Sickle Cell Treatment: Pain, Opioids, Hydroxyurea, and More

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41st Annual Eastern Medicaid Pharmacy Administrators Association Conference
Newport, RI
Disclosures

• I receive research funding from the following sources:
  – NHLBI/NIH
  – Pfizer
  – Howard University College of Medicine
Learning Objectives

• Recognize that frequent hospitalizations are a modifiable risk factor for premature death in sickle cell disease.

• Recognize that sickle cell patients are more sensitive to pain than the general medical patients.
Learning Objectives 2

• Recognize the principles of responsible opioid prescribing, and the difficulty of identifying opioid use disorder in the adult sickle cell population.

• Understand the mechanisms of action, clinical use and benefits of FDA approved treatments for sickle cell anemia (hydroxyurea and L-glutamine).
WHAT IS SICKLE CELL DISEASE?
Sickle Hb Polymer Formation

Homogeneous nucleation → Growth → Heterogeneous nucleation → Growth & alignment → Polymerized hemoglobin

↓ O₂ →
## Common HB Variants

<table>
<thead>
<tr>
<th>Hemoglobin Variant</th>
<th>Globin Chain</th>
<th>Amino Acid Substitution</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>S</td>
<td>β</td>
<td>Glu6Val</td>
<td>Polymerizes</td>
</tr>
<tr>
<td>S Antilles</td>
<td>β</td>
<td>Glu6Val AND Val23Ile</td>
<td>SCD variant</td>
</tr>
<tr>
<td>C</td>
<td>β</td>
<td>Glu6Lys</td>
<td>Crystalizes</td>
</tr>
<tr>
<td>E</td>
<td>β</td>
<td>Glu26Lys</td>
<td>Thalassemic variant</td>
</tr>
<tr>
<td>Hb Jamaica Plain</td>
<td>β</td>
<td>Glu6Val AND Leu68Phe</td>
<td>SCD variant, ↓ O₂ affinity</td>
</tr>
<tr>
<td>Hb Korle Bu</td>
<td>β</td>
<td>Asp73Asn</td>
<td>Benign variant</td>
</tr>
<tr>
<td>C Harlem</td>
<td>β</td>
<td>Glu6Val AND Asp73Asn</td>
<td>SCD variant</td>
</tr>
<tr>
<td>D Los Angeles</td>
<td>β</td>
<td>Glu121Gln</td>
<td>SCD variant</td>
</tr>
<tr>
<td>O Arab</td>
<td>β</td>
<td>Glu121Lys</td>
<td>SCD variant</td>
</tr>
<tr>
<td>G Philadelphia</td>
<td>α</td>
<td>Asn68Lys</td>
<td>Benign variant</td>
</tr>
</tbody>
</table>
Sickle Cell Anemia

SCA blood smear:

blood smear: 18 y.o. SCA, CKD and alloimmunization

sickle cell

polychromasia

sickle cell
Pathophysiology of SCD

- **Misshaped cells occlude vessels**
  - $\downarrow$O$_2$ to tissues

- **Short rbc survival**
  - Normal 90-120 days
  - SS=15-30 days
# Sickle Cell Disease

<table>
<thead>
<tr>
<th>Genotype</th>
<th>“Severity”</th>
<th>S (%)</th>
<th>Hgb</th>
<th>MCV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sickle cell anemia</td>
<td>Severe</td>
<td>&gt;90</td>
<td>6-8</td>
<td>&gt;80</td>
</tr>
<tr>
<td>SC</td>
<td>Mild to Mod</td>
<td>50</td>
<td>10-12</td>
<td>75-85</td>
</tr>
<tr>
<td>Sβ⁺ thalassemia</td>
<td>Mild to Mod</td>
<td>&gt;60</td>
<td>(A 10-30)</td>
<td>&lt;75</td>
</tr>
<tr>
<td>Sβ⁰ thalassemia</td>
<td>Mod to Severe</td>
<td>&gt;80</td>
<td>7-9</td>
<td>&lt;70</td>
</tr>
<tr>
<td>SHPFH</td>
<td>Asymptomatic</td>
<td>&lt;70</td>
<td>&gt;12</td>
<td>&lt;80</td>
</tr>
</tbody>
</table>
Complications of Sickle Cell Disease

- Stroke, Meningitis
- Post-Hypneme Glaucoma, Re Infarction
- Sickle Hepatopathy
- Pappilary Necrosis
- Priapism
- Bone Marrow Infarction, Osteomyelitis
- Acute Chest Syndrome
- Splenic Sequestration Splenic Infarction
- Cholelithiasis
- Multi-organ Failure Syndrome
Complications of Sickle Cell Disease

