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Guidelines for Pediatric Unrelated Cord Blood Transplantation—Unique Considerations

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Abstract

Cord blood (CB) is the stem cell source of choice for approximately 30% of pediatric patients undergoing hematopoietic cell transplantation. Cord blood is readily available and is a particularly appealing stem cell source for patients who lack appropriate HLA matched related or unrelated donors. Pediatric cord blood transplant (CBT) recipients have low rates of disease relapse in the malignant setting and very low rates of chronic GVHD. In addition, CB has unique properties that make it the stem cell source of choice for some non-malignant conditions such as metabolic disorders. This review provides evidence-based and experience-based pediatric specific guidelines for CBT including considerations for infectious disease management, CB unit selection and infusion, conditioning regimen selection, and GVHD management. In addition, it covers unique bedside considerations for pediatric patients and CB banking. In concert with the other topic specific CB guidelines previously published in this series, it provides a comprehensive overview of the clinical management of pediatric CBT.

Introduction

Although registry data indicates an overall decline in the use of umbilical cord blood in recent years, it continues to be the stem cell source for approximately 30% of children undergoing hematopoietic cell transplantation (HCT). This is likely explained by advantages that are more often attainable in children because of generally favorable CB cell doses and unique disease indications for HCT (FAQ1). Perhaps most pertinent is the observation that overall chronic GVHD (cGVHD) and relapse-free survival in children after CBT is high, with the greater propensity for infectious complications being mitigated by optimal clinical practices (FAQ2). The following guideline focuses on unique questions related to allogeneic umbilical cord transplantation for pediatrics.

FAQ1: What are the advantages of cord blood transplant CBT?

Potential benefit	*Malignant Disease*	*Non-Malignant Disease*[1]
Ready availability	Yes	Yes
Less stringent HLA-matching potentially relevant to ethnic/racial minorities with fewer MRD/MUD options	Yes	Yes
Favorable cell doses are more readily achievable in pediatric CBT recipients	Yes	Yes
Equivalent survival and low risk or relapse, even when MRD present at	Yes	Not applicable

time of CBT		
Low rates and/or lower severity of chronic GVHD compared to URDs	Yes	Yes
Improved cGVHD-leukemia free survival (cGVHD-LFS) (measure of quality of life)	Yes	Not applicable
Donor stem cell source of choice for inborn errors of metabolism	Not applicable	Yes

- CB units (CBU) are readily available and provide a viable treatment alternative for patients without an HLA matched sibling or URD, a situation that disproportionately impacts ethnic and racial minorities[1].
- Additionally, CBT recipients have equivalent overall survival (OS) with evidence of decreased relapse rates particularly in comparison to HLA matched related donor transplants making CBT particularly appealing in high-risk leukemia where relapse is of primary concern[2,3]. In fact, the presence of minimal residual disease (MRD) at the time of transplant does not impact disease free survival in recipients of CBT[4] unlike other stem cell sources where there is a significant risk of relapse (HR 3.65 [2.53-5.27]) and decreased overall survival (HR 2.36 [1.73-3.22]) when MRD is present[5].
- Recipients of CBT have low rates of chronic GVHD similar to those receiving HLA matched sibling donor transplants and significantly lower than HLA matched unrelated donor (MUD) recipients[6].
- Improved quality of life (such as timing of return to school) and reduced risk for mortality is also evident in the composite endpoint of cGVHD-LFS which was significantly improved in CBT recipients as compared to recipients of unrelated donor transplants[7].
- Durable donor chimerism is well established in both malignant and, especially, non-malignant diseases.
- We believe CBT should be considered in patients with very high-risk leukemias and MRD positivity at the time of transplant where graft-versus-leukemia is of particular importance. Emerging data indicate that the immunobiology of CBT may be distinct from other stem cell sources and contribute to the lower rates of relapse. For example, HLA-loss as a major mechanism of post-transplantation relapse has not been observed in CBT[8].

FAQ 2. Are there pediatric specific pre-CBT Infectious disease evaluations to consider?

Cord blood specific infectious disease evaluations are covered in “Guidelines for infection prophylaxis, monitoring and therapy in cord blood transplantation”[9] from this series. Specific to pediatrics is the importance of comprehensive infectious disease workup, intensive viral

monitoring, use of prophylaxis and early initiation of treatment. Regular post-transplant surveillance for adenovirus and HHV-6 are particularly important.

Many centers have CMV monitoring guidelines specific to cord blood recipients. Letermovir is a promising medication for the prevention of CMV reactivation and disease. This medication is not yet approved in the pediatric population and so intensive monitoring +/- high-dose acyclovir/valacyclovir or ganciclovir are utilized to prevent CMV disease.

