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Guideline Recommendations for the Prophylaxis of Invasive Aspergillosis in AML

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H&O How are guidelines from the NCCN and IDSA developed?

EW Both sets of guidelines are created by panels of experts in a particular field who are conversant with the literature and may have practical experience. The panel of the Infectious Diseases Society of America (IDSA) is composed primarily of infectious disease specialists at a variety of university settings throughout the United States. The National Comprehensive Cancer Network (NCCN) panel consists of representatives from the cancer centers supported by the National Cancer Institute. The panel generating the NCCN guidelines for the prevention and treatment of cancer-related infections includes representatives from each of these comprehensive cancer centers.

Typically, these panels meet on a regular basis, either in person or via a teleconference. The NCCN guidelines are reviewed annually in a teleconference. Feedback is solicited from the panel members and panel member institutions regarding any needed revisions or updates based on emerging evidence from clinical trials, practice guidelines, and other sources. Any controversial issues or recommendations that require additional discussion are presented. Panel members then vote to indicate whether they agree with any changes. The panel members meet in person when there is a significant redesign.

H&O How is the evidence reviewed?

EW The evidence, including references, is reviewed during the panel meetings. Discussions about the quality of the evidence continue throughout the meeting. A randomized, phase 3 trial evaluating survival outcomes is considered high-level evidence. Low-level evidence includes case series, single case reports, and anecdotal reports.

The IDSA and NCCN guidelines both offer detailed explanations regarding the panel's rationale for each recommendation. The guidelines have extensive reference lists that include the newer work that has been presented since the last version was generated.

A benefit to the guidelines from the IDSA and the NCCN is that they provide more up-to-date information than the review articles obtainable through a literature search. The guidelines aim to include data from recent clinical trials and original publications to encompass the most current drug armamentarium.

H&O What do the different categories of recommendations indicate?

EW The NCCN guidelines divide the categories of recommendations based on 2 factors: the level of evidence and the level of agreement among the panel members. There are 4 levels of evidence (Table 1). In Category 1, a very high level of evidence is required (ie, a randomized phase 3 trial), and there must be uniform agreement among the panel members regarding the recommendation. Recommendations in Category 2A are supported by significant evidence and uniform consensus among all the panel members. Category 2B recommendations are based on a lower level of evidence—not a randomized, phase 3 trial—and are supported by a majority of panel members. Category 3 indicates that a treatment has some evidence

Table 1. Categories of Evidence and Consensus in the NCCN Guidelines

Category 1	Based upon high-level evidence, there is uniform NCCN consensus that the intervention is appropriate
Category 2A	Based upon lower-level evidence, there is uniform NCCN consensus that the intervention is appropriate
Category 2B	Based upon lower-level evidence, there is NCCN consensus that the intervention is appropriate
Category 3	Based upon any level of evidence, there is major NCCN disagreement that the intervention is appropriate

NCCN, National Comprehensive Cancer Network.

to support its use, but that significant disagreement among panel members prevented a consensus regarding any benefit. Treatments in Category 3 are included mostly to inform readers of their existence, but are not recommended or voted upon by the panel.

The IDSA uses a similar approach with different terminology. The panel uses the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) system, which rates both the quality of the evidence and the strength of the panel recommendation. The quality of evidence is graded as high, moderate, low, or very low. High levels of evidence typically reflect results of randomized, phase 3 clinical trial data. Specific recommendations are categorized as strong or weak. Strong recommendations are based on the quality of the evidence and a consensus that the benefits outweigh the risks. The IDSA suggests that strong recommendations be adopted into policy and implemented into the treatment plans of most patients. A weak recommendation reflects a lack of consensus and the need for substantial debate regarding any benefits for patients. It is important to emphasize that guidelines by both of these panels are intended to supplement, not supplant, clinical judgment in the care of individual patients. The NCCN also states that the best management of any cancer patients occurs on clinical trials.

H&O What do the guidelines recommend for prevention of invasive aspergillosis in AML?

