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Guideline

Guidelines for Infection Prophylaxis, Monitoring and Therapy in Cord Blood Transplantation

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As an alternative stem cell source, cord blood (CB) has many advantages. However, delayed engraftment, lack of transferred immunity, and a significant incidence of acute graft-versus-host disease renders CB transplant (CBT) recipients at high risk of infectious complications. This guidance written by CBT and infectious disease experts outlines evidence-based recommendations for the prevention and treatment of opportunistic infections in adult patients undergoing CBT. Topics addressed include bacterial, fungal, viral, pneumocystis jirovcii and toxoplasmosis prophylaxis, suggested PCR monitoring for viruses, therapy for the most commonly encountered infections after CBT. We review key concepts including the recent important role of letermovir in the prevention of CMV reactivation. In instances where there is a paucity of data, practice recommendations are provided, including the duration of antimicrobial prophylaxis.

Prolonged neutropenia, delayed immune recovery (as compared to T-cell replete HLA-matched allograft recipients), and lack of transferred immunity render cord blood transplant (CBT) recipients at a higher risk for morbidity and mortality as a result of infectious complications [1-4]. Herein, we describe critical measures for the prevention and treatment of opportunistic infections commonly associated with CBT (Tables 1 and 2). The focus of this guideline is on adult CBT recipients. Special considerations concerning the infectious complications in children undergoing CBT will be addressed in a separate article.

FAQ1: DO GRAFT-VERSUS-HOST DISEASE (GVHD) PROPHYLAXIS STRATEGIES INFLUENCE THE RISK OF OPPORTUNISTIC INFECTION?

Multiple series have demonstrated that antithymocyte globulin (ATG)–based conditioning is associated with increased infectious complications, poor immune reconstitution and increased mortality in patients with hematologic malignancies [5-11]. Accordingly, ATG is no longer recommended in adult patients with hematologic malignancies undergoing CBT. In patients undergoing transplantation for nonmalignant indications, pharmacokinetic-based dosing should be done to minimize ATG exposure during and after transplantation [12].

FAQ2: IS WHITE CELL GROWTH FACTOR SUPPORT RECOMMENDED?

Given the delayed neutrophil recovery after CBT, post-transplantation granulocyte colony stimulating factor (G-CSF) is recommended to mitigate bacterial and fungal infections and shorten the duration of neutropenia [13]. Most centers begin G-CSF between days 1 and 7 after transplantation and continue through engraftment.

FAQ3: WHAT IS THE RECOMMENDED PROPHYLAXIS FOR BACTERIAL INFECTIONS AND SHOULD MONITORING FOR BACTEREMIA BE CONSIDERED?

The most common bacterial prophylaxis strategy is to use a fluoroquinolone from the onset of neutropenia until neutrophil recovery. The value of prophylactic antimicrobials targeting a broader range of gram-positive pathogens is not established. Knowledge of colonization with methicillin-

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Table 1
Summary of recommendations for antimicrobial prophylaxis

Infection	Recommended Agent	Comments
Bacterial	Levofloxacin	Alternatives: ciprofloxacin, cepfodoxime or amoxicillin/clavulanate (if fluoroquinolone intolerant)
Fungal	Posaconazole, voriconazole, or isavuconazole	Alternative (no mold activity): Fluconazole or echinocandins (eg, micafungin) if hepatic dysfunction
HSV/ VZV	Acyclovir or valacyclovir	
CMV	Letermovir	Recommended in seropositive adults ≥ 18 years old for at least the first 100 days. Extended prophylaxis may be beneficial beyond day 100.
Pneumocystis	Trimethoprim/ sulfamethozaole before transplantation. Starting at 1 month after transplantation, trimethoprim/ sulphamethoxazole, atovaquone, dapsone, or pentamadine.	Need to tailor choice to recipient toxoplasmosis serostatus. Prophylaxis should be continued for at least 1 year after transplantation, patients are off immunosuppression, and until there is a sustained CD4+ lymphocyte count recovery above 200 cells/μL for at least 6 months, whichever takes longer.
Toxoplasmosis	Trimethoprim/ sulfamethoxazole before transplantation. Starting at 1 month after transplantation trimethoprim/ sulphamethoxazole, or atovaquone.	Commence early after transplantation. Criteria for cessation similar to PCP prophylaxis. Monitor for medication adherence with atovaquone.

resistant *Staphylococcus aureus*and vancomycin-resistant *Enterococci*may help guide antimicrobial selection in managing first neutropenic fever. However, vancomycin-resistant *Enterococci*bacteremia is relatively infrequent, and empiric therapy may have unintended negative consequences [14,15]. A high burden of *Clostridium difficile* infections in CBT recipients receiving fluroquinalone prophylaxis has been reported, and oral vancomycin prophylaxis is being investigated as strategy to prevent *C. difficile* infections [16-18].

