Placental and Umbilical Cord Blood as a Source of Stem Cells

Effective: May 1, 2024

Next Review: January 2025
Last Review: March 2024

DESCRIPTION

This policy addresses the collection, storage, and transplantation of placental/umbilical cord blood ("cord blood"), including *ex vivo* expanded cord blood products (e.g., Omisirge™), 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 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.

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

III. Transplantation of Omisirge™ (omidubicel-onlv) is considered **medically necessary** when all of the following criteria (A.-D.) are met:

   A. The individual meets the health plan's medical necessity criteria for allogeneic stem-cell transplant but is without a hematopoietic stem-cell donor; and

B. The individual is 12 years of age or older; and

C. The individual has a diagnosis of a hematologic malignancy, such as Acute Myelogenous Leukemia (AML), Acute Lymphoblastic Leukemia (ALL), Myelodysplastic Syndrome (MDS), Chronic Myeloid Leukemia (CML), lymphoma, or other rare leukemias; and

D. The individual does not have a history of receiving a prior allogeneic hematopoietic transplant.

IV. Transplantation of Omisirge™ (omidubicel-onlv) is considered **investigational** in all other situations.

V. 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.

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.

POLICY GUIDELINES

Omisirge™ is a cell suspension for intravenous infusion. A single dose of Omisirge™ consists of

- a Cultured Fraction: a minimum of 8.0×10^8 total viable cells of which a minimum of 8.7% is CD34+ cells and a minimum of 9.2×10^7 CD34+ cells, and
- a Non-cultured Fraction: a minimum of 4.0×10^8 total viable cells with a minimum of 2.4×10^7 CD3+ cells

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 Miscellaneous Solid Tumors in Adults, Transplant, Policy No. 45.27
7. Hematopoietic Cell Transplantation for Acute Myeloid Leukemia, Transplant, Policy No. 45.28
8. Hematopoietic Cell Transplantation for Hodgkin Lymphoma, Transplant, Policy No. 45.30

9. Hematopoietic Cell Transplantation for Chronic Myelogenous Leukemia, Transplant, Policy No. 45.31
10. Hematopoietic Cell Transplantation for Autoimmune Diseases, Transplant, Policy No. 45.32
11. Hematopoietic Cell Transplantation for CNS Embryonal Tumors and Ependymoma, Transplant, Policy No. 45.33
12. Hematopoietic Cell Transplantation for Chronic Lymphocytic Leukemia and Small Lymphocytic Lymphoma, Transplant, Policy No. 45.35
13. Hematopoietic Cell Transplantation for Acute Lymphoblastic Leukemia, Transplant, Policy No. 45.36
14. Hematopoietic Cell Transplantation for Solid Tumors of Childhood, Transplant, Policy No. 45.37
15. Hematopoietic Cell Transplantation in the Treatment of Germ-Cell Tumors, Transplant, Policy No. 45.38
16. 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.

<u>Reduced-Intensity Conditioning Allogeneic Hematopoietic Cell Transplantation</u>

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.

Ex Vivo Expanded Cord Blood Transplant (Omisirge™)

Umbilical cord blood transplantation is limited by the cell doses that can be achieved in recipients with high body weight and is also associated with delayed engraftment, higher risk for graft failure, higher rates of infectious complications, and higher costs for procurement. Omisirge™ (omidubicel-onlv, previously NiCord®) is a blood-based stem cell therapy derived from a single allogeneic umbilical cord blood unit. The therapy uses a proprietary expansion technology based on nicotinamide and cytokines, proposed to enable donor cells to grow while maintaining their functionality, increase homing to the recipient's bone marrow, and retention of engraftment capacity. Omisirge™ is designed to accelerate the rate of neutrophil recovery and lower the risk of infection in patients with hematologic malignancies planning allogeneic hematopoietic stem cell transplant but lacking a matched sibling or unrelated donor source.

Omisirge™ includes two components derived from a single cord blood unit, an *ex vivo* cultured fraction of CD34+ cells that will engraft and a supportive non-cultured fraction of non-selected cord blood unit cells. The cultured fraction contains at least 8.0 x 10^8 total number viable cells (TNVC) and at least 9.2 x 10^7 CD34+ cells with a minimum of 8.7% CD34+ cells suspended in approximately 20 milliliters of cryopreservation solution. The non-cultured fraction contains at least 4.0 x 10^8 TNVC and at least 2.4 x 10^7 CD3+ cells in 10 milliliters of cryopreservation solution. The cultured fraction and non-cultured fraction are individually cryopreserved until thawed for infusion and administered sequentially. Each cell fraction is diluted with an infusion solution of human serum albumin and dextran, just before infusion by a closed port system.

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]

Omisirge™ (omidubicel-onlv, previously NiCord®) received approval from the U.S. FDA for a Biologics License in April 2023.[4] Omisirge™ is approved for patients age 12 or older with hematologic malignancies who are planned for umbilical cord transplantation following myeloablative conditioning to reduce the time to neutrophil recovery and the incidence of infection.

