Transfusion Support for Sickle Cell Disease

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DISCLOSURES

- Research support from Canadian Blood Services
Objectives

1. Outline the principles of RBC transfusion in sickle cell disease

2. Define acceptable indications for RBC transfusion in sickle cell disease

3. Recognize the syndrome of hyperhemolysis and evaluate different options for prevention and treatment
Hemoglobin: An Overview

- **Structure of hemoglobin**
  - 4 globin chains (2 x alpha and 2 x beta), each containing a heme group within a protected pocket
  - When deoxygenated, Hgb in “taut” configuration, beta globin chains held apart with ionic bonds
  - With oxygen binding, ionic bonds broken, beta globin chains move together and Hgb adopts “relaxed” configuration
Hemoglobin: An Overview

- **Beta globin**
  - One gene carried on chromosome 11
  - Accompanied by several functional “beta-like genes”, including one epsilon (ε) expressed in embryonic development, two gamma (Gγ and Aγ) expressed primarily during fetal development, and one delta (δ) expressed weakly during adulthood

Frenette, J Clin Invest 2007;117:850
Hemoglobin: An Overview

- Variant hemoglobins can be distinguished by
  - Electrophoresis (+/- isoelectric focusing)
  - Cation-exchange liquid chromatography on RBC lysates
  - Molecular studies

- Normal adult hemoglobins:
  - HgbA ($\alpha_2\beta_2$) 97%
  - HgbF ($\alpha_2\gamma_2$) 2.5%
  - HgbA2 ($\alpha_2\delta_2$) <1%
Sickle Cell Disease: Pathophysiology

- Due to specific point mutation in sixth codon of β-globin gene
- Resulting HgbS has a hydrophobic domain which predisposes to precipitation when deoxygenated
- HgbS polymerization results in formation of elongated fibres which stretch and deform the erythrocyte
- Membrane damage results in cellular dehydration, rigidity, adhesiveness/thrombogenicity
- Net result: hemolysis, vaso-occlusion
Sickled erythrocyte

- Unexposed transmembrane segment
- Transmembrane protein
- PS
- Normal cell membrane

- Exposed transmembrane segment
- Transmembrane protein
- PS flip
- Abnormal cell membrane

- Spectrin
- Membrane
- Cytoskeleton

- Hb polymer

Frenette P, J Clin Invest 2007;117:850
<table>
<thead>
<tr>
<th>Genotype</th>
<th>HgbS</th>
<th>Typical clinical severity</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\beta^S/\beta^A$</td>
<td>HgbS: 20-30%</td>
<td>Asymptomatic</td>
</tr>
<tr>
<td>$\beta^S/\beta^C$</td>
<td>HgbS: 50%</td>
<td>Mild-moderate</td>
</tr>
<tr>
<td>$\beta^S/\beta^+$</td>
<td>HgbS: 70-85%</td>
<td>Moderate</td>
</tr>
<tr>
<td>$\beta^S/\beta^o, \beta^S/\beta^S$</td>
<td>HgbS: 90-95%</td>
<td>Severe</td>
</tr>
</tbody>
</table>

![Graph A](image1.png)  ![Graph B](image2.png)  ![Graph C](image3.png)
A note on screening

- After 6 months age, sickle cell solubility testing (Sickledex®) will detect all sickling syndromes (HgbSS, Sβ, SC, etc) AND HgbAS (sickle cell trait)

- Children < 6 months or with a positive solubility test should undergo confirmatory testing by hemoglobin electrophoresis/high-performance liquid chromatography
A note on screening

- Is it necessary to screen at-risk ethnicities (African, Greek, Southern Italian, Turk, Arab, Indian) for sickle cell disease prior to surgery?

- Consider the following:
  - >95% of patients will have already manifested clinically by age 10
  - Universal newborn screening has been in place in Ontario since 2006
  - Diagnosing sickle trait (50x more common than sickle cell disease) pre-operatively may create needless delays in care

- Careful history and physical/early referral to hematology of known SSD cases probably much more important than routine pre-operative lab screening

O’Leary, Can J Anesth 2013;60:54
QUIZ!

Which homozygote sickle cell disease patient warrants an exchange transfusion?

1. 28 year old female G1P0, 25 weeks pregnant with Hgb 70g/L
2. 45 year old woman with Hgb 34g/L with an aplastic crisis
3. 21 year old female with vaso-occlusive crisis and Hgb 70g/L
4. 20 month old girl going for cholecystectomy with Hgb 80g/L
5. 38 year old female with acute chest syndrome requiring mechanical ventilation
Oxygen Delivery: Macrocirculatory vs Microcirculatory Perspectives
Oxygen Delivery: Macrocirculation

- **Oxygen carrying capacity** \( (\text{CaO}_2) \) of blood determined predominantly by hemoglobin concentration
- Much smaller proportion dissolved in plasma

- Oxygen delivery in turn is the oxygen carrying capacity multiplied by rate of blood flow. Rate of blood is determined by cardiac output

- Under normal conditions, oxygen consumption is 200-300 mL/min, which is 4-5 times less than what is delivered
Oxygen Delivery: Microcirculation

- While *total* blood flow defined by cardiac output, flow in any particular blood vessel determined by *vascular resistance* and pressure difference between ends of the vessel.

- By Hagen–Poiseuille equation Vascular resistance defined by radius and length of the blood vessel, and the viscosity of the fluid flowing through it.

  \[
  \text{velocity} = \frac{\pi \cdot \text{pressure} \cdot (\text{radius of the tube})^4}{8 \cdot \eta \cdot \text{length of tube} \cdot \text{viscosity}}
  \]

- Blood viscosity determined primarily by the hematocrit.
Oxygen Delivery: What is the Optimal Hct?

- Given the competing effects of red cell mass on oxygen delivery (increases oxygen carrying capacity but decreases blood flow), is there an *optimal* hematocrit that maximizes oxygen delivery?

