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Hematopoietic Stem Cell Transplant (HSCT) as a cure for Sickle Cell Disease

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Disclosures

- No disclosures

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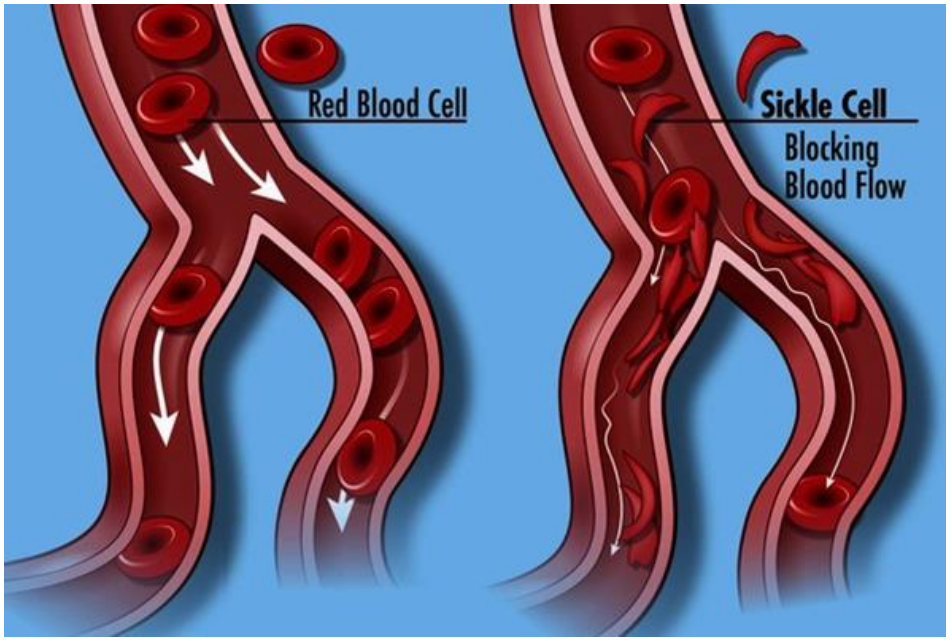
Objectives

- Brief review of Sickle Cell Disease
- Describe the pro's and cons of transplantation for SCD
- Discuss transplant options for patients with SCD
- Discuss the future directions of transplantation for SCD

What is sickle cell disease?

- Genetic condition where abnormal red blood cells are produced that become stiff during times of stress
- Defect is due to a mutation in DNA that leads to a Protein change from Glutamic acid to Valine



Sickle cell disease – Genetics Home Reference - NIH

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Sickle cell disease

- Incidence
  - 1 out of every 365 Black or African-American births
  - 1 out of every 16,300 Hispanic-American births

- 90,000 people in the U.S. have sickle cell disease currently

- 275,000 infants are born worldwide with sickle cell disease every year

Brousseau D.C. et al, American Journal of Hematology, 2010

Modell B. et al., Bulletin of the World Health Organization, 2008

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Major sickle cell related complications

- Vaso-occlusive pain crisis
- Acute chest syndrome
- Stroke
- Pulmonary Hypertension
- Priapism

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Supportive Care studies

- VOC/ACS prevention (Baby HUG)
  - Hydroxyurea group had less VOC and ACS than placebo control group
- Stroke prevention (STOP)
  - Chronic transfusions can prevent stroke in patients with abnormal TCD
- Stroke prevention with hydroxyurea (TWiTCH)
  - Hydroxyurea equally effective to chronic transfusions for patients with abnormal TCD's
- Stopping chronic transfusions for Stroke (SWiTCH)
  - Hydroxyurea inferior to chronic transfusions and iron chelation for patients that have already had a stroke

Wang WC et al, Lancet, 2011, Adams, RJ et al, NEJM,1998, Bernaudin MR et al, Lancet, 2016, Aboud F et al,Blood, 2011

Sickle cell disease progress/limitations

- Hydroxyurea use lead to increased fetal hemoglobin and decreased rates of hospitalization, but as much as 50%!
- Supportive care with penicillin prophylaxis, Streptococcus vaccination, and better recognition of Stroke and Acute Chest has patients living into adulthood.
- However, life expectancy is still often **less than half** that of the general population.
- Currently those with severe phenotype are often relegated to chronic transfusions

Quinn CT et al, Blood,2010

Hassel KL et al, American Journal of Preventive Medicine, 2010

Strouse JJ et al., Pediatrics, 2008.

