Pre-Emptive Antifungal Therapy in Neutropenic Onco-Hematology Patients
Johan Maertens, Koen Theunissen, Katrien Lagrou, Tom Lodewyck, and Johan Van Eldere

Antifungal Prophylaxis in Patients with Hematological Cancers
Gloria N Mattiuzzi and Hagop Kantarjian

Case Study: Rhino-Orbito-Cerebral Zygomycosis
Raoul Herbrecht, Caroline Berthillot, and Cécile Fohrer

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Foreword

Dear Colleagues,

Welcome to the first issue of The Journal of Invasive Fungal Infections.

This new, CME-accredited journal has been created to identify and highlight important developments within the arena of antifungal treatments. The journal will appear quarterly and will provide access to a critical and clinically relevant review of information regarding fungal infections as it pertains to both health and disease.

Each issue will include review articles authored by leading specialists. These manuscripts are peer-reviewed for quality and CME-accredited to provide an ongoing educational resource. In addition, summaries and analyses of recent papers, chosen for their impact upon the field, are provided for the reader together with highlights from recent international conferences.

The first issue contains two articles and a case study. The first article from Johan Maertens and colleagues (University Hospital Gasthuisberg, Catholic University Leuven, Leuven, Belgium) investigates the use of non-culture based microbiological tools along with more traditional techniques such as assessing clinical signs, cultures, and radiological imaging and emerging methods of detecting fungal antigens DNA to improve the early diagnosis of invasive fungal infections in patients with an underlying hematological disorder. It is hoped that starting treatment pre-emptively and using these tools to monitor the course of fungal disease and response to treatment will improve outcomes in this group.

The second article by Drs Mattiuzzi and Kantarjian (The University of Texas MD Anderson Cancer Center, Houston, TX, USA) explores the use of prophylaxis for the treatment of invasive fungal infections. Despite the high rates of morbidity and mortality in patients with hematological malignancies caused by such infections, indiscriminate use of antifungal prophylaxis can lead to high costs, drug toxicity, and the emergence of resistant species. Despite the associated diagnostic difficulties, it is imperative to determine those patients who would benefit most from a prophylactic approach and to ensure that the optimal treatment strategy for the appropriate spectrum of fungal infections is given.

The case study, presented by Raoul Herbrecht and coworkers (Hôpital de Hautepierre, Strasbourg, France) examines the treatment course of a patient with rhino-orbito-cerebral zygomycosis. This is followed by a synopsis and critique of recently published scientific findings from several key areas relating to fungal infections. The issue concludes with highlights of presentations from the 46th Annual Interscience Conference on Antimicrobial Agents and Chemotherapy (ICAAC) conference, held in San Francisco, CA, earlier this year.

We hope you find The Journal of Invasive Fungal Infections an educational and valuable tool. We welcome your feedback regarding the material presented as well as your suggestions for future topics to be covered. On behalf of the Editorial Board and the publisher, I would like to thank you for reading the first issue of what we believe will be an exciting and useful new journal in this developing field.

John R Perfect
Editor-in-Chief

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In 1993, I wrote an editorial entitled “Antifungal Prophylaxis: to Prevent or Not” [1]. This discussion was written before the introduction of highly active antiretroviral therapy (HAART) for HIV infection, and high-risk transplantation patients were just beginning to receive prophylactic antifungal strategies. It was written at a time when empirical antifungal drug use was standard care in febrile neutropenic patients, and pre-emptive treatment strategies with biomarkers and sophisticated radiographs were not routinely available. Of course, medicine has evolved over the last decade. For example, HAART has limited the need for widespread antifungal prophylaxis in HIV infection and, at present, the only antifungal agent to be routinely recommended is cotrimoxazole for *Pneumocystis jiroveci* in patients with poor immune reconstitution. Furthermore, in very high-risk bone marrow transplant recipients, azole prophylaxis is a well-accepted strategy. However, even in this risk group there is likely to be a further shift in favor of more mold-active prophylaxis in response to the recent FDA approval of posaconazole prophylaxis during graft-versus-host disease and in neutropenic patients receiving induction chemotherapy for acute myeloid leukemia and myelodysplastic syndrome. On the other hand, we still struggle to develop preventive strategies for fungal infections in intensive care units, certain solid organ transplant recipients, and those with new mechanical hardware such as left ventricular assist devices. The concept of antifungal prophylaxis is as alive and pertinent today as it was a decade ago.

In medicine today, we attempt to control severe underlying diseases at the edge of immune protection, and many patients are not far from being a “human Petri dish”. With monoclonal antibodies and chemotherapies mixed with immune modulators, we are able to alter the immune system with unprecedented rapidity. The patient either has too little or too much immunity, and obstructing the goal of getting it just right is the dreaded fungal infection. Despite a changing medical world, the six criteria listed in my previous editorial to justify antifungal prophylaxis remain.

1. **Safety**
   Prophylactic regimens must not cause further harm to the host. Fortunately, the azole compounds are relatively safe, but they do have side effects and drug interactions, and the candins must be given intravenously. The polyenes have defined toxicities but may be safer in aerosol forms.

2. **Efficacy**
   There are some convincing studies with randomized and blinded designs that support prophylaxis. However, in many situations antifungal prophylaxis strategies have not been validated using placebo groups and are introduced into clinical practice based on opinions, perceptions, and ethical issues. Some practices may be correct, but they are definitely not certain.

3. **Cost**
   It is a hospital executive’s nightmare to see the high acquisition costs for new drugs given to patients, when only a small minority may actually receive a benefit. Conversely, reduced hospitalizations through the prevention of infections, and productivity gain by not having to manage or live with a life-threatening fungal infection, may mean that it is cost-effective to prevent these serious adverse events. We simply need more robust studies on the pharmacoeconomics of fungal infections and their prevention to show economic advantages.

4. **Consequence**
   In the final analysis, this remains the most important criterion for justification of antifungal prophylaxis. Does it really make a difference in the final outcome of the patient, reduce pain and suffering, improve quality of life, and/or allow us to treat the underlying disease better, or does it simply make the caregiver feel better? In fact, the final arbitrator in the successful management of a fungal infection is successful control of the underlying disease. A fungal infection can cause a major “speed bump” in the algorithms for the timing of the treatments for the underlying disease. Many of the patients with severe diseases cannot afford to have their specifically timed
treatments compromised and prevention of a complication is critical.

5. Prevalence
It is always important that each institution understands the risk of fungal infections in their specific high-risk patient populations. Local epidemiology is important. I previously suggested that the risk group for prophylaxis would need a 10% frequency of fungal infection to make any single institution observe a statistical improvement in terms of a reduction of infections with a prophylaxis strategy [1]. This figure is still a reasonable starting point, but with large numbers of high-risk patients in certain centers, prophylaxis may be successfully used when the frequency is even a little lower than 10%.

6. Resistance
When we unleash a widespread use of an antimicrobial agent, we need to be aware of the potential for drug resistance development. Fortunately, fungi do not possess drug-resistance plasmids or transposons, although drug efflux pumps can upregulate within a strain to make the agent ineffective, and superinfections with drug-resistant fungi have been well-described. From the recent occurrence of zygomycotic superinfections in patients receiving voriconazole, to potential future concerns of breakthrough infections with Candida glabrata and Scedosporium spp during extended-spectrum triazole administration, there is always a risk of the increased appearance of resistant yeasts and molds with the widespread use of antifungals. We must take care to keep our limited number of antifungal agents intact for treatment strategies.

In my previous editorial I stated an opinion that is as true today as it was in the 1990s: “An ounce of prevention is worth a pound of cure is only true when you know the true weight of the prevention”. We must be rigorous in our clinical practice and supporting studies to ensure that antifungal prophylaxis validates its use in specific patient populations using consideration of the six criteria set out above. When the balance of information supports antifungal prophylaxis we should not be afraid to use it. On the other hand, we should not blindly accept its existence. Taken together, I would always prefer to prevent a fungal infection than treat it, and I suspect the patient and the attending clinician concur with this statement.

Reference
While antifungal prophylaxis has successfully decreased the incidence of invasive yeast infections, invasive fungal (mold) infections (angio-invasive pulmonary aspergillosis in particular) continue to be an emerging cause of morbidity in virtually all severely immunosuppressed hematology patients [1]. In addition, these fungal infections carry high crude and attributable mortality rates, especially in allogeneic hematopoietic stem cell transplant (HSCT) recipients and in patients with acute leukemia or myelodysplastic syndrome who undergo intensive chemotherapy [2,3]. Moreover, even if treated successfully, fungal infections have a high propensity to reactivate in the setting of continued immunosuppression, often resulting in unacceptable delays to potentially curative cytoreductive therapy [4].

The high mortality rates of invasive fungal infections (>70% for some mold infections) stem, in part, from substantial delays in establishing a diagnosis [5]. Indeed, many high-risk patients have decreased inflammatory responses and clinical features that, although variable and usually non-specific, may not manifest in the early stages of infection. Fever not responding to 4–5 days of broad-spectrum antibacterial coverage usually represents the first clinical clue in non-steroid treated neutropenic patients [5]. However, survival rates can be dramatically improved by the early initiation of adequate antifungal therapy, when the fungal burden is low and tissue damage is limited [6].

For many years, conventional microbiological (culture and microscopy), histological, and radiological techniques were the cornerstones of fungal infection diagnosis, but these tools had a limited impact on clinical decision making because they are insensitive and time consuming. In an effort to overcome these diagnostic obstacles, the empirical use of antifungal agents was introduced in the late 1980s [7]. Empirical antifungal therapy primarily targets profoundly neutropenic patients (intensive chemotherapy for acute leukemia or myelodysplastic syndrome and allogeneic HSCT following conventional intensity conditioning) with unexplained or relapsing fever in the absence of other clinical, microbiological, or radiological findings suggestive of fungal infection. Although the effectiveness of empirical antifungal therapy in this setting has been assessed in just two small series of patients [8,9], this strategy has rapidly been adopted as the standard of care worldwide and has repeatedly been endorsed by consensus guidelines [10]. However, the late 1990s witnessed a growing awareness of the low specificity and predictive value of persistent or relapsing fever for diagnosing fungal infections. Consequently, empirical antifungal therapy is associated with significant overtreatment, resulting in increased expenditure and risk of
adverse effects [11]. In addition, most empirical studies continue to observe an approximately 10% incidence of breakthrough fungal infection [12].

Recent improvements in the diagnosis of fungal infections have prompted a further reappraisal of the concept of empirical antifungal therapy [13]. The time period between the biological start of the infection and the appearance of clinical signs and symptoms (e.g. pleuritic chest pain or hemoptysis) represents a window of opportunity that may allow earlier and more targeted therapeutic intervention. In such a scenario, the decision to start antifungal therapy would not be triggered by fever but would rely both on better identification of those at risk and the availability of sensitive techniques able to facilitate rapid and early diagnosis of invasive fungal infections. This window could be identified via prospective screening strategies using new serodiagnostic assays – the Platelia Aspergillus enzyme immunoassay (PA-EIA, Bio-Rad Laboratories, Marnes-La-Coquette, France & Bio-Rad Laboratories, Hercules, CA, USA) for the detection of galactomannan (GM), or the Fungitell assay, (Associates of Cape Cod Inc., East Falmout, MA, USA) for the detection of (1,3)-β-D-glucan – and/or polymerase chain reaction (PCR) techniques for the detection of fungal-specific DNA [14]. In line with recent guidelines, these tools should be used in conjunction with modern imaging techniques such as high-resolution computed tomography (CT) scanning, which has been shown to improve earlier diagnosis and survival [15,16].