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 manifested 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.[5]

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.[5]

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.[6] 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.[7]

EVIDENCE SUMMARY

RELATED CORD BLOOD TRANSPLANT

The first cord blood transplant was a related cord blood transplant for a child with Fanconi's anemia.[8] After the success of this initial transplant, approximately 60 others were performed in the matched-sibling setting. The results demonstrated that cord blood contained sufficient numbers of hematopoietic stem and progenitor cells to reconstitute a pediatric patient and 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.[9] 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.[10]

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).[11] 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% (risk ratio [RR]=0.53, confidence interval [CI], 0.38 to

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).[12] 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 Type 1 DM studies: n=36, and three Type 2 DM 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 to -0.657; p<0.001) and C-peptide levels (pooled-estimate 1.008; 95% CI, 0.475 to 1.541; p<0.001), as well as the daily insulin-requirement (pooled-estimate -2.027; 95% CI, -3.32 to -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 randomized clinical trials (RCTs) with larger cohorts to address knowledge gaps in optimum transplantation regimen, route of administration, injected cell number, preference of autologous or allogeneic 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.[13] 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 (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.[14] 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.[15] 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).[16] 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.[17] 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.

Randomized Clinical Trials

Huang (2023) published results of an open-label RCT that assessed whether repeated infusions of MSCs during the early stage after haplo-hematopoietic stem cell transplantation (HSCT) decreases the incidence of severe chronic GVHD in patients with acute leukemia.[18] The enrolled patients with a haploidentical relative for HSCT received the modified busulfan/cyclophosphamide + antithymocyte globulin modified regimen and standard GVHD prophylaxis. Patients were randomly chosen to receive either MSCs (1×10^6cells/kg, every two weeks, starting from 45 days after transplant, four times total, n=74) or regular prophylaxis (n=74). The primary outcome was cumulative incidence of severe chronic GVHD. The estimated two-year cumulative incidence of severe chronic GVHD was 5.4% (95%CI, 1.8% to 14.0%) in the MSC group and 17.4% (95% CI, 10.1% to 28.5%) in the control group (hazard ratio [HR], 0.29; 95% CI, 0.10 to 0.88; p=0.03). There was no difference between the MSC and control groups in the cumulative incidence of leukemia relapse (HR, 1.17; 95% CI, 0.55 to 2.47; p=0.68). The cumulative incidence of stage II to IV acute GVHD in the MSC group was significantly lower than that in the control group (HR, 0.25; 95% CI, 0.09 to 0.67; p=0.01). The MSC group had better GVHD-free and relapse-free survival rates than the control group (HR, 0.62; 95% CI, 0.39 to 0.98; p=0.04).

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.[19] The two-year progression-free survival (the primary endpoint) was 35% (95% 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).[20] 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.[21] 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.[22] 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.[23] The two-year probability of overall survival (OS) was 82% (95% 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.[24] 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.[25] 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.[26] 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.[27] 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.[28]

In addition to these studies, there have been other retrospective and registry studies.[29-33] 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.[30]

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[34] and 78% in children with nonmalignant conditions.[35] 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.[36] 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.[37, 38]

In 1996, outcome data from the first 25 unrelated cord blood transplants completed at Duke University were reported.[39] 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.[39-43] 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.[34, 39, 41-44]

Randomized Controlled Trials

Wagner (2014) published results from a RCT of single versus double-unit cord-blood transplantation after a uniform myeloablative conditioning regimen and immunoprophylaxis for GVHD.[45] 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.[46] 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.[47] 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.[48] 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.[49] 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.[36] 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.[50]

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[51] and levels of angiogenic factors[52]

EX VIVO EXPANDED CORD BLOOD TRANSPLANT

The purpose of Omisirge™ (omidubicel-onlv) in individuals with hematologic malignancies is to provide a treatment option that is an alternative to or an improvement on standard allogeneic umbilical cord blood transplantation in patients who lack a matched sibling or matched unrelated donor source. *Ex vivo* expansion strategies using nicotinamide have been investigated to expedite hematopoietic recovery and enhance cell volume without inducing differentiation or cellular stress commonly associated with culturing hematopoietic progenitor cells outside their natural environment. Omisirge™ is a modified allogeneic hematopoietic progenitor cell therapy derived from cord blood utilizing a proprietary nicotinamide enrichment technology.

Omisirge™ for the Treatment of Hematologic Malignancies

Systematic Reviews

Saiyin (2023) published a systematic review and meta-analysis of RCTs and nonrandomized studies which evaluated the outcomes of umbilical cord blood transplantation in patients with hematologic malignancies.[53] 1,146 participants were pooled across nine trials of multiple *ex vivo* CD34+ cell expansion strategies including: four studies of omidubicel, discussed below, and one study each of UM171, StemEx, SR-1, MSC, and Notch. Six studies reported on survival at varying endpoints (100 days, one year, or two years). A pooled analysis of the risk of death at the last available follow-up favored *ex vivo* expanded umbilical cord blood transplantation over unmanipulated umbilical cord blood (OR, 0.66; 95% CI, 0.47 to 0.95; p=0.02; I^2 0%). Two analyses of the rate of acute GVHD showed no differences between the pooled rate of grade II-IV GVHD or grade III or IV GVHD events between groups. The authors reported a consistently low risk of bias, in terms of participant selection, classification of interventions, deviation from intended interventions, and handling of missing data, across all nine included studies. A moderate risk of bias was found for selective reporting of results, with five studies not reporting control cohort data for some outcomes and no study reporting blinding of measurement outcomes. No sub-group analysis was performed on the subset of *ex vivo* expansion studies utilizing omidubicel, and no correction was made for the overlapping patient populations in Anand (2017) and Horowitz (2014). As a result, the magnitude of the effect of these omidubicel outcomes remains uncertain.

