AMERICAN ACADEMY OF PEDIATRICS

Work Group on Cord Blood Banking

Cord Blood Banking for Potential Future Transplantation: Subject Review

ABSTRACT. In recent years, umbilical cord blood, which contains a large number of hematopoietic stem cells, has been used successfully for allogeneic transplantation to treat a variety of pediatric genetic, hematologic, and oncologic disorders. It is a potential alternative when autologous or allogeneic transplantation with HLA-matched marrow is unavailable for children. This advance has resulted in the establishment of not-for-profit and for-profit cord blood banking programs for autologous and allogeneic transplantation. Many issues confront institutions that wish to establish such a program. Parents also seek information from their physicians about this new modality. This document is intended to provide information to guide physicians in responding to parents' questions about cord blood banking. The document also makes recommendations about appropriate ethical and operational standards, including informed consent policies, for the institutions that operate a program.

In a number of genetic, hematologic, and oncologic disorders, reconstitution of bone marrow can be a potentially lifesaving procedure. Allogeneic (related or unrelated) or autologous (self) bone marrow is the usual source of hematopoietic progenitor cells to achieve this goal. If autologous marrow is not available, the best option for successful reconstitution therapy is to secure marrow from a sibling with an identical HLA match. Close matching is important to achieve successful engraftment and to minimize the risk of potentially fatal graft-vs-host disease. Unfortunately, there is only a 25% chance for an identical HLA match in a sibling.

An alternative involves seeking potential adult donors outside of the family. As of July 1997, data from a national registry of potential adult donors, the National Marrow Donor Program, showed that 76% of all preliminary donor searches identify at least one donor identically matched for HLA-A, HLA-B, and HLA-DR for the potential recipient.[1] For the recipients who decide to undergo marrow transplantation, the time from beginning the formal search process to transplantation is within 2 months for 5% of recipients, within 4 months for 50% of recipients, and within 16 months for 95% of the recipients. Although the number of patients who receive unrelated donor marrow transplants each year continues to increase (more than 1250 transplantations in 1997), additional sources of unrelated hematopoietic progenitor cells may serve to facilitate transplantation to additional needy recipients. Otherwise, some persons who could benefit from bone marrow transplantation may die while awaiting donors. Locating a match is even more difficult among ethnic or racial minorities.

Recently, it has been shown that umbilical cord blood contains a large number of hematopoietic stem cells.[2] Approximately 500 stem cell transplantations in a variety of pediatric genetic and hematologic disorders have been performed. The 1-year survival may be as high as 73% for HLA-matched siblings but only 29% for unrelated donors.[3] These encouraging results have generated considerable enthusiasm in the field. In contrast, there is almost no experience with autologous transplantation.

During the past several years, a number of programs have been established to collect, type, screen for infection, and cryogenically store cord blood for potential transplantation of unrelated recipients. Some of these programs are funded by the National Institutes of Health and based in not-for-profit organizations. A number of for-profit companies encourage parents to bank their children's cord blood for their own autologous use or for the allogeneic use of a family member should the need arise.

Families may be vulnerable to emotional marketing at the time of birth of a child and may look to their physicians for advice. No accurate estimates exist of the likelihood of children to need their own stored cells. The range of available estimates is from 1:1000 to 1:200 000.[4] Empirical evidence that children will need their own cord blood for future use is lacking. There also is no evidence of the safety or effectiveness of autologous cord blood transplantation for the treatment of malignant neoplasms (Table 1). For these reasons, it is difficult to recommend that parents store their children's cord blood for future use.

Most stem cell transplantation using umbilical cord blood has been performed on relatively small children. More cells are needed for marrow reconstitution in older children or young adults because of their larger size. Recent evidence suggests a relationship exists between the likelihood of successful engraftment and the number of nucleated cells infused.[2]

The importance of larger numbers of stem cells to the success of engraftment could encourage the attendance at delivery by a physician or other health care personnel to attempt to harvest more cord blood. It has been shown that the timing of umbilical cord clamping has an important effect on the neona-

The recommendations in this statement do not indicate an exclusive course of treatment or serve as a standard of medical care. Variations, taking into account individual circumstances, may be appropriate.

TABLE 1. Indications for Allogeneic and Autologous Stem Cell Support*

Disease	Allogeneic Transplantation	Autologous Transplantation
Leukemia (acute lymphoblastic, acute myelogenous, chronic myelogenous)	Effective	Controversial; no better than conventional therapy
Lymphomas (Hodgkin disease, non-Hodgkin lymphoma)	Effective	Used rarely and only when marrow not involved
Neuroblastoma (stage IV)	Controversial; studies ongoing to define role related to conventional therapy and autologous transplantation	Controversial; studies ongoing to define role related to conventional therapy and allogeneic transplantation
Bone and soft tissue sarcomas, Wilms tumor, brain tumors	Very rarely indicated	Rarely indicated and effectiveness unproven
Aplastic anemia and other cytopenias (not environmentally caused)	Effective	Not indicated
Immune deficiency (eg, severe combined immunodeficiency disease)	Effective	Not indicated
Hemoglobinopathies, thalassemia, sickle cell anemia	Effective	Not indicated
Metabolic storage disorders, Hurler syndrome, metachromatic leukodystrophy	Controversial; may be effective in selected patients	Not indicated

* See reference 3 in this article.

tal blood volume and the subsequent hematologic status. If cord clamping is done too soon after birth, the infant may be deprived of a placental blood transfusion, resulting in lower blood volume and increased risk for anemia in later life.[5] Immediate cord clamping will, of course, increase the volume of placental blood for harvesting for cord blood banking. There may be a temptation to practice immediate cord clamping aggressively to increase the volume of cord blood that can be harvested for cord blood banking. This practice is unethical and should be discouraged.

