Curative therapies for Sickle Cell Disease: Hematopoietic Stem Cell Transplant & Gene Therapy

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Summary

- Sickle cell disease review
  - Etiology
  - Impact of disease
- Curative therapies
  - Hematopoietic stem cell transplant
  - Gene therapy

Sickle cell disease

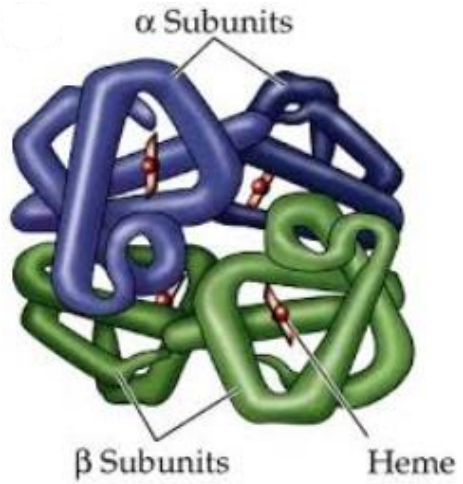
What is sickle cell disease?

A genetic hemoglobinopathy

Our DNA (genetic code): ½ from Dad, ½ from Mom

Sickle cell disease = Abnormal β globin subunits, either

1. HgbSS = 2 β globin genes coding for "sickle" hemoglobin, or
2. HgbS βthal$^{+/0}$ = 1 β globin gene coding for "sickle" hemoglobin & 1 β globin gene with a mutation resulting in decreased (+) or no (0) β globin

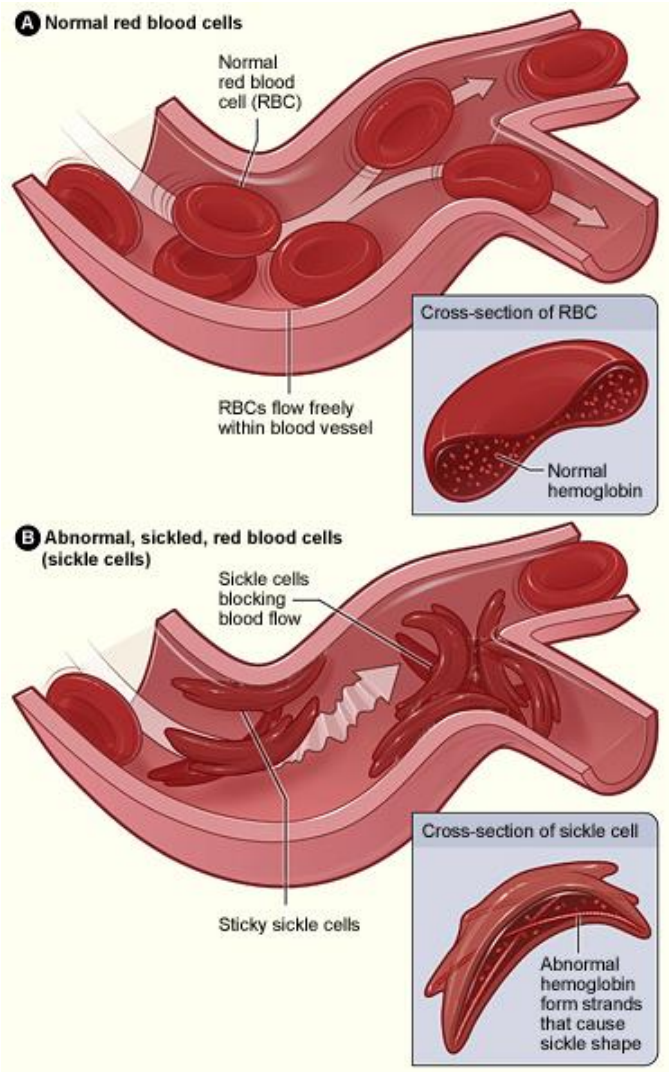


Hemoglobin is in red blood cells and functions to carry oxygen throughout the body

RBCs have to change shape to move through the blood vessels, but RBCs containing HgbSS become sickled

Shorter lifespan of the HgbSS RBCs and Sickled cells block blood flow to parts of the body

What is sickle cell disease?



