

Cord Blood Stem Cell Transplantation

No. 2 in a series providing the latest information on blood cancers

Highlights

- Umbilical cord blood, like bone marrow and peripheral blood, is a rich source of stem cells for transplantation. There may be advantages for certain patients to have cord blood stem cell transplants instead of transplants with marrow or peripheral blood stem cells (PBSCs).
- Stem cell transplants (peripheral blood, marrow or cord blood) may use the patient's own stem cells (called "autologous transplants") or use donor stem cells. Donor cells may come from either a related or unrelated matched donor (called an "allogeneic transplant"). Most transplant physicians would not want to use a baby's own cord blood ("autologous transplant") to treat his or her leukemia. This is because donor stem cells might better fight the leukemia than the child's own stem cells.
- Cord blood for transplantation is collected from the umbilical cord and placenta after a baby is delivered. Donated cord blood that meets requirements is frozen and stored at a cord blood bank for future use.
- The American Academy of Pediatrics's (AAP) policy statement (*Pediatrics*; 2007;119:165-170.) addresses public and private banking options available to parents. Among several recommendations, the report encourages parents to donate to public cord blood banks and discourages parents from using private cord blood banks for personal or family cord blood storage unless they have an older child with a condition that could benefit from transplantation.
- The Stem Cell Therapeutic and Research Act of 2005 put several programs in place, including creation of the National Cord Blood Inventory (NCBI) for patients in need of transplantation.
- Research studies of cord blood transplant outcomes, including transplants with two or more cord blood units, show promising results.

Stem Cell Transplantation

The transplantation of blood-forming stem cells is an accepted treatment to restore the body's ability to make blood and immune cells. Blood-forming or "hematopoietic" stem cells (HSCs) can develop into any of the three types of blood cells: red cells, white cells or platelets.

Cancer treatment with very high-dose chemotherapy or radiation therapy may result in severe injury to blood-forming cells in marrow, the spongy material inside the center of bones. Certain patients with leukemia, lymphoma, myeloma, myelodysplastic syndromes (MDS) or other blood cancers may benefit from high-dose chemotherapy or radiation therapy followed by stem cell transplantation. Patients with some other inherited or acquired marrow or immune system disorders may also benefit from stem cell transplantation.

Sources of Stem Cells for Transplantation

The cells used in transplants can come from three sources: marrow, peripheral blood and the blood in the umbilical cord after a baby's birth.

- To obtain cells from marrow, the physician removes marrow from a donor's hip bone in a surgical procedure using anesthesia, sterile needles and syringes. The donor's body replaces the donated bone marrow in four to six weeks.
- Currently, peripheral blood is the most common source of stem cells for transplant. Peripheral blood stem cells (PBSCs) are blood-forming stem cells released from the marrow into the bloodstream. Peripheral blood is also called "circulating blood." Normally, the marrow releases only a small number of these stem cells into the blood. To obtain enough stem cells from the peripheral blood for a transplant, a donor is given medication that encourages more blood-forming stem cells to move from the marrow to the blood. The cells are collected from the blood using a process called "apheresis." For apheresis, a needle is placed in the donor's vein, usually in the arm. The donor's blood passes through a machine that removes the stem cells and then returns the rest of the blood to the donor. The donor's body replaces the cells in two to three weeks.
- Cord blood stem cells are collected from the umbilical cord and placenta after a baby is born. Cord and placental blood contain large numbers of blood-forming stem cells. The donated cord blood is screened, frozen and stored at a cord blood bank for future use if it meets screening requirements. The stored cord blood collected from the umbilical cord and placenta after a baby is born is called a "cord blood unit."

Cord Blood Stem Cell Transplants

The first successful cord blood stem cell transplant was performed in 1988 in Paris, France. The patient was a boy with Fanconi anemia, a genetic and potentially life-threatening type of anemia. Cord blood stem cell transplants have now been given successfully to patients (mostly children) with some 70 diseases, including acute lymphocytic leukemia (also called "acute lymphoblastic leukemia," or ALL), acute myelogenous leukemia (AML), myelodysplastic syndromes (MDS), chronic myelogenous leukemia (CML), juvenile chronic myelogenous leukemia (JCML), chronic lymphocytic leukemia (CLL), Hodgkin and non-Hodgkin lymphoma, neuroblastoma, thalassemia, severe combined immune deficiency (SCID), Wiskott-Aldrich syndrome, metabolic diseases such as adrenoleukodystrophy and Hurler syndrome, and severe aplastic anemia. To date, more than 5,500 cord blood stem cell transplants from unrelated donors and several hundred from sibling donors have been performed worldwide.

Cord blood transplants can have complications similar to allogeneic stem cell transplants and should be done only at centers experienced in the transplantation of allogeneic sources of stem cells.