- Physiologic studies define this optimal point as the Hct at which any further increases result in a proportionally larger increase in viscosity (eg., optimal Hct = maximal Hct/viscosity ratio)
Hematocrit: Viscosity Ratio vs Hct for Oxygenated Sickle Cell RBCs

- At high shear blood flow, viscosity does not increase at the same rate as Hct over wide-range of Hct values, with either 100% HgbSS or diluted to 25%
- At low shear, increased RBC:protein interactions exacerbate viscosity, suggesting lower Hct results in better O₂ delivery

Alexy T, Transfusion 2006;46:912
While oxygenated sickle blood is already more viscous than normal blood, viscosity increases dramatically when deoxygenated.

Result is apparent optimal Hct of 25% even at high shear; even if HgbS diluted to 25%, no further benefit in increasing Hct past 30%.

Alexy T, Transfusion 2006;46:912
Implications of Viscosity Studies

- In vascular beds with low shear, particularly those with low oxygen tension (e.g., post-capillary venules, bone marrow), any increase in oxygen delivery achieved by transfusion is likely offset by increases in viscosity.

- This would suggest that top-up transfusions are unlikely to be of benefit as treatment for vaso-occlusive crises manifesting as bony pain.
Implications of Viscosity Studies

- In vascular beds with **high shear** (e.g., brain, kidneys, lungs), oxygen delivery may be optimized by increasing the Hct, but with deoxygenated sickle blood there is likely little benefit and possibly harm of transfusing to exceed a Hct of 30%, even if patient’s own blood has already been diluted by 75%.

- Moreover, any improvements in oxygen delivery achieved by transfusion in high-shear vascular beds may result in **worsened** oxygen delivery in low shear beds.
Implications of Viscosity Studies: Rules of Thumb

1. In most cases, the benefits of transfusing a patient with sickle cell disease will come from decreasing the viscosity of their blood rather than by increasing its oxygen-carrying capacity
   - Goal of transfusion is to decr HgbS%, not increase total Hgb

2. Transfusing a patient with sickle cell disease to Hgb > 100-110 g/L may worsen their condition, particularly if the patient is already in a hyperviscous state (dehydrated, low-flow, hypoxic)
   - Target HgbS% may only be safely achievable by removing patient’s own blood prior to transfusing (exchange transfusion)
A Note on Exchange Transfusions

- **Manual exchange:** No special equipment required, but slow
  - Phlebotomize 500 cc
  - Infuse 500 cc saline
  - Phlebotomize another 500 cc
  - Transfuse 2 units RBCs
  - Repeat as necessary

- **Automated erythrocytopharesis:** Specialized equipment/personnel, but fast
  - Blood volume estimated based on patient height, weight and Hct
  - Approximately 150 cc autologous RBCs removed with each cycle and replaced with either saline or homologous RBCs, depending on patient baseline status and goals of therapy
A Note on Exchange Transfusions

- Patient should be euvolemic prior to starting exchange
- If starting Hgb < 80 g/L, consider first transfusing then phlebotomizing
- If long-term central venous access device required, patient should be fully anticoagulated until removed: 33% chance of thrombosis, at 0.1% daily rate – much higher than pts being treated for malignancy (Jeng MR, Am J Haem 2002;69:103)
  - For erythrocytapheresis will require a dialysis line (PICC/Hickman®/Port-a-Cath® will not tolerate draw)
- Quantity of donor RBCs required increases dramatically with decreasing target HgbS% due to removal of transfused blood with subsequent draws
  - 10-20 units often required to achieve HgbS of 5%
Transfusing to Increase the Oxygen Carrying Capacity
Transfusing for CaO_{2}

What seem like symptoms of anemia may in fact reflect medication effects (eg., fatigue), hypovolemia (eg., tachycardia, hypotension), or other disease (eg., dyspnea).

As per NIH Guidelines, prophylactic transfusions to prevent complications of anemia in sickle cell disease not advised unless Hgb < 50 g/L!

In patients hospitalized for pain episodes and other events, the Hb concentration may fall well below the admission value. If the patient is stable and the reticulocyte count high (>20 percent or >250,000/μL), transfusions can be deferred. In general, patients should be transfused if there is sufficient physiological derangement to result in heart failure, dyspnea, hypotension, or marked fatigue. Such symptoms tend to occur during an acute illness when hemoglobin falls under 5 g/dL. Patients with an acute event associated with falling hemoglobin can die suddenly from cardiovascular collapse and should be monitored closely.
Is there ever a need to increase $\text{CaO}_2$?

- Most common causes of severe anemia in sickle cell disease:
  - Aplastic crisis
  - Sequestration crisis
  - Hyperhemolysis
Aplastic crisis

- Most commonly due to parvovirous B19 infection (tropism for erythroid precursors)
- 1 week latency from infection, then fever (90%), pain (60%), acute splenic sequestration (20%), and acute chest syndrome (10%)
- 2 weeks later, erythematous rash and arthopathy x 2-3d, then profound reticulocytopenia
- Reticulocytopenia lasts 1 week and then recovers as virus cleared by neutralizing antibodies
  - Lifelong immunity following infection (~75% by age 20)
- As patients with sickle cell disease have RBC lifespan of only 16-20d, severe anemia may occur during interim (Hgb decr > 30 g/L)
Nadir Hgb in P19 Infected Pts with Sickle Cell Disease

Solid circles = nadir Hgb in pts with sickle cell disease
Open circles = nadir Hgb in pts with other hemolytic anemias

Saarinen U, Blood 1986;67:1411
Aplastic crisis

- As fall in hemoglobin occurs over days, plasma volume has time to increase in compensation
- Further transfusions therefore risk volume overload; administer slowly and consider prophylactic diuretics
- For patients with humoural immunodeficiency IVIG 0.5 mg/kg weekly x 4 is reasonable
- Most patients with SCD have self-limiting disease

Anderson D, Trans Med Rev 2007;21(S1):S9
Sequestration Crisis

- Trapping of sickle erythrocytes in sinusoids results in massive enlargement of spleen (abd pain and distension) and severe anemia over a period of hours, accompanied by reticulocytosis.
  - May also be accompanied by thrombocytopenia and leukopenia.
  - Can occur with liver as well, although less common: incr bili/AST/ALT.

