Transfusion Support in Sickle Cell Disease

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15 year-old boy was diagnosed with sickle cell disease at 2 months of age on a routine prenatal screen. The mother was known to have sickle cell trait and the father was never tested. The patient now presents with 1 day of fever (103.1 deg F), non-productive cough and wheezing. The respiratory rate is 40, heart rate 140 and blood pressure 100/60.

What else do you want to know?
What tests do you want?

PMH: prior red cell exchange 5 years ago for acute chest syndrome
PSH: none
Meds: none
All: NKDA
FH: mother with sickle cell trait, two siblings with sickle cell trait, father untested for sickle cell

Temp 103 deg F, HR 140, BP 100/60
Lying in bed uncomfortable, short of breath
R sided crackles and wheezing
No hepatosplenomegaly
No joint abnormalities
Neurologic exam intact

Type and Screen (to be discussed)
SpO2 86% on Room Air
ABG on NRB 7.42/27/124/18/99%
WBC 19.2 Hb 6.5 Hct 18.8% Plt 509
82% N, 12% L, 6% M; 12.8% retic
TP 7.6 Alb 4.3 TB 2.5 DB 0.7 AST 30 ALT 17
ALP 76
Na 137 K 3.6 Cl 107 CO2 16 BUN 7 Cr 0.5 Glu 100
U/A 1.009 ph 5.5 trace albumin blood neg,
everything else neg
CXR RUL and RLL infiltrates

What are common methods for the diagnosis of hemoglobinopathies?
**Sickle Trait**

- Normal Adult Hemoglobins
  - A (α2β2)
  - A2 (α2δ2)
  - F (α2γ2)
- Normal Hgb must be very soluble to pack to the concentration required for adequate oxygen carrying capacity

**Sickle Cell Disease**

- Most patients are from African descent; endemic malaria areas
- 1/650 infants in African-American population
- Very Rare in Europe except in Italy and Greece
- βS protects heterozygotes from malaria
- Clinical Manifestations are highly variable
- Premature death in many patients – mean 42-45 y.o.

**Pathogenesis**

- single nucleotide substitution in the beta chain of hemoglobin results in an amino acid change
- \( \beta^{66(Val->Glu)} \)
- changes the charge at a critical pocket
  - Glu (-ve); Val (neutral); loss of negative charge
  - Results in hydophobic interactions with other hemoglobin molecules
Polymerization also depends on the rate of formation (how fast does deoxygenation occur)
- If rapid, then no alteration in the disc shape
- If slow, then polymerization with the characteristic sickle shape

Viscosity: Intracellular Factors
- Deoxygenation
- Presence of other hemoglobins/thal
  - F gets in the way of nucleation
  - C gets in the way of effective nucleation
  - A is more effective at binding alpha chains
  - Beta thal
- Dehydration
- Temperature

Flow: Radius and Viscosity
- Poiseuille’s law
  - Flow inversely proportional to viscosity
  - Increase viscosity by ½ then
  - Flow decreases 1/2
  - Proportional to radius to the 4th power
  - Decrease radius by ½ then
  - Flow decreases by 1/16 (~90%)
- Where are sickle cells exposed to small vessel and increased viscosity?

Flow and Hematocrit
- Viscosity of AA Blood decreases with increasing shear stress at Hct 45% (more viscosity when blood is static)
- Sickle cell blood is more viscous at all shear stresses at Hct 45%
- Sickle cell blood is less viscous at all shear stresses at Hct 25%

Interaction with Endothelium
Clinical Manifestations

- Anemia
- Acute Erythroid Aplasia
- Pain Crisis
- CVA
- Acute Chest
- Renal Dysfunction
- Spleen
- Avascular Necrosis
- Priapism
- Hepatobiliary
- Retinopathy
- Heart Failure

Acute Anemia

- There are differences in the degree of anemia depending on the type of Hemoglobinopathy (inc LDH, bilis; decr Hct)
  - SS (Hb 7-8) has greater degree of anemia than SC (10-11)
- Compensation
  - Increased 2,3-DPG, increased cardiac heart rate
- Acute Decompensation
  - Decreased Production (e.g. parvovirus B19)
  - Increased destruction/loss (e.g. hemolysis, bleeding, sequestration)
- May require transfusion depending on the baseline Hb and signs/symptoms

Pain Crisis

- Pain due to localized hypoxia secondary to obstruction of the microcirculation with SS cells; Abrupt; at night
- Occurs in Bone Marrow cells get caught in sinuses
- Ribs get inflamed⇒pleural chest pain
- Periosteal inflammation⇒“hand/foot syndrome”
- abdominal surface inflamed⇒acute abdomen
- Lasts about 5 days
- Treatment
  - Hydration
  - Analgesics
  - ? Exchange

Acute Chest Syndrome

- May be secondary to pneumonia, PE, or pulmonary fat embolus
- Findings
  - Fever
  - pulmonary infiltrates (may be progressive with more than one lobe involved)
  - **Hypoxia (may not be corrected by oxygen therapy)
  - respiratory distress
  - leukocytosis
- Treat with oxygen, antibiotics, and simple transfusion (if needed)
- red cell exchange transfusion to bring HbSS percent to below 30% and the end hematocrit to 30% if patient is in respiratory distress and does not respond to oxygen or simple transfusion