FAQ 3. Are there unique considerations for cell dose or cell infusion in pediatric UCB recipients?

Please refer to 'Guidelines for Cord Blood Unit Thaw and Infusion' in this series for details on considerations for cord blood infusion[10]. Please also refer to 'Guidelines for Cord Blood Unit Selection' in this series for in-depth discussion of CBU selection[11].

The most important factors related to UCB outcomes are HLA match and total nucleated cell (TNC) dose. For pediatrics UCB recipients with malignant indications for HCT, successful engraftment along with other outcomes improve with higher cord blood cell dose [12-17]. The absolute minimum cell dose for an un-manipulated single cord blood should be at least 2.5x10^7 TNC/kg, with target cell dose 4x10^7 TNC/kg. For non-malignant indications, a targeted cell dose greater than 4 x10^7/kg is recommended, with higher dose recommended for patients with lesser HLA matched cord (4/6) or severe aplastic anemia[18]. For pediatrics single cord is preferred over double cord when adequate cell dose is available[19]. These cell doses are based on the pre-cryopreservation cell dose data. CD34 cell dose can be another important consideration which can affect engraftment and outcomes.

The minimum acceptable CD34 cell dose is at least 1.5x10^5 CD34/kg[20,21]. During CBU selection, higher level HLA match takes precedence over cell dose[17,22] assuming minimum cell dose criteria have been met.

FAQ 4. What are the most common conditioning regimens used in pediatric UCB recipients?

A comprehensive review of cord blood regimens is provided in "Guidelines for adult patient selection and conditioning regimens in cord blood transplant recipients with hematologic malignancies and aplastic anemia"[23]. The most common conditioning approaches in pediatric patients are shown below. For non-malignant diseases in particular, conditioning regimens may be altered based on disease and patient clinical status.

Conditioning Regimens	Malignant disease	Non-Malignant Disease
Myeloablative	FLU (75 mg/m2), CY (120 mg/kg), 12-13.2 Gy TBI	BU targeted (90mg*h/L), CY (200 mg/kg), ATG*, +/- FLU
	BU targeted, CY (200 mg/kg)	

Reduced Intensity	FLU (150 mg/m2), CY (50 mg/kg), TT (10 mg/kg), 4Gy TBI[24]	BU targeted (60mg*h/L), FLU, ATG*

*Consider withholding ATG in the setting of significant viral infections

FAQ5: Are there specific GVHD management considerations in children?

In general, GVHD management in children does not differ from adults receiving CBT (reviewed in detail in "Guidelines for the prevention and management of graft-versus-host disease after cord blood transplantation"[25]). Most common GVHD prophylaxis regimens utilize a calcineurin inhibitor (CNI) and mycophenolate mofetil (MMF) in the first 2-6 months post-transplant. In-vivo T-cell depletion with ATG is an alternative immune suppressive strategy; however, its use is controversial if the underlying disease indication is malignancy and generally avoided due to higher risk of viral reactivation, delayed immune reconstitution and concern for increased NRM and relapse. If ATG is given, ATG pharmacokinetics should be considered to reduce post-transplant ATG exposure and enhance immune reconstitution[26]. The majority of children will develop acute GVHD; however, severe (grade III-IV) GVHD occurs in a minority of patients (13%)[19]. Of note MMF taper should be considered once systemic corticosteroids are added for the primary treatment of acute GVHD as no study has yet demonstrated that CNI+MMF+corticosteroid is superior to CNI+corticosteroids for acute GVHD management. Acute GVHD more commonly affects skin and gut rather than liver and typically is very responsive to corticosteroids. The intensity of corticosteroid therapy should attempt to balance the risk for viral reactivation without compromising GVHD control. For patients requiring second and third line therapy for GVHD, relatively less immunosuppressive approaches such as extracorporeal photopheresis (ECP) or mesenchymal stem cells if they are available could be considered, particularly in patients where viral infection is complicating or driving GVHD.

FAQ6. What is Pre-Engraftment Syndrome and how to best manage it?

A unique complication following UCB is pre-engraftment syndrome (PES)[27-29]. This can occur commonly and manifest with non-infectious fevers, rash, fluid retention and sometimes even tachypnea and hypoxia in the peri-engraftment period[30]. These symptoms are otherwise unexplained, and not responsive to antimicrobial changes. Pediatric UCB recipients should be monitored for PES. When there is evidence of PES, infectious etiologies should first be ruled out with blood cultures, urine cultures, viral PCRs, stool cultures/PCRs, nasal wash and/or radiology evaluations when clinically appropriate and short course steroids started without delay to treat and manage it. As described in previously published guidelines in this series, the recommended steroid and dose is methylprednisolone at 1-2mg/kg/day for 3 days and then weaned off rapidly within a week of engraftment[25]. While 1mg/kg is the standard adult PES dose, BMT CTN 0501 used 2mg/kg in a pediatric population and so this should be considered, particularly in the setting of significant PES symptoms[19]. If symptoms persist beyond 6 days,

the patient should be considered to have hyperacute/acute GVHD and treated with a steroid course as deemed appropriate by treating clinician.