- If untreated, can cause death from hypovolemic shock/anemia.

- ~25% incidence in pts with sickle cell disease, most common first 2 years of life, very rare after puberty.

- Often treated with immediate splenectomy; if managed conservatively with transfusions 50% recurrence rate with accompanying 20% mortality rate, but diminishing risk over time. However, patient may be left with chronic hypersplenism.

Owusu-Ofori S, Cochrane Database 2002; CD003425.
Sequestration Crisis

- Post-transfusion hemoglobin levels often higher than expected, suggesting *autotransfusion*: sequestered RBCs released back into circulation
- Care must therefore be taken not to accidentally induce polycythemia with attendant risks of hyperviscosity; in children, advisable to administer transfusions in smaller than normal aliquots (e.g., 3-5 mL/kg)
- Often a single transfusion is sufficient to reverse a sequestration crisis
Hyperhemolysis

- Syndrome defined as post-transfusion RBC destruction accompanied by fall in Hgb to below pre-transfusion levels
  - Only fully recognized as a distinct phenomenon in past decade
- Hemolytic indices markedly increased, sometimes accompanied by transient “abnormally normal” reticulocyte count
- Cases may initially present as fever and pain
- Two types
  - Acute (<7 days post-transfusion): often no evidence of new antibodies
  - Delayed (>7 days post-transfusion): new antibodies often detected in serum or eluate
Transfusion Refractoriness in Patient with HgbSβ-thal

Anti-Jka + UNID

Anti-S, autoAb

LDH (units/L), Retics (x10e9/L)

Hgb (g/L), Bilirubin (µmol/L)

Prednisone
Hyperhemolysis

- Controversy over effect on patient’s own RBCs
  - Serial hemoglobin electrophoresis demonstrates rapid clearance of transfused HgbA-containing RBCs
  - If only transfused RBCs cleared, however, then post-transfusion Hgb should be same as pre-transfusion level
  - Further fall in Hgb suggests enhanced destruction of autologous RBCs and/or suppressed erythropoiesis

- Controversy over significance of alloantibodies
  - Many cases often present within time frame of delayed hemolytic transfusion reaction, but 20% of cases have no new antibodies detectable
  - Even when new antibodies detectable, matching for them does not improve transfusion response
Hyperhemolysis

- Experience suggests that transfusing patients during hyperhemolysis is of little benefit and even appears to exacerbate the condition (even if serologically compatible)

- Case reports suggest beneficial effect of IVIG and steroids, with erythropoietin of potential benefit if accompanying reticulocytopenia
  
  - Canadian Guidelines: IVIG “may be considered among the options for treatment of serious, life-threatening, delayed hemolytic transfusion reactions in patients with SCD”

- Once diagnosed, hyperhemolysis is a relative contraindication to all future transfusions

2. Win N, Trans Med Rev 2010;24:64
Transfusing to Decrease Whole Blood Viscosity
Transfusing to Depr HgbS%

- Traditional goal of therapy is to depr HgbS to < 30% while keeping total Hgb < 110 g/L
  - In patients with HgbSC, may be preferable to state goal as HgbA > 70%

- Available RCT evidence limited to ability of transfusion to prevent complications in variety of high-risk settings:
  - Pregnancy
  - Perioperative
  - Stroke prevention

- Guidelines for treatment of complications based largely on observational studies and case series
  - Acute chest syndrome/multi-organ failure
  - Acute stroke
Transfusing to Decrease Whole Blood Viscosity

PROPHYLAXIS
Pregnancy

- HgbSS pts < 28 weeks gestation enrolled
  - Excluded if history of neurologic dysfunction or chronic disease of kidney, liver, lung, or coagulation
- All provided very close obstetric follow-up (bi-weekly until last month of pregnancy, then weekly)
- Intervention: 36 pts randomized to transfusion with goal of HgbS < 35% and total Hgb 100-110 g/L, starting weekly x 3 or until goals met
- Control: 36 pts randomized to receive transfusion only if Hgb < 60 g/L and retics < 3%, or in response to “medical or obstetrical indications”
  - 44% of controls ended up receiving some degree of transfusion
Pregnancy

- Chronic transfusion support resulted in
  - More RBC exposure (mean 12 units/pt vs 6.5 in control arm)
  - No significant decrease in adjusted gestational age or other obstetric complications
    - Trend towards worse outcomes with transfusion (perinatal death 15% vs 5%, neonatal death 6% vs 0%, stillbirth 10 vs 5%)
  - Fewer maternal pain crises (14% vs 50%) and other non-pain sickle complications (19% vs 42%)
- Conclusion: chronic transfusion useful to prevent maternal morbidity but no benefit to fetus, so long as very close obstetrical care provided
  - Caveat: likely underpowered, few high-risk patients; prophylactic transfusion initiated too late to benefit developing placenta?
Perioperative

- HgbSS pts scheduled for elective surgery enrolled
  - Patients transfused in 3 months prior to surgery excluded
  - 13% of procedures excluded from analysis (details not provided); >99% of procedures enrolled were ASA low/intermediate risk
- All patients received standard treatment protocol that included ≥ 8 hours pre-operative hydration
- 303 procedures randomized to maintain pre-op HgbS < 30% and total Hgb 90-100 g/L
  - 57% required an exchange transfusion to meet goal
- 301 procedures randomized to maintain Hgb 90-110 g/L, regardless of HgbS
  - 77% of patients transfused, average HgbS achieved for all pts in this group = 59%

