

Cord Blood Banking

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Background

Allogeneic bone marrow transplantation has been successful for about 25 years in treating life-threatening diseases affecting the blood, hematopoietic system, or immune system. The first transplants used surgical bone marrow harvests from related, HLA-matched donors.^{1,2} Unrelated HLA-matched donors started to be widely used after the National Marrow Donor Program (NMDP) registry of volunteers was set up in 1987. Potential donors are recruited for listing in this registry and then may be recruited specifically for a marrow donation when matched with a recipient. The matching process is more difficult when the patient's race is not well represented in the registry. For the patient, the major problem with these transplants is graft-versus-host disease, which may be as fatal as the underlying disease. For the donor, the major problem is recovery from the grueling surgical collection of bone marrow under anesthesia.³

The latter problem can be avoided by the growing use of peripheral blood stem cells (PBSC), which are collected by apheresis.

Cord Blood as a Transplant Source

Early observations by Broxmeyer et al.⁴ showed that the residual cord blood in the placenta after a normal birth was rich in hematopoietic progenitor cells. Subsequent studies showed that cell colonies could be grown from cord blood and that the colonies were large and primitive (containing a mix of hematopoietic cell varieties) and could be subcultured to form further colonies. These observations suggested that cord blood would be an adequate and readily available source of engraftment material for transplantation, at least for small patients.^{5,6}

In 1988, the first cord blood transplant was performed in France on a child with Fanconi's anemia⁷ and the sec-

ond, in 1991, for chronic myelogenous leukemia.⁸ By the summer of 1996,⁹ about 250 cord blood transplants had been performed. In most cases, the recipients have been children, as there is concern that an umbilical cord collection may not have enough progenitor cells to transplant larger individuals (> 50 kg). This is currently under investigation.

Cord blood transplants appear to be associated with a reduced incidence of graft-versus-host disease.¹⁰ Should this initial observation be confirmed, cord cell transplants may prove to be preferable to those from other sources.

Posttransplantation speed of granulocyte and platelet recovery in the patient is important. Cord blood typically leads to a slower recovery than bone marrow or PBSC. Median neutrophil recovery of 22.5 days after transplant with cord blood is 3 to 5 days longer than that seen after marrow transplantation. Mean time to platelet recovery, however, is considerably longer than seen after PBSC transplantation (48 days average for cord blood transplants versus up to 20 days for PBSC) and is of major clinical importance.¹⁰ A possible method of shortening this recovery time has been proposed by John Wagner, MD, of the University of Minnesota.⁹ He proposes to split the cord cells into two freezing chambers in the storage bag, separate and thaw a portion of the cells, and then grow them in a bioreactor in media containing recombinant growth factors. This strategy should leave a number of the very primitive cells for long-term engraftment while amplifying some early cells into more mature progenitor cells ready to give a rapid recovery of hematopoietic elements.⁹

Another measure of cord blood as graft material is in the success and failure rate of engraftment. In one series, graft failure occurred in 5 out of 44 patients.¹⁰ Of these five patients, four had marrow failure syndromes and the fifth had mucopolysaccharidosis. These patients would have had a high risk of marrow failure with any transplant source.

A major advantage of cord blood as a transplant source is the possibility of collecting from all racial groups, thus improving the chances of matching HLA types. Since graft-versus-host disease might be less severe, donors with two

and possibly three antigen mismatches could be used. Greater diversity of donors and less stringent matching would greatly increase the likelihood of finding a donor.¹¹

Cord Blood Banking for a Community Bank

Setting up a cord blood banking system is a challenge faced by blood bank and transplant professionals worldwide. The tasks include:

- Designing safe and effective collection techniques
- Obtaining informed consent by the mother
- Selecting infectious disease tests for the mother and the cord blood
- Selecting HLA and genetic tests for the cord blood
- Adapting effective and economical processing and freezing methods
- Forming an alliance with a computerized tracking system for HLA-typed cord bloods

Collection Techniques

The window of time when cord blood is available for collection is short (within 15 minutes of delivery of the placenta). The simple method employed in the early collection experiments was to place the open, cut end of the umbilical cord into a sterile bowl and allow the contents to collect by gravity drainage. This resulted in good volumes of cord blood but presented predictable problems with bacterial and maternal blood contamination. A second technique involves collection of cord blood from the umbilical vein before delivery of the placenta. This method gives good volumes of cord blood as well. The disadvantage is that the environment may not be adequately controlled, and the obstetrical staff may have other pressing duties during the several minutes following the birth of the baby.¹²

