

Therapeutic Decisions in the CARE OF PATIENTS AT HIGH RISK FOR INVASIVE FUNGAL INFECTIONS: A Case-based Approach

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Case Presentation:

Empiric Management of Patient With Febrile Neutropenia

A 55-year-old woman with a history of chronic obstructive pulmonary disease was transferred to a teaching hospital for management of acute myeloid leukemia FAB M5. On admission, she was febrile, with a temperature of 38°C. A chest x-ray showed slight underaeration but was otherwise unremarkable. A chest computed tomography (CT) scan was performed the following day and revealed changes consistent with emphysema as well as a focal area of consolidation in the right upper lobe and a couple of scattered areas of nodularity. The patient was started empirically on intravenous (IV) cefepime 2 g q8h. Three days after admission, she began induction chemotherapy with cytarabine 200 mg by continuous IV infusion daily for 7 days and idarubicin 24 mg IV daily for 3 days.

The patient's fever subsided with antibiotic treatment; however, about 2 weeks later, her fever recurred, with temperatures as high as 39.7°C. At this time, she was neutropenic with a white blood cell count of $0.3 \times 10^9/L$, anemic, and thrombocytopenic. Routine screening serum galactomannan measurements had been performed twice weekly since admission and remained negative. A repeat CT scan at this time demonstrated a nodular-appearing left upper lobe process, which had progressed and likely represented an infection. The right upper lobe consolidation seen radiologically on admission had resolved. There was a new and more extensive airspace consolidation in the left upper lobe as well as ground-glass opacification involving the left upper lobe and lingula. The patient subsequently underwent bronchoscopy with bronchoalveolar lavage (BAL). The cytology revealed fungal organisms consistent with *Candida*. There were no viral cytologic changes and no *Pneumocystis jiroveci*. BAL culture was negative for fungal pathogens. Galactomannan antigen levels

were elevated in the BAL fluid (7.82) but remained negative in the serum (0.25).

Based on her neutropenic status, physical examination, and chest CT findings as well as the positive galactomannan on BAL fluid, the patient had probable invasive aspergillosis. She was thus initiated on empiric therapy with voriconazole 500 mg (6 mg/kg) orally twice a day for 2 doses, followed by 350 mg (4 mg/kg) orally twice daily thereafter with rapid defervescence. She was discharged on voriconazole therapy. One week later, a follow-up CT scan revealed an increase in the size and number of diffuse bilateral pulmonary nodules, suggestive of a progressive, invasive fungal infection. There was a dense area of consolidation in the apical posterior segment of the left upper lobe, and there were additional areas of ground glass-like opacity throughout the upper lobe and lingula. Nodular areas were present in both lower lobes and had slightly increased from prior scans; however, the patient continued voriconazole therapy.

A follow-up CT scan 1 month later demonstrated a decrease in size of the left upper lobe mass, which also appeared to be less spiculated. This lesion was likely secondary to her aspergillosis. The remainder of the more peripheral, smaller, somewhat spiculated masses throughout both hemithoraces were either stable or slightly improved since the prior examination. There were no new lesions.

Over a period of 9 months, the patient was followed with serial CT scans, demonstrating marked improvement with each scan. She was able to continue her treatment for leukemia, successfully completing 3 consolidation courses of high-dose cytarabine. She remains alive and free of obvious signs of fungal infection today.



Letter From the Editor:

We are pleased to bring you the first of a 3-part educational series that focuses on the care of patients at high risk for invasive fungal infections. In this issue, Helen L. Leather, BPharm, BCPS, shares with us a challenging case of neutropenic fever in a woman with acute myeloid leukemia. In the discussion that follows, we review the data for empiric therapy of fungal infections among neutropenic patients, highlighting recent advances in diagnosis and treatment. Following the discussion, you have the opportunity to gain CE credit by completing an assessment and submitting this information to the University of North Carolina School of Pharmacy. We appreciate your participation in this and our future issues in this informative and timely educational series.