Vichinsky E, NEJM 1995;333:206
Perioperative

- Aggressive transfusion support resulted in
  - Higher RBC requirements (average 6.1 vs 3.8 units for adults)
  - Increase in transfusion-related complications (eg., delayed hemolytic transfusion reactions 5% vs 1%); note, RBC products not prophylactically matched
  - No reduction in survival, LOS or any other serious/life-threatening complication (eg., post-op acute chest syndrome 10% vs 10%). Note, ACS usually occurred POD3, 11% risk of intubation
- Conclusion: for low/intermediate risk surgery, top-up transfusion to Hgb 90-110 g/L is sufficient
Perioperative

Study limitations

- No untransfused arm, although comparison with non-randomized cohort who were not transfused found better outcomes with transfusion for variety of intermediate risk procedures (cholecystectomy\textsuperscript{1}, orthopedic procedures\textsuperscript{2})
- Few truly high-risk procedures examined (eg., older pts with baseline pulmonary disease)

Haberkern CM, Blood 1997;89:1533
Vichinsky E, Am J Haem 1999; 62:129
Perioperative

- TAPS Trial: Patients with HgbSS/Sß⁰ undergoing low-moderate risk surgery randomized to two different perioperative transfusion strategies
  - 33 pts to supportive care only (no transfusion)
  - 34 pts to pre-op transfusion: top-up if Hgb < 90 g/L, partial exchange if Hgb > 90 g/L (goal of HgbS < 60%)
- 81% mod risk (eg., cholecystectomy, joint replacement), 19% low risk (eg., adenoidectomy, inguinal hernia repair)
- Exclusions included Hgb < 65 g/L, history of ETT for ACS
- Recommended perioperative management
  - IV fluids if NPO > 2 hrs pre-op
  - Keep SpO₂ >96%
  - DVT prophylaxis if immobile > 24 hrs

Howard, Lancet 2013; 381: 930–38
Perioperative

- Trial stopped early due to incr rate of serious adverse events in untransfused arm (33% vs 3%)
  - Most significantly acute chest syndrome: 9/33 if untransfused, 1/34 if transfused
  - Only 1 patient developed acute chest syndrome after low-risk surgery
- Median time to post-operative complications = 2.5 d
- Of patients in untransfused arm, 12% were transfused intraoperatively anyway, another 27% post-operatively (most for sickle complications, e.g. ACS)
Perioperative

- Surgeries without pre-op transfusion complicated by post-operative acute chest syndrome (9 of 33 patients)
  - Adenoitonsillectomy (3)
  - Laparoscopic cholecystectomy (2)
  - Tonsillectomy (1)
  - Laparoscopic splenectomy (1)
  - Umbilical hernia repair (1)
  - Shoulder arthroplasty and subacromion decompression (1)
- A 10th patient developed intra-operative bleeding requiring conversion of laparoscopic to open cholecystectomy, followed by acute chest syndrome
- 2/10 patients required ICU admission

Howard, Lancet 2013; 381: 930–38
## Perioperative: General Guidelines

<table>
<thead>
<tr>
<th>Risk</th>
<th>Example</th>
<th>Pre-op transfusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low</td>
<td>• Skin, eyes, nose, ears, dental&lt;br&gt;• Distal extremities&lt;br&gt;• Perineal, and inguinal areas</td>
<td>Not required</td>
</tr>
<tr>
<td>Intermediate</td>
<td>• Abdominal or orthopedic procedures&lt;br&gt;• Oropharyngeal procedures</td>
<td>Top-up transfusion to 100 g/L (approx HgbS 60%); exchange if Hgb &gt; 90g /L</td>
</tr>
<tr>
<td>High</td>
<td>• Intracranial, cardiovascular, or intrathoracic procedures&lt;br&gt;• pars plana vitrectomy or scleral buckling&lt;br&gt;• intermediate-risk procedures in patients with significant comorbidities (eg., chronic pulmonary disease), or with baseline Hgb &gt; 90g/L</td>
<td>Exchange transfusion to HgbS of 30% (HgbA 70%)</td>
</tr>
</tbody>
</table>
**Stroke prevention**

- **STOP Trial**: Pediatric HgbSS/Sβ⁰ pts with persistently high middle cerebral or internal carotid artery blood flow, as detected by transcranial doppler (TCD)
  - Excluded if prev stroke; participants not allowed to take HU
- 63 randomized to transfusion with goal of HgbS < 30%/total Hgb < 120 g/L
- 67 randomized to standard care
- *Trial halted early* due to **92% reduction** in symptomatic stroke risk in transfusion arm
  - 11 out of 12 documented strokes were ischemic
  - Single stroke in transfusion arm did not have MRI findings

Stroke prevention

- Subsequent RCT (STOP2) found that discontinuing transfusions altogether results in rapid reversion to high-risk TCD in 14/41 (34%) pts, recurrent stroke in 2/41 (5%)
  - No such events in transfusion arm
  - Mean time to event from last transfusion = 4.5 months
  - Transfusion arm also associated with reduced risk of ACS (3% vs 47% of patients)

- Even transfusing to keep HgbS < 30% may only slow (rather than completely halt) progressive vasculopathy
  - 40 children monitored by MRI/MRA for median of 5.4 years after initial stroke
  - Despite mean pre-transfusion HgbS% of 29%, 11 patients developed new silent infarcts and 7 developed overt strokes

Adams RJ, NEJM 2005;353:2769
Hulbert M, Blood. 2011;117:772
Stroke prevention

- **SWITCH Trial**: Pediatric pts with HgbSS, previous stroke, ≥18 months transfusion therapy, and transfusional iron overload
- 67 randomized to ongoing transfusion to maintain HgbS < 30%, plus iron chelation with deferasirox
- 67 randomized to hydroxyurea (max tolerable dose) with monthly phlebotomy
  - No phlebotomy if Hgb < 70 g/L
- Both arms maintained same Hgb level (90 g/L) but average HgbS% twice as high in HU/phlebotomy arm (64.1% vs 32.3%)
- *Trial halted early* due to excess strokes in HU/phlebotomy arm (10% vs 0%) without any improvement in iron overload