Red blood cells deform/sickle →
Decreased blood flow →
Decreased oxygen delivery →
Cells die = Infarct

Sickle cell disease affects all organs

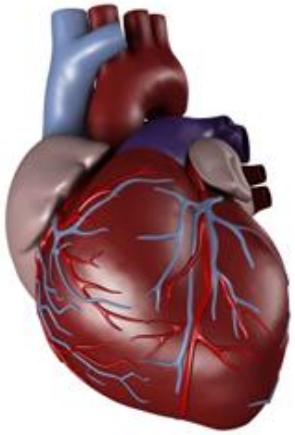
Silent strokes
Overt strokes

Retinopathy
Vision loss

Leg ulcers

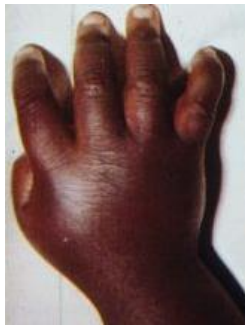
Splenic sequestration
Autoinfarction

Priapism



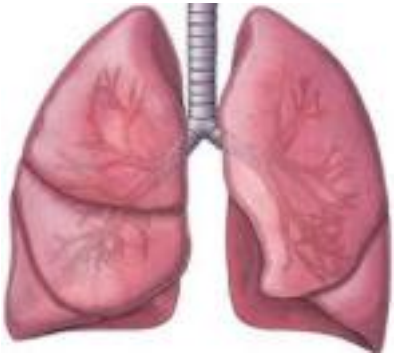
Heart
strain
And failure

Aplastic crisis



Dactylitis

Vaso-occlusive Crisis Pain

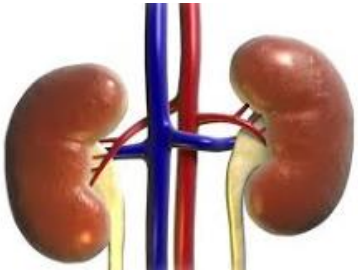


Gall stones

Acute chest syndrome
Pulmonary hypertension

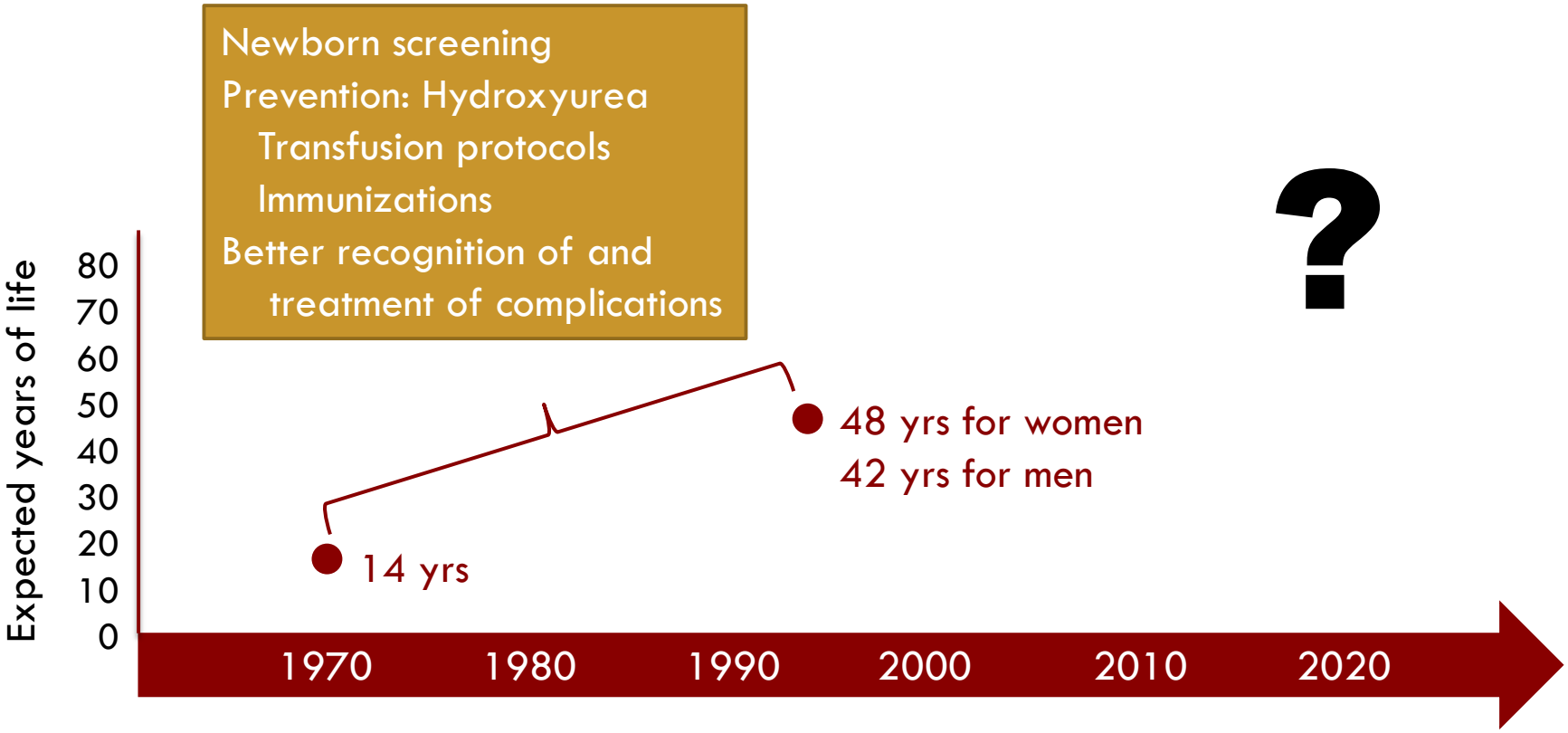
Osteomyelitis

Acute papillary necrosis
Nephropathy
High blood pressure



Pregnancy complications

Sickle cell disease survival



Improvement in life expectancy

but not yet equal to non-sickle cell population

Current interventions: Helpful but not a cure

- **Newborn screening:** Early identification, genetic counseling
- **Improved education:** Importance of hydration, avoiding triggers for RBC sickling such cold exposure, altitude
- **Hydroxyurea:** Increases HgbF (fetal hemoglobin), decreased concentration of HgbS within RBC
  - **Not always effective**
  - **Requires a pill daily**
- **Transfusion programs (simple or exchange):** Provides normal hgb/RBCs
  - **Iron overload**
  - **Time consuming**
- **Immunizations and preventative antibiotics**
  - **Not as effective as a functioning spleen**
