Hematopoietic Stem Cell Transplant for Sickle cell disease –What a pediatrician ought to know

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Division of Blood and Marrow Transplantation

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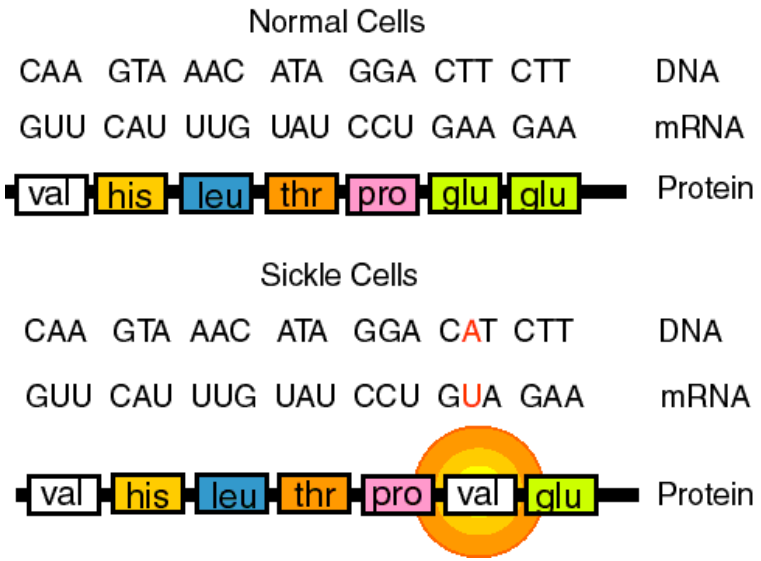
Outline

Background Sickle cell disease

Matched Sibling Transplants for Sickle cell disease

Current outcomes of transplant

Post transplant follow-up care



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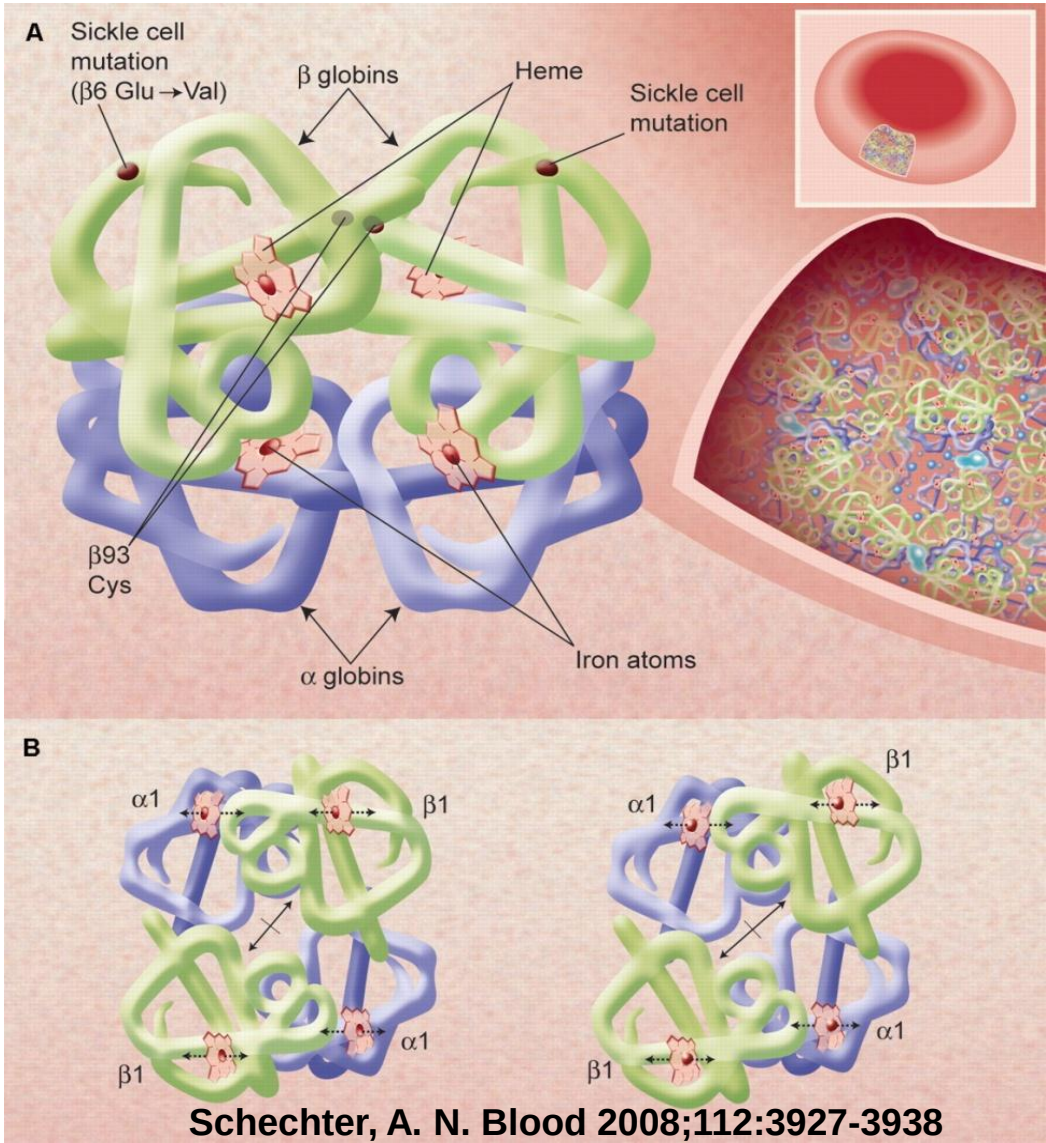
Hemoglobin

Human adult hemoglobin HbA - tetramer of 2 α- and 2 β-globin chains

2 α-globin genes on chromosome 16

1 β-globin gene on chromosome 11



Schechter, A. N. Blood 2008;112:3927-3938

Sickle Cell Disease (SCD)

Sickle cell disease - qualitative mutation

Thymine replaces adenine → hydrophilic glutamic acid replaced by hydrophobic valine

Hemoglobin S molecules in deoxy conformation aggregate

Cells sickle irreversibly with time

Result is vaso-occlusion – basis of pain crises, acute chest sydrome, stroke, etc.