Ware, Blood. 2012;119:3925
Stroke prevention

- **SIT Trial**: children between age 5 and 15 with sickle cell disease (SS/SSo) and no history of stroke or high-risk TCDs, but ≥ 1 silent infarcts by MRI (min. 3 mm)
  - Randomized to monthly transfusion support (Hgb ≥ 90 g/L and HgbS < 30%) vs observation only
    - Chelation therapy initiated if ferritin persistently ≤ 1500 µg/L
    - 32% of patients in observation received at least some transfusion support and 14% were started on HU

**RESULTS**

- Transfusion decreased incidence if new clinical or radiologic infarct, (6% vs 14%, p = 0.03, NNT = 13 for 3 yrs)
- Transfusion also reduced incidence of VOC, ACS, priapism and symptomatic AVN
- No difference in IQ scores

DeBaun, NEJM. 2014;371:699
Stroke prevention

- **TWITCH** Trial: Pediatric pts with HgbSS, baseline TCD flow > 200 cm/s with no previous neurologic event or severe cerebral vasculopathy, and ≥12 months transfusion therapy
  - Silent infarcts were allowed, however and were common
  - 61 randomized to ongoing transfusion to maintain HgbS < 30%, plus iron chelation with deferasirox
  - 60 randomized to hydroxyurea (max tolerable dose) with monthly phlebotomy
  - No phlebotomy if Hgb < 80 g/L
  - Both arms maintained same Hgb level (90 g/L) but average HgbS% > 2x as high in HU/phlebotomy arm (70.7% vs 27.6%)
  - **Trial halted early** due to improved TCDs in HU/phlebotomy arm (mean 138 cm/s vs 143 cm/s) and improvement in iron overload
  - But: other SAEs (mostly sickle cell VOC/ACS) more common off transfusion

Ware, Lancet Dec 2015 (Epub ahead of print)
Stroke prevention

**Conclusion**

- Transfusion remains first line therapy for primary and secondary stroke prevention in children with sickle cell disease and pending further evidence should be continued indefinitely.
- In patients being transfused for *secondary* prophylaxis, must maintain HgbS% of <30% indefinitely (and continue monitoring: may not be sufficient to completely prevent progressive disease).
- In patients being transfused for *primary* prophylaxis, careful transition to hydroxyurea after > 1 year of transfusion may be feasible.
- No equivalent evidence to guide initiation of stroke prophylaxis in adults: if no obvious other explanation (e.g., cardioembolism) prudent to initiate chronic transfusion support.
Who else should receive chronic/prophylactic transfusion support?

- **Pain crises/ACS**
  - RCTs conducted for prevention of pregnancy complications and stroke have also demonstrated that transfusion can effectively decrease the incidence of painful crises and acute chest syndrome.
  - Hydroxyurea, although never directly compared with transfusion for the above complications, has RCT evidence supporting its efficacy in preventing both. Since it is less invasive and carries less risk than transfusion, it should be considered first-line therapy.

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Who else should receive chronic/prophylactic transfusion support?

- “Pulmonary HTN”
  - SCD patients TRj > 2.5 m/s (RVSP ~ 30 mmHg) have a mortality rate 10x that of pts with TRj < 2.5 m/s, with observational data suggesting protective benefit of exchange transfusion or inhaled NO (Gladwin M, NEJM 2004;350:886)
  - Whether these echocardiographic observations represent true arterial hypertension or nitric oxide depletion remains controversial (Bunn HF, Blood. 2010;116:687)
  - Unclear if apparent benefit of transfusion is secondary to improvement in anemia, decr in viscosity, or replenishment of NO via suppression of hemolysis
Transfusing to Decrease Whole Blood Viscosity

TREATMENT
Acute Chest Syndrome

- Standard definition encompasses a broad range of disease severity: new pulmonary infiltrates on CXR accompanied by respiratory symptoms, chest pain or fever
- May be triggered by infection or marrow embolism; specific cause not identified in ~60% of cases despite extensive investigations

1. Vichsinky E, NEJM 2000;342:1855
2. Wayne AS, Blood 1993;81:1109
Acute Chest Syndrome

- Largest observational study of 671 episodes noted
  - 72% of pts received transfusions, ~2/3 of them top-up transfusions
  - Transfusion associated with improvement in gas exchange (PO$_2$ 68 $\rightarrow$ 71 mmHg and SpO$_2$% 91% $\rightarrow$ 94%)
  - Simple and exchange transfusions resulted in “similar” improvements (data not shown)

- However, an earlier case series reported that 40% of patients referred for exchange transfusion for ACS had failed earlier attempt at top-up transfusion

1. Vichsinky E, NEJM 2000;342:1855
2. Wayne AS, Blood 1993;1811109
A more recent case series also noted no difference in LOS following exchange transfusion vs top-up transfusion despite 4-5× more RBC use.

However, patients receiving exchange transfusion were potentially sicker (indication bias):

