

November 20, 2018

HOT TOPIC: Matched Related Donor Hematopoietic Stem Cell Transplant for Children with Sickle Cell Disease

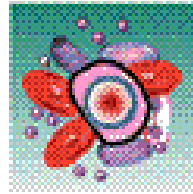
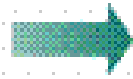
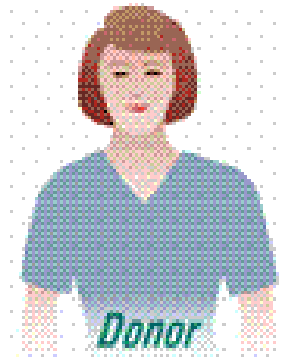
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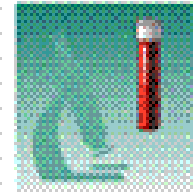
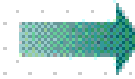


Allogeneic Transplant → Donor gives stem cells to patient



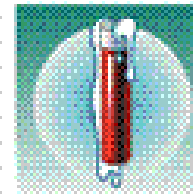
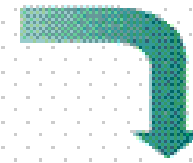
1 Collection

Stem cells are collected from donor's bone marrow or blood (harvest)



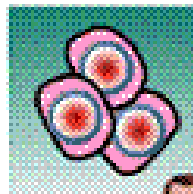
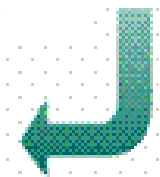
2 Processing

Bone marrow or blood is taken to processing laboratory where stem cells are concentrated and prepared for freezing process



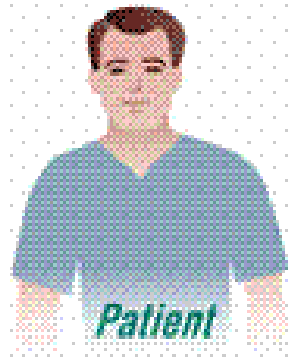
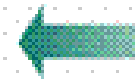
3 Cryopreservation

Bone marrow or blood is preserved by freezing to keep stem cells alive until they are infused into patient's bloodstream



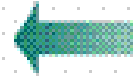
4 Chemotherapy

High dose chemotherapy and/or radiation therapy is given to the patient (conditioning regimen)



5 Infusion

Thawed stem cells are infused into the patient



Matched related donor stem cell transplant

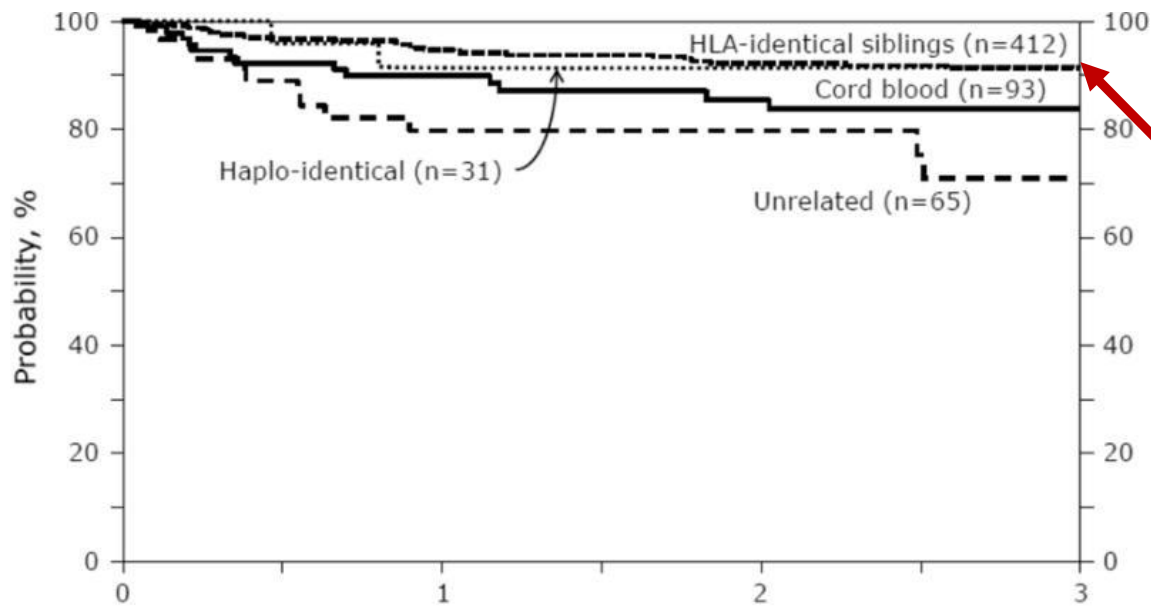
Matched related donors

- Donors are sibling with same parents
- Most common form of transplant for children with SCD