- Anemia, Leukocytosis
- Indirect Hyperbilirubinemia
- Isosthenuria, Chronic Renal Failure
- Functional Asplenia
- Avascular Necrosis
- Delayed Puberty
- Retinopathy

Chronic Complications
SICKLE CELL PAIN
Pain in SCD

• Most common disease manifestation

• 90% of SCD hospitalizations for pain
  – Treatment symptomatic; unchanged for decades!
  – 40% re-hospitalization rate

• Annual Healthcare Cost >$1 Billion
  – DC Medicaid for 600 adults = $71 Million/Year
  – 16% Hydroxyurea
  – 85% Opioids
“Pain Crisis Rate” and Mortality

• CCSCD: Rx + >2 hours
• 39% - no “pain”
• >Pain = >Mortality
• >HbF = ↓Pain + Mortality

Platt et al. NEJM 1991; Platt et al. NEJM 1994

• NIH Cohort (2001-2010)

| Table 3. Cox proportional hazards mortality in adults |
|----------------|----------------|----------------|
| Risk factor    | RR (95% CI)*   | p Value†       |
| ED/Hospitalization, ≥1 in past year | 2.68 (1.1-6.5) | 0.03           |
| TRV‡           | 2.41 (1.5-3.9) | <0.0001        |
| Ferritin       | 4.00 (1.8-9.0) | 0.001          |
| GFR            | 2.73 (1.6-4.6) | <0.0001        |

Acute care encounters highest for 18-30-year-olds

Rate higher for public vs. private payer

30 day rehospitalization rate highest for 18-30-year-olds, with 41.1% (95% CI, 40.5%-41.7%)
Transition to Adult Care

- **SCD complications ↑ after 16**
- **18+ (after transition):**
  - Fewer transfusions and less chelation
  - Less Hydroxyurea
EXPERIMENTAL PAIN = SCD
MORE PAIN SENSITIVE
PATHWAY BASED VIEW: IS SICKLE CELL PAIN PATHOLOGICAL?

1. Peripheral
2. Spine (CNS)
3. Brain (CNS)

Frontal cortex: co-morbidities (sleep, depression, emotional responses, etc.)

1. Pathological Pain in SCD?
2. Peripheral stimuli?
3. Central components?
## Mechanical Temporal Summation

<table>
<thead>
<tr>
<th>Pinprick Probe</th>
<th>SS (n=30) Mean Pain Score$^1$ (SD)</th>
<th>Control (n=30) Mean Pain Score (SD)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>256 mN probe</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 stimulus</td>
<td>1.65 (1.98)</td>
<td>2.06 (2.21)</td>
<td>0.38</td>
</tr>
<tr>
<td>10 stimuli</td>
<td>8.56 (5.40)</td>
<td>5.83 (4.31)</td>
<td>0.05</td>
</tr>
<tr>
<td>15 second aftersensation</td>
<td>4.62 (5.03)</td>
<td>1.20 (2.17)</td>
<td>0.0002</td>
</tr>
<tr>
<td>30 second aftersensation</td>
<td>3.68 (4.50)</td>
<td>0.61 (1.42)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Temporal summation (Δ pain score)</td>
<td>6.91 (5.02)$^2$</td>
<td>3.77 (3.26)$^3$</td>
<td>0.004</td>
</tr>
</tbody>
</table>

Kathleen Vaughan BS
Temporal Summation: Evidence for Central Sensitization

QST:
1) Thermal
2) Mechanical
   1) Pinprick
   2) Pressure
3) Tactile
4) Ischemia

Dynamic QST (central):
1) Conditioned Pain Modulation
2) Temporal Summation

Temporal: repeated stimulation = no recovery of action potential
When threshold reached = PAIN

Kuner 2010 Nat Med 16:1259
Central Sensitization Defined

• SCD patients more sensitive to pain

• Augmented Responses by Central Neurons (larger, longer action potentials) = Pain Hypersensitivity

• Pain Not Coupled to Intensity or Duration of Peripheral Stimuli (Pathological Pain)
Low HbF, Not Pain Crisis Rate or Opioids, Associated with TS

- Only 2 of 6 Variables Associated (46.9 MME)