Fathallah et al., Blood Cells, Molecules, and Diseases 43 (2009) 58–62

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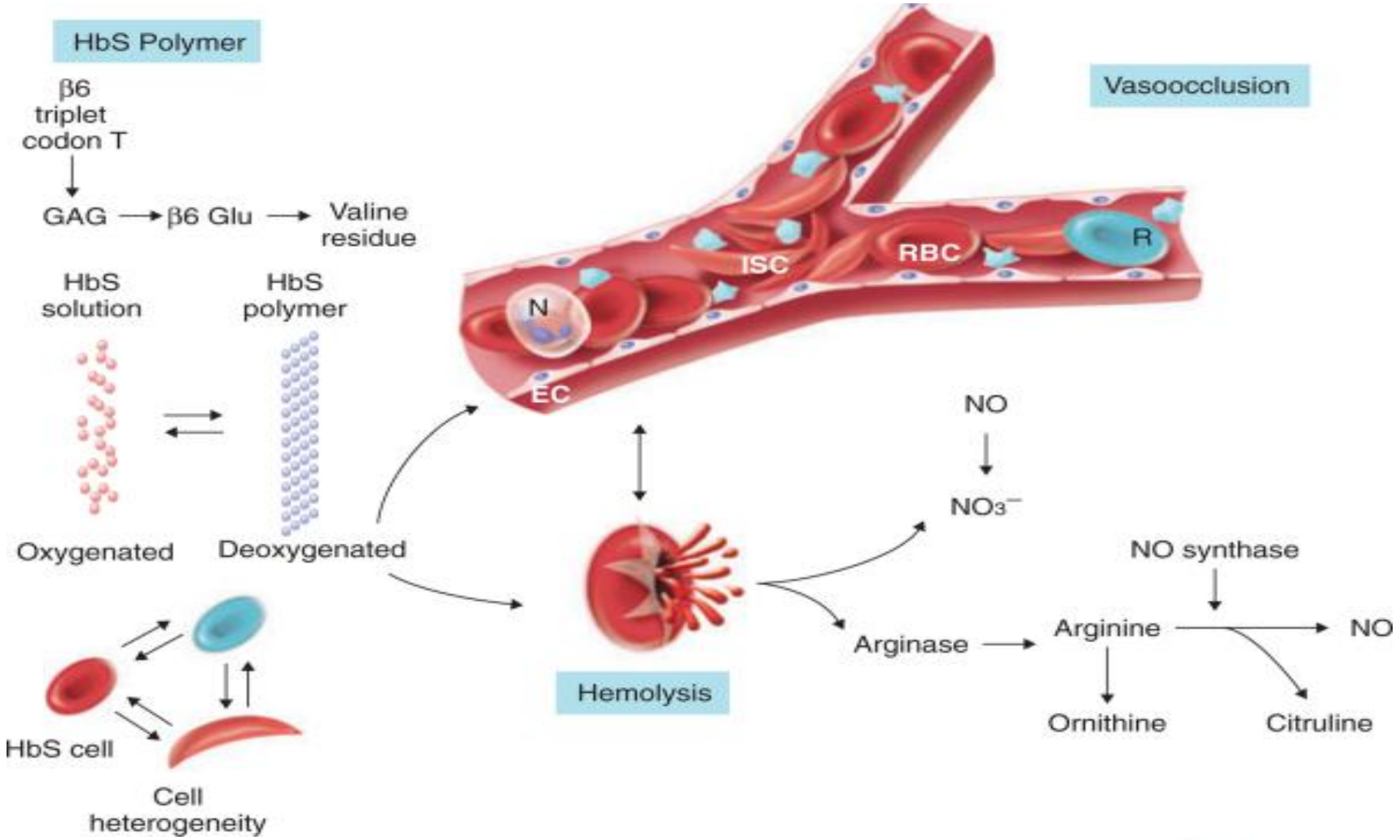
Pathophysiology SCD



Goldman: Cecil Medicine, 23rd ed.

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Sickle Cell Disease (SCD)

SCD affects ~70-100,000 people in U.S.

Typical clinical manifestations

- anemia
- severe painful crisis
- acute chest syndrome
- splenic sequestration
- stroke (clinically overt and silent)
- chronic pulmonary and renal dysfunction
- growth retardation
- neuropsychological deficits
- premature death

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Survival

1994 NIH Cooperative Study of SCD (CSSCD) estimated median survival HbSS 42 yrs for men, 48 yrs for women

SCD-related mortality in childhood contributed significantly to this shortened survival

Dallas Newborn Cohort (1983-2007) estimates SCD childhood survival ~94%

Adult mortality (1992-2009) MSH follow-up study including hydroxyurea treated ~43%

Platt et al, N Engl J Med 1994; 330:1639-1644

Steinberg MH, Am J Hematol. 2010 Jun;85(6):403-8.

Quinn et al, Blood 2010 April;115(17)

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Morbidity

However still negative effects of disease

- Stroke (including silent)
- Chronic kidney disease/failure
- Pain admissions, missing days of work/school, opioid dependence
- Pulmonary hypertension

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Treatment options

Red Blood cell transfusions

Hydroxyurea

Hematopoietic stem cell transplantation

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Long-term RBC Transfusion

Replacement of sickle red cells with normal RBCs

Decreases erythropoiesis, hemolysis, sickling

Effective in preventing stroke and other complications

Associated with increased risk of iron overload, infection, and alloimmunization

Lee at al, Blood 2006 Aug 1;108(3):847-52

Hankins et al, J Pediatr Hematol Oncol. 2005 Mar;27(3):158-61

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Hydroxyurea (HU)

Mechanism of action

- Inhibits ribonucleotide reductase and DNA synthesis
- Appears to alter kinetics of erythropoiesis
- Possibly increases γ-globin expression through chromatin and promoter effects
- **Resultant red cells contain higher levels of HbF ($\alpha_2\gamma_2$)**

Hydroxyurea (HU)

Clinical and laboratory benefits

- Reduces frequency of VOC and ACS
- Appears to improve mortality in adults
- Substantial hematologic efficacy at maximum tolerated dose

Zimmerman et al, Blood. 2004 Mar 15;103(6):2039-45

Steinberg MH, Am J Hematol. 2010 Jun;85(6):403-8.