FAQ4: WHAT IS THE RECOMMENDED FUNGAL PROPHYLAXIS?

Given the extended neutropenia associated with CBT, CBT recipients should typically be screened for occult mold infections using noncontrast chest computed tomography scanning before transplantation [19]. Evaluation for occult fungal infection of the sinuses can be done if clinically warranted. At a minimum, all patients should receive antifungal prophylaxis for yeast with fluconazole or an echinocandin from the onset of neutropenia. Some institutions use mold-active prophylaxis early after transplantation; posaconazole, voriconazole, or isavuconazole may also be considered. Mold-active azoles should not be used during conditioning but can be commenced early after transplantation with close attention to drug interactions with calcineurin inhibitors and sirolimus. In patients with prolonged neutropenia or who are receiving systemic corticosteroids after CBT, prophylaxis should be continued until neutropenia resolves and steroids are discontinued or tapered to physiological dosing. Many centers perform therapeutic drug monitoring to ensure adequate blood levels of voriconazole or posaconazole. Micafungin or caspofungin can be substituted in patients with hepatic dysfunction.

FAQ5: WHAT IS THE RECOMMENDED PROPHYLAXIS FOR HERPES SIMPLEX (HSV) AND VARICELLA ZOSTER VIRUS (VZV)?

CBT recipients are at high risk for HSV and VZV, including disseminated disease, when not receiving acyclovir prophylaxis [20]. Viral prophylaxis with valacyclovir (500 mg twice daily) or acyclovir (800 mg twice daily) for HSV and VZV is recommended from start of chemotherapy until at least 3 years after CBT. Longer prophylaxis can be considered in patients with GVHD or poor immune recovery. There are no safety and efficicacy data pertaining to the use of Shingrix vaccination to prevent herpes zoster after CBT. If patients are vaccinated, acyclovir prophylaxis should be continued for at least 1 month after the second dose, although it remains unknown whether this will provide the same level of protection [21].

FAQ6: WHAT IS THE RECOMMENDED PROPHYLAXIS FOR CYTOMEGALOVIRUS (CMV)?

Because of the high incidence of morbidity and mortality associated with CMV after CBT [22-24], letermovir prophylaxis starting at day 7 and continuing for at least 100 days after CBT is the recommended standard of care in all adult CMV-seropositive CBT recipients [25]. Although the optimal duration of prophylaxis is not established, some patients may benefit from prophylaxis beyond day 100, particularly in the setting of

Table 2
Summary of Viral Monitoring Recommendations Using Quantitative PCR

	Recommended Monitoring	Comments*
CMV	If recipient seropositive, twice weekly early after transplantation through day 100. Extended monitoring beyond day 100 on a weekly basis should be performed at least until patients have 3 negative test results and are off systemic corticosteroids.	Alternative: weekly could be considered only if on letermovir prophylaxis.
HHV-6	Can be considered early after transplantation, but utility of monitoring is not proven.	Alternative: as clinically indicated.
Adenovirus	Can be considered early after transplantation with pre-emptive therapy of high level viremia.	
EBV	Consider monitoring in the first 100 days, especially if GVHD with pre-emptive therapy of high level viremia.	
Toxoplasmosis	Can be considered early after transplantation if recipient seropositive, but utility is not proven.	

* Extended monitoring of CMV and EBV is recommended in the setting of systemic immunosuppression with corticosteroids or slow immune reconstitution.

therapy for GVHD or delayed immune reconstitution. Monitoring for viremia during and after cessation of letermovir should be performed. If letermovir prophylaxis is not possible, frequent monitoring for viremia and early pre-emptive therapy is mandatory, and prophylaxis with valacyclovir of 2 gm by mouth every 8 hours during the first year after CBT can be considered if tolerated [23,26].

FAQ 7: WHAT VIRAL MONITORING AND TREATMENT STRATEGIES ARE RECOMMENDED?

HHV-6B

HHV-6B viremia is common after CBT. Although reported incidences of end-organ disease vary, CBT recipients are at increased risk [27-30]. There is no evidence that prophylaxis with the currently available antiviral drugs reduces the incidence of end-stage organ disease [31]. Symptom-based testing should be performed. Some centers perform PCR surveillance during the first 60 days after CBT, and although pre-emptive therapy can be considered for high levels of viremia, the threshold to start treatment is not established [29]. The condition of chromosomally integrated HHV-6 should be considered in patients with viremia that does not respond to antiviral therapy or with viral loads above 10^5 copies/mL in whole blood samples [32].

