Transfusion Support of Thalassemia

Jacob Pendergrast, MD, FRCPC
University Health Network Blood Transfusion Service
Assistant Professor, University of Toronto
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
  – Heme = porphyrin + Fe\(^{2+}\)
  – Fe\(^{2+}\) capable of binding O\(_2\) (stays in reduced/ferrous state)
  – When deoxygenated, Hgb exists in “taut” configuration, with 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

- Function of hemoglobin
  - Oxygen delivery
  - Nitric oxide delivery (vasodilator)
  - CO2 delivery (minor role)
  - Acid-base buffer (binds H⁺)
- Oxygen affinity enhanced (right-shift of curve) through binding of 2,3-DPG
Hemoglobin: An Overview

• Alpha globin
  – Two identical genes carried on chromosome 16 (α1 and α2, with former making 2-3x less alpha globin than former)
  – Accompanied by several “alpha-like genes”, only functional one is zeta (ζ), expressed in early embryogenesis. Developmental expression regulated by HS-40

Frenette, J Clin Invest 2007;117:850
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. Developmental expression regulated by LCR

Frenette, J Clin Invest 2007;117:850
Hemoglobins (embryonic)
- Gower 1 $\zeta_2\varepsilon_2$
- Portland 1 $\zeta_2\gamma_2$
- Gower 2 $\alpha_2\varepsilon_2$

Hemoglobins (% at birth)
- Hb F $\alpha_2\gamma_2$ (75)
- Hb A $\alpha_2\beta_2$ (25)

Hemoglobins (% in adults)
- Hb A $\alpha_2\beta_2$ (97)
- Hb A$_2$ $\alpha_2\delta_2$ (2.5)
- Hb F $\alpha_2\gamma_2$ (<1)

Globin chain synthesis (%)

- Embryo
- Fetus
- Birth
- 6 mo
- Adult

Yolk sac → Liver → Bone marrow

Williams Hematology, 7th ed (Mc-Graw Hill, 2006)
Hemoglobin: An Overview

• Normal adult hemoglobins:
  – HgbA ($\alpha_2\beta_2$) 97%
  – HgbF ($\alpha_2\gamma_2$) 2.5%
  – HgbA2 ($\alpha_2\delta_2$) <1%

• Variant hemoglobins can be distinguished by
  – Electrophoresis (+/- isoelectric focusing)
  – Cation-exchange liquid chromatography on RBC lysates
  – Induced hypoxemia (eg., Sickledex®)
  – Molecular studies
Hemoglobin: An Overview

• Globin gene deletions or mutations may result in:
  – Imbalance of alpha and beta globin chain synthesis (thalassemia)
  – Alteration of secondary or tertiary structure of hemoglobin molecule (hemoglobinopathy)

• Some hemoglobin variants also involve an underlying globin chain synthesis imbalance and are therefore “thalassemic”
Alpha Thalassemia

• Deficiency in α-globin (primarily gene deletions): present in 5% of world’s population
• Embryo: alpha-like ζ globin combines with beta-like ε and γ globins to form functional hemoglobins Gower 1 and Portland
• Fetus: with α globin deficiency, excess γ-globin tetramers form non-functional Hgb-Barts
• Adult: excess β-globin tetramers form non-functional HgbH
Alpha Thalassemia

- Severity of disease depends on number of functioning $\alpha$-globin genes
  - $\alpha^0$ haplotype = two deletions
  - $\alpha^+\ haplotype = one deletion (worse phenotype if $\alpha_2$ gene affected)
  - Thalassemia hemoglobinopathy: non-deletional mutation in alpha-globin gene (eg., $\alpha^{CS}$, basis of Hgb Constant Spring)
# Alpha Thalassemia

<table>
<thead>
<tr>
<th>Disease</th>
<th>Phenotype</th>
<th>Hgb</th>
<th>Genotype</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alpha thal minima (Alpha-thal trait 2)</td>
<td>Normal</td>
<td>A</td>
<td>αα/ α-</td>
</tr>
<tr>
<td>Alpha thal minor (Alpha-thal trait 1)</td>
<td>Mild microcytic anemia</td>
<td>A</td>
<td>αα/ -- (cis) α-/ α- (trans)</td>
</tr>
<tr>
<td>HgbH disease (alpha thal major)</td>
<td>Moderate microcytic anemia</td>
<td>A, H</td>
<td>α-/ --</td>
</tr>
<tr>
<td>Hgb Barts disease (fetal hydrops)</td>
<td>Stillbirth</td>
<td>Barts, Portland</td>
<td>-- / --</td>
</tr>
</tbody>
</table>
Alpha Thalassemia