Sincerely,
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Educational Objectives

- Review the prevalence and changing resistance patterns of mycoses in high-risk hematology/oncology patients
- Discuss the rationale for early versus late initiation of empiric antifungal therapy
- Evaluate the latest findings on the use of antifungal agents for empiric therapy in neutropenic patients
- Describe the differences among lipid amphotericin agents for antifungal management of high-risk patients

CE Information



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Melissa D. Johnson, PharmD, has served as a consultant and/or speaker for the following pharmaceutical companies: Astellas Pharma US, Inc., Enzon Pharmaceuticals, Inc., Merck & Co., Inc., Pfizer Inc, and Schering-Plough. She has also received research funding from Merck & Co., Inc.

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Question & Answer

What is the prevalence of fungal infections in febrile neutropenic patients with cancer? What are the common causative pathogens?

During the past several decades, there has been a steady increase in the prevalence of invasive fungal infections (IFIs) in immunocompromised patients. Much of this is related to advances in chemotherapeutic regimens as well as antibiotic treatment strategies that can effectively control serious bacterial infections during neutropenia.¹ With these advances, more patients with cancer now survive bacterial infections to develop IFIs. Although fungal infections remain much less common than bacterial infections, they account for the majority of infectious-related deaths in patients with cancer.² As neutropenia persists, the likelihood that the infection is caused by a fungus increases substantially.³

Candida spp and *Aspergillus* spp are the major fungal pathogens of concern during neutropenia. *Candida* infections typically occur in the early phase of neutropenia, with the spectrum of disease ranging from superficial to disseminated. *Aspergillus* infections usually occur later, typically in patients treated for acute leukemia or those undergoing hematopoietic stem cell transplantation.⁴ Other fungal pathogens that are less common but are being seen with increasing frequency include *Fusarium* spp, *Zygomycetes*, *Scedosporium* spp, and a variety of dematiaceous molds.⁵

What risk factors does this patient have for a fungal infection?

Our patient has several major risk factors for fungal infection, the most prominent being her underlying hematologic malignancy and neutropenia resulting from cytotoxic chemotherapy. In addition, cytarabine increases the risk of gastrointestinal mucosal injury, facilitating the entry of fungal pathogens through the mucosal barrier.⁶ Prolonged neutropenia and use of broad-spectrum antibiotics also increase the risk for fungal infection.⁷

Which procedures or tests can be done to diagnose IFIs?

Given the poor prognosis of patients who develop IFIs, it is critical to make an early diagnosis. Unfortunately, diagnosis remains very challenging, particularly in the early stages of infection, as clinical symptoms are often nonspecific and blood cultures are rarely positive. Fever (defined as a single oral temperature of $\geq 38.3^{\circ}\text{C}$ or a temperature of $\geq 38.0^{\circ}\text{C}$ for ≥ 1 hour) is typically the principal sign of infection in neutropenic patients, and, in some

cases, it is the only evidence of infection.⁷ Other potential causes of persistent fever in neutropenic patients should be considered, however (Table 1).³

Table 1. Causes of Persistent Fever in Neutropenic Patients³

- Superinfection with fungi
- Resistant bacterial infection (eg, vancomycin-resistant enterococci)
- Bacterial infection associated with tissue necrosis/mucositis (endotoxemia)
- Nonculturable cell wall-deficient bacteria
- Nonbacterial infection (virus, acid-fast bacteria, toxoplasmosis)
- Malignancy-related fever
- Drug or transfusion fever

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All febrile neutropenic patients should undergo radiographic imaging such as chest radiography and/or computed tomography (CT) scans to evaluate them for infection. Bronchoscopies and bronchoalveolar lavage (BAL) are also helpful for further defining infection in patients with abnormal radiographic findings. The most characteristic radiographic findings in invasive aspergillosis are the halo sign that is characteristic of early disease and air-crescent formation, which appears later with neutrophil recovery.⁸ New serologic tests that detect circulating antigens for *Aspergillus*, such as cell-wall galactomannan, or measure 1,3- β -D-glucan concentrations can help support the diagnosis of aspergillosis.⁹

Although sometimes difficult to obtain, samples for histopathology and culture are important to identify the organism, and a combination of both methods is necessary for a definitive diagnosis. For example, the presence of branching septae and hyphae on histology is nonspecific and can represent a number of different fungal organisms, including *Fusarium*, *Aspergillus*, or *Scedosporium* species. Only culture methods would enable accurate identification of the pathogen. Some laboratories are using newer polymerase chain reaction-based methods to confirm the identity of the fungal pathogen, but these methods are not widely available yet for routine clinical use and there are no commercially available kits to standardize methods across laboratories.