Randomized Controlled Trials

Horwitz (2021) published results from an RCT that investigated omidubicel compared to standard unmanipulated umbilical cord blood transplantation.[54] Participants included pediatric and adult patients with high-risk hematologic malignancies who were candidates for myeloablative allogeneic hematopoietic stem cell transplantation but did not have a readily available matched sibling or unrelated donor. All participants had an umbilical cord blood unit, HLA matched at four or more loci, and underwent standard myeloablative conditioning. The median participant age was 41 years (range 12-65 years) and included the following cancer types: 48% acute myeloid leukemia, 33% acute lymphoblastic leukemia, 7% myelodysplastic syndrome, 5% chronic myeloid leukemia, 4% lymphoma, and 3% other rare leukemias. Participants received either omidubicel (n=62) or standard umbilical cord blood transplantation (n=63) and were stratified on the treatment center, disease risk index, age, and the intent to perform a single or double umbilical cord blood transplantation. 52 patients in the omidubicel group and 55 patients in the control group were analyzed as treated due to planned transplants that did not occur after randomization. Median follow-up time was 10 months post-transplantation (range 1 to 19 months). The primary endpoint of time to neutrophil engraftment had 90% power to detect a difference with the selected sample size. Time to neutrophil engraftment favored participants treated with omidubicel over standard umbilical cord blood transplantation. Total CD34+ cells correlated with time to engraftment, suggesting patients with a higher total cell count at transplantation had shorter engraftment times. The time to neutrophil recovery and the incidence of platelet engraftment also favored the omidubicel-treated arm.

Horwitz (2021) also examined several exploratory outcomes. The rate of acute grade 2 to 4 GVHD (13% difference; 95% CI, -6% to 30%; p=0.18) at 100 days or chronic GVHD at 1 year (6% difference; 95% CI, -21% to 7%; p=0.33) were similar between groups. No significant differences were observed for the rate of relapse at 15 months (8% difference; p=0.32), overall survival (HR, 0.57; 95% CI, 0.3 to 1.1; p=0.09), disease-free survival (HR, 0.79; 95% CI, 0.45 to 1.38; p=0.4), non-relapse-related mortality (11% vs. 24%; p=0.09), or treatment failure (HR, 0.79; 95% CI, 0.45 to 1.38; p=0.4). Significantly fewer grade 2 or 3 bacterial or fungal infections or grade 3 viral infections were reported in the omidubicel group; however, these were exploratory outcomes, and some stratified analyses may be suggestive of selective reporting (e.g. limiting the cumulative incidence of first viral infection outcome to grade three events only). More deaths were reported in the standard umbilical cord group (n=18) compared to the omidubicel group (n=11) with GVHD accounting for four deaths in each group. Participants allocated to omidubicel also showed a quicker time to discharge from the hospital than those in the standard of care comparator (27 days versus 35 days; p=0.005). The incidence of treatment-related serious adverse events was similar between omidubicel (40%) and standard umbilical cord blood (41%) groups. Study limitations include: a short median follow-up period for time-to-event outcomes such as overall survival, disease-free survival, non-relapse-related mortality, and treatment failure; not powered to detect differences in important clinical outcomes; lacked blinding of participants and investigators, and omission of some data on statistical comparisons for some outcomes.

Lin (2023) published a supplementary analysis of the RCT participants studied by Horwitz (2021), to assess health-related quality of life.[55] Data were prospectively collected on three instruments: the Functional Assessment of Cancer Therapy-General instrument, the Functional Assessment of Cancer Therapy-Bone Marrow Transplant (FACT-BMT) and the EuroQol 5-Dimension 3-Level tests. Participants completed these quality of life measures at 42, 100, 180 and 365 days post-transplantation. 75 participants from the RCT completed one or more assessments (37 in the omidubicel group and 38 in the standard UCB group). Notably, an assessment comparing characteristics of those who participated in this quality of life study and those that did not found that the excluded patients had a significantly lower (p<0.001) incidence of platelet engraftment (54.6% versus 90.7%), spent more days in the hospital (66.3 days versus 43.6 days), and had lower one year overall survival (42.4% versus 82.7%). On the FACT-G test, the total FACT-G score was significantly better in the omidubicel group compared to the control group (p=0.01) with mean differences ranging from 6 to 6.9 points. This exceeded the minimally important clinical difference of five at all follow-up times through one year. On the FACT-G subscale of physical well-being, a significant difference (p=0.02) also favored the omidubicel group. Similarly, the mean change in scores on the FACT-BMT total score favored the omidubicel group (p=0.01) and exceeded the MCID of seven at all follow-up assessments (range 7.2 to 10 points). No significant difference between groups was observed on the EQ-5D-3L index (p=0.06).

Lin (2023) published a pooled analysis of five clinical trials that evaluated long-term outcomes of allogeneic hematopoietic cell transplantation with omidubicel, including a planned secondary analysis of the RCT published by Horwitz (2021).[56] Three trials assessed patients with hematologic malignancies, and two trials enrolled patients with sickle cell hemoglobinopathy. Patients treated in the two phase I studies received omidubicel coadministered with an unmanipulated umbilical cord blood graft. All patients received a myeloablative conditioning regimen and GVHD prophylaxis, composed of a calcineurin inhibitor and mycophenolate mofetil. Patients received either single cord transplantation with omidubicel or double cord transplantation with omidubicel and an unmanipulated umbilical cord blood unit. To examine omidubicel-specific outcomes, all patients who fully engrafted with unmanipulated umbilical cord blood were excluded from this long-term follow-up study. 105 patients were included in this analysis, including 97 who reached full engraftment with omidubicel, two with mixed chimerism with omidubicel and unmanipulated umbilical cord blood, five with primary graft failure, and one who died before engraftment could be assessed. The most common indications for transplantation were acute myeloid leukemia (41%), acute lymphoblastic leukemia (27%), myelodysplastic syndrome (12%), and sickle cell hemoglobinopathy (8%). At the time of data cutoff, the median follow-up duration was 22.0 months (range, 0.3 to 122.5 months) for all included patients and 35.7 months (range, 11.7 to 122.5 months) among survivors. Three-year estimated overall survival and disease-free survival were 62.7% and 56.4%, respectively. Durable trilineage hematopoiesis and normal counts of immune subsets were reported up to eight years. Secondary graft failure occurred in five patients within the first year, and no late cases were reported. One case of donor-derived myeloid neoplasm occurred at 40 months post-transplantation.

