss these patients in the context of targeted treatment.

2.2.3 Pre-Emptive Treatment

Pre-emptive treatment may be initiated in the presence of surrogate markers in a high-risk host without clinical signs and symptoms of disease and without definitive verification by histopathology and/or culture of the causal pathogen. Given the imperfect performance of diagnostic methods for invasive candidiasis, risk scores, similar to the prediction rules mentioned in the section on prophylaxis (section 2.2.1), have attracted considerable interest. In contrast to the prediction rules, scoring systems for selection of patients for pre-emptive treatment emphasize *Candida* spp. colonization as a surrogate marker.

Leon et al.[69] created a so-called *Candida* score, based on the analysis of a total of 1669 non-neutropenic ICU patients, of whom 97 developed invasive candidiasis. Four independent risk factors were identified, i.e. *Candida* spp. colonization (1 point), surgery prior to ICU admission (1 point), total parenteral nutrition (1 point) and sepsis (2 points). The *Candida* score was equal to the sum of the statistical weight of each risk factor, and patients with at least 2.5 points were found to be at a 7.75-fold greater risk of invasive candidiasis. This cut-off value was associated with a sensitivity of 81% and a specificity of 74%.

Piarroux et al.[123] demonstrated that a targeted pre-emptive strategy can prevent proven invasive candidiasis in surgical ICU patients. In an historical control setting, two cohorts (n = 933) before and after introduction of weekly mycological screening were compared. Using the so-called corrected colonization index ([culture-positive sites/number of sites cultured] × [heavily colonized sites/total number of colonized sites])[71] with a threshold of 0.4, patients were selected for initiation of pre-emptive antifungal treatment with oral fluconazole 800 mg loading dose and 400 mg/day maintenance. Incidence of proven invasive candidiasis acquired in the ICU significantly decreased from 2.2% to 0% ($p < 0.001$), while incidence of proven 'imported' invasive candidiasis remained unchanged (4.8% vs 3.8%; $p = 0.42$). Emergence of fluconazole resistance was not observed.

2.2.4 Targeted Treatment

Until the 1990s, D-AmB was considered the gold standard in the treatment of patients with proven

invasive candidiasis. This notion was challenged by a series of clinical trials, beginning in 1994, when Rex et al.[124] published their results from a multicentre, randomized trial that compared the use of intravenous D-AmB 0.5–0.6 mg/kg/day and oral fluconazole 400 mg/day in the treatment of invasive candidiasis in immunocompetent, non-neutropenic patients. Efficacy analysis based on data obtained from 206 patients revealed no statistically significant differences in treatment outcome between the two groups (p = 0.22). A total of 81 patients (79%) receiving D-AmB and 72 patients (70%) receiving fluconazole were treated successfully, while fluconazole displayed a more favourable toxicity profile than D-AmB.

Increasing numbers of infections with fluconazole-resistant *Candida* strains (e.g. *C. krusei* or *C. glabrata*) drew attention to other azoles with a broader spectrum than fluconazole and led to the design of a multicentre, randomized, noninferiority study comparing intravenous voriconazole 6 mg/kg twice-daily loading dose followed by 3 mg/kg twice-daily maintenance versus intravenous D-AmB 0.7–1.0 mg/kg/day, followed by oral or intravenous fluconazole 400 mg/day in non-neutropenic patients with candidaemia. The primary endpoint was defined as sustained clinical and mycological response, 12 weeks after end of treatment. A total of 370 of 422 patients were included in the modified intention-to-treat population, and efficacy analysis yielded equal success rates of 41% for both treatment groups. Fewer serious adverse events and in particular renal toxicity were reported from patients in the voriconazole group. The authors concluded that voriconazole was as efficacious as and less toxic than D-AmB in the treatment of invasive candidiasis in non-neutropenic patients.[125] In contrast with the echinocandins, voriconazole can be given both as initial intravenous treatment and as an oral step-down agent.

With the development of the echinocandins, clinical trials evaluating their efficacy and safety were conducted. Mora-Duarte et al.[10] compared caspofungin 70 mg loading dose followed by 50 mg/day maintenance with D-AmB 0.6–1.0 mg/kg/day in the treatment of invasive candidiasis in non-neutropenic (n = 200) and neutropenic (n = 24) patients. Caspofungin was as efficacious as D-AmB, with favourable response rates of 73.4% and 61.7%, respectively. From a second analysis, including only those patients treated for at least 5 days, superiority of caspofungin to D-AmB was concluded, based on success rates of 80.7% and 64.9%, respectively. There was no difference in survival rates at 6- to 8-week follow-up, but significantly more patients in the D-AmB group experienced nephrotoxic effects and hypokalaemia.[10]

Micafungin was evaluated as first-line treatment for invasive candidiasis in a double-blind, randomized, multinational, noninferiority trial, comparing micafungin 100 mg/day versus L-AmB 3 mg/kg/day in non-neutropenic (n = 469) and neutropenic (n = 62) patients. Per-protocol analysis revealed treatment success in 181 patients (89.6%) treated with micafungin and in 170 patients (89.5%) treated with L-AmB, and noninferiority was met. Micafungin was associated with fewer treatment-related adverse events than L-AmB.[126]

In an international, randomized, double-blind trial, micafungin 100 mg/day (n = 191) was compared with micafungin 150 mg/day (n = 199) and caspofungin 70 mg loading dose followed by 50 mg/day (n = 188) in patients with candidaemia and other forms of invasive candidiasis. Treatment was successful in 76.4%, 71.4% and 72.3%, respectively, such that dosages of micafungin 100 mg/day and 150 mg/day were regarded as noninferior to a standard dosage of caspofungin.[127]

A recent phase III, randomized, double-blind, multicentre trial comparing anidulafungin 200 mg/day loading dose followed by 100 mg/day maintenance with oral fluconazole 800 mg loading dose and 400 mg/day maintenance for the treatment of invasive candidiasis was conducted in a predominantly non-neutropenic population with 238 non-neutropenic versus 7 neutropenic patients. Of the 261 patients enrolled, 245 (anidulafungin [n = 127], fluconazole [n = 118]) were eligible for efficacy analysis, which yielded significantly higher response rates (75.6% vs 60.2%) and better survival (74% vs 69%) for anidulafungin (p = 0.01). Protocol-prespecified criteria for superiority were met. Limits of this study are the small number of neutropenic patients, patients with non-candidaemic invasive candidiasis and the exclusion of paediatric patients.[128]

3. Discussion: When and How to Treat Invasive Fungal Infection

3.1 Overall Strategy for Neutropenic Hosts

In spite of numerous clinical trials on the treatment of IFIs, randomized comparisons of treatment strategies have not been published. Even if more data on the efficacy of pre-emptive treatment were to be provided by randomized controlled trials in the future, direct comparisons with prophylactic and empirical treatment strategies might remain elusive. Only a trial in which each approach was included in a separate treatment arm could clarify the question of when to ideally start treatment. However, such a trial would require tremendous organizational efforts. Furthermore, a double-blind approach could not be upheld in this setting. Under these circumstances, one should recall the reason why different treatment strategies were created in the first place: early antifungal exposure effectively reduces mortality.