In our case study, the patient had initial CT findings that were suggestive of an IFI. Results of galactomannan antigen testing in the serum did not support a diagnosis of aspergillosis. Although the high galactomannan level on BAL

suggests the presence of *Aspergillus*, the assay is not validated nor approved by the Food and Drug Administration (FDA) in nonserum samples, and further studies are needed. Cytology was positive for *Candida*, but this was attributed to potential fungal colonization or contamination of the bronchoscope. The patient was subsequently initiated on empiric therapy with voriconazole, which has activity against most species of *Candida* and *Aspergillus*. Within 48 hours, she became afebrile. Concurrently, the patient's white blood cell count improved, which likely increased host response to the infection. Results of a CT scan a week later showed worsening disease, which could also be related to immune reconstitution. It is important to point out that even with effective treatment, CT scans can get worse before they get better, and, indeed, this was the case with our patient.⁸

When should empiric antifungal therapy be initiated?

The goal of empiric antifungal therapy is to treat the occult IFI early in the course of disease and to prevent subsequent breakthrough infections. Early initiation of therapy appears to improve survival rates.¹

The first neutropenic fever is typically bacterial in origin, and empiric antifungal therapy is not prescribed at this time. The Infectious Diseases Society of America recommends initiating an antifungal agent in neutropenic patients who remain febrile for 5 or more days despite use of broad-spectrum antibacterials,⁷ although it has become common in some centers to initiate therapy after 3 days of persistent fevers or even sooner for high-risk patients.

Whether or not a patient has received antifungal prophylaxis is an important consideration in the timing of initiation of empiric antifungal therapy. Fluconazole prophylaxis has substantially reduced *Candida* infections; however, it does not protect against mold infections. The common use of this agent has also fostered the emergence of non-*albicans* *Candida* spp, such as *Candida glabrata* and *Candida krusei*. Itraconazole prophylaxis has also been evaluated with similar success, although it has a broader spectrum of activity extending to molds. More recently, posaconazole prophylaxis has been evaluated in high-risk patients with success.¹⁰ Among neutropenic patients who have received fluconazole prophylaxis, empiric antifungal therapy may be initiated later (≥ 10 days) provided there are no respiratory or sinus signs or

symptoms that might suggest a possible *Aspergillus* infection.¹

What are empiric antifungal treatment options?

Empiric antifungal therapy options for febrile neutropenia include azoles, such as voriconazole, itraconazole, or fluconazole; polyenes, including amphotericin B deoxycholate (AmBd) and lipid formulations of amphotericin B; and echinocandins, such as caspofungin, micafungin, and anidulafungin, although not all of these agents have been specifically evaluated in this setting.

Fluconazole is only appropriate as empiric therapy among patients who have not already received azole prophylaxis and are at low risk for mold pathogens.⁴ Itraconazole is generally not favored over voriconazole for those patients requiring coverage for molds because of tolerability of its oral solution formulation and variable absorption, especially in the presence of mucositis.¹¹ Voriconazole has demonstrated activity against *Candida* spp, *Cryptococcus neoformans*, and molds such as *Aspergillus* spp, *Fusarium* spp, and *Scedosporium apiospermum*. However, it lacks activity against Zygomycetes. Voriconazole has been evaluated in the management of neutropenic fever in a large, randomized, open-label trial. In this trial, voriconazole (6 mg/kg IV q12h for 2 doses, followed by 3 mg/kg IV q12h or 200 mg PO q12h, after at least 3 days of IV therapy) was compared to liposomal amphotericin B (3 mg/kg/dose).¹² Treatment success rates were 26% with voriconazole and 30.6% with liposomal

amphotericin B (95% confidence interval [CI] for the difference, -10.6% - 1.6%). Based on these results, the trial did not meet the prespecified criteria for noninferiority. Importantly, fewer breakthrough IFIs occurred among voriconazole recipients (1.9% vs 5%, respectively; $P=.02$). There were fewer infusion-related reactions and less nephrotoxicity with voriconazole, but more visual changes and hallucinations.