Common alpha thalassemic deletions

Chui, Blood 2003;101(3):791
Alpha Thalassemia

• Diagnosis of alpha thal trait or minima can be challenging
  – Microcytosis may be mild or absent in alpha thal minima
    • Population screening usually based on MCV < 82 fL, or MCH < 27 pg, with molecular tests for confirmation
    • Alternatively, ELISA for persistent ζ chains in adults can detect α⁰ carriers
  – Hgb Barts only detectable during newborn period
  – HgbH very fast moving on electrophoresis, usually missed
  – HgbH inclusions rarely visible on supravital stain of peripheral blood film if < 3 gene deletions
Alpha Thalassemia

• Hydrops Fetalis
  – HgbBarts both unstable, resulting in ineffective erythopoiesis, and very high oxygen affinity, resulting in poor oxygenation (degree of anemia therefore underestimates degree of hypoxia)
  – Heart failure: cardiomegaly, pericardial effusion, edema, ascites, pleural effusion
  – Impaired fetal development: congenital anomalies (common), CNS impairment (uncommon)
  – Placental hypertrophy: pre-eclampsia, dystocia, retained products: high maternal morbidity rate
  – Diagnosis of affected fetus: doppler US of fetal MCA; placentomegaly; high cardiothoracic ratio
Alpha Thalassemia

• Hydrops Fetalis
  – Highest risk when both mother and father are $\alpha^0$ carriers (two deletions in cis) $\rightarrow$ 25% chance 4 gene deletion in fetus
  – HgbH may occasionally be hydropic if non-deletional (25% of cases)
  – If embryonic genes also deleted, pregnancy may terminate unnoticed early in pregnancy
  – Intrauterine transfusion support generally required for fetal survival (~20 cases reported)
Alpha Thalassemia

• Evolution of intra-uterine transfusion technique
  – 1963: first inter-peritoneal transfusion (RBCs taken into fetal bloodstream via sub-diaphragmatic lacunae and right lymphatic duct; uptake depends on diaphragmatic movements)
  – 1981: first intravascular fetal transfusion (RBCs infused under ultrasound guidance into umbilical cord or intrahepatic umbilical vein)
    • Exchange transfusion not required to prevent volume overload, as excess fluid absorbed into fetoplacental circulation

• Generally repeated q2weeks until delivery
  – Post-procedure decline in Hct of 1-2%/day
Alpha Thalassemia

• Complications of intra-uterine transfusion
  – 1.6-2% perinatal mortality
  – Pre-term delivery (from intrauterine infection)
  – Maternal alloimmunization (fetal-maternal hemorrhage)

• Outcomes
  – 84% long-term survival (94% for non-hydropic, 74% for hydropic)
  – 90% of survivors will have normal short-term neurodevelopmental outcome; limited data for long-term results generally encouraging

Alpha Thalassemia

• Hgb H Disease
  – Generally a benign disease
  – Less ineffective hematopoiesis than Hgb Barts: average baseline Hgb = 90-100 g/L; with oxidative stress (infection, fever, sulphameds, etc) may induce HgbH precipitation and worsening hemolysis
  – Transfusion often required during pregnancy
  – Goal of transfusion is generally treatment of symptomatic anemia (eg., Hgb < 70-80 g/L)
  – A significant proportion of non-deletional HgbH (eg., --/α<sup>CS</sup>) will require chronic transfusion support
  – Transfusion requirements can be mitigated by splenectomy, but at increased risk of septicemia and venous thromboembolism
Beta Thalassemia

- Deficiency in β-globin (primarily mutations)
- Unbound α globin do not form stable tetramers and are much more toxic to developing erythroblast than free β-globin
- Result: higher rate of ineffective hematopoiesis and intramedullary hemolysis than alpha thalassemia
- Severity of disease depends on severity of β globin gene mutation
  - $\beta^0$ haplotype = complete absence no β-globin synthesis
  - $\beta^+$ and $\beta^{++}$ haplotypes = some residual β-globin synthesis
  - Thalassemia hemoglobinopathies: HgbE, Hgb Lepore
### Beta Thalassemia

<table>
<thead>
<tr>
<th>Disease</th>
<th>Phenotype</th>
<th>Hgb</th>
<th>Genotype</th>
</tr>
</thead>
<tbody>
<tr>
<td>Beta-thal minor</td>
<td>Mild microcytic anemia</td>
<td>A, A2, F</td>
<td>β⁺/ββ⁺/ββ⁰/β⁰</td>
</tr>
<tr>
<td>(Beta-thal trait)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Beta-thal intermedia</td>
<td>Moderate microcytic</td>
<td>A, A2, F</td>
<td>TMaj with mitigators</td>
</tr>
<tr>
<td></td>
<td>anemia</td>
<td></td>
<td>Tmin with exacerbators</td>
</tr>
<tr>
<td>Beta-thal major</td>
<td>Severe microcytic</td>
<td>(A), A2, F</td>
<td>β⁰/β⁰β⁰/β⁺β⁺/β⁺</td>
</tr>
<tr>
<td>(Cooley’s anemia)</td>
<td>anemia</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