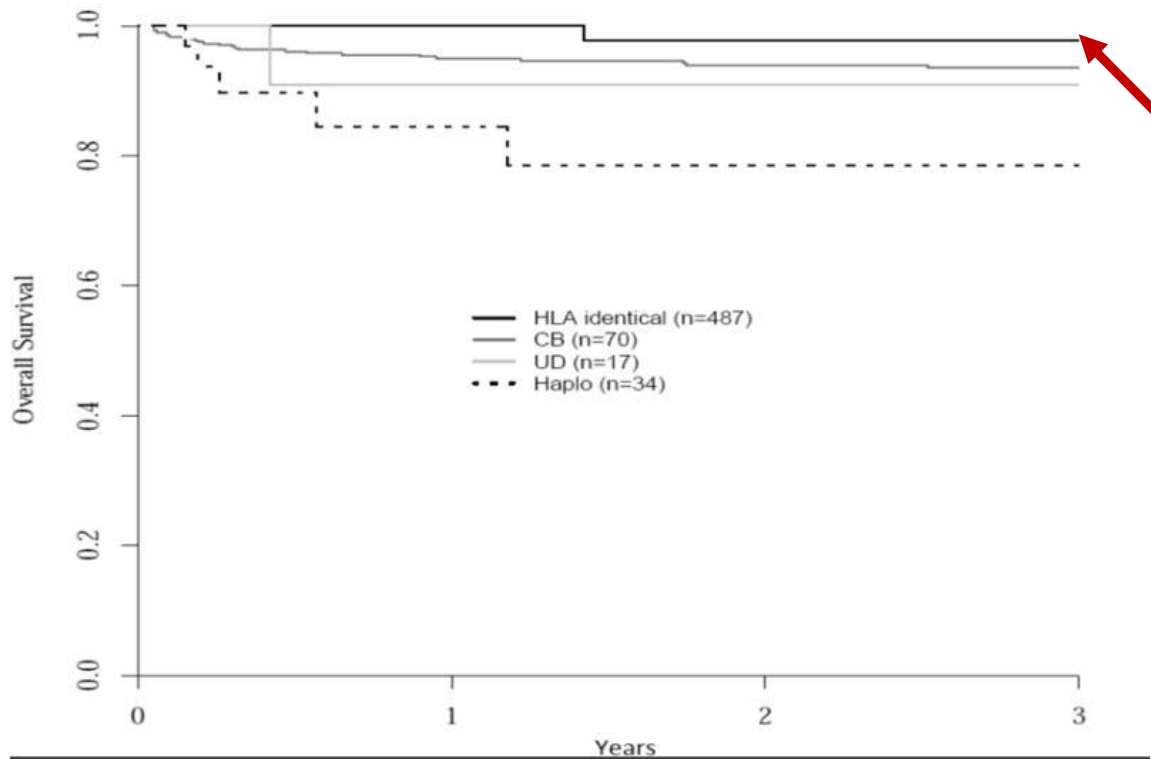
Treatment option for children with (severe?) sickle cell disease and matched sibling donor¹

- Overall survival ~95%
- Disease-free survival ~92%
- <1 in 10 children have complications, such as graft-versus-host disease

¹ Roberts I and Fuente J. Sickle cell disease: the price of cure. Blood 2016;128:2486-2488; doi: <https://doi.org/10.1182/blood-2016-10-740969>



91% survival for sibling donor
(Center for International Blood and Marrow Transplant Research)



95% survival for sibling donor
(European Blood and Marrow Transplant)

¹ Walters MC, De Castro LM, Sullivan KM, et al. Indications and Results of HLA-Identical Sibling Hematopoietic Cell Transplantation for Sickle Cell Disease. *Bio Blood Marrow Transplant.* 2016 Feb;22(2):207-211.

Hot Topic: Guidelines Conflict on Transplant

2014 NHLBI Expert Panel Report: More information needed¹

- “Although clinical trials have provided promising results, and cure appears to be possible in a large proportion of patients receiving HSCT, additional research is still needed that addresses the potential risks of this therapy (e.g., failure of engraftment and chronic graft-versus-host disease) before HSCT can become a widely used therapy.”