Amphotericin B continues to have the widest spectrum of activity against fungi, with low rates of resistance among most fungal pathogens. The efficacy of amphotericin B and lipid formulations of amphotericin B is described in **Table 2**.¹¹ Generally, these different formulations of amphotericin B have demonstrated similar efficacy in the empiric management of neutropenic fever. At our institution, polyenes are particularly favored in neutropenic patients when the fungal diagnosis includes the possibility of pathogens such as Zygomycetes (ie, significant sinus involvement). These emerging molds may be more common in the setting of voriconazole prophylaxis or empiric therapy. In a recent study, receipt of voriconazole prophylaxis was an independent risk factor for development of Zygomycetes infections (odds ratio, 7.43; 95% CI, 2.38-23.14).¹³ Further well-designed epidemiologic studies are needed to confirm any association between voriconazole therapy and zygomycosis. The efficacy and safety of amphotericin B lipid complex have been studied in 64 immunocompromised patients with zygomycosis, with an overall

Table 2. Summary of Trials of Empiric Antifungal Therapy for Febrile Neutropenic Patients¹¹

Study	N	Treatments		Primary End Point Success Rates (% of patients)		Rates of Breakthrough IFIs (% of patients)	
		Arm 1	Arm 2	Arm 1	Arm 2	Arm 1	Arm 2
White et al (1998) ¹⁸	213	ABCD	AmBd	50	43	3.1	3.2
Walsh et al (1999) ¹⁹	687	L-AmB	AmBd	50	49	3.2 [†]	7.8
Winston et al (2000) ²⁰	317	Fluconazole	AmBd	68	67	8.2	6.3
Wingard et al (2000) ^{21*}	244	ABLCL	L-AmB (3/5) [†]	33	40/42	3.8	3.6/2.5
Fleming et al (2001) ²²	82	ABLCL	L-AmB	63 [†]	39	—	—
Boogaerts et al (2001) ²³	384	Itraconazole	AmBd	47	38 [§]	2.8	2.8
Walsh et al (2002) ¹²	837	Voriconazole	L-AmB	26	31	1.9 [†]	5.0
Walsh et al (2004) ¹⁶	1095	Caspofungin	L-AmB	34	34	5.2	4.5

ABCD, amphotericin B colloidal dispersion; ABLCL, amphotericin B lipid complex; AmBd, amphotericin B deoxycholate; L-AmB, liposomal amphotericin B. *Safety study; [†]Two different doses of study drug (3 mg/kg/day and 5 mg/kg/day); [‡] $P < .05$ vs comparator; [§]Difference of 9.0 percentage points (95% confidence interval, -0.8 - 19.5). Reprinted from Wingard JR, Leather H. *Biol Blood Marrow Transplant*. Empiric antifungal therapy for the neutropenic patient. 10:73-90. Copyright 2004, adapted with permission from the American Society for Blood and Marrow Transplantation.

success rate of 72%.¹⁴ Success rates remained high in disseminated disease as well as pulmonary and sinus infections. The activity of posaconazole against Zygomycetes is likewise promising, although this agent is not yet FDA approved.¹⁵

Only one echinocandin, caspofungin, is FDA indicated for empiric therapy in febrile neutropenia. FDA approval was based on a randomized, double-blind trial that compared caspofungin (70 mg on day 1 and 50 mg/day thereafter) with liposomal amphotericin B (3 mg/kg/day).¹⁶ Overall success rates were 33.9% with caspofungin and 33.7% with liposomal amphotericin B, which fulfilled the statistical requirements for noninferiority of caspofungin. Rates of breakthrough fungal infections were similar between the 2 groups; however, successful treatment of baseline IFIs was better with caspofungin. Micafungin has been evaluated as empiric treatment in a small noncomparative, open-label study.¹⁷ The overall success rate was 78%. The newest echinocandin, anidulafungin, has not been evaluated in the empiric management of neutropenic fever.

What are the challenges in interpreting data from clinical trials of antifungals as empiric therapy for febrile neutropenia?