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Problems with Long-term HU use

Adherence to daily lifelong medicine with close monitoring

Remains underutilized in developed countries

? Does not significantly reduce the risk of stroke and other end-organ injury

Not FDA-approved for children with sickle cell disease

Ware and Helms, Blood. Epub 2012 Feb 7

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Transplant for Sickle cell disease

First reported in 1984

Child had leukemia as well as sickle cell

Transplant done for leukemia from a HLA matched sibling (with sickle trait)

The patient was cured of both diseases

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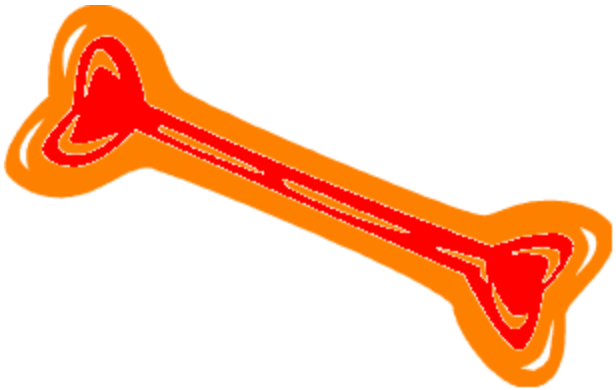
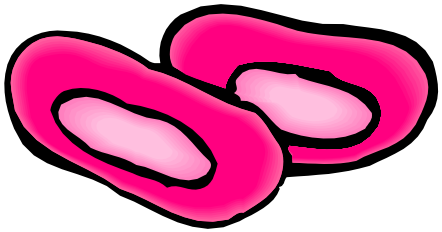
Healthy





Red Blood Cell

White Blood Cell

White Blood cells

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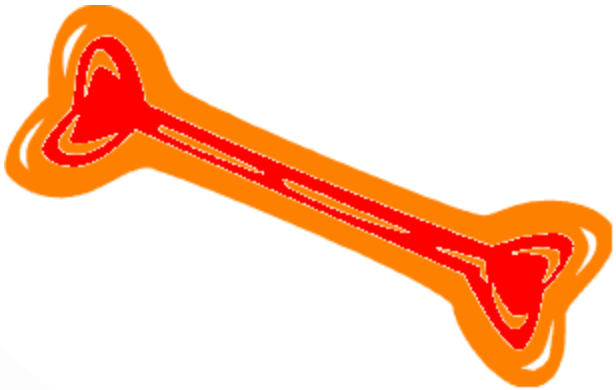
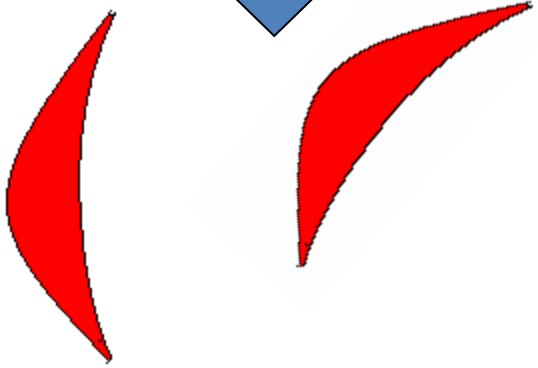
Sickle cell disease





Sickle Red Cells

White Blood Cell

White Blood cells

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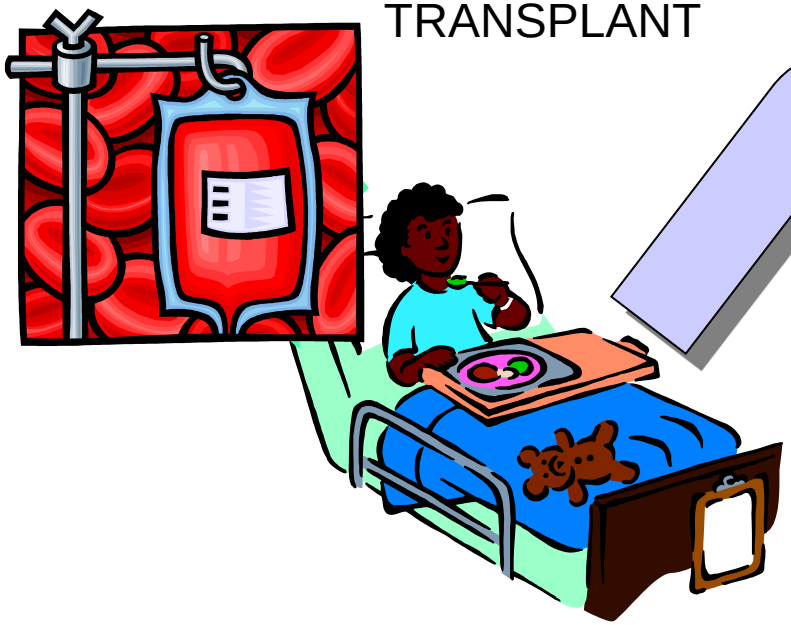
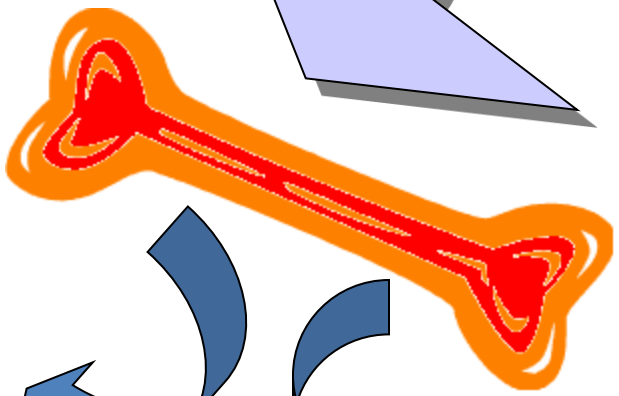
TRANSPLANT





