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Guideline

American Society of Transplantation and Cellular Therapy Series, 2: Management and Prevention of Aspergillosis in Hematopoietic Cell Transplantation Recipients

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A B S T R A C T

The Practice Guidelines Committee of the American Society of Transplantation and Cellular Therapy partnered with its Transplant Infectious Disease Special Interest Group to update its 2009 compendium-style infectious disease guidelines for hematopoietic cell transplantation (HCT). A completely fresh approach was taken with the goal of better serving clinical providers by publishing each standalone topic in the infectious disease series as a concise format of frequently asked questions (FAQs), tables, and figures. Adult and pediatric infectious disease and HCT content experts developed, then answered FAQs, and finalized topics with harmonized recommendations that were made by assigning an A through E strength of recommendation paired with a level of supporting evidence graded I through III. This second guideline in the series focuses on invasive aspergillosis, a potentially life-threatening infection in the peri-HCT period. The relevant risk factors, diagnostic considerations, and prophylaxis and treatment approaches are reviewed.

INTRODUCTION

Invasive aspergillosis (IA) is the most common invasive mold disease following hematopoietic cell transplantation (HCT) [1-3]. Although invasive pulmonary aspergillosis (IPA) is the most common manifestation, multiple organs can be involved [1]. This guideline is in the form of frequently asked questions (FAQs) focusing on the epidemiology of IA, clinical presentation, diagnosis, prophylaxis, and treatment of IA in adult HCT recipients. Special considerations unique to pediatric HCT and chimeric antigen receptor T cell therapy (CART) are briefly discussed. Because the quality of evidence that supports clinical management of IA remains suboptimal, especially in HCT, our synthesis of this complex body of recommendations prioritizes information from relevant prospective multicenter data for HCT, when available [4].

For grading of strength of recommendation (A to E) and quality of supporting evidence (level I to III), see Appendix 1. Key recommendations below are accompanied in the text by grading in parentheses.

FAQ1: WHAT ARE THE RISK FACTORS FOR IA, AND WHEN ARE HCT RECIPIENTS MOST AT RISK?

Factors that increase the risk for post-HCT IA include

- A pretransplantation history of IA, active underlying hematologic malignancy, comorbidities such as diabetes mellitus or iron overload, occupation or hobbies associated with high levels of environmental exposure to *Aspergillus*, and poor performance status [3,5-8].
- Allogeneic HCT more than autologous HCT. In allogeneic HCT, IA risk is highest for mismatched unrelated donors, followed by matched unrelated donors and then matched related donors [2].

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- Recipients of cord blood and haploidentical donor grafts [9-11].
- Higher-intensity conditioning and prolonged neutropenia.
- Acute or chronic graft-versus-host disease (GVHD) if treated with high-dose prednisolone equivalents ≥1 mg/kg/day and/or monoclonal antibodies (eg, infliximab) [12], ibrutinib, and ruxolitinib in steroid-refractory GVHD.
- Donor or host immunogenetic predisposition (eg, donor/host *TLR4, PTX3, CLEC7-alpha* polymorphisms) may be a risk factor [13-15].
- Community-acquired respiratory viral infections with influenza, respiratory syncytial virus and parainfluenza [16,17].
- Environmental exposures, such as construction, gardening, indoor plants, and marijuana use [8,18].

Time periods of highest risk for IA after HCT

- Onset is bimodal, either "early" within the first 100 days or "late" when 180 days or later. Early IA is usually associated with a previous history of IA, prolonged neutropenia, and acute GVHD. Late IA is associated with lack of mold-active prophylaxis, cytomegalovirus reactivation, and/or chronic GVHD necessitating prolonged corticosteroid treatment [2,9,19].

FAQ2: HOW CAN I PREVENT IA AFTER HCT?

This is accomplished by primary or secondary prophylaxis and minimization of environmental exposures.

Primary antifungal prophylaxis

- For autologous or low-risk allogeneic HCT, the risk of IA is low, and prophylaxis directed primarily against *Candida* spp (eg, fluconazole, micafungin) is generally sufficient through engraftment for autologous HCT (**A-I**) [20,21] and through 75 days for allogeneic HCT (**A-I**) [20-23].
- For allogeneic HCT with high risk for IA (see **FAQ1**), posaconazole or voriconazole should be used, given the need to cover *Aspergillus* [24,25]. Echinocandins are an alternative for patients with hepatic dysfunction or at risk for drug-drug interactions with triazoles (**B-I**) [21].
- Use of mold-active prophylaxis in allogeneic HCT is recommended until day 75 or beyond when continued IA risk factors exist, such as receipt of therapy for GVHD (**A-I**) [23,24].
- For patients with GVHD, posaconazole is recommended (**A-I**) [24], and the tablet formulation is preferred over the more erratically absorbed oral suspension (**B-I**) [26]. The next alternative is voriconazole (**B-I**) [25].
- Isavuconazole is approved only for treatment of IA [27]. Data on prophylaxis are limited [28,29]. Because it does not prolong QTc it, can be selected for patients with prolonged QTc, for patients receiving QTc-prolonging medications, or to minimize drug-drug interactions mediated by CYP3A4 (**C-III**) [30].