Although cord blood is currently considered discarded human material, it should not be collected for potential transplantation without the written informed permission of the parents.[6] Although there is agreement on the importance of short-term linkage, ie, communicating pertinent donor information to the cord blood bank, to our knowledge there is no consensus on the maintenance of long-term linkage. The purpose of long-term linkage is to allow donors to notify the cord blood bank if a genetic disease or hematologic malignant neoplasm develops. This notification is important so that the stored cord blood can be discarded, or if transplantation has already occurred, the recipient can be notified. However, without legislation guaranteeing the confidentiality of the records, concern exists that abuse may occur that exposes the donor to invasion of privacy. A recipient may want more information or more cells if engraftment was incomplete. All cells collected for blood banking will need to be tested for infectious diseases and for hereditary hematologic diseases before storage. Part of the informed consent process must address the issue of what is being tested and how the parents will be informed if test results are abnormal. Because of these unresolved issues, parental permission should be obtained before collection of the samples. Furthermore, because the peripartum period is emotionally stressful, the consent should ideally be obtained during a prenatal visit, and before the onset of labor.

RECOMMENDATIONS

When consulted by prospective parents who are interested in donating cord blood to a philanthropic bank or paying to have cord blood stored in a for-profit bank, the physician can provide the following information:

1. Although preliminary data show encouraging results in cord blood stem cell transplantation for a variety of genetic, hematologic, and oncologic diseases, the procedure at this time is considered investigational.
2. The indications for autologous transplantation are limited, and the potential for future expansion is unlikely.
3. Given the difficulty of making an accurate estimate of the need for autologous transplantation and the ready availability of allogeneic transplantation, private storage of cord blood as "biological insurance" is unwise. However, banking should be considered if there is a family member with a current or potential need to undergo a stem cell transplantation.
4. Conditions such as leukemia or severe hemoglobinopathy may indicate the need for directed-donor cord blood banking for sibling cord blood transplantation.
5. Philanthropic donation of cord blood for banking at no cost for allogeneic transplantation is encouraged. In such instances, the parents should be informed of the appropriate operational principles recommended for the bank listed herein.

Institutions or organizations (private or public) involved in cord blood banking should consider the following recommendations:

1. Recruitment practices should be developed with an awareness of the possible emotional vulnerability of pregnant women and their families and friends. Efforts should be made to minimize the effect of this vulnerability on recruitment decisions.
2. Accurate information about the potential benefits and limitations of allogeneic and autologous cord

blood banking and transplantation should be provided.
3. A policy should be developed regarding disclosing to the parents any abnormal findings in the harvested blood.
4. Specific permission for maintaining demographic medical information should be obtained, and the potential risks of breaches of confidentiality disclosed.
5. Written permission should be obtained during prenatal care, and before the onset of labor. The practice of collecting cord blood first and obtaining permission afterward is considered unethical and should be discouraged.
6. Consultation with the institutional review board or hospital ethics committee about recruitment strategies and the wording of consent forms is recommended.
7. Cord blood collection should not be done in complicated deliveries, and the cord blood stem cell collection program should not alter routine practice for the timing of umbilical cord clamping.
8. Because of the investigational status of cord blood banking and the high risk for its potential abuse, the regulatory agencies (eg, US Food and Drug Administration, Federal Trade Commission, state equivalent of these federal agencies) are encouraged to have an active role in providing oversight for the safety and welfare of the population.

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REFERENCES

1. Cairo MS, Wagner JE. Placental and/or umbilical cord blood: an alternative source of hematopoietic stem cells for transplantation. *Blood*. 1997;90:4665–4678
2. Kurtzberg J, Laughlin M, Graham ML, et al. Placental blood as a source of hematopoietic stem cells for transplantation into unrelated recipients. *N Engl J Med*. 1996;335:157–166
3. Gluckman E, Rocha V, Boyer-Chammard A, et al. Outcome of cord-blood transplantation from related and unrelated donors. *N Engl J Med*. 1997;337:373–381
4. Johnson FL. Placental blood transplantation and autologous banking: caveat emptor. *J Pediatr Hematol Oncol*. 1997;19:183–186
5. Yao AC, Lind J. *Placental Transfusion: A Clinical and Physiological Study*. Springfield, IL: Charles C. Thomas; 1982
6. Sugarman J, Kaalund V, Kodish E, et al. Ethical issues in umbilical cord blood banking. *JAMA*. 1997;278:938–943

ERRATUM

In the practice guideline entitled, "Practice Parameter: The Diagnosis, Treatment, and Evaluation of the Initial Urinary Tract Infection in Febrile Infants and Young Children" (1999;103:843–852), incorrect information was provided Table 2. Criteria for the Diagnosis of Urinary Tract Infection[53]. Table 2 should read:

TABLE 2. Criteria for the Diagnosis of Urinary Tract Infection[53]

Method of Collection	Colony Count (Pure Culture)	Probability of Infection (%)
Suprapubic aspiration	Gram-negative bacilli: any number Gram-positive cocci: more than a few thousand	>99%
	$>10^5$	95%
Transurethral catheterization	$10^4 - 10^5$	Infection likely
	$10^3 - 10^4$	Suspicious; repeat
	$<10^3$	Infection likely
Clean void		
Boy	$>10^4$	Infection likely
Girl	3 specimens $\geq 10^5$	95%
	2 specimens $\geq 10^5$	90%
	1 specimen $\geq 10^5$	80%
	$5 \times 10^4 - 10^5$	Suspicious; repeat
	$10^4 - 5 \times 10^4$	Symptomatic: suspicious; repeat Asymptomatic: infection unlikely
	$<10^4$	Infection unlikely

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