<table>
<thead>
<tr>
<th>Independent Variables(^1)</th>
<th>(\beta) (Standard Error)</th>
<th>(p) value</th>
</tr>
</thead>
<tbody>
<tr>
<td>256 nM probe TS ((\Delta) pain score)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sickle cell status</td>
<td>6.392 (1.427)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>HbF (%)</td>
<td>-0.300 (0.904)</td>
<td>0.002</td>
</tr>
</tbody>
</table>

\(^1\) Linear regression by stepwise backward elimination in all study subjects (both sickle cell anemia and normal volunteer, \(N=60\)) with variables including SCA status, hemoglobin, HbF, number of hospitalizations for pain treatment during the 12 months prior to enrollment, hydroxyurea dose (mg/kg/day) and opioid dose during the 24 hours prior to QST (morphine equivalents, mg). Regressions were adjusted for age and gender.

\(^2\) Regression limited to SCA (\(N=30\)) also showed \(\beta=-0.338\), \(p=0.006\), adjusted for age and gender.
An Evaluation of Central Sensitization in Patients With Sickle Cell Disease

C. Patrick Carroll, MD,1 Sophie Lanzkron, MD,2 Carlton Haywood Jr., PhD,2 Kasey Kiley, MPH,1 Megan Pejsa, BS,1 Gyasi Moscou-Jackson, PhD, MHS, RN,3 Jennifer A. Haythornthwaite, PhD,1 Claudia M. Campbell, PhD1


Chronic Opioid Therapy and Central Sensitization in Sickle Cell Disease

Sensitization of nociceptive spinal neurons contributes to pain in a transgenic model of sickle cell disease.

Key Points:
1. All human testing in SCD (SS and other SCD)
2. Berk SS mouse = no HbF
Central Sensitization in SCD
Summary = More Sensitive

• Temporal Summation: Evidence of Excitatory Signaling (Central Sensitization)
  – Observed in mice and humans
  – Association with HbF
  – After sensations

• fMRI: ↑CNS Connectivity (Central Sensitization)  
  – HbF association  
  – Central (15/25=60%) + Mixed (32%) Pain in SCD

Central Sensitization: Other Considerations

- **Co-morbidities: Depression and Sleep**
  
  - Depression in SCD (20%; 10% suicidal ideation)
    
    Minitti et al. BMC Psych 2014
  
  - Sleep Disturbance ~70% prevalence (associated with pain)
    
    Minitti et al. BMC Psych 2014
  
  - Co-morbidities and Pain signaling: dorsal columns → lateral thalamus → frontal cortex (emotions)
TREATMENT
Therapy for SCD

• FDA approved:
  – Hydroxyurea
  – L-glutamine

• Opioids

• Transfusion Therapy (q month)
  ↓ % HbS <50%

• Marrow Transplantation
  Still experimental
The New England Journal of Medicine

Volume 332  MAY 18, 1995  Number 20

EFFECT OF HYDROXYUREA ON THE FREQUENCY OF PAINFUL CRISES IN SICKLE CELL ANEMIA

SAMUEL CHARACHE, M.D., MICHAEL L. TERRIN, M.D., RICHARD D. MOORE, M.D., GEORGE J. DOVER, M.D., FRANCA B. BARTON, M.S., SUSAN V. ECKERT, ROBERT P. McMATHON, PH.D., DUANE R. BONDS, M.D., AND THE INVESTIGATORS OF THE MULTICENTER STUDY OF HYDROXYUREA IN SICKLE CELL ANEMIA

1998
Hydroxyurea
FDA Approved
Hydroxyurea Therapy

No Therapy

100% Hb S

Hydroxyurea

75% Hb S and 25% Hb F

Hb S to Hb F hybrid Polymer in cells

Hybrid Formation

+O₂ ← -O₂

Hb S Polymerization

+O₂ ← -O₂

SS Cells

Flow

Flow

No Flow
Hydroxyurea for SCD

- **NHLBI Indications (SS only):**
  - >3 pain events/year
  - Recurrent Acute Chest Syndrome
  - Severe anemia
  - Role in SC and other SCD unclear

- **Dose:** 15 - 35 mg/kg/day
- **↑ HbF (target 20-30%)**

- **Risks**
  - Teratogen (indication for birth control)
  - t-AML (extrapolated from MPDs; ? risk)
Hydroxyurea Benefits: Pain Crisis Rate and Mortality

