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Guideline

American Society for Transplantation and Cellular Therapy Series, #6: Management of Invasive Candidiasis 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 (ASTCT) partnered with its Transplant Infectious Disease Special Interest Group (TID-SIG) to update its 2009 compendium-style infectious disease guidelines for hematopoietic cell transplantation (HCT). A completely new 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 (FAQ), tables, and figures. Adult and pediatric infectious disease and HCT content experts developed and then answered FAQs and finalized topics with harmonized recommendations made by assigning an A through E strength of recommendation paired with a level of supporting evidence graded I through III. This sixth guideline in the series focuses on invasive candidiasis (IC) with FAQs to address epidemiology, clinical diagnosis, prophylaxis, and treatment of IC, plus special considerations for pediatric, cord blood, haploidentical, and T cell-depleted HCT recipients and chimeric antigen receptor T cell recipients, as well as future research directions.

INTRODUCTION

Conditioning chemotherapy-induced mucositis and gastrointestinal graft-versus-host disease (GVHD) represent the major risk factors for invasive candidiasis (IC) in hematopoietic cell transplantation (HCT) recipients due to gastrointestinal flora translocation. Routine primary antifungal prophylaxis beginning in the 1990s led to a significant decline in post-transplantation IC to an incidence of 1% to 2% and a significant shift in the epidemiology of *Candida* species [1]. Current challenges include the changing *Candida* epidemiology, suboptimal diagnostic tools, and poor clinical outcomes, despite the availability of effective and safe treatment options. The principles discussed for allogeneic HCT recipients prior to engraftment are applicable to autologous HCT recipients and patients receiving cellular therapies, such as chimeric antigen receptor (CAR) T cells, at least until neutrophil recovery and in the absence of prolonged glucocorticoid therapy.

In this update to the 2009 compendium-style infectious disease guidelines for HCT, a completely new 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 (FAQ), tables, and figures [2]. For grading of strength of recommendation (A to E) and quality of supporting evidence (level I to III), see Supplementary Data. The key recommendations provided below are accompanied by grading in parentheses.

EPIDEMIOLOGY

FAQ1: What is the epidemiology of Candida infections in HCT recipients?

Collectively, non-*albicans Candida* species are more frequently encountered in HCT recipients with IC [3,4]. Infections due to *Candida glabrata* (*Nakaseomyces glabrata*) are up to 25% to 50% fluconazole-resistant, and *Candida krusei* (*Pichia*

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kudriavzevii) infections are intrinsically fluconazole-resistant and may represent consecutively >50% of IC cases [4,5]. Infections due to *Candida* species, which were until recently considered rare and with challenging resistance patterns (eg, *Candida auris*, *Candida kefyr*, *Kluyveromyces marxianus*) are being increasingly reported [6,7].

CLINICAL PRESENTATION AND DIAGNOSIS

FAQ2: What are the risks and timing of Candida infections in HCT recipients?

Candida infections post-transplantation primarily occur from translocation of gastrointestinal flora during postconditioning mucositis before engraftment or subsequently in association with severe gastrointestinal GVHD postengraftment. Infection also may develop secondarily in association with an indwelling central venous catheter (CVC).

FAQ3: How does IC present in HCT recipients?

The vast majority present with candidemia due to translocation of gastrointestinal flora or CVC infection. Disseminated disease has been described predominately in profoundly neutropenic patients with *Candida tropicalis* candidemia, presenting with persistent fever, diffuse maculopapular rash, and bilateral micronodular and ground-glass patterns on chest computed tomography scan [8]. Hepatosplenic candidiasis is a rarely encountered form of IC due to local dissemination via the portal system. It manifests on engraftment with persistent fever and elevated alkaline phosphatase level, and computed tomography images show micronodular liver and/or splenic lesions [9]. Prolonged fever despite treatment may result from an immune reconstitution inflammatory syndrome [9].

FAQ4: How is the diagnosis of IC made in HCT recipients?