In the most recent literature, this new approach is usually referred to as “pre-emptive antifungal therapy”, although “targeted prophylaxis”, “early targeted therapy”, “presumptive therapy”, and even “targeted empirical therapy” have all been used to describe the same technique. Conceptually, pre-emptive therapy involves the treatment of those patients in whom there is evidence of the presence of a pathogen that predisposes for the development of invasive disease. The concept has successfully been applied to the management of viral infections following HSCT or solid organ transplantation. Indeed, transplant recipients with suspected cytomegalovirus (e.g. positive antigenemia or PCR assay) often receive pre-emptive antiviral therapy in view of their increased likelihood of developing life-threatening disease if left untreated [17]. However, the new serological assays for fungal diagnosis do not allow this form of pre-emptive approach, since seropositivity signifies that the patient already has fungal disease. A truly pre-emptive antifungal approach, similar to the antiviral strategy, is not yet feasible, although PCR-based attempts look promising [18]. Nevertheless, for the purpose of this article and to be consistent with recent literature, we will use the term “pre-emptive antifungal therapy” to describe an antifungal approach that is based on the incorporation of new, non-invasive, non-culture based microbiological tools (NCBMTs).

**New diagnostic tools from the mycology lab**

Detection of galactofuranosyl-containing molecules

Over the past 2 decades, significant experience has been gained with the PA-EIA, a second-generation seroassay with improved performance compared with the earlier latex agglutination assay. This sandwich enzyme immunoassay detects galactofuranosyl-containing molecules, including galactomannan (GM) – a polysaccharide cell wall component of *Aspergillus* spp (and a few other molds) that is released into the circulation during hyphal growth in tissues [19]. The test has been commercially available in Europe since the mid 1990s and was approved by the US Food and Drug Administration (FDA) for diagnostic use in May, 2003 [20]. Consensus criteria from the EORTC/MSG (European Organisation for the Research and Treatment of Cancer and the Mycosis Study Group) state that the detection of GM in the body fluids (predominantly serum/plasma and bronchoalveolar lavage [BAL] fluid) of cancer patients and HSCT recipients is as diagnostically valuable as the isolation of *Aspergillus* spp on culture or the microscopic demonstration of hyphae [21]. GM detection in serum and BAL fluid was included in the microbiological criteria following the excellent diagnostic accuracy of the PA-EIA as reported by studies in the late 1990s involving profoundly neutropenic patients undergoing chemotherapy for acute leukemia/myelodysplastic syndrome or recipients of HSCT [22–28]. In some of these studies, PA-EIA positivity preceded the conventional diagnosis of invasive aspergillosis (IA) by an average of 1 week [29]. However, more recent studies that have included non-neutropenic patients (e.g. solid tumor patients, solid organ transplant recipients, and intensive care unit patients) have reported significantly lower sensitivities and positive predictive values [19]. Hence, it remains unclear whether a case of IA can be defined by the PA-EIA and, more importantly, whether a reliable pre-emptive approach can be designed based upon serial monitoring for the presence of GM [30].

A recent meta-analysis of 27 studies assessed the diagnostic performance of the PA-EIA and reported a pooled sensitivity (for proven and probable cases of IA) of 61% and an overall specificity of 93% [31]. However, the study also identified subgroups of patients and conditions in which the assay performed significantly better: the accuracy of the test differed by study population (adults > children), by underlying disorder (hematological malignancy and allogeneic stem cell transplantation > solid organ transplantation), and by the stringency of the criteria used to define a case of IA (EORTC/MSG criteria > other criteria). Thus, methodological
and clinical inter-study heterogeneities undermine the generalizability of test results across patient populations [30,32]. For instance, differences in the pathogenesis of IA in neutropenic and steroid-treated patients account in part for variations in test performance [33,34].

In addition, a number of clinically important caveats remain regarding the performance of the PA-EIA, including the negative impact of mold-active antifungal prophylaxis or empirical therapy [35,36]. Other factors, such as the use of antibacterial therapy with semi-synthetic β-lactam antibiotics (piperacillin-tazobactam; amoxicillin-clavulanate) [37] or the presence of anti-GM antibodies, may also affect the performance and/or interpretation of the assay [28]. Fortunately, one area of controversy has recently been resolved; in Europe, the optical density index cut-off level for a positive result has been lowered to 0.5, identical to the proposed cut-off in the US [38]. However, different cut-off values may be needed for different clinical settings [39]. Finally, the optimal frequency of sampling has not yet been determined and it remains unclear whether or not a positive sample should be confirmed and, if so, whether this should be by a subsequent sample or by retesting the first sample [40]. However, overall, the high specificity and excellent negative predictive value of the PA-EIA in neutropenic patients, especially if used in combination with sensitive radiological tools, allows a diagnosis of IA to be ruled out.

**Detection of (1,3)-β-D-glucan**

Glucans, (1,3)-β-D-linked polymers of glucose, are part of the outer cell wall of most pathogenic yeasts and filamentous fungi (exceptions are *Cryptococcus* spp and the zygomycetes). Two commercially available colorimetric assays (Fungitell [previously Glucatell]), and FungiTec G, Seikagaku Kogyo Corporation, Tokyo, Japan) and one turbidimetric assay (Wako-WB003, Wako Pure Chemical industries, Osaka, Japan) can be used to detect (1,3)-β-D-glucan. These assays are based on the ability of horseshoe crab hemolymph to clot in response to trace amounts of (1,3)-β-D-glucan (as low as 1 pg/mL) [5,14].

These tests are widely used in Japan and the Fungitell assay has recently been approved by the FDA as an aid for the diagnosis of invasive fungal infections in cancer patients, based on an assessment in patients with acute leukemia and myelodysplastic syndrome [41]. At a cut-off level 60 pg/mL, the negative predictive value of twice weekly sampling was 100%. Additionally, sensitivity was 100% if one positive assay was considered a truly positive result. Of note, test results were not influenced by the prophylactic or empirical use of antifungals.

However, overall experience with these assays remains limited and many of the methodological shortcomings that have hampered the evaluation of the GM detection assay also apply to the detection of (1,3)-β-D-glucan. These include the inadequate use of a case–control design, the heterogeneity of the study population, the spectrum of alternative diagnoses, the number of collected serum samples, and the cut-off for positivity [42,43]. In addition, the use of endotoxin- and glucan-free glassware is required and a number of factors can lead to false-positive readings, including the use of albumin or immunoglobulins, exposure to glucan-containing gauze (following surgery), and hemodialysis [14]. Moreover, the assay cross-reacts with some antimicrobial preparations, both *in vitro* and *in vivo* (amoxicillin-clavulanate) and can test false-positive in patients with Gram-positive bacteremia [44,45].

However, given the broad spectrum of fungal species that can be detected by the assay and the excellent negative predictive value, these tests seem to be useful for excluding invasive fungal infections. The specificity and the positive predictive value of the glucan assay could be improved by combining it with the PA-EIA.

**Detection of fungal DNA**

The amplification of unique gene sequences by polymerase chain reaction (PCR) techniques offers the potential for rapid detection and identification of molds at the genus level [46,47]. Mainly in European centers, PCR detection is increasingly appreciated as being a valuable diagnostic tool for diagnosing fungal infections. Sensitivity and negative predictive values have usually been excellent. However, there remains a great deal of debate regarding routine clinical applicability. All PCR assays have been developed in-house, using different sample specimens, extraction methods, PCR designs, and detection and specification of the amplicon. Thus, due to the lack of a standardized, reproducible, and validated (commercially available) method, the routine use of PCR in the diagnosis of invasive fungal infections cannot yet be recommended. However, panfungal assays that amplify a conserved region of 18S ribosomal DNA, using real-time techniques combined with automated DNA extraction, may allow standardization and reproducibility between centers and thus broaden the clinical applicability of PCR-based diagnosis in the near future. Once again, PCR may be useful for excluding invasive fungal infections because of its ability to detect a broad spectrum of fungi and its high negative predictive value.

**Combination of non-culture based tools**

Prior to 2002, only a few small retrospective studies investigated the use of combinations of NCBMTs for the diagnosis of fungal infection, with generally inconsistent results. More recently, Buchheidt and colleagues compared...
LightCycler PCR (Roche, Basel, Switzerland), nested PCR, and PA-EIA in a series of hematology patients [48]. Nested PCR was superior to PA-EIA with respect to sensitivity (63.6% vs. 33.3%), but significantly more episodes tested false-positive by PCR. In addition, the rate of false-positivity correlated with the total number of samples per study episode. In line with previous observations, real-time quantitative LightCycler PCR was less sensitive. A Japanese group monitored the levels of Aspergillus DNA, GM, and (1,3)-β-D-glucan (by kinetic assay) in high-risk hematology patients and evaluated the diagnostic potentials by using receiver operating characteristic (ROC) analyses [49]. The ROC curve for the PA-EIA (at an optical density index of 0.6) was better than that for the other two tests. Recent studies that focused on combinations of these tests demonstrated improved performance with GM plus (1,3)-β-D-glucan detection [50], GM plus PCR detection [51], and PCR enzyme-linked immunosorbent assay plus GM detection [52].

The pre-emptive approach

The excellent negative predictive value of the PA-EIA, PCR, or (1,3)-β-D-glucan assay should convince clinicians to withhold empirical antifungal therapy in persistently febrile neutropenic patients with no other clinical, microbiological, or radiological evidence of fungal infection. Conversely, given the high positive predictive value in neutropenic patients, confirmed test positivity should trigger a diagnostic work-up and should lead to the early pre-emptive initiation of antifungal (anti-Aspergillus in the case of PA-EIA positivity) therapy, irrespective of the presence or absence of fever. Hence, the pre-emptive use of antifungals may precede or follow the classic criterion for starting empirical antifungal therapy. This reasoning is supported by a decision analysis model presented by Severens et al., in which pre-emptive therapy, in contrast to a conventional approach, resulted in fewer patients being treated without incorrectly withholding therapy [53].

However, thus far, few studies have assessed the so-called pre-emptive approach. One study looked at the feasibility of a PCR-guided strategy in pediatric cancer patients who did not receive antifungal prophylaxis [54]. Patients with neutropenic fever were screened for fungal infection by means of blood culture and PCR assay simultaneously. Antifungal therapy was withheld if PCR and blood culture results remained negative and if there was no other evidence of invasive fungal infection. Conversely, positive blood culture or two consecutive positive PCR assays resulted in initiation of antifungal treatment. Antifungal therapy was not administered in 52 PCR-negative episodes and fungal infection was not documented. Of 29 PCR-positive episodes, 22 were confirmed by positive culture; culture-negative, PCR-positive episodes were mainly seen in patients with hepatosplenic candidiasis. Of note, PCR-positivity preceded the final blood culture by 1–8 days, resulting in earlier adequate therapy.

Recently, we assessed the feasibility of a computed tomography (CT) scan combined with a GM detection-based approach (with an optical density cutoff level of ≥0.5) in a prospective trial in adult neutropenic hematology patients [55]. This non-comparative study was designed to explore the feasibility of starting antifungal therapy based on diagnostic information with a high predictive value (both positive and negative) as an alternative to the classic empirical approach, in an attempt to reduce the exposure to antifungal agents. Whereas a purely fever-driven approach would have resulted in antifungal treatment in at least 41 of 136 episodes (30%), a pre-emptive algorithm led to initiation of antifungals in <25% of these episodes. Furthermore, this approach identified 10 episodes of fungal infection that would not have been identified by the conventional approach due to the absence of fever or the presence of coexisting febrile conditions. Just one case of disseminated zygomycosis out of 22 cases of invasive fungal infection remained undetected. The overall mortality rate of 18% was considered acceptable for a neutropenic population with probable invasive fungal disease. These encouraging data have been confirmed by a study in allogeneic HSCT recipients [56] and by two recent Spanish series [57,58].