Firstly, this effect has been shown in empirical treatment, when the use of caspofungin resulted in an improved survival compared with L-AmB.[8] Secondly, this is a major finding from the *post hoc* analysis of the global aspergillus study group.[9] They recently showed that patients with chest CT scan findings occurring early in the pathogenesis of aspergillosis had an improved response rate and overall survival compared with other imaging findings.[129] Thirdly, reduced overall mortality has been achieved through prophylaxis with fluconazole in recipients of HSCT,[101] with posaconazole in AML and MDS patients undergoing remission induction chemotherapy cycles, and in patients receiving immunosuppressives for GvHD.[97,103]

With regard to these results, as well as to the extended spectrum of posaconazole and its low rate of adverse events and drug-drug interactions, it seems warranted to replace fluconazole with posaconazole prophylaxis among patients undergoing allogeneic HSCT, even though this recommendation differs from the current Clinical Practice Guidelines for the Treatment of Aspergillosis from the Infectious Diseases Society of America.[130,131] Prophylaxis with posaconazole could be started after completion of the conditioning regimen. In conclusion, posaconazole prophylaxis may be seen as the gold standard. If so, it would be difficult to design a clinical trial randomizing this strategy versus another, e.g. pre-emptive treatment.

3.2 Neutropenic Hosts not Receiving Prophylaxis

For those patients who do not belong to one of the defined risk groups profiting from systemic antifungal prophylaxis, other evidence-based strategies are appropriate. Regarding the lack of randomized controlled trials investigating the efficacy of pre-emptive antifungal treatment, this approach cannot be recommended outside well designed clinical trials. However, empirical treatment in persistently febrile patients has been extensively researched in a number of landmark trials. These trials were marked by their efforts to identify the best agent for the treatment of populations that were selected on the basis of rather broad inclusion criteria, i.e. prolonged and profound neutropenia.[6-8] We now know that such a generalized approach does not measure up perfectly to the complexity of the issue, and future trials may aim at the identification of those subpopulations that benefit most from empirical treatment, e.g. nonspecific versus no lung infiltrates. Nevertheless, in the absence of more selective data, empirical antifungal treatment in neutropenic high-risk patients should be initiated with caspofungin 70 mg/day loading dose followed by 50 mg/day maintenance[8] or with L-AmB 3 mg/kg/day.[6] In view of its favourable toxicity profile, caspofungin will usually be preferred as first-line treatment. Voriconazole and other azoles are not indicated in this setting.[7]

3.3 Probable or Proven Invasive Aspergillosis

While invasive fungal infections are uncommon in patients receiving posaconazole prophylaxis,[99] they will be seen outside the typical patient groups.

Irrespective of whether patients are receiving antifungal prophylaxis, all patients at an increased risk of IFI should be subject to rigorous screening. In patients at risk of invasive aspergillosis, galactomannan antigen detection in serum has been associated with sensitivity and specificity values of 75–94% and 98–100%, respectively.[132-134] We

Table II. Prophylaxis and treatment strategies for invasive fungal infection (IFI) in neutropenic patients

Underlying condition	Risk factor	Antifungal	Dosage	Reference
Prophylaxis				
Acute leukaemia or myelodysplastic syndrome	Induction therapy	Posaconazole	200 mg tid PO	97
Allogeneic SCT	Neutropenia	Posaconazole	200 mg tid PO	
Prior allogeneic SCT	Immunosuppressive medication for severe graft-versus-host disease	Posaconazole	200 mg tid PO	103
Empirical treatment				
Total duration of neutropenia >10 days	Persistent fever for >72–96 h	Caspofungin	70 mg loading dose followed by 50 mg/day IV	8
		L-AmB	3 mg/kg/day IV	6
Pre-emptive treatment				
Total duration of neutropenia >10 days or prior allogeneic SCT	Laboratory or radiographic results conclusive of IFI	Unknown	Unknown	No well designed prospective trial published
Targeted treatment[a]				
Any	Any	Voriconazole[b]	6 mg/kg bid loading dose, followed by 4 mg/kg bid IV	9
		L-AmB	3 mg/kg/day IV	20

a For proven or probable invasive aspergillosis.

b If patient is receiving azole prophylaxis, liposomal amphotericin B should be preferred.

bid = twice daily; **IV** = intravenously; **L-AmB** = liposomal amphotericin B; **PO** = oral; **SCT** = stem cell transplantation; **tid** = three times daily.

recommend testing at a frequency of three times per week. A positive test result for galactomannan antigen or any clinical signs or symptoms compatible with IFI should trigger further diagnostic measures. When suspecting invasive aspergillosis, a chest CT scan should be performed the very same day, since any delays will impair prognosis. If any infiltrate is found on CT scanning, bronchoalveolar lavage with galactomannan testing is of high diagnostic value.[135]

If the diagnosis of probable or proven invasive aspergillosis is established in accordance with the criteria used by Herbrecht et al.,[9] intravenous voriconazole 6 mg/kg twice daily loading dose followed by 4 mg/kg twice daily maintenance for at least 7 days is the agent of choice,[9] while intravenous L-AmB 3 mg/kg/day is the alternative treatment.[20] In patients developing breakthrough IFI under posaconazole prophylaxis, L-AmB may be preferred over voriconazole, as cross-resistance to other azoles might impair response to treatment. Table II summarizes our general recommendations on prophylaxis and treatment of IFI, while figure 2 focuses on the diagnosis, prophylaxis and treatment of IFIs in neutropenic patients.

3.4 Prophylaxis in High-Risk Intensive Care Unit Patients

The efficacy of azole prophylaxis in non-neutropenic high-risk ICU patients is supported by results from randomized controlled trials[68,114,115] and large meta-analyses.[117,118] Nevertheless, its implementation remains a controversial issue.

Firstly, concern about the selection of azole-resistant non-*albicans Candida* spp. has been raised. However, rational analysis yields few arguments in favour of this development. Unlike bacteria, *Candida* spp. lack the ability to exchange resistance patterns by plasmid transfer, and the two meta-analyses mentioned[117,118] showed no evidence of epidemiological shifts after fluconazole prophylaxis. On the other hand, the criticism has been made that all randomized controlled trials included in the meta-analyses by Playford et al.[118] and Cruciani et al.[117]