Several clinical trials have compared antifungal agents for empiric therapy in febrile neutropenia (Table 2).^{11,12,16,18-23} It is important, however, to consider the difficulties in interpreting these studies, especially with respect to distinguishing differences in efficacy.⁴ In clinical studies, the primary end point is typically based on a surrogate marker of efficacy that encompasses a 5-point composite for treatment success: (1) defervescence prior to the recovery of neutrophil count, (2) no breakthrough fungal infection, (3) response of baseline infection, (4) no fungemia-related deaths, and (5) no discontinuation of drug therapy due to adverse events.^{4,19} One difficulty with using this end point, however, is that treatment success may be influenced by factors that are completely unrelated to the IFI. For example, fever in neutropenic patients could be caused by a nonfungal infection or neoplasm; thus, defervescence

is not absolute proof of the eradication of a fungus, although it is often a major driver of this end point.⁴ Furthermore, because empiric therapy is started early, rates of breakthrough IFIs are very low, making it difficult to determine the relative efficacy of treatments. Oftentimes, these types of studies reveal more about relative toxicities rather than about comparative efficacy. The most clinically meaningful end points of the 5-point composite are the occurrence of breakthrough fungal infections and survival rates; however, trials evaluating these individual end points would require very large sample sizes. Fungal infection-free survival is also an important end point that should be considered in future trials.

In this case, voriconazole was chosen for empiric antifungal therapy. What is the rationale?

Amphotericin B has traditionally been the standard of empiric antifungal therapy for febrile neutropenia. In many institutions, use of the conventional formulation, AmBd, has been replaced by the lipid amphotericin B formulations, which are as effective but are associated with reduced rates of infusion-related toxicities and nephrotoxicity.²⁴ Data supporting the use of newer antifungal agents for documented infections have influenced our selection of empiric therapy in the febrile neutropenic patient. In addition, the relatively high acquisition cost of the lipid formulations and the potential to use less expensive oral agents have impacted our management strategies. Published data demonstrating the efficacy of voriconazole against invasive pulmonary aspergillosis also influenced our decision to start this agent.²⁵ With the clinical and laboratory data available to us at the time, the most likely infection was invasive aspergillosis, and voriconazole has proven efficacy in that setting.

Are there alternative strategies, such as empiric versus preemptive therapy?

The aim of empiric therapy is to ensure that patients with a possible IFI (based on risk factors and clinical criteria) receive therapy early in the course of disease. In neutropenic patients, initiation of empiric

therapy is based on the persistence of fever despite broad-spectrum antibiotic therapy, which suggests an increased risk for fungal infection. However, as mentioned previously, fever in neutropenic patients can be related to nonfungal causes. Indeed, although up to 40% or more of these patients receive empiric antifungal therapy, fewer than 10% of all febrile episodes are associated with proven fungal infections.²⁶

Preemptive therapy involves a more targeted approach to deliver antifungal therapy to neutropenic patients with a probable (versus possible) IFI. This approach incorporates additional evidence of fungal infection, such as a positive surveillance culture, sinusoid calcification, pulmonary infiltrate, and/or positive galactomannan antigen test. With this strategy, antifungal therapy is initiated only in patients with a high probability of IFI. This limits antifungal exposure among patients who are at low risk of IFI, potentially reducing drug-associated toxicities, drug interactions, and drug resistance. In a recent study, a protocol-driven preemptive approach targeting invasive aspergillosis reduced the rate of antifungal use from 35% to 7.7%.²⁷

In summary, patients with leukemia represent a subpopulation of patients who are susceptible to chemotherapy-induced neutropenia. In cases of neutropenia and persistent fevers despite antibiotic therapy, a possible IFI should be suspected, and it is important to attempt to confirm a diagnosis. *Candida* and *Aspergillus* are the most common infecting fungal pathogens in these patients. The incidence of more-resistant pathogens is becoming increasingly common in the setting of antifungal prophylaxis and may require different approaches for initial antifungal coverage. In this case, pulmonary findings on CT raised suspicion for invasive aspergillosis, and thus voriconazole was administered empirically. Although effective, amphotericin B is reserved for cases in which there is a high suspicion of an infection caused by Zygomycetes. We typically try to initiate antifungal therapy preemptively rather than empirically, reserving treatment for those patients who demonstrate a high probability of IFI, based on results of diagnostic assays.

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