- **Mitigators:** residual β-globin (mild β⁺), decr α-globin (alpha thal), elevated HgbF (HPFF, Xmn1-γ γ +/+, δβ deletion)
- **Exacerbators:** incr α-globin (eg., ααα/αα), “dominant” β⁰
- **HgbE/β-thal** most common cause of thal intermedia, but highly variable phenotypic expression (may also be either trait or major)
Beta Thalassemia

• Diagnosis of β-thal minor usually straightforward:
  – Mild microcytic anemia with incr A2 (> 3.5% when quantified by chromatography)

• As with alpha-thal trait, microcytosis may be falsely attributed to iron deficiency
  – Mentzer index (MCV/RBC) usually > 15 in iron deficiency
  – Iron deficiency may co-exist with thal trait, and may decrease A2
  – Serum ferritin 20-100 μmol/L indeterminate for iron deficiency
  – Trial of iron very reasonable method of ruling out iron deficiency if time allows (eg., not for pre-natal diagnosis)

• As MCV falsely increases during prolonged sample storage, MCH cut-off < 27 pg gaining more popularity for population screening
Beta Thalassemia

- Deficiency of β-globin results in increased proportion of Hgb derived from “beta-like” globins
  - In severest forms of beta thalassemia major (β⁰/β⁰), 95% of hematopoiesis is ineffective (intramedullary hemolysis)
  - Almost all circulating hemoglobin will be HgbF (α₂γ₂), with small proportion(<4%) being HgbA2 (α₂δ₂)

- However, these Hgb variants are less efficient at oxygen delivery, and in all but the mildest forms of beta-thal minor are never produced in sufficient quantities to completely correct anemia

- Without transfusion support, body attempts to compensate for chronic ineffective hematopoiesis by expanding the erythroid marrow
Beta Thalassemia

• Massive marrow hyperplasia underlies most of the phenotypic manifestations of β-thalassemia major
  – Hypercatabolic state (growth retardation)
  – Skeletal deformities
    • “chipmunk facies” (frontal bossing, occlusion of maxillary sinuses with subsequent dental deformities)
    • shortening of long bones due to premature fusion
    • osteoporosis with bony pain
    • classic radiologic findings (“hair-on-end”’s skull x-ray, Erlenmeyer flask deformity in femur, etc)
  – Increased adsorption of iron from gut
Beta Thalassemia

• Other disease manifestations
  – Hepatosplenomegaly (usually due to work hypertrophy)

• Massive marrow hyperplasia underlies most of the phenotypic manifestations of β-thalassemia major
  – Hypercatabolic state (growth retardation)
  – Skeletal deformities
    • “chipmunk facies” (frontal bossing, occlusion of maxillary sinuses with subsequent dental deformities)
    • shortening of long bones due to premature fusion
    • osteoporosis with bony pain
    • classic radiologic findings (“hair-on-end”’s skull x-ray, Erlenmeyer flask deformity in femur, etc)
  – Increased adsorption of iron from gut
Beta Thalassemia

• Iron overload from increased GI absorption in turn causes progressive organ dysfunction
• Hepatic iron overload normally triggers secretion of hepcidin, which serves as “master switch” to minimize further iron absorption from gut

Ganz, Blood. 2003;102:783
Ganz, Blood. 2003;102:783
Beta Thalassemia

- GDF15, secreted by erythroid precursors, inhibits secretion of hepcidin by hepatocytes
- In thalassemia major, the degree of marrow hyperplasia means that hepcidin continues to be suppressed even after the body is already iron overloaded

Tanno, Curr Opin Hematol. 2010;17:184
Beta Thalassemia

• In severest forms of beta-thalassemia major (β⁰/β⁰), regular transfusions required within first year of life: without them anemia induces fatal heart failure within second year

• Prior to 1960s, however, patients with TM were transfused only “to the amount required to maintain minimum physical activity”, for fear of exacerbating the progressive iron overload which at that point constrained life expectancy to 2nd or 3rd decade
  – ~ 250 mg iron per unit RBCs/whole blood transfused
  – Normal body iron = 3-4 g; clinical complications expected once 12-24 g accumulated

Piomelli, Ann NY Acad Sci 1974;232:186
Beta Thalassemia

• 1963: 45 children (under age 12) with beta-thalassemia major brought to Philadelphia and studied along with 18 children already living in the area. Total of 35 children had adequate documentation of transfusion history and agreed to participate in study

