

Dimitrios P Kontoyiannis

# A clinical approach to assess treatment for presumed and documented invasive mold infections in patients with hematologic malignancies: Focus on Spanish Society of Chemotherapy Guidelines

---

Division of Internal Medicine, The University of Texas MD Anderson Cancer Center, U.S.A

---

Despite four decades of progress made in the management of patients with hematologic cancer and invasive mold infections (IMIs), major treatment challenges remain<sup>1-4</sup>. In this context, the guidelines presented here<sup>5</sup> represent a helpful synthesis of bedside clinical experience and the published literature, which often lags behind the "real-life" challenges that clinicians face managing infections in this complex patient population. Because IMIs are less common, many hematologists may not have accumulated a "critical mass" of experience in management. The major problem is that randomized clinical trials in this area might have rather limited value for daily clinical care of *contemporary* hematology patients. To that end, consensus opinion could help informing the average clinician of the decision process.

A laudable feature of these guidelines in their effort to provide a risk assessment for IMIs that is founded on clinical parameters. Risk assessment of neutropenic patients with leukemia or stem cell transplantation remains an art whose components are derived from the careful knowledge of the natural history of the patient's underlying hematologic disease, comorbidities, and prior exposures to pathogens and prior antifungal courses (table 1). This "qualitative" concept should be an integral part of the initial evaluation, as it allows the identification of patients suitable for initial empiric or pre-emptive antifungal therapeutic approach while a search for the offending pathogen(s) is being attempted. It is clear that leukemia and transplant patients do not represent a homogeneous group and they are not at the same risk for life-threatening complications or infectious-related death from IMIs.

Another useful feature of these guidelines is that these recommendations are developed in the context of the use of *Aspergillus*-active prophylaxis with a triazole (e.g., posaconazole, voriconazole)- a widespread practice. Several consensus

guideline recommendations (ECIL3, IDSA)<sup>2-4</sup> advocate use of posaconazole prophylaxis in AML. Therefore as azole-resistant IMIs is of concern in patients with breakthrough resumed IMIs, hence the recommendation on the emphasis regarding "expanded" use of a liposomal formulation of amphotericin B is reasonable.

Guidelines should not substitute careful and frequent clinical evaluation in these patients. Given the inability of immunocompromised hosts to mount an adequate inflammatory response, the classic signs and symptoms of infection, other than fever, may be minimal or absent. Although time consuming, hematologists should perform a meticulous physical examination and take notice of every minor or subtle sign and symptom of IMIs and investigate them further. High-resolution chest computed tomography may indicate early signs of angioinvasive sino-pulmonary mold infection, such as the halo or reverse halo signs, even in patients with a normal chest radiograph. Needless to say, an efficient clinical microbiology laboratory that identifies pathogens in a timely fashion is of paramount importance for the selection of appropriate early regimen. In fact, knowledge of the local fungal epidemiology is critical in that early assessment and decision making. The guidelines put emphasis on the availability and results of non-culture-based diagnostic methods (*Aspergillus* galactomannan, GM) to allow pathogen-specific preemptive therapy to supplant empirical therapy. However, as chest CT is not a part of the algorithmic approach presented, they authors seem to mix the surveillance strategy (Positive GM without signs/symptoms or CT abnormalities consistent with an IMI in a patient on mold-active prophylaxis) versus use of these diagnostic tests as a true adjunct diagnostic strategy in a patients with suspected breakthrough infection (e.g., Positive GM without signs/sympoms or CT abnormalities consistent with an IMI in a patient on mold-active prophylaxis). Also, the time of positive GM, its repetiveness, the GM index all are issues deserving further clarification, especially if GM-driven decisions are done in the context of pre-emptive therapy without any other clinical evidence of IMI.