  - **Requires a pill twice daily**

Curative therapies

What causes sickle cell disease?

- HgbSS genes→ Sickle hemoglobin → Sickle RBCs

- 2 options for **CURE:**
  - Permanently replace the RBCs
  - Correct the genetic mutation

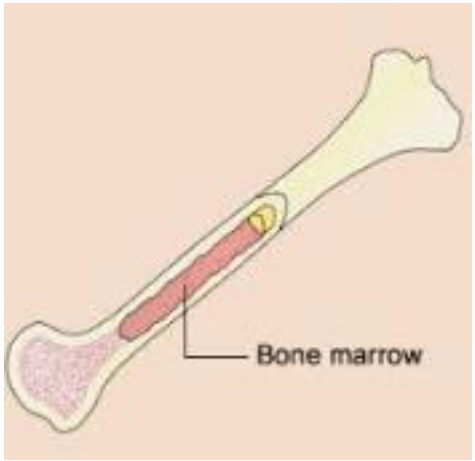
Hematopoietic Stem Cell Transplant

Gene Therapy

Hematopoietic stem cell transplant (HSCT)

What is HSCT?

- HSCT = hematopoietic stem cell transplant
- Also known as bone marrow transplant or BMT
- For treatment of Sickle Cell Disease, takes advantage of the fact that the problem is in the RBCs, which come from bone marrow



Hematopoietic stem cells in the bone marrow make 3 cell types:

1. **Red blood cells (RBCs)** – carry oxygen
2. **White blood cells (WBCs)** – fight infection
3. **Platelets** – clot blood

HSCT in Sickle Cell Disease

Donor without
HgbSS
Bone marrow stem cells
Peripheral blood stem cells
Umbilical cord blood stem cells

Chemotherapy

Stem cell infusion

Patient with HgbSS

Patient without HgbSS

History of HSCT in HgbSS

1984: Child with HgbSS developed leukemia→

Sibling bone marrow transplant cured leukemia + HgbSS

Donor	Conditioning	Overall survival (%)	Free of sickle cell disease (%)	Acute GVHD (%)
HLA-matched sibling	Myeloablative	90	70	15
HLA-matched sibling	Reduced intensity	98	92	5
Related umbilical cord	Mix	91	90	8
Unrelated umbilical cord	Mix	85	49	20
Haploidentical	Mix	91	50*	9