24 month RCT:
- 50% ↓ in pain crises
- 50% ↓ in ACS
- Decreased transfusions

17 year follow-up:
- Apparent prolonged survival with HU


<table>
<thead>
<tr>
<th>Variable</th>
<th>Hazard Ratio, 95% Confidence Interval</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Enrollment Visit</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alkaline Phosphatase</td>
<td>1.005 (1.003, 1.006)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>White Blood Cell Count</td>
<td>1.08 (1.00, 1.17)</td>
<td>0.048</td>
</tr>
<tr>
<td>Creatinine</td>
<td>1.13 (1.00–1.27)</td>
<td>0.043</td>
</tr>
<tr>
<td>Tricuspid Regurgitant Velocity</td>
<td>2.22 (1.23–4.02)</td>
<td>0.0082</td>
</tr>
<tr>
<td>Hydroxyurea Dose &lt;15 mg/kg/day</td>
<td>0.73 (0.26–2.05)</td>
<td>0.55</td>
</tr>
<tr>
<td>Hydroxyurea Dose 15–35 mg/kg/day</td>
<td>0.36 (0.17–0.73)</td>
<td>0.0050</td>
</tr>
<tr>
<td>Hydroxyurea Dose &gt;35 mg/kg/day</td>
<td>0.72 (0.20–2.55)</td>
<td>0.61</td>
</tr>
<tr>
<td>Hydroxyurea Dose Unknown</td>
<td>2.41 (0.96–6.09)</td>
<td>0.063</td>
</tr>
</tbody>
</table>

*aInput variables: age, hydroxyurea exposure, hydroxyurea dose, dose group, maximum fetal hemoglobin, hemoglobin, white blood cell count, alkaline phosphatase, total bilirubin, albumin, creatinine, ejection fraction, and tricuspid regurgitant velocity. The input variables were selected based on univariate analysis results if they were associated either with mortality or hydroxyurea use. The final model is shown in the table and is obtained through backward stepwise model selection and includes variables associated with hydroxyurea use if they were significant at the 0.10 level. The hazard ratio units represent increase per one unit change of the factor. Hydroxyurea dose groups are compared to no hydroxyurea.

Fitzhugh et al. PLOS One 2015, 10:e0141706.
L-Glutamine FDA Approved

RBC redox potential

NA \rightarrow PRPP \rightarrow PPI \rightarrow GLN \rightarrow GLU \rightarrow NAD

NA: nicotinic acid
PPI: pyrophosphate
PRPP: phosphoribosylpyrophosphate
GLN: glutamine
GLU: glutamate

2017

FDA Approves First Treatment for Sickle Cell Disease in 20 Years

Endari was granted FDA approval to treat sickle cell, a condition that affects about 100,000 Americans.
NAD Metabolism and Glutamine

NAD Metabolism*

- Oxidation plays an important part in pathophysiology of SCD
- NAD is an important physiological antioxidant in RBC
- In sickle RBC NAD, redox potential is significantly compromised
- Glutamine, a precursor for NAD, can improve NAD redox potential

NADH and Redox Potential**

Pilot studies provided compelling clinical proof-of-concept highlighting L-Glut potential benefits


L-Glut Phase 3 RCT Results
Reductions in Frequency and Severity of Crises

<table>
<thead>
<tr>
<th>Primary Endpoint</th>
<th>Secondary Endpoint</th>
<th>Additional Analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Decrease in the frequency of sickle cell crises</td>
<td>Decrease in the frequency of hospitalization</td>
<td>Decrease in the cumulative days in hospital</td>
</tr>
<tr>
<td>Decrease in the severity of painful sickle cell crises and length of stay in hospital</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

- Median reduction in frequency of crises from 4 to 3*
- Median reduction in frequency of hospitalization from 3 to 2**
- Reductions despite 2/3 of patients being on Hydroxyurea
- Decreases in the Severity of Sickle Cell Crises and length of stay in hospital

Strong safety and efficacy results represent a compelling risk/benefit profile

Pharmaceutical Grade L-Glutamine

- FDA approved July, 2017
- Dose 5-15 grams per day
  - Dissolved in liquid for oral consumption
- Available Nov. or Dec., 2017
  - Personal communication
Outpatient Opioid Use SCD

• Opioids High Grade Evidence for Benefit for Acute Sickle Cell Pain
  • Abstracted to outpatient setting for Chronic Pain
  • 21% SCD adults = Chronic Pain

• Snapshot of use – true prevalence in unknown

• Mean = 73.9 mg morphine equivalents (N=29)
  • Median=51.3 mg (range 0.7 – 306.3 mg)
Opioid Guidance from CDC

Dosages at or above 50 MME/day increase risks for overdose by at least 2x the risk at <20 MME/day.

