(Matched Sibling Donor) Hematopoietic Cell Transplantation for Sickle Cell Disease

Past, Present and Future

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(Re) Imagining Health
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Disclosures/Conflicts of Interest

- Funding for attendance at the American Society of Hematology meeting, December 2017
  - Jazz Pharmaceuticals

Objectives

- Identify basic principles of hematopoietic cell transplantation (HCT), specifically as applied to SCD
- Describe important measures of safety and success, including engraftment of donor blood cells and graft-versus-host disease
- Outline current and future directions of the practice of HCT, including timing, eligibility, safety and access

Otherwise described as:

- What is hematopoietic cell transplantation?
- How can it cure sickle cell disease?
- What are the risks?
- Why isn't everyone offered (HCT)?
- How can we realize a future where everyone with SCD worldwide can be **cured <u>safely</u>**?

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www.torontosun.com

Bone marrow transplantation (BMT) =

Blood and marrow transplantation (BMT)=

Hematopoietic stem cell transplantation (HSCT)=

Hematopoietic cell transplantation (HCT)

What is hematopoietic cell transplantion (HCT)?

- HCT is the procedure of infusing blood stem and progenitor cells from a donor into a recipient.

- Allogeneic HCT (**the donor is someone else**- not the recipient)
  - Stem cells from another individual are infused into the recipient after s/he receives preparatory chemotherapy, immunotherapy and/or radiation therapy
  - Can be a family member or an unrelated person

(Guilcher, Fernandez & Joffe, 2014)

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BMT Basics

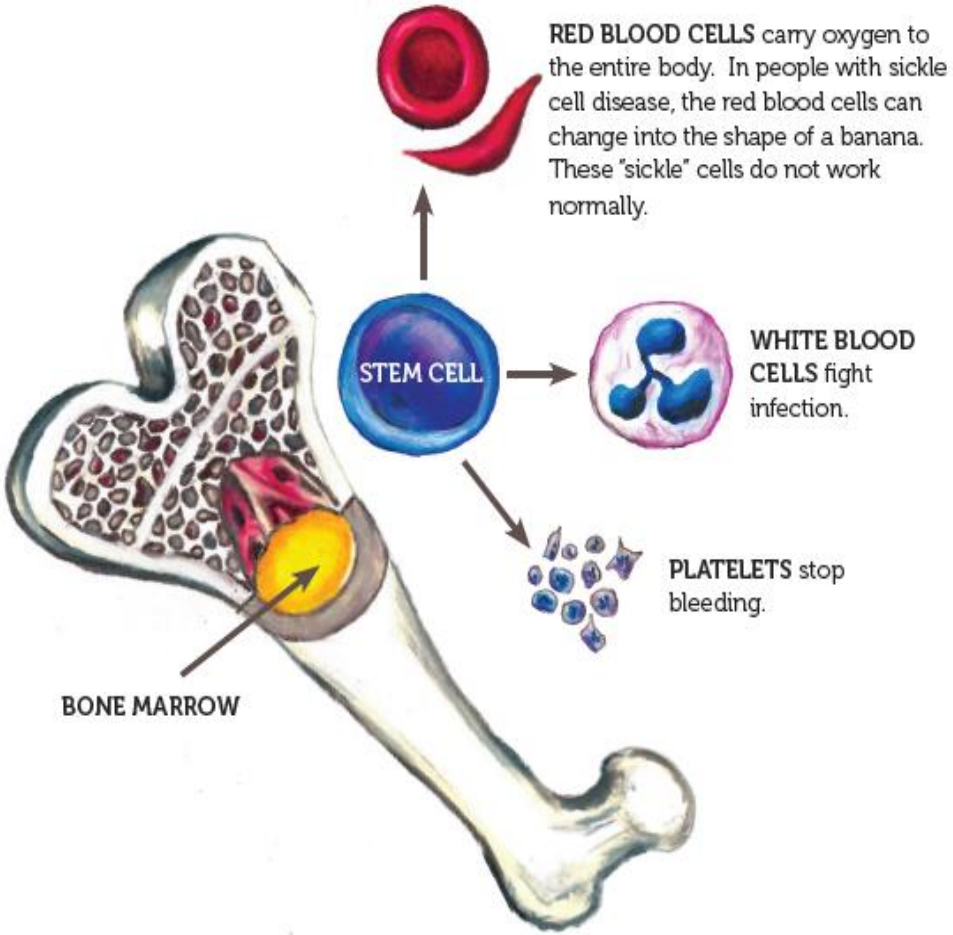
BMT is not a surgery.

Blood and marrow transplant (BMT) is not like other transplants. BMT is a process to replace a patient's bone marrow with a donor's bone marrow.