FAQ 7. Are there unique bedside considerations in pediatric patients receiving cord blood transplantation as compared to other donor sources?

In general, the management of patients before and after cord blood transplant is similar to recipients of other stem cell sources; however, there are a few unique considerations of which to be aware for those administering care at the beside. Cord blood unit thaw and infusion guidelines have been recently published and can be referenced for standard operating procedures for CB processing and infusion[10].

- Of particular note, for children, is the decision between “dilute” and “dilute and wash” for product preparation. The latter should be considered in patients less than 20kg to control infusion volume and avoid fluid overload.
- Fluid balance and vital signs should be monitored closely at the bedside as fluid overload can exacerbate common infusion reactions such as hypertension as well as rare, but serious reactions such as Takotsubo cardiomyopathy[31].
- Hypertension should be managed with anti-hypertensive medications (hydralazine) as well as adjusting infusion rate and providing diuresis if indicated.
- The timing from thaw/thaw & wash to infusion should be less than 2 hours if feasible to optimize the viability and potency of the cord blood cells.
- For double cord blood transplants, units should be thawed and infused serially, allowing sufficient time between unit infusions to assess for adverse reactions.
- Non red cell depleted cryopreserved CBUs contain sufficient RBCs to cause hemolytic transfusion reactions in small children. The volume of residual (post processing) RBCs in any CBU should be known before thaw. If ABO incompatibility exists, then thaw and wash or a post thaw RBC depletion should be strongly considered or, if possible, an alternative CBU should be selected.

FAQ 8. What are the long-term side effects of pediatric CBT and are they different from other donor sources?

Pediatric CBT recipients generally have a similar long-term side effect profile as patients receiving comparable conditioning regimens but alternate donor sources. There are, however, a few notable differences.

- Recipients of CBT are at significantly lower risk of chronic GVHD as compared to those receiving other MUD/MMUD stem cell sources. Studies have consistently shown the incidence of chronic GVHD by NIH Consensus grading to be around 20-25% in both children and adults with majority of cases being mild or moderate[32-35].
- Interestingly, multiple large centers have noted that recipients of cord blood transplants appear to develop ***atopic dermatitis*** that is distinct from chronic GVHD and typically responds to topical agents and does not require continuation or escalation of systemic immune suppression[36].

- Late acute gut GVHD is a manifestation of CB transplant that is relatively more common than classic chronic GVHD manfestations[37].
- Historically, recipients of cord blood transplants were considered to have delayed T-cell immune reconstitution (IR) as compared to other donor sources, placing them at increased risk for early post-transplant infectious complications[38-40]. More recent literature suggests this may not be the case in the absence of ATG. Furthermore, early T-cell IR (CD4+) in CBT patients is associated with improved survival. Decreasing ATG exposure or eliminating ATG from conditioning regimens for patients with malignant indications for transplant has the advantage of improving IR and survival outcomes and is the standard approach for most large CB transplant centers in the US[26]. Delayed IR in CBT recipients does not impact recommendations for revaccination in these patients and established guidelines should be followed for initiation of revaccination[41].

FAQ 9. Do you recommend public or private banking of CB from siblings?

Cord donation for public banking continues to be recommended to help increase the representation in our national and international cord blood banks especially for populations that continue to be underrepresented in the National Marrow Donor Program (NMDP)[42-44]. In addition, focus on banking of large, high quality CBUs will further improve the inventory of CBUs available for transplantation.

The one exception to this is consideration of direct donation (privately or to a commercial/public bank that may bank units free of charge) for families that have another child who may require future allogeneic stem cell transplantation where an HLA matched sibling graft is the preferred stem cell source. This would most commonly occur in non-malignant conditions such as sickle cell disease, Thalassemia, Wiscott-Aldrich syndrome, Hurler's syndrome, Adrenoleukodystrophy, and other inborn errors of metabolism[45]. The carrier state of the CBU donor should be determined prior to use of a sibling CBU. In certain conditions, use of a carrier donor is contraindicated. Families electing to bank CBUs in private banks should confirm appropriate quality assurance and regulatory review has occurred and that unit processing results in sufficient cell dose for future use.

Contact NMDP if further guidance needed regarding choosing of specific private banks or public banks that may waive fees for families who have a child with a potential indication for allogeneic transplant[46].

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