Invasive fungal infection (IFI) is a serious and common complication in hematological patients. The risk is highest among acute leukemia patients undergoing induction chemotherapy and patients undergoing allogeneic hematopoietic stem-cell transplantation. Owing to the difficulty in diagnosing IFIs and the fatality rate associated with delayed treatment, antifungal prophylaxis and empirical antifungal therapy are standard management approaches. Novel agents, such as posaconazole and echinocandins, broaden our armamentarium against IFIs and improve patients’ outcomes.

**Risk factors of invasive fungal infection**

Among hematological patients, the risk of IFI is the highest among those with prolonged neutropenia (absolute neutrophil count <0.1 × 10^9/l for more than 3 weeks or absolute neutrophil count <0.5 × 10^9/l for more than 5 weeks) and those undergoing allogeneic stem-cell transplantation. The risk is even higher in cases with unrelated or mismatched donor and presence of graft-versus-host disease (GVHD) [3]. GVHD leads to further compromise in host immunity and mucosal barrier damage, as well as the use of immunosuppressants. Therefore, there are two peaks of IFI during stem-cell transplantation. An early peak occurs during the neutropenic phase before engraftment, and a later peak is associated with the presence of GVHD, the use of steroids and persistent lymphopenia. Cytomegalovirus infection per se has also been reported to increase the risk of IFI [4]. There exists a scoring system that divides hematological patients into high-, intermediate- and low-risk groups (Table 1) [3].

**Diagnosis of fungal infection**

A prompt diagnosis of IFI is essential for patient survival since early initiation of appropriate antifungal treatment is shown to improve patient outcome [5]. However, this is often challenging. Clinical features are nonspecific and indistinguishable from bacterial infections.

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Neutropenic fever not responding to broad-spectrum antibiotics can be related to drugs or the primary hematological disease. Lung infiltrate on chest x-ray was reported in 15–28% of neutropenic patients after chemotherapy, which apart from IFIs, can be attributed to numerous causes such as multidrug-resistant bacteria, *Pneumocystis jiroveci*, viruses, underlying disease infiltration, alveolar hemorrhage, organizing pneumonia and irradiation pneumonitis [6].

The diagnostic yield of microbiological cultures is very low for IFIs as fungal pathogens are often difficult to recover from tissue. The use of antifungal prophylaxis reduces the fungal pathogen load and makes the diagnostic yield even lower. Histology is the cornerstone of making a definitive diagnosis of IFI (Table 2) [7]. However, invasive procedures are rarely possible in hematologic patients because of their coagulopathic state.

There is emerging interest in noninvasive, nonculture-based diagnostic tests. The most widely reported are serum galactomannan and 1,3-β-d-glucan. Galactomannan is a polysaccharide component of the cell wall of *Aspergillus* species, which is released during hyphal growth. Its presence in serum or body fluid is detected by a double sandwich ELISA in patients with invasive pulmonary aspergillosis, the positive and diagnostic cut-off value ranging from 0.17 to 1 in different reports [8]. In a prospective study of hematologic patients with invasive pulmonary aspergillosis, the positive and negative predictive values reached 100% when BAL galactomannan assay was combined with high-resolution CT imaging [9]. However, the galactomannan assay has not been validated for body fluid specimens other than serum. The evidence reported in the literature are mostly case reports or retrospective studies with heterogeneous patient populations. Prospective studies in this aspect are needed to compare the performance of this test in body fluid specimens other than serum.

1,3-β-d-glucan is a panfungal antigen and is present in many different fungal species. One study demonstrated that its sensitivity in diagnosing candidiasis ranged from 78 to 81% depending on the cut-off value [10]. Positive 1,3-β-d-glucan in serum suggests a fungal infection but it is not specific for any fungi. False-positive results are reported in hemodialysis patients owing to the cellulose membrane used in dialysis. Certain antibiotics such as cephalosporin, carbapenems and ampicillin–sulbactam cross-react with 1,3-β-d-glucan. Its clinical utility is currently limited as an adjunctive test to microbiological cultures and radiological investigations.

