Sickle Cell Disease Workshop:
Breaking Down Myths and Barriers

Pediatric Complications and Treatment

Courtney Thornburg, MD MS
November 1, 2012
Outline

Diagnosis of sickle cell disease

Complications of sickle cell disease in children

Treatment of complications

Prevention of complications

The next 100 years….
Physiology

$\beta^6$ glu → val

oxygenated:

de-oxygenated:
Newborn Screening

- Performed at 24 hrs of life via heel stick

- Technique
  - Hemoglobin electrophoresis
  - Isoelectric focusing

- Follow-up
  - Family, local physician, and state counselor are notified of any abnormal hemoglobin
  - Infant is referred to Sickle Cell Center
Newborn Screening for Sickle Cell Disease and Other Hemoglobinopathies

National Institutes of Health
Consensus Development Conference Statement
April 6-8, 1987

“....the panel concludes that every child should be screened for hemoglobinopathies to prevent the potentially fatal complications of sickle cell disease during infancy.”
Newborn screening of all infants in North Carolina since 1994.
Goals of Early Diagnosis

• Diagnose babies before they get sick

• Educate the parents

• Provide genetic counseling

• Prevent complications

• Save lives and improve lives
Improved Survival

Age Distribution of Complications

Clinical Presentation

- 6 month old with persistent crying and decreased feeding; **dactylitis**

- 15 month old with SCD, type SS, with fever, diarrhea and non-productive cough; **pneumococcal sepsis**

- 3 year old with SCD, type SS, presenting with fever; **splenic sequestration**

- 5 year old with SCD, type SS, with left knee pain; **stroke**
Dactylitis

- Peak occurrence at 6-12 mo of age
- Affects ~45% of children by age 2 y
- Rarely seen after age 3 y
- Treat with hydration and pain medication
- May be a predictor of severe disease

Davies, S. C et al. BMJ 1997;315:656-660
Predictors of Disease Severity

- Dactylitis < 12 mo
- Hgb < 7.0 g/dL
- WBC > 13.7 x 10^9/L

An Ounce of Prevention is Worth a Pound of Cure
Hydroxyurea Treatment for Sickle Cell Disease
Hydroxyurea Induces Fetal Hb

Rapid Publication

Hydroxyurea Enhances Fetal Hemoglobin Production in Sickle Cell Anemia

Orah S. Platt, Stuart H. Orkin, George Dover, G. Peter Beardsley, Barbara Miller, and David G. Nathan
Division of Hematology and Oncology, Children's Hospital, Division of Pediatric Oncology, Dana Farber Cancer Institute, Department of Pediatrics of the Harvard Medical School, Boston, Massachusetts 02115, and Department of Pediatrics, Johns Hopkins University and Hospital, Baltimore, Maryland 21205

\[
\begin{align*}
\text{H}_2\text{N} & \quad \text{O} \\
\text{C} & \quad \text{N} \\
\text{N} & \quad \text{OH}
\end{align*}
\]

hydroxyurea

JCI 1984. 74: 652-656.
Pleioptropic effects of Hydroxyurea

1) Fetal hemoglobin induction

2) Lower neutrophil and reticulocyte counts from ribonucleotide reductase inhibition and marrow cytotoxicity

3) Decreased adhesiveness and improved rheology of circulating neutrophils and reticulocytes

4) Reduced hemolysis through improved erythrocyte hydration, macrocytosis, and reduced intracellular sickling

5) Nitric oxide (NO) release with potential local vasodilatation and improved vascular response
Laboratory Effects

<table>
<thead>
<tr>
<th></th>
<th>Adults</th>
<th>Children</th>
</tr>
</thead>
<tbody>
<tr>
<td>MTD (mg/kg/d)</td>
<td>21.3</td>
<td>25.6</td>
</tr>
<tr>
<td>Δ Hb (g/dL)</td>
<td>+1.2</td>
<td>+1.2</td>
</tr>
<tr>
<td>Δ MCV (fL)</td>
<td>+23</td>
<td>+14</td>
</tr>
<tr>
<td>Δ HbF (%)</td>
<td>+11.2</td>
<td>+9.6</td>
</tr>
<tr>
<td>Δ Reticulocytes (10⁹/L)</td>
<td>−158</td>
<td>−146</td>
</tr>
<tr>
<td>Δ WBC (10⁹/L)</td>
<td>−5.0</td>
<td>−4.2</td>
</tr>
<tr>
<td>Δ ANC (10⁹/L)</td>
<td>−2.8</td>
<td>−2.2</td>
</tr>
<tr>
<td>Δ Bilirubin (mg/dL)</td>
<td>−2.0</td>
<td>−1.0</td>
</tr>
</tbody>
</table>

