INVASIVE MYCOSES IN HEMATOLOGIC MALIGNANCIES: OPTIMAL MANAGEMENT STRATEGIES

1. In hematologic malignancy patients, the most common cause of invasive fungal infection is:

A. *Candida* spp.
B. *Cryptococcus* spp.
C. *Aspergillus* spp.***
D. *Fusarium* spp.

Commentary: Infections with *Aspergillus* spp. typically account for about 60% of all the IFIs documented in this patient population. (See section 1B; Pagano 2006; Pagano 2010; Girmenia 2014)

2. Which of the following pre-chemo factors confers the highest risk for proven/probable mold infections?

A. House renovation***
B. Higher body weight
C. High exposure job
D. Performance status greater than or equal to 2.

Commentary: In the study by Caira and colleagues, the highest OR for proven/probable invasive mold infection was in patients who had exposure to house renovation in the pre-chemotherapy setting (OR 4.01). (See Section 1B; Caira 2015)

3. You are evaluating the appropriateness of prophylactic antifungal use at your institution. Among the following hematologic/malignancy patients, which patient type, in which time period post transplant (in days) would have the highest risk for an IFI?

A. An autotransplant patient, day 80, with a prior IFI
B. An allotransplant patient, related donor, day 65, prior IFI
C. An allotransplant patient, unrelated donor, day 65, no prior IFI
D. An allotransplant patient, cord blood transplant, day 20, prior IFI***

Commentary: Allotransplant patients transplanted with unrelated donors or cord blood, who are in the early period post transplant, and who have a history of a prior IFI have particularly high risk for IFI. (See Section 1B; Girmenia 2014; Kontoyiannis 2010)

4. Regarding the impact of mold-active prophylaxis in allogeneic HSCT patients

A. Itraconazole is considered an effective, mold-active prophylaxis agent
B. In the Ullmann study, posaconazole was more effective than fluconazole in preventing IFI-related deaths in patients with severe GvHD***
C. Prophylaxis is most beneficial in auto stem cell transplants for patients with mucositis
D. Among HSCT patients, prophylaxis is most effective in related donor transplants
Commentary. Posaconazole was more effective than fluconazole for IFI prophylaxis in patients with severe GVHD. Mixed treatment comparisons show that voriconazole and posaconazole are generally more efficacious than either fluconazole or itraconazole for prevention of proven or probable invasive aspergillosis and for reducing all-cause mortality. (See Section 1B and Section 2; Ullmann 2007; Bow 2015).

5. Regarding blood culture vs non-culture based diagnostics for fungal infections, which is an advantage of culture?

A. Higher sensitivity with blood culture in the hematology population
B. Less time consuming
C. Enables susceptibility testing***
D. All fungal species grow well in culture and at the same rate

Commentary: Blood culture has several disadvantages because it is insensitive, time consuming, and fungal organisms often grow slowly. However, blood culture does enable susceptibility testing, which is important given the emergence of antifungal resistance. (See Section 2)

6. Which of the following non-culture-based diagnostics can be used as a point-of-care test at the bedside for bronchoalveolar lavage (BAL) specimens?

A. Galactomannan
B. Lateral flow assay***
C. PCR
D. Beta-D-Glucan

Commentary: The lateral flow test, which functions much like a pregnancy test (ie, provides a quick visual display on a prepared card, for immediate evaluation of a sample from BAL) can be used as a point-of-care test for Aspergillus fumigatus at the bedside using BAL samples. (See section 2; Thornton 2008)

7. You care for a range of patients who are at risk for invasive fungal infections, including invasive aspergillosis. You are asked to help work on some standard orders for use of the galactomannan (GM) test. In which of the following patient types would you indicate that the test is likely to have the highest sensitivity and utility?

A. Solid organ transplant patient with neutropenia
B. Neutropenic patient with a hematologic malignancy***
C. ICU patient
D. HIV-infected patient

Commentary: The GM test performs best in patients with hematologic malignancies and prolonged neutropenia. (See Section 2; Marchetti 2012)
8. In a patient with suspected invasive aspergillosis based on radiologic findings and respiratory symptoms, BAL galactomannan index values above what cutoff value would you consider highly suggestive of IA?