Majhail (2023) published a prospective secondary analysis of the Horwitz (2021) omidubicel RCT that examined resource utilization, including hospital length of stay, hospital care setting, visits by provider type, rate of transfusions, and readmissions, among the 108 treated patients (omidubicel-onlv, n = 52; umbilical cord blood, n = 56) from day 0 to day 100 post-transplantation.[57] Patient demographics were similar in the two groups except for a higher proportion of female patients (52% versus 37%) and older median age (40 years versus 36 years) in the omidubicel group. Compared with patients receiving standard umbilical cord transplantation, patients who received omidubicel had a shorter average total hospital length of stay (mean, 41.2 days versus 50.8 days; p=0.027) and more days alive and out of the hospital (mean, 55.8 days versus 43.7 days; p=0.023). Fewer patients in the omidubicel group required intensive care unit admission (10% versus 23%) and spent fewer days in the intensive care unit (mean, 0.4 day versus 4.7 days; p=0.028) and transplant unit (mean, 25.3 days versus 32.9 days; p=0.022) compared with those who received standard umbilical cord blood transplantation.

<u>Nonrandomized Studies</u>

Horwitz (2019) compared omidubicel (n=36) to a cohort of matched historical controls (n=146) from The Center for International Blood and Marrow Transplant Research (CIBMTR) database in patients with high-risk hematologic malignancies and no matched sibling or unrelated donor matches for allogeneic HSCT.[58] The median follow-up of omidubicel recipients was 14 months (range, 5 to 36 months). Neutrophil engraftment was higher in the omidubicel recipients (94%) compared to the historical control group (85%) and showed a significantly higher rate of engraftment. The median time to neutrophil recovery was 11.5 days (95% CI, 9 to 14 days) for omidubicel recipients and 21 days (95% CI, 20 to 23 days) for the historical control group ($p<0.001$). Time to platelet engraftment showed a similar trend. The median time to platelet recovery was 34 days (95% CI, 32 to 42 days) and 46 days (95% CI, 42 to 50 days) for the omidubicel and control cohorts, respectively (p<0.001). The two-year cumulative incidence of non-relapse mortality was 24% (95% CI, 11% to 39%) in the omidubicel group, which showed a significantly reduced risk of non-relapse mortality compared to standard umbilical cord blood (HR, 0.41; 95% CI, 0.19 to 0.88; p=0.02). The cumulative rate of relapse at two years was 33% (95% CI, 16% to 52%); relapse showed conflicting findings in a multivariate analysis with one showing a significant between-group difference and the other showing no difference depending on which variables were adjusted for in the model. Disease-free survival was similar between the omidubicel (43%; 95% CI, 24% to 60%) and historical control groups (45%; 95% CI, 37% to 53%; p=0.77). Rates of acute GVHD, incidence of chronic GVHD two years post-transplantation, and two-year overall survival were not different between treatment groups.

Anand (2017) conducted a prospective cohort study comparing patients who were treated with omidubicel for hematologic malignancies (n=18) to patients at the same institution who historically received standard umbilical cord blood (n=86).[59] The omidubicel group overlapped with the patient population in the phase I trial conducted by Horwitz (2014), discussed below. Similar to Horowitz (2014), the median time to neutrophil engraftment favored the omidubicel group, but there was no significant difference in the rate of engraftment failure (6% vs 12%, p=0.68). A total of 56% of omidubicel and 73% of standard umbilical cord blood patients had one or more grade 2 or 3 infections (p=0.16); the authors stratified this by infection type and found that grade 2 or 3 bacterial infections were significantly less common in the omidubicel group (p=0.009) but found no difference in the frequency of grade 2 or 3 viral or fungal infections. The infection density, the mean number of total infections during the first 100 days post-transplantation, was not significantly different between omidubicel and standard umbilical cord blood transplant (3.7 vs 4.9; p=0.09).

Horwitz (2014) allocated omidubicel treatment to 12 adult patients with hematologic malignancies undergoing umbilical cord transplant in a phase I clinical trial.[60] Two participants did not receive the allocated omidubicel intervention. Patients receiving omidubicel (n=10) were compared to a cohort of historical controls from the same institution who received unmanipulated umbilical cord blood (n=17). Time to neutrophil engraftment favored the omidubicel group over unmanipulated umbilical cord blood transplant, but no difference was observed for the time to platelet engraftment. The rate of acute GVHD was high but not compared to historical controls. Overall survival and progression-free survival were 82% and 73%, respectively. This study is limited by small sample size and lack of reported values for the control arm.