White Blood Cell

Hematopoietic Stem Cell Transplant (HSCT)

Allogeneic HSCT remains only cure for SCD

Limited by appropriate donor

Traditional preparative regimens are toxic

Disease processes cause pre-existing organ injury

Significant transplant-related risks – e.g. GVHD, infection, rejection

Hansbury et al, Pediatr Blood Cancer 2012; 58: 611–615

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Selection criteria proposed for HSCT

- < 16 yrs of age
- HLA-identical related donor
- Have at least one of following signs or symptoms:
  - stroke or CNS event lasting > 24 h
  - acute chest syndrome
  - recurrent severe pain episodes
  - impaired neuropsychological function + abnormal MRI brain
  - stage I or II sickle lung disease
  - sickle nephropathy
  - bilateral proliferative retinopathy
  - osteonecrosis of multiple joints
  - RBC alloimmunization during long-term transfusion therapy

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Controversy about HSCT in SCD

Disagreement about correct timing and optimal patient population

Indicated for children with severe symptoms of SCD (strokes, recurrent ACS) with an HLA-matched donor?

Or better for pts who have not yet experienced such symptoms, but nonetheless will experience them

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MSD HSCT for SCD

Table 1 Results of bone marrow transplantation in sickle cell anemia

	Fred Hutchinson Cancer Research Center [1]	University of Louvain, St. Luc Hospital [3]	Fred Hutchinson Cancer Research Center [2]	Reference Center for Sickle Cell Disease, Intercommunal Hospital [4••]	Medical College of Wisconsin [7••]
Patients, *n*	22	50	50	87	67
Median age (range), years	10.4 (3.3–13.9)	7.5 (1.7–23)	9.9 (3.3–15.9)	9.5 (2–22)	10 (2–27)
Neurologic complications*	7	18	9	16	11
Graft failure (%)	18	10	10	7	13
Overall survival (%)	91 at 4 years	93 at 5 years	94 at 6 years	93 at 6 years	97 at 5 years
Event-free survival (%)	73 at 4 years	82 at 5 years	84 at 6 years	86 at 6 years	85 at 5 years

* Seizures or intracranial bleeding.

Javier Bolaños-Meade and Robert A. Brodsky, Current Opinion in Oncology 2009, 21:158–161

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French MSD BMT experience

Overall survival at 3 yr was 95%

Event-free survival was 92.9%

However, comparing the results before (n=23) and after 2000 (n=121) showed significant improvement of EFS at 3 yr:

- 73.9% for transplants performed before 2000
- 96.8% after 2000

Bernaudin et al, Blood (ASH Meeting Abstracts) 2010 116: Abstract 3518

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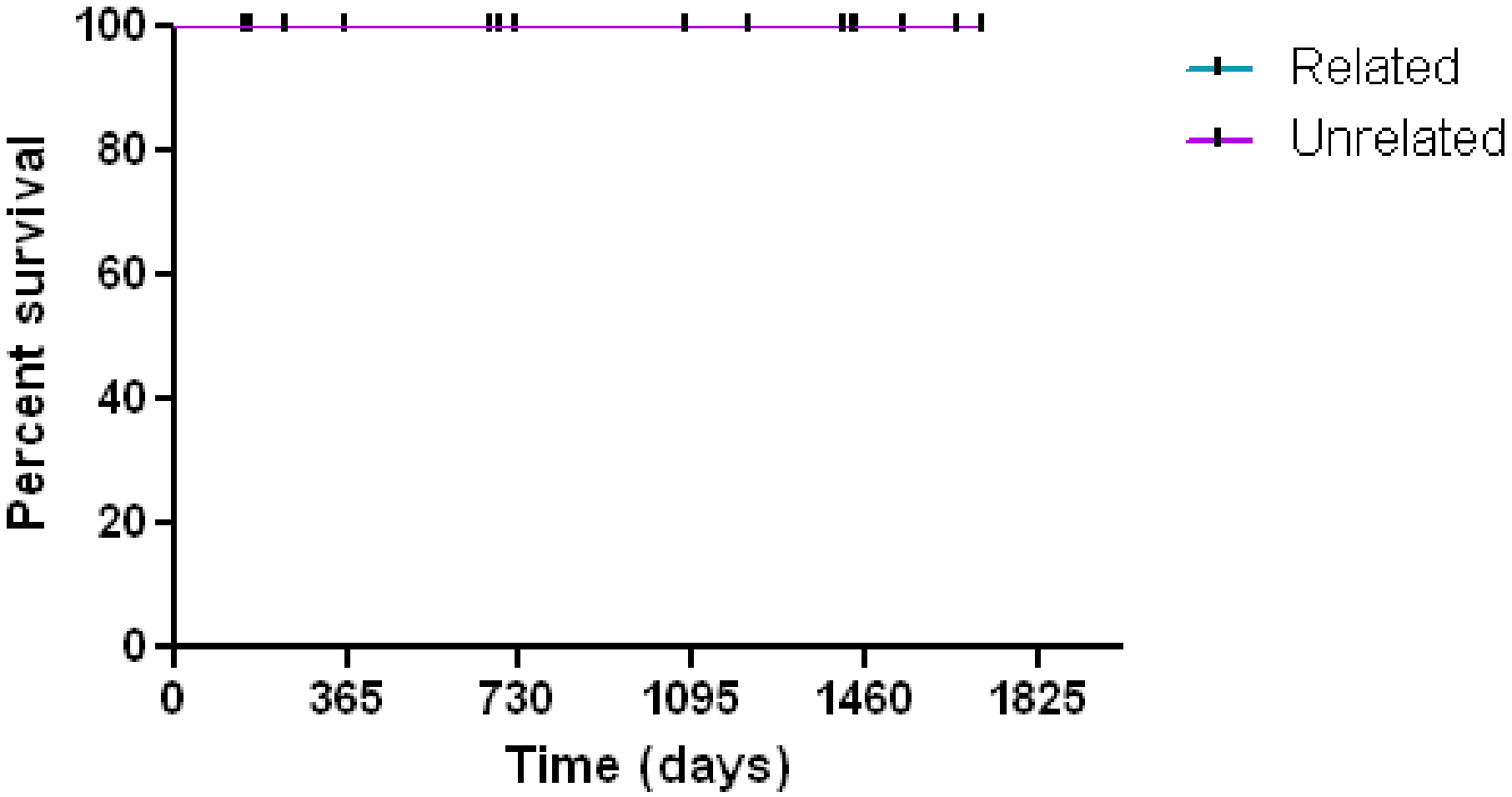
Sickle Cell BMT Survival (2008-2012)



For Related (n=7) and Unrelated (n=8) Sickle Cell BMT, OS is 100%.