**TABLE 1. Baseline patient characteristics of patients who underwent XC and ST**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Exchange (n = 20)</th>
<th>Simple (n = 20)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)*</td>
<td>31.4 ± 10.6</td>
<td>30.3 ± 8.1</td>
<td>0.74</td>
</tr>
<tr>
<td>Female (%)</td>
<td>30</td>
<td>35</td>
<td>0.74</td>
</tr>
<tr>
<td>Genotype</td>
<td>18 SS, 2 S/β</td>
<td>19 SS, 1 S/β</td>
<td>0.33</td>
</tr>
<tr>
<td>Prior ACS (%)</td>
<td>70</td>
<td>90</td>
<td>0.16</td>
</tr>
<tr>
<td>Ejection fraction &lt;55% (%)</td>
<td>10</td>
<td>16 (n = 18)</td>
<td>0.33</td>
</tr>
<tr>
<td>On hydroxyurea before admission</td>
<td>40</td>
<td>45</td>
<td>0.75</td>
</tr>
<tr>
<td>Bronchodilator use (%)</td>
<td>75</td>
<td>65</td>
<td>0.49</td>
</tr>
<tr>
<td>Pulmonary artery pressure &gt;25 mmHg (%)</td>
<td>10</td>
<td>17 (n = 18)</td>
<td>0.67</td>
</tr>
<tr>
<td>Patients with ICU admissions (%)</td>
<td>60</td>
<td>45</td>
<td>0.33</td>
</tr>
<tr>
<td>Patients on BiPAP (%)</td>
<td>30</td>
<td>15</td>
<td>0.10</td>
</tr>
<tr>
<td>Admission indirect bilirubin (mg/dL)*</td>
<td>2.8 ± 1.7</td>
<td>3.8 ± 2.0</td>
<td>0.10</td>
</tr>
<tr>
<td>Maximum temperature (°C)*</td>
<td>39.1 ± 0.5</td>
<td>38.4 ± 0.6</td>
<td>0.02</td>
</tr>
<tr>
<td>WBC peak (×10⁹/L)*</td>
<td>23.3 ± 7.2</td>
<td>21.0 ± 8.8</td>
<td>0.37</td>
</tr>
<tr>
<td>LDH</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Peak (IU/L)*</td>
<td>1171 ± 1117</td>
<td>688 ± 267</td>
<td></td>
</tr>
<tr>
<td>Median (interquartile range)</td>
<td>725 (456-1653)</td>
<td>641 (509-827)</td>
<td>0.08</td>
</tr>
</tbody>
</table>

* Data are presented as mean ± SD or percent.

BiPAP = bilevel positive airway pressure; ICU = intensive care unit.

Turner JM, Transfusion 2009;49:863
Acute Chest Syndrome

- In absence of RCT evidence, authorities recommend transfusions for all patients with ACS, and exchange transfusions for patients with poor prognostic markers.

- Physical exam
  - Altered mental status
  - Persistent HR > 125/min
  - Persistent RR > 30 or other evidence of incr work of breathing
  - Temp > 40C
  - Hypotension vs baseline

- Lab/radiologic findings
  - Arterial pH < 7.35
  - SpO2 persistently < 88% despite aggressive ventilatory support
  - Serial decline in SpO2% or A-a gradient
  - Hgb decr by ≥ 20 g/L
  - Plts < 200/fL
  - Elevated BNP or troponin
  - Evidence of multiorgan failure
  - Pleural effusion
  - Progressive pulm infiltrates

Johnson, Hematol Oncol Clin N Am 2005:19;857
Multi-Organ Failure

- Largest case series = 17 episodes in 14 pts
- Defined as acute and severe dysfunction in at least 2 of lung/liver/kidney in the setting of sickle cell pain episode
  - Lung: acute infiltrate or O2 requirements > 3L/min
  - Liver: ALT > 5x norm/baseline, bili > 5x, direct bili > 2x, or PT prolonged by > 3s
  - Kidney: Cr > 175 µmol/L
- All 17 episodes “occurred in the setting of pain that had a distribution typical of previous pain episodes but was unusually severe for the patient”
- While 3 cases had evidence of organ dysfunction at time of admission, most had initially normal laboratory findings but then experienced sudden and rapid deterioration on 3rd or 4th day of hospitalization

Multi-Organ Failure

- In addition to organ failure, most patients experienced some degree of confusion/lethargy and decreasing Hgb and platelet counts with preserved reticulocytosis and coagulation times.

- All cases treated with transfusion had rapid and in most cases complete resolution of organ dysfunction over following months: up front exchange likely preferred.

<table>
<thead>
<tr>
<th>Transfusion</th>
<th># Pts</th>
<th>Mean units transfused</th>
<th>Means days to discharge from transfusion start</th>
<th>Residual organ dysfunction</th>
<th>Deaths</th>
</tr>
</thead>
<tbody>
<tr>
<td>Top-up</td>
<td>8</td>
<td>8 (over 7d)</td>
<td>15</td>
<td>2/7 cases</td>
<td>0</td>
</tr>
<tr>
<td>Exchange</td>
<td>9</td>
<td>9</td>
<td>7</td>
<td>0/9 cases</td>
<td>1</td>
</tr>
</tbody>
</table>

Sickle Hepatopathy

37% of patients had second diagnosis unrelated to sickle cell disease (e.g., viral hepatitis, autoimmune hepatitis)
Sickle Hepatopathy

- **Sickle Cell Intrahepatic Cholestasis (SCIC)**
  - Severe RUQ pain, acute hepatomegaly, coagulopathy, extreme hyperbilirubinemia (predominantly conjugated) with only moderately elevated liver enzymes
  - Occasionally progresses to acute liver failure.
  - Males > Females
  - Acute forms (accompanied by sequestration) may occur in setting of VOC and be precipitated by intercurrent infection or exposure to hepatoxin
  - Chronic (benign) form more common in children; in adults may progress to severe liver dysfunction requiring transplant

Gardner, Blood. 2014; 123:2302
Vaso-Occlusive Crisis

- Most authorities recommend against transfusion as treatment for uncomplicated vaso-occlusive crisis
  - Presumed to offer no advantage over appropriate supportive care with IV fluids, oxygen and analgesia
  - Top-up transfusions may in fact worsen symptoms that occur predominantly in low-shear vascular beds (e.g., bone)
- However, also recognized that many cases of acute chest syndrome and multi-organ failure are secondary to marrow embolism, a potential complication of bone infarction
- A small RCT (N = 15 events) found top-up transfusion prevented ACS in pts presenting with VOC accompanied by elevated secretory phospholipase A2

Styles LA, Brit J Haem 2007;136:343
Other Indications for Therapeutic Transfusion