There are now several microbiological and radiological tools that have the potential to be used to identify an invasive fungal/Aspergillus infection at an early stage or that can rule out the presence of an invasive fungal/Aspergillus infection in high-risk neutropenic hematoo-ncology patients. The high negative predictive value of a normal CT scan and serial negative NCBMTs rules out the presence of an invasive pulmonary fungal infection, whereas the high positive predictive value of a suggestive CT scan (e.g. halo-sign) and positive NCBMTs warrants the initiation of mold-active antifungal therapy (the agent of choice depends on the species specificity of the assay). All scenarios in-between remain inconclusive (fungal or non-fungal; infectious or non-infectious) and warrant a more aggressive approach, including invasive diagnostic procedures for adequate sampling for culture and microscopy (e.g. CT-guided bronchoscopy with lavage) and for obtaining tissue specimens for histopathological examination [59].

Prospective multicenter studies comparing pre-emptive or early therapy approaches versus empirical therapy should determine the impact of more targeted approaches in terms of outcome and cost-effectiveness [60]. However, as recently...
evidenced, these studies will be difficult to undertake because they require the full cooperation and compliance of all parties (clinicians, microbiologists, radiologists, nursing team etc.) and the strict adherence to a protocol of minimum standards of diagnosis [61]. Such endeavors will only be possible if healthcare providers combine their efforts and establish a consortium to support such a study using a standardized diagnostic approach that has gained widespread acceptance [62].

Conclusion

The management of invasive fungal (mold) infections in patients with an underlying hematological disorder has been hampered by the inability to diagnose these infections since definite diagnosis invariably centers on histological identification of hyphae in tissue or on culture. As such, most practitioners tend to rely on generalized prophylaxis and empirical therapy. Currently, there is a shift in emphasis from waiting for definite diagnosis or starting empirical therapy to screening high-risk adult neutropenic patients so that clinicians can administer appropriate antifungal therapy early, when it can potentially improve patient outcome. NCBMTs are at the forefront of this paradigm shift. Commercially available and emerging methods to detect fungal antigens and sophisticated techniques to detect fungal DNA may be useful when used serially over the period of highest risk. Together with the assessment of clinical signs, cultures, and radiological imaging (CT scan), they may prove useful in screening patients with hematological malignancies, both for starting antifungal therapy and for monitoring the course of the disease and the response to treatment.

Disclosure

J Maertens is a member of the advisory boards for Gilead, MSD, Shering-Plough, Zeneus, Pfizer, and Astellas, and has received speakers’ honoraria from all of these companies. K Theunissen, K Lagrou, T Lodewyck, J van Eldere have no relevant financial interests to disclose.

References

PRE-EMPTIVE ANTIFUNGAL THERAPY IN NEUTROPENIC ONCO-Hematology Patients


Antifungal Prophylaxis in Patients with Hematological Cancers

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Invasive fungal infections (IFIs) cause morbidity and mortality in patients with hematological malignancies. Due to the high mortality rate and diagnostic difficulties associated with IFI, particularly mold infections, prophylaxis emerges as one of the most appealing strategies. However, the routine and indiscriminate use of antifungal prophylaxis may lead to undesirable effects, including high cost, toxicity, and emergence of resistant species. Thus, it is essential to identify which patients are most likely to benefit from a prophylactic approach. Several options are available in the setting of antifungal prophylaxis. The choice of the optimal prophylactic strategy should be made using a risk-based approach and be appropriate for the spectrum of fungal infections at each treatment center. J Invasive Fungal Infect 2007;1(1):10–6.

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Patients at risk
Among patients with cancer, those with hematological malignancies appear at highest risk for IFI. Risk factors for IFI result from the interaction of immunosuppression (secondary to the underlying disease and cytotoxic chemotherapy), organ damage, and environmental exposure to pathogens (Table 1) [1].

Not all hematological malignancies are associated with the same risk of IFI. Patients with acute myelogenous leukemia (AML) undergoing remission induction chemotherapy are at high risk of developing IFI because of the low numbers of granulocytes at diagnosis, the intensity of the chemotherapeutic regimen, and the resulting prolonged neutropenia (approximately 3 weeks). During chemotherapy, ≤25% of AML patients develop IFI, and the mortality rate is unacceptably high, especially for those with mold infections. During consolidation therapy, recovery from neutropenia is much faster (approximately 2 weeks), even though anti-leukemia treatment is as intensive as that given during remission induction; and the risk of IFI is substantially lower (<1%) during this phase of therapy. Indeed, an evaluation of the causes for hospitalization during a 6-month period (June–November, 2001) among 49 patients with AML in remission who were receiving consolidation chemotherapy, revealed that infection was responsible for hospitalization in only 11 (22%) of the patients, (four bacteremia, one sinusitis, and six fever of unknown origin). None of the infections involved fungi [Mattiuzzi, unpublished data].

Among AML patients, those at highest risk for IFI are patients with relapsed or resistant disease. This is due to the need for repeated application of intensive cytotoxic...
therapies, which can result in prolonged neutropenia and other immunosuppression in patients who have been exposed to fungi by colonization or by prior fungal infection during preceding therapies.

Patients with acute lymphocytic leukemia (ALL) are susceptible to IFI due to neutropenia and long-term exposure to high-dose corticosteroids. The incidence of IFI in 13% of ALL patients is similar to the incidence seen among

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**Table 1. Risk factors for invasive fungal infection in patients with hematological cancers.**

<table>
<thead>
<tr>
<th>Risk factor</th>
<th>Infection</th>
<th>Population</th>
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<td><strong>Microbial exposure</strong></td>
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<tr>
<td>Colonization and exposure</td>
<td>Invasive candidiasis</td>
<td>AML, autoBMT</td>
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<tr>
<td>Mucosal</td>
<td>Aspergillosis</td>
<td>Hematological malignancies</td>
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<td>Cancer (exposure to antibiotics)</td>
<td>Fusariosis</td>
<td>Hematological malignacies</td>
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<td>Nasal</td>
<td>Aspergillosis</td>
<td>AML</td>
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<td>Cutaneous</td>
<td>Fusariosis</td>
<td>AML, ALL, lymphomas</td>
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<td>History of fungal infection</td>
<td>Aspergillosis</td>
<td>Non-Hodgkin’s lymphoma</td>
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<td>Fusariosis</td>
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<td>Blastomycosis, Coccidioidomycosis</td>
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<td><strong>Net state of immunosuppression</strong>*</td>
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<td>Broad immunosuppression</td>
<td>Yeast and mold infections</td>
<td>Allo, autoBMT/PBSCT</td>
</tr>
<tr>
<td>Age (older)</td>
<td>Yeast and mold infections</td>
<td>AlloBMT</td>
</tr>
<tr>
<td>Myeloablative chemotherapy</td>
<td>Yeast and mold infections</td>
<td>Several patient populations</td>
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<tr>
<td>Low CD34+ stem cell dose</td>
<td>Yeast and mold infections</td>
<td>Several patient populations</td>
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<tr>
<td>Stem cell manipulation (CD34+ selection)</td>
<td>Various infections</td>
<td>Several patient populations</td>
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<tr>
<td>Histocompatibility</td>
<td>Invasive aspergillosis</td>
<td>AlloBMT</td>
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<tr>
<td>Extensive prior chemotherapy</td>
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<td>Several patient populations</td>
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<tr>
<td>Interleukin-2 therapy</td>
<td>Invasive aspergillosis</td>
<td>Several patient populations</td>
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<tr>
<td>Profound and persistent neutropenia**</td>
<td>Aspergillosis, invasive candidiasis, fusariosis</td>
<td>AML, &gt; solid tumors</td>
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<td>Lymphopenia and CD4 cytopenia</td>
<td>Cryptococcosis</td>
<td>AlloBMT</td>
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<tr>
<td>All causes</td>
<td>Aspergillosis</td>
<td>Therapy with nucleoside analogues</td>
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<td>Aspergillosis, invasive candidiasis, PCP, other</td>
<td>All patients</td>
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<tr>
<td>≥3 to 5 weeks</td>
<td>Yeast and mold infections</td>
<td>CLL, lymphoma</td>
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<tr>
<td>Nucleoside analogues</td>
<td>Yeast and mold infections</td>
<td>CLL</td>
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<td>Campath-1H</td>
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<td>Acute leukemias</td>
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<tr>
<td>Refractory malignancy</td>
<td>Yeast and mold infections</td>
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<td>RF</td>
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<td>Pulmonary</td>
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<tr>
<td>Pancreas (diabetes mellitus)</td>
<td>Candidiasis, zygomycosis</td>
<td>All patients</td>
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<tr>
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<td>Invasive candidiasis</td>
<td>GVHD</td>
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<td>Cryptococcosis, candidiasis</td>
<td>Sezary Syndrome</td>
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<tr>
<td></td>
<td>Aspergillosis and infection with Malassezia spp</td>
<td>Trauma (CVC site)</td>
</tr>
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</table>

*Immunosuppression may be limited to one arm of the immune system, or found in more than one arm (neutropenia, lymphopenia, asplenia, and others) in patients receiving myeloablative therapy. **Profound and persistent: <100 cells/µL ≥10 days.

ALL: acute lymphocytic leukemia; allo: allogeneic; AML: acute myeloid leukemia; aspergillosis: invasive *Aspergillus* infection; auto: autologous; BMT: bone marrow; transplantation; candidiasis: invasive candidiasis; CLL: chronic lymphocytic leukemia; CVC: central venous catheter; GVHD: graft versus host disease; PBSCT: peripheral blood stem cell transplantation; PCP: *Pneumocystis carinii* pneumonia; RF: renal failure.

Adapted with permission from [1].
patients with AML. IFIs in patients with AML and ALL predominantly involve *Candida* and *Aspergillus* spp. However, the fungal-related mortality rate for ALL patients is much lower compared with that in AML patients [2]. Possible explanations for this difference in mortality rate are:

- The high remission rates achieved in ALL (approximately 90%) compared with AML (67%).
- The faster recovery from neutropenia in ALL compared with AML (18 days and 21 days, respectively).
- The younger age of ALL patients (median 39.5 years) compared with AML patients (median 57 years) [3,4].

Although patients with relapsed ALL are thought to have an increased risk of IFI due to low response rates to salvage therapies (approximately 30%) and prolonged exposure to high-dose corticosteroids [5], no findings have been published on the frequency of IFI in such patients.

Patients with chronic lymphocytic leukemia (CLL) are also susceptible to infection due to therapy-related immunosuppression. Although bacterial infections predominate among such patients, IFI (especially from *Candida* spp or *Aspergillus* spp) may occur during prolonged neutropenia secondary to treatment and concurrent use of corticosteroids [6]. An incidence of IFI in patients with CLL of 7–12% has been reported among patients being treated with purine analogues such as cladribine [7] or with monoclonal antibodies such as alemtuzumab [8]. However, patients with heavily treated CLL, or CLL that is resistant to fludarabine, have a greater risk of IFI [6].

Lymphoid malignancies are usually associated with deficiencies in cell-mediated immunity, which may increase the risk of infection from a variety of organisms, including fungi. However, the spectrum of fungal infections in patients with lymphoid malignancies differs from that described for other hematological malignancies, with *Cryptococcus neoformans*, *Histoplasma capsulatum*, and *Coccidioides immitis* appearing to be the most common pathogens. However, the type of therapy applied to such patients modifies their risk for IFI if prolonged neutropenia or other immunosuppression ensues, and this includes an increased rate of candidiasis and aspergillosis.

Therapy for chronic myelogenous leukemia is associated with a very low risk of IFI, unless the disease is no longer in the early phase and more intensive therapies are applied. Consequently, such patients will be at the same risk of IFI as are patients with newly diagnosed AML.

