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Medical Policy Manual Transplant, Policy No. 45.16

Placental and Umbilical Cord Blood as a Source of Stem Cells

Effective: April 1, 2022

Next Review: January 2023
Last Review: February 2022

IMPORTANT REMINDER

Medical Policies are developed to provide guidance for members and providers regarding coverage in accordance with contract terms. Benefit determinations are based in all cases on the applicable contract language. To the extent there may be any conflict between the Medical Policy and contract language, the contract language takes precedence.

PLEASE NOTE: Contracts exclude from coverage, among other things, services or procedures that are considered investigational or cosmetic. Providers may bill members for services or procedures that are considered investigational or cosmetic. Providers are encouraged to inform members before rendering such services that the members are likely to be financially responsible for the cost of these services.

DESCRIPTION

This policy addresses the collection, storage, and transplantation of placental/umbilical cord blood ("cord blood") as a source of stem cells for allogeneic and autologous stem cell transplantation.

MEDICAL POLICY CRITERIA

Note: See Cross References to access the specific medical policies for hematopoietic stem cell transplantation.

I. Transplantation of cord blood stem cells

A. Transplantation of cord blood stem cells from related or unrelated donors is considered **medically necessary** in patients who meet the health plan's medical necessity criteria for allogeneic stem-cell transplant but who are without a hematopoietic stem-cell donor.

B. Transplantation of cord blood stem cells from related or unrelated donors is considered **investigational** in all other situations.

II. Collection and storage of cord blood stem cells

A. Collection and storage of cord blood from a neonate is considered **medically necessary** when an allogeneic transplant is imminent in an identified recipient and the health plan's medical necessity criteria for the transplant are met.

B. *Prophylactic* collection and storage of cord blood from a neonate is considered **not medically necessary** when proposed for an unspecified future use as an autologous stem-cell transplant in the original donor, or for an unspecified future use as an allogeneic stem-cell transplant in a related or unrelated recipient.

NOTE: A summary of the supporting rationale for the policy criteria is at the end of the policy.

LIST OF INFORMATION NEEDED FOR REVIEW

It is critical that the list of information below is submitted for review to determine if the policy criteria are met. If any of these items are not submitted, it could impact our review and decision outcome.

- History and physical/chart Notes
- Diagnosis and indication for transplant

CROSS REFERENCES

1. Medical Policy Manual: Transplant Section Table of Contents
2. Hematopoietic Cell Transplantation for Multiple Myeloma, Transplant, Policy No. 45.22
3. Hematopoietic Cell Transplantation for Non-Hodgkin Lymphomas, Transplant, Policy No. 45.23
4. Allogeneic Cell Transplantation for Myelodysplastic Syndromes and Myeloproliferative Neoplasms, Transplant, Policy No. 45.24
5. Allogeneic Hematopoietic Cell Transplantation for Genetic Diseases and Acquired Anemias, Transplant, Policy No. 45.25
6. Hematopoietic Cell Transplantation for Epithelial Ovarian Cancer, Transplant, Policy No. 45.26
7. Hematopoietic Cell Transplantation for Miscellaneous Solid Tumors in Adults, Transplant, Policy No. 45.27
8. Hematopoietic Cell Transplantation for Acute Myeloid Leukemia, Transplant, Policy No. 45.28
9. Hematopoietic Cell Transplantation for Breast Cancer, Transplant, Policy No. 45.29
10. Hematopoietic Cell Transplantation for Hodgkin Lymphoma, Transplant, Policy No. 45.30
11. Hematopoietic Cell Transplantation for Chronic Myelogenous Leukemia, Transplant, Policy No. 45.31
12. Hematopoietic Cell Transplantation for Autoimmune Diseases, Transplant, Policy No. 45.32
13. Hematopoietic Cell Transplantation for CNS Embryonal Tumors and Ependymoma, Transplant, Policy No. 45.33
14. Autologous Hematopoietic Cell Transplantation for Malignant Astrocytomas and Gliomas, Transplant, Policy No. 45.34
15. Hematopoietic Cell Transplantation for Chronic Lymphocytic Leukemia and Small Lymphocytic Lymphoma, Transplant, Policy No. 45.35
16. Hematopoietic Cell Transplantation for Acute Lymphoblastic Leukemia, Transplant, Policy No. 45.36
17. Hematopoietic Cell Transplantation for Solid Tumors of Childhood, Transplant, Policy No. 45.37
18. Hematopoietic Cell Transplantation in the Treatment of Germ-Cell Tumors, Transplant, Policy No. 45.38
19. Hematopoietic Cell Transplantation for Primary Amyloidosis or Waldenstrom Macroglobulinemia, Transplant, Policy No. 45.40