The New York Blood Center developed the first public cord blood bank under a National Heart, Lung, and Blood Institute (NHLBI) grant. Cord blood is collected using trained blood center personnel in a nearby "clean room."¹¹ By agreement with the obstetrical service, the placenta is given to the blood center collection team immediately after delivery. The placenta is hung in a funnel-shaped device, the umbilical vein is scrubbed with antiseptic, and the cord blood is collected into a bag containing citrate-phosphate-dextrose (CPD) anticoagulant. This collection method yields a sterile collection > 99% of the time. The major disadvantage is a lower collection volume.

Most sources agree that cord blood units with fewer than 50 mL are of questionable value as a transplant source. Typical clean room collections average about 60

mL, while obstetrical collections before placental delivery average closer to 90 mL.^{12,13,14}

Informed Consent

The baby is the actual donor and cannot give consent. In the past, the placenta was considered medical waste. Now that the cord blood is considered to have value either to society or to the individual, consent needs to be obtained. The mother is considered to be the baby's guardian in the majority of the cases, and consent needs to be discussed with her. She must consent to an interview about infectious disease risks and possible inherited genetic defects. In the cases where the mother is under legal age, she is regarded as an emancipated minor and is responsible for making decisions for the child. The mother should be informed (1) about whether her child's cord blood will be placed in a bank set up for community use (allogeneic) or for her baby's own use (autologous), (2) how the records will be maintained, (3) what kinds of tests will be done on the cord blood, and (4) what samples will be saved for future tests. If the cells are to be stored in an allogeneic community bank, she needs to be informed about the likelihood that her own child may need the cord blood unit and whether it can be located for her child if required.¹⁵

The ethical issues raised by this process involve complex issues of privacy, volunteerism, and individual versus community rights and requirements.^{16,17}

Infectious Disease Tests

The infectious disease tests recommended for the mother are those used for blood donors. Questions arise as to which tests should be done on the infant or cord blood. Cytomegalovirus (CMV) testing should be done on the infant because the baby will carry the virus less than 1% of the time, even though the mother will carry antibodies in 25–75% of cases. This is an important infectious disease problem in the early posttransplant recovery period for CMV-negative transplant recipients. The New York Blood Center Cord Bank obtains a CMV culture from a saliva swab done on the infant. Testing the mother for CMV is not useful, as she may have antibody to CMV but may not transmit the infection to her infant if the infection was not active during her pregnancy.¹⁵

The tests to be done on the cord blood are more problematic. The majority of infectious disease tests identify antibody to the infective agent. Newborns carry antibody transferred across the placenta from their mothers and usually do not develop the capability of making their own

antibodies for weeks after birth. Tests currently under development, such as polymerase chain reaction assays for molecular components of infectious agents, may prove more useful for testing cord blood.

HLA and Genetic Tests

HLA testing will be necessary for all but designated autologous cord blood units. High resolution DNA-based HLA methods are quickly becoming standard for pre-transplantation testing. These procedures can add considerable cost to the processing of a cord blood unit. Serologic or intermediate resolution molecular methods may need to be employed initially, with a sample labeled and frozen for more extensive testing, if required, for specific matching with a recipient.

The most common genetic disease that renders a cord blood unsuitable for transplant is sickle cell anemia. A test for hemoglobin S is done before infants leave the hospital. The sample reserved for future HLA testing could also be used for genetic tests if the cells are considered for transplant. The informed consent process needs to include information about possible future genetic testing and about notification of any significant abnormal results.^{16,17,18}

Processing and Freezing

Processing cord blood units has been the subject of considerable research. Early reports stated that the red cells could not be separated from progenitor cells without a significant loss of the progenitor cells. Later work at Duke University and the University of Minnesota showed good buffy coat separation with retention of progenitor cell activity. The red cells are removed, thus reducing the volume to be frozen and minimizing the problem of return of hemolyzed red cells to the recipient.^{13,15}

