

Overview of Recommendations on Improving Cord Blood Unit Quality

September 13, 2016

A Compiled Presentation to the
Advisory Council on
Blood Stem Cell Transplantation

Presentation Overview

- Review findings by the ACBSCT “Cord Blood Work Group for Improving the Availability of High TNC Cord Blood Units for a Diverse Population” that looked at TNC as a factor in defining a high quality unit
 - Review recommendation on contracting and funding for NCBI program
- Present findings of the High Quality Cord Blood Unit Work Group
 - Quality Sub Committee of the NMDP Cord Blood Advisory
 - Use of CD 34 testing
 - Agree with recommendations of ACBSCT Work Group re-tiered reimbursement for high TNC
 - Funding of unlicensed units by licensed banks
- Recognizing Considerations of Transplant Doctors

Recommendations of ACBSCT Work Group for
Improving the Availability of High TNC
Cord Blood Units For a Diverse Population
(February 23, 2016)

Work Group Co-Chairs:
Karen Ballen, MD
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Findings - Cord Selection

- Larger units are being used more than smaller units
- Of the transplants conducted, a higher percentage of pediatrics use CBUs than the percentage of adults who use CBUs; overall, there are more transplants for adults than pediatrics
- Transplant centers use various combinations of match and TNC dose, with no universally accepted combination
- Patients using smaller units tend to be younger
- Few patients get 6 of 6 antigen matches

Findings - Use

- Minority patients do not find as close matches as Caucasian patients
- African American patients are more likely to find a suitable match from African American donors, which typically have lower TNC levels
- Minority patients receive smaller units to a greater extent than Caucasians
- More low TNC NCBI units have been banked for minorities than for Caucasians
- Adult cord blood use in transplant in the United States is static or declining; pediatric and non-malignant cord blood use is increasing in US
- Cord blood transplants in Europe are declining

Findings - HRSA

- HRSA funding is essential to continue the current growth of the inventory
- HRSA funding may influence decisions about what size units to bank
- HRSA funding does influence the diversity of the registry
- Most HRSA funded banks have maintained a TNC cutoff of 90×10^{-7} th
- HRSA funding has provided a larger inventory of diverse UCB units and likely has saved lives

Findings - Registry Characteristics

- The NCBI registry has more minority CBUs than non-NCBI banks
- The registry has many more smaller units than larger units
- Additions to registry have and will continue to incrementally improve matching options
- Due to growth of registry, past patients would now have a greater selection of CBUs
- Additions to registry will incrementally improve cell dose options
- Some banks have shifted to a higher TNC cutoff voluntarily
- European banks are shifting toward a higher TNC cut-off for cost-effectiveness and to match clinical interest in high TNC units

Findings - Bank Perspective

- Based on the survey conducted by NMDP, most banks support a shift to a higher TNC cut-off, but additional compensation would be required to account for the extra resources needed to bank larger units.
- Discussion at Cord Blood Advisory Group confirmed that HRSA funded banks and Transplant Physicians support a shift to an inventory of larger cord blood units
- Extra resources per unit banked are needed to significantly expand collection activity since fewer CBUs will be banked out of the collected units.

Findings - What We Don't Know

- The impact of haplo-identical transplants on demand for CBUs
- The impact of expansion technologies on demand for CBUs
- The impact of alternatives to transplant on demand for CBUs, e.g. CAR-T cell therapies
- The impact of regenerative medicine on demand for CBUs
- How any individual bank is impacted by changes in TNC funding by HRSA
- Whether raising the TNC requirements (without any other action) will result in banks collecting and banking more CBUs with higher TNCs

Recommendation

- HRSA should adopt a funding framework that incentivizes the collection of high TNC units for a diverse population and that recognizes higher associated costs
 - Greater incentive to add units to the inventory that have higher TNC, including for minorities, which are associated with better outcomes
 - Recognizes growth and diversity of inventory since its inception and creates incentive to shift banking toward most-needed units
 - Recognizes that per unit reimbursement will need to reflect higher cost per unit banked for higher TNC, minority units
 - Need to expand collection activity
 - Fewer total units will be banked