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Life expectancy

- 1970’s 25-34
- 1980’s 34-44
- 1990’s 44-54
- 2000’s 44-54
- *General population 70’s.

Hassell, et al. American Journal of Preventive Medicine, 2010

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Supportive care limitations

- Hydroxyurea – compliance can be an issue, and even in best use will not help everyone
- Chronic transfusions lead to high iron burden
- Iron chelation difficult and time consuming
- None of these approaches will cure sickle cell disease, only keep it under control.

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HSCT as a cure for Sickle Cell Anemia

Donor selection?

- Matched related donors
  - Traditionally a sibling sharing the same parents has a 25% chance of being a 10/10 match
    - In the African American community this decreases down to approximately 18%.
- Unrelated donors
    - 18% Chance of 10/10 match in the registry
    - 75% Chance of 9/10 match
- Cord blood donors
    - Matching done at HLA A,B, DR, More naiive stem cell population, can tolerate up to 4/6 match
- Haploidentical donors-
  - 5/10 (half matched), increases donor options

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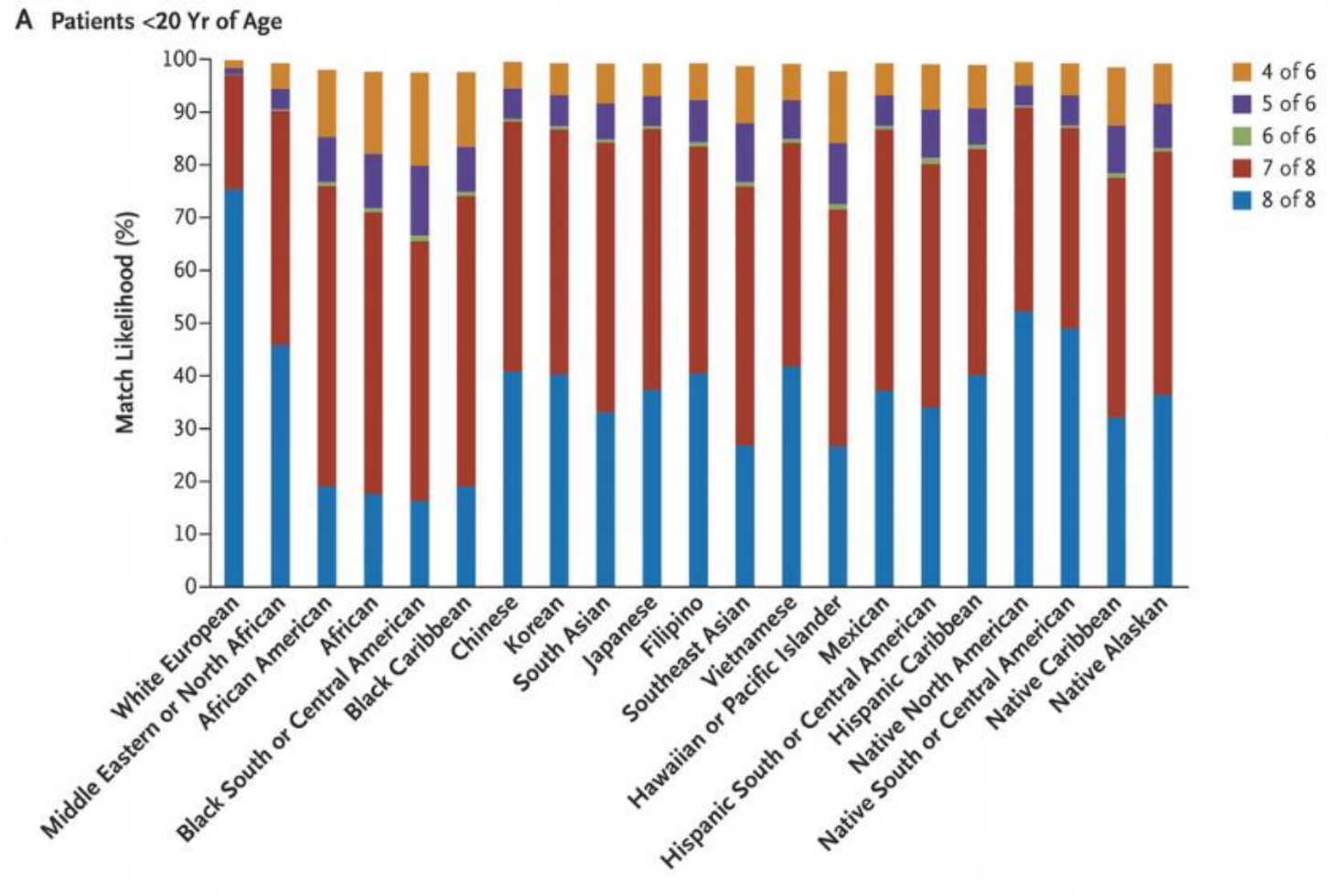
Donor options