Secondary antifungal prophylaxis

- Prior IA is not a contraindication for HCT [31]. The mold-active agent that led to resolution or stabilization of IA pre-HCT should be continued peri- and post-HCT or until the risk for IA is no longer present (**B-II**) [5,6]; infectious disease (ID) consultation is recommended. If an echinocandin is used as bridging therapy during conditioning, the switch back to the original mold-active agent should be done as soon as possible to avoid breakthrough IA. Effective surveillance to detect IA relapse post-HCT is of paramount importance.

Minimization of environmental exposure

- During hospitalization, recommended infection control standards for prevention of mold infection should be strictly implemented (**A-III**) [18,32].
- Enhanced surveillance during periods of construction should be instituted (**A-III**) [33,34].
- On hospital discharge, avoid gardening, digging, cleaning carpets, woodwork, having live plants in the house, or smoking marijuana until deemed immunocompetent (**A-III**) [35-38].

FAQ3: HOW CAN IA PRESENT?

- Symptoms may be many and varied when neutropenic, including persistent fever unresponsive to antibacterial medications, pleuritic chest pain, cough (typically dry), a new friction rub, and hemoptysis (uncommon). Sinusitis due to IA may present with facial pain, headache, nasal obstructive symptoms, or nasal bleeding with abnormal nasal eschar or necrotic areas.
- Invasive infection can result in direct extension or dissemination to viscera, bone, and central nervous tissue.
- Classic symptoms or signs may be absent in patients receiving systemic steroids for GVHD.

FAQ4: HOW DO I DIAGNOSTICALLY EVALUATE A PATIENT WITH SUSPECTED IA?

- Begin with accurate history of exposures, then assess for IA-attributable signs and symptoms.
- Diagnostic confirmation of IA is guided by the suspected site of involvement and requires expedited simultaneous evaluation using modalities A to E below.

(A) Imaging

- When sinopulmonary infection is suspected, a computed tomography (CT) scan is preferred. The classic nodule with a halo or crescent sign is uncommon and not pathognomonic for IPA even when present [39]. CT findings range from nodules to consolidation or diffuse lung infiltrates. When disseminated IA is suspected, magnetic resonance imaging of brain/orbits is preferred for the central nervous system (CNS), but CT is preferred for the abdomen and pelvis. Sinus IA may be associated with mucosal thickening and/or bony erosion.
- CT findings should not be the sole criteria to inform an IA diagnosis. Additional evaluation (B to E below) is strongly recommended to confirm a diagnosis and to guide therapy (**A-II**) [40].

(B) Procedures

- Bronchoalveolar lavage (BAL) is recommended for patients with suspected IPA because the risk is very low in experienced hands, even in thrombocytopenic patients. A

standardized BAL protocol decreases interoperator variability and increases yield [41,42].
- Biopsy for tissue sampling. Sinusitis: sinonasal endoscopic exam/biopsy. Other sites (eg, lung, visceral organs, bone, brain): biopsy if diagnosis not established by noninvasive testing or BAL.

(C) Microbiology

Culture:

- KOH prep, GMS stain, cytology and fungal cultures should be done on fluid samples from sterile sites (BAL, pleural, cerebrospinal, synovial) and tissue from biopsies [43].
- Isolating *Aspergillus* species and identifying its susceptibility profile can guide the choice of antifungals. For example, *Aspergillus terreus* is resistant to amphotericin B, while *Aspergillus lentulus* and *Aspergillus calidoustus* are resistant to azoles.

Aspergillus galactomannan antigen (AGM)

- This is done on serum, BAL fluid, and cerebrospinal fluid as appropriate. A positive AGM test is defined by the European Organization for Research and Treatment of Cancer and Mycoses Study Group Education and Research Consortium (EORTC/MSGERC) using cutoffs displayed in the table below. However, the AGM index must be interpreted in the context of risk factors, pretest probability, and knowledge of the concurrent use of antimold prophylaxis where an index lower than the cutoff described may be important.

Sample	AGM index cutoff
Single serum or plasma	≥1.0
BAL fluid*	≥1.0
Single serum when concomitant BAL fluid AGM ≥0.8	≥0.7
BAL fluid when concomitant serum or plasma ≥0.7	≥0.8
Cerebrospinal fluid [44]	≥0.0

* By increasing the AGM index cutoff to 1.0 in BAL fluid, the specificity increases at the expense of sensitivity [45].

