• Access to Care
• Sickle Cell Disease in Central California
• Cayenne Wellness Center and Sickle Cell Disease & Awareness
• May 19th, 2020
<table>
<thead>
<tr>
<th>Disclosures</th>
<th>Agios</th>
<th>Bluebird bio</th>
<th>GBT</th>
<th>Novartis</th>
<th>BSL Bering</th>
<th>Pfizer</th>
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<td>Consulting</td>
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<td>Research Funding</td>
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<td></td>
<td>ApoPharma</td>
<td>Silarus</td>
<td>Sangamo</td>
<td>Forma</td>
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</table>
Thirty minutes to...

• Discuss why guidelines are needed
• Discuss NHLBI guidelines
• Discuss Problems with Guidelines
Why are Guidelines Needed?
Sickle Cell Is a Rare Disease (in the US)

Only about 100,000 persons in a nation of 309,000,000 (0.032%)
Sickle Cell Has Become a Chronic Disease

The care of the adult with sickle cell disease is the care of end organs.

Even without pains, sickle cells are constantly sickling
- Adults with SCD 18 – 30 years had highest inpatient and ED use and 30 day rates of return to hospital post-discharge
- Death and hospitalization rate increased when patients are not transferred to adult providers

![Healthcare Utilization](image)

![Age at Death for People with SCD, 2004-2008](image)

Brousseau et al. *JAMA*. 2010;303:1288-94
Quinn et al. *Blood* 2010;115:3447-52
Centers for Disease Control and Prevention (CDC.gov)
Vasa Recta: Area of hypoxia, acidosis, and hypertonicity

Renal concentrating power limited to 400 to 450 mOsmole (normal is 1200 mOsm)
Unaffected by transfusions after age 10
Loses of the 14% of juxta-medullary nephrons, leaving short cortical nephrons intact so not much effect on glomerular filtration rate
Loss of acidifications if from collecting duct dysfunction
Overt Neurologic Disease

- **HbSS: Cumulative Risk**
  - 20 years: 11%
  - 30 years: 15%
  - 45 years: 24%

- **HbSC: Cumulative Risk**
  - 20 years: 2%
  - 30 years: 4%
  - 45 years: 10%
Overt Stroke Risk increases with Age

Strouse, et al, American Journal of Hematology, 2009
SCI in Normal Adults Vs. SCD

- Dementia rate
- Neuropsychological impairment

Graph showing the prevalence of SCI over age (years) for different conditions and groups.
Pulmonary Hypertension
Conclusions for PiSCES

- Pain is the rule rather than the exception, a chronic condition, under-recognized and undertreated
- Crisis doesn’t mean the same to patients and providers
- Utilization of health facilities is exception rather than a rule
Survival Related to Pain Rates

Platt, NEJM, 1991

Figure 3. Survival of Patients with Sickle Cell Anemia (≥20 Years Old at Entry) Who Had Different Pain Rates. 

r denotes the number of episodes of pain per patient-year.
### QUALITY OF LIFE

<table>
<thead>
<tr>
<th></th>
<th>SCD N = 308</th>
<th>Hemo-Dialysis N = 1000</th>
<th>Cystic Fibrosis N = 223</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bodily Pain</td>
<td>47.4</td>
<td>60.4</td>
<td>82.2</td>
</tr>
<tr>
<td>General Health</td>
<td>39.2</td>
<td>50.0</td>
<td>43.4</td>
</tr>
<tr>
<td>Vitality</td>
<td>42.7</td>
<td>46.5</td>
<td>58.4</td>
</tr>
<tr>
<td>Social Function</td>
<td>63.5</td>
<td>66.0</td>
<td>80.4</td>
</tr>
<tr>
<td>Role-emotional</td>
<td>57.8</td>
<td>58.2</td>
<td>77.0</td>
</tr>
</tbody>
</table>
US Mortality Rates for Adults and Children 1979-2005

Lanzkrom, Public Health Reports, 2013
Survival Disparity in Adult Sickle Cell Disease: Sickle Cell Centers vs. Regional Surveillance

- Nationally, survival data has not improved in last 25 years.
- Survival patients in sickle cell centers markedly improved.
- Disparity in survival based on prevention/treatment of complications in adults.

<table>
<thead>
<tr>
<th>Years</th>
<th>Median Survival (years)</th>
<th>Dx</th>
<th>Location</th>
<th>N Pts</th>
<th>Author</th>
</tr>
</thead>
<tbody>
<tr>
<td>1978-1988</td>
<td>45</td>
<td>SS only</td>
<td>United States</td>
<td>2,920</td>
<td>Platt/CSSCD study 1994</td>
</tr>
<tr>
<td>2004-2008</td>
<td>43</td>
<td>all SCD</td>
<td>California, Georgia</td>
<td>12,143</td>
<td>Paulukonis 2016</td>
</tr>
</tbody>
</table>

**Regional Surveillance:**

- Kings (67)
- Duke (58)
- CA/GA (42)
- U.S. (45)

**Comprehensive Sickle Cell Centers:**

What are Guidelines?