Blood cultures remain the major diagnostic tool, with a historical sensitivity of approximately 60% (Table 1) [10]. The use of automated blood culture methods, special fungal blood culture media, and matrix-assisted laser desorption/ionization time-of-flight methods have been associated with a higher diagnostic yield and faster species identification [11–14]. Isolating the pathogen on a culture allows for antifungal susceptibility testing and results provide the basis for specific treatment recommendations. The utility of nonculture diagnostic media for the diagnosis of IC is discussed in FAQ5 and FAQ14. Hepatosplenic candidiasis may be diagnosed when clinical presentation and timing are typical and when characteristic radiologic features are present, but we recommend tissue biopsy for definitive diagnosis (A-III) [15].

FAQ5: What is the utility of β-D-glucan in the diagnosis of IC in HCT recipients?

The sensitivity and specificity of β-D-glucan for diagnosis of IC in patients with leukemia and HCT recipients are 50% to 90% and 70% to 100%, respectively (Table 1) [16–19]. Results are less useful in children, based on a recent trial [20]. Test performance is influenced by prevalence of IC in the patient population, screening strategies (including the number of consecutive tests requested), and the cutoff used [19]. β-D-glucan is not specific for *Candida* species and may be positive in almost any invasive fungal infection except cryptococcosis and mucormycosis [21]. Many confounders can cause false-positive results, for example, i.v. immunoglobulin administration and hemodialysis with cellulose membranes [21,22]. Data addressing the utility of routine β-D-glucan screening in HCT are limited; low specificity and high false-positive test rates further compromise its clinical utility (C-III).

TREATMENT

FAQ6: Which antifungal agents should be considered as first-line treatment for IC in HCT recipients?

Our recommendations are consistent with the most recent Infectious Diseases Society of America guidelines (Table 2) [23]. Given that the vast majority of HCT recipients have been exposed to azole prophylaxis, and although echinocandins have not been systematically studied in neutropenic patients, first-line therapy with an echinocandin (eg, anidulafungin, caspofungin, micafungin) is recommended (A-I) [23–26]. Echinocandins are the preferred agents in children, with more pediatric data available for micafungin and caspofungin compared to anidulafungin, and antifungal dosing unique in children (A-II) (Table 2) [27]. Based on similarities in their in vitro and safety profile, echinocandins can be used interchangeably (B-III). Notably, echinocandin resistance is being increasingly reported [28,29]. Treatment may be adjusted based on *Candida* species identification (A-II) [23]. Additional options may become available in the future, including novel antifungal agents, such as ibrexafungerp or rezafungin, that have activity against most *Candida* species, administration advantages (eg, weekly intermittent i.v. administration or oral administration), and a favorable adverse event profile [30–32]. However, based on the limited available data, particularly on hematologic patients, recommendations cannot be made at this point. Treatment should be administered for a minimum of 14 days after both resolution of neutropenia and relevant clinical signs and symptoms and blood culture sterilization (A-I) [23]. A dilated eye exam should be performed in all patients with IC within the first week after neutropenia resolution to rule out

Table 1
Diagnosis of Candidemia and Invasive Candidiasis

Diagnostic Test	Sensitivity	Specificity	Comments
Blood cultures	60%-90% [10,11, 13,14]		Bottles with specific media to optimize the growth of fungal pathogens appear to have greater sensitivity than regular blood cultures.
β-D glucan	50%-90% [16–19]	70%-100% [16–19]	The performance of β-D glucan for the diagnosis of candidemia in patients with hematologic malignancies depends on the cutoff used and number of tests performed.
PCR	90%-95% [43,44]	>95% [43, 44]	Lack of assay standardization, inability to detect and identify multiple *Candida* spp in the same PCR test, and questionable cost-effectiveness significantly limit the utility of these tests in clinical practice.
T2Candida/ magnetic resonance panel	90% [45, 46]	>95% [45, 46]	Turnaround time for test results is 4-5 hours [45]. Prior antifungal treatment and neutropenia do not appear to affect the performance of this assay. Test can detect only 5 of the most frequently encountered *Candida* spp.