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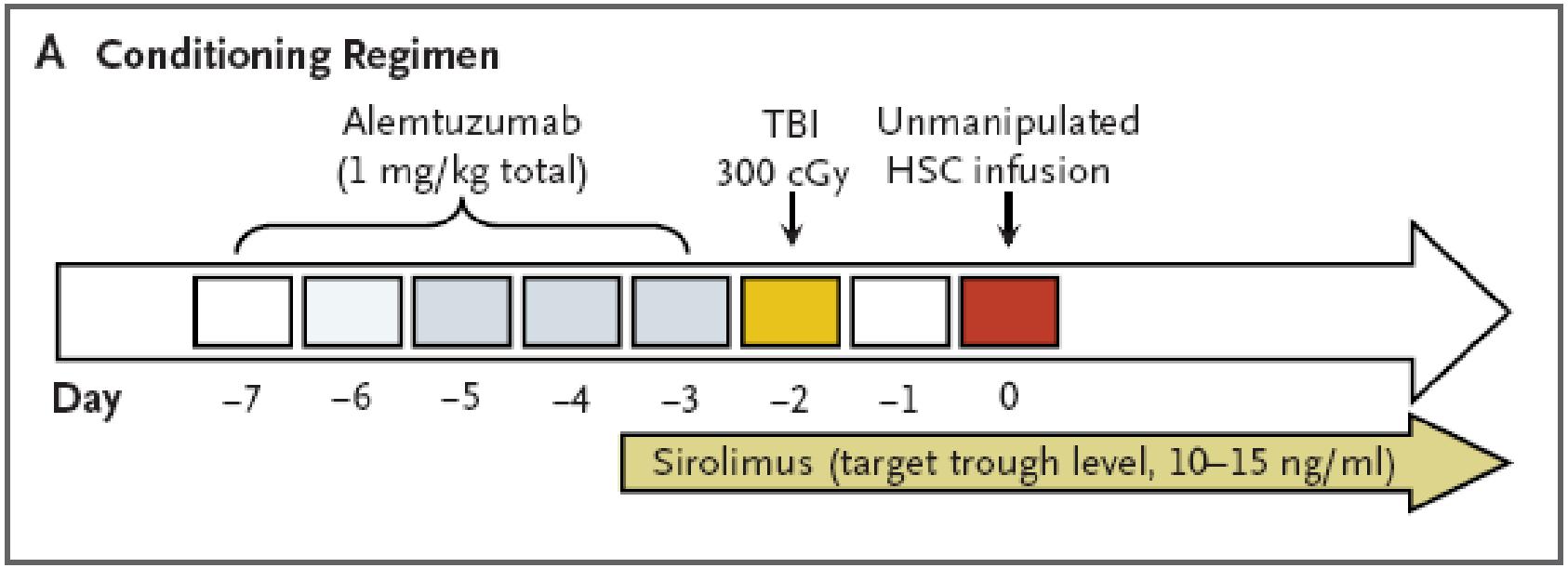
Allogeneic Hematopoietic Stem-Cell Transplantation for Sickle Cell Disease

Matthew M. Hsieh, M.D., Elizabeth M. Kang, M.D., Courtney D. Fitzhugh, M.D., M. Beth Link, R.N., Charles D. Bolan, M.D., Roger Kurlander, M.D., Richard W. Childs, M.D., Griffin P. Rodgers, M.D., Jonathan D. Powell, M.D., Ph.D., and John F. Tisdale, M.D.

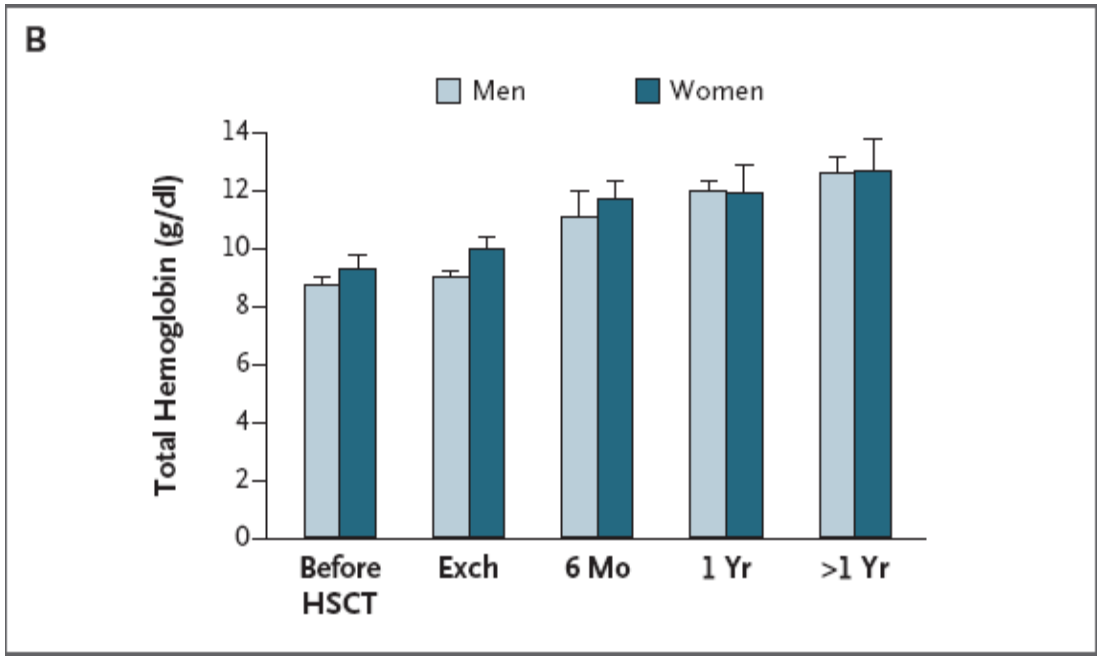


Reduced Intensity Conditioning

All 10 pts alive at a median follow-up of 30 months (range 15 - 54)