A. 0.25  
B. 1.0  
C. 1.5***  
D. 2.0

Commentary: According to Donnelly and Leeflang, the 1.5 optical density cutoff for GM in BAL is highly suggestive of invasive aspergillosis. Lower values, such as 0.5, would be appropriate for screening (in plasma/serum). (See Section 2; Donnelly 2010)

9. Which of the following is true about trial data for isavuconazole versus voriconazole?

A. Voriconazole was found statistically more effective than isavuconazole for prophylaxis in HSCT patients in terms of all-cause mortality  
B. Isavuconazole was found statistically more effective for treatment of invasive Aspergillus in terms of all-cause mortality  
C. Isavuconazole was associated with the lower rate of adverse drug reactions versus voriconazole***  
D. Isavuconazole was found statistically more effective for treatment of invasive Aspergillosis in terms of overall response rate

Commentary: The study of isavuconazole vs voriconazole in invasive aspergillosis found similar treatment effects but better tolerability for isavuconazole in terms of adverse drug reactions and specific adverse events. This was a treatment study, not a prophylaxis study. (See Section 3, Maertens 2015)

10. Which of the following is true about amphotericin B formulations as used for IFD in the setting of hematologic malignancies?

A. Voriconazole was found to have similar efficacy as amphotericin B for invasive aspergillosis  
B. Liposomal AmB was found ineffective for IA in the AmBiLoad trial  
C. Liposomal AmB is considered a reasonable choice for patients with breakthrough infections after azole prophylaxis***  
D. Liposomal AmB is unlikely to be tolerated in patients who are intolerant of azoles

Commentary: Liposomal AmB is considered a reasonable choice in the setting of breakthrough infections for patients who received azole prophylaxis given that guidelines suggest the benefit of a class switch in this setting. While the 2002 Herbrecht study showed the superiority of voriconazole vs traditional AmB in patients with IA, TheAmBiLoad trial (Cornely 2007) showed the benefits of liposomal AmB in IA. Moreover, liposomal AmB may be tolerated in patients who are intolerant to azoles or for whom there is a high azole drug interaction potential. (See Sections 3 and 4; Cornely 2007; Herbrecht 2002; Walsh 2008)
11. Which of the following is true about the use of echinocandins for prophylaxis in newly diagnosed AML patients?

A. Echinocandins have the broadest spectrum of action among antifungals and are therefore appropriate for prophylaxis against both yeasts and various invasive molds
B. Drug interactions with cancer therapeutics are much more likely with echinocandins than with azoles
C. Echinocandins can be easily transitioned from IV to oral therapy in the outpatient setting
D. The Gomes study provided a signal suggesting that breakthrough infections are higher in echinocandin-prophylaxed vs mold-active azole-prophylaxed patients, although additional study is needed to corroborate the results from this single center study***

Commentary: While the Gomes study did find a higher incidence of breakthrough infections in the echinocandin vs azole-prophylaxes patients, this was a single center study and had some methodologic flaws, limiting the extrapolation of its conclusions. While echinocandins are often preferred because of their lower propensity for drug interactions vs azoles, they have a much narrower spectrum of activity vs the mold-active azoles. (See Sections 1b and 3, Gomes 2014)

12. Which of the following adverse events has been associated with voriconazole?

A. Hallucinations
B. Increased skin cancer risk
C. Bone pain
D. All of the above***

Commentary: While the hallucination risk with high levels of voriconazole has been appreciated for some time, more recently research has also shown that voriconazole has been identified as an independent risk factor for development of cutaneous malignancy in lung transplant patients. It has also been associated with periostitis and bone pain, most likely because of its effect on fluoride metabolism. [See Section 3; Williams 2015; Moon 2014]

13. For an adult HSCT patient without any recognizable absorption issues, you prescribe posaconazole delayed release tablets for prophylaxis. After the initial loading dose, what is the dose of the oral tablets?

