Broad-Spectrum Antifungal Prophylaxis in Patients With Cancer at High Risk for Invasive Mold Infections: Counterpoint

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Abstract
Management of invasive mold infections in patients with prolonged neutropenia and hematopoietic stem cell transplant (HSCT) recipients with graft-versus-host disease (GVHD) has been hampered by the difficulty in diagnosing these infections. Definite diagnosis invariably centers on histologic identification of hyphae in tissue or on culture from a sterile body site. Therefore, most practitioners have relied on prophylaxis and empiric therapy. Currently, emphasis is shifting from routine prophylaxis and empiric therapy to screening of patients with neutropenia at high risk so that clinicians can administer appropriate antifungal therapy early, when it can potentially improve patient outcome. Non–culture-based microbiologic tools are at the forefront of this paradigm shift. Commercially available methods to detect fungal antigens and sophisticated techniques to detect fungal DNA may be used as screening tools during the highest risk period. Together with assessment of clinical signs, cultures, and especially CT scanning, these methods are useful for starting antifungal therapy preemptively. While awaiting further evaluation of these tools during the postengraftment period of allogeneic HSCT, mold-active prophylaxis targeting the subgroup of patients with severe acute or chronic GVHD may be justified.

The primary prophylactic use of antifungal agents in patients with cancer, defined as the administration of an antifungal drug during a period of high risk to prevent the development of fungal infections, has been evaluated in more than 80 studies. In the 1990s, 2 pivotal studies revived the discussion between believer and nonbeliever. Apparently acceptable safety and tolerability profile, has apparently improved the incidence of invasive fungal infections. Among the 16 trials reports that this practice is only effective when the background incidence of invasive fungal infections (IFIs) exceeds 15% (Table 1). The effectiveness of prophylaxis using mold-active agents (itraconazole, amphotericin B, micafungin) has remained a subject of debate, primarily because an indisputable reduction in overall mortality.

Hence, antifungal prophylaxis practice varies considerably among different centers. The recent arrival of posaconazole, a broad-spectrum antifungal agent with an apparently acceptable safety and tolerability profile, has revived the discussion between believer and nonbeliever. Two phase III studies of posaconazole prophylaxis are now available, reporting a reduced incidence of invasive...
aspergillosis in patients at risk (although only in those able to tolerate oral drug intake) and a decreased overall mortality in neutropenic patients with myeloid malignancies undergoing intensive chemotherapy, but not in non-neutropenic allogeneic HSCT recipients with graft-versus-host disease (GVHD). In the authors’ opinion, current data supporting mold-active prophylaxis should be weighed against gaps in knowledge and recent improvements in the diagnosis and outcome of invasive aspergillosis, which is the most common mold infection in patients with cancer. Studies on the detection of galactomannan or β-D-glucan in neutropenic patients with cancer have shown a median time-lag of approximately 1 week between the biologic onset of infection (evidenced by a positive test result) and the appearance of clinical signs and symptoms. The authors believe that an accurate diagnosis can be reached within this period, allowing an earlier and more targeted therapeutic intervention.

### New Diagnostic Tools

**Detection of Galactofuranosyl-Containing Molecules**

Aspergillus antigen detection in blood using the Bio-Rad Platelia sandwich enzyme-linked immunosassay (ELISA) has been studied extensively for more than 12 years and has gained widespread acceptance as a sensitive method to undertake prospective surveillance in patients with hematologic malignancies undergoing chemotherapy and to diagnose invasive aspergillosis. A comprehensive review of the literature showed excellent performance characteristics (receiver operating characteristic areas under the curve > .8) of Aspergillus antigen detection in blood for diagnosing invasive aspergillosis in profoundly neutropenic adult patients with cancer, provided the test was performed at least 2 or 3 times a week and supported by suggestive chest CT scan findings (usually taken in patients with > 4–5 days of persistent neutropenic fever).