Gragert et al, NEJM, 2014

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Pre Stem cell transplant testing

- Disease evaluation
  - % Sickle Hemoglobin
- Organ evaluations
  - **Iron evaluation- MRI liver**
  - Echo cardiogram- heart
  - Kidney scan/ Electrolytes
  - Lung testing
  - MRI/MRV of Brain- evaluate for new or recent stroke
- Infection evaluation
  - Includes lab work and dental visit, chest x-ray etc.
- Donor testing occurs at the same time

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Conditioning/Preparative regimen

- Chemotherapy +/- radiation
  - Myeloablative
    - Busulfan/Cytoxan – used in ABO mismatched patients
  - Non-myeloablative/reduced intensity
    - Fludarabine/Melphalan/Alemtuzumab
    - Total body irradiation/Alemtuzumab
    - Thiotepa/rATG/Fludarabine/Cyclophosphamide

Pro's and cons for HSCT for Sickle Cell Anemia

Pros

- Only current curative approach!
- Ends need for chronic transfusion
- Stops worsening iron overload
- Stops further damage via VOC or ACS to organs

Cons

- Transplant related mortality
- Graft vs. Host disease
- Graft rejection
- Late Effects
  - Infertility
  - Secondary malignancy

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HSCT indications- Children

- **Children <15 yo**
  - **Stroke or CNS event lasting > 24 hours**
  - **Impaired neuropsychological function with abnormal MRI and angiography**
  - **Recurrent acute chest syndrome**
  - **Stage I-II sickle cell lung disease**
  - **Recurrent VOC pain episodes or recurrent priapism**
  - **Sickle nephropathy (GFR 30-50% of predicted values)**

Arnold et al, British Journal of Haematology, 2016

Angelucci et al. Haematologica et al, 2014

Walters et al, BBMT, 2016

Horan et al, BBMT, 2015.

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HSCT indications- Adolescent/Adult

- **Adults >15 yo**
  - **Clinically significant neurological event (stroke) or any neurological deficit lasting >24 hours**
  - **History of >/= 2 episodes of acute chest syndrome for 2 years despite supportive care measures**
  - **History of >/= 3 severe pain crisis per year for 2 years despite supportive care**
  - **Red cell transfusion therapy, >8 transfusions per year for >/= 1 year**
  - **Tricuspid valve regurgitant jet >/= 2.7 m/s on echo**

Arnold et al, British Journal of Haematology, 2016

Angelucci et al. Haematologica et al, 2014

Walters et al, BBMT, 2016

Horan et al, BBMT, 2015.

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Sickle Cell Transplants

Number of Transplants Reported for IEA - Sickle cell anemia
From 2012 - 2016

Year of Transplant	Donor Type			
	Autologous	Allogeneic		
		HLA-matched sibling	Related Donor	Unrelated
2013	0	65	18	33
2014	0	88	26	31
2015	2	89	35	40
2016	1	86	35	31
2017	1	88	37	31

CIBMTR data, 2019

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Matched Sibling Donors

Overview of Matched sibling HSCT

- Donor availability is the issue!
- Currently standard of care at most institutions provided severity is met.
- Still not without complications
  - GVHD, rejection

First Case

- Johnson, F.L et al, NEJM, 1984.
  - AML patient, who also had Sickle cell disease
  - Myeloablative conditioning (Cytoxan/TBI prep)
  - Bone Marrow was stem cell source
  - **Cured of both diseases!**