BACKGROUND

Blood harvested from the umbilical cord and placenta shortly after delivery of neonates contains stem and progenitor cells capable of restoring hematopoietic function after myeloablation. This "cord" blood has been used as an alternative source of allogeneic stem cells. Cord blood is readily available and is thought to be antigenically "naive," thus minimizing

the incidence of graft-versus-host disease (GVHD) and permitting the broader use of unrelated cord blood transplants. Unrelated donors are typically typed at low resolution for human leukocyte antigens (HLA) -A and -B and at high resolution only for HLA-DR; HLA matching at four of six loci is considered acceptable. Under this matching protocol, an acceptable donor can be identified for almost any patient.[1] Several cord blood banks have now been developed in Europe and in the United States.

Potential indications for use of cord blood are included in the disease-specific reference policies. A variety of malignant diseases and non-malignant bone marrow disorders are treated with myeloablative therapy followed by infusion of allogeneic stem and progenitor cells collected from immunologically compatible donors. Stem cells may be obtained from the transplant recipient (autologous) or from a donor (allogeneic). For those with bone marrow disorders, stem cells are sought from family members or an unrelated donor identified through a bone marrow donor bank. In some cases, a suitable donor is not found.

HEMATOPOIETIC CELL TRANSPLANTATION

Hematopoietic cell transplantation (HCT) is a procedure in which hematopoietic stem cells are intravenously infused to restore bone marrow and immune function in cancer patients who receive bone marrow-toxic doses of cytotoxic drugs with or without whole-body radiotherapy. Hematopoietic stem cells may be obtained from the transplant recipient (autologous HCT) or a donor (allogeneic HCT [allo-HCT]). These cells can be harvested from bone marrow, peripheral blood, or umbilical cord blood shortly after delivery of neonates.

Immunologic compatibility between infused hematopoietic stem cells and the recipient is not an issue in autologous HCT. In allogeneic stem cell transplantation, immunologic compatibility between donor and patient is a critical factor for achieving a successful outcome. Compatibility is established by typing of human leukocyte antigens (HLA) using cellular, serologic, or molecular techniques. HLA refers to the gene complex expressed at the HLA-A, -B, and -DR (antigen-D related) loci on each arm of chromosome 6. An acceptable donor will match the patient at all or most of the HLA loci.

Conditioning for Hematopoietic Cell Transplantation

Conventional Conditioning

The conventional (“classical”) practice of allo-HCT involves administration of cytotoxic agents (e.g., cyclophosphamide, busulfan) with or without total body irradiation at doses sufficient to cause bone marrow ablation in the recipient. The beneficial treatment effect of this procedure is due to a combination of the initial eradication of malignant cells and subsequent graft-versus-malignancy effect mediated by non-self-immunologic effector cells. While the slower graft-versus-malignancy effect is considered the potentially curative component, it may be overwhelmed by existing disease in the absence of pretransplant conditioning. Intense conditioning regimens are limited to patients who are sufficiently medically fit to tolerate substantial adverse effects. These include opportunistic infections secondary to loss of endogenous bone marrow function and organ damage or failure caused by cytotoxic drugs. Subsequent to graft infusion in allo-HCT, immunosuppressant drugs are required to minimize graft rejection and graft-versus-host disease, which increases susceptibility to opportunistic infections.

The success of autologous HCT is predicated on the potential of cytotoxic chemotherapy, with or without radiotherapy, to eradicate cancerous cells from the blood and bone marrow. This permits subsequent engraftment and repopulation of the bone marrow with presumably normal hematopoietic stem cells obtained from the patient before undergoing bone marrow ablation. Therefore, autologous HCT is typically performed as consolidation therapy when the patient's disease is in complete remission. Patients who undergo autologous HCT are also susceptible to chemotherapy-related toxicities and opportunistic infections before engraftment, but not graft-versus-host disease.