A. 300 mg 12 h x 2 doses/day
B. 300 mg QD***
C. 200 mg 12 h x 3 doses/day
D. 200 mg 12 h x 2 doses/day

Commentary: The correct answer is 300 mg QD. The dosing for the oral tablets should not be confused with that for the older oral suspension, which was 200 mg 3X daily. Note that there is no recommended dose for treatment of IFIs using the posaconazole delayed release tablets. [See Section 3, Noxafil PI 2015]
14. When considering the use of isavuconazole in a hematologic malignancy patient, which of the following pharmacologic considerations/strategies is relevant?

A. Follow the guidelines available regarding therapeutic dose monitoring
B. Expect a similar adverse event profile as voriconazole
C. **The long terminal half-life allows once daily dosing after the loading dose***
D. Consider an alternative oral step down therapy, since isavuconazole is only available in the IV formulation

**Commentary.** The long terminal half-life of isavuconazole allows for once-daily dosing of isavuconazole after the loading dose. For isavuconazole, available as IV and oral formulations, we can anticipate better tolerability than with voriconazole. However, it is not yet known whether therapeutic dose monitoring will be required. (See Sections 3 and 5; Cresemba PI).

15. For an adult patient with ALL who is receiving dose-intensive multi-agent multi-cycle chemotherapy, how would you counsel him about his risk for IFIs as well as potential prophylaxis regimens?

A. **He is at substantial risk for IFI***
B. ALL regimens containing vincristine are unlikely to have drug interactions with azoles
C. He is likely to experience a very high risk for fungal infections in the consolidation cycle
D. Amphotericin B would be an inappropriate option for this condition

**Commentary:** Such patients are at risk for IFIs, particularly during the induction phase. They are challenging to treat because of the likelihood of interactions between vincristine and azoles, which can lead to peripheral neuropathy. The NCCN recommends echinocandins in this setting, but these agents cannot be provided in the outpatient setting since they are only available in IV formulations. (See Sections 4 and 5; Doan 2015)

16. In the Marr study of combination antifungal therapy for invasive aspergillosis, voriconazole plus anidulafungin (as compared with voriconazole alone):

A. Provided an overall benefit in the intent-to-treat population
B. Provided the greatest benefit in patients with low disease burden [serum galactomannan (GM) <0.5]
C. **Provided the greatest benefit in patients with moderate disease burden (serum GM between 0.5-1.5)***
D. Provided the greatest benefit in patients with high disease burden (serum GM >1.5)

**Commentary:** In the Marr study, the combination had the most beneficial effect in patients with moderate disease burden as defined by GM levels between 0.5 and 1.5. (See Section 4; Marr 2015)

17. Which of the following is true about targeted therapy in the management of invasive aspergillosis?

A. Amphotericin B is equally effective as voriconazole in IA according to the Herbrecht study
B. Isavuconazole has been found equally effective as posaconazole in this setting
C. **Currently, combination therapy is considered an option for salvage therapy***
D. Echinocandins are the preferred first-line regimen in this setting
Commentary: In the management of IA, combination therapy is still considered an option for salvage therapy and not primary therapy. Voriconazole is listed as a preferred therapy in several guidelines, with newer data for isavuconazole being considered. Echinocandins are generally used more frequently in the salvage setting than in the primary setting. (See Section 4; Walsh 2008; Girmenia 2009; Maertens 2011; Herbrecht 2007)

18. In a patient who has received posaconazole as prophylaxis and who appears to have a breakthrough mold infection, which of the following would be the preferred therapy?

A. Voriconazole  
B. Fluconazole  
C. Liposomal amphotericin B***  
D. An echinocandin

Commentary: In the setting of breakthrough infections in patients who have received an extended-spectrum mold-active azole prophylaxis, a change of class should be considered because of the potential for cross-resistance with other azoles. Liposomal amphotericin B is a good option in this setting because of its broad-spectrum of activity; an echinocandin may not have the coverage necessary for all types of mold infections, so it is a less desirable choice. (See Sections 3 and 4; Walsh 2008)