Patients with multiple myeloma (MM) have classically been considered to be at risk of infection with encapsulated bacteria due to hypogammaglobulinemia. However, during advanced stages of the disease, patients with MM also show impairment in cellular immunity, granulocytopenia, and reduction of granulocyte function, all of which increase the risk of IFI. Indeed, recent reports have described an increase in the incidence of IFI, particularly invasive aspergillosis, in MM patients patients undergoing intensive chemotherapy with high-dose corticosteroids [9].

Risk factors for IFI among patients undergoing hematopoietic stem-cell transplantation (HSCT) have been well described, and the incidence of IFI varies according to the type of transplant. The lowest incidence (0–5%) and best outcomes have been reported for recipients of autologous HSCT, regardless of the type of underlying disease [10–12]. However, increasing numbers of *Aspergillus* infections among patients undergoing autologous HSCT have been reported [13].

IFI is more common among patients undergoing allogeneic HSCT, with an incidence of 10–25%. The risk of IFI varies during the transplantation period. During the pre-engraftment period (≤30 days following transplant), mucosal injury, neutropenia, and the development of acute graft-versus-host disease (GVHD) are the major risk factors for IFI. The presence of acute and chronic GVHD and impaired cellular immunity influences the patient vulnerability to IFI during the post-engraftment period (30–100 days following transplant). During the late phase (>100 days after engraftment), impairments in cellular and humoral immunity and chronic GVHD are the main factors influencing the risk of IFI.

*Candida* spp and *Aspergillus* spp remain the most common causes of IFI among patients undergoing HSCT, and *C. albicans* and *A. fumigatus* are the most common species implicated in IFI within this group of patients. However, it is important to recognize that infections with non-*albicans Candida* species (*C. glabrata* and *C. kruzei*) and non-*fumigatus Aspergillus* species are becoming more prevalent [13–15]. This shift in causative agent is of clinical significance because these species of *Candida* and *Aspergillus* may be more virulent and more difficult to treat.

Available options and suggested use for antifungal prophylaxis

There are a number of classes of antifungal agents that may be considered for prophylaxis in hematological oncology patients. The characteristics of currently available agents have been summarized in Table 2.

Azoles

Fluconazole has been widely used in patients with leukemia and in recipients of HSCT. The benefits of using fluconazole as a prophylactic agent include reduction in fungal colonization and hematogenous candidiasis and, more importantly,
improved survival rates [16–18]. The excellent bioavailability of fluconazole, superior safety profile, low cost, and its availability in oral and intravenous formulations make fluconazole a good option for prophylaxis. However, with the increasing rates of mold infections in high-risk patients and the emergence of fluconazole-resistant Candida infections, the use of fluconazole is becoming limited to smaller subgroups of leukemia patients at low risk of IFI, such as patients with AML in remission, those undergoing autologous HSCT, and those with CLL.

Itraconazole has potent antifungal activity against yeasts and molds. Like fluconazole, it is available in oral and intravenous formulations, but reports of numerous side effects and drug interactions have limited its use. When taken orally, the solution form is recommended over the capsule form due to its superior bioavailability. The superiority of the itraconazole suspension was demonstrated in a meta-analysis, in which the incidence of Aspergillus infection was only reduced in trials involving the use of oral suspension [19]. Furthermore, itraconazole oral solution produces significantly fewer mold infections compared with fluconazole oral solution [20,21]. Despite such encouraging evidence of efficacy and the low cost of itraconazole oral solution, this therapeutic agent suffers some limitations as a prophylactic agent, including hepatic and gastrointestinal toxicity (nausea, vomiting, and diarrhea) [20,21]. Furthermore, concerns have been expressed regarding possible cardiotoxicity associated with the use of intravenous itraconazole. However, in one study of intravenous itraconazole prophylaxis for patients with AML, no cardiotoxicity could be demonstrated and stable cardiac ejection fractions by serial echocardiograms were observed, despite the median age of the cohort (median 60 years) and the lengthy duration of exposure to itraconazole (median 21 days) [22]. In summary, intravenous itraconazole can be considered for prophylaxis, especially for patients who cannot tolerate or absorb oral medications and who need broad-spectrum antifungal coverage (yeasts and molds). Alternatively, the oral suspension formulation may be used in the outpatient setting following hospital discharge, with close monitoring for the emergence of side effects.

Some properties of voriconazole make it an attractive option for antifungal prophylaxis. The agent is active against Aspergillus and Candida spp, and is available in both IV and oral formulations with a >90% oral bioavailability. Although voriconazole has not yet been approved by the US Food and Drugs Administration for prophylaxis, several institutions have successfully used it for this purpose, reserving prophylactic voriconazole use for patients at particularly high risk of IFI, such as those with acute leukemia and allogeneic HSCT [23,24]. Although voriconazole is generally well tolerated, its use has been associated with transient elevations of liver transaminases and with reversible visual disturbances. Furthermore, the possibilities of cross-resistance of some Candida spp to fluconazole and voriconazole and the emergence of zygomycosis have raised concerns regarding the prophylactic use of voriconazole. In an evaluation of breakthrough Candida infections among patients receiving different antifungal prophylactic regimens, an apparent reduction was noted in the rate of C krusei infection with voriconazole prophylaxis (0 of 105 patients) compared with prophylactic fluconazole (16 of 519 patients; p=0.069). Fewer infections due to C glabrata were also observed with voriconazole prophylaxis (0 of 105 patients) compared with fluconazole or itraconazole recipients (18 of 1647). These findings represent the first solid evidence indicating that
there is no clinically significant cross-resistance between fluconazole and voriconazole, and support in vitro studies indicating that voriconazole is effective against C krusei [25].

Despite its apparent efficacy, there is concern regarding the use of voriconazole and the emergence of zygomycosis, which has been reported in patients treated with HSCT who developed GVHD [26–28]. However, the emergence of zygomycosis was first observed several years before the introduction of voriconazole [29] and additional data are needed to establish whether or not the emergence of zygomycosis in these HSCT patients was linked solely to the use of voriconazole. Overall, voriconazole has been effective at preventing breakthrough IFI and has been well tolerated when used in patients with newly diagnosed acute leukemia [24].

Posaconazole was approved in 2006 for IFI prophylaxis in patients undergoing HSCT and in patients with hematological malignancies who were expected to have prolonged neutropenia from chemotherapy. In a randomized trial of antifungal prophylaxis in patients with AML that compared oral posaconazole with oral fluconazole or itraconazole [30], posaconazole more effectively prevented IFI (mostly aspergillosis) and led to significantly improved survival. Unfortunately, the overwhelming majority of patients in the control group received fluconazole, an agent known to be devoid of activity against aspergillosis. Furthermore, details on the patient population studied are not yet available. Since posaconazole is not available in an intravenous formulation and patients with severe mucositis have low absorption rates, it is particularly important to determine the tolerance for oral therapy in the subjects of this study [31]. However, posaconazole was generally well tolerated; drug-related adverse events were typical of those associated with the azoles (increased values in liver function tests, nausea, and vomiting), and the incidence of side effects was comparable in the two study arms. Posaconazole must be given three times per day, and in combination with high-fat, high-calorie meals for optimal absorption. However, this is frequently not possible among patients with hematological cancers undergoing intensive cytotoxic chemotherapy, and who may therefore be suffering from severe mucositis, nausea, vomiting, and severe diarrhea.

Polyenes

Of the three amphotericin B lipid formulations currently available from commercial sources, liposomal amphotericin B (L-AmB) has been the most frequently used for prophylaxis. Some studies have suggested that low-dose L-AmB (1–3 mg/kg) given three times per week was as effective in reducing the rates of IFI or fungal-related mortality as amphotericin B lipid complex [32–35]. In general, L-AmB is well tolerated at the doses used in these studies. Limitations on its use for prophylaxis are its high cost and the need for frequent intravenous administration, which is often inconvenient for patients.

New drug delivery strategies have been developed in the past few years. Two studies have explored the safety and pharmacokinetics of weekly high-dose L-AmB for prophylaxis. In one study, L-AmB was given at a dose of 7.5 mg/kg once weekly to 15 adults undergoing HSCT [36]. L-AmB was well tolerated, with mild and transitory infusion-related reactions. Four patients required drug discontinuation because of increased creatinine levels. In another study, 14 children were given L-AmB at 10 mg/kg once per week, and the results confirmed the safety of this strategy [37]. Importantly, tissue concentrations of L-AmB given at single dose of 15 mg/kg every 2 weeks were similar to those when L-AmB was given daily at 1 mg/kg to patients undergoing peripheral stem cell transplant [38]. Further studies are needed to accurately evaluate the safety and efficacy of using high-dose intermittent L-AmB for IFI prophylaxis.

The safety of aerosolized AmB in lipid complexes for Aspergillus prophylaxis has been demonstrated in patients undergoing lung transplantation [39], and (in combination with intravenous fluconazole) in recipients of HSCT [40]. Indeed, adverse events such as nausea, vomiting, and taste disturbances occurred in 2–7.5% of patients given the aerosolized form compared with 69% of patients given aerosolized conventional amphotericin B [41]. In a lung transplant study, six of the 51 patients (12%) given aerosolized AmB developed IFIs, but none were lung parenchymal infections [35]. In the HSCT study, none of the patients given aerosolized AmB in combination with fluconazole developed IFIs in the lungs, and only one patient developed cutaneous fusariosis, suggesting that the aerosolized form was not systematically absorbed. Thus, from a safety point of view, aerosolized AmB is relatively well tolerated. Additional studies are needed to confirm its prophylactic activity in this patient population.

Echinocandins

Three echinocandins are currently available in the US, but information on their use for prophylaxis is only available for two of the agents, caspofungin and micafungin. The safety of these echinocandins and their lack of interaction with other drugs are attractive attributes, and have been confirmed in two recent studies [22,42]. When micafungin was compared with fluconazole in patients undergoing HSCT, fewer patients in the micafungin group required drug discontinuation due to adverse events, and the number of drug-related side effects were comparable between the two groups [42]. Hyperbilirubinemia, allergy-related reactions,
and the development of drug resistance.

Despite the activity of echinocandins against a broad range of Candida spp, breakthrough infections from C parapsilosis and C guilliermondii have been reported, confirming reports of high minimal inhibitory concentrations for these organisms. Another caveat for echinocandins is their limited activity against Trichosporon spp and Fusarium spp, and against the agents of zygomycosis. Because echinocandins have an excellent safety profile and broad-spectrum activity against yeasts and molds, presumably these drugs will be most frequently used in patients with a particularly high risk of IFI. Thus, special attention should be paid to the possibility of breakthrough or emerging IFIs in such patients, particularly those caused by Trichosporon spp or Fusarium spp, and the agents of zygomycosis. Finally, the longer half-lives of anidulafungin and micafungin may allow for less frequent dosing schedules.

Conclusion

New and increasingly intensive treatments for hematological malignancies will undoubtedly continue to be developed and, as a consequence, the risk of IFI will continue to increase. Therefore, until difficulties in the diagnosis of IFI are resolved, antifungal prophylaxis will still have a key role in reducing fungal-related morbidity and mortality rates among high-risk patients. The choice of the optimal prophylactic strategy (which drug, at what dose, and for how long) is likely to be related to the specific type of risk group and to the spectrum of fungal infections at each treatment center. Risk factors for IFI, which differ among various patients, play an important role in the decision to use prophylaxis and in the selection of the optimal strategy. The risk of IFI is the result of the interaction between environmental exposure to fungi, intensity of immunosuppression, and the presence of organ dysfunction.

In short, a risk-based approach to prophylaxis is needed that differs among various patients, play an important role in the decision to use prophylaxis and in the selection of the optimal strategy. The risk of IFI is the result of the interaction between environmental exposure to fungi, intensity of immunosuppression, and the presence of organ dysfunction.