Reduced-Intensity Conditioning Allogeneic Hematopoietic Cell Transplantation

Reduced-intensity conditioning (RIC) refers to the pretransplant use of lower doses of cytotoxic drugs or less intense regimens of radiotherapy than are used in traditional full-dose myeloablative conditioning treatments. Although the definition of RIC is variable, with numerous versions employed, all regimens seek to balance the competing effects of relapse due to residual disease and non-relapse mortality. The goal of RIC is to reduce disease burden and to minimize associated treatment-related morbidity and non-relapse mortality in the period during which the beneficial graft-versus-malignancy effect of allogeneic transplantation develops. RIC regimens range from nearly total myeloablative to minimally myeloablative with lymphoablation, with intensity tailored to specific diseases and patient condition. Patients who undergo RIC with allo-HCT initially demonstrate donor cell engraftment and bone marrow mixed chimerism. Most will subsequently convert to full-donor chimerism. In this review, the term reduced-intensity conditioning will refer to all conditioning regimens intended to be nonmyeloablative.

Cord Blood as Source of Stem Cells for Stem Cell Transplant

A variety of malignant diseases and nonmalignant bone marrow disorders are treated with myeloablative therapy followed by infusion of the allogeneic stem and progenitor cells collected from immunologically compatible donors, either family members or an unrelated donor identified through a bone marrow donor bank. In some cases, a suitable donor is not found.

Blood harvested from the umbilical cord and placenta shortly after delivery of neonates contains stem and progenitor cells capable of restoring hematopoietic function after myeloablation. This cord blood has been used as an alternative source of allogeneic stem cells. Cord blood is readily available and is thought to be antigenically "naive," thus potentially minimizing the incidence of graft-versus-host disease (GVHD) and permitting the broader use of unrelated cord blood transplants. Unrelated donors are typically typed at low resolution for human leukocyte antigen (HLA)-A and -B and at high resolution only for HLA-DR; HLA matching at 4 of 6 loci is considered acceptable. Under this matching protocol, an acceptable donor can be identified for almost any patient.

REGULATORY STATUS

According to the U.S. Food and Drug Administration (FDA), cord blood stored for potential use by a patient unrelated to the donor meets the definitions of "drug" and "biological products." As such, products must be licensed under a biologics license application or an investigational new drug application before use. Facilities that prepare cord blood units only for autologous and/or first- or second-degree relatives are required to register and list their products, adhere to Good Tissue Practices issued by the FDA, and use applicable processes for donor suitability determination.[2, 3]

Other cord blood banks are offering the opportunity of collecting and storing a neonate's cord blood for some unspecified future use in the unlikely event that the child develops a condition that would require autologous transplantation. In addition, some cord blood is collected and stored from a neonate for use by a sibling in whom an allogeneic transplant is anticipated due to a history of leukemia or other condition requiring allogeneic transplant.

As with any biologic product there are issues unique to cord blood as an unrelated donor source, some of which include:

- The cell dose available is much closer to the minimum needed for engraftment;
- There is interbank variability in the quantification of hematopoietic potential;
- Donors who may have hematologic/immunologic disorders may not have manifest their disease at the time of donation or follow-up;
- Units may have been banked years earlier at a time when the collection and storage process may not reflect current accreditation standards; and
- The initial product characterization at the end of processing may not reflect the product at the time of release due to freeze, storage, or transport insults.[4]

For the reasons cited above instituting international standards and accreditation for cord blood banks is critical. This will assist transplant programs in knowing whether individual banks have important quality control measures in place to address such issues as monitoring cell loss, change in potency, and prevention of product mix-up.[4]

Two major organizations are working towards these accreditation standards: NetCord/FACT and the American Association of Blood Banks (AABB). NetCord, Foundation for the Accreditation of Cellular Therapy (FACT) has developed and implemented a program of voluntary inspection and accreditation for cord blood banking.[5] The program includes standards for collection, testing, processing, storage and release of cord blood products. AABB also runs an accreditation process, where an AABB representative inspects the program.[6]

EVIDENCE SUMMARY

RELATED CORD BLOOD TRANSPLANT

The first cord blood transplant was a related cord blood transplant for a child with Fanconi's anemia.[7] After the success of this initial transplant, approximately 60 others were performed in the matched-sibling setting. The results, demonstrating that cord blood contained sufficient numbers of hematopoietic stem and progenitor cells to reconstitute a pediatric patient, were reported to a volunteer international registry. When used as the source of donor cells, lower incidence of acute and chronic GVHD was observed with cord blood compared with bone marrow.[8] This led to the hypothesis that cord blood could be banked and used as a source of unrelated donor cells, possibly without full HLA matching.[9]