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**Table 1 Factors Favoring Antifungal Prophylaxis with Yeast- Versus Mold-Directed Prophylactic Strategies**

<table>
<thead>
<tr>
<th>Factors</th>
<th>Yeasts (Candida) (Fluconazole)</th>
<th>Molds (Invasive Aspergillosis) (e.g., Posaconazole)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infection-Related</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Common (to avoid prophylaxis of &gt; 90% of patients who do not need it)</td>
<td>Yes (&gt; 15%)</td>
<td>No</td>
</tr>
<tr>
<td>Serious even when diagnosed early and treated preemptively (e.g., based on serologic markers ± radiology)</td>
<td>Yes (high morbidity and mortality; acute, chronic disseminated candidosis; death)</td>
<td>Yes, depending on how it is diagnosed</td>
</tr>
<tr>
<td>Difficult to diagnose</td>
<td>Yes (&lt; 50% + blood cultures)</td>
<td>No (serology, chest computed tomography)</td>
</tr>
<tr>
<td>Prophylaxis-Related</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Effective (decreases morbidity and mortality)</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Minimal drug interactions</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Minimal toxicity</td>
<td>Yes</td>
<td>Yes (preliminary)</td>
</tr>
<tr>
<td>Less expensive than cost of preemptive strategy</td>
<td>Yes (especially when using generics)</td>
<td>Not tested</td>
</tr>
<tr>
<td>Does not interfere with diagnosis of infection when breakthrough develops</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Does not interfere with response assessment (e.g., immune reconstitution inflammatory syndrome)</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Available in intravenous/oral formulations</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Unlikely to lead to increased resistance</td>
<td>Yes</td>
<td>Too early to evaluate, but resistance to azoles likely to develop</td>
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The test was released for clinical use in Europe in 1997 and approved by the FDA for diagnostic use in 2003. The performance characteristics were deemed adequate to include *Aspergillus* antigen detection in the consensus criteria for defining IFIs in patients with cancer and HSCT recipients (EORTC/Mycoses Study Group [MSG] criteria).\(^9\)

However, according to a recent meta-analysis involving 27 diagnostic studies, accuracy of the test differed according to study population (adults > children), underlying disorder (hematologic malignancy and allogeneic stem cell transplant > solid organ transplantation), and the stringency of the criteria used to define a case of invasive aspergillosis (EORTC/MSG criteria > other criteria).\(^8\) Major differences in the pathogenesis of invasive aspergillosis (e.g., between neutropenic and steroid-treated patients) and methodological and clinical heterogeneities between these studies account for most of the variations in test performance, as discussed in detail elsewhere.\(^9\) However, some clinically important caveats exist, such as reduced sensitivity during treatment with mold-active antifungal agents\(^6\) and the high number of false-positive results with the use of some semisynthetic \(\beta\)-lactam antibiotics\(^2\) (including piperacillin-tazobactam and amoxicillin-clavulanate) and gluconate-containing plasma-expanders.\(^9\) Despite these caveats, the high specificity and excellent negative predictive value of the Platelia sandwich ELISA in patients with neutropenia, especially if used in combination with a pulmonary CT scan, allows a diagnosis of pulmonary invasive aspergillosis to be ruled out.\(^9\)

**Detection of (1,3)-\(\beta\)-D-Glucan**

\(\beta\)-D-glucan assays are widely used in Japan, and the FDA recently approved the Fungitell assay to help diagnose IFIs in patients with cancer based on an assessment in patients with acute leukemia and myelodysplastic syndromes.\(^11\) The negative predictive value of twice-weekly sampling is 100% and test results are not influenced by the use of mold-active antifungal agents. Again, several factors can lead to false-positive readings, including the use of albumin or immunoglobulins, exposure to glucan-containing gauze, hemodialysis, and some antimicrobial preparations (amoxicillin-clavulanate).\(^11\) Nevertheless, given the broad spectrum of fungal species that can be detected with these assays and the excellent negative predictive values, these tests seem to be useful for excluding IFIs.