Potential Advantages for Patients

For certain patients, there may be advantages to using donor cord blood stem cells instead of donor peripheral blood or donor marrow stem cells. Some potential advantages are

- **Availability.** Cord blood stored in a public cord blood bank has been prescreened, tested and frozen and is ready to use; on the other hand, it can take several months to find and confirm a marrow or peripheral blood donor.
- **Human Leukocyte Antigen (HLA) Matching.** The outcomes of related and unrelated donor stem cell transplants are strongly affected by the degree of HLA matching between the transplant recipient and the donor cord blood. HLA matching plays an important role in successful engraftment, severity of graft-versus-host disease (GVHD) and overall survival. A close match between the patient and the cord blood unit can improve a patient's outcome after transplantation. However, even though a closely matched cord blood unit is preferred, clinical studies suggest that the match may not have to be as close as the match that is necessary for bone marrow or peripheral blood transplants.
- **Graft-Versus-Host Disease.** Studies have found that after a cord blood stem cell transplant, fewer patients got GVHD and, among those patients who did develop GVHD, the complication tended to be less severe than it was in patients who had bone marrow or peripheral blood transplants. GVHD is a serious and sometimes fatal complication of allogeneic stem cell transplantation. With GVHD, the donor's immune cells (the graft) attack the patient's healthy tissue (the host).
- **Diversity.** As a result of extending collection efforts to hospitals where births from diverse ethnic backgrounds are well represented, donated cord blood units have the potential to provide a source of stem cells that reflects racial diversity.
- **Infectious Disease Transmission.** Cord blood stem cell transplants carry less risk of transmission of blood-borne infectious diseases compared with stem cells from the peripheral blood or marrow of related or unrelated donors.

Potential Disadvantages for Patients

Some potential disadvantages are

- **Clinical Data.** Cord blood stem cell transplantation is almost two decades old, yet is a relatively new procedure in comparison to transplantation of peripheral blood or marrow stem cells. It is possible that genetic diseases may be present but not apparent at the time of birth and could be transplanted to a patient via donor cord blood stem cells. Procedures to track this possibility require follow-up until the donor infant is months or even years old. Such follow-up has proven difficult.

A partial solution used by many public cord blood banks is to obtain a detailed health history from potential donors in advance of cord blood collection, similar to standard procedures used to screen volunteer blood donors.

The health history questionnaire covers individual and family histories of disease and the expectant parents' ethnic background. If responses to the health history generate medical concern, the cord blood is not collected.

A future alternative approach may be genetic testing for diseases that affect the blood and immune system and for certain metabolic diseases that might be transplantable.

- **Storage.** It is not known how long cord blood can be frozen and stored before it loses its effectiveness. Cord blood samples have been preserved for as long as 10 years and have still been successfully transplanted.
- **Engraftment.** The number of cells required to give a transplant patient the best chance for engraftment and for surviving the transplant is based on his or her weight, age and disease status. A cord blood unit might contain too few stem cells for the recipient's size. Due to the smaller number of stem cells in the cord blood unit, cord blood stem cell transplants engraft more slowly than stem cells from marrow or peripheral blood. Until engraftment occurs, patients are at risk of developing life-threatening infections. Thus, cord blood transplant recipients may be vulnerable to infections for an average of up to one to two months longer than marrow and peripheral blood stem cell recipients. For more information on this topic, see the section *Research and Clinical Trials* on page 7.

Options for Cord Blood Donation and Collection

The umbilical cord is routinely discarded after a baby is delivered unless the parents choose to do otherwise. Expectant parents may choose to have the blood remaining in the umbilical cord and placenta collected after delivery. Parents are encouraged to talk with healthcare providers about the options that may be available. Healthy parents with healthy children and no transplant candidate in the family can choose to donate their newborn's cord blood to cord blood banks or research programs if their hospital participates in public cord blood banking or a university-based research program.

Parents with a child or family member who has a blood cancer, an immune deficiency or any of certain genetic diseases and who might be a candidate for transplantation should discuss with their physicians the potential benefits of saving their newborn's cord blood for possible family use. It is important to note that there is a 25 percent chance that any two siblings will be fully matched for their HLA tissue type. A baby's cord blood will automatically share 50 percent of its HLAs with each parent; however, it will occasionally be a better match for a parent if both parents, by chance, have some of the same HLAs. A baby's cord blood is less likely to be a good match for more distant relatives. Cord blood units from unrelated donors that are stored in public banks may be a better source of matches for parents and distant relatives, as well as for siblings who do not have matching HLAs.