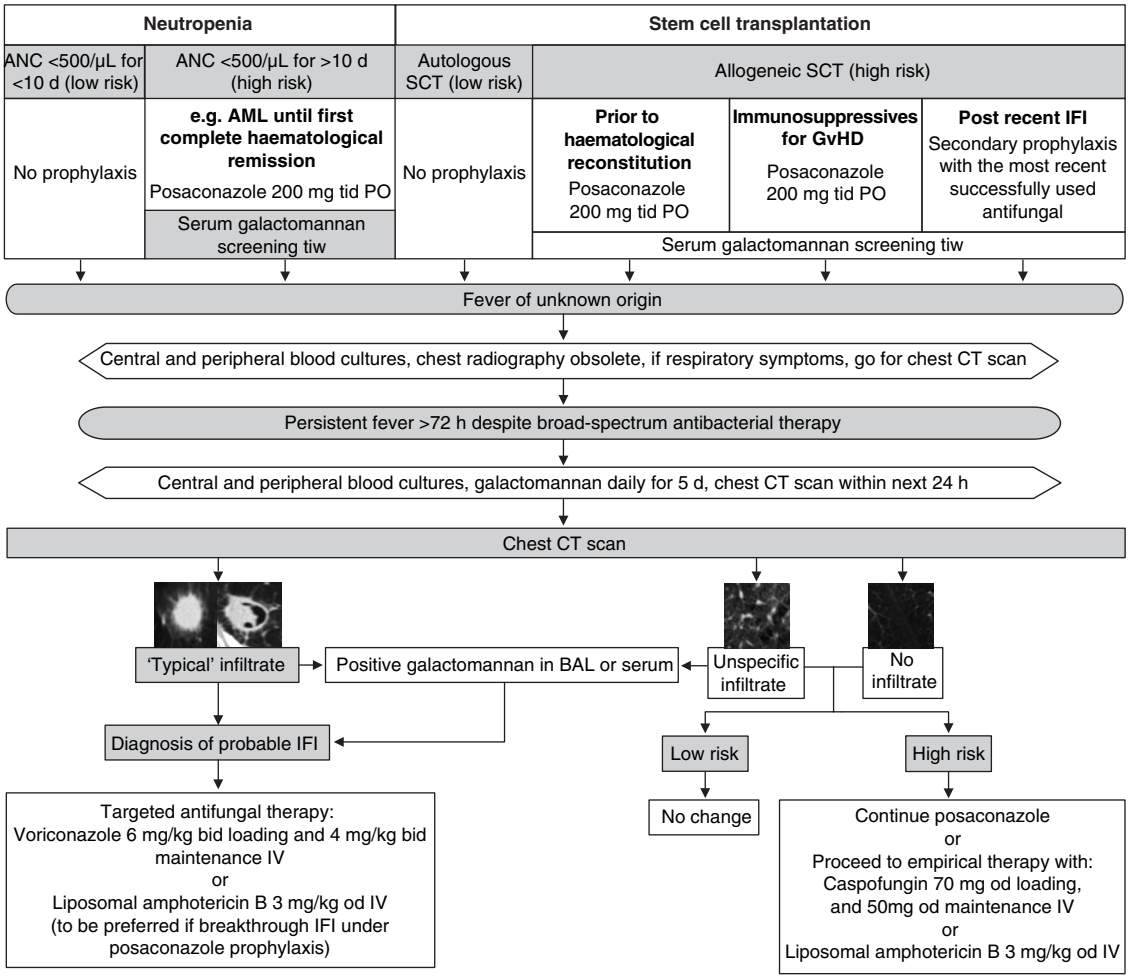

Fig. 2. Antifungal prophylaxis and treatment in the neutropenic patient. **AML** = acute myelogenous leukaemia; **ANC** = absolute neutrophil count; **BAL** = bronchoalveolar lavage; **bid** = twice daily; **GvHD** = graft-versus-host disease; **IFI** = invasive fungal infection; **IV** = intravenous; **od** = once daily; **PO** = oral; **SCT** = stem cell transplantation; **tid** = three times daily; **tiw** = three times weekly.

were limited by their monocentric design and/or their limited statistical power. Furthermore, each of them focused on a group of clinically distinct patients. It is debatable whether results from such heterogenous trials should be pooled into a meta-analysis. Alternatively, stratification scores for the identification of high-risk subpopulations have been introduced[66,70,72,118] (table I). Patients identified by such a score might experience a more pronounced benefit from prophylaxis than unselected ICU patients. However, to date, their efficacy has not been proven in the context of clinical trials.

Under these circumstances, prophylactic use of fluconazole in high-risk ICU patients cannot be generally recommended, but should be restricted to patients with multiple risk factors for invasive candidiasis. The following estimation by Playford et al.[118] may serve as a rough guideline: if the cumulative incidence of invasive candidiasis in a certain subpopulation of the ICU approaches or exceeds 10%, in spite of active prevention, prophylaxis should be initiated. Using this approach, the number needed to treat to prevent one case of invasive candidiasis ranges between 17 patients (for a risk of

11%) and 9 patients (for a risk of 20%).[118] With regard to its favourable toxicity and drug-drug interaction profile, oral fluconazole 400 mg/day is our agent of choice in this setting. The efficacy of the echinocandins for antifungal prophylaxis will have to be evaluated in future trials, even though their limitation to intravenous administration represents a major disadvantage of this class.

3.5 Pre-Emptive and Empirical Treatment of Invasive Candidiasis

Data on the efficacy of pre-emptive and empirical treatment strategies in high-risk ICU patients is scarce. Considering the negative impact of treatment delays on the outcome of patients with invasive candidiasis,[136,137] a basis of evidence for the future use of these strategies is an unmet medical need. Using the corrected colonization index established by Pittet et al.,[71] Piarroux et al.[123] managed to demonstrate the use of pre-emptive treatment in reducing the incidence of invasive candidiasis among ICU patients. This approach would have to be tested in a randomized controlled trial before a reliable treatment recommendation could be made.

3.6 Targeted Treatment of Invasive Candidiasis

Once invasive candidiasis can be proven, a choice must be made between six different, but similarly efficacious antifungal agents, all supported by data from randomized controlled trials: LAmB, fluconazole, voriconazole, caspofungin, micafungin and anidulafungin.[10,124-126,128] Considering the risk of azole-resistant *Candida* spp. strains, an echinocandin should be considered first-line treatment in non-neutropenic patients, while patients with susceptible *Candida* spp. may be switched to fluconazole. Drug-drug interactions and toxicity rates render voriconazole a less suitable step-down agent. It should also be mentioned that a significant rate of cross-resistance between fluconazole and voriconazole, particularly against *C. glabrata* strains, has been reported.[138]

In neutropenic patients, caspofungin or micafungin should be preferred to anidulafungin as first-line treatment, as no clinical evidence exists to support its use in this setting. L-AmB is a second-line treatment option in both settings. After 10 days of treatment, switching from an intravenous to an oral formulations may be considered.[128] The prerequisites are shown in figure 3.

Concerns have been raised regarding the decreased susceptibility of *C. parapsilosis* towards echinocandins,[139] particularly since subgroup analyses of the clinical trials by Reboli et al.[128] and Mora-Duarte et al.[10] had yielded delayed microbiological eradication of *C. parapsilosis* with anidulafungin and caspofungin, respectively. However, these findings did not translate into a decreased clinical efficacy, as both echinocandins were found to be as effective against *C. parapsilosis* as fluconazole[128] and D-AmB,[10] respectively. Data published by Kuse et al.[126] do not mention species-specific time to eradication, but no significant differences in persistence rates and clinical efficacy were reported for the treatment of different *Candida* spp. with micafungin or L-AmB. The same is true for results from the trial by Pappas et al.,[127] comparing micafungin with caspofungin. Furthermore, recent results from a global antifungal surveillance programme showed general susceptibility of *C. parapsilosis* to all echinocandins.[140]

Table III summarizes our recommendations on the prophylaxis and treatment of IFI in high-risk ICU patients.