In short, a risk-based approach to prophylaxis is needed that will address the requirements of each group of patients. The objective of this strategy is to choose an antifungal medication from the existing armamentarium and use it in the most effective way possible, while avoiding toxicity, overuse, and the development of drug resistance.

Disclosure

Dr Mattiuzzi has been a speaker for Pfizer and Merck, and has received research grants from MGI, and Astellas. Dr Kantarjian has received research grants from Novartis, MGI and BMS.

References


Rhino-Orbito-Cerebral Zygomycosis

Case study presented by Raoul Herbrecht, Caroline Berthillot, and Cécile Fohrer
Hôpital de Hautepierre, Strasbourg, France


A 62-year-old woman was hospitalized for febrile neutropenia related to *Enterobacter cloacae* and *Escherichia coli* bacteremia. Four days before hospitalization, the patient had received a chemotherapy cycle combining high-dose methotrexate and cytarabine for a central nervous system relapse of non-Hodgkin’s lymphoma.

At admission the patient had mild anemia (hemoglobin 10.4 g/dL), severe thrombocytopenia (platelet count 5000/μL), and severe neutropenia (white blood cell count <100/μL; no differential count). The patient was administered piperacillin/tazobactam and amikacin. Her fever disappeared rapidly and blood cultures were found to be negative for *E cloacae* and *E coli*.

Six days after admission, the patient was still severely neutropenic and she developed edema of the right upper eyelid and a new fever. A cranial computed tomography scan showed bilateral maxillary, ethmoidal and frontal sinusitis, hypodensity in both frontal lobes, nearly complete right nasal obstruction, mild thickening of soft tissue in the right nasal and orbital area, but no evidence of bone destruction.

Because a filamentous fungal infection was suspected, amphotericin B lipid complex (ABLC) therapy was initiated. Nevertheless, clinical condition worsened rapidly with an increase of fever, an increase of inflammatory signs of the conjunctiva and eyelids, and the appearance of a very small necrotic zone at the inner junction of the right lower and upper eyelids (Fig. 1). A magnetic resonance imaging scan showed ethmoidal sinusitis, bilateral frontal sinusitis, and necrosis of the inner wall of the right orbit, and it confirmed that the infection had extended to the brain (Figs. 2 and 3).

**Mycology**

Histopathology showed numerous broad, hyaline, non-septate hyphae that were branching at right angles, which was suggestive of zygomycosis. *Rhizomucor pusillus* grew from nasal swab and biopsy samples, confirming the suspicion of zygomycosis.

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Email: raoul.herbrecht@chru-strasbourg.fr
Outcome
Surgery was not considered to be possible because of the substantial brain involvement. Infection progressed locally (Fig. 4) and then spread to the lung (Fig. 5), despite the patient’s recovery from neutropenia. Therapy was then switched to posaconazole, after 3 weeks of ABLC. The patient’s condition continued to worsen and she died 49 days after the first clinical signs. Causes of death were the infection and the relapse of the lymphoma. \textit{R} \textit{pusillus} still grew from post mortem nasal biopsy samples.

Discussion
Zygomycosis is an invasive disease caused by fungi from the Mucorales order and the Entomophthorales order. In a large literature review, \textit{R} \textit{pusillus} was found to be involved in 4\% of the reported cases, the most frequently isolated organisms being \textit{Rhizopus} spp [1].

Zygomycosis mainly affects patients who are intravenous drug abusers, who have undergone organ or hematopoietic stem cell transplantation, or who have diabetes, renal failure, HIV infection, or a hematological malignancy or solid tumor [1,2]. The most frequent primary sites of infection are the paranasal sinuses, the lungs, the skin, and the digestive tract.

Zygomycotic agents are usually susceptible to amphotericin B, and many of them are also susceptible to posaconazole [3]. The agents are resistant to the other newer azoles and to the echinocandins. Surgical removal of the infected and necrotic tissue is an important part of the therapeutic strategy. However, despite \textit{in vitro} sensitivity to amphotericin B, outcome is generally poor, with an overall mortality rate of >50\% [1]. Prognosis of infection is closely related to the severity and evolution of underlying immunosuppressed condition, and therefore failure rates are higher in transplant recipients and leukemia patients than in patients with diabetes [1].

Disclosures
Dr Herbrecht has been a member of an advisory board or speaker’s bureau for Astellas, Gilead, Merck, Pfizer, Schering-Plough, and Zeneus. Drs Berthillot and Fohrer have no relevant financial relationships to disclose.

References
CANDIDIASIS

Genital Candida species detected in samples from women in Melbourne, Australia, before and after treatment with antibiotics
Pirotta MV, Garland SM

Vulvovaginal candidiasis (VVC) is a very common condition, with approximately three out of every four women developing at least one episode of VVC during their lifetime. However, the epidemiology of this disease is changing. In this paper, the authors described the characteristics of VVC within a prospective cohort of 233 women receiving antibiotic therapy in Melbourne (VIC, Australia).

Participants self-collected a low vaginal swab before and 8 days after completion of antibiotic treatment; data on potential risk factors for VVC were collected at the same time. The rate of Candida spp colonization was 21% (95% confidence interval [CI] 17–27%) at baseline, rising to 37% (95% CI 31–44%) after treatment. Overall, Candida albicans was the most common species, being detected in 73% of subjects, with Candida glabrata identified in approximately 20%. Self-reported proneness to VVC after antibiotic treatment and baseline colonization with Candida spp were predictors of symptomatic VVC.

Although C albicans remains the most common causative agent for VVC, there has been a shift in recent years towards non-albicans Candida spp, particularly C glabrata. Two factors are thought to have contributed to this change:

- The frequent use of over-the-counter topical antifungals.
- The increased use of oral fluconazole in the community [1].

C albicans shows greater susceptibility to these products compared with non-albicans Candida spp.

Non-albicans VVC appears to be prominent in specific patient populations, especially in patients with recurrent disease. In a recent epidemiological study in pregnant women, 36.7% of all Candida isolates were non-albicans Candida spp, with C glabrata accounting for 25.1% of all Candida isolates and 68.5% of non-albicans isolates [2]. The prevalence of C glabrata increased slightly with progression of pregnancy from the first to the second and third trimesters.

Postmenopausal women in long-term care facilities represent another population at high risk of colonization with non-albicans Candida spp. Dan et al. tested 106 bedridden residents of a long-term care facility. Of the study patients, 32% had vaginal colonization with Candida spp, and C glabrata was the predominant species isolated from these women (51.2% of isolates) [3].

Knowledge of the risk factors for non-albicans VVC is necessary for prompt and efficient treatment for patients who do not respond to traditional antifungal therapy. Routine speciation may be warranted in specific patient populations.


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This study describes a real-time polymerase chain reaction (PCR) method for the detection and speciation of Candida and Aspergillus spp in a variety of clinical samples. The test achieved 100% specificity for both Candida and Aspergillus spp. Positive PCR results for Candida and Aspergillus were corroborated by clinical or laboratory evidence of infection in 83% and 50% of cases, respectively. More studies are needed to determine the optimal PCR technique for the detection of fungal pathogens.

Traditional techniques for diagnosing systemic fungal infections are subject to a variety of limitations; there is therefore great interest in developing and optimizing molecular diagnostic methods. Several polymerase chain reaction (PCR) techniques have been developed that involve various DNA extraction and amplification methods.

The authors of the present article describe the performance of a real-time PCR assay for the detection of Candida and Aspergillus spp. The automated MagNA Pure DNA isolation kit (Roche, Mannheim, Germany) was used for DNA extraction, and PCR amplification was performed using the LightCycler system (Roche, Mannheim, Germany) with oligonucleotide probes designed based on the sequences of the 18S rRNA genes of different fungal pathogens. PCR identified Aspergillus and Candida to the genus level. For Candida-positive samples, typing to the species level was achieved using species-specific probes. The test achieved 100% specificity for both Candida and Aspergillus spp and had a sensitivity of 2 CFU/mL of blood. To assess the utility of the assay in a clinical setting, the authors analyzed 1650 consecutive samples (1330 blood samples, 295 samples from other body fluids, and 25 biopsy samples) obtained from patients with suspected invasive fungal infections. Of these, 5.3% tested positive for Candida spp and 1.7% were positive for Aspergillus spp. Verification of the results using conventional methods was possible in 83% and 50% of cases, respectively.

DNA extraction from fungi is technically difficult due to the presence of a hardy cell wall that is resistant to lysis, and a number of manual and automated extraction methods have been described. In a recent study, six extraction methods for Aspergillus fumigatus were compared [1]. The bead-beating method followed by extraction with AL lysis buffer (Qiagen, Hilden, Germany) was the most successful and least time-consuming extraction technique investigated. Although the MagNA Pure method gave a lower DNA yield, it was as time-efficient as the bead-beating method. Attempts to increase the DNA yield of the automated technique resulted in more preparation steps, thereby increasing the extraction time and obviating the need for automation. In another study, White et al. compared different PCR techniques for Aspergillus and Candida spp [2]. The authors found that the detection limit of the Roche LightCycler was greatly reduced with whole-blood samples.

In conclusion, more studies are needed to determine the optimal PCR technique for the detection of fungal pathogens.

mechanism of action of echinocandins against fungal biofilms is still not completely understood, it is thought that echinocandins could lead to lysis and dissolution of the extracellular matrix by inhibiting polysaccharide production [1].

Whether or not all echinocandins exhibit the same activity against fungal biofilms remains to be determined. However, there is evidence that echinocandins have differential activity against the various Candida spp. For instance, in a recent in vitro study, micafungin was active against C. kefyr and C. glabrata biofilms, but not against C. albicans, C. dubliniensis, C. tropicalis, or C. parapsilosis biofilms on polystyrene sections. Conversely, in a study on central venous catheter sections, micafungin was active against C. glabrata, C. parapsilosis, and C. albicans biofilms, but not against C. dubliniensis, C. tropicalis, or C. kefyr biofilms [2].

In 2004, Shinabeck et al. developed a rabbit model of C. albicans biofilm infection [3]. They showed that liposomal AmB lock therapy almost completely clears the biofilm. However, more data are needed to determine the activity of liposomal AmB compared with AmB deoxycholate and echinocandins.

Finally, although efforts are made to ensure the applicability of the animal models to infection in humans, the value of echinocandins and AmB in treating Candida biofilm infections needs to be demonstrated in human studies.

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Finally, although efforts are made to ensure the applicability of the animal models to infection in humans, the value of echinocandins and AmB in treating Candida biofilm infections needs to be demonstrated in human studies.
Efficacy of environmental measures to decrease the risk of hospital-acquired aspergillosis in patients hospitalised in haematology wards


The present study evaluated the effectiveness of a set of preventive measures on the rate of invasive aspergillosis (IA) in patients admitted to haematology wards. Although the number of construction projects increased between 1995 and 2001, the IA rate decreased significantly. This suggests that a well-orchestrated team effort towards preventing IA is possible and can be effective.

Invasive aspergillosis (IA) remains an important cause of death in patients with hematological malignancies. It has therefore been the target of various preventive measures in hospitalized, heavily immunosuppressed patients. Aspergillus spp spores are ubiquitous and can be present at high concentrations in dust particles, and environmental contamination is a recognized risk factor for the development of IA in hematological patients [1]. Furthermore, several reports have linked IA to hospital construction and renovation [2,3].

The present study evaluated the effectiveness of a multifaceted strategy aimed at decreasing the rate of IA in patients with hematological malignancies, during a period of intensive construction work at a university hospital in France. During 1994–2001, a host of preventive measures were implemented:

- Positive-pressure rooms.
- Strict hygiene practices.
- Dust control.
- Partitioning of construction work areas from patient care areas.
- Periodic environmental surveillance cultures.