Both private and public cord blood banks collect and store cord blood. Public cord blood banks collect and store cord blood that is donated for use by anyone who might need it in the future (unrelated allogeneic use). Private cord blood banks charge an annual fee to collect and store cord blood for a family's own private use (sometimes called a "directed donation"), in the event it is needed for an HLA-matched family member (related allogeneic use) at a later time. Collecting and storing cord blood for

directed donation is offered at little or no cost through many public and private cord blood banks. Umbilical cord blood can also be used for research studies by a laboratory or technology company. These studies help improve the transplantation process for future patients. This cord blood is not stored for transplantation, and the collection process for research is free. Parents need to talk to their healthcare providers to determine whether this option is available.

Points to keep in mind:

- Parents should talk with the doctor or midwife about the decision to donate umbilical cord blood about two months before the baby is due (before the 34th week of pregnancy).
- Not all hospitals collect cord blood for public banking; therefore, parents need to find out whether their hospital collects donations of cord blood for public banking.
- The Center for Cord Blood at the National Marrow Donor Program maintains a list of participating hospitals that collect cord blood units for their network of public cord blood banks. (See the current list at www.marrow.org/cord.)
- Public cord blood banks do not charge for collecting and storing donated cord blood. The public cord blood bank that works with the hospital will need to be contacted to ensure determination of eligibility. The mother is required to complete a thorough health history and to be screened, free of charge, for infectious agents such as the hepatitis viruses and HIV. The screening process may be initiated during pregnancy or before or immediately after the delivery, but it is completed in the hospital. If the mother is in good health and meets eligibility criteria, she will be asked to sign a consent-to-donate form. Each cord blood bank has different instructions for returning the consent form.
- A family choosing to store its baby's cord blood for private family use must make arrangements in advance with a private bank. Usually the family will sign a contract with the company, pay an initial fee, obtain the company's special cord blood collection kit and get their obstetrician's agreement to do the collection. Initial and annual storage fees vary and may be covered by health insurance.

American Academy of Pediatrics Policy Statement. The AAP encourages most parents to donate to public cord blood banks because cord blood stem cells can be used to treat a variety of serious conditions. The AAP guidelines can be viewed at <http://aappolicy.aappublications.org/cgi/content/full/pediatrics;119/1/165>.

The AAP discourages most parents from private cord blood banking unless they have an older child who could benefit from cord blood transplantation. Cord blood cannot be used autologously (for the donor infant) in children with genetic diseases, because the same disease would be returned with the transplant. Moreover, most transplant physicians do not recommend autologous cord blood transplants for children with leukemia. Most of these children will have cells with the leukemic changes (mutations) in their blood at birth. Moreover, a child who develops leukemia has evidence that his or her own immune system has already failed to prevent the leukemia. Thus, physicians fear that an autologous cord blood transplant would have little if any graft-versus-leukemia effect. "Graft-versus-leukemia effect" is the term used to describe the successful suppression of leukemic cells by donor immune cells.

The Collection and Storage Process. During delivery, the focus is on the mother and baby. After the baby is delivered,

- The umbilical cord is clamped. The blood from the umbilical cord and placenta is then collected either before or after the placenta is delivered, depending upon the procedure at the hospital.
- Blood is collected into a sterile bag; this bag of blood is the cord blood unit. The collected blood is given an identification number and stored temporarily.
- The cord blood unit is transported to a cord blood bank for testing, freezing and long-term storage.
- Testing procedures include HLA typing to determine the level of matching to potential recipients, cell counts and testing for infectious agents such as the AIDS virus, cytomegalovirus and hepatitis viruses.
- The cord blood unit is also checked to make sure it has enough blood-forming cells for a transplant. If there are too few cells, the cord blood unit may be used for research to improve the transplantation process for future patients or be discarded.
- Next, the blood is frozen and held at a very low temperature, usually in liquid nitrogen, for future use. When needed for a transplant, the cord blood unit can be shipped, often within a few days, to the transplant center where it is thawed and infused into the patient.
- To minimize the risk to mothers and newborn infants, normal childbirth procedures should not be altered in order to collect cord blood, particularly when collecting cord blood for unrelated recipients.

Federal Cord Blood Legislation to Help Patients. In 2005, an Institute of Medicine report, which was requested by the United States Congress, suggested that the Department of Health and Human Services (HHS) establish a National Cord Blood Policy Board to create rules for donation, collection and use of cord blood. The C.W. Bill Young Cell Transplantation Program was authorized in December 2005, when the Stem Cell Therapeutic and Research Act of 2005 was enacted into law by the federal government. This Act helped patients by creating the National Cord Blood Inventory (NCBI). In the autumn of 2006, the National Marrow Donor Program (NMDP) was awarded key contracts to carry out the work mandated in the C.W. Bill Young Program, including the contract to act as the nation's Cord Blood Coordinating Center. The NMDP Cord Blood Coordinating Center has a network of cord blood banks, including some banks that are receiving federal funding support to build the NCBI. The Cord Blood Coordinating Center works with its network of cord blood banks to recruit expectant parents for umbilical cord blood donations, with an emphasis on racial and ethnic diversity, and to distribute cord blood units on the program's registry. The registry is a listing of potential marrow donors and cord blood units. Doctors can search the NMDP registry to find a suitable match for their patients who need a transplant.