A period of liquid storage of the cord blood before freezing and processing allows the units to be transported to the processing lab. It also allows time for informed consent to be obtained from the mother if that consent was not given prepartum. Cord cells have been shown to be well preserved at 1–6°C in CPD for 24 hours. Freezing has been accomplished with 10% dimethyl sulfoxide (DMSO) cryoprotectant and liquid nitrogen liquid or vapor phase storage. Progenitor cells from bone marrow and peripheral blood mononuclear cells have shown cryopreservation behavior similar to that of cord cells. Buffy coat separation methods for cord blood are more successful when specially adapted because of density differences of cord blood progenitor cells from those of bone marrow.^{4,10,13}

Computerized Tracking

A community allogeneic cord cell bank must be accessible to transplant candidates. A specially designed computer system is needed to positively identify and correlate this complex system of cord blood units, mother's signed consent forms, infectious disease results, and HLA type.^{15,19} A national system was developed for the NMDP to register and match donors to potential patients needing bone marrow transplantation. Another system may be developed for the centers to be awarded NHLBI grants for development of cord cell banks. The characteristics of the new system will be determined by a work group composed of NHLBI awardees.

Commercial Cord Blood Banking Activity

Cord cell banking is currently being promoted for autologous or familial use by a number of private, for-profit companies. The marketing focus of these companies has been high-income well-educated couples. The advertised price for this processing and frozen storage of cord blood cells is \$900–\$1,500.^{20,21} The claims made by some of these companies have attracted the attention of the public and of the Food and Drug Administration of the U.S. Department of Health and Human Services.

The promotional materials sent to the parents point out that cord blood storage is a once-in-a-lifetime opportunity, and if the storage is not done, the expected child's chance of being cured from a future cancer will be lost.^{20,21} Paul McCurdy, MD, of the NHLBI, the institute's expert in bone marrow transplantation treatment for malignancies, stated in the *Washington Post Magazine*²² that a child's own cord blood may not be the ideal transplant source since it does not provide the graft-versus-tumor effect. One of the major advantages of bone marrow transplantation in hematologic malignancies is the graft-versus-tumor effect. This beneficial effect is not seen in autologous transplants.

Materials sent to inquiring parents and professionals point out that failure to save a child's cord blood may be discarding the opportunity to treat future conditions such as AIDS, diabetes, and hypertension.²¹ Even more speculative are some promotions stating that stored cord blood is a transplant source for the future treatment of a parent's malignancy.²¹

To begin to evaluate these claims, the FDA (in December 1995) organized a conference of experts to share scientific information regarding cord blood transplantation. The FDA asked for public comment on their plan to regulate the field by requiring investigational new

drug applications from each agency collecting and processing umbilical cord blood.

Looking Ahead

Patients with genetic diseases, such as sickle cell anemia, may have an increased opportunity to find a suitable match for transplantation of cord cells that are available through a national cord cell bank program.²³ The proliferative potential of cord cells make them an excellent target for future genetic engineering treatment. Some initial experiments are under way with adenosine deaminase deficiency, in which cord blood progenitor cells have had normal genes inserted and the cells infused into the deficient individual with lasting engraftment.^{24,25} Cord blood progenitor cells may also be an excellent source for more ambitious cell culture programs, where the hematopoietic cell of choice can be grown with proper nutrition and growth factor stimulation.

In order to achieve these future goals, cord blood banks need to be designed to provide maximum benefit for the patient while protecting the donor and recipient from harm. Laboratory processes, computer systems, and donor management issues need to be designed or modified with this new blood component in mind.

If difficulties in storage, preservation, expansion, and marrow reconstitution can be overcome, cord cells may become the transplantation option of choice.

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The cons of cord blood banking are associated with the pricing. Cord blood banking is not cheap and includes a continuous payment process, starting from the collection rates to the annual payments. If you are a low-risk family, this may be an extra insurance that will not be needed. Public cord blood banks store cord blood for allogeneic transplants. They do not charge to store cord blood. The stem cells in the donated cord blood can be used by anyone who matches. Donating cord blood to a public bank adds to the supply and can potentially help others. Donating to a public bank is especially important for ethnic minorities, who are not well represented in cord blood banks. Public cord blood donation increases the chance of all groups finding a match. What are cord blood testing and cord blood banking? Cord blood is the blood left in the umbilical cord after a baby is born. The umbilical cord is the rope-like structure that connects a mother to her unborn baby during pregnancy. Some people want to bank (save and store) blood from their baby's umbilical cord for future use in treating diseases. The umbilical cord is full of special cells called stem cells. Unlike other cells, stem cells have the ability to grow into many different types of cells.