The authors conducted a prospective survey to determine the number of IA cases on two hematology wards between 1993 and 2001. The results indicated that, although there were significant increases in the number and risk level of hospital renovation projects between 1995 and 2001 (p<0.01), there was a decrease in the rate of IA between 1993 and 2001 (from 0.85% to 0.28%) and a significant decrease in the incidence of IA between 1993–1996 and 1997–2001 (p=0.02, Mann–Whitney U-test). The results of this study emphasize the importance of a proactive team approach towards the prevention of IA in high-risk patients. However, such results can only be maintained through continued efforts to implement the range of preventive measures. This requires commitment from members of the hospital administration department, the engineering department, and members of the infection control committee. Although such an endeavor is costly and labor-intensive, the money, time, and energy invested are largely justified by the benefits of preventing infections and saving patient lives.


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Early onset endophthalmitis caused by Aspergillus species following cataract surgery


This paper reports on a retrospective case series five patients with early onset Aspergillus endophthalmitis following cataract surgery. The authors recommend that Aspergillus should be considered in the differential diagnosis of early onset postoperative endophthalmitis, with cultures obtained at presentation.

Postoperative endophthalmitis caused by Aspergillus spp is rare and is associated with poor outcomes. The authors of this study describe a consecutive series of five patients who developed Aspergillus endophthalmitis following cataract surgery. The patients, who were treated by the authors between 1992 and 2005, were identified from medical records. The mean time between surgery and presentation was 29 days. All five patients had decreased vision and eye pain, and three had flocculent material in the anterior chamber. One patient was on oral corticosteroids and another was receiving chemotherapy. In terms of treatment, the patients received intravitreal amphotericin B in combination with an oral azole, and one also received intravenous amphotericin B. Enucleation was performed in three patients despite aggressive therapy. The remaining two patients underwent vitrectomy and surgical debridement and had poor visual outcomes (final visual acuity was 20/30 in one patient and 20/200 in the other).

There is now evidence to suggest that orally administered voriconazole penetrates well into the aqueous and vitreous humors. In one study, voriconazole achieved aqueous and vitreous levels that exceeded the 90% minimum inhibitory
concentrations required for the treatment of infections caused by *Aspergillus* and *Candida* spp. [1]. The safety of intravitreal voriconazole has also been recently investigated in an animal model [2]. Concentrations up to 25 mg/mL appeared to cause no retinal damage in treated rats.

So far, the clinical experience with voriconazole in the treatment of fungal endophthalmitis is promising. Voriconazole alone or in combination with caspofungin has been used successfully for the treatment of four of five patients with *Candida* endophthalmitis [3]. More recently, Sen et al. described their experience with intravitreal voriconazole for the treatment of drug-resistant fungal endophthalmitis [4]. The infection was successfully eradicated in all five reported cases. Evisceration of the affected eye was avoided in one case. In another study, oral posaconazole was used to treat a woman with amphotericin-resistant *Fusarium solani* keratitis that progressed to invasive endophthalmitis [5]. The patient exhibited a prompt response and had good recovery of retinal function. The ocular penetration of posaconazole was confirmed by an aqueous tap.

In conclusion, the new azoles constitute effective alternative therapeutic agents in the treatment of fungal endophthalmitis.


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### CRYPTOCOCCOSIS

#### Outcome of AIDS-associated cryptococcal meningitis initially treated with 200 mg/day or 400 mg/day of fluconazole


This retrospective study compared two doses of fluconazole (200 mg/day and 400 mg/day) for the initial treatment of AIDS-associated cryptococcal meningitis in South Africa. Overall, in-hospital mortality was high (25%). Kaplan–Meier analysis showed a similar length of survival at the two treatment doses (p=0.27).

In developing countries where the availability and cost of antifungals are problematic, fluconazole is frequently used as a first line agent in the treatment of AIDS-associated cryptococcal meningitis. In the present retrospective study, the authors report on the outcome of patients treated with one of two different doses of fluconazole (200 mg/day or 400 mg/day) in South Africa. Subjects with HIV presenting with a first episode of cryptococcal meningitis at a single secondary level hospital between January 1999 and December 2002 were identified by chart review. Between 1999 and April 2001, because of limited funds, patients were given low-dose fluconazole; patients with a poor prognosis were not offered therapy and were referred for palliative care. A donation of fluconazole in April 2001 allowed the standard dose to be administered after this time. None of the patients received antiretroviral therapy. Of 205 subjects included in the study, 77 received low-dose treatment and 128 received standard treatment. The rate of in-hospital mortality during first hospital admission was high overall (25%) and was similar for the two doses. Lack of antifungal treatment, lower level of consciousness, and a cerebrospinal fluid antigen titer >1000 were all independent predictors of in-hospital mortality. According to Kaplan–Meier analysis, the higher dose was not associated with a survival benefit. Median survival was 82 days with low-dose fluconazole and 76 days with standard-dose fluconazole.

There is evidence that resistance rates of *Cryptococcus neoformans* to fluconazole in South Africa have been increasing (from 0% in 1999 to 13% in 2004) [1]. Similar trends have been reported in other developing countries [2,3]. Heteroresistance to fluconazole has been observed among *C. neoformans* isolates, even where there has been no prior exposure to fluconazole [4].

In a recent study, Bicanic et al. investigated 32 episodes of relapsing cryptococcal meningitis among HIV-infected patients [5]. The authors found that 76% of culture-positive relapses were due to fluconazole-resistant isolates. Patients with drug-resistant infections had a 54% mortality rate at the 6-month follow-up, despite prolonged amphotericin B treatment.

The authors of the present paper report similar outcomes with low and high doses of fluconazole. However, the outcome measures they used were length of hospital stay, in-hospital mortality, and degree of disability on discharge. Relapse rates and post-treatment fluconazole susceptibility were not assessed.

Amphotericin B remains the agent of choice for the initial treatment of cryptococcal meningitis in HIV patients. When fluconazole is used in place of amphotericin B, high doses of fluconazole should be administered to maximize clinical and
microbiological response rates and to minimize the emergence ofazole resistance [6].


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Cryptococcus gattii infection: characteristics and epidemiology of cases identified in a South African province with high HIV seroprevalence, 2002–2004

Morgan J, McCarthy KM, Gould S et al; Gauteng Cryptococcal Surveillance Initiative Group


This study describes the characteristics of patients with Cryptococcus gattii infection in an HIV-endemic area of South Africa. Of the isolates tested, 2.4% were identified as C. gattii. The majority of patients had HIV infection, and the most common form of infection was meningitis. The clinical characteristics and outcome of patients with C. gattii infection were similar to those infected with other Cryptococcus spp.

Recent genotypic analyses revealed significant genetic differences within Cryptococcus neoformans isolates, which led to the pathogen being divided into two species: C. neoformans (which includes C. neoformans var brugii and C. neoformans var neoformans) and C. gattii. The epidemiology of C. gattii is not as well understood as that of C. neoformans. It has typically been reported from tropical and subtropical areas, but it recently emerged as an important pathogen in Vancouver (BC, Canada). The present paper describes the characteristics of patients with C. gattii infection in a South African province.

Cryptococcosis cases were identified by population-based surveillance from March 2002 to March 2004, in which surveillance officers collected data from laboratories and medical records on a weekly basis. Isolates identified as Cryptococcus spp isolates at the originating institutions were sent to the National Health Laboratory Service Mycology Reference Unit of the National Institute for Communicable Diseases (NICD; Johannesburg, South Africa) for species confirmation and serotyping using canavanine-glycine–bromthymol blue agar. The species of the majority of C. gattii isolates and a subset of non-gattii Cryptococcus isolates was confirmed by serotyping using the Crypto-Chek kit (Mitsuibishi Kagaku Iatron, Tokyo, Japan) at the Centers for Disease Control and Prevention Fungus Reference Unit (Atlanta, GA, USA); minimal inhibitory concentration (MIC) testing was also performed here using two different methods.

There were 2753 cases of cryptococcosis over the study period. Of 1912 viable isolates received by the NICD, 2.4% were identified as C. gattii. All isolates had low MICs to all antifungals tested (fluconazole, itraconazole, and voriconazole). The majority of C. gattii-infected patients (61%) had HIV infection, and most presented with symptoms of meningitis (headache 76%; stiff neck 67%; and fever 54%). Over one-third of the patients with C. gattii infection died during hospitalization for the index event. There were no significant differences between C. gattii-infected patients and non-gattii Cryptococcus-infected patients in terms of demographic or clinical characteristics.

The authors stress that their results probably underestimate the true prevalence of C. gattii, given the limitations of the diagnostic techniques available in this geographic area. Indeed, a recent genotypic analysis of 176 cryptococcal isolates in Botswana and Malawi found that 13.6% of the tested isolates were C. gattii serotype C [1].

Initially, C. gattii was thought to preferentially infect immunocompetent hosts. This theory was recently refuted in an experimental murine model in which no difference in infection rate was observed in immunocompetent and immunodeficient mice [2]. The results of the present study corroborate these findings.

Routine speciation of Cryptococcus spp isolates for detection of C. gattii is not recommended because it has similar clinical characteristics to C. neoformans. However, given the concern for the tendency of C. gattii to exhibit higher MIC values, speciation should be considered in areas that are endemic for C. gattii when an adequate response to therapy is not achieved.

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Epidemiology and outcome of Rhodotorula fungemia in a tertiary care hospital

The results of this retrospective study indicate that cancer patients, patients receiving corticosteroids or other immunosuppressive therapy, patients with central venous catheters, and patients receiving broad-spectrum antibiotic therapy are most susceptible to Rhodotorula fungemia. Occasionally, immediate catheter removal can be avoided. Conversely, catheter removal is sometimes sufficient to eradicate the infection.

Rhodotorula is a genus of yeasts that can be found in air, soil, salt water, fresh water, and dairy products. Although traditionally considered to be a saprophyte that can colonize plants, humans, and other mammals, it has recently emerged as an opportunistic pathogen in immunocompromised hosts.

In the present retrospective study, the authors reviewed the medical records of patients at a tertiary care hospital in southern Brazil over a 4-year period to investigate the risk factors for, and treatment of, Rhodotorula fungemia. Seven patients with Rhodotorula mucilaginosa bloodstream infections were identified; the rate was 0.056 episodes per 1000 hospital admissions. All seven patients had a central venous catheter; four patients (57%) had solid tumors and been exposed to cytotoxic drugs; three patients (43%) had leukemia and been exposed to corticosteroids and cytotoxic drugs; six patients (86%) were neutropenic and had been exposed to broad-spectrum antibiotics; and two patients (28%) had been taking prophylactic fluconazole. In terms of treatment, all seven patients had their catheter removed, and five also received antifungal therapy (amphotericin B [AmB] plus 5-flucytosine n=2; AmB n=2; fluconazole n=1; and voriconazole following AmB n=1). The two patients treated only by catheter removal survived. However, three of the five patients treated with antifungal therapy plus catheter removal died within 10 days of incident sample culture.

The largest series of cases of Rhodotorula fungemia was reported in 1992 at the Memorial Sloan-Kettering Cancer Center (New York, NY, USA) [1]. This paper reported on 23 patients who developed catheter-related Rhodotorula sepsis between 1985 and 1989. In contrast to the study by Lunardi and colleagues, all 23 patients survived, without recurrence of the infection.

In addition to sporadic infections in critically ill patients with intravascular catheters, there have been outbreaks of Rhodotorula mucilaginosa in healthcare settings. Perniola et al. recently reported an outbreak of bloodstream infections due to R mucilaginosa in a neonatal intensive care unit in Italy [2]. Birth weight, gestational age, duration of parenteral nutrition, duration of antibiotic therapy, and prophylactic administration of fluconazole were all risk factors for infection.