Pre-hydroxyurea
Hb = 7.7 gm/dL
MCV = 84 fL
ANC = 8113
ARC = 247K
HU = 600mg
20 mg/kg/d

8 weeks
Hb = 7.9 gm/dL
MCV = 96 fL
ANC = 3700
ARC = 203K
HU = 780 mg
25 mg/kg/d

20 weeks
Hb = 9.6 gm/dL
MCV = 105 fL
ANC = 3200
ARC = 150K
HU = 950 mg
30 mg/kg/d

22 months
Hb = 10.0 gm/dL
MCV = 113 fL
ANC = 1200
ARC = 124K
HU = 1040 mg
27 mg/kg/d
Hydroxyurea: 30 Years of Research

- Phase III MSH trial
- Phase I/II trial in infants (HUSOFT)
- Long-term effectiveness in children
- Initial HUSTLE trial results
- Prevention of organ damage
- BABY HUG Results
- PK, PD, and PGx results
- SWITCH trial results


- Proof of Principle studies
- Phase I/II trial in children (HUG-KIDS)
- Short-term pediatric efficacy
- MSH follow-up
- Lowering of TCD velocities
- BABY HUG begins enrollment
- HUSOFT extension
- TWHUCH trial begins
- Prevention of secondary CVA
BABY HUG

• BABY HUG (NCT00006400) was a Phase III multicenter, randomized, double-blinded clinical trial of hydroxyurea in infants with sickle cell anemia (SCA).

• Secondary endpoints included subjects’ rates of vaso-occlusive pain (VOC), dactylitis, and acute chest syndrome (ACS).

Dactylitis was also decreased in patients who were asymptomatic at study entry.
Ongoing Assessment in the Real World

• BABY HUG Follow-up Study I
  – Complete
  – Up to 6 years of follow-up

• BABY HUG Follow-up Study II
  – Ongoing
  – Additional 5 years of follow-up
  – Will follow children into adolescence
Hydroxyurea is Underutilized

- The NIH Consensus Conference on Hydroxyurea identified significant challenges to the implementation of hydroxyurea therapy.

- There are barriers at the provider-level, the patient-level including parental acceptance and medication adherence, and systems-level including access to care and insurance.

Provider-Reported Barriers

- patient adherence with taking medication (86%);
- patient adherence with blood tests (85%);
- lack of contraception in females (85%);
- patient’s anticipation of side effects (75%);
- age of patient (68%);
- concern for male infertility (46%);
- lack of formal guidelines in children (30%);
- concern with carcinogenic potential (27%);
- cost (18%);
- lack of time/resources to explain risks/benefits (16%);
- lack of FDA approval in children (12%);
- and doubt of effectiveness of hydroxyurea (11%).
Provider-Reported Barriers

• 26% of providers indicated that the rate of families declining hydroxyurea was greater than 20%.

• Providers reported that families decline hydroxyurea due to the following reasons:
  • fear of cancer (51%);
  • fear of other side effects (62%);
  • do not want to take medication (48%);
  • do not want required laboratory monitoring (28%);
  • and do not think it will work (17%).
Pneumococcal Sepsis

- Functional asplenia
- Increased risk of sepsis, particularly with *Streptococcus pneumoniae*

**Prevention**
- Immunizations
- Penicillin prophylaxis
- Early evaluation for fever
Impact of Penicillin Prophylaxis on Invasive Pneumococcal Disease in Children Less than 3 years Old