PCR of fungal ribosomal DNA allows rapid and early detection of IFIs. In addition, it allows the molecular identification of the fungal pathogens. It has been shown to have high sensitivity and
specificity of 92.3 and 94.6%, respectively, in a study of hematological patients with invasive aspergillosis. A negative PCR result is useful to exclude invasive aspergillosis [18]. However, this test is still investigational and standardization of this PCR test is needed before it can be used clinically.

**Antifungal prophylaxis**

There are numerous randomized controlled trials investigating the efficacy of antifungal prophylaxis in hematological patients. Fluconazole, amphoterin B, liposomal amphoterin B, itraconazole, voriconazole, posaconazole and micafungin have been studied in these patients as antifungal prophylaxis [18–23].

A meta-analysis in 2007 looked at 64 randomized controlled trials of antifungal prophylaxis in patients undergoing chemotherapy or stem-cell transplantation. It was shown that antifungal prophylaxis reduced overall mortality significantly compared with placebo, with a relative risk of 0.84 (95% CI: 0.74–0.95). The number of patients that needed to be treated to prevent one death was 43. Antifungal prophylaxis was also shown to reduce the incidence of documented IFIs by 50% and fungal-related death by 45%. The efficacy was most pronounced in the group undergoing allogeneic stem-cell transplantation and patients with acute leukemia undergoing induction chemotherapy. Results in patients undergoing autologous stem-cell transplant did not reach statistical significance [24].

Fluconazole is the prophylactic antifungal most extensively studied in hematological patients. It has consistently been shown to decrease the risk of *Candida* infection. In a study of 300 allogeneic bone marrow transplant recipients from a single center comparing fluconazole prophylaxis versus placebo for 75 days immediately post-transplantation, it was demonstrated that fluconazole effectively reduced the incidence of invasive *Candida* infection. After follow-up for 8 years, the incidence of *Candida*-related death was lower in the fluconazole group. The incidence of severe gut GVHD as well as mortality due to gut GVHD was also lower with fluconazole prophylaxis. This led to an overall survival benefit in the group receiving fluconazole prophylaxis [21]. Therefore, fluconazole has been the standard prophylactic antifungal in stem-cell transplant recipients. No other antifungal has been shown to have an overall survival advantage over fluconazole in stem-cell transplant recipients.

Patients receiving fluconazole are reported to have a change in microbial colonization and there was an increased rate of colonization by *Candida glabrata* and *Candida krusei*, both of which are less susceptible to fluconazole [25]. Breakthrough IFIs become a major concern in these patients as fluconazole has no activity against molds. There is an increasing incidence of aspergillosis, zygomycosis and fusariosis in centers employing fluconazole prophylaxis. In a hospital in the USA, the incidence of invasive aspergillosis tripled, while that of fusariosis and zygomycosis doubled over a 15-year period [26].

Itraconazole has some activity against molds and broader coverage against *Candida* species than fluconazole. It can be administered orally or intravenously. An open-labeled randomized trial comparing itraconazole with fluconazole in allogeneic stem-cell transplant recipients showed that the incidence of IFI was lower in the group receiving itraconazole but there was no significant difference in the overall mortality [27]. This finding was also demonstrated in a meta-analysis [28]. In this meta-analysis of 13 randomized trials, itraconazole was shown to reduce the incidence of IFI and the mortality from IFIs. In the subgroup of patients who received itraconazole solution, there was significantly less invasive *Aspergillus* infection (odds ratio [OR]: 0.52; 95% CI: 0.30–0.90; p = 0.02), while this was not demonstrated in the subgroup who received itraconazole tablets. Itraconazole commonly causes gastrointestinal side effects. The erratic absorption with oral tablets is also a problem in its clinical utility. Oral suspension demonstrates better oral bioavailability than the tablet form and is the preferred option.