*New approach at UMN bringing haplo success up to that of MSD BMT

Common questions about donors

- **What is HLA-matching?**
  - Tested by a cheek swab or blood draw
  - The cells in our body have proteins on the surface (HLA) that help our immune system identify **self versus foreign**. We get ½ from our Mom, ½ from our Dad. Infusion of HLA-mismatched cells will result in rejection of the donor cells or attack of the patient by the donor cells (graft-versus-host disease).
- **Likelihood that a sibling will be an HLA-match?**
  Statistically 25%, in reality 16%
- **Would you use a sibling who has Sickle Trait?** Yes
- **Likelihood of finding an HLA-matched unrelated bone marrow donor?** 66%

Who is eligible for HSCT?

Established indications

1. Overt stroke
2. Increased TCD velocity (>200 m/s)
3. Frequent Vaso-occlusive crises (≥2 hospital admission requiring IV narcotics)*
4. Recurrent priapism requiring medical therapy
5. Acute chest syndrome (≥1 episode)*
6. Red cell alloimmunization
7. Osteonecrosis of ≥2 joints

Potential Indications

1. Silent infarct with severe anemia or neurocognitive dysfunction
2. Tricuspid regurgitant jet velocity >2.5 m/sec
3. Sickle-related liver injury or iron overload
4. Renal insufficiency (dialysis, nephrotic syndrome, sickle nephropathy)

* On a therapeutic dose of hydroxyurea

Sickle cell disease affects all organs

Hgb SS is a *chronic disease* with silent accumulation of *end-organ damage* over time

Outcomes of HSCT are compromised by this major organ dysfunction

HSCT cannot fix the irreversible damage from HgbSS

As HSCT as a therapy improves and we shift to less toxic regimens, less severe patients considered for HSCT **BEFORE** HgbSS complications arise.

HSCT Timeline

Work-up week:
Studies to evaluate
Major organ function
and
Ensure no hidden
Infections

Unique to HSCT of HgbSS

- Compared to other patients undergoing HSCT:
  - Increased CNS complications (encephalopathy, seizures, stroke)
  - Possibility of sickle complications

- ✔ Hydroxyurea for 1 month prior
- ✔ Simple or exchange transfusion to get HgbS % <30%
- ✔ Higher transfusion thresholds (Hgb >9, plt >50,000)
- ✔ Tight blood pressure control
- ✔ Anti-seizure medication

Improvements in HSCT over time

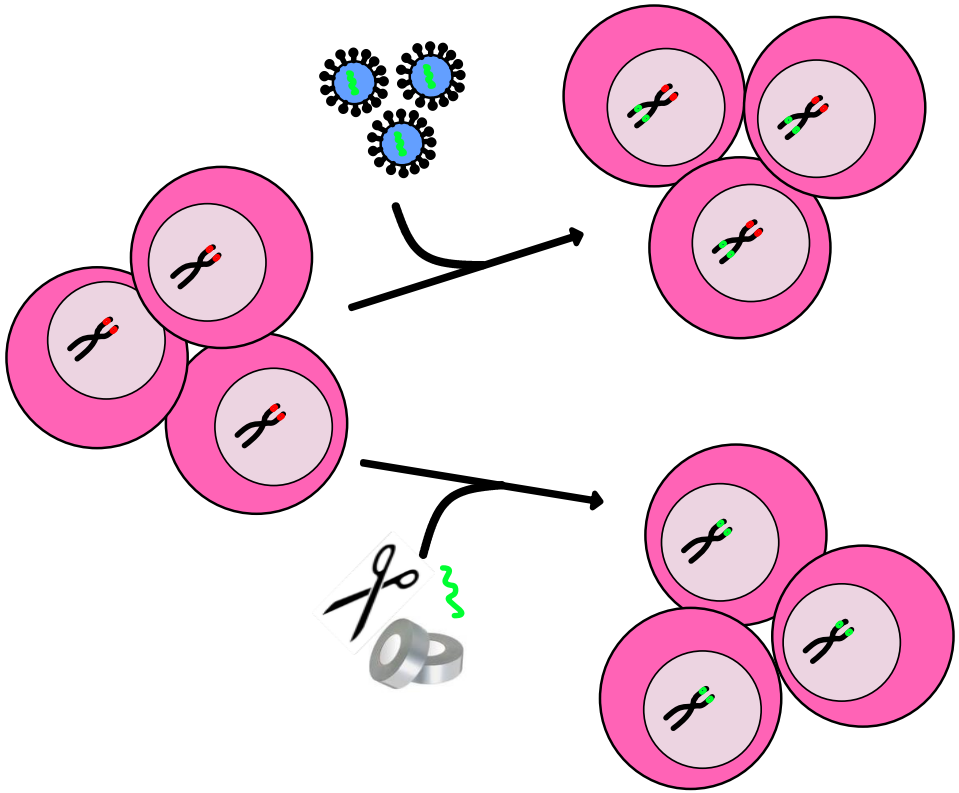
- **Myeloablative → Reduced intensity**
  - Better fertility preservation, less organ toxicity
- **Availability of alternative donors**
  - Haploidentical, umbilical cord blood
- **Offering HSCT early in life, before accumulation of irreversible end-organ damage**