4. Conclusion

Early diagnosis and treatment of patients with IFI have a major impact on morbidity and mortality rates. This concern has led to the emergence of

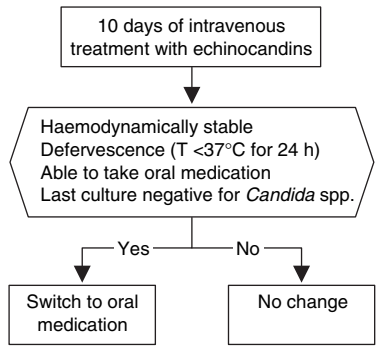

Fig. 3. Switching treatment for invasive candidiasis from intravenous to oral. **T** = body temperature.

Table III. Prophylaxis and treatment of invasive fungal infections in intensive care unit (ICU) patients

Indication	Antifungal agent	Dosage (mg/day)	References
Prophylaxis			
High-risk ICU patients[a]	Fluconazole	400 PO	118
Established diagnosis of invasive candidiasis			
Non-neutropenic patients	Anidulafungin	200 loading dose and 100 IV maintenance	128
	Micafungin	100 IV	126,127
	Caspofungin	70 single loading dose, 50 IV maintenance	10,127
Neutropenic patients	Micafungin	100 IV	126,141
	Caspofungin	70 single loading dose and 50 IV maintenance	8,10,127
Second-line neutropenic and non-neutropenic patients	L-AmB	3 mg/kg/day IV	126

a Subpopulations with a cumulative incidence >10%.

IV = intravenous; **L-AmB** = liposomal amphotericin B; **PO** = oral.

different treatment strategies, i.e. prophylactic, empirical and pre-emptive treatment, as well as targeted treatment in response to a definite diagnosis of IFI. In order to define the ideal agent to be used in each of these settings, representative clinical trials have been discussed. Recommendations are shown in table II and table III. Unfortunately, methodological comparisons cannot be made, based on current evidence. Therefore, we propose an eclectic treatment approach to reduce morbidity and mortality from IFI without compromising tolerability. Antifungal prophylaxis thus remains restricted to high-risk subgroups, i.e. patients undergoing induction chemotherapy for acute leukaemia or MDS, allogeneic HSCT recipients and high-risk ICU patients.

Acknowledgements

The authors did not receive any funding or external help for the completion of this article. Dr Rüping has received travel grants from Schering-Plough/Essex and Gilead. Dr Vehreschild has received travel grants from Merck Sharp & Dohme/Merck, Pfizer, Schering-Plough and Viropharma. Dr Cornely is supported by the German Federal Ministry of Research and Education (BMBF grant 01KN0706) and has received research grants from, is an advisor to, or served at the speakers' bureau of Astellas, Basilea, Bayer, F2G, Genzyme, Gilead, Pfizer, Merck, Mölnlycke, Nektar, Optimer, Schering-Plough, SpePharm, United Medical, Vicuron and Zeneus.

References

1. Maschmeyer G, Haas A, Cornely OA. Invasive aspergillosis: epidemiology, diagnosis and management in immunocompromised patients. Drugs 2007; 67 (11): 1567-601
2. Pfaller MA, Diekema DJ. Epidemiology of invasive candidiasis: a persistent public health problem. Clin Microbiol Rev 2007 Jan; 20 (1): 133-63
3. Morris A, Lundgren JD, Masur H, et al. Current epidemiology of *Pneumocystis pneumonia*: emerging infectious diseases 2004 Oct; 10 (10): 1713-20
4. Marr KA, Carter RA, Crippa F, et al. Epidemiology and outcome of mould infections in hematopoietic stem cell transplant recipients. Clin Infect Dis 2002 Apr 1; 34 (7): 909-17
5. Husain S, Alexander BD, Munoz P, et al. Opportunistic mycelial fungal infections in organ transplant recipients: emerging importance of non-*Aspergillus mycelial* fungi. Clin Infect Dis 2003 Jul 15; 37 (2): 221-9
6. Walsh TJ, Finberg RW, Arndt C, et al. Liposomal amphotericin B for empirical therapy in patients with persistent fever and neutropenia. National Institute of Allergy and Infectious Diseases Mycoses Study Group. N Engl J Med 1999 Mar 11; 340 (10): 764-71
7. Walsh TJ, Pappas P, Winston DJ, et al. Voriconazole compared with liposomal amphotericin B for empirical antifungal therapy in patients with neutropenia and persistent fever. N Engl J Med 2002 Jan 24; 346 (4): 225-34
8. Walsh TJ, Teppler H, Donowitz GR, et al. Caspofungin versus liposomal amphotericin B for empirical antifungal therapy in patients with persistent fever and neutropenia. N Engl J Med 2004 Sep 30; 351 (14): 1391-402
9. Herbrecht R, Denning DW, Patterson TF, et al. Voriconazole versus amphotericin B for primary therapy of invasive aspergillosis. N Engl J Med 2002 Aug 8; 347 (6): 408-15
10. Mora-Duarte J, Betts R, Rotstein C, et al. Comparison of caspofungin and amphotericin B for invasive candidiasis. N Engl J Med 2002 Dec 19; 347 (25): 2020-9
11. Ascioglu S, Rex JH, de Pauw B, et al. Defining opportunistic invasive fungal infections in immunocompromised patients with cancer and hematopoietic stem cell transplants: an international consensus. Clin Infect Dis 2002 Jan 1; 34 (1): 7-14
12. Cornely OA, Ullmann AJ, Karthaus M. Evidence-based assessment of primary antifungal prophylaxis in patients with hematologic malignancies. Blood 2003 May 1; 101 (9): 3365-72
13. Ullmann AJ, Cornely OA. Antifungal prophylaxis for invasive mycoses in high risk patients. Curr Opin Infect Dis 2006 Dec; 19 (6): 571-6
14. Pagano L, Caira M, Candoni A, et al. The epidemiology of fungal infections in patients with hematologic malignancies: the SEIFEM-2004 study. Haematologica 2006 Aug; 91 (8): 1068-75
15. Denning DW. Invasive aspergillosis. Clin Infect Dis 1998 Apr; 26 (4): 781-803; quiz 4-5
16. Marr KA, Carter RA, Boeckh M, et al. Invasive aspergillosis in allogeneic stem cell transplant recipients: changes in epidemiology and risk factors. Blood 2002 Dec 15; 100 (13): 4358-66

