Hemoglobinopathies
(everything you wanted to know but were afraid to ask)
Melissa Frei-Jones, MD MSCI
Pediatric Grand Rounds
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Disclosure
• I have no relationships with commercial companies to disclose.
• I will be discussing off-label use of medications in children.
  – FDA - “Safety and effectiveness of hydroxyurea in children has not been established.”

Learning Objectives
• Plan the evaluation and counseling of patients with abnormal hemoglobinopathy testing on newborn screen.
• Recognize the clinical and laboratory findings associated with quantitative hemoglobinopathies.
• Integrate changes in sickle cell practice guidelines into primary and specialty care.

Screening for Hemoglobinopathies
• The test:
  – Thin layer isoelectric focusing (IEF) and high performance liquid chromatography (HPLC)
  – Approach 100% sensitivity and specificity
• The results:
  – 76 possible results
  – 31 represent actual disease
  – 45 represent trait or carrier status

Screening for Hemoglobinopathies
• The benefit:
  – Identify children with a disease that benefits from early detection
    • SCD to start prophylactic penicillin by 2 months of age to prevent pneumococcal infection
    • Thalassemia Major to start blood transfusion
• The harm:
  – Incidental detection of trait/carryer status and hemoglobin disorders of questionable clinical significance
  – Parental anxiety and un-necessary testing in infants

Interpreting Reports
<table>
<thead>
<tr>
<th>RESULT NOTE</th>
<th>WHAT IT MEANS?</th>
</tr>
</thead>
<tbody>
<tr>
<td>Recommend consultation with pediatric hematologist.</td>
<td>Call and discuss timing of repeat testing and refer if abnormal to hematologist.</td>
</tr>
<tr>
<td>Consult with pediatric hematologist.</td>
<td>Refer for counseling and visit by 6-12 months of age.</td>
</tr>
<tr>
<td>Refer to pediatric hematologist.</td>
<td>Hematology should see patient by 2 months of age.</td>
</tr>
<tr>
<td>Notify family of test results.</td>
<td>Provider discretion. Referral not necessary.</td>
</tr>
</tbody>
</table>
So when should I repeat testing?

- **In disease** –
  - Specialist may repeat testing at 6-12 mo
  - CBC, retic and Hemoglobin Analysis
- **In common traits (S, C, D, Alpha Thal)** -
  - Not required
- **Uncommon traits (Other)** –
  - Repeat at 6-12 months when Hb F levels fall to see if abnormal hemoglobin persists
    - May represent prenatal hemoglobin
  - CBC, Hemoglobin Analysis, Pulse Oximetry

What is missing on NBS?

- Beta Thalassemia Trait
- Beta Thalassemia Intermedia
- Why?
  - Detected by development of microcytosis after Hb F falls (Hb F = increased MCV).
  - Elevated Hb A2 (>3%)
    - Won’t be elevated in newborn period due to Hb F

What is Hemoglobin Bart’s?

- Decreased alpha globin production results in excess gamma (γ) globin.
  - $2\gamma + 2\beta = \text{Hb F}$
- Bart’s hemoglobin = $\gamma_4$ tetramer
  - Detected on newborn screen
  - Disappears as Hb F downregulated

Beta Thalassemia

- Abnormal β-globin production
  - Inability to make Hemoglobin A
  - Imbalance between α-globin and β-globin gene production
    - Excess α-globin forms an unstable tetramer
    - Causes damage to red blood cell membrane and increases red cell turnover/shortens half-life
- Key Term – Ineffective Erythropoiesis
Nomenclature

- Beta (β) – nl beta globin gene
- Beta+ (β+) – less than normal production but greater than no production 
  – "Beta plus"
- Beta0 (β0) – no beta globin production 
  – "Beta null or zero"

Beta Thalassemia Minor

- One allele deletion – (ββ° or β/β+)
  - Diagnosis
    - Not detectable on newborn screen
    - Elevated Hb A2
  - Clinical Findings
    - None
  - Laboratory Findings
    - Microcytosis (MCV 50-60)
    - Mild anemia (0.5-1.5 gm/dl below normal)
    - Elevated RBC count
    - Normal RDW
    - Smear
      - Target cells
      - microcytes but without anisocytosis.