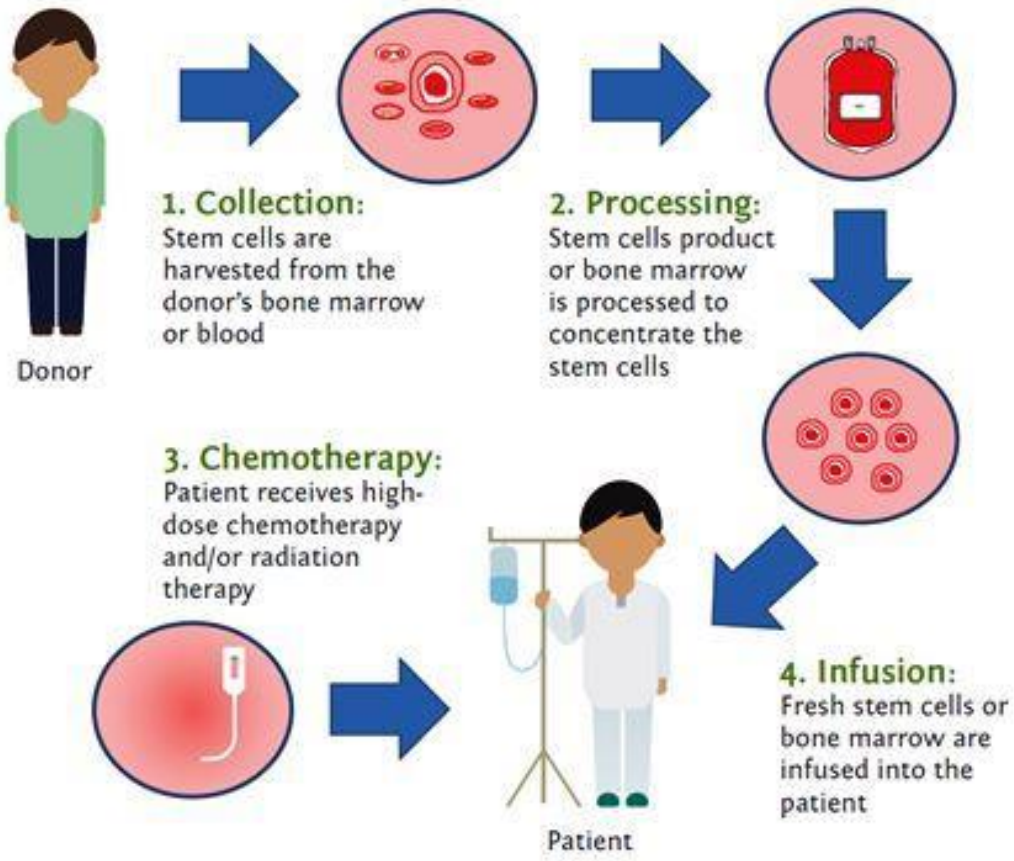
Bone marrow is the factory that makes blood cells.

Bone marrow is located in the center space inside bones. The bone marrow contains blood stem cells, which are special cells that grow to become red blood cells, white blood cells, or platelets.

(SUN Sickle Cell BMT Booklet, 2017)



(SUN Sickle Cell BMT Booklet, 2017)


Donor
1. Collection:
Stem cells are harvested from the donor's bone marrow or blood
2. Processing:
Stem cells product or bone marrow is processed to concentrate the stem cells
3. Chemotherapy:
Patient receives high-dose chemotherapy and/or radiation therapy
4. Infusion:
Fresh stem cells or bone marrow are infused into the patient
Patient

HCT can correct sickle hemoglobin production

BONE-MARROW TRANSPLANTATION IN A PATIENT WITH SICKLE-CELL ANEMIA

F. Leonard Johnson, M.B.B.S.,
A. Thomas Look, M.D., Jon Gockerman, M.D.,
Mary R. Ruggiero, P.N.P.,
Luciano Dalla-Pozza, M.B.B.S.,
and Frederic T. Billings III, M.D.

(Johnson et al., 1984)

Why not call it bone marrow transplantation?