17. Patterson TF, Kirkpatrick WR, White M, et al. Invasive aspergillosis: disease spectrum, treatment practices, and outcomes. I3 Aspergillus Study Group. Medicine (Baltimore) 2000 Jul; 79 (4): 250-60
18. Martino R, Parody R, Fukuda T, et al. 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. Blood 2006 Nov 1; 108 (9): 2928-36
19. Cornet M, Fleury L, Maslo C, et al. Epidemiology of invasive aspergillosis in France: a six-year multicentric survey in the Greater Paris area. J Hosp Infect 2002 Aug; 51 (4): 288-96
20. Cornely OA, Maertens J, Bresnik M, et al. Liposomal amphotericin B as initial therapy for invasive mold infection: a randomized trial comparing a high-loading dose regimen with standard dosing (AmBiLoad trial). Clin Infect Dis 2007 May 15; 44 (10): 1289-97
21. Cordonnier C, Ribaud P, Herbrecht R, et al. Prognostic factors for death due to invasive aspergillosis after hematopoietic stem cell transplantation: a 1-year retrospective study of consecutive patients at French transplantation centers. Clin Infect Dis 2006 Apr 1; 42 (7): 955-63
22. Martino R, Subira M, Rovira M, et al. Invasive fungal infections after allogeneic peripheral blood stem cell transplantation: incidence and risk factors in 395 patients. Br J Haematol 2002 Feb; 116 (2): 475-82
23. Paya CV. Fungal infections in solid-organ transplantation. Clin Infect Dis 1993 May; 16 (5): 677-88
24. Winston DJ, Emmanouilides C, Busuttil RW. Infections in liver transplant recipients. Clin Infect Dis 1995 Nov; 21 (5): 1077-89; quiz 90-1
25. Infectious disease community of practice, fungal infections. Am J Transplant 2004; 4 Suppl. 10: 110-34
26. Fishman JA. Infection in solid-organ transplant recipients. N Engl J Med 2007 Dec 20; 357 (25): 2601-14
27. Singh N. Antifungal prophylaxis for solid organ transplant recipients: seeking clarity amidst controversy. Clin Infect Dis 2000 Aug; 31 (2): 545-53
28. Singh N, Husain S. Aspergillus infections after lung transplantation: clinical differences in type of transplant and implications for management. J Heart Lung Transpl 2003 Mar; 22 (3): 258-66
29. Fortun J, Martin-Davila P, Moreno S, et al. Risk factors for invasive aspergillosis in liver transplant recipients. Liver Transpl 2002 Nov; 8 (11): 1065-70
30. Singh N, Paterson DL. Aspergillus infections in transplant recipients. Clin Microbiol Rev 2005 Jan; 18 (1): 44-69
31. Hellinger WC, Bonatti H, Yao JD, et al. Risk stratification and targeted antifungal prophylaxis for prevention of aspergillosis and other invasive mold infections after liver transplantation. Liver Transpl 2005 Jun; 11 (6): 656-62
32. Gavalda J, Len O, San Juan R, et al. Risk factors for invasive aspergillosis in solid-organ transplant recipients: a case-control study. Clin Infect Dis 2005 Jul 1; 41 (1): 52-9
33. Patterson JE. Epidemiology of fungal infections in solid organ transplant patients. Transpl Infect Dis 1999 Dec; 1 (4): 229-36
34. Singh N. Impact of current transplantation practices on the changing epidemiology of infections in transplant recipients. Lancet 2003 Mar; 3 (3): 156-61
35. Lortholary O, Meyohas MC, Dupont B, et al. Invasive aspergillosis in patients with acquired immunodeficiency syndrome: report of 33 cases. French Cooperative Study Group on Aspergillosis in AIDS. Am J Med 1993 Aug; 95 (2): 177-87
36. Bruck HM, Nash G, Foley D, et al. Opportunistic fungal infection of the burn wound with phycomycetes and Aspergillus: a clinical-pathologic review. Arch Surg 1971 May; 102 (5): 476-82
37. Stone HH, Cuzzell JZ, Kolb LD, et al. Aspergillus infection of the burn wound. J Trauma 1979 Oct; 19 (10): 765-7
38. Becker WK, Cioffi Jr WG, McManus AT, et al. Fungal burn wound infection: a 10-year experience. Arch Surg 1991 Jan; 126 (1): 44-8
39. Labbe AC, Su SH, Laverdiere M, et al. High incidence of invasive aspergillosis associated with intestinal graft-versus-host disease following nonmyeloablative transplantation. Biol Blood Marrow Transplant 2007 Oct; 13 (10): 1192-200
40. Narreddy S, Mellon-Reppen S, Abidi MH, et al. Non-bacterial infections in allogeneic non-myeloablative stem cell transplant recipients. Transpl Infect Dis 2007 Mar; 9 (1): 3-10
41. Thursky KA, Worth LJ, Seymour JF, et al. Spectrum of infection, risk and recommendations for prophylaxis and screening among patients with lymphoproliferative disorders treated with alemtuzumab. Br J Haematol 2006 Jan; 132 (1): 3-12
42. Keating MJ, Flinn I, Jain V, et al. Therapeutic role of alemtuzumab (Campath-1H) in patients who have failed fludarabine: results of a large international study. Blood 2002 May 15; 99 (10): 3554-61
43. Meersseman W, Van Wijngaerden E. Invasive aspergillosis in the ICU: an emerging disease. Intensive Care Med 2007 Oct; 33 (10): 1679-81
44. Meersseman W, Vandecasteele SJ, Wilmer A, et al. Invasive aspergillosis in critically ill patients without malignancy. Am J Respir Crit Care Med 2004 Sep 15; 170 (6): 621-5
45. Wisplinghoff H, Bischoff T, Tallent SM, et al. Nosocomial bloodstream infections in US hospitals: analysis of 24,179 cases from a prospective nationwide surveillance study. Clin Infect Dis 2004 Aug 1; 39 (3): 309-17
46. Almirante B, Rodriguez D, Park BJ, et al. Epidemiology and predictors of mortality in cases of Candida bloodstream infection: results from population-based surveillance, Barcelona, Spain, from 2002 to 2003. J Clin Microbiol 2005 Apr; 43 (4): 1829-35
47. Asmundsdottir LR, Erlendsdottir H, Gottfredsson M. Increasing incidence of candidemia: results from a 20-year nationwide study in Iceland. J Clin Microbiol 2002 Sep; 40 (9): 3489-92
48. Laupland KB, Gregson DB, Church DL, et al. Invasive Candida species infections: a 5 year population-based assessment. J Antimicrob Chemother 2005 Sep; 56 (3): 532-7
49. Poikonen E, Lyytikainen O, Anttila VJ, et al. Candidemia in Finland, 1995-1999. Emerg Infect Dis 2003 Aug; 9 (8): 985-90
50. Sandven P, Bevanger L, Digranes A, et al. Candidemia in Norway (1991 to 2003): results from a nationwide study. J Clin Microbiol 2006 Jun; 44 (6): 1977-81
51. Arendrup MC, Fuursted K, Gahrn-Hansen B, et al. Seminational surveillance of fungemia in Denmark: notably high rates of fungemia and numbers of isolates with reduced azole susceptibility. J Clin Microbiol 2005 Sep; 43 (9): 4434-40
52. Diekema DJ, Messer SA, Brueggemann AB, et al. Epidemiology of candidemia: 3-year results from the emerging infections and the epidemiology of Iowa organisms study. J Clin Microbiol 2002 Apr; 40 (4): 1298-302
53. Kao AS, Brandt ME, Pruitt WR, et al. The epidemiology of candidemia in two United States cities: results of a population-based active surveillance. Clin Infect Dis 1999 Nov; 29 (5): 1164-70
54. Hajjeh RA, Sofair AN, Harrison LH, et al. Incidence of bloodstream infections due to Candida species and in vitro susceptibilities of isolates collected from 1998 to 2000 in a population-based active surveillance program. J Clin Microbiol 2004 Apr; 42 (4): 1519-27
55. Lin MY, Carmeli Y, Zumsteg J, et al. Prior antimicrobial therapy and risk for hospital-acquired *Candida glabrata* and