EW The NCCN and IDSA panels unanimously recommend that patients with acute myeloid leukemia (AML) with neutropenia following induction or reinduction chemotherapy receive antifungal prophylaxis with posaconazole. In the NCCN, it is a category 1 recommendation supported by a significant amount of randomized clinical trial evidence. Like the NCCN guidelines, the IDSA guidelines also strongly recommend posaconazole as the first choice for prophylaxis, citing the same very high-quality data as the NCCN.

Where the IDSA and NCCN guidelines diverge is in their recommended alternatives to posaconazole. The NCCN supports voriconazole, fluconazole, micafungin, and amphotericin B, albeit at lower levels of recommendation. Despite some consensus regarding their use, the categorization for all 4 agents is a 2B recommendation, reflecting the panel's acknowledgement that the supporting evidence is inferior to that for posaconazole. The IDSA also strongly recommends voriconazole, albeit with a lower (moderate) level of evidence, as an alternative to posaconazole. However, the IDSA guidelines also strongly endorse itraconazole based on moderate-quality evidence, specifically recognizing that this therapy may be limited by absorption and tolerability. In contrast to the NCCN, the IDSA lists micafungin, caspofungin, and aerosolized amphotericin B as options (weak recommendations with low-quality evidence). Fluconazole is not mentioned in the IDSA guidelines for patients with AML (Table 2).

H&O What is the role of health economics in the development of guideline recommendations?

EW Overall, the guidelines attempt to take a more academic role and assess evidence based on scientific data and clinical trial results. Health economics do not directly impact the recommendations, and panel members tend not to know the ultimate cost of a particular treatment for individual patients. However, in text accompanying the guidelines, both the IDSA and the NCCN allude to the impact of health economics on their recommendations. For example, the IDSA specifically cites "resources and cost" as one of the determinants affecting their recommendations. As stated in the text included in the NCCN guidelines, the economic reality is that the second-generation mold-active azole drugs, voriconazole and posaconazole, tend to be exceedingly expensive. Some patients may not be able to receive treatment with these therapies owing to their insurance plans or other financial impediments. The NCCN and the IDSA therefore make the point of recommending lower-cost alternative therapies, specifically fluconazole, itraconazole, amphotericin formulations, and the echinocandins (micafungin and caspofungin). The IDSA clearly states that the use of amphotericin B for antifungal prophylaxis should be reserved for use in "resource-

Table 2. Summary of Recommendations for Prophylaxis of Invasive Aspergillosis in Patients With AML and Prolonged Neutropenia

NCCN Guidelines	
Posaconazole	Category 1
Voriconazole, fluconazole, micafungin, amphotericin B	Category 2B

IDSA Guidelines	
Posaconazole	Strong recommendation, high-level evidence
Voriconazole, itraconazole	Strong recommendation, moderate-level evidence
Micafungin, caspofungin, aerosolized amphotericin B	Weak recommendation, low-level evidence
Amphotericin B formulations	Only in resource-limited settings when other agents are not available

IDSA, Infectious Diseases Society of America; NCCN, National Comprehensive Cancer Network.

limited settings," where other presumably more expensive alternatives are not available. The NCCN is even more explicit. The panel notes that first-generation azoles (ie, fluconazole) are often extensively used for prophylaxis, due to their low cost, despite the recognition of potential resistant *Candida* strains. They go on to report that second-generation azoles known to exhibit more potent antimold activity tend not to be used as widely for the prevention and treatment of aspergillosis, as they are "extremely costly" with prolonged administration.

H&O Are there any other barriers to the implementation of these guidelines in clinical practice?

EW A potential barrier to the use of micafungin or amphotericin B products is that they are administered intravenously. The associated costs of daily intravenous access over weeks at a time make these therapies impractical and unfeasible in some patients with prolonged neutropenia. One benefit of using azoles is the ease of oral administration, although the absorption of itraconazole oral suspension can sometimes be problematic. Prolonged use of antifungal prophylaxis agents may also result in drug-associated toxicities, specifically hepatotoxicity (azoles), nephrotoxicity (amphotericin), and CYP3A4 inhibition (azoles), enhancing the toxicities of concomitant anticancer therapy.