UNRELATED OR HAPLOIDENTICAL CORD BLOOD TRANSPLANT

Systematic Reviews

Shen (2021) published the results of a systematic review with meta-analysis of data from clinical trials on mesenchymal stem cells (MSCs) in the treatment of heart failure (HF).[10] Data from twelve studies involving 823 HF patients who underwent MSC or placebo treatment were included. The primary outcome was safely assessed by death and rehospitalization and the

secondary outcome was efficacy, which was assessed by six-minute walk distance and Left Ventricular Ejection Fraction (LVEF), Left Ventricular End-systolic Volume (LVESV), Left Ventricular End-diastolic Volume (LVEDV) and Brain Natriuretic Peptide (BNP). No statistically significant difference in rate of death was found between groups (p=0.12), however, rehospitalization was reduced by 47% (RR [CI]=0.53[0.38, 0.75], p<0.001). In addition, significant improvements in secondary outcome measures were observed in the MSC group over the placebo group.

A meta-analysis published by Kassem (2020) evaluated the therapeutic efficacy of umbilical cord-derived stem cell (UCSC) transplantation in the treatment of diabetes mellitus (DM).[11] Eleven eligible clinical studies were included, six of which were on UCSC (N=172 including 71 controls). Only five of these studies provided pre- and post-intervention data, so the analysis only included these five studies (two T1DM studies: N=36, and three T2DM studies: N=59) Primary outcomes were glycemic control (HbA1c%) and β cell function (C-peptide levels), as well as daily insulin requirement after receiving UCSC transplantation compared to baseline. UCSC transplant significantly improved HbA1c% (pooled-estimate - 1.085; 95%CI (- 1.513, - 0.657); p < 0.001) and C-peptide levels (pooled-estimate 1.008; 95%CI (0.475, 1.541); p < 0.001), as well as the daily insulin-requirement (pooled-estimate - 2.027; 95%CI (- 3.32, - 0.733); p = 0.002). The number of included studies was limited and in most cases with small sample sizes. The authors concluded that there is a crucial need for additional well-designed RCTs with larger cohorts to address knowledge gaps in optimum transplantation regimen, route of administration, injected cell number, preference of autologous or allogenic UCSC therapy, and putative synergistic co-interventions.

Li (2020) performed a meta-analysis of seven studies in adult and pediatric patients with hematological malignancies (N=2,422) undergoing umbilical cord blood transplantation or haploidentical transplantation.[12] The results revealed a similar incidence of chronic GVHD and disease-free survival at two years between the two types of transplant in children. In adults, grade II to IV acute GVHD occurred at a higher rate with umbilical cord blood transplantation versus haploidentical transplantation (relative risk [RR], 1.17; 95% CI, 1.02 to 1.34; p=0.02). Rates of grade III to IV acute GVHD, chronic GVHD, relapse, non-relapse mortality, and disease-free survival at two years were similar between the two transplant types in adults.

Wu (2020) performed a meta-analysis of 12 studies (N=2,793) comparing haploidentical HCT versus umbilical cord blood transplantation for hematologic malignancies.[13] Compared with umbilical cord blood transplantation, HCT improved OS (OR, 0.74; 95% CI, 0.68 to 0.80), progression-free survival (OR, 0.77; 95% CI, 0.72 to 0.83), non-relapse mortality (OR, 0.72, 95% CI, 0.64 to 0.80), and acute GVHD (OR, 0.87; 95% CI, 0.77 to 0.98) but also increased the risk for chronic GVHD (OR, 1.40; 95% CI, 1.22 to 1.62).

Poonsombudlert (2019) performed a meta-analysis of seven studies (N=3,434) comparing haploidentical transplant utilizing post-transplant cyclophosphamide versus umbilical cord transplant in patients without a matched relative.[14] Compared with umbilical cord transplant, haploidentical transplant utilizing cyclophosphamide was associated with a decreased risk of acute GVHD (odds ratio [OR], 0.78; 95% CI, 0.67 to 0.92) and relapse (OR, 0.74; 95% CI, 0.57 to 0.97) and an improved rate of chronic GVHD (OR, 1.41; 95% CI, 1.02 to 1.95) and OS (OR, 1.77; 95% CI, 1.1 to 2.87).

A meta-analysis by Lou (2017) compared unrelated hematopoietic stem cell transplants to umbilical cord blood transplants in pediatric and adult patients with acute lymphoblastic

leukemia (ALL) or acute myeloid leukemia (AML).[15] Nine studies were included, with a total of 6,762 patients (n=4,736 for hematopoietic stem cell transplant, n=2,026 for umbilical cord blood transplant). No differences were found between the groups for risk of relapse or overall survival, but neutrophil and platelet recovery periods were shorter for those that had hematopoietic stem cell transplants.