Candida krusei fungemia: a case-case-control study. Antimicrob Agents Chemother 2005 Nov; 49 (11): 4555-60
56. Abi-Said D, Anaissie E, Uzun O, et al. The epidemiology of hematogenous candidiasis caused by different *Candida* species. Clin Infect Dis 1997 Jun; 24 (6): 1122-8
57. Antoniadou A, Torres HA, Lewis RE, et al. Candidemia in a tertiary care cancer center: in vitro susceptibility and its association with outcome of initial antifungal therapy. Medicine (Baltimore) 2003 Sep; 82 (5): 309-21
58. Blumberg HM, Jarvis WR, Soucie JM, et al. Risk factors for candidal bloodstream infections in surgical intensive care unit patients: the NEMIS prospective multicenter study. The National Epidemiology of Mycosis Survey. Clin Infect Dis 2001 Jul 15; 33 (2): 177-86
59. Eggimann P, Garbino J, Pittet D. Epidemiology of *Candida* species infections in critically ill non-immunosuppressed patients. Lancet Infect Dis 2003 Nov; 3 (11): 685-702
60. Marr KA, Seidel K, White TC, et al. Candidemia in allogeneic blood and marrow transplant recipients: evolution of risk factors after the adoption of prophylactic fluconazole. J Infect Dis 2000 Jan; 181 (1): 309-16
61. Pappas PG, Rex JH, Lee J, et al. A prospective observational study of candidemia: epidemiology, therapy, and influences on mortality in hospitalized adult and pediatric patients. Clin Infect Dis 2003; 37: 634-43
62. Wey SB, Mori M, Pfaller MA, et al. Risk factors for hospital-acquired candidemia: a matched case-control study. Arch Int Med 1989; 149 (10): 2349-53
63. Martino P, Girmenia C, Micozzi A, et al. Prospective study of *Candida* colonization, use of empiric amphotericin B and development of invasive mycosis in neutropenic patients. Eur J Clin Microbiol Infect Dis 1994; 13 (10): 797-804
64. Diekema DJ, Pfaller MA. Nosocomial candidemia: an ounce of prevention is better than a pound of cure. Infect Control Hosp Epidemiol 2004 Aug; 25 (8): 624-6
65. Ostrosky-Zeichner L. Prophylaxis and treatment of invasive candidiasis in the intensive care setting. Eur J Clin Microbiol Infect Dis 2004 Oct; 23 (10): 739-44
66. Paphitou NI, Ostrosky-Zeichner L, Rex JH. Rules for identifying patients at increased risk for candidal infections in the surgical intensive care unit: approach to developing practical criteria for systematic use in antifungal prophylaxis trials. Med Mycol 2005 May; 43 (3): 235-43
67. Wenzel RP, Gennings C. Bloodstream infections due to *Candida* species in the intensive care unit: identifying especially high-risk patients to determine prevention strategies. Clin Infect Dis 2005 Sep 15; 41 Suppl. 6: S389-93
68. Pelz RK, Hendrix CW, Swoboda SM, et al. Double-blind placebo-controlled trial of fluconazole to prevent candidal infections in critically ill surgical patients. Ann Surg 2001 Apr; 233 (4): 542-8
69. Leon C, Ruiz-Santana S, Saavedra P, et al. A bedside scoring system ("Candida score") for early antifungal treatment in nonneutropenic critically ill patients with *Candida* colonization. Crit Care Med 2006 Mar; 34 (3): 730-7
70. Ostrosky-Zeichner L, Sable C, Sobel J, et al. Multicenter retrospective development and validation of a clinical prediction rule for nosocomial invasive candidiasis in the intensive care setting. Eur J Clin Microbiol Infect Dis 2007 Apr; 26 (4): 271-6
71. Pittet D, Monod M, Suter PM, et al. *Candida* colonization and subsequent infections in critically ill surgical patients. Ann Surg 1994 Dec; 220 (6): 751-8
72. Dupont H, Bourichon A, Paugam-Burtz C, et al. Can yeast isolation in peritoneal fluid be predicted in intensive care unit patients with peritonitis? Crit Care Med 2003 Mar; 31 (3): 752-7
73. Richet H, Roux P, Des Champs C, et al. Candidemia in French hospitals: incidence rates and characteristics. Clin Microbiol Infect 2002; 8: 405-12
74. Tortorano AM, Biraghi E, Astofi A, et al. European Confederation of Medical Mycology (ECMM) prospective survey of candidaemia: report from one Italian region. J Hosp Infect 2002; 51: 297-304
75. Marchetti O, Bille J, Fluckinger U, et al. Epidemiology of candidemia in Swiss tertiary care hospitals: secular trends, 1991–2000. Clin Infect Dis 2004; 38: 311-20
76. Chen YC, Chang SC, Luh KT, et al. Stable susceptibility of Candida blood isolates to fluconazole despite increasing use during the past 10 years. J Antimicrob Chemother 2003; 52: 71-7
77. Hsueh PR, Lau YJ, Chuang YC, et al. Antifungal susceptibilities of clinical isolates of *Candida* species, *Cryptococcus neoformans*, and *Aspergillus* species from Taiwan: surveillance of multicenter antimicrobial resistance in Taiwan program data from 2003. Antimicrob Agents Chemother 2005 Feb; 49 (2): 512-7
78. Pfaller MA, Boyken L, Hollis RJ, et al. In vitro susceptibilities of *Candida* spp. to caspofungin: four years of global surveillance. J Clin Microbiol 2006 Mar; 44 (3): 760-3
79. Colombo AL, Nucci M, Salomao R, et al. High rate of non-albicans candidemia in Brazilian tertiary care hospitals. Diagn Microbiol Infect Dis 1999 Aug; 34 (4): 281-6
80. Pfaller MA, Messer SA, Boyken L, et al. Geographic variation in the susceptibilities of invasive isolates of *Candida glabrata* to seven systemically active antifungal agents: a global assessment from the ARTEMIS Antifungal Surveillance Program conducted in 2001 and 2002. J Clin Microbiol 2004; 42: 3142-6
81. Klevay MJ, Ernst EJ, Hollanbaugh JL, et al. Therapy and outcome of *Candida glabrata* versus *Candida albicans* bloodstream infection. Diagn Microbiol Infect Dis 2008 Mar; 60 (3): 273-7
82. Gudlaugsson O, Gillespie S, Lee K, et al. Attributable mortality of nosocomial candidemia, revisited. Clin Infect Dis 2003 Nov 1; 37 (9): 1172-7
83. Pfaller MA, Diekema DJ, Gibbs DL, et al. Results from the ARTEMIS DISK Global Antifungal Surveillance study, 1997 to 2005: an 8.5-year analysis of susceptibilities of *Candida* species and other yeast species to fluconazole and voriconazole determined by CLSI standardized disk diffusion testing. J Clin Microbiol 2007 Jun; 45 (6): 1735-45
84. Seifert H, Aurbach U, Stefanik D, et al. In vitro activities of isavuconazole and other antifungal agents against Candida bloodstream isolates. Antimicrob Agents Chemother 2007 May; 51 (5): 1818-21
85. National Center for Biotechnology Information. The NCBI taxonomy homepage [online]. Available from URL: http://www.ncbi.nlm.nih.gov/Taxonomy/Browser/wwwtax.cgi?.id = 5475 [Accessed 2008 Jul 16]
86. De Pauw B, Walsh TJ, Donnelly JP, et al. Revised definitions of invasive fungal disease from the European Organization for Research and Treatment of Cancer/Invasive Fungal Infections Cooperative Group and the National Institute of Allergy and Infectious Diseases Mycoses Study Group (EORTC/MSG) Consensus Group. Clin Infect Dis 2008 Jun 15; 46 (12): 1813-21
87. Kuhlman JE, Fishman EK, Siegelman SS. Invasive pulmonary aspergillosis in acute leukemia: characteristic findings on CT, the CT halo sign, and the role of CT in early diagnosis. Radiology 1985 Dec; 157 (3): 611-4
88. Vandewoude KH, Blot SI, Depuydt P, et al. Clinical relevance of Aspergillus isolation from respiratory tract samples in critically ill patients. Crit Care 2006 Feb; 10 (1): R31