- **Acute stroke**
  - Many experts recommend immediate, therapeutic exchange transfusion for children presenting with ischemic stroke: one retrospective study noted recurrent strokes occurred in 57% (8/14) patients treated initially with simple transfusion compared with only 21% (8/38) of those treated with exchange transfusion (Hulbert ML J Pediatr 2006;149:710)
  - In adults, standard management (ASA, BP control etc) advised while investigating for non-sickle etiology
Other Indications for Therapeutic Transfusion

**Acute stroke**

- Note that between ages 20 and 40, most strokes in sickle cell patients are hemorrhagic; exchange transfusion generally not advised during acute phase even if related to sickle cell disease.
Other Indications for Therapeutic Transfusion

- In absence of good evidence, many advocate transfusion for specific complications **only** if standard-of-care, non-transfusion approaches have failed:
  - **Priapism**: voiding, hydration, analgesics, heat, vasodilators, aspiration/irrigation with adrenergic agents. Beware of ASPEN syndrome (Association of SCD, Priapism, Exchange transfusion, and Neurologic events)
  - **Malleolar ulcers**: wound care, antibiotics, compression stockings
  - **Proliferative retinopathy**: phototherapy, cryotherapy, vitrectomy, scleral buckling
  - **Avascular necrosis**: physiotherapy
  - **Renal dysfunction**: ACE-I

- Hydroxyurea and/or phlebotomy should also be considered for the above and may be safer than transfusion
“What’s the takeaway on all this?”
### Overview of Transfusion Indications for SSD

<table>
<thead>
<tr>
<th>Generally Accepted</th>
<th>Possibly Effective</th>
<th>Not Indicated</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Acute cerebrovascular accident</td>
<td>• Recurrent or persistent priapism</td>
<td>• Compensated anemia</td>
</tr>
<tr>
<td>• Primary and secondary stroke prevention</td>
<td>• Pulmonary hypertension</td>
<td>• Infections other than aplastic crisis or acute chest syndrome</td>
</tr>
<tr>
<td>• Retinal artery occlusion</td>
<td>• Progressive renal failure</td>
<td>• Treatment of uncomplicated pain crisis</td>
</tr>
<tr>
<td>• Acute and recurrent splenic sequestration</td>
<td>• Pregnancy with exacerbation of anemia or evidence of placental insufficiency</td>
<td>• Pre-operative for minor procedures</td>
</tr>
<tr>
<td>• Intrahepatic cholestasis</td>
<td></td>
<td>• Non-surgical management of avascular necrosis</td>
</tr>
<tr>
<td>• Acute chest syndrome</td>
<td></td>
<td>• Uncomplicated pregnancy</td>
</tr>
<tr>
<td>• Aplastic crisis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Pre-operative for moderate to high-risk procedure</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Hemorrhage (e.g., splenic rupture)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Prevention of pain crises</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Adapted from Wanko, Hem Onc Clinics of NA 2005;19:803
QUIZ!

With regard to transfusion of patients with sickle cell disease (SCD) which is true?

1. Unlike patients transfused for thalassemia, SCD patients are not at risk of developing iron overload.
2. Transfusion triggers are the same for patients with and without sickle cell disease.
3. Delayed haemolytic transfusion reactions are common unless phenotypically matched blood is provided.
4. Units for transfusion should be irradiated.
5. Alloantibody development occurs rarely in the transfused SCD patient.
Selection of RBCs
RBC Antigens

ABO

RhD

RhCE

C

CE

e

K

Kk

Jk

Jka Jkb

Fya Fyb

MNS

S

Kidd

Duffy

Kell

Fy

Prevention of Alloimmunization

- Approx 25% of patients with SSD will become alloimmunized from transfusion.
- Traditionally assumed to represent differences in antigen expression between typical donor and sickle cell patient.

<table>
<thead>
<tr>
<th>Antibody</th>
<th>Average frequency (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anti-E</td>
<td>21</td>
</tr>
<tr>
<td>Anti-K</td>
<td>18</td>
</tr>
<tr>
<td>Anti-C</td>
<td>14</td>
</tr>
<tr>
<td>Anti-Le\textsuperscript{a}</td>
<td>8</td>
</tr>
<tr>
<td>Anti-Fy\textsuperscript{a}</td>
<td>7</td>
</tr>
<tr>
<td>Anti-Jk\textsuperscript{b}</td>
<td>7</td>
</tr>
<tr>
<td>Anti-D</td>
<td>7</td>
</tr>
<tr>
<td>Anti-Le\textsuperscript{b}</td>
<td>7</td>
</tr>
<tr>
<td>Anti-S</td>
<td>6</td>
</tr>
<tr>
<td>Anti-Fy\textsuperscript{b}</td>
<td>5</td>
</tr>
<tr>
<td>Anti-M</td>
<td>4</td>
</tr>
<tr>
<td>Anti-E</td>
<td>2</td>
</tr>
<tr>
<td>Anti-C</td>
<td>2</td>
</tr>
</tbody>
</table>