In such outbreak settings, additional epidemiological data are usually required for a complete investigation. Pulsed-field gel electrophoresis was recently used for the first time to analyze genetic similarities between R mucilaginosa clinical isolates [3].

Although less frequent than candidiasis, Rhodotorula spp should be considered alongside Candida spp in the differential diagnosis of fungemic patients with intravascular catheters. Given the potential for nosocomial dissemination, infection control practices should be emphasized in such patients.


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Human and canine pulmonary blastomycosis, North Carolina, 2001–2002

The present report described a cluster of 8 human and 4 canine cases of pulmonary blastomycosis in North Carolina (USA) during 2001–2002. Outbreaks of this disease are difficult to study because of delayed diagnosis, difficulty isolating Blastomyces dermatitidis in nature, and the lack of a test with high specificity and sensitivity for assessing exposure.

The epidemiology of blastomycosis is not entirely clear, largely due to difficulties in diagnostic testing. Most of the available information is based on reports of clinical infection in humans and dogs in high prevalence areas. In the present study, MacDonald et al. described a cluster of eight human and four canine cases of pulmonary blastomycosis in a rural community in North Carolina (USA) during 2001–2002. Although the epidemic curve was consistent with ongoing exposure, no common source for human and canine exposure was identified.

Although most cases of blastomycosis are concentrated in North America, the disease has been occasionally reported in Africa [1], Central and South America [2], India [3], and the Middle East [4].
In a case–control study performed by the US Centers for Disease Control and Prevention (CDC) in Missouri, 93 cases of blastomycosis in humans were studied [5]. Black race and a history of pneumonia were the only risk factors for infection. However, blastomycosis in dogs has been associated with residence in proximity to a waterway and exposure to an excavation site [6].

In an attempt to shed light on the molecular epidemiology of blastomycosis, McCullough et al. examined the genetic diversity of 59 Blastomyces dermatitidis isolates from various endemic areas in North America, India, and Africa [7]. Using a polymerase chain reaction-based typing system and restriction fragment length polymorphism analysis, isolates were classified into three major groups. The authors showed that in one outbreak, the soil isolates did not correspond to the clinical isolates. In addition, more than one strain was found in environmental and clinical samples. As demonstrated by this and by previous studies, environmental testing is of limited value in identifying the source of clinical outbreaks.


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A fatal pseudo-tumour: disseminated basidiobolomycosis
van der Berk GE, Noorduyn LA, van Ketel RJ et al. BMC Infect Dis 2006;6:140.

This case report describes a 61-year-old man with gastrointestinal basidiobolomycosis that manifested as an obstructing colonic tumor and a hepatic mass. Despite hemicolecotomy and treatment with fluconazole and amphotericin B, the patient developed multi-organ failure and died. This is only the second reported case of fatal gastrointestinal basidiobolomycosis.

Basidiobolomycosis is caused by a rare fungus of the Zygomyceetes class, Basidiobolus ranarum. Basidiobolus is a saprophytic filamentous fungus that can be grown from amphibian, reptile, and bat droppings. Most human cases of basidiobolomycosis have been reported from Africa, South America, and tropical Asia. The most common form of infection in humans is subcutaneous chronic zygomycosis [1]. However, systemic infections have occasionally been reported.

In this report, the authors describe a 61-year-old patient with gastrointestinal basidiobolomycosis. The man presented with progressive left abdominal pain and constipation. Colonoscopy an obstructing colonic mass, and a hemicolecotomy was performed. Histology showed inflammation, possibly caused by a fungal or parasitic infection, but a specific organism was not identified. A computed tomography (CT) scan was performed a few weeks after the operation because of abdominal discomfort, and showed a liver mass 6 cm in diameter. Treatment with metronidazole, directed at an amoebic liver abscess, was unsuccessful, but subsequent treatment with fluconazole resulted in a small decrease in the size of the abscess. The patient developed marked eosinophilia (27.7%), and so a liver biopsy was performed and the patient was referred to a university hospital. A repeat CT scan showed that the liver mass had grown (9 cm diameter). Colon and liver biopsy samples showed extensive necrosis and histiocytes, multinucleated giant cells, and numerous eosinophils. In Grocott-stained sections, unusually large hyphae could be seen, and these were surrounded by strongly eosinophilic material in haematoxylin- and eosin-stained sections (Splendore–Hoeppli phenomenon). Based on these findings, a diagnosis of Basidiobolus spp infection was made. Although itraconazole remains the antifungal agent of choice, this was contraindicated because of renal insufficiency, and so amphotericin B was used. The patient developed multi-organ failure and died a few days later. After autopsy, Basidiobolus ranarum was cultured from liver, gallbladder, and colon.

Gastrointestinal basidiobolomycosis has mostly been reported in children. The US Centers for Disease Control and Prevention has conducted an epidemiological investigation of a cluster of seven cases of gastrointestinal basidiobolomycosis in adult patients from Arizona [2]. The infection can involve the colon, rectum, stomach, duodenum, liver, and pancreas. Potential risk factors included prior ranitidine use and longer residence in Arizona. In addition, histopathological analysis of six cases of gastrointestinal basidiobolomycosis in Arizona has been conducted [3]. There was marked mural thickening and fibrosis in the gastric and intestinal specimens when compared with controls. Splendore–Hoeppli phenomenon was seen. Colonic perforation was found in two cases.

Radiographic findings in gastrointestinal basidiobolomycosis may mimic Crohn’s disease [4]. Common
features include concentric colonic wall thickening, perivisceral inflammation, fistulization, perforation, and abscess formation.

The treatment of basidiobolomycosis is difficult. More studies are needed to determine the susceptibility of this rare fungus to the new generation azoles and echinocandins.


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THERAPEUTICS

Pulmonary adverse events of anti-tumor necrosis factor-α antibody therapy
Mutlu GM, Mutlu EA, Bellmeyer A et al.

This paper provides a review of the available data on the risk of pulmonar infections following anti-tumor necrosis factor-α (TNF-α) antibody therapy. Increased awareness among prescribing physicians and careful patient selection for anti-TNF-α therapy will help to prevent and allow early detection of these serious infections.

The authors of this paper provide a useful review of the role of tumor necrosis factor-α (TNF-α) in the initiation and maintenance of the inflammatory response to various infections, the use of anti-TNF-α antibody therapy in diseases such as rheumatoid arthritis, and the risk of pulmonary infections following therapy with these agents.

Although many patients continue to benefit dramatically from anti-TNF-α therapy, TNF-α blockade compromises host resistance to infections, particularly granulomatous diseases [1]. The authors make an important point in the present review: TNF-α antagonists differ in terms of the risks they pose for reactivation of latent granulomatous infections. Indeed, between January 1998 and September 2002, the US Food and Drug Administration received reports of 255 granulomatous infections following infliximab therapy and 68 infections following treatment with etanercept (129 vs. 60 infections per 100 000 treated patients, relative risk 2.1) [2]. Three hypotheses were postulated to explain this disparity [3]:

- Differential induction of target cell death (infliximab induces apoptosis of monocytes and lymphocytes, whereas etanercept does not).
- Differential inhibition of TNF-α signaling (infliximab binds to both soluble and transmembrane TNF-α, whereas etanercept binds only to soluble TNF-α).
- Differential net blockade of TNF-α bioactivity (rapid and irreversible binding of infliximab to TNF-α vs. release of TNF-α 10 min after etanercept administration).

There are limited available data regarding the newest agent, adalimumab. Reactivation of latent tuberculosis has been reported with adalimumab in a dose-related response [4].

Since the clinical use of TNF blockers is expected to increase, the continued monitoring and reporting of adverse events is crucial to ensure patient safety and to reduce morbidity and mortality associated with opportunistic infections in these high-risk patients.


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New agents for the treatment of fungal infections: clinical efficacy and gaps in coverage
Spanakis EK, Aperis G, Mylonakis E.

New treatment options are now available for the various fungal infections encountered in the clinical setting. This review of the data on the clinical efficacy of these agents reports that the use of voriconazole as a primary treatment for invasive aspergillosis is increasing, posaconazole has a broad anti-fungal spectrum, and the echinocandins are effective against most Candida spp.

The antifungal armamentarium has recently expanded to include several new agents for the treatment of various fungal infections. In the present review, the authors provide a summary of the trials that have investigated the efficacy of the new antifungal agents (newer triazoles and echinocandins) in the clinical setting.

Whereas voriconazole is being increasingly used for the treatment of proven or suspected invasive aspergillosis (IA), echinocandins are very helpful in the treatment of Candida
spp, particularly of azole-resistant isolates. The strength of posaconazole lies in its broad activity against filamentous fungi, including zygomycetes.

In addition to the studies evaluated in this review, new data have been recently reported. Two randomized trials recently examined treatment options for invasive candidiasis [1,2]. The first study compared caspofungin at a dose of 50 mg/day after a loading dose of 70 mg on day 1 with two doses of micafungin (100 mg/day and 150 mg/day) in adult patients with invasive candidiasis [1]. Micafungin was not inferior to caspofungin in terms of efficacy or safety, and no advantage was seen with higher doses of caspofungin. The second study compared micafungin with liposomal amphotericin B (L-AmB) in pediatric patients with invasive candidiasis [2], and reported that micafungin was as effective as L-AmB in the overall population.

Treatment options for IA have also recently been evaluated [3,4]. When compared with high-dose lipid formulations of AmB, posaconazole appeared to be more efficacious and safer as salvage therapy for IA in patients with hematologic malignancy [3]. In view of preliminary evidence suggesting benefit from the use of combination therapy with voriconazole plus caspofungin in IA, Raad et al. concluded that the combination of voriconazole and caspofungin is an effective treatment strategy in patients with hematologic malignancy and IA [4].

Finally, in two different studies, micafungin-based antifungal combinations were found to be safe and reasonably efficacious in the treatment of IA [5,6].


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Prospective study of amphotericin B formulations in immunocompromised patients in 4 European countries


This prospective study investigated the outcomes of adult patients receiving amphotericin B deoxycholate (AmB-d) or lipid formulations of AmB in 20 European hospitals. The authors recommend that newer, less toxic antifungals should be used in place of AmB to improve treatment outcomes.

Since its first introduction in 1959, amphotericin B deoxycholate (AmB-d) has successfully been used for the treatment of various fungal infections. However, a number of studies have shown that AmB-d associated with significant nephrotoxicity, which sometimes precludes its use. Lipid formulations of AmB are now available, and these have proved to be less nephrotoxic than AmB-d [1].

The aim of this longitudinal, prospective, observational study was to compare the outcomes of patients treated with different formulations of AmB in 20 European centers (four in Italy, four in the UK, six in Germany, and six in Spain). Of 418 patients studied, 62% initially received AmB-d, 27% received liposomal AmB, and 11% received other lipid formulations of AmB. At baseline, 390 patients had normal kidney function, and 57% of these went on to develop nephrotoxicity. Patients with nephrotoxicity had a higher mortality rate and a longer hospital stay than patients who did not develop nephrotoxicity. Duration of therapy and choice of formulation used as initial therapy were predictors of the development of nephrotoxicity; AmB-d was a stronger predictor than the other formulations. Of the patients initially treated with AmB-d, 36% had switched to lipid formulations, primarily because of increased serum creatinine levels (in 45.7% of patients) or other AMB-attributable adverse events (in 41.3% of patients).

For several decades, and in the absence of therapeutic options for azole-resistant fungal infections, AmB-d was considered to be the “gold standard” antifungal agent. However, three lipid formulations of AmB have been developed:

In vitro and in vivo evidence has demonstrated that these agents are at least as effective as AmB-d in the treatment of invasive mycoses. However, the main advantage conferred by the lipid formulations is a reduced risk for nephrotoxicity compared with traditional AmB-d therapy.