Beta Thalassemia Major

- Complete gene deletion – (β°/β°)
  - Diagnosis
    - Newborn Screen
      - Hb F only
  - Laboratory features
    - Hemoglobin electrophoresis = No Hb A, > 90% Hb F
    - MCV may be elevated due to presence of Hb F
    - Severe anemia
      - Hb 4-5 gm/dl without transfusions
      - Ineffective erythropoiesis

Beta Thalassemia Intermedia

- Beta globin gene mutations are variable
  - >200 mutations described in beta globin gene
    - (β+)/β° or β+/β+)
  - Laboratory Findings
    - Anemia but Hb usually > 7gm/dl
    - Microcytosis
  - Clinical presentation
    - +/- splenomegaly
    - May have iron overload in absence of transfusions due to increased intestinal absorption.

Alpha Thalassemia Syndromes

- 2 Alpha globin genes
  - HBA1, HBA2
  - 2 alleles per gene
- Highest frequency of mutations in Southeast Asia

Pathophysiology

- Abnormal amount of Hb A produced
- Excessive beta globin production

Cis vs Trans Conformation

- 1 gene deleted on both alleles = Trans conformation
  - Common among African-Americans
- 2 genes deleted on one allele = Cis conformation
  - Common in Southeast Asia
Alpha Thalassemia Syndromes

- Silent carrier – single deletion
  - Newborn screen
    - <3% Hb Barts
  - Hematologically and clinically silent
- α-Thal Trait - two gene deletion
  - Newborn Screen – Hb Barts
  - Laboratory Findings
    - Mild microcytosis (MCV 60-70)
    - Mild anemia (0.5-1 gm/dl below nl)
    - Often confused with iron deficiency
  - Clinical Findings
    - None

Hemoglobin H Disease

- HbH = tetramer of beta globin (β4)
  - Unstable hemoglobin
    - High affinity for oxygen
    - Susceptible to oxidative stress
- Laboratory Findings
  - Heinz bodies on peripheral smear
  - Microcytosis
  - Anemia
- Clinical findings
  - Splenomegaly
  - +/-Jaundice
  - Hemolysis on exposure to sulfonamides, etc.

Alpha Thal Major

- No functioning alpha globin
- Clinical Findings
  - Severe intra-uterine anemia
  - Heart failure
  - Fetal hydrops and intrauterine fetal demise
- Unable to make Hb F
  - Hb F = 2 α + 2 γ

Management of Thalassemia

- Trait/Carrier
  - No routine care/avoid over-treating microcytosis with oral iron
- Thal Major
  - Chronic transfusion therapy
  - Stem cell transplantation

Sickle Cell Disease ≠ Sickle Cell Anemia

- Sickle Cell Disease (SCD)
  - Umbrella term
- Genotypes are more informative
  - Homozygous Hb SS (aka Sickle Cell Anemia)
  - Compound Heterozygotes
    - Hb SC
    - Hb SB thalassemia plus
    - Hb SB thalassemia null
Prevalence

- 90,000 Americans affected (2010 estimate)
- Hispanic Americans
  - Overall 1 in 20,000 born with SCD
  - Hispanic children of non-Mexican Ancestry 1 in 1100
  - Hispanic children of Mexican Ancestry 1 in 33,000
- Black Americans
  - 1 in 375 births Hb SS
  - 1 in 12 Hb S Carrier
  - 1 in 50 Hb C Carrier
  - 1 in 100 β-thal Carrier
- Hispanic children of non-Mexican Ancestry 1 in 1100
- Hispanic children of Mexican Ancestry 1 in 33,000

How far we’ve come and where are we going next……

Mortality in 1994

- 1994 Median age of death
  - Males 42 yrs
  - Females 48 yrs
- 18% of deaths due to organ failure (renal)
- 33% of deaths had no organ failure
  - 78% during Acute Pain or Acute Chest or both
  - 22% had stroke

Improved Survival in 2010

- Dallas Newborn Cohort of SCD patients

Morbidity & Mortality - Infection

- Functional/Acquired Asplenia
  - Splenic auto-infarction
    - By age 5 in HbSS
    - By age 10-12 in HbSC
  - Splenectomy for recurrent sequestration
- Encapsulated organisms
  - Hib
  - S. pneumoniae
  - N. meningitidis
  - Salmonella
- Infection incidence 50 times
- Leading cause of death in children < 5 with SCD
  - Bacteremia

Infection Prevention

Prophylactic Penicillin
- 1986 RCT
  - 125mg BID PCNVK and placebo
  - Terminated early after only 8 months
  - 84% reduction in incidence of pneumococcal bacteremia
  - No deaths in PCNVK arm; 3 deaths in placebo arm

Immunizations
- Pneumovax and Prevnar
  - Prevnar 7 (2001-2007)
  - Invasive pneumococcal disease decreased by 65% from 131.8 cases/year to 45.5 cases/year
  - Increasing prevalence of non-vaccine serotypes (2004-2010)
- Meningococcal
- Influenza
**“Asthma”**