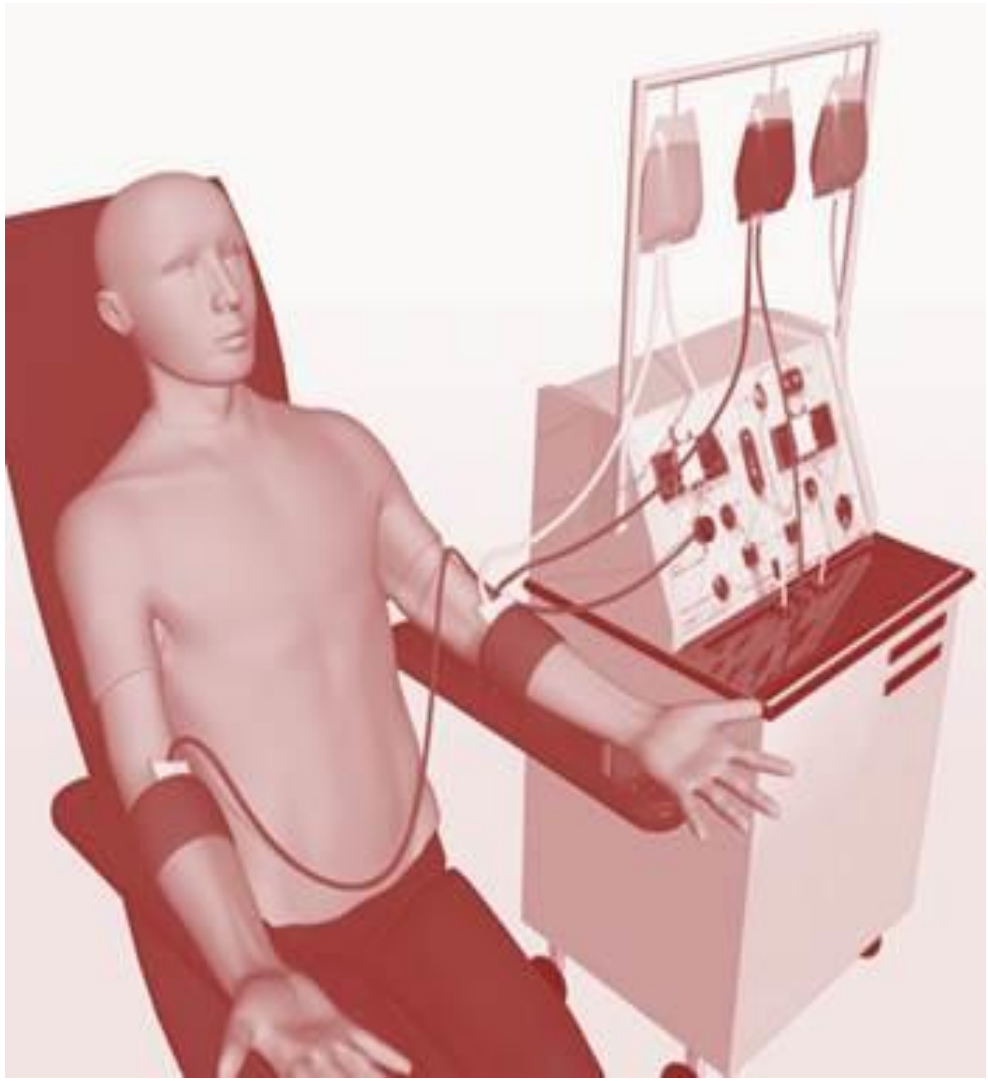
- Blood stem cells can be donated from
  - Bone marrow (harvested)
  - Peripheral blood stem cells (apheresis procedure)
  - Umbilical cord blood collection
    - Public banks (vast majority)
    - Private banks (rarely used for HCT)

(Smith, 2011); (Fox, Chervenak & McCullough, 2008)

Bone Marrow Harvest

www.cnn.com/2012/12/25/health/bone-marrow-donation

Peripheral Blood Stem Cell Collection



www.regenexx.com/2012/08/apheresis-has-more-stem-cells-than-bone-marrow/

Umbilical Cord Blood Collection

www.mja.com.au/journal/2006/184/8/no-longer-biological-waste-product-umbilical-cord-blood

Who is eligible?

- Seattle Consensus Criteria informed the first multi-centre clinical trial
- Milder phenotypes eligible for matched sibling donor HCT in some centres
  - Due to high rates of success and fewer complications
- Experimental options only for more severe phenotypes without a matched sibling donor
  - Unrelated donor, umbilical cord blood, haploidentical
  - At present, alternative donor HCT should be performed on a clinical trial

Who is eligible?

- Typically HbSS or HbSβ^0 genotypes

- Sickling phenotype history of
  - Stroke
  - Recurrent acute chest syndrome
  - Recurrent vaso-occlusive crises
  - Red blood cell alloimmunization
  - Pulmonary hypertension
  - Sickle lung disease
  - Sickle nephropathy