Omisirge™ for the Treatment of Sickle-Cell Disease

<u>Nonrandomized Studies</u>

Parikh (2021) published the results of a single-arm, phase I/II study that investigated whether increasing the umbilical cord blood cell dose with omidubicel would improve engraftment in pediatric patients receiving myeloablative HSCT for Sickle Cell Disease.[61] 13 patients with severe Sickle-Cell Disease received omidubicel in combination with an unmanipulated UCB graft. Three patients received a single omidubicel graft. Grafts were minimally matched with patients at four of six HLA alleles. Median age at transplant was 13 years. A median CD34+ expansion of approximately 80-fold was observed with omidubicel, along with rapid neutrophil engraftment (median, seven days). Long-term engraftment was derived from the unmanipulated graft in most of the double cord blood recipients. Two of the three single omidubicel recipients also had sustained engraftment. Incidence of acute GVHD was high, but resolved in all surviving patients. Event-free survival in the double cord group was 85% (median follow-up four years). All three patients in the single cord group were alive one year after transplantation.

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.[62]

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.[63] 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.[64]

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.[65] 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).[43]

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.[66] 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.[67]

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.[68] 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 2019, the American College of Obstetricians and Gynecologists (ACOG) published an ACOG committee opinion on Umbilical Cord Blood Banking.[69] ACOG makes the following recommendations regarding umbilical cord blood banking:

- Umbilical cord blood collected from a neonate cannot be used to treat a genetic disease or malignancy in that same individual (autologous transplant) because stored cord blood contains the same genetic variant or premalignant cells that led to the condition being treated.
- The routine collection and storage of umbilical cord blood with a private cord blood bank is not supported by the available evidence.
- The current indications for umbilical cord blood transplantation are limited to select genetic, hematologic, and malignant disorders.
- Private umbilical cord blood banking may be considered when there is knowledge of a family member with a medical condition (malignant or genetic) who could potentially benefit from cord blood transplantation.
- Public umbilical cord blood banking is the recommended method of obtaining umbilical cord blood for use in transplantation, immune therapies, or other medically validated indications.
- Obstetrician–gynecologists and other obstetric care providers should be aware of state and local laws regarding umbilical cord blood banking, including the law in some states that requires physicians to inform patients about umbilical cord blood banking options.
- Umbilical cord blood collection should not compromise obstetric or neonatal care or alter routine practice of delayed umbilical cord clamping with the rare exception of medical indications for directed donation.
- It is important to inform patients that the medical condition of the woman or neonate may prevent adequate umbilical cord blood collection.

In 2015, ACOG published a committee opinion on umbilical cord blood banking, which was updated in 2019.[70] 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)[71] 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.[72] 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 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.

There is enough research to show that Omisirge™ (omidubicel-onlv) can improve infection rates, time to engraftment, and other health outcomes in patients with hematologic malignancies when a suitable stem cell donor cannot be found. Therefore, treatment with Omisirge™ (omidubicel-onlv) may be considered medically necessary for patients who meet the policy criteria.

There is not enough research to show that Omisirge™ (omidubicel-onlv) can improve health outcomes in patients who do not meet the policy criteria, including but not limited to, patients who do not have a hematologic malignancy or patients who have a matched hematopoietic stem cell donor. Therefore, Omisirge™ (omidubicel-onlv) is considered investigational for all other indications.

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.

REFERENCES

1. Godley LA, van Besien K. The next frontier for stem cell transplantation: finding a donor for all. *JAMA.* 2010;303(14):1421-2. PMID: 20388899
2. U.S. Food and Drug Administration (FDA). Cord Blood Banking: Information for Consumers (July 23, 2012). [cited 01/19/2024]. 'Available from:' http://www.fda.gov/biologicsbloodvaccines/resourcesforyou/consumers/ucm236044.htm .
3. U.S. Food and Drug Administration. Guidance for Industry: Minimally manipulated, unrelated allogeneic placental/umbilical cord blood intended for hematopoietic reconstitution for specified indications. [cited 01/19/2024]. 'Available from:' https://www.fda.gov/downloads/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/CellularandGeneTherapy/UCM357135.pdf.
4. U.S. Food and Drug Administration (FDA). Biologics License Application Approval Summary. Omisirge (omidubicel-onlv). Gamida Cell, Ltd. 2023. [cited 3/1/2024]. 'Available from:' https://www.fda.gov/media/167203/download?attachment.
5. Wall DA. Regulatory issues in cord blood banking and transplantation. *Best Pract Res Clin Haematol.* 2010;23(2):171-7. PMID: 20837328
6. Netcord FFTAoCTF. International Standards For Cord Blood Collection, Banking, And Release For Administration. Seventh Edition. January 2020. [cited 01/19/2024]. 'Available from:' https://fact.policytech.com/dotNet/documents/?docid=229&public=true.
7. AABB (American Association of Blood Banks). Standards & Accreditation. Umbilical Cord Blood Donation FAQs. [cited 01/19/2024]. 'Available from:' http://www.aabb.org/sa/facilities/celltherapy/Pages/cordbloodfaqs.aspx.
8. Gluckman E, Broxmeyer HA, Auerbach AD, et al. Hematopoietic reconstitution in a patient with Fanconi's anemia by means of umbilical-cord blood from an HLA-identical sibling. *N Engl J Med.* 1989;321(17):1174-8. PMID: 2571931
9. Wagner JE, Rosenthal J, Sweetman R, et al. Successful transplantation of HLA-matched and HLA-mismatched umbilical cord blood from unrelated donors: analysis of engraftment and acute graft-versus-host disease. *Blood.* 1996;88(3):795-802. PMID: 8704232
10. Broxmeyer HE, Douglas GW, Hangoc G, et al. Human umbilical cord blood as a potential source of transplantable hematopoietic stem/progenitor cells. *Proceedings of the National Academy of Sciences of the United States of America.* 1989;86(10):3828-32. PMID: 2566997
11. Shen T, Xia L, Dong W, et al. A Systematic Review and Meta-Analysis: Safety and Efficacy of Mesenchymal Stem Cells Therapy for Heart Failure. *Curr Stem Cell Res Ther.* 2021;16(3):354-65. PMID: 32867655
12. Kassem DH, Kamal MM. Therapeutic efficacy of umbilical cord-derived stem cells for diabetes mellitus: a meta-analysis study. *Stem Cell Res Ther.* 2020;11(1):484. PMID: 33198815
13. Li D, Li X, Liao L, et al. Unrelated cord blood transplantation versus haploidentical transplantation in adult and pediatric patients with hematological malignancies-A meta-analysis and systematic review. *Am J Blood Res.* 2020;10(1):1-10. PMID: 32206440
14. Wu R, Ma L. Haploidentical Hematopoietic Stem Cell Transplantation Versus Umbilical Cord Blood Transplantation in Hematologic Malignancies: A Systematic Review and Meta-Analysis. *Cell Transplant.* 2020;29:963689720964771. PMID: 33040595
15. Poonsombudlert K, Kewcharoen J, Prueksapraopong C, et al. Post transplant cyclophosphamide based haplo-identical transplant versus umbilical cord blood transplant; a meta-analysis. *Jpn J Clin Oncol.* 2019;49(10):924-31. PMID: 31265729