Table 2
Treatment of Candidemia and Invasive Candidiasis [23]

Agent	Dose, Induction	Dose, Maintenance	Route	Side Effects/Toxicities
Echinocandins*				Rare infusion reactions
Anidulafungin				
Adult (A-I)	200 mg × 1 dose	100 mg once daily	i.v.	
Child†	3 mg/kg × 1 dose	1.5 mg/kg once daily	i.v.	
Caspofungin				
Adult (A-I)	70 mg × 1 dose	50 mg once daily	i.v.	
Child <3 mo	None	25 mg/m2 once daily	i.v.	
Child ≥3 mo to <18 yr	70 mg/m2 × 1 dose	50 mg/m2 once daily (increase to 70 mg/m2 daily, depending on clinical response; maximum dose, 70 mg daily)	i.v.	
Micafungin				
Adult (A-I)	None	100 mg once daily	i.v.	
Infant <4 mo	None	2 mg/kg/day once daily (increase to 4-10 mg/kg daily, depending on clinical response)	i.v.	
Child ≥4 mo to <18 yr	None	2 mg/kg/day once daily (maximum dose, 100 mg daily)	i.v.	
Azoles‡				
Fluconazole (A-I)§				Hepatotoxicity
Adult	800 mg × 1 dose	400 mg once daily	i.v./oral	
Child	None	12 mg/kg once daily (maximum dose, 800 mg/day)	i.v./oral	
Voriconazole (A-I)‖,¶				Hepatotoxicity, visual hallucinations, neurologic toxicity, QTc prolongation, rash, photosensitivity reactions, periostitis
Adult	6 mg/kg twice daily × 2 doses	4 mg/kg twice daily	i.v.¶/oral	
Child¶ 2 to <12 yr	9 mg/kg twice daily × 2 doses	8 mg/kg twice daily (maximum oral dose, 350 mg once daily)	i.v.¶/oral	
Child ≥12 to ≤14 yr, <50 kg	9 mg/kg twice daily × 2 doses	8 mg/kg twice daily (maximum oral dose, 350 mg once daily)	i.v.¶/oral	
Child ≥12 to ≤14 yr, ≥50 kg	6 mg/kg twice daily × 2 doses	4 mg/kg twice daily	i.v.¶/oral	
Child ≥15 yr	6 mg/kg twice daily × 2 doses	4 mg/kg twice daily	i.v.¶/oral	
Polyenes				
Amphotericin B lipid formulation#				Nephrotoxicity, electrolyte abnormalities
Adult	None	3-5 mg/kg once daily	i.v.	
Child	None	3-5 mg/kg once daily	i.v.	

* Echinocandins are considered interchangeable for the treatment of IC. Notably, only a limited number of patients with neutropenia have been included in the major echinocandin clinical trials [24–26]. In adult patients with critical illness or obesity, higher doses of echinocandins may be used; doses as high as 150 mg/day, 200 mg/day, and 150 mg/day for caspofungin, anidulafungin, and micafungin, respectively, have been well tolerated [23,26,51] (A-I/II). Echinocandins should not be used in patients with endophthalmitis (particularly with involvement of the vitreous fluid) or central nervous system involvement because of poor penetration.

† Anidulafungin is not approved for use in children.

‡ Based on lack of relevant data, posaconazole is not included among the recommended options for the treatment of invasive candidiasis [23]. Isavuconazole is not approved for the treatment of candidemia based on failure to demonstrate noninferiority compared to caspofungin for primary treatment of invasive candidiasis [56].

§ Fluconazole can be used in patients with fluconazole-susceptible *Candida* spp as step-down therapy.

‖ Voriconazole can be used in patients with candidemia due to *C. glabrata* (*Nakaseomyces glabrata*) and/or *C. krusei* (*Pichia kudriavzevii*) as step-down oral treatment. Cross-resistance between voriconazole and fluconazole for *C. glabrata* (*Nakaseomyces glabrata*) may be encountered.