• All children underwent blinded physical, laboratory and radiologic assessment

• Results presented at 1st Cooley’s conference in 1964: children with Hgb of 80-100 g/L appeared to be in better health than patients with lower levels, despite having received more transfusion

Wolman, Ann NY Acad Sci 1964;119:736
Beta Thalassemia

• On basis of these findings, children started on “hypertransfusion” program with goal of maintaining pre-transfusion Hct > 28%
  – 20 ml/kg PRBCs q4weeks = 2-4 units per month in adult
• Results presented at subsequent Cooley’s conferences in 1969 and 1974: hypertransfusion resulted in
  – Prevention and partial regression of skeletal abnormalities
  – Prevention and partial regression of organomegaly
  – Suppressed erythropoiesis (deceased F cells)
  – Improved quality of life
• Best results seen when transfusions started early

Piomelli, Ann NY Acad Sci 1969;165:427
Piomelli, Ann NY Acad Sci 1974;232:186
Beta Thalassemia

- Enthusiasm for “hypertransfusion” grew with recognition that:
  - Transfusional iron burden partly offset by decreased GI absorption
  - Continuous infusion of desferrioxamine B (first isolated in 1960 from *Streptomyces pilosus*) could achieve negative iron balance and prevent organ damage even with chronic transfusion support
    - DFO initially given as IM bolus; due to short plasma half-life, efficacy greatly increased by administering as continuous SQ or IV infusion
Beta Thalassemia

• Erythrokinetic studies: RBC clearance = 1% per day
• Implies that maintaining a higher Hct requires more transfusion support than maintaining lower Hct
• However, if maintaining a higher Hct also results in decreased whole blood volume, then may be possible to reap benefits of greater Hct (improved oxygen delivery, further suppression of erythroid hyperplasia) without increased transfusion needs
• On this reasoning, “supertransfusion” regimen became popular in 1980s: transfuse to keep Hgb > 120 g/L (Hct > 35%) at all times and keep average Hgb at 140 g/L
Beta Thalassemia

- Preliminary results promising: higher Hct resulted in decreased iron turnover...

Beta Thalassemia

- ...with similar transfusion requirements

Beta Thalassemia

• However, clinical experience later revealed that supertransfusion did in fact involve increased transfusion requirements, resulting in 150-200 mg/kg Fe per year compared to hypertransfusion.

Hyper- vs supertransfusion in a cohort of 32 Italian patients with beta-thalassemia major

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean pre-tx Hgb (g/L)</td>
<td>113 g/L</td>
<td>94 g/L</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>Blood consumption per year (RBC/kg/yr)</td>
<td>137</td>
<td>104</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>Mean serum ferritin (µg/L)</td>
<td>2280</td>
<td>1004</td>
<td>&lt; 0.0001</td>
</tr>
</tbody>
</table>

Cazzola, Transfusion 1997;37:135
Beta Thalassemia

- Return to hypertransfusion in 1990s
- Proposed that pre-transfusion Hgb of 90-100 g/L was sufficient to maintain erythroid activity to < 5x normal (as calibrated against serum transferrin receptor levels), which should be sufficient, since:
  - Erythroid activity below this threshold does not result in net iron accumulation from increased GI absorption
  - Thal minor and non-transfused intermedia patients generally do not exceed this threshold and do not suffer skeletal abnormalities or growth retardation

Cazzola, Br J Haem 1995;89:473
Beta Thalassemia

• Initial attempts at reducing transfusion requirements involved selecting only “fresh” units of blood (< 7 days)
• Process later refined by selectively collecting only the youngest circulating RBCs from blood donors
  – “Neocyte” defined as a RBC < 30 days old, as determined by standard calibration curves for RBC pyruvate kinase
  – When whole blood centrifuged at 700 mL, neocytes (which are less dense) tend to segregate into lower layer of buffy coat
  – Leukocytes and platelets removed by freeze/thaw with deglycerolization
• Commercial apheresis kit later developed to allow for preparation of neocytes from standard pre-storage leukoreduced units of whole blood

Corash, Blood 1981;57(3):599
Beta Thalassemia

• Cross-over trial conducted in 16 patients, comparing neocytes with washed RBCs, both administered with Hct 0.8 at dose of 15 ml/kg whenever patient Hgb < 100 g/L)

• Result: neocyte transfusions provided an average of 6 days longer between transfusions, with calculated 15% annual decrease in iron loading

• However, these modest benefits came at a cost of:
  – Doubling the number of donor exposures
  – Quintupling the component production costs

Collins, Transfusion 1994;34:517
Beta Thalassemia

• Partial erythrocytapharesis can also more effectively reduce the age of circulating RBCs in thalassemic patients (“neocyte/gerocyte” exchange), allowing for decreased RBC consumption and iron loading versus simple transfusion.