Voriconazole is active against *Candida*, *Aspergillus* and *Fusarium* species. There was no case of breakthrough aspergillosis in a retrospective study of allogeneic stem-cell transplant recipients receiving voriconazole prophylaxis [29]. An ongoing double-blind randomized study is comparing voriconazole with fluconazole as antifungal prophylaxis in allogeneic stem-cell transplant recipients. Preliminary results have shown comparable efficacy between the two drugs in terms of prevention of IFIs and overall mortality [30]. The final results of the study are expected soon and will provide more information on the role of voriconazole as primary antifungal prophylaxis. Voriconazole is available in both oral and intravenous forms, however, it can cause visual hallucinations during infusion. The intravenous preparation contains cyclodextrin that would accumulate in patients with renal impairment. Therefore, the use of intravenous voriconazole in renal failure patients should be cautious. There is a concern that the use of voriconazole as antifungal prophylaxis is associated with an increasing incidence of zygomycosis [31,32]. Zygomycosis carries a very grave prognosis and has a case–fatality rate of 73% in stem-cell transplant patients [32].

Posaconazole is the newest drug available in the triazole family. It is only available in oral solution and has the broadest coverage in terms of antifungal activity among all azoles. In addition to *Candida*, *Aspergillus* and *Fusarium*, it is also active against Zygomycetes. In a randomized trial of neutropenic myelodysplastic and acute myeloid leukemia patients, posaconazole was superior to fluconazole and itraconazole in preventing IFIs, invasive aspergillosis and overall mortality [33]. In another study comparing posaconazole with fluconazole in patients with severe GVHD after allogeneic stem-cell transplantation, posaconazole was found to have similar efficacy in preventing IFIs compared with fluconazole and was superior in the prevention of invasive aspergillosis. Although the overall mortality was similar in both groups, the mortality from IFIs was significantly lower in the group receiving posaconazole [34]. Posaconazole was well tolerated in both studies. The only concern with this drug is that it is only available orally. Patients in the early post-stem-cell transplant period or those with severe mucositis would have difficulty in taking this drug.

Hepatotoxicity is a problem with all azoles. They are contraindicated in patients with liver impairment and not suitable in hematopoietic stem-cell transplant patients with liver GVHD. Drug interaction is another concern in the use ofazole prophylaxis. Azoles are metabolized by cytochrome P450 and interact with drugs that
Table 2. European Organization of the Research and Treatment of Cancer/Mycosis Study Group criteria for diagnosis of invasive aspergillosis.