• The IOM (2011) defined clinical practice guidelines as "statements that include recommendations intended to optimize patient care that are informed by a systematic review of evidence and an assessment of the benefits and harms of alternative care options."

• Provides framework for standards of care

• Helps the doctor know what to do
National Heart Lung and Blood Institute of the National Institutes of Health

- 2009 – 2014
- 161 pages
- Dozens of co-chairs, members, reviewers, methodologists, and subject matter experts
- Extensive reviews of what is published
- Expert working groups
- Preliminary drafts, editing, and revisions

Reviewed by the major organizations:

- Academy of Emergency Medicine (AAEM)
- American Academy of Pediatrics (AAP)
- American Academy of Physician Assistants (AAPA)
- American Osteopathic Association (AOA)
- American Society of Hematology (ASH)
- American Society of Pediatric Hematology/Oncology (ASPHO)
- International Association of Sickle Cell Nurses and Physician Assistants (IASCNAPA)
- National Black Nurses Association (NBNA)
- National Initiative for Children’s Health Quality (NICHQ)
- National Medical Association (NMA)
- Sickle Cell Disease Association of America (SCDAA)
Framework of Guidelines

Ask Key Question

- KQ2. In asymptomatic individuals with SCD, what is the effect of screening for renal disease, by measuring serum creatinine and urine albumin and protein, on mortality and the development of end-stage renal disease (ESRD)?
- Made recommendation
- Listed strength of recommendation
  - Research quality of data, how definite, when and who it applies to.
Review what was known

Five Topic Areas → Subtopics and Key Questions*

Literature Search for Studies in Persons With SCD†

No Evidence or Evidence Review Not Feasible†

Evidence Reports†

Existing Systematic Reviews and Guidelines or Panel Expertise*

Evidence-Based Recommendations*

Consensus Statements*: • Adapted From Other Sources • Panel Expertise
Make recommendations

• Screen all individuals with SCD, beginning by age 10, for proteinuria. If the result is negative, repeat screening annually. If the result is positive, perform a first morning void urine albumin-creatinine ratio and if abnormal, consult with or refer to a renal specialist.

List strength of recommendation
(Consensus–Panel Expertise)
What’s Covered

Chapter 2: Health Maintenance for People With Sickle Cell Disease

- Prevention of Invasive Pneumococcal Infection
- Screening for Renal Disease
- Screening for Pulmonary Hypertension
- Electrocardiogram Screening
- Screening for Hypertension
- Screening for Retinopathy
- Screening for Risk of Stroke Using Neuroimaging
- Screening for Pulmonary Disease
- Reproductive Counseling
- Contraception
- Clinical Preventive Services
- Immunization

Chapter 4: Managing Chronic Complications of Sickle Cell Disease

- Chronic Pain
- Avascular Necrosis
- Leg Ulcers
- Pulmonary Hypertension
- Renal Complications
- Stuttering/Recurrent Priapism
- Ophthalmologic Complication
What’s Not Covered

- Voxelotor (Oxbryta) – Approved 11/2019
  - Affects Oxygen Affinity
  - 274 patients studied

- Crizanlizumab (Adakveo) – Approved 11/2019
  - Affects cells sticking to blood vessels
  - 198 patients studied

- L-glutamine (Endari) – Approved 7/2017
  - ? Likely increases nitric oxide
  - 230 patients studied

Bone Marrow Transplants
Genetic Therapies
Any study since 2014
ASH Guidelines 2019-2020
Example of Change: Renal Screening after 2014

Quarterly UA (albuminuria, albuminuria/creatinine ratio)

Serum creatinine (Serum creatinine does not ↑ abn GFR
> .7 mg/dL in children > 1 mg/dL in adults ∆ 0.3 mg/dL

Cystatin-C better than creatinine
A Phase 3 Trial of L-Glutamine in SCD

Glutamine is a Precursor of NADH and Decreases Oxidative Stress in sRBC

- 25% reduction in number of pain crises (3.0 vs 4.0; P 0.005)
- 30% lower hospitalization rates (2.0 vs 3.0; P 0.005)
- Reduced number of episodes of acute chest syndrome (ACS; ~8% vs 23% P 0.003)

Y. Niihara et al, 2018. NEJM
Primary End Point - Annual Rate of SCPC  
SUSTAIN Study Monthly Infusions in 3 Arms, One Year

<table>
<thead>
<tr>
<th>Primary End Point</th>
<th>High-Dose SelG1 (N=67)</th>
<th>Low-Dose SelG1 (N=66)</th>
<th>Placebo (N=65)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median rate of SCPC per year</td>
<td>1.63</td>
<td>2.01</td>
<td>2.98</td>
</tr>
<tr>
<td>Reduction vs. placebo</td>
<td>45.3%</td>
<td>32.6%</td>
<td></td>
</tr>
<tr>
<td>P value</td>
<td>0.010</td>
<td>0.180</td>
<td></td>
</tr>
<tr>
<td>Interquartile Range</td>
<td>(0.00 - 3.97)</td>
<td>(1.00 – 3.98)</td>
<td>(1.25 – 5.87)</td>
</tr>
<tr>
<td>Number of patients with SCPC rate of zero at end of study</td>
<td>24</td>
<td>12</td>
<td>11</td>
</tr>
</tbody>
</table>
## Annual Rate of Days Hospitalized