Zhang (2012) published a systematic review and meta-analysis of studies comparing unrelated donor cord blood transplantation to unrelated donor bone marrow transplantation in patients with acute leukemia.[16] The authors identified seven studies with a total of 3,389 patients. Pooled rates of engraftment failure (n=5 studies) were 127 events in 694 patients (18%) in the cord blood transplantation group and 57 events in 951 patients (6%) in bone marrow transplantation patients. The rate of engraftment graft failure was significantly higher in cord blood transplantation recipients ($p<0.0001$). However, rates of acute GVHD were significantly lower in the group receiving cord blood transplantation. Pooled rates of GVHD (n=7 studies) were 397 of 1,179 (34%) in the cord blood group and 953 of 2,189 (44%) in the bone marrow group, $p<0.0001$. Relapse rates, reported in all studies, did not differ significantly between groups. Several survival outcomes including overall survival, leukemia-free survival and non-relapse mortality favored the bone marrow transplantation group.

Nonrandomized Studies

Fuchs et al (2020) reported on outcomes of two parallel phase 2 trials comparing unrelated umbilical cord blood transplantation versus haploidentical bone marrow transplantation in 368 patients aged 18 to 70 years old.[17] The two-year progression-free survival (the primary endpoint) was 35% (95% confidence interval [CI], 28% to 42%) after cord blood transplants and 41% (95% CI, 34% to 48%) after haploidentical bone marrow transplants ($p=0.41$). The two-year non-relapse mortality was 18% (95% CI, 13% to 24%) with cord blood transplant versus 11% (95% CI, 6% to 16%) with haploidentical transplants ($p=0.04$), resulting in a two-year OS of 46% (95% CI, 38% to 53%) with cord blood transplant versus 57% (95% CI, 49% to 64%) with haploidentical bone marrow transplants ($p=0.04$).

Yan (2020) published the results of a single-arm study evaluating treatment of premature ovarian insufficiency (POI) using umbilical cord-derived mesenchymal stem cells (UCMSCs).[18] The number of mature oocytes per month after the stem cell therapy was the primary outcome. Sixty-one patients diagnosed with POI. UCMSCs were isolated and cultured using a standard protocol and then transplanted to the patients' ovary by orthotopic injection under the guidance of vaginal ultrasound. No serious side effects or complications relevant to the treatment were reported. While a trend of increased follicular development and improved egg collection was reported, quantification of this trend or comparison to a control was not provided. Six-month follow-up data was severely limited by participant attrition.

A registry study by Robin (2019) compared outcomes of patients with myelodysplastic syndrome who received transplants from a haploidentical donor, an HLA-mismatched unrelated donor, or unrelated cord blood donor.[19] Included in the study were 833 patients from the European Group for Blood and Marrow Transplantation (EBMT) registry who received transplants between 2011 and 2016. Both haplo-transplantation and cord blood transplantation had a similar risk of GVHD, which was lower than the risk with unrelated donor transplants. Progression-free survival was greatest in patients with haplo-transplantation, and this group also had better overall survival than patients who had cord blood transplants ($p=0.002$), but not unrelated donor transplants.

Another registry-based study, by Ruggeri (2017), reported outcomes after cord blood transplant for infant acute leukemia.[20] The study included 252 children diagnosed with acute leukemia before one year of age and the median follow-up was 42 months. In this group, the cumulative incidence function (CIF) of acute GVHD within 100 days was 40% (±3%) and the CIF of one-year transplant-related mortality was 23% (±3%). After four years, leukemia-free survival was 50% (±3%), and survival was higher in those with acute myelogenous leukemia compared to those with acute lymphoblastic leukemia (66% vs. 40%), and higher in those who received transplants in the first complete remission.

Mo (2016) reported on outcomes after umbilical cord blood and haploidentical hematopoietic cell transplantation (haplo-HCT) in 129 children less than 14 years old with high risk acute lymphoblastic leukemia.[21] The two-year probability of overall survival (OS) was 82% (95% confidence interval [CI] 72.2% to 91.8%) in the haplo-HCT group and 69.9% (95% CI 58.0% to 81.2%) in the cord blood group. The difference in OS between groups did not differ significantly (p=0.07). The two-year incidence of relapse was also similar in the two groups: 16% (95% CI 6.1% to 26.1%) in the haplo-HCT group and 24.1% (95% CI 12.5% to 37.5%) in the cord blood group (p=0.17).