**Detection of Fungal DNA**

Although promising, fungal DNA detection is still considered investigational because of the lack of a standardized, reproducible, and validated (commercially available) method.\(^26\)

**Chest CT Scan**

In neutropenic patients, CT scans should be performed at the first sign of pulmonary mold infection, such as unexplained or relapsing fever; isolation of *Aspergillus* species or other mold; suggestive clinical signs/symptoms; a new pulmonary infiltrate on standard radiography; or more than 1 positive non–culture-based assay.\(^23\) Suggestive radiologic signs of angioinvasive pulmonary mycosis include single or multiple nodules surrounded by a halo of lower attenuation. This halo sign indicates invasive pulmonary aspergillosis in neutropenic patients and occurs early in the course of the disease.\(^26,29\) Other CT findings, such as ground-glass opacities, are highly indicative of inflammation or pneumonia but have no discriminative power. As recently evidenced, a CT-scan–based approach can substantially improve the early diagnosis of probable invasive aspergillosis and seems to have a significant impact on the outcome of patients with aspergillosis.\(^10\) However, the use of chest CT scan has been less well validated in non-neutropenic patients; similar CT findings are less specific and nodular lesions (even with halo) should be differentiated from those of bacterial, viral, and parasitic infections; lymphoma; nocardiosis; and carcinoma, among other causes.\(^11\)

**Premises of Prophylaxis**

The basic premises of antimicrobial prophylaxis, recently discussed by a panel of experts (Table 1),\(^32\) are delineated in the Point article (see page 175 of that article).

If the infection is considered severe and cannot easily be treated and diagnosed and prophylaxis does not incur clinically significant adverse events, a bias may exist toward prophylaxis, depending on the number needed to treat or prevent 1 infectious episode or prevent 1 infectious death. If, however, the infection can be easily treated and diagnosed or prophylaxis has significant adverse events, a bias will exist against the prophylactic approach, irrespective of the number needed to treat. How does this apply to mold infections in patients with cancer?
Seriousness
Invasive mold infections are serious infections. However, major improvement in the outcome of hematologic patients with invasive aspergillosis, which is the most common pathogenic mold, has been seen over the past decade in leukemia patients and HSCT recipients.\(^{12,13}\) This improved outcome has been attributed to the introduction of nonmyeloablative preparative regimens, the growing use of peripheral blood stem cells as a preferred source of hematopoietic stem cells, earlier diagnosis, and treatment with novel antifungal agents, such as liposomal amphotericin B, voriconazole, and caspofungin. For instance, between 2002 and 2006, Aspergillus-related mortality dropped from 30% to 10% in Italian leukemia centers.\(^{12}\) Between 1990 and 2004, the probability of survival increased fourfold in allogeneic HSCT recipients with invasive aspergillosis.\(^{31}\) In addition, hematologic patients who do not experience response to adequate primary and salvage antifungal treatment often do so because of the uncontrollable status of the underlying disease (e.g., refractory leukemia), severe combined immunodeficiency (e.g., use of corticosteroids), or concomitant presence of organ failure (e.g., severe impairment of pulmonary function tests), irrespective of the activity of the antifungal drug used.\(^{31}\)

Incidence
Placebo-controlled studies in HSCT recipients and neutropenic patients have shown highly significant reductions in the incidence of proven and probable IFIs in favor of fluconazole prophylaxis.\(^ {12,34}\) Unfortunately, few institutions have kept records of their baseline fungal infection rates, partly because of difficulties in diagnosis and lack of autopsy data. Nevertheless, major differences clearly exist among continents, countries, and even centers within the same geographic region. For instance, a nationwide study in Finland showed that the incidence of candidemia in 685 allogeneic HSCT recipients not receiving antifungal prophylaxis was only 1.3%; this low figure argues against routine Candida prophylaxis in Finland.\(^{35}\) Similarly, although Zygomycetes infections seem to be on the rise, most centers have not observed the high incidence rates of these infections seen at M. D. Anderson Cancer Center\(^ {46}\) or the University of Innsbruck in Austria.\(^ {37}\) Therefore, most centers would not consider prophylaxis programs specifically targeting these pathogens. In Finland (as in most Nordic countries), the incidence of invasive aspergillosis in allogeneic transplant recipients not receiving antifungal prophylaxis is approximately 7%; this figure does not justify routine prophylaxis unless therapy in these patients is suboptimal and the morbidity and mortality associated with invasive aspergillosis are very high.