WHY IS IT IMPORTANT TO CALCULATE THE TOTAL DAILY DOSAGE OF OPIOIDS?

Patients prescribed higher opioid dosages are at higher risk of overdose death.

In a national sample of Veterans Health Administration (VHA) patients with chronic pain receiving opioids from 2004–2009, patients who died of opioid overdose were prescribed an average of 98 MME/day, while other patients were prescribed an average of 48 MME/day.

Calculating the total daily dose of opioids helps identify patients who may benefit from closer monitoring, reduction or tapering of opioids, prescribing of naloxone, or other measures to reduce risk of overdose.

98 MME (death) vs. 48 MME (all others); but 74 MME SCD average

Unclear if this is applicable to sickle cell disease
Opioids – Caveats in SCD

• Opioid induced hyperalgesia
  – Personal communication: starts at 100 mg morphine daily
  – Unknown what occurs in SCD

• SCD patients may clear opioids more rapidly than healthy people
  – Genetic variant contributes to variability in hepatic clearance of morphine in SCD.
    Darbari et al. AJH 83: 200-202, 2008
Opioids in SCD

- **Tolerance** = adaptation after exposure induces changes that result in decreased effect over time

- **Physical Dependence** = characterized by a withdrawal syndrome produced by abrupt cessation, rapid dose reduction, decreasing blood level, or an antagonist

- Both present with mean SCD dose of 74 MME
Opioids in SCD

- **Addiction (opioid use disorder)** = a primary neurobiologic disease characterized by pathologic behavior
  - impaired control over use
  - compulsive use
  - continued use despite harm
  - Craving

- **Chronic Disease patient asking for a specific dose is NOT Addiction**
DSM V Criteria

• Two or more of the following within a 12-month period:
  1. Using larger amounts of opioids or over a longer period than was intended
  2. Persistent desire to cut down or unsuccessful efforts to control use
  3. Great deal of time spent obtaining, using, or recovering from use
  4. Craving, or a strong desire or urge to use substance
  5. Failure to fulfill major obligations (work, school, home) due to opioid use
  6. Continued use despite recurrent or persistent social or interpersonal problems
  7. Reducing social, occupational, or recreational activities due to opioid use
  8. Recurrent opioid use in physically hazardous situations
  9. Continued opioid use despite physical or psychological problems
  10. Tolerance (marked increase in amount; marked decrease in effect)
  11. Withdrawal syndrome as manifested by cessation or use to relieve withdrawal

• Tolerance and withdrawal not considered under appropriate medical supervision.
Natural History of Opioid Use Disorder

- Euphoria
- Normal
- Withdrawal

Tolerance & Physical Dependence

Acute use
Chronic use
Best Practices for Opioids

• **Document diagnosis for SCD**
  – Requires an HPLC, blood smear, electrophoresis
  – Trait case

• **Ground Rules**
  – No more than 30 day supply
  – Document # tablets in note
  – Follow-up visit (continuity)

• **Addiction Screening and Pain Management**
TIMELINE SICKLE CELL DISEASE RESEARCH
Peculiar Elongated and Sickle-Shaped Red Blood Corpuscles in a Case of Severe Anemia
James B. Herrick, M.D.

Sickle Cell Anemia, a Molecular Disease

Linus Pauling, Harvey A. Itano, S. J. Singer, and Ibert C. Wells

Gates and Crellin Laboratories of Chemistry,
California Institute of Technology, Pasadena, California
Bill (S. 2676) was signed as Public Law 92-294 (86 Stat. 136) on May 16, 1972.

“This disease is especially pernicious...No cure has yet been found. An estimated 25,000 to 50,000 individuals are currently afflicted with the disease. Many ... are crippled long before death, and some die from it prematurely.”
1972

HU CSCD Established and Newborn Screening Initiated

Roland B. Scott, M.D.
1977

Cooperative Study of SCD Initiated

- 23 centers (incl. Howard CSCD)
- 4085 subjects
- 1981 – adult enrollment ends
- 1988 – infant enrollment ends

Roland B. Scott, M.D.
EFFECT OF HYDROXYUREA ON THE FREQUENCY OF PAINFUL CRIPES IN SICKLE CELL ANEMIA

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L-Glutamine FDA Approved

RBC redox potential

\[
\begin{align*}
\text{NA} & \quad \xrightarrow{\text{PRPP}} \quad \xrightarrow{\text{PPI}} \quad \text{GLN} \\
\text{ATP} & \quad \xrightarrow{\text{AMP} + \text{PPI}} \quad \text{NAD}
\end{align*}
\]