¶ Weight-based dosing of voriconazole is preferred for both i.v. and oral administration. Voriconazole trough therapeutic drug monitoring should be performed, particularly in children [52,53]. Administration of i.v. voriconazole is not recommended if creatinine clearance <50 mL/min.

Amphotericin B lipid formulations may be used to treat IC based on available data and fungicidal profile, but are not favored as first-line therapy because of associated potential toxicities.

Table 3
Prevention of *Candida* Infection in HCT Recipients

Agent	Dose	Route	Start Day	Stop Day
Fluconazole (A-I) [34–36]	200-400 mg once daily	i.v./oral	Conditioning–stem cell infusion	Day 75-100
Micafungin (A-I) [38]	50 mg once daily*	i.v./oral	Conditioning	Day 100
Voriconazole (A-I) [37]	200 mg twice daily†	i.v./oral	Conditioning	Day 100
Posaconazole (A-I) [40]	300 mg once daily‡	i.v./oral	GVHD ≥grade 2	Steroid dose taper <20 mg/day

* Micafungin has been studied as primary antifungal prophylaxis at a dose of 50 mg/day, which remains the recommended prophylactic dose (A-I). Notably, micafungin may be administered at a dose of 100 mg/day in clinical practice despite a lack of relevant data to support this prophylactic dose.

† A loading dose of voriconazole 6 mg/kg twice daily for the first day should be administered. For maintenance dose, weight-based dosing at 4 mg/kg twice daily is preferred to a universal dose of 200 mg twice daily (B-III). Therapeutic drug monitoring of trough voriconazole blood concentrations may be used to decrease potential voriconazole-associated toxicities [52,53] (A-I).

‡ This dose refers to the oral pill or i.v. formulation of posaconazole. A loading dose of posaconazole at 300 mg twice daily for the first day should be administered. Trough posaconazole blood concentrations may be monitored to ascertain adequate blood concentrations [52,54,55] (B-II). If posaconazole suspension is used, 200 mg thrice daily administered with (fatty) meals is recommended.

Candida endophthalmitis (A-II) [23]. In cases of endophthalmitis, an ophthalmology consultation to assess the extent of infection and need for surgical intervention and longer treatment courses (4 to 6 weeks) with agents with optimal eye penetration, including fluconazole and voriconazole, are strongly recommended (A-II) [23].

FAQ7: Is combination therapy recommended for the treatment of IC in HCT recipients?

Echinocandins are highly efficacious and safe agents for most cases of IC, and thus combination therapy is not routinely recommended (D-III). However, for *C. auris* candidemia, before the antifungal susceptibility profile is available, combination therapy with more than 1 agent based on local epidemiology could be considered in critically ill neutropenic patients [33] (B-III).

FAQ8: Should a central line be removed in HCT recipients with candidemia?

We strongly favor CVC removal in neutropenic patients with candidemia when feasible (A-II) [23]. In non-neutropenic nonthrombocytopenic patients, CVC removal is strongly recommended (A-II) [23]. Daily blood cultures should be obtained to confirm sterility, particularly if the CVC is not removed.

ANTIFUNGAL PROPHYLAXIS

FAQ9: Who should receive anti-Candida primary prophylaxis, when, and for how long?

Administration of primary anti-*Candida* prophylaxis is recommended for all allogeneic HCT recipients, starting with either conditioning or stem cell infusion and continuing until 75 to 100 days post-transplantation (A-I) (Table 3) [34–38]. Although the timing of prophylaxis initiation has varied in clinical trials, we recommend that antifungal prophylaxis be started on initiation or immediately after completion of the conditioning regimen, in the event of concerns for drug interactions between azoles and conditioning agents, particularly cyclophosphamide (A-I) [39]. In patients with GVHD treated with corticosteroids at doses ≥1 mg/kg daily, we recommend antifungal prophylaxis with posaconazole for effective *Candida* and mold coverage, until symptom resolution and corticosteroid dose taper to <20 mg/day (A-I) [40]. In autologous HCT recipients, primary antifungal prophylaxis may be discontinued after resolution of neutropenia (B-III).