Diagnosis
In a diagnostics-based scenario, the decision to start antifungal therapy is not triggered by fever but relies on the results of a screening strategy in a predefined high-risk population. This strategy uses one or more of the (available in real-time) new non–culture based microbiological tools (see section on “New Diagnostic Tools”) that facilitate rapid and early diagnosis of IFIs. In line with recent guidelines, these tools are to be used in conjunction with modern imaging techniques, such as high-resolution, spiral, or thin-section CT scanning of the lungs, which is the major target organ of mold infections in patients with cancer. This approach is usually referred to as preemptive, and involves treatment of patients with evidence of a pathogen that predisposes them to developing invasive disease.\(^ {38}\) The concept has successfully been applied to the management of viral infections after HSCT or solid organ transplantation. Transplant recipients with suspected cytomegalovirus (e.g., positive antigenemia or polymerase chain reaction assay) undergo preemptive antiviral therapy because of their increased likelihood of developing life-threatening disease if untreated. The new serologic assays for fungal diagnosis do not allow this approach, because seropositivity signifies that the patient already has fungal disease. Nevertheless, to be consistent with recent literature, this article uses preemptive antifungal therapy to describe an antifungal approach based on incorporation of new, noninvasive diagnostic tools.

The excellent negative predictive value of the ELISA or (1,3)-β-D-glucan assay should convince clinicians to withhold antifungal therapy in persistently febrile neutropenic patients with no other clinical, microbiologic, or radiologic evidence of fungal infection (with or without antifungal prophylaxis, depending on specificity of the diagnostic assay). Conversely, given the high positive predictive value in patients with neutropenia, confirmed test positivity should trigger a diagnostic workup and early initiation of antifungal therapy, irrespective of fever or other clinical signs and symptoms. Hence, the preemptive use of antifungal agents may precede or follow the classic criterion for starting empirical antifungal therapy.
This reasoning is supported by a decision analysis model in which preemptive therapy, in contrast to a conventional approach, resulted in fewer patients being treated without incorrectly withholding therapy.\(^{19}\)

Successful examples of this restricted use of antifungals have been reported. In a recent noncomparative study, the authors explored the feasibility of starting anti-Aspergillus 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.\(^{40}\) Patients at risk were screened daily for circulating galactomannan (notably, a recent analysis showed that daily screening provided no benefit over twice-weekly screening\(^{41}\)), and a pulmonary CT scan was performed as per criteria discussed earlier. A purely fever-driven approach would have resulted in antifungal treatment in at least 41 of 136 episodes (30%); a preemptive algorithm led to use of antifungal agents in less than one quarter of these 41 episodes. Furthermore, the authors’ approach also identified 10 episodes of invasive aspergillosis that would not have been identified with the conventional approach because of the absence of fever or presence of confounding febrile conditions. One case of disseminated zygomycosis of 22 IFI cases remained undetected. These encouraging data were confirmed in a recent study in neutropenic allogeneic HSCT recipients.\(^{41}\) Finally, in a randomized clinical study in France, a preemptive approach did not result in increased overall mortality compared with empirical therapy, although a higher number of proven and probable IFIs were diagnosed.\(^{42}\) Also, the high number of galactomannan-seropositive cases of invasive aspergillosis (as opposed to culture-proven cases) in the recent AmbiLoad study may (at least partly) explain the good outcome of liposomal amphotericin B in patients with hematologic malignancies.\(^{43}\)

Thus, novel microbiologic and radiologic tools can identify an IFI or Aspergillus infection at an early stage or rule out these infections in high-risk neutropenic hematopoietic patients. The high negative predictive value of a normal CT scan plus serial negative non-culture–based microbiologic tools (NCBMTs) rule out an invasive pulmonary fungal infection, whereas the high positive predictive value of a suggestive CT scan (e.g., halo sign) plus positive NCBMTs warrant initiation of mold-active antifungal therapy (the preferred agent depends on the species specificity of the assay). All scenarios in between remain inconclusive (fungal or nonfungal; infectious or noninfectious) and warrant a more aggressive diagnostic approach, including invasive procedures for adequate sampling of culture and microscopy (e.g., CT-guided bronchoscopy with lavage\(^{44}\)) and for obtaining tissue specimens for histopathologic examination (e.g., CT-guided percutaneous lung biopsy).\(^{17}\)