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Proven IFI</td>
<td>Histopathologic or cytopathologic examination showing hyphae from needle aspiration or biopsy specimen with evidence of associated tissue damage (either microscopically or unequivocally by imaging); or positive culture result for a sample obtained by sterile procedure from a normally sterile and clinically or radiologically abnormal site consistent with infection, excluding urine and mucous membranes</td>
</tr>
<tr>
<td>Probable IFI</td>
<td>At least one host factor criterion, one microbiological criterion and one major (or two minor) clinical criteria from abnormal site consistent with infection</td>
</tr>
<tr>
<td>Possible IFI</td>
<td>At least one host factor criterion and one microbiological or one major (or two minor) clinical criteria from abnormal site consistent with infection</td>
</tr>
<tr>
<td>Host factors</td>
<td>Neutropenia (&lt;0.5 x 10^9/l for &gt;10 days); persistent fever for &gt;96 h refractory to appropriate broad-spectrum antibacterial treatment in high-risk patients; body temperature either &gt;38°C or &lt;36°C and any of the following predisposing conditions: prolonged neutropenia (&gt;10 days) in previous 60 days, recent or current use of significant immunosuppressive agents in previous 30 days, proven or probable IFI during previous episode of neutropenia or coexistence of symptomatic AIDS; signs and symptoms indicating GVHD, particularly severe (&gt;grade 2) or chronic extensive disease; prolonged (&gt;3 weeks) use of corticosteroids in previous 60 days</td>
</tr>
<tr>
<td>Microbiological</td>
<td>Positive result of culture for Aspergillus from sputum or BAL fluid samples; positive result of culture or findings of cytologic/direct microscopic evaluation for Aspergillus species from sinus aspirate specimen; positive findings of cytologic/direct microscopic evaluation for Aspergillus from sputum or BAL fluid samples; positive result for Aspergillus antigen in specimens of BAL fluid, CSF or &gt;two blood samples; positive findings of cytologic or direct microscopic examination for fungal elements in sterile body fluid samples</td>
</tr>
</tbody>
</table>
| Clinical LRTI | Must be related to site of microbiological criteria and temporally related to current episode  
• Major  
  Any of the following new infiltrates on CT imaging: halo sign, air crescent sign or cavity within area of consolidation  
• Minor  
  Symptoms of LRTI (cough, chest pain, hemoptysis or dyspnea); physical finding of pleural rub; any new infiltrate not fulfilling major criterion; pleural effusion |
| Sinonasal infection | Suggestive radiological evidence of invasive infection in sinuses (i.e., erosion of sinus walls or extension of infection to neighboring structures, and extensive skull base destruction)  
• Major  
  Upper respiratory symptoms (e.g., nasal discharge and stuffiness); nose ulceration or eschar of nasal mucosa or epistaxis; periorbital swelling; maxillary tenderness; black necrotic lesions or perforation of hard palate  
• Minor  
  Focal neurological symptoms and signs (including focal seizures, hemiparesis and cranial nerve palsies); mental changes; meningal irritation findings; abnormalities in CSF biochemistry and cell count (provided that CSF is negative for other pathogens by culture or microscopy and negative for malignant cells) |
| CNS infection | Radiological evidence suggesting CNS infection (e.g., mastoiditis or other parameningeal foci, extradural empyema, intraparenchymal brain or spinal cord mass lesion)  
• Major  
  Focal neurological symptoms and signs (including focal seizures, hemiparesis and cranial nerve palsies); mental changes; meningal irritation findings; abnormalities in CSF biochemistry and cell count (provided that CSF is negative for other pathogens by culture or microscopy and negative for malignant cells)  
• Minor |
| Disseminated FI | Papular or nodular skin lesions without any other explanation; intraocular findings suggestive of hematogenous fungal chorioretinitis or endophthalmitis |

BAL: Bronchoalveolar lavage; CSF: Cerebrospinal fluid; FI: Fungal infection; GVHD: Graft-versus-host disease; IFI: Invasive fungal infection; LRTI: Lower respiratory tract infection.

are substrates for cytochrome P450. Cyclosporin A and vinca alkaloids are frequently encountered drugs in hematology that interact with azoles. Close monitoring of Cyclosporin A level is needed.

The echinocandins are a new family in the antifungal armamentarium. There are three members currently available: caspofungin, micafungin and anidulafungin. The echinocandins inhibit 1,3-β-D-glucan synthase and thereby interfere with fungal cell wall formation; they are fungicidal for yeasts and fungistatic for molds; they must be administered intravenously; and they demonstrate excellent activity against *Candida* species in various trials and also have *in vitro* activity against *Aspergillus*. They have neither significant hepatotoxicity nor nephrotoxicity and have the least drug interaction of all antifungal classes. Micafungin demonstrated superior activity in preventing IFIs in a randomized double-blind study comparing it with fluconazole among stem-cell transplant recipients. Fewer invasive *Aspergillus* infections were observed in the group receiving micafungin but this did not reach statistical significance. There was no difference in overall mortality [23]. Caspofungin was reviewed in another open-labeled study which compared it with itraconazole. Caspofungin demonstrated similar efficacy in prevention of IFIs in patients with acute myeloid leukemia or myelodysplastic syndrome receiving induction chemotherapy, but further studies are needed to determine its role in prophylaxis [35].
Amphotericin B deoxycholate is the first drug to be made available that was effective against IFI and hence it is the earliest being evaluated as prophylaxis in high-risk hematological patients. It has a broad spectrum of activity. The incidence of IFIs decreased from 30 to 9% after implementation of routine amphotericin B prophylaxis in a retrospective analysis conducted in the 1980s [36]. However, it is now rarely used in prophylaxis settings because it causes significant infusion toxicity as well as nephrotoxicity [39]. Its lipid formulation is much better tolerated. In a study comparing liposomal amphotericin B (3 mg/kg three times per week) with fluconazole and itraconazole in patients with acute myeloid leukemia or myelodysplastic syndrome undergoing chemotherapy, there was no significant difference in the incidence of IFIs and overall survival between the two groups [21]. In another study, patients received liposomal amphotericin B (50 mg on alternate days) during neutropenia and there was a significant reduction in the incidence of IFIs and invasive aspergillosis. It was well tolerated and the discontinuation rate was only 2.8% [37]. Amphotericin B products can also be administered via the inhalation route and this avoids systemic adverse effects during infusion. In a randomized placebo-controlled trial, aerosolized liposomal amphotericin B given twice weekly prevented invasive pulmonary aspergillosis and was well tolerated [38]. This is a valuable option in patients with chronic lung diseases, such as bronchiolitis obliterans in stem-cell transplant patients.