Cerebrovascular Accident

- Occlusion of intravascular vessels
- Rupture of weakened vessels
- Peds: aphasia, weakness, lack of coordination; acute hemispheric infarctive stroke is not uncommon
- Adults: silent strokes; can get more hemorrhagic or watershed
- Present with hemiplegia, hemiparesis, aphasia, seizure, coma, and other neurologic symptoms
- May have a history of TIA’s
- Perform exchange to <30% SS and hct 30% after e/o hemorrhage

Splenic Sequestration

- Prior to autoinfarction
- Sudden sequestering of an enormous amount red cells
- hypovolemic shock, tachycardia, hypotension and poor perfusion
- sudden, massive, painful splenomegaly (4-10 cm below costal margin)
- The hematocrit suddenly drops (⇒ 2 g/dL)
- thrombocytopenia develops (approx 100K)
- there is a brisk reticulocytosis
- Immediate transfusion of red cells is indicated: 10-20 ml/kg over 2-3 hours
- Sequestered red cells will release with the transfusion ⇒ Overshoot phenomenon
- High risk of recurrence after the first event ⇒ splenectomy, transfusion protocol, observation
• Priapism
  – exchange is indicated after 1 hour of hydration and simple transfusion
• Avascular Necrosis → head femur most commonly and wrist
• Leg Ulcers → lower leg/malleolus
• Renal Dysfunction → papillary necrosis
• Hepatobiliary Disease → cholecystitis; hepatic sequestration

Treatment Options
• Reduce intracellular hemoglobin concentration
• Reduce percentage of sickle cells circulating
• Increase Hemoglobin F
• Get rid of endogenous sickle cell production

Hydroxyurea
– Only drug that is used worldwide to increase number of F cells and F per F cell
– Hb F interferes with HbS polymerization
– Non-toxic
– Myelosuppressive effects are reversible (perhaps a neutropenia plays a role)
– Reduction in hemolysis
– Increase in hemoglobin
– Reduction in irreversibly sickled cells
– Decrease frequency and severity of pain crisis
– Reduction in the incidence of acute chest syndrome

Transfusion
• Accomplish two goals:
  – Increase the oxygen carrying capacity by increasing the hematocrit/circulating hemoglobin → simple transfusion
  – Replace SS cells with AA cells to improve vascular stasis → reverse the effects of the sickled cells → exchange transfusion
  – Chronic transfusion with goal of reducing iron load → Exchange transfusion

Simple Transfusion
• Indications
  – Hb 7-8 is well within the range of anemia that is well tolerated
  – Increase oxygen carrying capacity to correct poorly tolerated decrease in Hct in setting of organ dysfunction
  – Reduce endogenous red cell production (Hb A 50-70%)
• In general, do not allow the Hct>30% when HbS% >30%
  – In this setting the blood viscosity increases the risk of significant VO event

Simple Transfusion Drawbacks
– Infectious risk
– Transfusion reactions
  • Allergic
  • FNHTR
  • AHTR
  • DHTR
  – Iron overload
  – Development of red cell alloantibodies
  – Volume overload
Exchange Transfusion

• Clinical situation requires rapid replacement of sickled cells with normal cells
• Most common indications:
  – CVA/TIA
  – ACS
  – Acute multiorgan damage (kidney, liver necrosis)
  – Retinal artery occlusion
• Evaluate the patient; is an exchange necessary have to be done emergently?
  – E.g. Patient sickle dz with new infiltrate and fever; 100% sat on RA is very different from fever, progressive infiltrates, O2 sat 70% on 15L O2 with increasing respiratory distress about ready to be intubated

Exchange Drawbacks

• Transfusion Reactions
• Infectious Risk
• Development of alloantibodies
• Citrate toxicity, air embolus, line infection
• Better for iron overload, volume overload

Pre-Transfusion Testing

• Get a blood type/Rh type
  – Dc (R0r or R0R0) is a common Rh phenotype in sickle cell disease
• Get an Antibody Screen Result ASAP
  – If antibodies are present, delay in identification can significantly delay providing compatible units

Selection of Blood Components

– Sickle Negative Blood
  • Sickle trait cells may sickle in patient’s physiologic conditions
  • Sickle trait cells may be difficult to transfuse or to filter through LR filter
  – Leukocyte reduced (FNHT/RAlloimmunization)
  – Irradiated only if indicated by other criteria; sickle cell disease is not one of the criteria for irradiation
  – Antigen negative blood, if needed
  – Some institutions will order Rh negative, Kell negative blood; should we phenotype match?

Practical Transfusion/Apheresis Issues

• See the patient yourself and evaluate the need for exchange
• Make sure active ABO/Rh and Antibody Screen sample is available
• Confirm that no antibodies are present; or if they are present identify the antibody and predict the availability
• Make sure a line is placed ASAP
• Most calls will be acute cases, usually acute lung; FRC=20 or 30%, End Hct 30%
• Evaluate ECV and prime instrument if the extracorporeal volume is large (>10% TBV)
• Recommend manual exchange if pt too small (e.g. <20 kg)
HPC Transplant

- Related and Unrelated Allogeneic HPC Transplant
- Cord blood transplant