- 4 times (CI 1.7-9.5) more likely to develop ACS
- Increased admissions for pain
  - SCD Asthma 3.2 episodes; SCD alone 1.8 episodes; p=0.03.
- Increased mortality
  - HR 2.36, 95%CI 1.21-4.62, p=0.01.
- Screening by pulmonology recommended

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**Stroke in SCD**

  - 25% of HbSS patients by age 45
  - 10% of HbSC patients by age 45
- Pediatric Prevalence
  - 10% Overt by 18 years
- Pediatric Stroke Risk
  - 0.13% <24 months
  - 1%-2-5 years
  - 0.79% ages 6-9
  - 2nd peak at age 50 – 1.3%

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**Stroke Prevention**

- Primary Prevention of Overt Stroke
  - Trans-cranial Doppler Ultrasonography (TCD)
    - Abnormal threshold defined in Hb SS patients
    - Prevent stroke with chronic blood transfusions
  - Annual screening
- Secondary Prevention of Overt Stroke
  - Chronic transfusion therapy with Hb S< 30%
    for first 2 years post event and < 50% life-long

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**Impact of Screening on Overt Stroke**

<table>
<thead>
<tr>
<th>Year</th>
<th>Stroke incidence—NIS databases (stroke/100 patient years)</th>
<th>Stroke incidence—KID databases (stroke/100 patient years)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1997</td>
<td>0.54 (0.32, 0.76)</td>
<td>0.51 (0.34, 0.67)</td>
</tr>
<tr>
<td>2000</td>
<td>0.19 (0.07, 0.31)</td>
<td>0.33 (0.32, 0.44)</td>
</tr>
<tr>
<td>2003</td>
<td>0.73 (0.09, 2.96)</td>
<td>0.32 (0.22, 0.43)</td>
</tr>
<tr>
<td>2006</td>
<td>0.13 (0.04, 0.27)</td>
<td>0.25 (0.16, 0.34)</td>
</tr>
<tr>
<td>2009</td>
<td>0.24 (0.06, 0.39)</td>
<td>0.28 (0.20, 0.37)</td>
</tr>
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</table>

NIS, nationwide inpatient sample; KID, kids' inpatient database; SCD, sickle cell disease; CI, confidence interval.

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**Silent Stroke**

- Absence of neurologic deficit
- Most common in HbSS, Sbnull
- Epidemiology
  - Reported prevalence 20% by 18 years
  - Incidence of 47 events/100-pt years
    - Among 652 pts followed prospectively
- “Symptoms”
  - Neurocognitive deficits
  - Academic failure
  - Increase risk of overt stroke
- Treatment
  - Undefined
  - Silent Infarct Transfusion Trial ongoing

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**HYDROXYUREA IN SCD**
Why Hydroxyurea?

- Inhibits ribonucleotide reductase and inhibits DNA synthesis
- Alters RBC precursors by increase Hb F production (increases MCV)
- Cytoreductive effect on bone marrow (pmn>plt>rbc)
- Hb-F beneficial for SCD patients.
- Decrease polymerization of deoxygenated hemoglobin S
- Oral formulation
  - Can be taken once a day
  - Liquid formulations possible

Baby HUG

- Hydroxyurea Infant Study
  - Phase III Multi-Center RCT
    - 20 mg/kg/day HU vs placebo
    - Ages 9-18 months with HbSS/Sbnull
    - Followed for 2 years
  - Primary Outcomes
    - Spleen function (p=0.2), Renal Function (p=0.84)
  - Secondary Outcomes
    - Pain (p=0.002), Dactylitis (p=0.0001), Transfusion (p=0.03), ACS (p=0.02), TCD (p=0.0002)
  - Follow-up Study ongoing

2007 NIH Consensus Findings

Table 2. Summary of Study Outcomes for Pediatric/Children Beyond Infancy Receiving Hydroxyurea for Sickle Cell Disease

<table>
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<tr>
<th>Outcomes</th>
<th>Impact</th>
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<tbody>
<tr>
<td>Spleen function</td>
<td>--- (not significantly different)</td>
</tr>
<tr>
<td>Renal function</td>
<td>--- (not significantly different)</td>
</tr>
<tr>
<td>Lactic acidosis</td>
<td>--- (not significantly different)</td>
</tr>
<tr>
<td>Hematologic toxicity</td>
<td>--- (not significantly different)</td>
</tr>
<tr>
<td>Cytopenias</td>
<td>--- (not significantly different)</td>
</tr>
<tr>
<td>Gastrointestinal symptoms</td>
<td>--- (not significantly different)</td>
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<tr>
<td>Death rates</td>
<td>--- (not significantly different)</td>
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2012 Update