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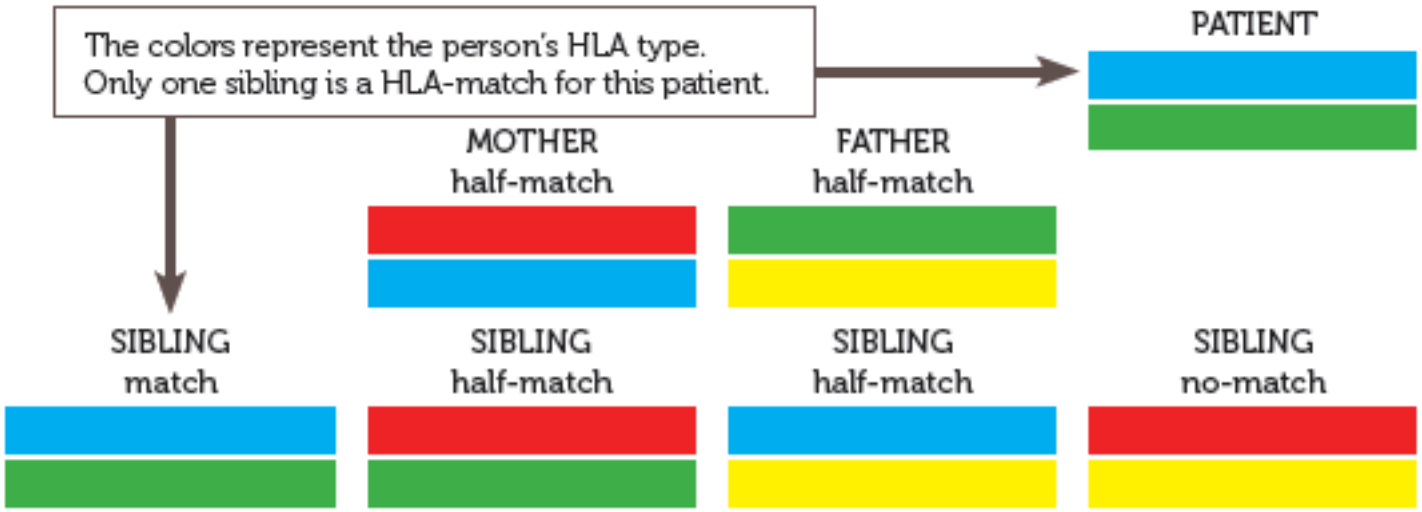
Some complications (but not too many)

HLA Matching- 1st we need a donor



(SUN Sickle Cell BMT Booklet, 2017)

How many African-Americans can find unrelated donors?

Table 1. Formal Search Results Showing the Best HLA-Matched URD or Best CB Units in Patients who Underwent Combined Searches (n = 525): URD Predominantly Serves Patients of Northwestern, Eastern, or Mixed European Ancestry, Whereas CB Extended Access to a Stem Cell Source to Both Europeans and Non-Europeans

	Patients of European Ancestries			
	Northwestern European (n = 104)	Eastern European (n = 76)	Southern European (n = 60)	European Mix (n = 101)
Best URD				
10/10	64 (62%)	45 (59%)	20 (33%)	51 (50%)
9/10	28 (27%)	20 (26%)	20 (33%)	31 (31%)
≤8/10	12 (12%)	11 (14%)	20 (33%)	19 (19%)
Best CB*				
5-6/6	88 (85%)	62 (82%)	36 (60%)	84 (83%)
4/6	15 (14%)	12 (16%)	15 (25%)	14 (14%)
No CB	1 (1%)	2 (3%)	9 (15%)	3 (3%)

	Patients of Non-European Ancestries				
	Asian (n = 42)	African (n = 61)	White Hispanic (n = 48)	Middle Eastern (n = 10)	Non-European Mix (n = 23)
Best URD					
10/10	8 (19%)	5 (8%)	10 (21%)	6 (60%)	9 (39%)
9/10	6 (14%)	20 (33%)	14 (29%)	1 (10%)	8 (35%)
≤8/10	28 (67%)	36 (59%)	24 (50%)	3 (30%)	6 (26%)
Best CB*					
5-6/6	36 (86%)	35 (57%)	33 (69%)	8 (80%)	19 (83%)
4/6	6 (14%)	14 (23%)	10 (21%)	2 (20%)	2 (9%)
No CB	0	12 (20%)	5 (10%)	0	2 (9%)

URD indicates adult unrelated volunteer donor; CB, cord blood.

*Best CB units were defined according to HLA-match but also had to have an adequate total nucleated cell (TNC) dose of at least 1.5×10^7/kg/unit.

(Barker et al., 2010)

Donor Options for SCD

- Matched sibling donors are the ideal donors
  - Safest, best outcomes
    - Stay tuned for Dr. Saraf
  - Only ~15-20% of full siblings will be an HLA match and not have SCD
- Matched unrelated donors are hard to find for most people with SCD
  - Higher risks of graft rejection
  - Higher risks of GVHD

Haploidentical HCT

- The donor is usually in the room...
  - Half-matched (at least) 1st degree relative
  - Fathers are typically preferred
- The easiest access to donors, so potentially the easiest solution
- However, these are **complex transplants** with more potential for complications
  - GVHD
  - Rejection
  - Infections
  - Post-transplant lymphoproliferative disease