Sakaguchi (2016) compared outcomes after cord blood transplantation with those after unrelated bone marrow transplantation and HLA-identical related bone marrow transplantation.[22] The study included 577 children from a Japanese registry, and the median follow-up was 40 months. The three-year overall survival rates were 75.0% for cord blood transplantation, 74.8% for related bone marrow transplantation, and 69.0% for unrelated bone marrow transplantation. Overall survival and leukemia-free survival were not significantly different after adjustment for risk factors.

A study by Liu (2014) compared outcomes after unrelated donor cord blood transplantation to those after matched-sibling donor peripheral blood transplantation.[23] The study included patients age 16 years or older who had hematologic malignancies. A total of 70 patients received unrelated cord blood and 115 patients received HLA-identical peripheral blood stem cells, alone or in combination with bone marrow. Primary engraftment rates were similar in the two groups, 97% in the cord blood group and 100% in the peripheral blood stem-cell group. Most outcomes were similar between both groups, including grades III to IV acute GVHD and three-year disease-free survival rates. However, the rate of chronic GVHD was lower in the unrelated-donor cord blood group. Specifically, limited or extensive chronic GVHD occurred in 12 of 58 (21%) evaluable patients in the cord blood group and 46 of 109 (42%) evaluable patients in the peripheral blood stem cell group (p=0.005).

Several studies have examined specific risk factors and outcomes related to cord blood transplantation. A report by Balaguer Rosello (2017) indicated that the incidence of central nervous system infections was significantly higher with cord blood transplantation compared with HLA-matched sibling donor stem cell transplantation.[24] A study by Crombie (2017) found that the readmission rate within 30 days after cord blood transplant discharge was 33.3%, and this rate rose to 46.3% for readmission within 100 days.[25] Infection was the most common reason for readmission (38.3%), followed by fever without a source (14.8%) and GVHD (8.6%). According to a study by Zhu (2017), The European Group for Blood and Marrow Transplantation (EBMT) risk score may be useful for predicting prognosis after single umbilical cord blood transplantation for acute leukemia.[26]

In addition to these studies, there have been other retrospective and registry studies.[27-31] These have generally found that unrelated cord blood transplantation is effective in both children and adults with hematologic malignancies and children with a variety of nonmalignant conditions. Moreover, these studies have identified the importance of a minimum cell dose. For example, Park (2014) published results from an analysis of data from the Korean Cord Blood Registry demonstrating that the presence of at least 3.91 X 105/kg of infused CD34+ cells was significantly associated with overall survival (p=0.03) in unrelated donor cord blood transplants in children and adolescents.[28]

Martin (2006) published results from the first prospective trial of unrelated cord blood transplant was the Cord Blood Transplantation study (COBLT) from 1997 to 2004. COBLT was designed to examine the safety of unrelated cord blood transplantation in infants, children, and adults. In children with malignant and nonmalignant conditions, two-year event-free survival was 55% in children with high-risk malignancies[32] and 78% in children with nonmalignant conditions.[33] Across all groups, the cumulative incidence of engraftment by day 42 was 80%. Engraftment and survival were adversely affected by lower cell doses, pretransplant cytomegalovirus seropositivity in the recipient, non-European ancestry, and higher HLA mismatching. Slower engraftment leads to longer hospitalizations and greater utilization of medical resources.[34] In the COBLT study, outcomes in adults were inferior to the outcomes achieved in children. This study also established three new cord blood banks and standard operating procedures addressing donor recruiting and screening, cord blood collection, processing, testing, cryopreservation, storage, and thawing for transplantation.[35, 36]

In 1996, outcome data from the first 25 unrelated cord blood transplants completed at Duke University were reported.[37] This study concluded that cord blood contained sufficient numbers of stem cells and progenitor cells to reconstitute the marrow of children who underwent myeloablative treatments, without full HLA matching between donor and recipient. Patients who underwent unrelated cord blood transplant experienced a lower incidence and severity of both acute and chronic GVHD, compared with patients receiving unrelated matched bone marrow. Cell dose was strongly correlated with clinical outcome, including but not limited to time to and probability of engraftment as well as overall survival.[37-41] Since this time, research has been ongoing to study the effectiveness of placental/umbilical cord blood for the treatment of various conditions.