Recommendation - Example 1

- Goals
 - incentivize collection of high TNC units for diverse populations
 - Increase the pace of adding large units to the inventory
- Use a higher TNC cutoff, e.g.:
 - Minority at 125x10^{>7}th
 - Caucasian at 150x10^{>7}th
- Recognize that per unit reimbursement will need to reflect
 - Higher cost per unit banked
 - Need to expand collection activity

Recommendation - Example 1 Impact

- Assumes one-third of current per unit subsidy supports collection
- Two-thirds of subsidy not used for processing smaller units will now support new collections or larger units
- Units that would have been banked at 90 TNC: 9,841
- Units that will be continue to be banked at higher cutoffs: 4,911
- Additional larger units collected (\$2,500 subsidy): 1,670
- Net units not banked (smaller units) compared to current: 3,260

Implications of Example 1

- Higher Cell Count Threshold
- Collections will need to be Expanded
- Higher Cost and Reimbursement per Cord Blood Unit Banked
- Current estimates:
 - Approximately one-third of the per unit HRSA subsidy goes to collection
 - A higher threshold means funds not used for banking smaller units will be used to collect larger units
- Net effect
 - Smaller number of total units banked
 - Larger number of large units banked

Recommendation - Example 2

- Goals
 - Continue to bank CBUs with a variety of TNC levels, but incentivize collection of high TNC units for diverse populations
- Adopt a graduated reimbursement framework with higher reimbursement with each sequential group, such as:
 - Group 1: 90 TNC to <125 TNC (Minority) and 125 to <150 TNC (Caucasian) @\$750
 - Group 2: 125 to <150 TNC (Minority) and 150 TNC or more (Caucasian) @\$1,250
 - Group 3: 150 TNC or more (Minority) @\$2,500
- Recognize that per unit reimbursement will need to reflect
 - Higher cost per unit banked
 - Need to expand collection activity

Recommendation - Example 2 Impact

- All minority units above 90 TNC will receive a subsidy
- Units that would have been banked at 90 TNC: 9,841
- Units that will continue to be banked under this example: 8,642
- Additional larger units collected (\$2,500 subsidy): 274
- Net units not banked (smaller units) compared to current: 925

Implications of Example 2

- Higher Cell Count Threshold
- Collections will need to be Expanded
- Higher Cost and Reimbursement per Cord Blood Unit Banked
- Current estimates:
 - Approximately one-third of the per unit HRSA subsidy goes to collection
 - A higher threshold means funds not used for banking smaller units will be used to collect larger units
- Net effect
 - Smaller number of total units banked
 - Larger number of large units banked
 - Incremental growth in number of large units banked
- Less disruptive to some banks, depending on demographics
- May be difficult to administer given the number of ethnic and funding variations

Recommendation - Implementation

- Amend existing contracts within next year rather than rebid
- Increase per unit funding for higher TNC units and for diversity
 - Continue to focus on diversity
 - Requires expanded collection activity
 - At least doubling of current collection activity depending on populations targeted
 - Recognize that per unit funding will need to increase to add more large minority units
- The HRSA contracts would need to be individualized to fit the accrual targets and patterns of each CB bank

Funding - Approach

It is recommended that HRSA and cord blood banks commit to pricing that incentivizes the collection and banking of high TNC CBUs for a diverse population, and that provides for higher reimbursement based on increased associated costs for collection and banking. This reimbursement framework provides a greater opportunity for minority patients to have access to higher TNC CBUs, while continuing to support collection of CBUs that can be used by a diverse population. This is particularly important given that some minority patients (particularly African Americans) are more likely to find a suitable match from African American donors, whose CBUs typically have lower TNC levels.

Review of New Collection Practices

- One year to amend contracts
- Review outcomes of new collection practices at approximately 18 months and 3 years after implementation
- Review might include:
 - Inventory of Minority and Caucasian Cord Blood Units
 - Usage of NCBI and non NCBI Cord Units
 - Cord Transplant Outcomes
 - Implementation Issues at the Cord Blood Banks

Demonstration Projects

HRSA-funded Demonstration Projects offer an important opportunity for cord blood banks to test innovative strategies for increasing their collection and banking of high TNC CBUs for a diverse population. Regardless of the TNC reimbursement threshold set by HRSA, HRSA should take immediate steps to make ample funds available through a Demonstration Project for innovative initiatives that will provide information to the field.