16. Lou X, Zhao C, Chen H. Unrelated donor umbilical cord blood transplant versus unrelated hematopoietic stem cell transplant in patients with acute leukemia: A meta-analysis and systematic review. *Blood reviews.* 2017. PMID: 29174416
17. Zhang H, Chen J, Que W. A meta-analysis of unrelated donor umbilical cord blood transplantation versus unrelated donor bone marrow transplantation in acute leukemia patients. *Biol Blood Marrow Transplant.* 2012;18:1164-73. PMID: 22289799
18. Huang R, Chen T, Wang S, et al. Mesenchymal Stem Cells for Prophylaxis of Chronic Graft-vs-Host Disease After Haploidentical Hematopoietic Stem Cell Transplant: An Open-Label Randomized Clinical Trial. *JAMA Oncol.* 2023. PMID: 38153755
19. Fuchs EJ, O'Donnell PV, Eapen M, et al. Double unrelated umbilical cord blood vs HLA-haploidentical bone marrow transplantation: the BMT CTN 1101 trial. *Blood.* 2021;137(3):420-28. PMID: 33475736
20. Yan L, Wu Y, Li L, et al. Clinical analysis of human umbilical cord mesenchymal stem cell allotransplantation in patients with premature ovarian insufficiency. *Cell Prolif.* 2020;53(12):e12938. PMID: 33124125
21. Robin M, Porcher R, Ruggeri A, et al. HLA-Mismatched Donors in Patients with Myelodysplastic Syndrome: An EBMT Registry Analysis. *Biol Blood Marrow Transplant.* 2019;25(1):114-20. PMID: 30172776
22. Ruggeri A, Volt F, Locatelli F, et al. Unrelated Cord Blood Transplantation for Acute Leukemia Diagnosed in the First Year of Life: Outcomes and Risk Factor Analysis. *Biol Blood Marrow Transplant.* 2017;23(1):96-102. PMID: 27777140
23. Mo XD, Tang BL, Zhang XH, et al. Comparison of outcomes after umbilical cord blood and unmanipulated haploidentical hematopoietic stem cell transplantation in children with high-risk acute lymphoblastic leukemia. *International journal of cancer.* 2016;139(9):2106-15. PMID: 27356906
24. Sakaguchi H, Watanabe N, Matsumoto K, et al. Comparison of Donor Sources in Hematopoietic Stem Cell Transplantation for Childhood Acute Leukemia: A Nationwide Retrospective Study. *Biol Blood Marrow Transplant.* 2016;22(12):2226-34. PMID: 27667011
25. Liu HL, Sun ZM, Geng LQ, et al. Similar survival, but better quality of life after myeloablative transplantation using unrelated cord blood vs matched sibling donors in adults with hematologic malignancies. *Bone Marrow Transplant.* 2014;49:1063-9. PMID: 24842525
26. Balaguer Rosello A, Bataller L, Lorenzo I, et al. Infections of the Central Nervous System after Unrelated Donor Umbilical Cord Blood Transplantation or Human Leukocyte Antigen-Matched Sibling Transplantation. *Biol Blood Marrow Transplant.* 2017;23(1):134-39. PMID: 27794456
27. Crombie J, Spring L, Li S, et al. Readmissions after Umbilical Cord Blood Transplantation and Impact on Overall Survival. *Biol Blood Marrow Transplant.* 2017;23(1):113-18. PMID: 27789360
28. Zhu X, Huang L, Zheng C, et al. European Group for Blood and Marrow Transplantation Risk Score Predicts the Outcome of Patients with Acute Leukemia Receiving Single Umbilical Cord Blood Transplantation. *Biol Blood Marrow Transplant.* 2017;23(12):2118-26. PMID: 28807768
29. Kato K, Choi I, Wake A, et al. Treatment of patients with adult T cell leukemia/lymphoma with cord blood transplantation: a Japanese nationwide retrospective survey. *Biol Blood Marrow Transplant.* 2014;20(12):1968-74. PMID: 25172635