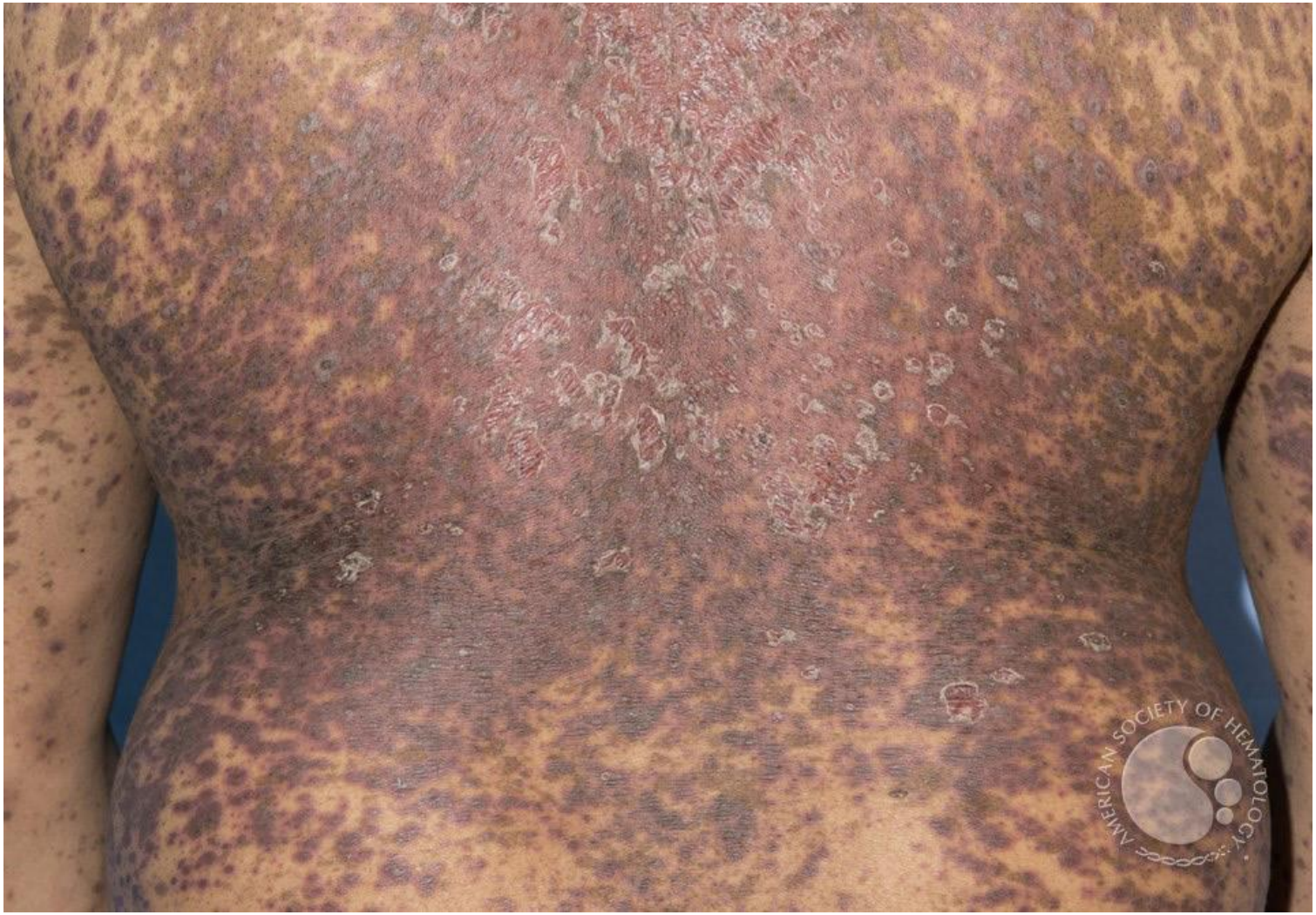
The two biggest challenges to HCT in SCD

- Graft rejection
  - Person with SCD (recipient) destroys the new blood system
    - Either immediately- primary graft failure
    - Or after a period of initial acceptance- secondary graft failure
- Graft-versus-host disease
  - Immune blood cells (T-cells) in the donated cells react against the person with SCD
  - Can be life threatening or very dangerous
  - Most common cause of death in HCT for SCD

Graft Rejection

Immense-immunology-insight.blogspot.com

Graft-Versus-Host Disease



(SUN Sickle Cell BMT Booklet, 2017)

Graft-versus-Host Disease

- Can be acute or chronic
- Can be life threatening or life limiting
  - Skin
  - Liver
  - Gastrointestinal tract
  - Lungs
  - Musculoskeletal system

- **The most important cause of death in HCT for sickle cell disease**

(Guilcher et al., 2018)