Table 1. Characteristics at Entry, According to Treatment Group

<table>
<thead>
<tr>
<th>CHARACTERISTIC</th>
<th>PENICILLIN (n = 105)</th>
<th>PLACEBO (n = 110)</th>
</tr>
</thead>
<tbody>
<tr>
<td>% of patients</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age (mo)*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3–5</td>
<td>15.4</td>
<td>10.8</td>
</tr>
<tr>
<td>6–11</td>
<td>23.1</td>
<td>21.6</td>
</tr>
<tr>
<td>12–17</td>
<td>14.4</td>
<td>20.7</td>
</tr>
<tr>
<td>18–23</td>
<td>22.1</td>
<td>17.1</td>
</tr>
<tr>
<td>≥24†</td>
<td>25.0</td>
<td>28.8</td>
</tr>
<tr>
<td>Boys</td>
<td>48.5</td>
<td>51.4</td>
</tr>
<tr>
<td>Palpable spleen</td>
<td>30.8</td>
<td>30.9</td>
</tr>
<tr>
<td>Pneumococcal vaccine</td>
<td>67.0</td>
<td>71.6</td>
</tr>
<tr>
<td>Previous infection</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pneumonia</td>
<td>19.2</td>
<td>12.6</td>
</tr>
<tr>
<td>Bacteremia</td>
<td>5.8</td>
<td>5.4</td>
</tr>
<tr>
<td>Osteomyelitis</td>
<td>2.9</td>
<td>0</td>
</tr>
<tr>
<td>Meningitis</td>
<td>—</td>
<td>0.9</td>
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</table>

Laboratory findings

<table>
<thead>
<tr>
<th></th>
<th>PENICILLIN</th>
<th>PLACEBO</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hematocrit (%)</td>
<td>26.1</td>
<td>27.3</td>
</tr>
<tr>
<td>Hemoglobin (g/dl)</td>
<td>8.8</td>
<td>9.1</td>
</tr>
<tr>
<td>White-cell count (×10^9/liter)</td>
<td>14.6</td>
<td>14.1</td>
</tr>
<tr>
<td>Granulocytes (%)</td>
<td>31.7</td>
<td>35.0</td>
</tr>
</tbody>
</table>

*The mean value for age in the penicillin group was 17.8 months; that in the placebo group was 18.5.

†One child was older than 36 months.

Changes in Causes of Death

Management of Fever

Prompt evaluation for any fever > 38.5°C (101°F)

- CBC, Blood Culture, ± CXR
- Other clinically indicated evaluations
  - Immediate administration of IV/IM Ceftriaxone or alternative
- Close observation
- Hospitalization of children with high risk feature
Indications for Admission

- Age < 1 year
  - Surgically splenectomized
  - History of pneumococcal sepsis
  - Toxic appearance
  - Acute chest syndrome
  - Other infection requiring parenteral antibiotics
  - Unsure follow-up
Splenic Sequestration

- Most common in young children (< 2 years of age)
- Anemia, thrombocytopenia and splenomegaly
- May cause hypovolemic shock and death if occurs acutely
Management of Splenic Sequestration

• Acute
  – Fluid resuscitation
  – Red cell transfusion

• Long-term
  – Careful observation
  – Splenectomy
Observation

Spleen Stick

- A tongue depressor can be used to measure and track spleen size
- Place the tip on the left nipple and make a mark where the spleen tip is felt
Spleen Stick

- On one side of the stick write the child’s name, sickle cell type, and average hemoglobin level.
- One the back put dates above the line where the spleen tip was.
Splenectomy

• Indications
  – Life-threatening sequestration
  – Recurrent sequestration
  – Hypersplenism

• Timing
  – Age > 18-24 mo
  – After immunizations
Intraoperative photograph of partial splenectomy used with permission of Dr. Henry Rice, Pediatric Surgery, Duke Children’s Hospital.
Splenectomy Registry

• Multi-center registry of children with congenital hemolytic anemia

• Follow post-splenectomy outcomes

• Basis for comparative effectiveness research
Stroke

- Natural history
  - 0.6-0.8 events per 100 patient-years
  - Affected 7.8% by age 14 years in the Jamaican cohort and 11% by age 20 years in the CSSCD

- Types:
  - Large vessel
  - Small vessel (silent)
  - Hemorrhagic
Incidence of 1\textsuperscript{st} Stroke
300x higher than for all children in US