Graft (MSD) retained in 9 of 10 pts

Sirolimus continued throughout study



Hsieh et al, NEJM 2009 Dec: 361(24)

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Reduced Intensity Conditioning

Have transplanted 23 patients on this regimen with 100% survival

Graft (Matched sibling) retained in 20 of 23 pts

17 patients 1 year post-transplant of which 5 off sirolimus

No acute or chronic GVHD

Now enrolling pediatric patients

Hsieh et al, Oral Abstract ASH annual meeting 2011 Dec

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Best case scenario for MSD

Sibling donor matches 25% of the time

Assumes sibling suitable to donate

- Appropriate size, health
- No sickle cell disease

~15% SCD patients will have a MSD

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Alternative Donor Grafts

For HSCT to be widely used it is necessary to expand donor pool

Sources being studied

- Unrelated umbilical cord blood
- Unrelated adult donors
- Haploidentical donors

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Risks for Sickle cell transplant

Graft rejection occurs 5-10% in matched sibling transplants, higher with other graft sources

Can be immediate or slowly during the first year as well

Patients typically recover blood counts go back to having sickle cell disease

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Risks for Sickle cell transplant

Graft-versus-host-disease (GVHD) is a significant complication especially when severe

Immune cells of the graft attack the patient (host)

Acute (skin,liver, gut) and Chronic (mutli-organ) forms

Severe forms occur <10% in matched sibling BMT, higher in other donors

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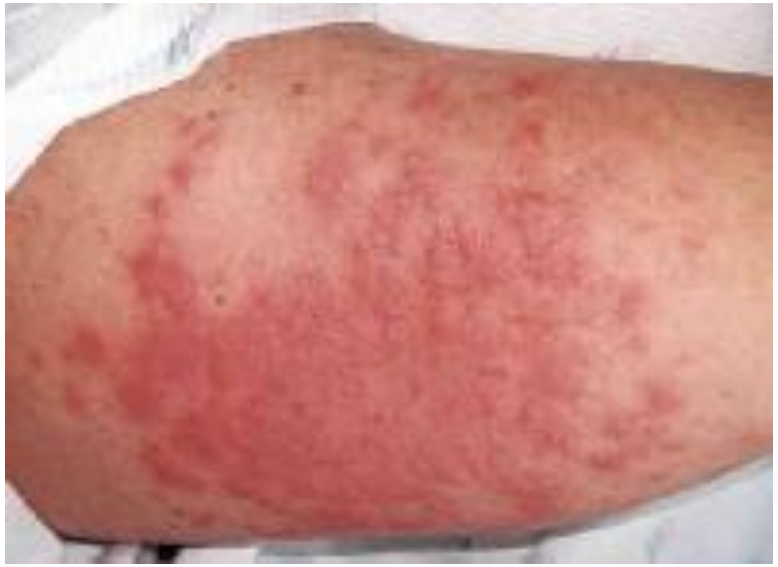
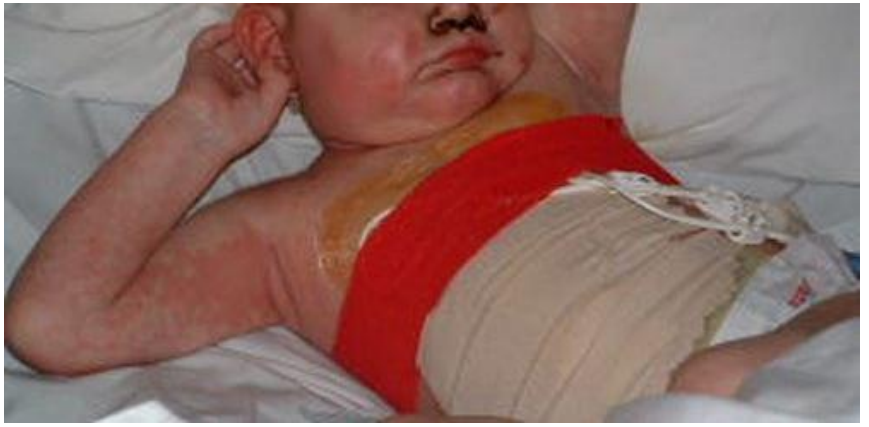
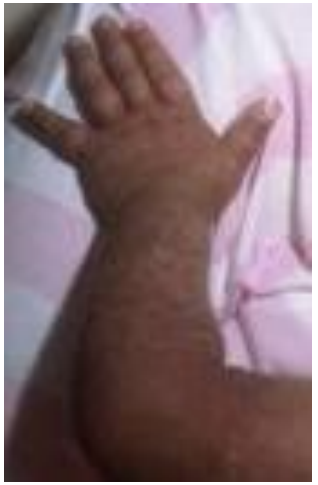
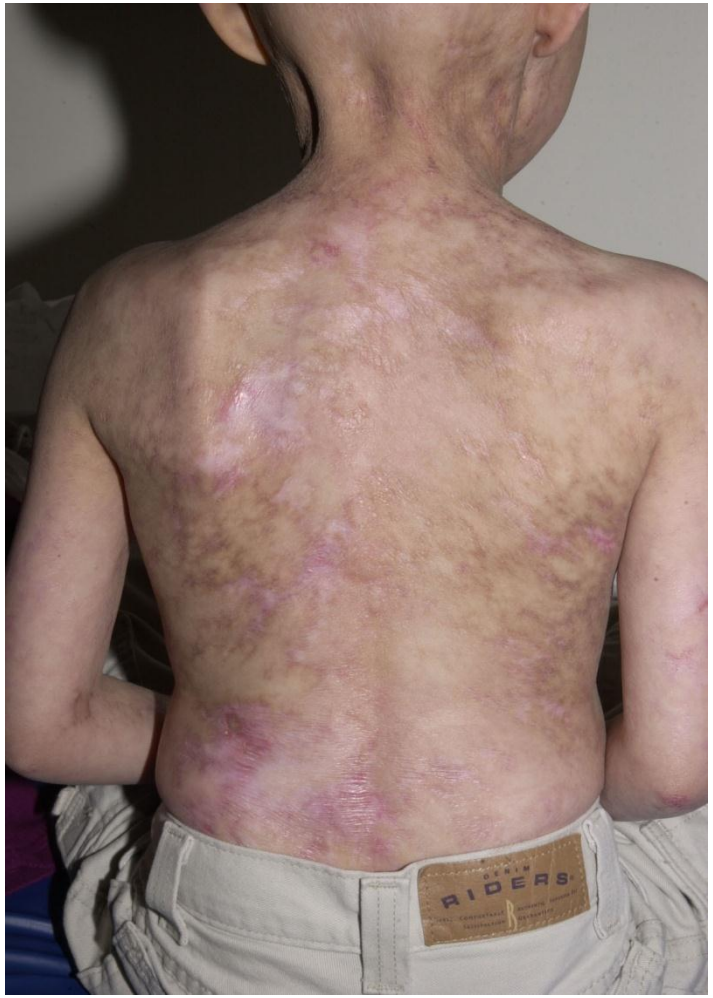
Acute GVHD