• However, only 12/16 of patients in a pilot study achieved this benefit, and at a cost of
  – 2-3x more donor exposures
  – Increased rate of adverse transfusion reactions (17% vs 3.1%)

Friedman, Blood, 2003;102:121a
Beta Thalassemia

• Donor exposure and disease transmission
  – In 1984, 12% of thalassemics in New York had HIV. Prevalence was 3% by 1990, 2% by 1998 (decreased prevalence due to both improved product safety and 25% 6-year mortality rate)
  – 80% of thalassemic patients transfused in 1980s were infected with HCV. Spontaneously clearance in 30% of cases; 40% of remainder may achieve persistent viral clearance with ribavirin and interferon. Treatment with ribavirin may increase transfusion requirements by 50%

Prati, Vox Sang 2000;179:29
Busch, JAMA 2003;289(8):959
Current Risks

Residual Risks per Donor Exposure

- HIV: 1 in 7.8 million
- HCV: 1 in 2.3 million
- HTLV: 1 in 4.3 million
- HBV: 1 in 153 000
- Bacterial contam: 1:100 000 (RBCs)

Others: CMV, PB19, EBV, HHV-8, WNV, malaria, Chagas, prions...

O’Brien, Transfusion 2007;47:316
Beta Thalassemia

- What about thal intermedia?
  - Usually defined as requiring < 8 transfusions/year
  - Baseline Hgb 70-100 g/L
  - Skeletal abnormalities less severe than untransfused β-thal major
  - Historically, splenectomy performed in early adolescence in attempt to minimize transfusion dependence (splenectomy has also been advised in thalassemia major patients requiring > 200 ml/kg/year of RBCs)
Beta Thalassemia

• What about thal intermedia?
  – However, in addition to increasing risk of bacterial infection (especially encapsulated organisms), splenectomy also increases risk of thrombosis and pulmonary hypertension
  – Observational studies suggest fewer long-term complications if patients managed as if they had beta-thal major (ie., regular transfusion support with iron chelation)
  – Splenectomy now advised primarily if hypersplenism causing physical discomfort, or resulting in unmanageable iron overload from excessive transfusion requirements
  – Note that risks of splenectomy can be minimized by:
    • Pre-procedure vaccination
    • Post-procedure DVT prophylaxis (short-term) and chronic transfusion support (long-term)
<table>
<thead>
<tr>
<th>Complication/parameter</th>
<th>RR</th>
<th>95% CI</th>
<th>( P )</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>EMH</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age &gt; 35 y</td>
<td>0.85</td>
<td>0.46-1.58</td>
<td>.610</td>
</tr>
<tr>
<td>Ferritin ≥ 1000 μg/L</td>
<td>0.85</td>
<td>0.51-1.44</td>
<td>.548</td>
</tr>
<tr>
<td>Splenectomy</td>
<td>0.44</td>
<td>0.26-0.73</td>
<td>&lt;.001*</td>
</tr>
<tr>
<td>Transfusion</td>
<td>0.06</td>
<td>0.03-0.99</td>
<td>&lt;.001*</td>
</tr>
<tr>
<td>Hydroxyurea</td>
<td>0.52</td>
<td>0.30-0.91</td>
<td>&lt;.001*</td>
</tr>
<tr>
<td><strong>PHT</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age &gt; 35 y</td>
<td>2.59</td>
<td>1.09-6.19</td>
<td>.032*</td>
</tr>
<tr>
<td>Splenectomy</td>
<td>4.11</td>
<td>1.99-8.47</td>
<td>&lt;.001*</td>
</tr>
<tr>
<td>Transfusion</td>
<td>0.33</td>
<td>0.18-0.58</td>
<td>&lt;.001*</td>
</tr>
<tr>
<td>Hydroxyurea</td>
<td>0.42</td>
<td>0.20-0.90</td>
<td>&lt;.001*</td>
</tr>
<tr>
<td>Iron chelation</td>
<td>0.53</td>
<td>0.29-0.95</td>
<td>&lt;.001*</td>
</tr>
<tr>
<td><strong>HF</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Splenectomy</td>
<td>2.88</td>
<td>0.99-8.32</td>
<td>.051</td>
</tr>
<tr>
<td>Transfusion</td>
<td>0.06</td>
<td>0.02-0.17</td>
<td>&lt;.001*</td>
</tr>
<tr>
<td>Hydroxyurea</td>
<td>1.84</td>
<td>0.99-3.47</td>
<td>.057</td>
</tr>
<tr>
<td>Iron chelation</td>
<td>0.45</td>
<td>0.19-1.12</td>
<td>.086</td>
</tr>
<tr>
<td><strong>Thrombosis</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age &gt; 35 y</td>
<td>2.60</td>
<td>1.39-4.87</td>
<td>.009*</td>
</tr>
<tr>
<td>Female</td>
<td>1.27</td>
<td>0.74-2.19</td>
<td>.387</td>
</tr>
<tr>
<td>Hb ≥ 90 g/L</td>
<td>0.41</td>
<td>0.23-0.71</td>
<td>.282</td>
</tr>
<tr>
<td>Ferritin ≥ 1000 μg/L</td>
<td>1.86</td>
<td>1.09-3.16</td>
<td>.023*</td>
</tr>
<tr>
<td>Splenectomy</td>
<td>6.59</td>
<td>3.09-14.05</td>
<td>&lt;.001*</td>
</tr>
<tr>
<td>Transfusion</td>
<td>0.38</td>
<td>0.16-0.48</td>
<td>&lt;.001*</td>
</tr>
<tr>
<td>Hydroxyurea</td>
<td>0.56</td>
<td>0.29-1.10</td>
<td>.090</td>
</tr>
<tr>
<td>Iron chelation</td>
<td>0.97</td>
<td>0.56-1.68</td>
<td>.912</td>
</tr>
<tr>
<td><strong>Cholelithiasis</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age &gt; 35 y</td>
<td>2.76</td>
<td>1.56-4.87</td>
<td>&lt;.001*</td>
</tr>
<tr>
<td>Female</td>
<td>1.96</td>
<td>1.18-3.25</td>
<td>&lt;.001*</td>
</tr>
<tr>
<td>Splenectomy</td>
<td>5.19</td>
<td>2.72-9.90</td>
<td>&lt;.001*</td>
</tr>
<tr>
<td>Transfusion</td>
<td>0.36</td>
<td>0.21-0.62</td>
<td>&lt;.001*</td>
</tr>
<tr>
<td>Hydroxyurea</td>
<td>0.55</td>
<td>0.29-1.02</td>
<td>&lt;.001*</td>
</tr>
<tr>
<td>Iron chelation</td>
<td>0.30</td>
<td>0.18-0.51</td>
<td>&lt;.001*</td>
</tr>
</tbody>
</table>