DOUBLE CORD BLOOD TRANSPLANT

Recent studies have examined the effects of transplanting two partially HLA-matched donor cord blood units in an effort to increase the total transplanted nucleated cells (TNC) appropriate for the patient's body mass. In general, when two units are used in a single transplant, one unit engrafts and the other is rejected. The exact role of the non-engrafting unit is unclear. However, standard practice continues to be to transplant one unit. In general, a minimum cell dose of 2.5–3.0x10^7 nucleated cells/kg in the cord blood has been associated with superior clinical outcome and is the current gold standard.[32, 37, 39-42]

Randomized Controlled Trials

Wagner (2014) published results from a randomized controlled trial (RCT) of single versus double-unit cord-blood transplantation after a uniform myeloablative conditioning regimen and immunoprophylaxis for GVHD.[43] Primary outcome measure was one-year overall survival. Authors reported similar one-year overall survival between the two groups with 65% among

recipients of double cord-blood transplant versus 73% among recipients of single cord-blood transplant.

Nonrandomized Studies

A report by Baron (2017) compared single- and double-unit cord blood transplants in adults using data from a multicenter registry.[44] There were 408 patients with acute myeloid leukemia (AML) and 126 patients with acute lymphoblastic leukemia (ALL) included in the analysis. The authors found no significant differences between single- and double- cord blood transplantation for relapse or nonrelapse mortality, with a trend (p=0.08) toward a higher incidence of GVHD with double units.

Scaradavou (2013) reported a retrospective analysis using data from the Center for International Blood and Marrow Transplant Research (CIBMTR) and the U.S.-based National Cord Blood Program.[45] The authors reported data on adults with acute leukemia who received one (n=106) or two (n=303) umbilical cord blood units. All units used for single transplantation contained a minimum cell dose of $2.5–3.0x10^7$ nucleated cells/kg. For the double transplants, the two units combined contained more than $2.5–3.0x10^7$ nucleated cells/kg, but in about half of cases, individual units contained less than the minimum amount required. The primary outcomes of rates of transplantation-related mortality (p=0.63), relapse (p=0.64) and overall mortality (p=0.62) were similar in the groups that received single and double transplantations. For patients treated in the earlier period, 2002-2004, there was a significantly higher risk of grade 2-4 acute GVHD in recipients of double cord blood units (p<0.001). In the later period, 2004-2009, rates of grade 2 to 4 acute GVHD did not differ significantly between groups (p=0.30).

Several other non-randomized studies have been published on double cord blood transplant. A 2013 study evaluating double unit transplants in adults with hematologic malignancies reported an engraftment rate of 93% (127 of 136) and a median overall survival rate of 17.5 months.[46] A trial from the University of Minnesota has shown that using two units of cord blood for a single transplant in adults improved rates of engraftment and overall survival.[47] Pilot studies show engraftment being achieved by at least 90% with overall survival at one year ranging from 60% to 80%, depending on the initial disease, comorbidities, and disease status at the time of transplant.[34] Additionally, a 2016 study reported a lower incidence of GVHD in patients who underwent double cord blood transplantation compared with patients who had matched unrelated-donor peripheral blood transplantation.[48]

A number of recent observational studies have also evaluated the role of various risk factors in the outcomes of double cord blood transplants. The results of these studies indicate that transplant outcomes may be associated with additional HLA-matching[49] and levels of angiogenic factors[50]

CORD BLOOD VERSUS BONE MARROW TRANSPLANTATION FOR TREATMENT OF LEUKEMIA

In addition to trial data, there have been numerous retrospective and registry studies comparing cord blood to bone marrow transplants in patients with leukemia. In general, studies have supported the conclusion that unrelated cord blood transplantation is effective treatment option in both children and adults with hematologic malignancies.[51]

Nonrandomized Studies

The majority of cord blood transplants have been mismatched at one or two HLA loci. A 2013 study compared survival rates after bone marrow transplantation or unrelated cord blood transplantation in patients older than age 50 years with acute myelogenous leukemia who received reduced-intensity conditioning.[52] The adjusted three-year overall survival rate was 51% after related donor bone marrow transplantation, 53% after unrelated donor bone marrow transplantation and 45% after unrelated donor cord blood transplantation; the difference among groups was not statistically different (p=0.73). A similar study of adults of any age found no statistically significant differences in three-year survival rates between cord blood (44%), matched adult donor (44%), and mismatched adult donor (43%) transplants.[53]

In 2007 retrospective comparative analysis from the Center for International Blood and Marrow Transplant Research compared outcomes after unrelated cord blood versus unrelated bone marrow transplant.[54] This study showed similar five-year leukemia-free survival for those receiving allele-matched marrow and those who received unrelated cord blood with a one or two antigen mismatch.