89. Garnacho-Montero J, Amaya-Villar R. A validated clinical approach for the management of aspergillosis in critically ill patients: ready, steady, go! [letter]. Crit Care 2006; 10 (2): 132
90. Hope WW, Walsh TJ, Denning DW. Laboratory diagnosis of invasive aspergillosis. Lancet Infect Dis 2005 Oct; 5 (10): 609-22
91. Uffredi ML, Mangiapan G, Cadranel J, et al. Significance of *Aspergillus fumigatus* isolation from respiratory specimens of nongranulocytopenic patients. Eur J Clin Microbiol Infect Dis 2003 Aug; 22 (8): 457-62
92. Husain S, Kwak EJ, Obman A, et al. Prospective assessment of Platelia *Aspergillus* galactomannan antigen for the diagnosis of invasive aspergillosis in lung transplant recipients. Am J Transplant 2004 May; 4 (5): 796-802
93. Kwak EJ, Husain S, Obman A, et al. Efficacy of galactomannan antigen in the Platelia *Aspergillus* enzyme immunoassay for diagnosis of invasive aspergillosis in liver transplant recipients. J Clin Microbiol 2004 Jan; 42 (1): 435-8
94. Digby J, Kalbfleisch J, Glenn A, et al. Serum glucan levels are not specific for presence of fungal infections in intensive care unit patients. Clin Diagn Lab Immunol 2003 Sep; 10 (5): 882-5
95. Vardakas KZ, Michalopoulos A, Falagas ME. Fluconazole versus itraconazole for antifungal prophylaxis in neutropenic patients with haematological malignancies: a meta-analysis of randomised-controlled trials. Br J Haematol 2005 Oct; 131 (1): 22-8
96. Glasmacher A, Cornely O, Ullmann AJ, et al. An open-label randomized trial comparing itraconazole oral solution with fluconazole oral solution for primary prophylaxis of fungal infections in patients with haematological malignancy and profound neutropenia. J Antimicrob Chemother 2006 Feb; 57 (2): 317-25
97. Cornely OA, Maertens J, Winston DJ, et al. Posaconazole vs fluconazole or itraconazole prophylaxis in patients with neutropenia. N Engl J Med 2007 Jan 25; 356 (4): 348-59
98. Vehreschild JJ, Böhme A, Buchheidt D, et al. A double-blind trial on prophylactic voriconazole (VRC) or placebo during induction chemotherapy for acute myelogenous leukaemia (AML). J Infect 2007 Nov; 55 (5): 445-9
99. Cornely OA, Stollorz A, Beisel C, et al. Impact of posaconazole prophylaxis on the epidemiology of invasive aspergillosis. 47th Interscience Conference on Antimicrobial Agents and Chemotherapy; 2007 Sep 17-20; Chicago (IL)
100. Goodman JL, Winston DJ, Greenfield RA, et al. A controlled trial of fluconazole to prevent fungal infections in patients undergoing bone marrow transplantation. N Engl J Med 1992 Mar 26; 326 (13): 845-51
101. Slavin MA, Osborne B, Adams R, et al. Efficacy and safety of fluconazole prophylaxis for fungal infections after marrow transplantation: a prospective, randomized, double-blind study. J Infect Dis 1995; 171 (6): 1545-52
102. Wingard JR, Carter SL, Walsh TJ, et al. Results of a randomized, double-blind trial of fluconazole (FLU) vs voriconazole (VORI) for the prevention of invasive fungal infections (IFI) in 600 allogeneic blood and marrow transplant (BMT) Patients. ASH Annual Meeting; 2007 Dec 8-11; Atlanta (GA)
103. Ullmann AJ, Lipton JH, Vesole DH, et al. Posaconazole or fluconazole for prophylaxis in severe graft-versus-host disease. N Engl J Med 2007 Jan 25; 356 (4): 335-47
104. Ullmann AJ, Heussel CP, Cornely OA. Voriconazole versus liposomal amphotericin B for empirical antifungal therapy. N Engl J Med 2002 May 30; 346 (22): 1745-7; discussion 1747
105. Marr KA. Empirical antifungal therapy: new options, new tradeoffs. N Engl J Med 2002 Jan 24; 346 (4): 278-80
106. Boogaerts M, Winston DJ, Bow EJ, et al. Intravenous and oral itraconazole versus intravenous amphotericin B deoxycholate as empirical antifungal therapy for persistent fever in neutropenic patients with cancer who are receiving broad-spectrum antibacterial therapy: a randomized, controlled trial. Ann Intern Med 2001 Sep 18; 135 (6): 412-22
107. Link H, Böhme A, Cornely OA, et al. Antimicrobial therapy of unexplained fever in neutropenic patient: guidelines of the Infectious Diseases Working Party (AGIHO) of the German Society of Hematology and Oncology (DGHO). Ann Hematol 2003 Oct; 82 Suppl. 2: S105-17
108. Maertens J, Theunissen K, Verhoef G, et al. Galactomannan and computed tomography-based preemptive antifungal therapy in neutropenic patients at high risk for invasive fungal infection: a prospective feasibility study. Clin Infect Dis 2005 Nov 1; 41 (9): 1242-50
109. Viscoli C, Herbrecht R, Akan H, et al. Caspofungin as first-line therapy of invasive aspergillosis in haematological patients: a study of the EORTC Infectious Diseases Group. Trends in Medical Mycology Congress 2007; 2007 Oct 28-31; Turin
110. van't Wout JW, Novakova I, Verhagen CA, et al. The efficacy of itraconazole against systemic fungal infections in neutropenic patients: a randomised comparative study with amphotericin B. J Infect 1991 Jan; 22 (1): 45-52
111. Caillot D, Bassaris H, McGeer A, et al. Intravenous itraconazole followed by oral itraconazole in the treatment of invasive pulmonary aspergillosis in patients with hematologic malignancies, chronic granulomatous disease, or AIDS. Clin Infect Dis 2001 Oct 15; 33 (8): e83-90
112. Denning DW, Lee JY, Hostetler JS, et al. NIAID Mycoses Study Group multicenter trial of oral itraconazole therapy for invasive aspergillosis. Am J Med 1994 Aug; 97 (2): 135-44
113. Ostrosky-Zeichner L. Combination antifungal therapy: a critical review of the evidence. Clin Microbiol Infect 2008 May; 14 Suppl. 4: 65-70
114. Eggimann P, Francioli P, Bille J, et al. Fluconazole prophylaxis prevents intra-abdominal candidiasis in high-risk surgical patients. Crit Care Med 1999 Jun; 27 (6): 1066-72
115. Garbino J, Lew DP, Romand JA, et al. Prevention of severe *Candida* infections in nonneutropenic, high-risk, critically ill patients: a randomized, double-blind, placebo-controlled trial in patients treated by selective digestive decontamination. Intensive Care Med 2002 Dec; 28 (12): 1708-17
116. Swoboda SM, Merz WG, Lipsetta PA. Candidemia: the impact of antifungal prophylaxis in a surgical intensive care unit. Surg Infect 2003 Winter; 4 (4): 345-54
117. Cruciani M, de Lalla F, Mengoli C. Prophylaxis of *Candida* infections in adult trauma and surgical intensive care patients: a systematic review and meta-analysis. Intensive Care Med 2005 Nov; 31 (11): 1479-87
118. Playford EG, Webster AC, Sorrell TC, et al. Antifungal agents for preventing fungal infections in non-neutropenic critically ill and surgical patients: systematic review and meta-analysis of randomized clinical trials. J Antimicrob Chemother 2006 Apr; 57 (4): 628-38
119. Rex JH, Sobel JD. Prophylactic antifungal therapy in the intensive care unit. Clin Infect Dis 2001 Apr 15; 32 (8): 1191-200
120. Ostrosky-Zeichner L, Sobel J, Pappas P, et al. Lessons from a multicenter, randomized, double-blind trial and insights into diagnostic performance of surrogate markers; M-1158. Interscience Conference on Antimicrobial Agents and Chemotherapy 2007; 2007 Sep 17-20; Chicago (IL)
121. Cruciani M, Mengoli C, Malena M, et al. Antifungal prophylaxis in liver transplant patients: a systematic review and meta-analysis. Liver Transpl 2006 May; 12 (5): 850-8
122. Cruciani M, Serpelloni G. Management of *Candida* infections in the adult intensive care unit. Expert Opin Pharmacother 2008 Feb; 9 (2): 175-91
123. Piarroux R, Grenouillet F, Balvay P, et al. Assessment of preemptive treatment to prevent severe candidiasis in critically ill surgical patients. Crit Care Med 2004 Dec; 32 (12): 2443-9