FAQ10: Which antifungal agents can be used for Candida prophylaxis in HCT recipients?

Fluconazole, voriconazole, posaconazole, and micafungin all provide effective prophylaxis (A-I) [34,35,37,38,40]. We favor the administration of fluconazole prophylaxis based on the accumulated body of evidence and clinical experience, as well as its excellent bioavailability and efficacy and safety profile (A-I). Prophylaxis with mold-active agents, such as voriconazole (A-I) or posaconazole (A-I), may be used in patients at high risk for invasive aspergillosis or other mold infections to provide mold coverage [37,40]. An echinocandin may be considered in cases of colonization or prior infections with azole-resistant *Candida* species or in cases of azole-intolerance or other contraindications (eg, drug interactions, abnormal liver function, QTc prolongation) (B-III). Posaconazole is recommended postengraftment if acute GVHD is being treated with corticosteroids at doses ≥1 mg/kg/day (A-I) [40]. The suggested time frame and doses of antifungal prophylaxis are summarized in Table 3.

FAQ11: Are there special considerations for Candida prophylaxis in pediatric HCT recipients?

This has not been well studied in children, but similar approaches as in adults have been adopted and appear feasible (A-III).

SPECIAL CONSIDERATIONS

FAQ12: Should further adjustments in Candida prophylaxis be made in cord blood, haploidentical or T cell-depleted HCT recipients?

There are no current data to suggest that prophylaxis approaches should differ in recipients of cord blood, haploidentical or T cell-depleted grafts (C-III).

FAQ13: Should CAR-T cell recipients receive Candida primary prophylaxis?

Because CAR-T cell recipients frequently develop mucositis and prolonged neutropenia after administration of cytotoxic chemotherapy, they are at risk for *Candida* infections. Despite a paucity of relevant data, administration of anti-*Candida* prophylaxis from the start of chemotherapy until resolution of neutropenia and mucositis should be strongly considered (A-III) [41,42]. A mold-active agent (eg, posaconazole) is recommended in CAR-T cell recipients who are at elevated risk for mold infections because of prior allogeneic HCT, corticosteroid therapy at doses ≥1 mg/kg/day, or IL-6 inhibitors (A-III) [41,42].

UNMET NEEDS AND FUTURE DIRECTIONS

FAQ14: What is the utility of PCR or T2Candida-MR panel for diagnosing IC in HCT recipients?

These assays have showed excellent performance in diagnosing candidemia in clinical studies [43–46] (Table 1).

However, a lack of real-life data, including cost-effectiveness, has limited the widespread implementation of these approaches in HCT recipients. T2Candida appears promising in children based on a recent clinical trial [47].

FAQ15: Should Candida primary prophylaxis be continued postengraftment in patients without GVHD?

In the pivotal clinical trials, fluconazole prophylaxis in HCT was continued until posttransplantation day 75 or 100 [34,35]. A post hoc analysis of one of these trials demonstrated lower incidence of gastrointestinal GVHD and a sustained 8-year survival benefit in the fluconazole arm over placebo [48]. However, HCT recipients without severe mucositis or gastrointestinal GVHD are less likely to translocate gut flora, including *Candida* species, after engraftment. More data are needed to evaluate the effect of fluconazole prophylaxis beyond engraftment on clinical outcomes. Pending more data, prolonging fluconazole prophylaxis until post-transplantation day 75 should be considered, if feasible and well-tolerated (A-I).

FAQ16: What is the utility of adjunctive treatments, such as granulocyte transfusions, in managing severe IC in HCT recipients?

Based on the available data and their short half-life, granulocyte transfusions do not appear to provide a significant benefit (D-II) [49,50]. However, they may be considered in patients with sustained candidemia and prolonged profound neutropenia when count recovery is anticipated [23].

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SUPPLEMENTARY MATERIALS

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.jtct.2023.01.011.

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