Table 3. Potential Indications and Strength of Recommendation for Hydroxyurea Therapy in Children with HUS

<table>
<thead>
<tr>
<th>Category</th>
<th>Indication</th>
<th>Strength of recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute vaso-occlusive disease</td>
<td>Decrease frequency of vaso-occlusive events</td>
<td>Strong</td>
</tr>
<tr>
<td>Laboratory markers of severity</td>
<td>Decrease HbS concentration</td>
<td>Moderate</td>
</tr>
<tr>
<td>Organ dysfunction</td>
<td>Increase percent normal HbF</td>
<td>Weak</td>
</tr>
<tr>
<td>Leukocyte dysfunction</td>
<td>Increase number of normal neutrophils</td>
<td>Weak</td>
</tr>
<tr>
<td>Renal dysfunction</td>
<td>Decrease creatinine and proteinuria</td>
<td>Weak</td>
</tr>
<tr>
<td>Microcirculation</td>
<td>Decrease microvascular obstruction</td>
<td>Weak</td>
</tr>
</tbody>
</table>

HUS includes transfusion-related acute lung injury (TRALI), transfusion-associated circulatory overload (TACO), transfusion-related acute lung injury (TRALI), organ dysfunction (TRALI), acute vaso-occlusive disease (AHD), and microcirculatory obstruction (TACO).

Transfusion Complications

- Venous Access
- Difficult Transfusion
  - Transfusion reactions
  - Allo-immunization
- Iron Overload
  - Liver, cardiac and endocrine sequelae
  - Challenges of chelation
- Transition to adult care......
Stopping Transfusions
• STOP II Trial
  – Discontinuation of prophylactic transfusion
  • Reappearance of abnormal TCD
  • Increase risk of overt stroke
  • Increase risk of silent stroke
• Recurrent stroke despite transfusion
  – 2.2 per 100 pt/years

Hydroxyurea in Stroke
SWITCH Trial
• Phase III Multi-Center non-inferiority RCT
• Chronic transfusion/chelation versus convert to hydroxyurea/phaebotomy
• Primary endpoint
  Stroke and iron overload
• DSIB
  – Trial halted early
  – 7 strokes in HU/phaebotomy arm/0 in transfusion/chelation

Twitch Trial
• Hydroxyurea versus chronic transfusion for abnormal TCD
• Pts on chronic transfusion randomized to change to hydroxyurea
• Ongoing

Barriers to Hydroxyurea Use
• Adherence to medication
  – Monthly MD visits
  • Cost of weekly to monthly CBC
  – Taking a medication daily
• Delay in onset of effect (3 months)
  – Underdosing contributes
• Patient/Provider fears
• Lack of provider consensus

Pulmonary Hypertension
• 2004, Pulm HTN in 1/3 of adults with SCD
  – Pts with TR jet > 2.5 m/s vs with < 2.5 m/s
  – RR 10.1 of sudden death, 95% CI 2.2-47, p <0.001
•Must confirm with right heart cath
  – 2012, 40% abnormal by echo but only 10% with Pulm HTN on cath

Sickle Cell Pain
• Acute pain
  – Most common manifestation of SCD
  • Adults reported 54% of days in pain
  • 25% parents miss work
  • 54% miss 2 or more days of school
• Chronic pain
  – Increasing recognition

• Symptomatic care
  – Opioids
  – Nsaid
  – Alternative methods
    • Heat
    • Acupuncture
    • PT
    • Biofeedback
• Hydroxyurea
• Transfusions
Transition from Pediatric to Adult Care

- Before 1970, 50% of children with SCD live to adulthood
- Now > 90% survive to adulthood
- 32% unsuccessful in transition
  - Success = establish care with adult provider by attending appointments/not using ED

Barriers
- Financial
- Loss of medicaid
- Lack of adult sickle cell program
- Parental
- Provider
  - Delay in discussion
  - Methods of promoting independence

Take Home Points

- Newborn screen results are highly reliable*.
  - *(Assuming correct patient sample.)
- Carriers of beta and alpha thalassemia are asymptomatic and do not require routine follow-up.
- Preventive care, transfusions and hydroxyurea have resulted in increased survival of patients with SCD (but there is still a lot of work to do).

Questions

Off-Label Use of Medications in Children

- 20% of FDA approved medication have a pediatric label.
  - Pediatric Research Equity Act (PREA) 1998
    - New drugs must have plan to include children or explain why not included.
    - Drug companies get an extra 6 months of exclusive marketing if they also include children in their studies.