124. Rex JH, Bennett JE, Sugar AM, et al. A randomized trial comparing fluconazole with amphotericin B for the treatment of candidemia in patients without neutropenia. Candidemia Study Group and the National Institute. N Engl J Med 1994 Nov 17; 331 (20): 1325-30

125. Kullberg BJ, Sobel JD, Ruhnke M, et al. Voriconazole versus a regimen of amphotericin B followed by fluconazole for candidaemia in non-neutropenic patients: a randomised non-inferiority trial. Lancet 2005 Oct 22-28; 366 (9495): 1435-42

126. Kuse ER, Chetchotisakd P, da Cunha CA, et al. Micafungin versus liposomal amphotericin B for candidaemia and invasive candidosis: a phase III randomised double-blind trial. Lancet 2007 May 5; 369 (9572): 1519-27

127. Pappas PG, Rotstein CM, Betts RF, et al. Micafungin versus caspofungin for treatment of candidemia and other forms of invasive candidiasis. Clin Infect Dis 2007 Oct 1; 45 (7): 883-93

128. Reboli AC, Rotstein C, Pappas PG, et al. Anidulafungin versus fluconazole for invasive candidiasis. N Engl J Med 2007 Jun 14; 356 (24): 2472-82

129. Greene RE, Schlamm HT, Oestmann JW, et al. Imaging findings in acute invasive pulmonary aspergillosis: clinical significance of the halo sign. Clin Infect Dis 2007 Feb 1; 44 (3): 373-9

130. Walsh TJ, Anaissie EJ, Denning DW, et al. Treatment of aspergillosis: clinical practice guidelines of the Infectious Diseases Society of America. Clin Infect Dis 2008 Feb 1; 46 (3): 327-60

131. Karthaus M. Treatment of aspergillosis. Clin Infect Dis 2008; 47 (3): 427

132. Maertens J, Verhaegen J, Lagrou K, et al. Screening for circulating galactomannan as a noninvasive diagnostic tool for invasive aspergillosis in prolonged neutropenic patients and stem cell transplantation recipients: a prospective validation. Blood 2001 Mar 15; 97 (6): 1604-10

133. Rovira M, Jimenez M, De La Bellacasa JP, et al. Detection of *Aspergillus* galactomannan by enzyme immunoabsorbent assay in recipients of allogeneic hematopoietic stem cell transplantation: a prospective study. Transplantation 2004 Apr 27; 77 (8): 1260-4

134. Maertens J, Van Eldere J, Verhaegen J, et al. Use of circulating galactomannan screening for early diagnosis of invasive aspergillosis in allogeneic stem cell transplant recipients. J Infect Dis 2002 Nov 1; 186 (9): 1297-306

135. Maschmeyer G, Beinert T, Buchheidt D, et al. Diagnosis and antimicrobial therapy of pulmonary infiltrates in febrile neutropenic patients: guidelines of the Infectious Diseases Working Party (AGIHO) of the German Society of Hematology and Oncology (DGHO). Ann Hematol 2003 Oct; 82 Suppl. 2: S118-26

136. Morrell M, Fraser VJ, Kollef MH. Delaying the empiric treatment of *Candida* bloodstream infection until positive blood culture results are obtained: a potential risk factor for hospital mortality. Antimicrob Agents Chemother 2005 Sep; 49 (9): 3640-5

137. Garey KW, Rege M, Pai MP, et al. Time to initiation of fluconazole therapy impacts mortality in patients with candidemia: a multi-institutional study. Clin Infect Dis 2006 Jul 1; 43 (1): 25-31

138. Magill SS, Shields C, Sears CL, et al. Triazole cross-resistance among *Candida* spp.: occurrence among bloodstream isolates, and implications for antifungal therapy [case report]. J Clin Microbiol 2006 Feb; 44 (2): 529-35

139. Perlin DS. Resistance to echinocandin-class antifungal drugs. Drug Resist Updat 2007 Jun; 10 (3): 121-30

140. Pfaller MA, Diekema DJ, Gibbs DL, et al. Geographic and temporal trends in isolation and antifungal susceptibility of *Candida parapsilosis*: a global assessment from the ARTEMIS DISK Antifungal Surveillance Program, 2001 to 2005. J Clin Microbiol 2008 Mar; 46 (3): 842-9

141. van Burik JA, Ratanatharathorn V, Stepan DE, et al. Micafungin versus fluconazole for prophylaxis against invasive fungal infections during neutropenia in patients undergoing hematopoietic stem cell transplantation. Clin Infect Dis 2004 Nov 15; 39 (10): 1407-16

Correspondence: Dr *Oliver A. Cornely*, Department I of Internal Medicine, Clinical Trials Unit Infectious Diseases II, Hospital of the University of Cologne, Kerpener Straβe 62, Cologne, 50937, Germany.
E-mail: oliver.cornely@ctuc.de