Largest case series

- European bone marrow transplant/ Center for international blood and marrow transplant registry (EBMT/CIBMTR)
  - 1000 patients, 846 patients <16 years of age, median age 9 years old
    - Transplanted between 1986-2013
    - Majority had bone marrow donors
    - Majority myeloablative conditioning (Busulfan/Cytoxan/thymoglobulin)
  - Grade II-IV acute GVHD was 14.8%, Chronic GVHD 14.3%
    - Survival and acute and chronic GVHD risk high for older patients >16 yo
  - 5 year overall survival, and EFS were 92.9% and 91.4%.
    - Survival better for patients transplanted after 2006

Gluckman E et al., Blood, 2016

Reduced intensity- National Institute of Health (NIH protocol)

- Patients 16-65 years old with HLA matched related donors
- **G-CSF mobilized Peripheral blood stem cell source**
- Non-myeloablative conditioning (Alemtuzumab/TBI (300 cGray)
  - No chemotherapy
  - Significant immune suppression.
- Sirolimus as GVHD prophylaxis
- No transplant related mortality
- 87% long term stable engraftment w/o GVHD
- Median myeloid engraftment 86%, T cell 48%

Hsieh MM et al, JAMA, 2014

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NIH protocol in Kids

- Guilcher et al.
- 16 patients, All pediatric cohort!
- Non-myeloablative conditioning (Alemtuzumab/ TBI (300 cGray))
- Matched sibling
  - **G-CSF mobilized peripheral blood stem cells**
- No GVHD, 100% survival

Newer matched sibling protocols

- Minimizing toxicity in HLA-identical sibling donor transplantation for children with sickle cell disease (SUN) protocol (NIH protocol backbone)
  - Age 2-21.99
  - Non myeloablative approach
  - Matched related donors
  - Non- myeloablative conditioning (Alemtuzumab/TBI (300 cGray))
  - Sirolimus GVHD pox
  - Open at Levine Children's Hospital, as well as DC Children's, Alberta Children's, and multiple other sites.

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Alternative donors

Alternative donor overview

- Donor pool limited
  - 18% chance of 10/10 donor in the Be the match Registry
- Toxicity
  - cGHVD rates quite high with current approaches
  - Survival rates < matched related donors and less than haploidentical donors
- Ideally done on clinical trial

Cord Blood?

- Significant rate of graft failure!
  - BMT CTN 0601- SCURT cord blood arm.
    - 87% overall survival
    - **5/8 (62.5%) graft failure!**
  - CIBMTR, Eurocord, NYBC, 2011.
    - 51 patients (16 patients SCD)
    - Overall survival 94%, DFS 50% for SCD.
    - **Graft failure occurred in 7/16 (44%)**

Kamani N.R. et al., BBMT, 2012

Ruggeri A, et al., BBMT, 2011

Sickle Cell Unrelated Donor Transplant Trial (SCURT)

- BMT CTN 0601
  - 2008-2014
  - 29 pts, all <19 yo
  - Bone marrow donors
  - Reduced intensity conditioning (Fludarabine/Melphalan/alemtuzumab)
  - 1 year EFS – 76%, OS 86%, 2 year EFS – 69%, OS 79%
  - Rejection rate 10%
  - Day 100 incidence of GVHD was 28%
  - **Chronic GVHD 62%! (38% extensive)**

Shenoy S. et al. Blood 2016.

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Sickle Cell Transplantation to Prevent Disease Exacerbation (STRIDE)

- BMT CTN 1503
- HLA matched donor- related or unrelated
- **Only go to transplant if they have a matched option, otherwise are on observation arm – “Biologic randomization”**
- Age 16-40
- Reduced intensity conditioning (Busulfan/Fludarabine/rATG)
- Study ongoing
- Available at Duke Medical Center

Other Unrelated donor Mismatched protocols

- Washington University
  - 7/8 Matched unrelated donors, and soon 7/8 related donors
  - Reduced intensity conditioning
    - Distal alemtuzumab (day -21 to-18)
    - Fludarabine, Melphalan
  - Bone marrow is stem cell source
  - Abatacept- anti CTLA-4 to combat issue with cGVHD

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Haploidentical

Haploidentical transplant

- Half matched protocols- make donor availability less of an issue, as most patients will have a parent or sibling that will allow them to qualify

  - **Post transplant Cytoxan** - Developed at Johns Hopkins, uses post transplant chemotherapy to destroy alloreactive T cells that can lead to GVHD

  - **Alpha/Beta T cell depletion** – removal of a portion of the T cells that cause GVHD, and leaves T cell components that can still allow graft vs. Leukemia and fight viruses.