<table>
<thead>
<tr>
<th>Age (yr.)</th>
<th>SS</th>
<th>SC</th>
<th>Sβ\textsuperscript{+}</th>
<th>Sβ\textsuperscript{o}</th>
<th>Totals</th>
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<tr>
<td>&lt; 2</td>
<td>0.13\textsuperscript{*} (1)**</td>
<td>0.00</td>
<td>0.00</td>
<td>0.00</td>
<td>0.08 (1)</td>
</tr>
<tr>
<td>2 - 5</td>
<td>1.02 (20)</td>
<td>0.27 (2)</td>
<td>0.00</td>
<td>0.00</td>
<td>0.75 (22)</td>
</tr>
<tr>
<td>6 - 9</td>
<td>0.79 (15)</td>
<td>0.00</td>
<td>0.00</td>
<td>0.00</td>
<td>0.55 (15)</td>
</tr>
<tr>
<td>10 - 19</td>
<td>0.41 (15)</td>
<td>0.09 (1)</td>
<td>0.00</td>
<td>0.00</td>
<td>0.30 (16)</td>
</tr>
<tr>
<td>20 - 30</td>
<td>0.52 (14)</td>
<td>0.16 (1)</td>
<td>0.46 (1)</td>
<td>0.43 (1)</td>
<td>0.45 (17)</td>
</tr>
<tr>
<td>30 - 39</td>
<td>0.59 (8)</td>
<td>0.00</td>
<td>0.00</td>
<td>0.00</td>
<td>0.39 (8)</td>
</tr>
<tr>
<td>40 - 49</td>
<td>0.74 (3)</td>
<td>1.01 (2)</td>
<td>0.00</td>
<td>0.00</td>
<td>0.76 (5)</td>
</tr>
<tr>
<td>50 -</td>
<td>1.28 (2)</td>
<td>0.76 (1)</td>
<td>0.00</td>
<td>0.00</td>
<td>0.91 (3)</td>
</tr>
<tr>
<td>OVERALL</td>
<td>0.61 (78)</td>
<td>0.17 (7)</td>
<td>0.11 (1)</td>
<td>0.10 (1)</td>
<td>0.46 (87)</td>
</tr>
<tr>
<td>Age-adjusted</td>
<td>0.61</td>
<td>0.15</td>
<td>0.09</td>
<td>0.08</td>
<td></td>
</tr>
</tbody>
</table>

* Number Per 100 Patient-Year followup; **Number of cerebrovascular accidents

Treatment of Stroke

• Critical care management

• Erythrocytapheresis to reduce hemoglobin S <30%
Secondary Stroke Prevention

- Transfusion therapy
Complications

• Iron overload

• Allo/autoantibodies
Predicting and Preventing Stroke

Screen with Transcranial Doppler Ultrasound

Treat high risk children with transfusion

Before transfusion

After transfusion
Impact on Stroke Incidence

![Graph showing the incidence of first stroke per 100 per year from 1991 to 2000. The graph indicates a decrease in incidence post-1997, with a notable peak around 1993. An arrow points to 1997 with the label: STOP trial published.]
Spectrum of CNS Disease

Increasing morbidity / mortality

Increasing neuropsychological deficits

Neuro exam: normal abnormal

- high TCD, nl exam, nl MRI
- high TCD, nl exam, silent infarct
- nl TCD, nl exam, nl MRI
- nl TCD, nl exam, silent infarct
- hemorrhage
- stroke
The Next 100 Years
Stem Cell Transplantation

- Issues
  - Eligibility
  - Type of conditioning
  - Source of cells
  - Long-term follow-up

![Graph showing survival rates and rejection/recurrence over time.]
Targeted Therapies

- Open up the vessels
  - Nitric oxide
  - Anticoagulation
- Prevent damage to the blood vessels
- Decrease inflammation

Clinicaltrials.gov
Dialing down sickle cell disease
Study in mice says dialing up fetal hemoglobin may bring new therapies

Correction of Sickle Cell Disease in Adult Mice by Interference with Fetal Hemoglobin Silencing

Jian Xu, Cong Peng, Vijay G. Senkaran, Zhen Shao, Erica B. Esrick, Bryan G. Chong, Gregory C. Ippolito, Yuko Fujiiwara, Benomini L. Ebert, Philip W. Tucker, Stuart H. Orkin

ABSTRACT
Persistence of human fetal hemoglobin (Hbf, α2γ2) in adults lessens the severity of sickle cell disease (SCD) and the β-thalassemias. Here, we show that the repressor BCL11A is required in vivo for silencing of γ-globin expression in adult animals, yet dispensable for red cell production. BCL11A serves as a barrier to Hbf reactivation by known Hbf-inducing agents. In a proof-of-principle test of BCL11A as a potential therapeutic target, we demonstrate that inactivation of BCL11A in SCD transgenic mice corrects the hematologic and pathologic defects associated with SCD through high-level pancellular Hbf induction. Thus, interference with Hbf silencing by manipulation of a single target protein is sufficient to reverse SCD.
Summary

• Early identification
  – Universal newborn screening
  – Family education

• Focus on prevention and early trt
  – Prophylactic penicillin
  – Immunization
  – Management of fever and pain
  – Transcranial Doppler Ultrasound

• Therapeutic interventions
  – Transfusion
  – Hydroxyurea
  – Stem cell transplantation
  – ????