Demonstration Projects

- All cord blood banks be encouraged to participate
- Encourage a wide variety of proposed Demonstration Project models that are intended to improve the applicant bank's collection and banking of high TNC units for a diverse population
- Banks should be encouraged to partner and to submit larger scale projects
- Awards should be for a minimum of 2 years
- HRSA should use an expert review panel to review the projects and award appropriate funding, with opportunities available to suggest panel members with appropriate expertise

Outcome of ACBSCT Cord Blood Work Group

- Presentation to HRSA ACBSCT March 2016
- Advisory Council reviewed and voted to recommend that HRSA adopt a funding framework that incentivizes the collection of high TNC units for a diverse population and that recognizes higher associated costs, and that:
 - Provides greater incentives to add units to the inventory that have higher TNC, including for minorities, which are associated with better outcomes
 - Recognizes growth and diversity of inventory since its inception and creates incentive to shift banking toward most-needed units
 - Recognizes that per unit reimbursement will need to reflect higher cost per unit banked for higher TNC, minority units
 - Recognizes the need to expand collection activity
 - Acknowledges that fewer total units will be banked

Recommendations of Quality Committee of NMDP Cord Blood Advisory Group

Presenter:

Karen Ballen, MD

Quality Committee of NMDP Cord Blood Advisory Group

- NMDP CBAG:
 - Cord Blood Bankers, Transplant Physicians, Transplant Scientists
- Quality Group:
 - Asked to define high quality UCB unit
 - Membership: Sharon Miller, Joanne Kurtzberg, Donna Regan, Machi Scaradavou, Merry Duffy, Anne Gass
- Met three times over 4 months and sent recommendations to Dr. McCullough August, 2016
- 19 CBAG members voted and approved these recommendations

Tiered TNC Approach to Reimbursement

- Recommend Tiered TNC Approach to Reimbursement
 - Example:
 - Group 1: 90 TNC to <125 TNC (Minority) and 125 to <150 TNC (Caucasian)
 - Group 2: 125 to <150 TNC (Minority) and 150 TNC or more (Caucasian)
 - Group 3: 150 TNC or more (Minority)
- Details and reimbursement amounts to be defined by each bank's contract with HRSA

NCBI Funding Should be Available for Unlicensed Units Banked by Licensed Banks

- Recommend reimbursing licensed banks for non-licensed, Investigational New Drug (IND) cord blood units that meet NCBI requirements in certain cases where Safety, Quality, Identity, Purity, and Potency (SQulPP) are not affected.
- Rationale
 - NCBI funding is limited to licensed units
 - Licensed banks occasionally process and bank units that meet acceptable SQulPP standards but don't meet the technical specifications under the license
 - The inability to be licensed is not related to the quality of the unit
 - These units would have been funded if processed and banked by an unlicensed bank

CD34 Testing of CBUs

- Recommend implementing a requirement for a minimum absolute viable post-processing CD34 of $\geq 1.25 \times 10^6$ to align with specifications for FDA licensure
- Rationale
 - CD34 is considered an important characteristic for selection of a CBU for transplant
 - There is sufficient literature on the minimum level of CD34 for purposes of defining therapeutic benefit
 - Test results now a required field for entry into the national registry
 - Is consistent with FDA Guidance: Biologics License Application for Minimally Manipulated Unrelated Cord Blood Intended for Hematopoietic and Immunologic Reconstitution in Patients with Disorders Affecting the Hematopoietic System, March 2014

Recognizing Considerations of Transplant Doctors

Presenter:

Karen Ballen, MD

How does a Transplant Doctor Pick the Optimal UCB unit for each Patient?

- Complex process that involves patient age, weight, disease, disease status, protocol options, other donor choices.
- Cell dose one of the most important factors for survival.
- Even in pediatrics and double cord, choose larger cords.
- Nucleated cell dose standard
- Many centers will also look at CD 34 cell dose
- Some centers will also look at CFU-GM

Selection of the Optimal UCB Unit

- Other factors:
 - HLA match (? HLA C or allele level typing)
 - HLA antibodies (controversial)
 - KIR Match (controversial)
 - Bank of Origin (controversial)
 - Infectious Disease Markers
 - Genetic Screen
 - Cord Blood Potency