Rocha (2001) published results from a retrospective multicenter study of 541 children with acute leukemia. The difference at day 60 in rates of neutrophil recovery was 96% for those receiving unrelated bone marrow (n=262) versus 80% for unrelated cord blood (n=99).[41]

AUTOLOGOUS CORD BLOOD TRANSPLANT

Data regarding the use of cord blood for autologous (when the donor and recipient are the same) stem cell transplantation are limited. However, blood banks are available for collecting and storing a neonate's cord blood for a potential future use. A position paper from the American Academy of Pediatrics noted that there is no evidence of the safety or effectiveness of autologous cord blood transplantation for treatment of malignant neoplasms.[55] This report comments on evidence demonstrating the presence of DNA mutations in cord blood from children who subsequently develop leukemia. In addition, a survey of pediatric hematologists noted few transplants have been performed using cord blood stored in the absences of a known indication.[56]

PRACTICE GUIDELINE SUMMARY

AMERICAN ACADEMY OF PEDIATRICS

A position statement on cord blood banking for potential future transplantation was published by the American Academy of Pediatrics in 2017.[57] The Academy recommended cord blood banking for public use, with a more limited role for private cord blood banking for families with a known fatal illness that could be rescued by cord blood transplant.

AMERICAN COLLEGE OF OBSTETRICIANS AND GYNECOLOGISTS

In 2015, the American College of Obstetricians and Gynecologists (ACOG) published a committee opinion on umbilical cord blood banking, which was updated in 2019.[58] The statement discussed counseling patients about options for umbilical cord blood banking, as well as benefits and limitations of this practice. Relevant recommendations include the following:

- "Umbilical cord blood collection should not compromise obstetric or neonatal care or alter routine practice for the timing of umbilical cord clamping."

- "The current indications for cord blood transplant are limited to select genetic, hematologic, and malignant disorders."
- "Umbilical cord blood collection is not part of routine obstetric care, and is not medically indicated."

AMERICAN SOCIETY FOR BLOOD AND MARROW TRANSPLANTATION

On behalf of the American Society for Blood and Marrow Transplantation (ASBMT), Ballen (2008)[59] published recommendations related to the banking of umbilical cord blood:

- Public banking of cord blood is encouraged when possible.
- Storage of cord blood for autologous (i.e., personal) use is not recommended.
- Family member banking (collecting and storing cord blood for a family member) is recommended when there is a sibling with a disease that may be successfully treated with an allogeneic transplant.
- Family member banking on behalf of a parent with a disease that may be successfully treated with an allogeneic transplant is only recommended when there are shared HLA antigens between the parents.

AMERICAN SOCIETY OF TRANSPLANTATION AND CELLULAR THERAPY

In 2020, the American Society of Transplantation and Cellular Therapy released an evidence-based review on hematopoietic cell transplantation for treating newly diagnosed adult acute myeloid leukemia.[60] This publication also provided recommendations that were graded based on the quality and strength of underlying evidence. The summary stated that a haploidentical-related donor is preferred over UCB in the absence of a fully HLA-matched donor, but UCB unit transplantation is an option for centers with this expertise.

SUMMARY

There is enough research to show that umbilical cord blood cell transplantation can improve survival and other health outcomes in certain patients. In addition, clinical guidelines based on research recommend considering cord blood as a possible source of blood stem cells when a suitable stem cell donor cannot be found. Therefore, the collection and use of cord blood as a source of stem cells may be considered medically necessary criteria for patients who meet the policy criteria.

There is not enough research to show that umbilical cord blood cell transplantation can improve health outcomes in patients who do not meet the policy criteria. Therefore, the use of cord blood as a source of stem cells is considered investigational for these patients.

The routine collection and storage of cord blood for possible future use is not considered current standard medical care and has not been shown to improve health outcomes. Therefore, routinely collecting and storing cord blood for a potential future use is considered not medically necessary.

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CODES

Codes	Number	Description
CPT	None	
HCPCS	S2140	Cord blood harvesting for transplantation, allogeneic
	S2142	Cord blood derived stem-cell transplantation, allogeneic
	S2150	Bone marrow or blood-derived stem cells (peripheral or umbilical), allogeneic or autologous, harvesting, transplantation, and related complications; including: pheresis and cell preparation/storage; marrow ablative therapy; drugs; supplies; hospitalization with outpatient follow-up; medical/surgical, diagnostic, emergency, and rehabilitative services; and the number of days of pre- and post-transplant care in the global definition

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