**Abnormal liver function**

<table>
<thead>
<tr>
<th>RR</th>
<th>95% CI</th>
<th>( P )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ferritin ≥ 1000 μg/L</td>
<td>1.74</td>
<td>1.00-3.02</td>
</tr>
<tr>
<td>Transfusion</td>
<td>1.56</td>
<td>0.76-3.17</td>
</tr>
</tbody>
</table>

**Leg ulcers**

<table>
<thead>
<tr>
<th>RR</th>
<th>95% CI</th>
<th>( P )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ferritin ≥ 1000 μg/L</td>
<td>1.29</td>
<td>0.67-2.47</td>
</tr>
<tr>
<td>Transfusion</td>
<td>3.88</td>
<td>1.68-9.29</td>
</tr>
<tr>
<td>Splenectomy</td>
<td>0.39</td>
<td>0.20-0.78</td>
</tr>
<tr>
<td>Hydroxyurea</td>
<td>0.10</td>
<td>0.02-0.43</td>
</tr>
<tr>
<td>Iron chelation</td>
<td>0.68</td>
<td>0.35-1.34</td>
</tr>
</tbody>
</table>

**DM**

<table>
<thead>
<tr>
<th>RR</th>
<th>95% CI</th>
<th>( P )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ferritin ≥ 1000 μg/L</td>
<td>5.79</td>
<td>0.71-47.21</td>
</tr>
<tr>
<td>Transfusion</td>
<td>0.24</td>
<td>0.03-2.20</td>
</tr>
<tr>
<td>Splenectomy</td>
<td>0.40</td>
<td>0.10-1.62</td>
</tr>
</tbody>
</table>

**Hypothyroidism**

<table>
<thead>
<tr>
<th>RR</th>
<th>95% CI</th>
<th>( P )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ferritin ≥ 1000 μg/L</td>
<td>1.01</td>
<td>0.46-2.23</td>
</tr>
<tr>
<td>Transfusion</td>
<td>6.04</td>
<td>2.03-17.92</td>
</tr>
<tr>
<td>Splenectomy</td>
<td>13.3</td>
<td>1.79-100.00</td>
</tr>
<tr>
<td>Hydroxyurea</td>
<td>0.05</td>
<td>0.01-0.45</td>
</tr>
<tr>
<td>Iron chelation</td>
<td>0.49</td>
<td>0.22-1.07</td>
</tr>
</tbody>
</table>