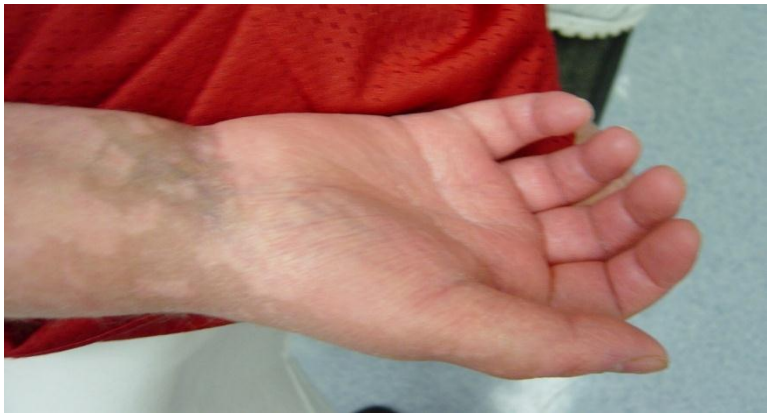


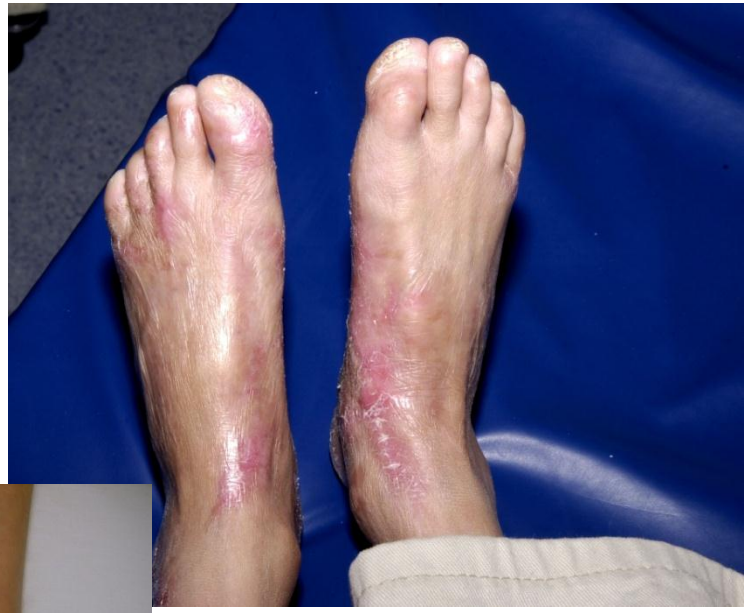


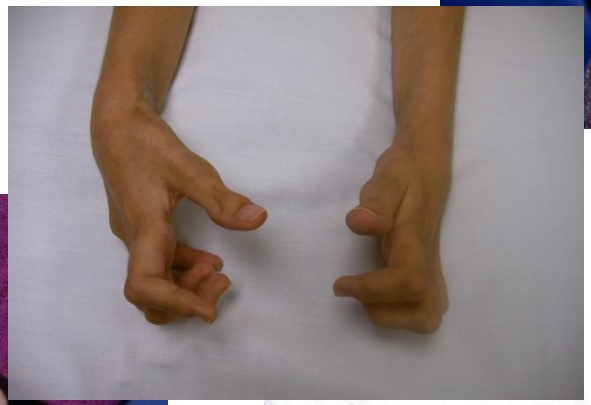


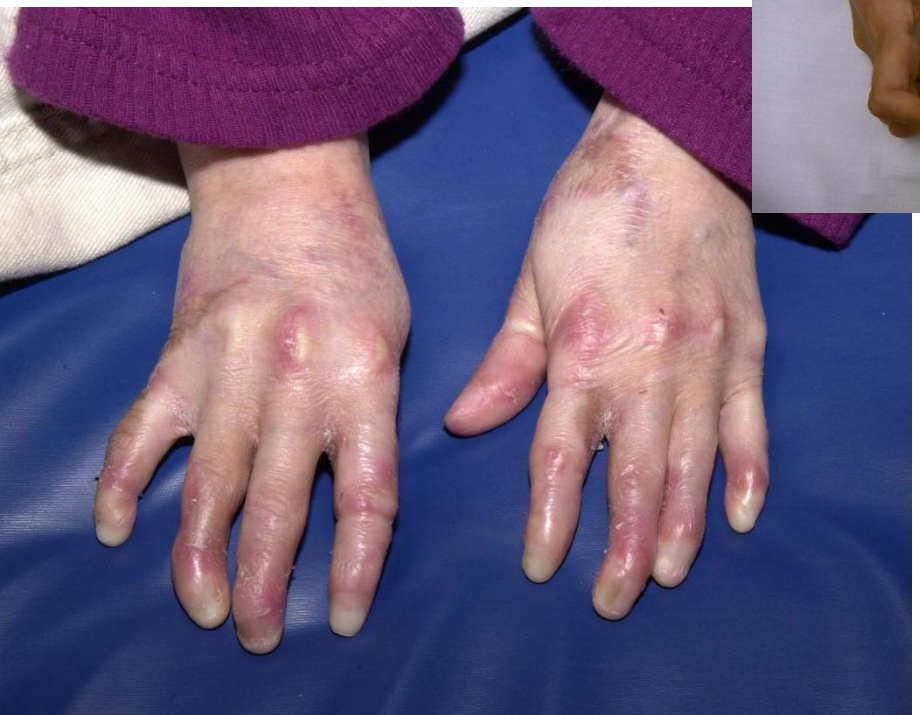
Chronic GVHD

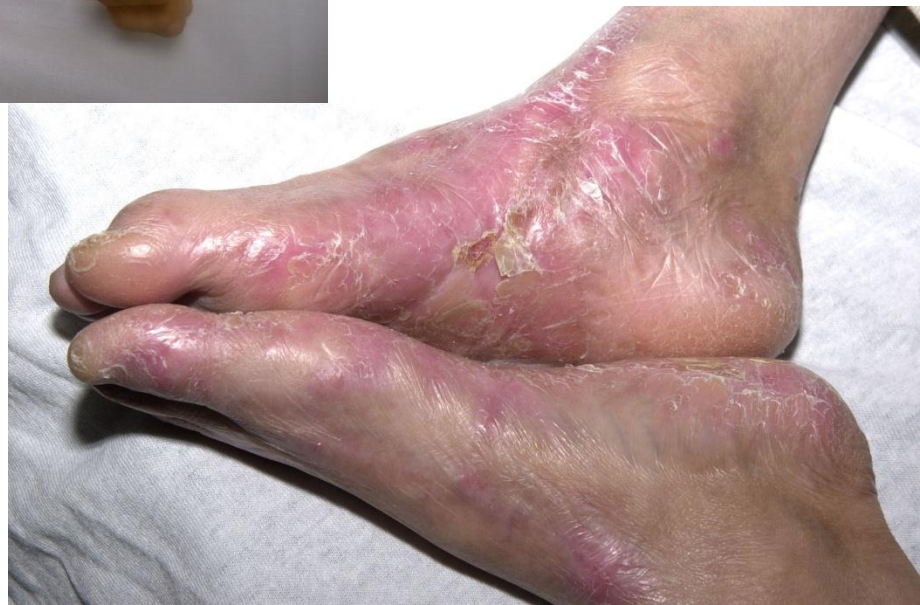












Late effects

As transplants are usually done in children, the effects on growth and development are important

Makes general pediatric care extremely important

At one year after matched sibling BMT patients return to PCP if no major complications

Considered immune-competent at that point

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Late effects

Study of 53 children undergoing myeloablative HSCT for SCD found growth not affected for young children

Could affect growth if done near or during adolescent growth spurt

Gonadal function severely compromised especially in girls (up to 70%)

Can require hormone replacement to go through puberty

Eggleston et al, Br J Haematol 2007; 136:673–676

Brachet et al, J Pediatr Hematol Oncol 2007; 29:445–450

Bernaudin et al, Blood 2008; 111:1744

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Vaccinations

Protective effects of prior vaccination lost with HSCT

Requires catch-up series of vaccines

Follow recommendations of the CDC for catch-vaccination

Expect a letter outlining when vaccination may be started, typically earliest at 6 months

Vaccine titers are measured at transplant clinic visits to judge response and guide further vaccinations

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Vaccine	First Dose	Second Dose	Third Dose	Fourth Dose	Fifth Dose	Comments
Inactivated influenza	6 months	+4 weeks				Give first dose October to April
Pneumococcal conjugate (PCV7 or PCV 13)	6 months	+8 weeks	+16 weeks			
Pneumococcal polysaccharide (PPSV23)	8 weeks after last PCV dose					Do not administer prior to 18 months of age.
Diphtheria, tetanus, pertussis (DTaP)●	12 months	+4 weeks	+8 weeks	+ 8 months	+14 months	5th dose not necessary if 4th dose administered at 4 years or older.