- A negative AGM test result in a patient on antimold prophylaxis or an immunosuppressed nonneutropenic patient (eg, GVHD on corticosteroids) does not exclude a diagnosis of IA (**A-II**) [45-47]. Thus, it is generally accepted that there is lack of benefit from AGM surveillance in both children and adults in these settings.
- Beta-1,3 D-glucan testing in BAL is not useful, and testing in serum lacks specificity and is not routinely recommended to rule in IA (**D-II**) [44,48].
- Both AGM and beta-1,3 D-glucan testing can give false-positive results [34]. Positive AGM can occur with non-*Aspergillus* molds. Piperacillin-tazobactam is no longer associated with false-positive AGM [49].

(D) Molecular tests

- *Aspergillus* polymerase chain reaction (PCR) for IA is endorsed by EORTC/MSGERC as a diagnostic tool performed on serum, plasma, whole blood, and BAL fluid . It is not widely commercially available and is mostly an in-house developed assay [44]. Next generation sequencing directly from blood is commercially available, still considered investigational and not currently endorsed [50].
- MALDI-TOF (matrix-assisted laser desorption ionization time of flight): On isolation of an *Aspergillus* strain, this technique can rapidly identify it to the species level [51].

(E) Histopathology

- Evidence of fungal hyphae in the tissue confirms invasive mold disease. Although *Aspergillus* has typically acute-angle branching hyphae with septations, morphological distinction between *Aspergillus*and *Aspergillus*-like molds (eg, *Fusarium, Acremonium* spp) is particularly difficult and unreliable alone for diagnosis. PCR at a laboratory experienced in performing DNA extraction from formalin-fixed tissue is recommended to establish diagnosis when hyphae are seen on biopsy but culture is negative (**A-II**) [44,52,53].

FAQ5: HOW TO BEGIN ANTIFUNGALS AND USE ANCILLARY THERAPIES FOR MANAGEMENT OF IA IN HCT?

- If a patient receiving fluconazole or echinocandin prophylaxis develops documented IA, voriconazole is recommended as first-line therapy (**A-II**) [54] with isavuconazole (**A-II**) [27], posaconazole (**A-III**) [55] and liposomal amphotericin B (**A-II**) [56] as alternatives.
  - CNS IA is best treated with voriconazole or isavuconazole due to excellent CNS penetration (**A-II**) [57,58]. Liposomal amphotericin B is an alternative (**C-II**) [59].
- Although optimal therapy for breakthrough IA on a mold-active triazole is not fully defined, liposomal amphotericin B is recommended to avoid an azole class effect (**C-III**) [60].
- In a randomized controlled trial of patients not receiving mold-active prophylaxis, the combination of a mold-active azole (voriconazole) and an echinocandin (anidulafungin) improved outcomes compared with azole monotherapy in the subsets of patients with IA diagnosed by serum AGM (**C-I**) [61]. Otherwise, the value of combination antifungal is of unclear utility despite widespread use, particularly in cases with high mortality [61-65].
- Drug-drug interactions while on antifungal therapy can be clinically very significant, and discussion with an HCT pharmacist and/or ID specialist should be considered to mitigate interactions (Table 1).
- Consider surgical intervention for impending vascular catastrophe (lung), focal pulmonary disease not responding to antifungals, focal CNS disease, sinus or orbit involvement, and localized cutaneous or bone/osteoarticular infection (**A-III**) [66,67].
- The role of granulocyte-macrophage colony-stimulating factor (GM-CSF) and granulocyte transfusions is unclear, although these can be considered in the context of refractory/progressive disease or prolonged neutropenia when marrow recovery is anticipated (**C-III**) [68]. Pulmonary toxicity and alloimmunization are risks with granulocyte transfusions [34].

Table 1
Drug-Drug Interactions to Watch Out for When Treating Invasive Aspergillosis