More recently, voriconazole has proved to be effective in the treatment of invasive aspergillosis. In addition, echinocandins have been increasingly used for Candida infections and as empirical therapy in patients with neutropenic fever. However, when compared with AmB, gaps in treatment coverage still exist in these new agents, mainly against zygomycetes. The newestazole, posaconazole, is active against both Aspergillus spp and zygomycetes. So far, in vitro and in vivo data supporting the use of posaconazole have been promising.

AmB-d is affordable and widely available. Although it is less likely to be nephrotoxic in neonates than in adults, it can be tolerated in brief, low-dose courses in adults. Therefore, AmB-d is still recommended as first-line therapy in AIDS-associated cryptococcal meningitis. It can also be given intrathecally in the setting of fungal meningitis. With the advent of all the antifungal agents described above, the place of AmB-d in the treatment of invasive mycoses is being continuously redefined.

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Corneal ulceration in South East Asia. II: a strategy for the prevention of fungal keratitis at the village level in Burma

Maung N, Thant CC, Srinivasan M et al.

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The authors of this study evaluated the effectiveness of antibiotic and antifungal ointments in the prevention of corneal ulcers in Burmese patients with traumatic corneal abrasions. All 126 patients included in the study tolerated the ointments well and healed uneventfully. This preventive strategy is effective and easy to implement in developing countries.

Corneal ulceration is one of the most common causes of preventable blindness in South East Asia. The present study was the second of three studies, conducted in South East Asia in collaboration with the World Health Organization, to evaluate the effectiveness of a short course of topical ointments to patients with corneal abrasions in the prevention of ulceration.

In the first study, 115 patients with corneal abrasions were treated with 1% chloramphenicol ointment three times daily for 3 days [1]. The study was conducted in Bhutan, where 98% of all culture-positive corneal ulcers are caused by bacterial pathogens. None of the patients developed corneal ulcerations, and all patients healed uneventfully. It was concluded that antibiotic ointments can successfully prevent bacterial corneal ulcers.

The present prospective study was conducted in Burma, where two-thirds of all corneal ulcerations are caused by fungi. Individuals from three selected villages (n=16 987 in total) were followed for 1 year by village health workers (VHW) trained to identify patients with post-traumatic corneal abrasions and to administer antibacterial and antifungal ointments (1% chloramphenicol and 1% clotrimazole) to those who met the eligibility criteria. Of the 273 individuals who presented to the VHS with an ocular injury during the study, 126 had a corneal abrasion. All 126 received the preventive treatment three times daily for 3 days, and all tolerated the ointments well and had an uneventful recovery. The authors concluded that bacterial and fungal ulcers can be prevented by treating potential sites of infection.

In the third study, 374 patients with corneal abrasions were randomized to receive 1% chloramphenicol and 1% clotrimazole ointments (n=169) or 1% chloramphenicol and placebo ointments (n=205) [2]. The site of this third study was India, where fungi account for 50% of corneal ulcerations. The vast majority of patients (n=368) healed without sequelae. Interestingly, bacterial and fungal ulcers were prevented in both groups of patients. The investigators concluded that antibacterial ointments can prevent bacterial and fungal ulcers, and that antifungal ointments are apparently unnecessary.

Therefore, simple preventive measures can be very effective in preventing corneal ulcers in developing countries.

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The 2006 Interscience Conference on Antimicrobial Agents and Chemotherapy (ICAAC) program covered many aspects of clinical mycology, including recent clinical trials, new and established antifungal agents, diagnostic laboratory testing, and antifungal susceptibility. This review will provide a summary of the key abstracts on clinical mycology presented at the meeting.

Management of invasive fungal infections

Invasive candidiasis

Two randomized trials examined treatment options for invasive candidiasis [1,2]. The first was a randomized double-blind study that compared caspofungin (70 mg loading dose, followed by 50 mg/day) with two doses of micafungin (100 mg/day and 150 mg/day) in adult patients with invasive candidiasis [1]. A total of 593 patients were included in the intent-to-treat population (192, 199, and 202 patients in the caspofungin, micafungin [100 mg/day], and micafungin [150 mg/day], respectively). The primary endpoint was the clinical and mycological response at the end of therapy. Overall response rates were similar for the three groups (71.4%, 73.9%, and 70.9%, respectively). Success rates were not significantly different across the various Candida spp. All three treatments were equally well tolerated. This study is the first trial to directly compare the efficacy of two echinocandins in the treatment of invasive candidiasis. Micafungin was found to be non-inferior to caspofungin in terms of efficacy. Higher doses of micafungin did not provide any additional benefit.

Micafungin was also compared with liposomal amphotericin B (L-AmB) in pediatric patients with invasive candidiasis [2]. The analysis included 98 patients who had culture-proven invasive candidiasis and had been randomized to receive one of the study drugs (2 mg/kg/day micafungin, n=48; 3 mg/kg/day L-AmB, n=50). The majority of cases were caused by non-albicans Candida spp (63% in the micafungin arm and 70% in the L-AmB arm). Micafungin was as effective as L-AmB in the overall population (72.9% vs. 76.0%). In addition, micafungin and L-AmB were equally efficacious in neutropenic patients (85.3% vs. 76.9%), patients aged <2 years (80.8% vs. 77.4%), and in premature infants (70.0% vs. 66.7%). To date, this is the largest trial in pediatric patients with invasive candidiasis, and suggests that micafungin is an effective alternative to L-AmB for the treatment of this infection.

Invasive aspergillosis

Treatment options for invasive aspergillosis were evaluated in several presentations [3,4]. Raad et al. conducted a comparative, retrospective cohort study comparing posaconazole with high-dose lipid formulations of AmB as salvage therapy for invasive aspergillosis (IA) in patients with hematological malignancies [3]. Patients received posaconazole (n=51) or high-dose lipid formulations of AmB (n=49; L-AmB or AmB lipid complex at doses of ≥7.5 mg/kg/day). Risk factors (age, underlying malignancy, bone marrow transplantation, duration of neutropenia, immunosuppressant use, graft-versus-host disease) were similar in the two groups. The response rate to salvage therapy was significantly better with posaconazole than with lipid formulations of AmB (39% vs. 8%; p=0.001). Mortalities that could be attributed to aspergillosis were lower in the posaconazole group (at a rate of 39% compared with 63% in those who received AmB; p=0.02). Posaconazole treatment was the only factor that was significantly associated with improved outcome (odds ratio [OR] 8.85, 95% confidence interval [CI] 2.64–29.41). Higher rates of hepatotoxicity and nephrotoxicity were observed with high-dose lipid formulations of AmB compared with posaconazole. Thus the authors concluded that posaconazole appears to be more...
Invasive fungal infection is a serious complication in cancer patients, particularly in those undergoing hematopoietic stem cell transplantation. Antifungal prophylaxis is the use of antifungal agents to prevent the onset of invasive fungal infections in patients at high risk. The appropriate selection of antifungal prophylaxis often depends on the specific fungal pathogens involved and the patient's clinical status. This article reviews the use of antifungal prophylaxis in cancer patients, including the role of voriconazole/caspofungin combination therapy in the treatment of invasive fungal infection compared with placebo, but no survival benefit was observed (B1 evidence level).

One of the concerns surrounding the widespread use of antifungal prophylaxis is the development of azole resistance. This was addressed as part of the analysis of two studies that compared posaconazole with fluconazole or itraconazole for prophylaxis in patients with acute myelogenous leukemia (AML; n=1202) [8]. The distribution and susceptibilities of Candida isolates were assessed at baseline and at the end of therapy. The investigators found that the shift to non-albicans species and the development of azole resistance were uncommon. Minimum inhibitory concentrations (MICs) were increased for two C albicans isolates and 14 C glabrata isolates. Breakthrough Candida infections occurred in only 11 patients (in four patients while they were receiving prophylaxis and in seven others after end of therapy). Eight of these breakthrough infections were due to C glabrata. Therefore, the use of antifungal prophylaxis selected for azole resistance and for non-susceptible Candida spp to a limited extent only.

In a small, randomized trial in patients with AML, voriconazole was compared with placebo for prophylaxis during induction chemotherapy [9]. Ten patients were randomized to voriconazole and 15 to placebo. By day 21, none of the patients on voriconazole and five patients on placebo had developed lung infiltrates (p=0.04). After 4 weeks of follow-up, no patients in the voriconazole arm and four patients in the placebo arm had developed chronic disseminated candidiasis (p=0.07). These are promising results and call for larger studies to corroborate the value of voriconazole as a prophylactic agent in neutropenic patients with AML.

Another randomized trial studied the efficacy of aerosolized L-AmB as a prophylactic regimen against IA in patients with prolonged neutropenia [10]. The analysis included 271 patients with 406 neutropenic episodes; 139 patients were randomized to inhaled L-AmB via an Adaptive Aerosol Delivery system (AAD®, Respironics Respiratory Drug Delivery [UK] Ltd, Bognor Regis, West Sussex, UK) twice weekly for 30 min each, and 132 patients were randomized to receive placebo. The rate of proven or probable IA was 4% in the L-AmB arm and 14% in the placebo arm (p=0.003). No difference in mortality rates between the two groups was detected. Therefore, inhaled L-AmB can be considered a viable alternative to traditional antifungal prophylaxis in patients with prolonged neutropenia.

**Emerging fungal infections**

Several presentations dealt with the recently described outbreaks in the US and Asia of Fusarium keratitis in contact lens wearers [11–15]. Early in 2006, the US Centers for
Disease Control and Prevention (CDC) received reports of several cases of Fusarium keratitis among contact lens wearers. An investigation was launched and revealed 86 confirmed cases in 29 states [11]. The most commonly isolated species was F solani (12 of 16; 75%). Molecular analysis revealed multiple genotypes of F solani. The organism was cultured from opened contact lens solution bottles and lens cases but not from unopened solution bottles. A case–control study was then performed to identify risk factors for acquiring Fusarium keratitis [12]. Forty-four cases were included in the analysis and were matched to 83 controls who were adult contact lens wearers from the same neighborhoods as the cases. Multivariable regression showed that the use of Bausch & Lomb’s (Rochester, NY, USA) ReNu with MoistureLoc contact lens solution was associated with the highest risk for developing Fusarium keratitis (OR 19.0, 95% CI 4.5–80.9). Other risk factors included the reuse of old solution for contact lens storage (OR 2.9, 95% CI 1.3–6.3). All of the findings detailed above led the investigators to conclude that extrinsic contamination of contact lens solutions had occurred, and that the cause of this outbreak is multifactorial.

Another large outbreak of Fusarium keratitis occurred in Asia and was subject to an extensive investigation [13]. Genotyping of isolates from 61 contact lens wearers in Singapore suggested possible relatedness of the strains, pointing towards a common source of infection, at least in some patients.

Sutton et al. reported on the susceptibility of F solani isolates to antifungals at a reference laboratory in San Antonio (TX, USA) [14]. The isolates were resistant to a number of antifungal agents, including fluconazole, caspofungin, itraconazole, posaconazole, and AmB. Slightly lower MICs were observed with voriconazole. Synergy testing using various combinations of antifungals gave mostly indifferent results, except in two cases where enhanced activity with the combination of voriconazole plus terbinafine was observed. The refractoriness of Fusarium infections to antifungal therapy was reinforced by the findings of Imamura et al. that Fusarium spp have the ability to form biofilms on soft contact lenses [15].

Twenty-five patients (36%) in the US and five patients (8%) in Singapore who had Fusarium keratitis required corneal transplantation [11,13]. It appears that the innate reduced susceptibility of the organism combined with biofilm formation on contact lenses have contributed to the high treatment failure rates associated with these outbreaks.

References
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