In January 2007 the Food and Drug Administration (FDA) issued a draft guidance recommending a streamlined path to licensure for organizations that collect, store and provide cord blood for certain medical conditions. The draft guidance describes the FDA's approach to the regulation of cord blood. However, the FDA has not yet issued final rules for licensure and federal supervision of cord blood banking. At present, some cord blood banks are accredited by NETCORD-FACT or the AABB (formerly

known as the American Association for Blood Banks). For more information about these accreditation organizations, please see the NETCORD, FACT and AABB Web sites listed under *Resources* on pages 8 and 9.

Research and Clinical Trials

Clinical trials of transplantation with two cord blood units (double cord blood transplant) have shown promising results with more rapid engraftment than that seen with single-unit transplants and improved survival. Phase II and phase III clinical trials are under way to continue studying this approach for pediatric and adult patients.

The Leukemia & Lymphoma Society is supporting cord blood stem cell transplantation research, including research to explore ways to increase the number of stem cells in each cord blood unit to enable adults and larger children to optimize their outcome following cord blood stem cell transplantation.

Resources

The Leukemia & Lymphoma Society

The Leukemia & Lymphoma Society is a national voluntary health agency with chapters throughout the United States and Canada. The Society provides education and support services for the public and for cancer treatment professionals.

Callers may speak directly with an Information Specialist, Monday-Friday, 9-6 PM ET, (800) 955-4572. To contact an Information Specialist, click on Live Help (10 AM-5 PM) on the Society's Web site or email us at infocenter@LLS.org. To find the Society chapter nearest you, contact

The Leukemia & Lymphoma Society
1311 Mamaroneck Avenue
White Plains, NY 10605
Information Resource Center
(800) 955-4572 or www.LLS.org

The Society provides free fact sheets and booklets that can be ordered via the 800 number or through Free Materials on the Web site, www.LLS.org. For more information about stem cell transplantation, see the Society's free booklet, *Blood and Marrow Stem Cell Transplantation*.

AABB

www.aabb.org

This international nonprofit organization, formerly known as the American Association of Blood Banks, works to advance transfusion medicine and related biological therapies by increasing public awareness, supporting high standards and promoting education and advocacy about these therapies.

The AABB maintains a list of private cord blood banks that are accredited by the organization. To access this list, visit

http://www.aabb.org/Content/Accreditation/Cord_Blood/AABB_Accredited_Cord_Blood_Facilities.

Center for International Blood and Marrow Transplant Research (CIBMTR)

www.ibmtr.org

CIBMTR combines the expertise and unique resources of two leaders in the field of blood and marrow transplantation: The National Marrow Donor Program and the Medical College of Wisconsin's International Bone Marrow Transplant Registry and Autologous Blood and Marrow Transplant Registry.

These organizations conduct and support clinical studies that involve large numbers of patients from multiple transplant centers. These studies will help improve outcomes for blood and marrow transplantation. The goal is to help more transplant patients live longer, healthier lives.

Foundation for the Accreditation of Cellular Therapy (FACT)

www.factwebsite.org

A nonprofit corporation that establishes standards for high-quality medical and laboratory practice in cellular therapies. In 2000, FACT partnered with NETCORD to develop international standards for cord blood collection, processing, testing, banking, selection and release.

National Marrow Donor Program (NMDP)

www.marrows.org

The NMDP helps people who need a life-saving marrow or cord blood transplant but do not have a matched donor in their family. From diagnosis through survivorship, support programs and resources for patients and their families are available through NMDP's Office of Patient Advocacy.

For information on marrow and cord blood donation, including a current list of U.S. participating hospitals that actively collect cord blood units for NMDP network cord blood banks, visit www.marrows.org or www.marrows.org/cord_Network/Cord_Blood_Banks/CB_Participating_Hospitals/nmdp_cord_blood_hospitals.

NETCORD

<https://www.netcord.org>

This international collection of cord blood banks works to set standards for cord blood banking and provide access to cord blood units to member banks. The group's Web site is a "virtual office" that allows members to search all of the cord blood units available through affiliated blood banks.

New York Blood Center National Cord Blood Program (NCBP)

(866) 767-6227

www.nationalcordbloodprogram.org

This public cord bank collects, processes, tests and stores cord blood that is donated to it for use by anyone who might need it. The NCBP supplies information for patients, their families and caregivers, healthcare professionals, expectant parents and the general public.

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