Pathophysiology of GVHD

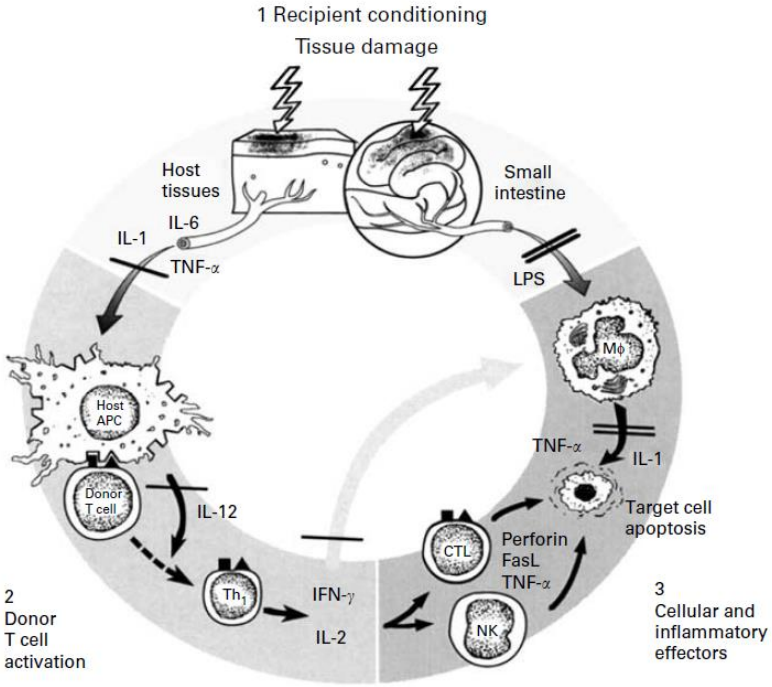


Figure 1 Acute GVHD pathophysiology—the three sequential phases of GVHD are detailed. (taken from Hill and Ferrara[1]. Copyright American Society of Hematology, used by permission). GVHD, graft-versus-host disease.

(Jacobsohn, 2008); (Hill & Ferrara, 2000)

How can GVHD risk be reduced?

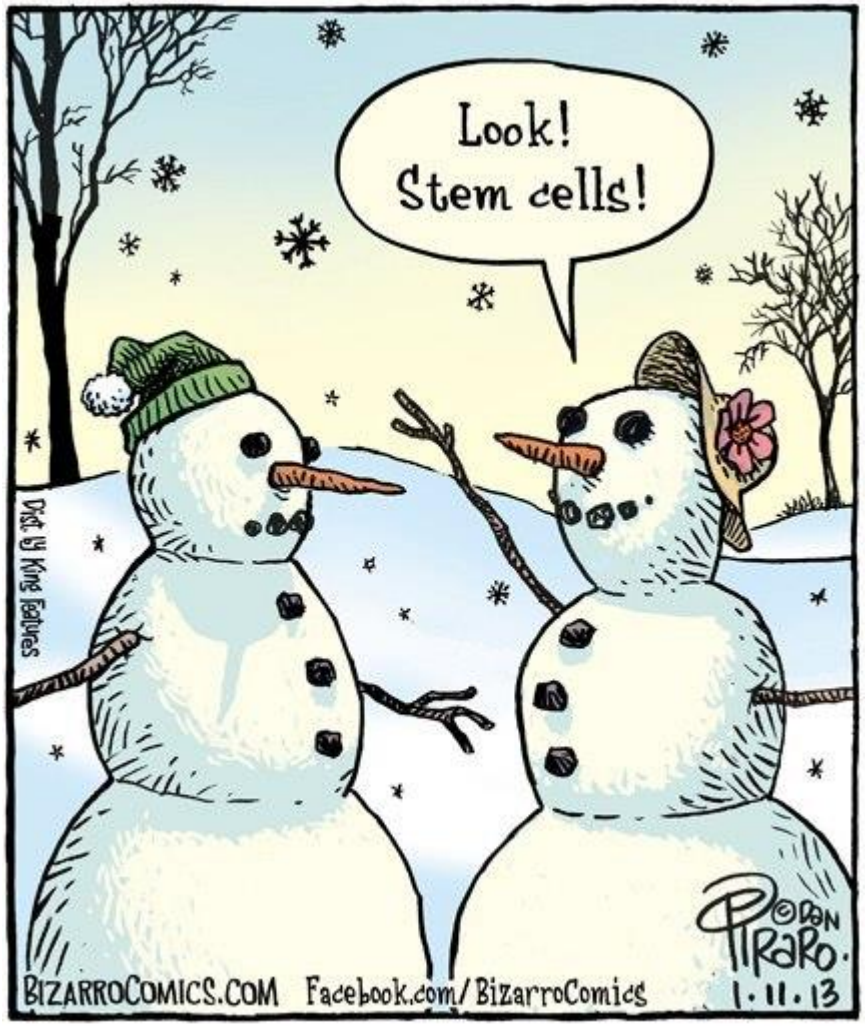
- Better HLA matching (ideally 8/8 or 10/10)
- Family matches (siblings best)
- Younger donors
- Younger recipients
- Male donors
- Preventative medications
- Graft manipulation
- Stem cell source (bone marrow typically preferred)

Other Risks of *Myeloablative* Allogeneic HCT

- Death
  - Infection/Sepsis
  - End organ dysfunction
    - Veno-occlusive disease of liver
    - Renal insufficiency
      - Sepsis
      - Calcineurin inhibitor (eg cyclosporin)

- **Infertility** (85%)
- Cancer (5-8%)
  - 0.4% in French SCD HCT experience (Bernaudin, personal communication)

(Thomas, 2004)


Look!
Stem cells!
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When is the best time for HCT for SCD?