CMV

Although letermovir prophylaxis is very effective, once- or twice-weekly CMV PCR monitoring of the blood is recommended through day 100 and at regular intervals subsequently as long as severe immunosuppression exists. This is especially important when letermovir is stopped. In patients on Letermovir, low-level viremia can be closely observed without pre-emptive therapy to ensure spontaneous resolution. In patients not on letermovir, pre-emptive therapy with ganciclovir, valgancyclovir, or foscarnet is recommended at any level of detection in the first 6 months after transplantation or subsequently if there is delayed immune reconstitution [22,23]. Foscarnet is the preferred therapy in patients with significant cytopenias. CMV-specific cytotoxic lymphocytes have been investigated for refractory or resistant CMV disease [33].

BKV

In the context of clinical symptoms of cystitis, testing for viruria is recommended. Measurement of viremia can also be considered in patients with renal impairment. The mainstay of treatment consists of supportive care [34]. A reduction in immune suppression should be considered if possible in patients with severe complications.

Adenovirus

Monitoring for viremia can be considered early after transplantation or as clinically indicated. Pre-emptive therapy is recommended for high-level or progressively worsening adenoviremia, although there are no established thresholds. Patients with end-stage organ disease should be treated with cidofovir. Given the toxicities of cidofovir, clinical trials are ongoing for alternative therapies such as brincidofovir [29,35] and virus-specific T-cells.

EBV

Monitoring for viremia can be considered or performed as clinically indicated. Many centers will monitor patients on systemic therapy for GVHD. Pre-emptive therapy of viremia with rituximab is recommended in patients with persistent and high-viral loads, although there are no established thresholds. Patients with post-transplantation lymphoproliferative disease require treatment as described elsewhere [36]. EBV-specific cytotoxic lymphocytes can be considered for refractory or resistant disease if available [33,37,38].

FAQ8: WHAT IS THE MOST APPROPRIATE STRATEGY FOR PREVENTING *PNEUMOCYSTIS JIROVECII* PNEUMONIA (PCP) AND TOXOPLASMOSIS?

PCP

Prophylaxis for PCP typically consists of trimethoprim-sulfamethoxazole before transplantation. Starting at 1 month after transplantation, prophylaxis can be initiated with trimethoprim-sulfamethoxazole, atovaquone (if also sero-positive for toxoplasmosis), dapsone, or inhaled or intravenous pentamidine (if seronegative for toxoplasmosis). Prophylaxis should be continued until at least 1 year after transplantation, until patients are off immunosuppression, and there is a sustained CD4+ T-cell count recovery above 200 cells/μL for at least 6 months, whichever takes longer. Some centers also continue prophylaxis until responses to protein conjugate vaccines have been documented. Dapsone can be used after evaluating for G6PD deficiency but can be associated with hemolysis and methemoglobinemia.

Toxoplasma

Toxoplasmosis serology should be measured before transplantation. If IgG seropositive, patients should receive prophylaxis with trimethoprim-sulfamethoxazole before transplantation followed immediately after transplantation by atovaquone, and, on sustained resolution of severe cytopenias, trimethoprim-sulfamethoxazole [34]. Some centers perform PCR blood monitoring early after transplantation in seropositive patients, but this is not the standard of care.

FAQ9: WHAT IS THE TREATMENT OF INVASIVE FUNGAL INFECTIONS?

Patients with breakthrough infections who are on extended spectrum azoles including voriconazole or posaconazole should have azole blood levels measured to ensure absorption [39]. For infection occurring in patients on extended spectrum azoles with therapeutic drug levels, specialist consultation is recommended.

FAQ10: WHAT ARE SPECIAL CONSIDERATIONS IN CBT RECIPIENTS WITH GVHD?

In patients with GVHD on high-dose systemic corticosteroids, additional monitoring can be considered for viral infections (Table 2) irrespective of the time from transplantation. In addition, affected patients should receive antimicrobial prophylaxis for encapsulated bacteria with either trimethoprim-sulfamethoxaxole or penicillin VK and with mold-active azoles if on systemic corticosteroids.

FAQ11: IS TREATMENT OF HYPOGAMMAGLOBINEMIA WITH INTRAVENOUS IMMUNE GLOBULIN SUPPLEMENTATION RECOMMENDED?

Intravenous immune globulin supplementation may be considered for patients with severe hypogammaglobinemia with recurrent or severe bacterial infections, a history of sinopulmonary bacterial infections, or those with GVHD on systemic corticosteroids [40].

FAQ12: HOW SHOULD CBT RECIPIENTS BE VACCINATED?

All patients require complete reimmunization after CBT, and CBT recipients can generate appropriate responses [41].

Vaccination strategies have been addressed in detail elsewhere [42,43]. There are no published data about the safety or efficacy of the nonlive recombinant VZV vaccine (Shingrix) after CBT, although it has been approved for autologous transplantation recipients [44] and should be considered after CBT. Vaccination for human pappilomavirus is now routinely recommended.

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