The authors admit that these approaches require full cooperation from all parties (clinicians, microbiologists, radiologists, nursing team) and strict adherence to a protocol, and that these endeavors are only possible if health care providers combine efforts. Rapid availability of CT scanning and real-time reporting of mycologic test results are absolute prerequisites.

**Safety Profile and Interactions: Many Unknowns Remain**

Although the safety, tolerability, and drug interaction profiles of most agents commonly used in antifungal prophylaxis (particularly the azoles) have been well characterized, hazardous adverse effects or interactions still become evident after many years of use. For instance, an unanticipated interaction of itraconazole and metabolites of cyclophosphamide, resulting in clinically significant hepatic abnormalities and a trend toward lower fungal-free survival in allogeneic HSCT recipients, was only recently reported, although the drug had been used for more than a decade.\(^{44}\) More alarming is the fact that clinicians are often unaware of or inattentive to potentially hazardous interactions. In addition, recent observations have ascribed severe drug-related toxicities (and therapeutic failure) of itraconazole/voriconazole to unexpectedly high (or low) serum concentrations because of interpatient pharmacokinetic variabilities.\(^{45–47}\)

Finally, some studies have (unintentionally) selected for a less-sick population; particularly with drugs that have only an oral formulation. Whether the results of these studies are generalizable to other (sicker?) populations who might show different drug absorption patterns (e.g., because of severe mucositis or grade III–IV intestinal GVHD) or who cannot comply with an oral intake (e.g., because of nausea or vomiting) remains to be explored.

**Collateral Damage**

Numerous reports indicate that the use of antifungal prophylaxis results in the selection of inherently resistant
organisms, leading to changes in the epidemiology of colonizing and infecting organisms. The emergence of Zygomycetes infections in patients who have received voriconazole for several weeks or months in a row is the most recent example of this potential.

Equally disturbing is the dramatic impact of mold-active prophylaxis on the performance of the galactomannan Platelia sandwich ELISA. Animal studies have shown that even a single dose of mold-active agents (polyenes, azoles, and candins) leads to lower circulating galactomannan levels as late as 96 hours after exposure, most likely in response to inhibition of fungal growth by the antifungal agent. This finding is in line with recent data reporting higher assay sensitivity in patients who do not receive preventative mold-active agents. However, this confounding factor induces a false sense of security, potentially delaying adequate antifungal therapy.

Conclusions

For many years, the managing of invasive mold infections in high-risk patients with cancer has been hampered by the inability to diagnose the infection early. Most practitioners have relied on generalized prophylaxis or empirical use of antifungal agents, despite significant overtreatment, increased cost, and potential for increased toxicity. Currently, emphasis is shifting from these latter approaches to screening adult patients at high risk so that appropriate antifungal therapy can be administered early. NCBMTs and sensitive radiologic tools are at the forefront of this paradigm shift. Commercially available methods to detect fungal antigens and sophisticated techniques to detect fungal DNA, combined with sensitive radiologic tests, are useful for screening prolonged neutropenic patients. Currently, these tools are currently less well validated in non-neutropenic patients; fortunately, non-neutropenic patients with cancer at high to very high risk can be more easily identified (e.g., HSCT with severe GVHD; T-cell depleted transplant recipients; prior mold infection). While awaiting further evaluation of non-culture based methods in these particular subgroups, targeted prophylaxis (or secondary prophylaxis in case of prior fungal infections) can be used, taking into account the importance of institutional epidemiology, current gaps in knowledge, and recent improvements in the outcome of patients with invasive mold infections.

References


34. Rex JH, Anaissie EJ, Boutsati E, et al. Systemic antifungal prophylaxis reduces invasive fungal in acute myelogenous leukemia: a retrospec-