Coadministered Drug	Effect on Drug Levels	Effect on Antifungal	Potential Clinical Effects	DDI Severity Ranking	Management Strategies*
Posaconazole (strong CYP3A4 inhibitor; P-gp inhibitor and substrate)					
Venetoclax	↑ Venetoclax (AUC: 90-144%)	No significant change	Hematologic toxicity, GI toxicity, tumor lysis syndrome	Major	CLL/SLL at steady state dose: reduce venetoclax to 70-100 mg/day; AML patients: 10 mg on day 1, 20 mg on day 2, 50 mg on day 3, then 70-100 mg/day starting on day 4
Ibrutinib	↑ Ibrutinib (3- to 10- fold increase in exposure)	No significant change	Hematologic toxicity, bleeding, infection	Major	If coadministered with posaconazole oral suspension 200 mg t.i.d. or 400 mg b.i.d. or posaconazole delayed release tablets or i.v. once daily, reduce ibrutinib to or 140 mg/day p.o. for chronic GVHD.
Ruxolitinib	↑ Ruxolitinib	No significant change	Thrombocytopenia, anemia, elevated liver enzymes, diarrhea	Major	No initial dose adjustments necessary for patients with GVHD.
Bortezomib	↑ Bortezomib	No significant change	Myelosuppression, peripheral neuropathy, GI toxicity	Moderate	Use with caution; monitor bortezomib toxicity.
Idelalisib	↑ Idelalisib (AUC: 1.8-fold)	No significant change	Myelosuppression, infection, elevated liver enzymes, enterocolitis	Major	No recommendation for dose adjustment.
Duvelisib	↑ Duvelisib (AUC: 2-fold)	No significant change	Myelosuppression, infection, elevated liver enzymes, enterocolitis	Major	Reduce duvelisib dose to 15 mg p.o. b.i.d.
Tacrolimus	↑ Tacrolimus (C_{max} 2-fold; AUC: 4.5-fold)	No significant change	Nephrotoxicity, neurotoxicity, hyperkalemia, electrolyte abnormalities	Major	Dosage reduction of tacrolimus is recommended.
Sirolimus	↑ Sirolimus (C_{max}: 572%; AUC: 788%)	No significant change	Hypertension, peripheral edema, hepatotoxicity, impaired wound healing, ILD	Severe	Dosage reduction of sirolimus is recommended.
Cyclosporine	↑ Cyclosporine	No significant change	Nephrotoxicity, hepatotoxicity, neurotoxicity, hypertension	Major	Dosage reduction of cyclosporine is recommended.
Voriconazole (strong CYP3A4 and CYP2C9 inhibitor; CYP2C19 inhibitor; CYP2C19, CYP2C9, and CYP3A4 substrate)					
Venetoclax	↑ Venetoclax (AUC: 90-690%)	No significant change	Hematologic toxicity, GI toxicity, tumor lysis syndrome	Major	See posaconazole for details.
Ibrutinib	↑ Ibrutinib (C_{max}: 6.7-fold; AUC: 5.7-fold)	No significant change	Hematologic toxicity, bleeding, infection	Major	If coadministered with voriconazole 200 mg p.o. b.i.d, reduce ibrutinib dose to 140 mg/day p.o. for B cell malignancy or 280 mg/day p.o. for chronic GVHD.
Ruxolitinib	↑ Ruxolitinib	No significant change	Thrombocytopenia, anemia, elevated liver enzyme, diarrhea	Major	See posaconazole for details.
Bortezomib	↑ Bortezomib	No significant change	Myelosuppression, peripheral neuropathy, GI toxicity	Moderate	Use with caution; monitor bortezomib for toxicity. No recommendation for dosage adjustment.
Idelalisib	↑ Idelalisib	↑ Voriconazole	Myelosuppression, infection, elevated liver enzymes, enterocolitis	Major	Avoid coadministration. No recommendation for dosage adjustment.
Duvelisib	↑ Duvelisib (AUC: 1.8-fold)	No significant change	Myelosuppression, infection, elevated liver enzymes, enterocolitis	Major	Reduce duvelisib dose to 15 mg p.o. b.i.d.
Tacrolimus	↑ Tacrolimus (Cp: 2-fold; AUC: 3-fold)	No significant change	Nephrotoxicity, neurotoxicity, hyperkalemia, electrolyte abnormalities	Major	Dosage reduction of tacrolimus is recommended.
Sirolimus	↑ Sirolimus (Cp: 7-fold; AUC: 11-fold)	No significant change	Hypertension, peripheral edema, hepatotoxicity, impaired wound healing, ILD	Severe	Dosage reduction of sirolimus is recommended.
Cyclosporine	↑ Cyclosporine	No significant change	Nephrotoxicity, hepatotoxicity, neurotoxicity, hypertension	Major	Dosage reduction of cyclosporine is recommended.
Itraconazole (strong CYP3A4 inhibitor, P-gp and BCRP inhibitor, and CYP3A4, P-gp substrate)					
Venetoclax	↑ Venetoclax (AUC: 90-690%)	No significant change	Hematologic toxicity, GI toxicity, tumor lysis syndrome	Major	See posaconazole for details.