Josephson CJ, TMR 2007;21:118
<table>
<thead>
<tr>
<th>RH gene complex</th>
<th>Antigens expressed</th>
<th>Gene frequency in the US population</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Caucasians</td>
</tr>
<tr>
<td><strong>R₀</strong></td>
<td>cDe</td>
<td>0.04</td>
</tr>
<tr>
<td>r</td>
<td>ce</td>
<td>0.37</td>
</tr>
<tr>
<td><strong>R₁</strong></td>
<td>Cde</td>
<td>0.42</td>
</tr>
<tr>
<td><strong>R₂</strong></td>
<td>cDE</td>
<td>0.14</td>
</tr>
<tr>
<td>r'</td>
<td>ce</td>
<td>0.02</td>
</tr>
<tr>
<td>r''</td>
<td>cE</td>
<td>0.01</td>
</tr>
<tr>
<td>R₂</td>
<td>CDE</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>r₃</td>
<td>CE</td>
<td>&lt;0.01</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Blood group</th>
<th>Antigens expressed</th>
<th>Antigen frequency (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Caucasians</td>
</tr>
<tr>
<td>Kell</td>
<td>K</td>
<td>9.0</td>
</tr>
<tr>
<td></td>
<td>k</td>
<td>99.8</td>
</tr>
<tr>
<td></td>
<td>Kp</td>
<td>2.0</td>
</tr>
<tr>
<td></td>
<td>Js</td>
<td>&lt;0.1</td>
</tr>
<tr>
<td></td>
<td>Jsᵇ</td>
<td>&gt;99.9</td>
</tr>
<tr>
<td>Kidd</td>
<td>Jkᵃ</td>
<td>77.0</td>
</tr>
<tr>
<td></td>
<td>Jkᵇ</td>
<td>74.0</td>
</tr>
<tr>
<td>MNS</td>
<td>M</td>
<td>78.0</td>
</tr>
<tr>
<td></td>
<td>N</td>
<td>72.0</td>
</tr>
<tr>
<td></td>
<td><strong>S</strong></td>
<td>55.0</td>
</tr>
<tr>
<td></td>
<td><strong>S</strong></td>
<td>89.0</td>
</tr>
<tr>
<td></td>
<td>S-S-Uᵇ</td>
<td>0</td>
</tr>
<tr>
<td>Duffy</td>
<td>Fyᵃ</td>
<td>66.0</td>
</tr>
<tr>
<td></td>
<td>Fyᵇ</td>
<td>83.0</td>
</tr>
<tr>
<td></td>
<td>Fy[(a-b)]ᵇ</td>
<td>&lt;0.01</td>
</tr>
</tbody>
</table>

¹ Null phenotypes in the MNS and Duffy blood group systems.
Detection of Alloantibodies

- In patients with sickle cell disease, 30-50% of antibodies will be detectable on at least one occasion 1 year after they were first observed.
- Episodic transfusions in different hospitals increases risk of DHTRs and possibly hyperhemolysis.

Vichinsky E, Semin in Hematol 2001;1(S1):14
### Prevention of Alloimmunization

- Extensive matching has diminishing yields and can be challenging

<table>
<thead>
<tr>
<th>Matching protocol</th>
<th>% of immunizations that would have been prevented beyond ABO/D matching</th>
<th>% of transfused SSD who would never make an antibody</th>
<th>Frequency of required phenotype in Caucasians</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rh (C,c,D,E,e)</td>
<td>37.2%</td>
<td>82.3%</td>
<td>15%</td>
</tr>
<tr>
<td>Rh and K</td>
<td>53.3%</td>
<td>87.5%</td>
<td>13.6%</td>
</tr>
<tr>
<td>Rh, K and S</td>
<td>55.5%</td>
<td>88.3%</td>
<td>6.1%</td>
</tr>
<tr>
<td>Rh, K, S and Fya</td>
<td>62.8%</td>
<td>91.2%</td>
<td>2.1%</td>
</tr>
<tr>
<td>Rh, K,S, Fya, Jkb</td>
<td>70.8%</td>
<td>93.4%</td>
<td>0.6%</td>
</tr>
</tbody>
</table>

Note: in this study, only 137 of 351 (39%) of SSD patients transfused RBCs matched for just ABO/RhD made an alloantibody

Castro, Transfusion 2002;42:684
Prevention of Alloimmunization

- Studies in other patient populations suggests that most patients, even if Black, remain free of sensitization despite multiple transfusions.
- Estimated that 13% of general population are responders, in whom a transfusion carries a 30% risk of sensitization.

Higgins JM, Blood. 2008;112:2546 and 2010;15:4315
Prevention of Alloimmunization

- In Ontario, 2010 QMPLS survey reported that
  - 89% of hospitals attempt some degree of prophylactic antigen matching for SCD pts even in the absence of alloantibodies (eg., C, E,K)
  - 93% of hospitals would attempt to match for addition antigens in SCD pts who were alloimmunized (eg., Jk^a, Jk^b, Fy^a, S)

- More extensive matching for the already alloimmunized: some patients may be intrinsically more susceptible to sensitization

- Note: matching for Fy^b not required for SCD pts Fy^{a-b}- due to presence of Fy^b-like antigen on non-erythroid cells

1. QMPLS Committee Comments — TMED-1003-2010-05-25
2. Osby M, Arch Pathol Lab Med. 2005;129:190
Reasons for Failure of Prophylactic Matching

- Laboratory/transcription error in phenotype of either donor or recipient
- Failure to notify blood transfusion service of patient diagnosis
- Inability to source antigen-typed units for urgent transfusion
- Genotype/phenotype discrepancy (e.g., partial Rh antigens)
  - ~1/4 patients with will phenotype as C+ but will be capable of making an anti-C; of these patients, 30% will seroconvert when given C+ RBCs and are at risk of DHTR/hyperhemolysis! (Tournamille et al, Transfusion, 2010;50:13)
Other Considerations

- Transfusion of HgbS-containing units (eg, from sickle trait donors) may confound attempts to monitor response to transfusion but does not itself pose any significant harm to patients.
- Transfusion of fresh RBCs may prolong interval between transfusions.
- **The above considerations are of lesser importance than the provision of antigen-typed units.**
- Genotyping of donors may allow more careful selection of RBCs and may be only feasible method for supplier to meet growing demand for antigen typed units, particularly for SCD pts.
Other Considerations

- However, sickle cell patients still stand to benefit from implementation of “low-tech” solutions:
  - Judicious ordering of blood products by clinicians (e.g., not for asymptomatic anemia or uncomplicated pain crisis)
  - Increase recruitment of donors from ethnic minority groups
  - Better communication between clinicians and laboratory regarding patient diagnosis
  - Better communication between hospital blood transfusion services regarding patient phenotype and antibody history

- Safest option? Get a hematology consult before you operate on or transfuse a patient with sickle cell disease
Canadian Blood Services

it's in you to give

1-888-2-DONATE