---

Correspondence:  
Dimitrios P Kontoyiannis, MD, ScD  
Professor and Deputy Division Head  
Division of Internal Medicine  
The University of Texas MD Anderson Cancer Center  
E-mail: dkontoyi@mdanderson.org

Table 1

**Host factors for risk stratification important in determining the type and intensity for empiric and pre-emptive antifungal therapy in patients with hematologic malignancy.**

- Dose, duration and temporal sequence of immunosuppressive therapy
- Depth, rapidity and duration of neutropenia, prolonged cytopenia, lack of count recovery
- Multiple episodes of neutropenia
- Prior antifungal prophylaxis
- The presence of mucosal injury
- Host defects caused by underlying hematologic disease, activity of malignancy
- Metabolic factors, especially hyperglycemia and iron overload
- History of prior infections, multiple, sequential or polymicrobial infections
- Known mold colonization
- Old age (>65 yrs old), poor performance status
- Co-morbidities, especially liver/renal dysfunction

Other questions are worthwhile to reflect upon:

A) How these recommendations stand in the context of the use of HEPA/LAF rooms, treatment of high risk AML patients?

B) Is there a center effect in these recommendations, especially pertaining to empiric and pre-emptive approaches? Are these guidelines geared to larger centers with high patient volume and better diagnostic and therapeutic expertise dealing with IMIs, and perhaps differences in outcome?

C) What is the impact of local epidemiology to guidelines presented? Do we really know local epidemiology in the era of very low autopsy rates?

D) What is the impact of false positive due to antibiotics or cross-reactive GM (non-Aspergillus) hyalophycomycetes?

E) Should we be concerned about mixed mold infections?

F) What the work up of a presumed fungal pneumonia should be in the setting of a prior triazole (e.g., voriconazole or posaconazole) that has unpredictable pharmacokinetic behavior?

G) What the impact of the timing of work up would be in decision making and decided antifungal strategy?

H) Should we aim on a high dose (5-7, 5mg/kg/d) of a liposomal amphotericin B in patients with severe presumed breakthrough IMI?

I) What the cost-effectiveness of the recommended approaches?

In conclusion, the continuing change in epidemiology with the emergence of resistant fungal pathogens, partially as a result of selection pressures in patients with prolonged periods of immune suppression prevents the use of "standard regimens" applicable to such patients with presumed or documented IMIs. A therapeutic strategy that combines an intense combined diagnostic and therapeutic effort with broad regimens such as a liposomal formulation of amphotericin B, could be of help in combating the ever present resistance of mold pathogens in leukemia and transplant patients. The observed benefits of such guidelines would depend on whether the practicing physician would understand, agree and integrate them into his daily routine. The risk stratification and relatively simple algorithm are steps to the right direction. To that end, the practicing hematologist has more information about an individual patient that even complex guidelines can accommodate, especially in the setting of high risk AML, allogeneic SCT. Perhaps emphasis to individualized approach<sup>6</sup> might be the single most important message to than the filtered guidelines provided by respectable experts through a rather *non-valdated* consensus building.

## DECLARATION OF TRANSPARENCY

DPK has received research grants from Merck, Pfizer, Astellas and Gilead and he is on advisory board of Merck and on speaker's bureau of Gilead.

## REFERENCES

1. Sipsas NV, Bodey GP, Kontoyiannis DP. Perspectives for the management of febrile neutropenic patients with cancer in the 21st century. *Cancer* 2005; 103:1103-13.
2. Walsh TJ, Anaissie EJ, Denning DW, Herbrecht R, Kontoyiannis DP, Marr KA et al. Treatment of aspergillosis: clinical practice guidelines of the Infectious Diseases Society of America. *Clin Infect Dis* 2008; 46:327-60.
3. Freifeld AG, Bow EJ, Sepkowitz KA, Boeckh MJ, Ito JI, Mullen CA et al. *Clin Infect Dis* 2011; 52:e56-93.
4. Maertens J, Marchetti O, Herbrecht R, Cornely OA, Flückiger U, Frère P et al. *Bone Marrow Transplant* 2011; 46:709-18.
5. Barberán J, Mensa J, Vallejo Llamas JC, Jarque Ramos I, García Ruiz JC, Cabrera JR et al. Recommendations for the treatment of invasive fungal infection caused by filamentous fungi in the hematological patient. *Rev Esp Quimioter* 2011; 24: 233-62.
6. Leventakos K, Lewis RE, Kontoyiannis DP. Fungal infections in leukemia patients: how do we prevent and treat them?. *Clin Infect Dis*. 2010; 50:405-15.