The National Cancer Care Network issued a guideline concerning antifungal prophylaxis in 2008. It serves as a reference for choosing an antifungal prophylaxis for hematological patients of different levels of IFI risk (Table 3) [101].

**Empirical or pre-emptive antifungal treatment**

Neutropenic patients with persistent fever despite broad-spectrum antibiotic administration are considered to be at high risk of IFIs. Based on the risk stratification of patients, two management approaches have emerged: empirical versus pre-emptive treatment. The empirical approach is to start antifungal treatment in patients with neutropenic fever not responding to antibiotics, irrespective of the results of microbiological or radiological investigation. On the other hand, pre-emptive therapy is the administration of antifungals on the basis of clinical, imaging and/or laboratory findings indicative of IFIs in at-risk patients.

Some have criticized that the empirical approach might lead to overtreatment in many cases, and lead to patients suffering from unnecessary drug toxicity. They advocate pre-emptive therapy in view of the advances in diagnostics for fungal infection. Ideally, the combination of clinical features and laboratory and radiological investigation results allow the identification of patients in early stages of IFIs such that physicians can start appropriate antifungal treatment in time. This approach to management is highly dependent on the accuracy and sensitivity of investigations for fungal infection. However, as discussed earlier, fungal infection remains very difficult to diagnose, even with state-of-the-art technology. Any delay in treatment that occurs will jeopardize a patients’ chance of being cured. A recent study in France compared the two management strategies [39]. Neutropenic patients recruited into the empirical treatment arm received antifungal treatment when they had persistent or recurrent fever despite antibacterial treatment, while those in the pre-emptive treatment arm only received antifungal therapy if there was clinical or radiological evidence of pneumonia or acute sinusitis, mucositis, septic shock, cutaneous lesions suggestive of IFIs, unexplained CNS symptoms, periorbital inflammation, splenic or hepatic abscess, severe diarrhea, *Aspergillus* colonization or a positive ELISA for galactomannan antigen test. This study showed that the antifungal use was significantly lower in the preemptive treatment group. In subgroup analysis, the incidence of IFIs is significantly higher in subjects of the pre-emptive arm during the course of induction chemotherapy. For those receiving consolidation chemotherapy or autologous transplant, in whom the expected incidence of IFIs is low, pre-emptive treatment was noninferior to empirical treatment. However, the authors of this study used 1.5 as the cut-off for positivity of serum galactomannan ELISA. This significantly reduced the sensitivity of the test [39]. More vigorous studies are needed to investigate the clinical outcome of these two management approaches in hematological patients of various risk profiles before any recommendations can be given.

**Empirical antifungal therapy**

Amphotericin B, liposomal amphotericin B, itraconazole and caspofungin are approved for the empirical treatment of IFIs in susceptible patients. Amphotericin B is historically the standard empirical antifungal treatment but it is associated with significant toxicity. Liposomal amphotericin B was shown to have comparable efficacy but significantly less infusion-related toxicity and nephrotoxicity than amphotericin B [40].