2014 EBMT Inborn Error and EBMT Paediatric Working Parties²

- Young patients with *symptomatic* SCD who have an HLA-identical sibling donor should be transplanted as early as possible, preferably at pre-school age.
- Unmanipulated BM or UCB (whenever available) from HLA-identical sibling donors are the recommended stem cell source.

¹Angelucci E, Matthes-Martin S, Baronciani D, et al. Hematopoietic stem cell transplantation in thalassemia major and sickle cell disease: indications and management recommendations from an international expert panel. *Haematologica*. 2014 May; 99(5):811-20

²Yawn BP, Buchanan GR, Afenyi-Annan AN, et al. Management of sickle cell disease: summary of the 2014 evidence-based report by expert panel members. *JAMA*. 2014 Sep 10; 312(10):1033-48.

Indications for transplant¹

Children	Adults (15-40 years)
<ul style="list-style-type: none">• Children with HbSS or HbSβ⁰-thalassemia <16 years of age• Stroke or CNS event lasting >24 hours• Impaired neuropsychological function with abnormal cerebral MRI/MRA• Recurrent acute chest syndrome• Stage I or II sickle lung disease²• Recurrent vaso-occlusive painful episodes or priapism• Sickle nephropathy (glomerular filtration rate 30-50% of predicted normal)	<ul style="list-style-type: none">• Clinically significant neurological event (stroke) or and neurological deficit lasting >24 hours• ≥2 episodes of acute chest syndrome in 2 years despite supportive care measures (asthma therapy and/or hydroxyurea)• ≥3 episodes of severe pain crises/year in 2 years despite supportive care measures (pain management and/or hydroxyurea)• ≥8 transfusions/year for ≥1 year to prevent vaso-occlusive complications (pain, stroke and ACS)• Pulmonary hypertension (tricuspid valve regurgitant jet ≥2.7 m/s on Echocardiogram)

¹ Walters MC, De Castro LM, Sullivan KM, et al. Indications and Results of HLA-Identical Sibling Hematopoietic Cell Transplantation for Sickle Cell Disease. *Bio Blood Marrow Transplant.* 2016 Feb;22(2):207-211.

² Powars D, Weidman JA, Odom-Maryon T, Niland JC, Johnson C. Sickle cell chronic lung disease: prior morbidity and the risk of pulmonary failure. *Medicine.* 1988;67(1):66-76

Barriers to transplant

To date, << 1% of SCD in the United States has received transplant

Barriers include

- Unclear if transplant has higher mortality and morbidity than if managed with supportive care, such as hydroxyurea
- Donors: Only ~18% of individuals with SCD have a HLA-identical sibling donor
- Infertility risk
- Graft-versus-host disease occurs ~10% of patients and may cause chronic debilitating disorder
- Unknown late effects

¹ Walters MC, De Castro LM, Sullivan KM, et al. Indications and Results of HLA-Identical Sibling Hematopoietic Cell Transplantation for Sickle Cell Disease. *Bio Blood Marrow Transplant.* 2016 Feb;22(2):207-211.

Establish Benefit/Harms for HSCT

Evaluate impact on gonadal function

Optimize transplant conditioning regimens

- Prevent chronic graft-versus-host disease
- Unrelated donors

Perform prospective comparison to standard care (on-going, **STRIDE**)

Impact of transplant on quality of life

¹Arnold SD, Bhatia M, Horan J, Krishnamurti L. Haematopoietic stem cell transplantation for sickle cell disease - current practice and new approaches. Br J Haematol. 2016 Aug;174(4):515-25.

Other resources

Fitzhugh CD, Walters MC. The case for HLA-identical sibling hematopoietic stem cell transplantation in children with symptomatic sickle cell anemia. *Blood Adv* 2017;1(26):2563-2567 (*free full text*)

DeBaun MR, Clayton EW. Primum non nocere: the case against transplant for children with sickle cell anemia without progressive end-organ disease. *Blood Adv* 2017;1(26):2568-2571 (*free full text*)

Shenoy S, Gaziev J, Angelucci E, et al. Late Effects Screening Guidelines after Hematopoietic Cell Transplantation (HCT) for Hemoglobinopathy: Consensus Statement from the Second Pediatric Blood and Marrow Transplant Consortium International Conference on Late Effects after Pediatric HCT. *Biol Blood Marrow Transplant*. 2018 Jul;24(7):1313-1321