(*continued*)

Table 1 (*Continued*)

Coadministered Drug	Effect on Drug Levels	Effect on Antifungal	Potential Clinical Effects	DDI Severity Ranking	Management Strategies*
Ibrutinib	↑ Ibrutinib	No significant change	Hematologic toxicity, bleeding, infection	Major	No recommendation for dosage adjustment.
Ruxolitinib	↑ Ruxolitinib	No significant change	Thrombocytopenia, anemia, elevated liver enzymes, diarrhea	Major	See posaconazole for details.
Bortezomib	↑ Bortezomib	No significant change	Myelosuppression, peripheral neuropathy, GI toxicity	Moderate	Use with caution; monitor for bortezomib toxicity. No recommendation for dosage adjustment.
Idelalisib	↑ Idelalisib (AUC: 1.8-fold)	↑ Voriconazole	Myelosuppression, infection, elevated liver enzymes, enterocolitis	Major	Avoid coadministration. No recommendation for dosage adjustment.
Duvelisib	↑ Duvelisib (AUC: 2-fold)	No significant change	Myelosuppression, infection, elevated liver enzymes, enterocolitis	Major	Reduce duvelisib dose to 15 mg p.o. b.i.d.
Tacrolimus	↑ Tacrolimus	No significant change	Nephrotoxicity, neurotoxicity, hyperkalemia, electrolyte abnormalities	Moderate	Dosage reduction of tacrolimus is recommended.
Sirolimus	↑ Sirolimus		Hypertension, peripheral edema, hepatotoxicity, impaired wound healing, ILD	Major	Dosage reduction of sirolimus is recommended.
Cyclosporine	↑ Cyclosporine		Nephrotoxicity, hepatotoxicity, neurotoxicity, hypertension	Major	Dosage reduction of cyclosporine is recommended.
Isavuconazole (moderate CYP3A4 inhibitor; CYP3A4 and UGT substrate)					
Venetoclax	↑ Venetoclax (AUC: 78%)	No significant change	Hematologic toxicity, GI toxicity, tumor lysis syndrome	Major	Reduce venetoclax by at least 50%. Monitor for venetoclax toxicity.
Nilotinib	N/A	N/A	N/A	Minor	
Dasatinib	N/A	N/A	N/A	Minor	
Ponatinib	N/A	N/A	N/A	Minor	
Bosutinib	↑ Bosutinib (C_{max}: 1.5-fold; AUC 2-fold)		Myelosuppression, GI toxicity	Major	No recommendation for dosage adjustment.
Ibrutinib	↑ Ibrutinib (C_{max}: 3.4-fold; AUC: 3-fold)	No significant change	Hematologic toxicity, bleeding, infection	Major	Reduce ibrutinib dose to 280 mg/day for treatment of B cell malignancies. Initiate ibrutinib at the recommended dose of 420 mg/day p.o. for the treatment of chronic GVHD.
Ruxolitinib	↑ Ruxolitinib (C_{max}: 8%; AUC: 27%)	No significant change	Thrombocytopenia, anemia, elevated liver enzyme, diarrhea	Moderate	No dosage adjustment necessary; monitor for ruxolitinib toxicity.
Bortezomib	↑ Bortezomib	No significant change	Myelosuppression, peripheral neuropathy, GI toxicity	Moderate	Use with caution; monitor for bortezomib toxicity. No recommendation for dosage adjustment.
Idelalisib	No significant change	↑ Isavuconazole (AUC: 5-fold)	Myelosuppression, infection, elevated liver enzymes, enterocolitis	Severe	Concurrent use is contraindicated. Consider alternative therapy.
Duvelisib	↑ Duvelisib	↑ Isavuconazole	Myelosuppression, infection, elevated liver enzymes, enterocolitis	Moderate	Monitor for increased toxicity of duvelisib and isavuconazonium during coadministration.
Tacrolimus	↑ Tacrolimus (AUC: 125%)	No significant change	Nephrotoxicity, neurotoxicity, hyperkalemia, electrolyte abnormalities	Moderate	Dosage reduction of tacrolimus may be considered.
Sirolimus	↑ Sirolimus (AUC: 84%)	No significant change	Hypertension, peripheral edema, hepatotoxicity, impaired wound healing, ILD	Moderate	Dosage reduction of sirolimus may be considered.
Cyclosporine	↑ Cyclosporine (AUC: 29%)	No significant change	Nephrotoxicity, hepatotoxicity, neurotoxicity, hypertension	Moderate	Dosage reduction of cyclosporine may be considered.
Mycophenolate mofetil	↑ Mycophenolate mofetil	No significant change	Diarrhea, leukopenia, hyperglycemia	Moderate	
Caspofungin					
Tacrolimus	↓ Tacrolimus	No significant change	Reduction in tacrolimus efficacy	Major	Monitor tacrolimus levels. Consider a 25% increase in tacrolimus dose.
Sirolimus	↓ Sirolimus	No significant change	Reduction in sirolimus efficacy	Major	Monitor cyclosporine levels. Consider a 25% increase in sirolimus dose.