- Retrospective analysis of 727 patients who underwent HCT from a **sibling donor** at 98 EBMT centres over 30 years

- Group 1 (< 5 years of age)
  - 96% EFS, 99% OS
  - Less GVHD
- Group 2 (6-15 years)
  - 92% EFS, 95% OS
- Group 3 (> 15 years)
  - 84% EFS, 88% OS
  - More GVHD

(Cappelli et al., ASH Meeting 2017)

Journal of Blood Medicine

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REVIEW

Hematopoietic stem cell transplantation in sickle cell disease: patient selection and special considerations

"Therefore, **we would recommend that siblings of all patients with homozygous SCD be HLA-tested** to see if they are a match, and if they are, that the patient should be evaluated for HSCT.

We recommend this be done in early childhood, and be irrespective of whether the child is symptomatic or not."

(Bhatia et al, 2015)

EBMT/EUROCORD/CIBMTR Registry Data

- 1000 recipients of HLA-matched sibling donor HCT between 1986 and 2013
  - 87% myeloablative
  - 84% received bone marrow allografts
- 5 year EFS 91%, OS 93%
  - 5 year GVHD-free survival was 86% < 16 years, 77% for those > 16 years

Table 3. Multivariate analysis for EFS and OS

	EFS		OS	
	HR (95% CI)	*P* value	HR (95% CI)	*P* value
PB vs BM	1.93 (0.87-4.26)	.104	2.62 (1.17-5.89)	.019
CB vs BM	0.55 (0.13-2.31)	.412	Not applicable*	
Age	1.09 (1.05-1.12)	<.001	1.10 (1.06-1.14)	<.0001
Transplant year, ≥2007 vs ≤2006	0.95 (0.90-0.99)	.013	0.96 (0.91-1.00)	.101
Conditioning regimen, RIC vs MAC	1.13 (0.46-2.81)	.793	0.83 (0.29-2.39)	.735
In vivo T-cell depletion, yes vs no	1.34 (0.63-2.82)	.445	1.10 (0.49-2.48)	.806

The adjusted Cox regression analysis was stratified by registry (EBMT and CIBMTR); age was considered as a continuous variable, and when considering the graft source, PB and CB were compared, separately, with BM (baseline) for the EFS.

*Not evaluable, as there was only 1 event in the CB group; therefore, for OS, the CB transplants were included with BM transplants.

(Gluckman et al., 2017)

What are some unique aspects of HCT for SCD?

- HbS should be <30% prior to conditioning
  - To avoid a crisis or CNS event during recovery from HCT
  - Either simple or exchange transfusion can achieve this goal
- Consider Hydroxyurea for 3-6 months prior to HCT
  - To reduce marrow cellularity and facilitate engraftment
  - Weak data to support this practice
- Magnesium should be maintained in normal range
  - Risk of seizures
  - Cyclosporin will lower Mg

(Walters et al., 1996)

Other supportive care precautions

- BP must be kept normal for age
  - Risk of CNS events
- Hg must be maintained 90-110 g/L post-HCT
  - Avoid high (hyperviscosity)
  - Avoid low (hypoxia)
- Platelets should be kept > 50 x 10^9/L
  - High rates of CNS bleeding in original studies
  - Columbia (NYC) has had success with threshold of 30 if no Hx CNS neurovascular events
  - STAR is studying this supportive care practice

(Walters et al., 1996); (Bhatia and Nickel, personal communications)

Long Term Outcomes

- Treatment-related mortality (TRM) is low with a sibling donor
- GVHD is the most important cause of TRM
  - Focus of future efforts
- Second malignancy rate 0.4% (personal communication from Dre. Bernaudin)
- Infertility rates **very high (especially in post-pubertal females)** with busulfan exposure
- Typically stabilization of disease *at time of HCT* if

  Hb S < 50% and donor myeloid chimerism > 20-25%

(Bernaudin et al., 2007; Gluckman et al, 2013, Walters et al, 2010)

What is our definition of success?

- **S**ickle cell **T**ransplant **A**dvocacy and **R**esearch alliance

  - **Immune Suppression-Free Event-Free Survival**

    - **Alive with successful engraftment and no chronic GVHD**

How much donor engraftment is enough?

TRANSPLANTATION

At least 20% donor myeloid chimerism is necessary to reverse the sickle phenotype after allogeneic HSCT

Courtney D. Fitzhugh,[1,2] Stefan Cordes,[3] Tiffani Taylor,[2] Wynona Coles,[2] Katherine Roskom,[1] Mary Link,[2] Matthew M. Hsieh,[2] and John F. Tisdale[2]

[1]Sickle Cell Branch, National Heart, Lung, and Blood Institute (NHLBI), [2]Molecular and Clinical Hematology Branch, National Institute of Diabetes and Digestive and Kidney Diseases/NHLBI, and [3]Hematology Branch, NHLBI, National Institutes of Health, Bethesda, MD

ELSEVIER

Biology of Blood and Marrow Transplantation

Available online 4 September 2017

In Press, Corrected Proof

Relationship between Mixed Donor–Recipient Chimerism and Disease Recurrence after Hematopoietic Cell Transplantation for Sickle Cell Disease

Allistair Abraham [1], Matthew Hsieh [2, 3], Mary Eapen [4], Courtney Fitzhugh [2, 3], Jeanette Carreras [4], Daniel Keesler [4], Gregory Guilcher [5], Naynesh Kamani [6], Mark C. Walters [7], Jaap J. Boelens [8], John Tisdale [2, 3], Shalini Shenoy [9], National Institutes of Health, Center for International Blood and Marrow Transplant Research

(Fitzhugh et al, 2017); (Abraham et al, 2017)

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So can we reduce the intensity of the conditioning?