**Osteoporosis**

<table>
<thead>
<tr>
<th>RR</th>
<th>95% CI</th>
<th>( P )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ferritin ≥ 1000 μg/L</td>
<td>3.51</td>
<td>2.06-5.99</td>
</tr>
<tr>
<td>Transfusion</td>
<td>1.97</td>
<td>1.19-3.27</td>
</tr>
<tr>
<td>Splenectomy</td>
<td>1.60</td>
<td>0.96-2.69</td>
</tr>
<tr>
<td>Hydroxyurea</td>
<td>4.73</td>
<td>2.72-8.24</td>
</tr>
<tr>
<td>Iron chelation</td>
<td>3.10</td>
<td>1.64-5.85</td>
</tr>
<tr>
<td>ferritin ≥ 1000 μg/L</td>
<td>0.02</td>
<td>0.01-0.09</td>
</tr>
<tr>
<td>Transfusion</td>
<td>0.40</td>
<td>0.24-0.68</td>
</tr>
</tbody>
</table>

Taher, Blood 2010, 115:886
Taher, Blood 2010, 115:886
Beta Thalassemia

• Extramedullary hematopoietic masses that have not converted to adipose or fibrotic tissue may respond (with increasing speed) to hydroxyurea, hypertransfusion, radiation therapy, or surgery

• Generally only required for significant compression syndromes (eg., spinal cord impingement), which may not present until 3rd or 4th decade of life
  – Transfusion regimens may very aggressive: 2-4 units per week until symptoms resolve (usually several months)
Blood Product Selection

• Blood Group and Antibody Screen required prior to issue of all blood components
  – testing takes 45 minutes; if screen positive, a full investigation may be required (hours to days)

• Once group and screen complete, same sample can be used for crossmatching RBCs
  – takes 1 hour if screen positive, <15 min if negative

• Samples will outdate after 3 days (eg., sample must have been drawn at most 3 days prior to transfusion)
  – Some hospitals allow a 96 hour outdate, depending upon accreditation body
Blood Product Selection

• Sample collection errors (e.g., putting label on wrong tube of blood) very common (1:2000)
  – Risk especially high with blood bank samples: may result in ABO-incompatible transfusion (AHTR: acute hemolytic transfusion reaction)

• While individual hospitals maintain permanent records of detected antibodies, hospitals generally do not share these records with one another

• Patients who are transfused at multiple hospitals therefore at higher risk of delayed hemolytic transfusion reactions (DHTR) due to transient detectability of minor blood group antibodies
  – Provision of antibody cards may mitigate this risk
### TABLE 1. Antibody specificity and detectability over the course of time (all antibodies)

<table>
<thead>
<tr>
<th>Antibody specificity</th>
<th>Absolute number</th>
<th>Percentage of all antibodies</th>
<th>Undetectable over the course of time</th>
<th>Percentage of this antibody</th>
</tr>
</thead>
<tbody>
<tr>
<td>K</td>
<td>166</td>
<td>28</td>
<td>48</td>
<td>29</td>
</tr>
<tr>
<td>E</td>
<td>136</td>
<td>23</td>
<td>52</td>
<td>38</td>
</tr>
<tr>
<td>D</td>
<td>118</td>
<td>20</td>
<td>15</td>
<td>13</td>
</tr>
<tr>
<td>Fy&lt;sup&gt;a&lt;/sup&gt;</td>
<td>55</td>
<td>9</td>
<td>7</td>
<td>13</td>
</tr>
<tr>
<td>C</td>
<td>49</td>
<td>8</td>
<td>9</td>
<td>18</td>
</tr>
<tr>
<td>c</td>
<td>28</td>
<td>5</td>
<td>9</td>
<td>32</td>
</tr>
<tr>
<td>Jk&lt;sup&gt;a&lt;/sup&gt;</td>
<td>17</td>
<td>3</td>
<td>6</td>
<td>35</td>
</tr>
<tr>
<td>S</td>
<td>10</td>
<td>2</td>
<td>1</td>
<td>10</td>
</tr>
<tr>
<td>Jk&lt;sup&gt;b&lt;/sup&gt;</td>
<td>6</td>
<td>1</td>
<td>4</td>
<td>67</td>
</tr>
<tr>
<td>e</td>
<td>5</td>
<td>1</td>
<td>1</td>
<td>20</td>
</tr>
<tr>
<td>Fy&lt;sup&gt;b&lt;/sup&gt;</td>
<td>2</td>
<td>&lt;1</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>s</td>
<td>1</td>
<td>&lt;1</td>
<td>1</td>
<td>100</td>
</tr>
</tbody>
</table>

- 26% of antibodies will become undetectable over the course of time
- Antibodies detected by very sensitive compatibility testing techniques tend to be the least persistent
Blood Product Selection

• In the period May 2003- Nov 2005 all Québec hospitals progressively computerized with the same blood bank software.

• Each hospital can query the blood bank database of all other hospitals to check blood group, antibodies, transfusion history, and other special requirements.