Intravenous itraconazole was demonstrated to have at least equal efficacy to amphotericin B but it was significantly better tolerated in neutropenic patients in two randomized studies [41,42]. Voriconazole was compared with liposomal amphotericin B in neutropenic and post-stem-cell transplant patients. Although the overall composite outcome of the group receiving voriconazole was inferior to liposomal amphotericin B, these two drugs in fact had similar efficacy in patients considered to have high risk of IFIs. The overall success rate of patients at moderate risk of IFIs receiving voriconazole was lower but this was due to mortality from progressive underlying primary diseases. The incidence of documented breakthrough IFIs was lower with voriconazole and the adverse effects were significantly less with voriconazole [43]. However, because noninferiority was not established, voriconazole is not approved for empirical antifungal treatment. Posaconazole was evaluated in a small open-labeled study. Overall, 77% of 66 patients with febrile neutropenia responded to empirical posaconazole therapy. Further research is needed to investigate the efficacy of posaconazole as an empirical antifungal treatment [44].

In a randomized double-blind study, caspofungin showed equivalent overall efficacy as an empirical treatment of neutropenic fever compared with liposomal amphotericin B. Caspofungin in fact performed better in resolution of baseline fungal infection, survival at day 7 of follow-up and discontinuation due to toxicity. Caspofungin was associated with fewer adverse events and was better tolerated than liposomal amphotericin B [45]. In a Japanese
study, 44 out of 51 patients (86.3%) with febrile neutropenia despite treatment with broad-spectrum antibiotics responded to micafungin [46]. However, echinocandins have no activity against non-\textit{Candida} yeasts and non-\textit{Aspergillus} molds.

**Pre-emptive antifungal therapy**

Owing to the increased use of antifungal prophylaxis, some experts questioned whether empirical antifungal therapy for neutropenic fever may lead to unnecessary drug exposure and consequent toxicities, as well as increased cost [47]. The pre-emptive approach is advocated by some in order to target antifungal usage to those high-risk patients with definite clinical, radiological or microbiological features of IFIs. It was found that antifungal usage was reduced by 78% by this approach [48]. However, studies on this are very limited. Moreover, this pre-emptive approach depends heavily on the sensitivity and specificity of the tests for IFIs. Unfortunately, the currently available pre-emptive tests for IFIs, as discussed previously, have many pitfalls. The mortality of untreated IFIs or delayed treatment of IFIs reaches 100% and therefore the problems with the pre-emptive tests must be solved before this pre-emptive approach can be widely adopted.

**Expert commentary**

There is currently no consensus on when to commence antifungal treatment in high-risk hematological patients with neutropic fever. Advantages and disadvantages of both the empirical and pre-emptive approach are currently being intensely discussed and debated by experts worldwide. Whether to adopt empirical or pre-emptive treatment depends heavily on the availability of intensive screening and rapid diagnostics. If patients are provided with vigorous surveillance for any early sign of IFIs, a pre-emptive approach is a reasonable option. Otherwise, empirical treatment is still the safest way to avoid delayed management.

Antifungal prophylaxis, on the other hand, is consistently shown to prevent IFIs and have survival benefit. Guidelines on antifungal prophylaxis are available and can be referred to when making a clinical decision.

**Five-year view**

With the widespread use of antifungal prophylaxis, the emergence of drug-resistant fungal species is becoming a concern. A universal guideline for antifungal prophylaxis in hematological patients would be a useful reference for clinicians.

More accurate and reliable noninvasive tests for IFIs are needed. PCR-based methods are being developed and investigated. With the availability of diagnostic tests with improved sensitivity and specificity, antifungal treatment can be targeted to those at a real risk of IFIs.