(*continued*)

Table 1 (*Continued*)

Coadministered Drug	Effect on Drug Levels	Effect on Antifungal	Potential Clinical Effects	DDI Severity Ranking	Management Strategies*
Cyclosporine	No significant change	↑ caspofungin (AUC: 35%)	Hepatotoxicity	Major	Monitor liver function tests.
Micafungin					
Tacrolimus	N/A	N/A	N/A	Minor	
Sirolimus	↑ Sirolimus (C_{max}: no effect: AUC: 21%)	No significant change	Hypertension, peripheral edema, hepatotoxicity, impaired wound healing, ILD	Moderate	
Cyclosporine	N/A	N/A	N/A	Minor	
Itraconazole	↑ Itraconazole (C_{max}: 11%; AUC: 22%)	No significant change	Hepatotoxicity	Moderate	Monitor liver function tests and itraconazole levels.

DDI, drug-drug interactions; AUC, area under the curve; Cmax, maximum plasma concentration; Cp, concentration in plasma; GI, gastrointestinal; CLL, chronic lymphoblastic leukemia; SLL, small lymphocytic lymphoma; AML, acute myelogenous leukemia; ILD, interstitial lung disease; N/A, non-applicable.

* Consultation with a transplantation pharmacist is strongly recommended to determine an appropriate preemptive dosage reduction.

FAQ6: HOW TO ASSESS THE RESPONSE OF IA TO ANTIFUNGAL THERAPY IN HCT?

- Response assessment is based primarily on clinical improvement and follow-up imaging at no sooner than 2 weeks, because initial radiographic worsening might not be reflective of actual clinical progression (**A-III**) [69].
- A declining serum AGM level can be a surrogate marker of response but is not generally recommended because it is insufficient alone to inform cessation of antifungals (**D-II**) [70].

FAQ7: WHAT IS THE DURATION OF ANTIFUNGAL THERAPY FOR IA IN HCT?

- Duration is highly individualized [71]. Our consensus recommendation is to continue therapy until radiographic resolution or at least 12 weeks, whichever is later (**A-III**) [27,54].
- In continued high-risk scenarios like ongoing systemic GVHD therapy, continue the antifungal agent until resolution of the severe immune deficit with joint decision making between the HCT and ID providers (**A-III**) [60].

FAQ8: WHAT TO CONSIDER WHEN IA DEVELOPS OR PROGRESSES ON TRIAZOLE PROPHYLAXIS OR TREATMENT?

- ID consultation for further evaluation and management is recommended in these complex cases because of multiple potential issues [60]:
  - Poor compliance
  - Profound immunosuppression
  - High inoculum exposure
  - Suboptimal antifungal pharmacokinetics (especially with azoles) due to drug-drug interactions or rapid metabolizers
  - Azole-resistant *Aspergillus* isolate (uncommon in the United States)
  - Superinfections with non-*Aspergillus* opportunistic molds [72].
- With the emergence of azole-resistant *A. fumigatus* due to mutation in CYP51a (although rare in the United States) and associated poor outcomes, antifungal susceptibility testing should be considered in the setting of primary treatment failure with triazole or in the appropriate epidemiologic setting (**A-II**) [73,74].
- Pending ID consult, start liposomal amphotericin B (5 mg/kg/day)-based treatment (**C-III**) [60].

FAQ9: WHAT IS THE ROLE OF THERAPEUTIC DRUG MONITORING (TDM) WHEN USING A TRIAZOLE?

- Voriconazole: Significant variability in pharmacokinetics with CYP2C19 polymorphisms. TDM can optimize therapeutic dosing to improve efficacy and minimize toxicity. Voriconazole trough level should be obtained at day 5 to 7 of therapy and dose adjusted to target a trough level of 2 to 5.5 μg/mL (**A-I**) [75,76].
- Posaconazole: Trough level should be obtained at 3 to 8 days of therapy and dose adjusted to target a trough level

of >0.8 μg/mL for prophylaxis; a higher level is needed for treatment of IA (**A-II**) [77].
- Isavuconazole: The role of TDM is unclear but should be considered in progressive IA, suspected noncompliance, or poor absorption (**B-II**) [78].

FAQ10: WHAT CONSTITUTES FAILURE OF ANTIFUNGAL THERAPY, AND WHAT ARE THE NEXT STEPS?

- For probable and proven IA (updated definitions) [44], progression of clinical symptoms or radiographic findings after at least 2 weeks of appropriate therapy is considered failure of therapy.
- IA not responding to appropriate therapy requires a thorough reevaluation, ideally under the direction of an ID consultant; TDM if on azoles to assess for a subtherapeutic level; and BAL or tissue sampling (if not done previously). Repeat AGM or PCR tests as indicated. This will enable evaluation for possible initial misdiagnosis of IA and presence of a coinfection, or provide an indication that lack of host immune response (latter being the most common) is the cause.
- The antifungal treatment may require modification; such as changing the class of antifungal agent being used.