NA: nicotinic acid
PPI: pyrophosphate
PRPP: phosphoribosylpyrophosphate
GLN: glutamine
GLU: glutamate
HIV / AIDS Comparison

1981  *Pneumocystis* Pneumonia --- Los Angeles

1984  HIV discovered

1987  1st drug available (AZT)

1995  Drug cocktail (protease inhib/HAART)

2007  CCR5 drug FDA approved (39 FDA approvals)

2013 NIH Research Budget $2.9 Billion
750,000 affected in USA (2007 est.)
REALITY OF SCD 2017

- National Sickle Cell Act
- Preventive Penicillin
- Transfusion for Stroke Prevention
- Hydroxyurea
REALITY OF SCD 2017

• 100,000 patients in US

• 90% of Hospitalizations are for Pain
  – Treatment symptomatic; unchanged for decades!
  – 40% re-hospitalization rate

• Annual Healthcare Cost >$1 Billion
  – DC Medicaid for 600 adults = $71 Million/Year
  – Only 16% of adults on Hydroxyurea
• 100,000 with SCD in USA (2017)
• Is this enough relative to the disease burden?
Research Output Perspective

- Limited research $ directly correlated with progress and # FDA approved medications
KEY ISSUES FOR SICKLE CELL CARE
Where Do Patients Receive Care?

• Children’s Hospitals!
  – A true success for SCD
  – Newborn screening, Hydroxyurea, stroke treatment

• What Happens When You Turn 18?
  – Adult care
  – No central location
Few Financial Incentives to Provide Sickle Cell Care

• Medicaid/Medicare enriched population
  – Severely affected patients do not work
  – Howard Hospital reimbursement $0.31 collected on each $1.00 billed

• 40% Thirty day Re-admission Rate
  – No reimbursement?

• Consequences: ↑ Acute Care and 16% Hydroxyurea prescription rate
No Adult Care Physicians for SCD?

<table>
<thead>
<tr>
<th>Clinical focus of trainee graduates who pursue private practice or academic careers</th>
<th>Adult training program, %</th>
<th>Pediatric training program, %</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Private</td>
<td>Academic</td>
</tr>
<tr>
<td>Nonmalignant hematology</td>
<td>5.8</td>
<td>4.6</td>
</tr>
<tr>
<td>Malignant hematology</td>
<td>5.1</td>
<td>18.5</td>
</tr>
<tr>
<td>Solid-tumor oncology</td>
<td>20.5</td>
<td>30.0</td>
</tr>
<tr>
<td>Malignant hematology and solid-tumor oncology</td>
<td>73.4</td>
<td>34.0</td>
</tr>
<tr>
<td>Hematopoietic stem cell transplantation</td>
<td>1.6</td>
<td>7.7</td>
</tr>
</tbody>
</table>

Percentages indicate the mean percentage of trainees (as reported by training program directors) who pursued the indicated categories of clinical focus.

Todd RF et al. Blood 2004, 103:4383-4388
This problem is going to become more acute in the future…. Thus, unlike medical oncology, which is currently felt to exist in equilibrium between supply and demand, hematology is facing a dearth of well-trained specialists who care for and study non-malignant hematologic problems, in real time as well as in the future.

Certainly, ASH is attempting to address some of these concerns. For instance, the ASH Alternative Training Pathway Grant seeks to fund innovative training experiences combining hematology with another field; pharmacology and combined pediatric/adult hematology were the two proposals funded last year.
Why Does Care Seem to be Better for Hemophilia?

• Another comparable blood disease

• Late 1990’s: Primary Prophylaxis – Prevents Complications

• Financial Incentive for Hospitals to Sell Factor to Patients
1973: the National Hemophilia Foundation launched a campaign to establish a nationwide network of treatment centers. Goal to provide comprehensive services in 1 facility. There are about 147 federally funded treatment centers across the country authorized under section 501(a)(2) of the Social Security Act.

20,000 affected in USA (2013 est.)
Average 136 patients / center
CONCLUDING REMARKS

Center for Sickle Cell Disease

#CureSickleCellNow
My Advice

• See a Sickle Cell specialist

• Focus on Centers NOT Hem/Onc Divisions or private practices
  – DC area: Johns Hopkins and Howard

• Hydroxyurea (50% fewer pain crises)
  – Need to improve 16% prescription rate

• L-glutamine

• Advocacy for Better Care and a Cure
  – Philanthropy $ More Reliable than Federal?
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