**Financial & competing interests disclosure**

The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

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**Table 3. National Cancer Care Network guidelines for antifungal prophylaxis (January 2008 version).**

<table>
<thead>
<tr>
<th>Disease entity</th>
<th>Antifungal prophylaxis recommended</th>
<th>Duration of prophylaxis</th>
</tr>
</thead>
<tbody>
<tr>
<td>MDS with neutropenia</td>
<td>Posaconazole (Cat 1)</td>
<td>Until resolution of neutropenia</td>
</tr>
<tr>
<td>AML with neutropenia</td>
<td>Voriconazole (Cat 2B)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Amphotericin B products (Cat 2B)</td>
<td></td>
</tr>
<tr>
<td>Allogeneic stem-cell transplant (before engraftment)</td>
<td>Fluconazole (Cat 1)</td>
<td>Until resolution of neutropenia and at least 75 days post-transplant</td>
</tr>
<tr>
<td></td>
<td>Itraconazole (Cat 1)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Micafungin (Cat 1)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Voriconazole (Cat 2B)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Posaconazole (Cat 2B)</td>
<td></td>
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<tr>
<td></td>
<td>Amphotericin B products (Cat 2B)</td>
<td></td>
</tr>
<tr>
<td>Significant GVHD post-transplant</td>
<td>Posaconazole (Cat 1)</td>
<td>Until resolution of GVHD</td>
</tr>
<tr>
<td></td>
<td>Voriconazole (Cat 2B)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Itraconazole (Cat 1)</td>
<td></td>
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<tr>
<td></td>
<td>Micafungin (Cat 1)</td>
<td></td>
</tr>
<tr>
<td>Autologous stem-cell transplant with significant mucositis</td>
<td>Fluconazole (Cat 1)</td>
<td>Until resolution of neutropenia</td>
</tr>
<tr>
<td></td>
<td>Micafungin (Cat 1)</td>
<td></td>
</tr>
<tr>
<td>Autologous stem-cell transplant without mucositis</td>
<td>Consider no antifungal prophylaxis (Cat 2B)</td>
<td></td>
</tr>
<tr>
<td>All patients with overall intermediate to high risk of IFIs</td>
<td>Fluconazole (Cat 1)</td>
<td>Until resolution of neutropenia</td>
</tr>
<tr>
<td></td>
<td>Amphotericin B products (Cat 2B)</td>
<td></td>
</tr>
</tbody>
</table>

Cat 1: Uniform consensus on the basis of high level of evidence that the recommendation is appropriate.
Cat 2A: Uniform consensus, based on lower level of evidence, such as clinical experience, that the recommendation is appropriate.
Cat 2B: Nonuniform consensus (but no major disagreement) on the basis of lower level evidence, including clinical experience, that the recommendation is appropriate.
Cat 3: Major disagreement that the recommendation is appropriate.
AML: Acute myeloid leukemia; GVHD: Graft-versus-host disease; IFI: Invasive fungal infection; MDS: Myelodysplastic syndrome.
Empirical antifungal therapy for neutropenic fever remains the mainstay approach in hematologic patients because of the difficulty in confirming the diagnosis of IFIs.

Meta-analysis on the galactomannan antigen assay as a diagnostic.

- Meta-analysis on the galactomannan antigen assay as a diagnostic.

**References**

Papers of special note have been highlighted as:

- of interest
- of considerable interest


- of interest
- of considerable interest

**Key issues**

- The risk of invasive fungal infections (IFIs) is highest among patients with acute myeloid leukemia undergoing induction chemotherapy and allogeneic stem-cell transplant recipients.
- Fluconazole is the antifungal that is most widely studied as a prophylactic. It is the gold-standard antifungal prophylaxis in stem-cell transplant patients. However, it is not active against molds and some Candida species.
- Posaconazole is a novel triazole that has a broad spectrum of antifungal activity. It is shown to be superior to fluconazole and itraconazole for prophylaxis in hematologic patients.
- Empirical antifungal therapy for neutropenic fever remains the mainstay approach in hematologic patients because of the difficulty in confirming the diagnosis of IFIs.

**Empirical antifungal therapy for neutropenic fever remains the mainstay approach in hematologic patients because of the difficulty in confirming the diagnosis of IFIs.**

• Review on the role of antifungal prophylaxis in high-risk patients.


• Efficacy of voriconazole as an empirical antifungal treatment.


• Review of new antifungals and diagnostics.


Website


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