30. Park M, Lee YH, Kang HR, et al. Unrelated donor cord blood transplantation for non-malignant disorders in children and adolescents. *Pediatric transplantation.* 2014;18(2):221-9. PMID: 24372660
31. Al-Sweedan S, Al-Seraihy A, Al-Ahmari A, et al. Factors Determining the Outcome of Hematopoietic Stem Cell Transplantation in Patients With Acute Lymphoblastic Leukemia at King Faisal Specialist Hospital and Research Center, Riyadh, Saudi Arabia. *Journal of pediatric hematology/oncology.* 2017;39(1):33-37. PMID: 27906795
32. Inamoto Y, Kimura F, Kanda J, et al. Comparison of graft-versus-host disease-free, relapse-free survival according to a variety of graft sources: antithymocyte globulin and single cord blood provide favorable outcomes in some subgroups. *Haematologica.* 2016;101(12):1592-602. PMID: 27662017
33. Itonaga H, Aoki K, Aoki J, et al. Prognostic Impact of Donor Source on Allogeneic Hematopoietic Stem Cell Transplantation Outcomes in Adults with Chronic Myelomonocytic Leukemia: A Nationwide Retrospective Analysis in Japan. *Biol Blood Marrow Transplant.* 2017. PMID: 29196081
34. Kurtzberg J, Prasad VK, Carter SL, et al. Results of the Cord Blood Transplantation Study (COBLT): clinical outcomes of unrelated donor umbilical cord blood transplantation in pediatric patients with hematologic malignancies. *Blood.* 2008;112(10):4318-27. PMID: 18723429
35. Martin PL, Carter SL, Kernan NA, et al. Results of the cord blood transplantation study (COBLT): outcomes of unrelated donor umbilical cord blood transplantation in pediatric patients with lysosomal and peroxisomal storage diseases. *Biol Blood Marrow Transplant.* 2006;12(2):184-94. PMID: 16443516
36. Kurtzberg J. Update on umbilical cord blood transplantation. *Curr Opin Pediatr.* 2009;21(1):22-9. PMID: 19253461
37. Fraser JK, Cairo MS, Wagner EL, et al. Cord Blood Transplantation Study (COBLT): cord blood bank standard operating procedures. *J Hematother.* 1998;7(6):521-61. PMID: 9919946
38. Kurtzberg J, Cairo MS, Fraser JK, et al. Results of the cord blood transplantation (COBLT) study unrelated donor banking program. *Transfusion.* 2005;45(6):842-55. PMID: 15934981
39. 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(3):157-66. PMID: 8657213
40. Mayani H, Lansdorp PM. Biology of human umbilical cord blood-derived hematopoietic stem/progenitor cells. *Stem Cells.* 1998;16(3):153-65. PMID: 9617891
41. Rubinstein P, Carrier C, Scaradavou A, et al. Outcomes among 562 recipients of placental-blood transplants from unrelated donors. *N Engl J Med.* 1998;339(22):1565-77. PMID: 9828244
42. Gluckman E, Rocha V, Boyer-Chammard A, et al. Outcome of cord-blood transplantation from related and unrelated donors. Eurocord Transplant Group and the European Blood and Marrow Transplantation Group. *N Engl J Med.* 1997;337(6):373-81. PMID: 9241126
43. Rocha V, Cornish J, Sievers EL, et al. Comparison of outcomes of unrelated bone marrow and umbilical cord blood transplants in children with acute leukemia. *Blood.* 2001;97(10):2962-71. PMID: 11342418
44. Prasad VK, Kurtzberg J. Emerging trends in transplantation of inherited metabolic diseases. *Bone Marrow Transplant.* 2008;41(2):99-108. PMID: 18176609

45. Wagner JE, Jr., Eapen M, Carter S, et al. One-unit versus two-unit cord-blood transplantation for hematologic cancers. *N Engl J Med.* 2014;371(18):1685-94. PMID: 25354103
46. Baron F, Ruggeri A, Beohou E, et al. Single- or double-unit UCBT following RIC in adults with AL: a report from Eurocord, the ALWP and the CTIWP of the EBMT. *Journal of hematology & oncology.* 2017;10(1):128. PMID: 28637512
47. Scaradavou A, Brunstein CG, Eapen M, et al. Double unit grafts successfully extend the application of umbilical cord blood transplantation in adults with acute leukemia. *Blood.* 2013;121:752-8. PMID: 23223509
48. Wallet HL, Sobh M, Morisset S, et al. Double umbilical cord blood transplantation for hematological malignancies: a long-term analysis from the SFGM-TC registry. *Experimental hematology.* 2013;41(11):924-33. PMID: 23831606
49. Barker JN, Weisdorf DJ, DeFor TE, et al. Transplantation of 2 partially HLA-matched umbilical cord blood units to enhance engraftment in adults with hematologic malignancy. *Blood.* 2005;105(3):1343-7. PMID: 15466923
50. Gutman JA, Ross K, Smith C, et al. Chronic graft versus host disease burden and late transplant complications are lower following adult double cord blood versus matched unrelated donor peripheral blood transplantation. *Bone Marrow Transplant.* 2016;51(12):1588-93. PMID: 27400068
51. Brunstein CG, Cutler CS, DeFor TE, et al. Matching at Human Leukocyte Antigen-C Improved the Outcomes after Double Umbilical Cord Blood Transplantation for Recipients of Two to Four of Six Human Leukocyte Antigen-Matched Grafts. *Biol Blood Marrow Transplant.* 2017;23(1):126-33. PMID: 27989929
52. Politikos I, H TK, Karantanos T, et al. Angiogenic Factors Correlate with T Cell Immune Reconstitution and Clinical Outcomes after Double-Unit Umbilical Cord Blood Transplantation in Adults. *Biol Blood Marrow Transplant.* 2017;23(1):103-12. PMID: 27777141
53. Saiyin T, Kirkham AM, Bailey AJM, et al. Clinical Outcomes of Umbilical Cord Blood Transplantation Using Ex Vivo Expansion: A Systematic Review and Meta-Analysis of Controlled Studies. *Transplant Cell Ther.* 2023;29(2):129.e1-29.e9. PMID: 36396108
54. Horwitz ME, Stiff PJ, Cutler C, et al. Omidubicel vs standard myeloablative umbilical cord blood transplantation: results of a phase 3 randomized study. *Blood.* 2021;138(16):1429-40. PMID: 34157093
55. Lin C, Sajeev G, Stiff PJ, et al. Health-Related Quality of Life Following Allogeneic Hematopoietic Cell Transplantation with Omidubicel versus Umbilical Cord Blood. *Transplant Cell Ther.* 2023;29(1):52.e1-52.e9. PMID: 36179986
56. Lin C, Schwarzbach A, Sanz J, et al. Multicenter Long-Term Follow-Up of Allogeneic Hematopoietic Cell Transplantation with Omidubicel: A Pooled Analysis of Five Prospective Clinical Trials. *Transplant Cell Ther.* 2023;29(5):338.e1-38.e6. PMID: 36775201
57. Majhail NS, Miller B, Dean R, et al. Hospitalization and Healthcare Resource Utilization of Omidubicel-Onlv versus Umbilical Cord Blood Transplantation for Hematologic Malignancies: Secondary Analysis from a Pivotal Phase 3 Clinical Trial. *Transplant Cell Ther.* 2023;29(12):749.e1-49.e5. PMID: 37703995
58. Horwitz ME, Wease S, Blackwell B, et al. Phase I/II Study of Stem-Cell Transplantation Using a Single Cord Blood Unit Expanded Ex Vivo With Nicotinamide. *J Clin Oncol.* 2019;37(5):367-74. PMID: 30523748