• Results can be viewed but not copied/saved (current sample must still be tested).
Blood Product Selection

Ratio per 100,000 RBCs

ABO Inc: PRE 3.63, POST 0.94, p=0.012
AHTR: PRE 4.51, POST 1.41, p=0.03
DHTR: PRE 10.39, POST 4.71, p=0.006

Robillard, Transfusion 2006;46S:13A
Blood Product Selection

• **Leukoreduced**
  – Decreases risk of febrile non-hemolytic transfusion reactions, certain transfusion-transmitted infections (eg., CMV), and alloimmunization
  – All products in Canada now leukoreduced

• **Plasma-volume reduced**
  – Concentration of RBC required if risk of volume overload despite pre-transfusion diuretics
  – Very little actual plasma in current products (< 20 mL) but if transfusion reactions persist despite pre-medication can consider plasma-reduction or even washing
  – If anaphylaxis secondary to anti-IgA antibodies, can also select products from IgA-deficient donors
  – Note: by achieving uniform Hct of 80%, washing reveals the natural variation in RBC content between regular units (Hct 40-60%)
## Blood Product Selection

<table>
<thead>
<tr>
<th>Total volume</th>
<th>Hematocrit</th>
<th>Packed cell volume</th>
<th>Plasma volume (incl additive)</th>
<th>Difference in volume vs 59% product</th>
</tr>
</thead>
<tbody>
<tr>
<td>240 mL</td>
<td>40%</td>
<td>96 mL</td>
<td>144 mL</td>
<td>46 mL</td>
</tr>
<tr>
<td>240 mL</td>
<td>50%</td>
<td>120 mL</td>
<td>120 mL</td>
<td>22 mL</td>
</tr>
<tr>
<td>240 mL</td>
<td>59%</td>
<td>142 mL</td>
<td>98 mL</td>
<td>0 mL</td>
</tr>
</tbody>
</table>

- Note: actual duration between transfusions will depend upon other factors beyond RBC content of unit (eg., age of unit, volume status of patient, degree of residual marrow activity, degree of splenic activity, inter-transfusion bleeding, etc)
Recommendations regarding the volume of transfused red cells are complicated by the use of different anticoagulant-preservatives and additive solutions. For CPD-A units with a haematocrit of approximately 75%, the volume per transfusion is usually 10-15 ml/kg, administered over 3-4 hours. Units with additive solutions may have lower haematocrits in the range of 60-70%, and consequently larger volumes with a higher haematocrit level are needed to administer the same red cell mass (see Table 4). For most patients, it is usually easier to avoid these differences in red cell concentration by ordering a certain number of units (e.g. one or two) rather than a particular volume of blood. Younger children may require a fraction of a unit to avoid under- or over-transfusion. Patients with cardiac failure or very low initial haemoglobin levels should receive smaller amounts of red cells at slower rates of infusion.
Blood Product Selection

• **CMV-negative**
  – Reduces the risk of transfusion-transmitted CMV
  – May be slightly more effective than leukoreduced blood products, but additional safety margin only justified for intra-uterine transfusions or to pregnant women who are themselves CMV-neg

• **Irradiated**
  – Decreases risk of transfusion-associated graft-versus host disease
  – Only required for intrauterine transfusions, directed donations or for patients with specific types of immunodeficiency (eg., Hodgkin’s disease, following bone marrow transplant
Blood Product Selection

- **Prophylactically antigen-matched**
  - Historically only recommended for sickle cell disease due to high risk of alloimmunization (~25%) and severity of delayed hemolytic transfusion reactions (e.g., hyperhemolysis)
  - Traditionally, rate of alloimmunization in thalassemic patients thought to be close enough to general population to not merit prophylactic matching (5-10%)
  - However, more recent studies suggest rate of alloimmunization in thalassemics may be similar to those with sickle cell disease. Clinical significance also increases as greater proportion of thalassemic patients now becoming pregnant, with incr risk of HDN
  - Growing interest in some matching for thalassemic patients as well (Rh and Kell), although not yet a standard of care
The Future...

• Thalassemia
  – Very common in
  – 300 million carriers worldwide, mostly in Asian, Indian and Mideast areas of malaria belt (origin of ~75% of recent immigrants to North America)
  – Life expectancy continues to improve

Borgna-Pignatti, Haematologica 2004;89:1187
BIRTHS WITH A PATHOLOGICAL HEMOGLOBIN DISORDER PER 1,000 LIVE BIRTHS

Global Distribution of Pathological Hemoglobin Disorders, 1996 (WHO)

SOURCE: MARCH OF DIMES' GLOBAL REPORT ON BIRTH DEFECTS THE HIDDEN TOLL OF DYING AND DISABLED CHILDREN 2006

With permission from the Source: March of Dimes: Global Report 2006
Canadian Blood Services

it's in you to give

1-888-2-DONATE