*__Available on clinical trials only now aside from centers where it is standard of care such as Johns Hopkins University__

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Haploidentical protocols

- **BMT CTN1507**
  - Pedi arm <15, Adult arm >15
  - Hydroxyurea (-70 to -10)
  - Reduced intensity conditioning
    - Rabbit anti-thymocyte globulin, Thiotepa, Fludarabine, low dose Cyclophosphamide, Total body irradiation 200 cGray.
  - Bone marrow stem cell source
  - GVHD prevention: post transplant Cyclophosphamide, Sirolimus, mycophenolate mofitil
  - 60 day hydroxyurea prophase, as well as inclusion of thiotepa to reduce rejection rate

- **Johns Hopkins/ Vanderbilt consortium**
  - Reduced intensity conditioning
    - Rabbit anti-thymocyte globulin, Fludarabine, Cyclophosphamide, Total body irradiation 300 cGray
  - Bone marrow stem cell source
  - Post transplant Cyclophosphamide
  - Pediatric arm less restrictive
  - No hydroxyurea prophase
  - TBI higher at 300 cGray

Outcomes for SCD BMT 2011-2015

Donor Type	Cell Source	Number of Patients Evaluated	Survival Probability Estimate At a 95% Confidence Interval (CI) (Explain)		
			100 Days After Transplant	1 Year After Transplant	3 Years After Transplant
Autologous	Bone marrow	1	*	*	*
HLA - identical sibling	Bone marrow	288	98.6% ----- CI = 96.3 - 99.5%	97.2% ----- CI = 94.5 - 98.6%	94.9% ----- CI = 91.5 - 97.0%
	Peripheral blood	48	100.0% ----- CI = 100.0 - 100.0%	95.8% ----- CI = 84.4 - 98.9%	95.8% ----- CI = 84.4 - 98.9%
	Cord blood	17	100.0% ----- CI = 100.0 - 100.0%	100.0% ----- CI = 100.0 - 100.0%	*
Other related	Bone marrow	40	100.0% ----- CI = 100.0 - 100.0%	97.4% ----- CI = 83.2 - 99.6%	97.4% ----- CI = 83.2 - 99.6%
	Peripheral blood	45	97.8% ----- CI = 85.3 - 99.7%	91.1% ----- CI = 78.0 - 96.6%	80.6% ----- CI = 64.2 - 90.0%
	Cord blood	5	*	*	*
Unrelated	Bone marrow	97	95.9% ----- CI = 89.4 - 98.4%	80.4% ----- CI = 71.0 - 87.0%	73.8% ----- CI = 63.7 - 81.5%
	Peripheral blood	11	*	*	*
	Cord blood	33	97.0% ----- CI = 80.4 - 99.6%	87.9% ----- CI = 70.9 - 95.3%	87.9% ----- CI = 70.9 - 95.3%

CIBMTR data

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Gene manipulation

Gene Therapy

- Pros
  - Autologous transplant
  - Minimal Chemotherapy
  - No need for GVHD prophylaxis
  - Minimal engraftment of new cells needed
- Cons/Challenges
  - Low level engraftment with attempt to augment Beta globin production.
    - Better with gamma globulin production – leading to increased Hgb F
  - Ability to make enough normal hemoglobin to offset the sickle cell production
  - Concern for insertional mutations
    - Improved with letiviral vectors
  - G-CSF or Plerixafor mobilization for collection

Ribeil, et al. NEJM, 2017.

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Conclusions

- Stem cell transplant is the only definitive cure for Sickle cell disease
- Donor sources are limited for patients with Sickle cell disease needing transplant
- Matched sibling transplant is the gold standard, and likely can be done in younger less symptomatic patients
- Alternative donors
  - Cords lead to high graft rejection
  - Bone marrow donors current strategies lead to high GVHD
  - Haploidentical transplant holds promise as it opens transplant up to many more patients
- Peripheral blood stem cell options increasing with non-myeloabative conditioning
- Collaborative studies will help move the field forward

- Gene transfer may be wave of the future, but still in development

Thank you!

- Levine Children's Hospital/Atrium Health
- Sickle Cell Transplant Alliance for Research
- Blood and Marrow Transplant Clinical Trials Network
- Vanderbilt Haploidentical Consortium
- Washington University
- All our Patient's and their Families!

BLOOD AND MARROW
TRANSPLANT
CLINICAL TRIALS NETWORK

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