HiB conjugate	12 months	+8 weeks	+16 weeks			Once dose is given to 15 month or older patient, it is the last dose
Meningococcal conjugate	12 months					
Inactivated polio	12 months	+4 weeks	+ 7 months	+13 months*		*The final dose in the series should be administered on or after 4th birthday & >6 months after last dose. 4th dose not necessary if 3rd dose given at age 4 or later.
Hepatitis B	12 months	+4 weeks	+16 weeks			Minimum interval between 2nd & 3rd dose is 8 weeks.
MMR	24 months	+4 weeks				Do not give if patient has active GVHD or is on immune suppression.
Varicella	24 months	+3 months				Do not give if patient has active GVHD or is on immune suppression.

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Other follow-up considerations

CNS – MRI/MRA brain, Neuropsych testing

Optho – Retinopathy evaluation

Dental – At risk for caries, dental cleaning

Pulm – Pulm function testing

Cardiac – Echo + EKG, Hypertension screening

Endo – obesity screening, growth evaluation, thyroid function

Ortho – screen for AVN

Reproductive – Ovarian reserve, semen analysis, hormone levels, puberty evaluation

Immunological - Vaccination

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HSCT and SCD

SCD pts, families, physicians often reluctant to HSCT because of

- inherent morbidity/mortality risk
- no time or resources
- content with current therapy

Relatively low mortality rate following HSCT may be acceptable given reduced average life span for SCD

Hansbury et al, Pediatr Blood Cancer 2012; 58: 611–615

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Summary

Survival in SCD has improved in children to up to ~94%

Adult mortality remains high

Transplant is only current cure and matched sibling transplant successful ~95%

Post transplant general pediatric care important to monitor for late effects and re-vaccination

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