FAQ11: SPECIAL CONSIDERATIONS

Pediatric HCT recipients

- Indications for pediatric HCT are more diverse. Apart from hematologic malignancy, children undergo HCT for variety of nonmalignant indications (eg, sickle cell anemia, primary immunodeficiency). The risk of IA varies based on the underlying disease [79,80].
- Clinical presentation and risk factors are similar to those for adult HCT recipients, although a higher rate of CNS involvement is noted in disseminated infection [81].
- At risk patients with symptoms and signs of IA should undergo evaluation as described under FAQ4. The diagnostic approach is similar to that in adults and includes imaging as well as AGM and *Aspergillus* PCR [34,44].
- Radiographic findings are more likely to be nonspecific in pediatric IA [82,83].
- Treatment of IA: first-line therapy is voriconazole followed by liposomal amphotericin B [34]. Posaconazole can be used in children and adolescents age ≥13 years. Posaconazole dosing data for children age <13 years remains elusive, and thus is a last resort for use (with caution!). Modest outcomes have been reported with caspofungin [84]. Pediatric specific isavuconazole data are sparse. In a recent case series of 29 patients, a response rate of 70.8% was observed with a good safety profile [85].
- There are no studies comparing combination therapy to monotherapy in children with IA. However, addition of an echinocandin to triazole or liposomal amphotericin B can be considered in patients with high-risk features as in adults.
- Children have accelerated metabolism of antifungal drugs (triazoles and echinocandin) and weight-based dosing is recommended for children age <14 years. Oral bioavailability of voriconazole is lower than in adults, necessitating a loading dose of 9 mg/kg/dose twice daily for 1 day, followed by 8 mg/kg twice daily (**A-II**) [86,87]. Monitoring for toxicities (TDM) and response to therapy is recommended [88]. Echinocandin dosing**:** caspofungin is dosed based on body surface area; 70 mg/m^2 on day 1 followed by 50 mg/m^2 daily [60]. The recommendation for micafungin dosing ranges from 2 to 10 mg/kg/day, with higher doses in neonates. Input from a pediatric pharmacist to guide pediatric dosing is recommended.

CAR T Cell Therapy (CART)

- There are 2 Food and Drug Administration-approved products for treating acute lymphoblastic leukemia (ALL) and B cell lymphoma, tisagenlecleucel and axicabtagene-ciloleucel, respectively [89,90]. The data on epidemiology, risk factors, and management of IA in this population are limited. The independent contribution of CART to IA risk remains to be determined. In the only 2 studies reviewing CART infectious complications, the incidence of IA was 0.7% to 3.7% [91,92].
- It remains difficult to predict a priori who will develop prolonged cytopenia or significant corticosteroid requirement for cytokine release syndrome (CRS) following CART. Therefore, low threshold of starting mold-active prophylaxis should be adopted in heavily pretreated patients with ALL, especially those who received cytotoxic chemotherapy before CART infusion or recipients of previous HCT [93].
- The principles of diagnosis and management are similar as described in the foregoing FAQs.

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APPENDIX 1. GRADING OF STRENGTH OF RECOMMENDATION AND LEVEL OF EVIDENCE

FAQ1 to FAQ4

Recommendation	Grade	Supporting
For autologous HCT at low risk for IA prophylaxis against *Candida* spp (eg, fluconazole, micafungin) is recommended through neutrophil recovery (1000 cells/mm^3).	AII	20-23
For allogeneic HCT at low risk for IA prophylaxis against *Candida* spp (eg, fluconazole, micafungin) is recommended beyond neutrophil recovery until day 75.	AII	20-23
For allogeneic HCT at high risk for IA (see FAQ1), posaconazole or voriconazole should be used to provide coverage against *Aspergillus* infection.	AI	24,25
Echinocandins are an alternative to mold-active azoles for patients with hepatic dysfunction or at risk for drug-drug interactions with triazoles.	BI	21
Continuation of mold-active prophylaxis in allogeneic HCT is recommended until day 75, or beyond when IA risk factors persist (eg, receiving GVHD therapy.	AI	23,24
For patients with GVHD, posaconazole is the recommended mold- active prophylaxis	AI	24
The tablet formulation of posaconazole is preferred over the more erratically absorbed oral suspension.	BI	26
Voriconazole is a suitable alternative to posaconazole prophylaxis in allogeneic HCT when mold-active antifungal prophylaxis is required.	BI	25
Isavuconazole can be considered as an alternative to posaconazole or voriconazole for patients with prolonged QTc and those receiving QTc-prolonging medications, or to minimize drug-drug interactions mediated by CYP3A4.	CIII	30
The mold-active agent that led to resolution or stabilization of IA pre-HCT should be continued peri- and post-HCT.	BII	5,6
During hospitalization, recommended infection control standards for prevention of mold infection should be strictly implemented.	AIII	18,32
Enhanced surveillance during periods of construction should be instituted.	AIII	32-34
On hospital discharge, gardening, digging, cleaning carpets, woodwork, having live plants in the house, or smoking marijuana should be avoided until immunosuppression is ceased.	AIII	35-38
CT findings should not be the only criteria to inform an IA diagnosis; additional evaluation (see B to E in FAQ4) is strongly recommended to confirm a diagnosis and to guide therapy.	AII	40
A negative *Aspergillus* GM test result while on antimold prophylaxis or in an immunosuppressed non-neutropenic patient (eg, GVHD on corticosteroids) does not exclude a diagnosis of IA.	AII	45-47
Beta-1,3 D-glucan testing in BAL fluid lacks specificity and is not routinely recommended for diagnosing IA.	DII	44,48
PCR at a laboratory experienced in performing DNA extraction from formalin-fixed tissue is recommended when hyphae are seen on biopsy but culture is negative.	AII	44,52,53