59. Anand S, Thomas S, Hyslop T, et al. Transplantation of Ex Vivo Expanded Umbilical Cord Blood (NiCord) Decreases Early Infection and Hospitalization. *Biol Blood Marrow Transplant.* 2017;23(7):1151-57. PMID: 28392378
60. Horwitz ME, Chao NJ, Rizzieri DA, et al. Umbilical cord blood expansion with nicotinamide provides long-term multilineage engraftment. *J Clin Invest.* 2014;124(7):3121-8. PMID: 24911148
61. Parikh S, Brochstein JA, Galamidi E, et al. Allogeneic stem cell transplantation with omidubicel in sickle cell disease. *Blood Adv.* 2021;5(3):843-52. PMID: 33560399
62. Locatelli F, Crotta A, Ruggeri A, et al. Analysis of risk factors influencing outcomes after cord blood transplantation in children with juvenile myelomonocytic leukemia: a EUROCORD, EBMT, EWOG-MDS, CIBMTR study. *Blood.* 2013;122:2135-41. PMID: 23926304
63. Peffault de Latour R, Brunstein CG, Porcher R, et al. Similar overall survival using sibling, unrelated donor, and cord blood grafts after reduced-intensity conditioning for older patients with acute myelogenous leukemia. *Biol Blood Marrow Transplant.* 2013;19(9):1355-60. PMID: 23791622
64. Marks DI, Woo KA, Zhong X, et al. Unrelated umbilical cord blood transplant for adult acute lymphoblastic leukemia in first and second complete remission: a comparison with allografts from adult unrelated donors. *Haematologica.* 2014;99:322-8. PMID: 24056817
65. Eapen M, Rubinstein P, Zhang MJ, et al. Outcomes of transplantation of unrelated donor umbilical cord blood and bone marrow in children with acute leukaemia: a comparison study. *Lancet.* 2007;369:1947-54. PMID: 17560447
66. Lubin BH, Shearer WT. Cord blood banking for potential future transplantation. *Pediatrics.* 2007;119(1):165-70. PMID: 17200285
67. Thornley I, Eapen M, Sung L, et al. Private cord blood banking: experiences and views of pediatric hematopoietic cell transplantation physicians. *Pediatrics.* 2009;123(3):1011-7. PMID: 19255033
68. Shearer WT, Lubin BH, Cairo MS, et al. Cord Blood Banking for Potential Future Transplantation. *Pediatrics.* 2017;140(5). PMID: 29084832
69. ACOG Committee Opinion No. 771: Umbilical Cord Blood Banking. *Obstet Gynecol.* 2019;133(3):e249-e53. PMID: 30801478
70. Committee Opinion No. 648: Umbilical Cord Blood Banking. *Obstet Gynecol.* 2015;126:e127-9. PMID: 26595583
71. Ballen KK, Barker JN, Stewart SK, et al. Collection and preservation of cord blood for personal use. *Biol Blood Marrow Transplant.* 2008;14(3):356-63. PMID: 18275904
72. Dholaria B, Savani BN, Hamilton BK, et al. Hematopoietic Cell Transplantation in the Treatment of Newly Diagnosed Adult Acute Myeloid Leukemia: An Evidence-Based Review from the American Society of Transplantation and Cellular Therapy. *Biol Blood Marrow Transplant.* 2020. PMID: 32966881

CODES

Codes	Number	Description
CPT	None	
HCPCS	C9399	Unclassified drugs or biologicals
	J3490	Unclassified drugs (no specified code)
	S2140	Cord blood harvesting for transplantation, allogeneic
	S2142	Cord blood derived stem-cell transplantation, allogeneic

Codes	Number	Description
	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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