Gene Therapy

Gene therapy

Stem cells infected by lentivirus carrying a Normal β hemoglobin gene

Stem cells taken from the patient



Manipulated cells returned to the patient

Stem cells manipulated to replace the abnormal β hemoglobin gene with a normal hemoglobin β chain

Gene therapy

- **Benefits over HSCT:**
  - Achieve cure without needing to find a donor
  - No GvHD or need for immune suppression
- **Limitations:**
  - Still requires chemotherapy to get rid of stem cells with the abnormal β hemoglobin gene and make room for new, corrected stem cells
  - Can have problems with the viral transduction
  - Insertional mutagenesis (hopefully a problem of the past, but remains to be seen)

Are there gene therapy trials open for Sickle cell disease?

- **UCLA Phase I/II trial (NCT02247843)**
  - Opened in 2014, planning to enroll 6 patients
  - Lentiviral vector based (Lenti/βAS3-FB, anti-sickling gene)
  - Cytoreduction with busulfan
  - Restricted: Age >18, no available matched related donor, inadequate response to hydroxyurea

Results pending

- **Cincinnati Children's Phase I/II trial (NCT02186418)**
  - Opened in 2014, planning to enroll 10 patients
  - Lentiviral vector based (Gamma-globin)
  - Cytoreduction (not described further)
  - Restricted: Age 18-35, failed or chose not to take hydroxyurea. Need to stay in Cincinnati for 3-6 months

Results pending

Are there gene therapy trials open for Sickle cell disease?

- **Bluebird Bio Phase I/II trial (NCT02140554) – Sites: Chicago, NIH, Charleston SC, Bethesda MD, Oakland CA, NY NY, Philadelphia PA**
  - Opened in 2014, planning to enroll 50 patients
  - Lentiviral based (LentiGlobin BB305)
  - Restricted: Previously only for adults, now down to age 12 yrs (12-50 yrs), severe disease, for those <18 years excluded if have a willing, HLA-matched sibling donor available

OPENING SOON AT UMN
For ages 2 to 50 yrs!!

- **Boston Children's Pilot Study (NCT03282656)**
  - Opened in 2018, planning to enroll 6 patients
  - Lentiviral vector based (short hairpin (sh) RNA targeting γ–globin gene repressor, BCL11A to increase fetal hgb production)
  - Cytoreduction with busulfan
  - Restricted: Three age stratum (initially for 18-40, then 12-18 yrs, then 3-12 yrs), severe disease, no available matched related donor, inadequate response to hydroxyurea

Results pending

Summary

- **Curative therapy options expanding**
- **Outcomes with HSCT improving**
  - Reduced intensity conditioning
  - Alternative sources of stem cells (umbilical cord blood, haploidentical donors) make HSCT an option for more patients with HgbSS
- **Gene therapy trials opening to children!**

What do I struggle with?

- Decided who should proceed to HSCT and when?
- Or who should wait for gene therapy?
- Or who will do wonderfully well with hydroxyurea?

University of Minnesota Pediatric Blood and Marrow Transplant

- www.mhealth.org/childrens/care/treatments/blood-and-marrow-transplant-pediatrics

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