FAQ 5

Recommendation	Grade	Supporting
If a patient receiving fluconazole or echinocandin prophylaxis develops documented IA, voriconazole is recommended as initial first-line therapy.	AII	54
Isavuconazole is an alternative to voriconazole as first-line treatment in a patient receiving fluconazole or echinocandin prophylaxis who develops documented IA.	AII	27
Posaconazole is an alternative to voriconazole or isavuconazole.	AIII	55
Liposomal amphotericin B is an alternative to voriconazole and isavuconazole in a patient receiving fluconazole or echinocandin prophylaxis who develops documented IA.	AII	56
CNS IA is best treated with voriconazole or isavuconazole owing their excellent CNS penetration unless it developed or progressed while receiving these agents.	AII	57,58
Liposomal amphotericin B is an alternative to treat CNS aspergillosis when voriconazole or isavuconazole cannot be used.	CII	59
Optimal therapy for breakthrough IA occurring on a mold-active triazole has not been defined. In such cases, liposomal amphotericin B should be used.	CIII	60
Combining an echinocandin with a triazole or liposomal amphotericin B can be done when there is firm evidence of probable or proven IA despite no conclusive data showing benefit.	CI	61
Consider surgical intervention in the following settings: impending vascular catastrophe (lung), focal lung disease not responding to antifungals, focal CNS disease, sinus or orbit involvement, and localized cutaneous or bone/osteoarticular infection.	AIII	66,67
The role for GM-CSF and granulocyte transfusions is unclear, but these can be considered in refractory/progressive IA or during prolonged neutropenia when marrow recovery is anticipated.	C III	68

FAQs 6, 7, and 8

Recommendation	Grade	Supporting
Response assessment is based on clinical improvement and follow-up imaging no sooner than 2 weeks after starting antifungal therapy, because initial radiographic worsening might not be reflective of progression.	AIII	69
A declining serum AGM level can be a surrogate marker of response but is insufficient alone to inform cessation of antifungals.	BII	70
Continue antifungal therapy until radiographic resolution or at least 12 weeks, whichever is later.	AII	27,54
In continued high-risk scenarios such as ongoing systemic GVHD therapy, continue antifungal therapy until resolution of the severe immune deficit.	AIII	60
Antifungal susceptibility testing should be considered in the setting of primary treatment failure with triazole or in the appropriate epidemiologic setting for azole resistance (eg, prolonged azole exposure or acquisition of IA in a region where azole resistance is recognized).	AII	73,74
Where azole resistance is suspected, pending ID consult, start liposomal amphotericin B (5 mg/kg/day)-based treatment.	C-III	60

FAQ 9

Recommendation	Grade	Supporting
Voriconazole trough level should be obtained at day 5-7 of therapy and dose adjusted to target a trough level of 2 to 5.5 micrograms/ml.	AI	75,76
Posaconazole trough level should be obtained at 3-8 days of therapy and dose adjusted to target a trough level of >0.8 micrograms/ml for prophylaxis; a higher level is needed for treatment of IA.	AII	77
The role of TDM for isavuconazole is unclear but should be considered in progressive IA, suspected non-compliance, or poor absorption.	BII	78

FAQ11

Recommendation	Grade	Supporting
Voriconazole oral bioavailability is lower in children than in adults, necessitating a loading dose of 9 mg/kg/ dose BID for 1 day followed by 8 mg/kg BID.	AII	86,87
Accelerated metabolism of voriconazole in children necessitates weight-based dosing for age < 14 years.	AII	
Monitoring for toxicities (TDM) and response to therapy is recommended.	Same as adults	

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