Sickle Cell Disease
How Pathophysiology Affects Transfusion Practice

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• Pathophysiology
• Sickle cell vasoocclusion and hemolysis
• Common complications
• General approaches to treatment
• Transfusion
  indications
  methods
  complications
Mutations that change the amino acid sequence of the β-globin gene cause sickle cell anemia and HbSC disease.


HbS Polymer Initiates the Pathophysiology of SCD

Steinberg MH. Trends Pharmacol Sci. 2006 Apr;27(4):204-10
Loci of Membrane Damage and its Consequences

- HYDRATION
- RIGIDITY
- INFLAMMATION
- ADHERENCE
- HEMOLYSIS

- Cation channels
- HbS
- Oxidant generation
- Glycophorin
- Clustered proteins
- Heinz body
- Protein 3
- IgG

Intravascular Hemolysis Reduces NO Bioavailability and is Associated with Complications of SCD

Hyper-Hemolysis Associated with Increased Mortality

Complications Associated with Hemolytic Anemia

- Leg ulcers
- Cholelithiasis
- Priapism
- ↓ Renal function/albuminuria
- Stroke, ↑ TCD, silent cerebral infarction
- Pulmonary hypertension
Cellular Interactions

(Embury)

Sickle Vasoocclusion Leads to Reperfusion Injury and Inflammation

Common Sickle Vasoocclusion-Associated Complications

- Clinical manifestations are heterogeneous
- Acute painful episode-most patients
- Acute chest syndrome-~50% of patients, severe
- Osteonecrosis-~50% of patients, crippling, painful
- Retinopathy; splenomegaly in HbSC disease
- Multiorgan failure with thrombotic microangiopathy
Anemia in Sickle Cell Disease

- Mostly a result of peripheral destruction

- Secondarily, ineffective erythropoiesis
  \[\uparrow\] intramedularly loss of SCD erythroblasts in stable mixed chimeras transplanted with HbAS cells
  abnormal ferrokinetics (1 case)
  abnormal erythroblasts in transgenic mice

Treatment

• Increase HbF
• Reduce cell density
  - Gardos (Ca activated K)channel inhibition
  - K/CL co-transport inhibition
  - Others
• Prevention cellular interactions
• Reduce inflammation
Transfusion

Usually
• Severe symptomatic anemia (simple)
• Treatment and prevention of CVA (exchange)
• Preoperative (simple)
• Severe ACS, especially with MOF (simple/exchange)

Sometimes
• Pregnancy (simple)
• Renal failure (simple)

Avoid
• Acute pain, chronic anemia

Problems
• Iron overload, alloimmunization, loss of venous access, delayed hemolytic Tx reaction, hyper-hemolysis
Blood Viscosity in Sickle Cell Disease

- Doubling of viscosity halves flow velocity
- Sickle blood has intrinsically increased viscosity, especially when HbS is deoxygenated

**Exchange vs. Simple Transfusion**

- Pre-operative Tx study: exchange Tx had increased rate of alloimmunization; simple Tx equally effective (Vichinsky, NEJM, 1995)
- Preference for exchange Tx in acute stroke (Hulbert, J Pediatr, 2006)
- Exchange reduces Fe overload in 2^0 CVA prevention
- Preference for exchange in severe ACS with multiorgan failure. Possible better survival in fat embolization syndrome (Tsitsikas et al Blood Rev, 2014)
- Priapism: retrospective analysis, 10 cases (Ballas, J Clin Apheresis, 2015)
- Multiple Cochrane analyses find no evidence for superiority of exchange Tx (or even benefits of any transfusion)
HbSC Disease

- 1/800 African Americans
- Pathophysiology differs from HbS homozygotes
- Usual hemoglobin level 10-12 g/dL
- More prone to MOF syndrome
- High hemoglobin levels often require exchange when Tx is required
Manual vs. Automated Exchange

- Retrospective analysis
- >60% for CVA
- Automated (n=30) twice as fast as manual (n=21), but used about 2x the units of pRBCs
- Adverse events similar

The automated group more often met pre-exchange targets ($p=0.048$) but neither group was very good at this.

(Kuo et al, Br. J Haematol, 2015)
Alloimmunization

- Alloimmunization rate was 18.6% in 1,814 CSSCD patients transfused between 1979 - 1984
- Alloimmunization rate was 27.3% in 319 Duke/UNC patients transfused between 2001 - 2011

(Rosse et al, Blood, 1990; Telen et al, Transfusion, 2014)
Genetics of Alloimmunization

- GWAS of 390 adults from CSSCD and Duke/UNC cohorts
- 255 SNPs in the HLA locus, 684 SNPs in 53 genes previously associated with immune responses, totaling 939 SNPs. Regression analysis was used to evaluate the association of each SNP with alloimmunization.
- The most significant genetic associations with alloimmunization (FDR q = .28) occurred for 46 SNPs in the HLA locus and in 10 other genes.

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<tr>
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(Milton et al, ASH 2014)
Summary and Conclusions

- Vasoocclusion and hemolytic anemia are cardinal features of sickle cell disease.
- Simple and exchange Tx have roles in treating a defined number of complications.
- For almost all Tx indications, high-grade evidence supporting the superiority of one or the other of these approaches is lacking.
- Sometimes, especially in HbSC disease, high PCV dictates exchange Tx.
- Exchange Tx reduces Fe accumulation, increases risk of alloimmunization, is slower to initiate and might be better at achieving pre-exchange target HbS levels.