H&O Is drug resistance a concern in this setting?

EW In the infectious disease arena, there is always concern about the development of resistance to current medications and the rise of multidrug-resistant organisms. Although the second-generation azoles, posaconazole and voriconazole, are largely effective against invasive aspergillosis, they are not 100% foolproof in preventing aspergillosis infection. Clinicians must remain vigilant about the development of invasive aspergillosis at all times in patients with AML who have prolonged neutropenia. Despite prophylaxis, the development of azole-resistant invasive aspergillosis infections still occurs in some patients and remains highly challenging.

H&O Which patients with AML are at high risk for invasive aspergillosis?

EW Invasive aspergillosis is a leading cause of morbidity and mortality in patients treated with high-dose chemotherapy for AML. The incidence of this life-threatening infection ranges from 5% to 25%, with the major risk factor being the duration of prolonged neutropenia. Mortality rates associated with invasive, aggressive aspergillosis in this setting exceed 50%. Development of invasive aspergillosis has been shown to negatively impact on the achievement of complete remission, increase medical costs and the risk of death, and contribute to the poor overall survival rates of patients with AML following intensive chemotherapy.

Patients with AML who are at high risk for aspergillosis are those who are receiving high-dose induction or reinduction chemotherapy. These chemotherapy regimens lead to a very prolonged period of neutropenia, meaning an absolute neutrophil count (ANC) of less than 500 cells/μL. Patients who are receiving induction or reinduction chemotherapy are expected to develop prolonged neutropenia that can last for up to 8 weeks. Some of these patients may also have baseline neutropenia. The long duration of neutropenia places these patients at much higher risk as compared with patients who have solid tumors, who have a normal blood count at baseline and experience only transient neutropenia.

The risk of invasive aspergillosis is also high among patients with AML who are receiving immunosuppressive therapy after recent allogeneic stem cell transplant. Patients treated with high levels of immunosuppressive therapy for long periods will develop impairment of neutrophil function that places them at high risk for invasive aspergillosis—even in the presence of a normal neutrophil count.

The risk of invasive aspergillosis is significantly lower among patients with AML who have achieved remis-

sion and/or are receiving less intensive chemotherapy regimens. The value of antifungal prophylaxis for patients with AML following consolidation chemotherapy has not been well established. These regimens are less myelosuppressive and therefore associated with shorter durations of neutropenia. Recent data have suggested that patients with AML who are receiving therapy with hypomethylating agents also experience lower rates of invasive aspergillosis and therefore may not warrant long-term antifungal prophylaxis.

H&O What factors should initiate prophylaxis?

EW Prophylaxis should be initiated in all patients with AML who (a) develop neutropenia following high-dose induction or reinduction chemotherapy, (b) are neutropenic and/or are receiving immunosuppressive therapy following allogeneic stem cell transplant, and (c) are receiving immunosuppressive therapy for treatment of graft-vs-host disease following allogeneic stem cell transplant. Antifungal prophylaxis should also be considered in patients with AML who develop mucositis after treatment with chemotherapy or an autologous stem cell transplant. Mucositis indicates damage to the gastrointestinal tract that may put these patients at higher risk of developing invasive aspergillosis.

H&O Do you have any other recommendations regarding prevention of invasive aspergillosis?

EW In our facility, we routinely use antifungal agents for mold prophylaxis in high-risk patients with AML. In some cases, we also closely monitor drug levels in patients with AML who are receiving long-term prophylaxis with posaconazole, voriconazole, or fluconazole. Because individuals may metabolize azole drugs differently, monitoring drug levels can help to ensure that the azoles achieve sufficient therapeutic levels to effectively prevent invasive aspergillosis.

Disclosure

Dr Wang has no relevant conflicts of interest to report.

Suggested Readings

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