- Reduced Intensity Conditioning (RIC)
- Nonmyeloablative conditioning
  - Lower intensity chemotherapy ± radiation therapy to allow for engraftment yet minimize risks of morbidity and mortality
    - Often lower rates of GVHD
      - Less tissue damage with subsequent antigen presentation for immune reaction
    - Increased opportunity for fertility preservation

Success is more than survival

- We need to know how timing of HCT can affect
  - Neurocognitive outcomes
  - Stroke risk in those who have established neurovascular disease
  - Lung function (particularly restrictive lung disease) and risk of pulmonary hypertension
  - Renal outcomes
  - Immune recovery (spleen)
  - **Pain/patient reported outcomes/Health Related Quality of Life**
  - Health Economics analyses

Success is more than survival

- STELLAR
  - Sickle Cell Post Transplantation Long Term and Late Effects Registry
  - Emory University
  - Biomarkers of cardiovascular health, HRQoL, immune function, gonadal and sexual function

- STAR Retrospective Registry
  - Includes over 300 patients with rich data on organ function long-term
  - Manuscripts in progress

Project Sickle Cure

- STAR prospective study of 1st 3 years post-HCT
  - Immune recovery
  - Neurocognitive outcomes with imaging and biomarker correlates
  - Renal outcomes
  - Patient/sibling donor/family member HRQoL
    - Pain
    - Fatigue
    - Anxiety/Depression
    - Decisional regret
  - Biorepository and Neuroimaging Repository

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HCT for SCD

- Requires a balanced discussion based on:
  - patient age
  - disease genotype/phenotype
  - donor options
  - available clinical trials

- New therapies such as novel disease modifying agents and gene therapy need to be continually positioned against HCT (which is also evolving)

European Expert Panel Recommendations

Table 5. Recommendation summary for HSCT in SCD.

Indication for MSD-HSCT	Symptomatic SCD
Time of transplantation:	With HLA-identical sibling: as soon as possible
Stem cell source from MSD:	Bone marrow, cord blood
Indication for HSCT from unrelated BM or CB donors:	At least one criteria according Walters *et al.* (Table 3) Within controlled clinical trials only
Conditioning regimen:	Standard: IV Busulfan, cyclophosphamide, ATG Reduced: within controlled clinical trials only
GvHD-prophylaxis for MSD-HSCT	Standard: CSA + MTX; antibodies (ATG, alemtuzumab) as rejection- and GvHD-prophylaxis
Post-transplant evaluation:	In cooperation of hematologists and transplant experts

MSD: HLA-identical sibling donor; HSCT: hematopoietic stem cell transplantation; GvHD: graft-versus-host disease; CSA: cyclosporine A; MTX: methotrexate; ATG: anti thymo globuline.

- Many would argue that reduced intensity conditioning NOT be limited to clinical trials in 2018

(Angelucci et al., 2014; Guilcher et al., 2018)

How do we offer safe cure to everyone?

- Every patient needs a donor
  - Haploidentical HCT
    - Is the most promising direction for HCT if graft rejection and GVHD barriers can be overcome
  - Gene therapy
    - Needs to be refined to document cures
    - Promising for thalassemia major
    - Fertility risk due to chemotherapy
- **Every person with SCD needs access to cure**
  - Safe curative options
  - Equitable pathways to access these treatments
    - North America and worldwide

Global Health Opportunity

- Most eligible recipients in the world cannot access HCT due to resources
  - **3 years of chronic transfusion = HCT cost and follow-up in low income countries**
  - **80% of children with SCD in parts of Sub Saharan Africa die by age 10**

- Global Sickle Cell Disease Network
  - Led by Dr. Isaac Odame (SickKids)

- Successful Transplants have been reported in West Africa

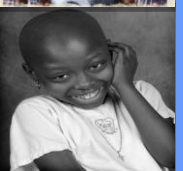
- East African Collaboration with
  - Dr. Julie Makani (Tanzania)
  - Drs. Clement Okello and Henry Ddungu (Uganda)
  - Dre. Eliane Gluckman (France)
  - Drs. Doreen Mutua and Jessie Githanga (Nairobi)

Many other important contributors









STAR 2019 Annual Meeting

Alberta Children's HOSPITAL

- 60+ attendees from across North America representing STAR member children's hospitals, STAR Board, volunteers, SCD families and experts in the field
- All 3 annual meetings in Banff/Canmore