<table>
<thead>
<tr>
<th></th>
<th>High-Dose SelG1 (N=67)</th>
<th>Low-Dose SelG1 (N=66)</th>
<th>Placebo (N=65)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median rate per year</td>
<td>4.00</td>
<td>6.87</td>
<td>6.87</td>
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<tr>
<td>Reduction vs. placebo</td>
<td>41.8%</td>
<td>0.0%</td>
<td></td>
</tr>
<tr>
<td>P value</td>
<td>0.450</td>
<td>0.837</td>
<td></td>
</tr>
<tr>
<td>Interquartile Range</td>
<td>(0.00 – 25.72)</td>
<td>(0.00 – 18.00)</td>
<td>(0.00 – 28.30)</td>
</tr>
</tbody>
</table>
Voxelotor Demonstrates a Rapid, Robust and Sustained Improvement in Anemia at Target Hemoglobin Occupancy

**Graph:**
- **Voxelotor 1500 mg**
- **Voxelotor 900 mg**
- **Placebo**

**Table:**

<table>
<thead>
<tr>
<th>Value</th>
<th>Voxelotor 900 mg</th>
<th>Voxelotor 1500 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>% Hb occupancy(^a)</td>
<td>13.8% (46.5)</td>
<td>25.3% (32.8)</td>
</tr>
</tbody>
</table>

\(^a\)Hb occupancy geometric mean (%CV) = calculated % of RBC Hb bound by voxelotor
What’s known about new Sickle Cell medications

<table>
<thead>
<tr>
<th>Medication</th>
<th>VOC</th>
<th>Hospital</th>
<th>Hemoglobin</th>
<th>Hemolysis</th>
<th>Transfusions</th>
<th>Acute Chest</th>
<th>Organ</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hydroxyurea</td>
<td>↓(44%)</td>
<td>↓(58%)</td>
<td>↑</td>
<td>↓</td>
<td>↓(36%)</td>
<td>↓(54%)</td>
<td>↑</td>
</tr>
<tr>
<td>L-glutamine</td>
<td>↓(25%)</td>
<td>↓(33%)</td>
<td>→</td>
<td>?</td>
<td>?</td>
<td>?</td>
<td>?</td>
</tr>
<tr>
<td>Crizanlizumab</td>
<td>↓(33%)</td>
<td>?</td>
<td>→</td>
<td>?</td>
<td>?</td>
<td>? (↑?)</td>
<td>?</td>
</tr>
<tr>
<td>Voxelotor</td>
<td>→</td>
<td>?</td>
<td>↑(51% &gt; 1)</td>
<td>↓</td>
<td>?</td>
<td>?</td>
<td>?</td>
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**Approved Medications for Sickle Cell Disease**

- **Hydroxyurea** — all patients with SS hemoglobin and no contraindication beginning at age 9 months
- **L-glutamine** — any patient with recurrent VOCs and admissions after hydroxyurea
- **Crizanlizumab** — patients with ongoing pains despite hydroxyurea or transfusions
- **Voxelotor** — patients on transfusions who are accumulating iron despite chelation; patients with chronic symptomatic anemia despite hydroxyurea; patients with markers of ongoing hemolysis
Checklist:

**Good Health Care**
1. Work closely with your doctors – primary care and sickle cell specialist -- to develop your own unique care plan.
2. Build relationships with a hematologist and a team of **other specialists** so they are available for you when needed.

**Healthy Lifestyle**
1. Stay active.
2. Drink 8–10 glasses of water daily.
3. Follow a heart-healthy eating plan that includes limiting alcohol.
4. Aim for 7–8 hours of sleep a night.

**Prevent Infections**
- Children under 5 years old should take penicillin regularly.
- Adults and children should get scheduled vaccines, including flu shots.
- Wash hands often.

**Topics to Discuss with Your Doctor**
**Pain Control**
1. How has your pain been since your last visit?
2. What do you do to control pain?
3. Have you been screened for any organ changes from sickle cell that are recommended in the guidelines?
Thank You
Covid-19 Update
Cases as of May 8, 2020

Count of Cases Reported: 146

Age Summary:
- Average Age: 30.50
- Standard Deviation: 13.45

Age Distribution

Sex Distribution:
- Female: 38.62%
- Male: 60.69%
- Other: 0.69%

Race & Ethnicity Distribution:
- Black/African American
- Other
- White
- Asian
- Hispanic/Latino
- Not Hispanic/Latino
- Not Reported
- Unknown/Chose not to Answer

Source: https://covidssicklecell.org/updates-data/
Case Locations in the World as of May 8, 2020

Source: https://covidsicklecell.org/updates-data/
Case Locations in US as of May 8, 2020

Source: https://covidtitrex.org/updates-data/
Outcome of Known Cases as of May 8, 2020

**Disease Severity**
- 55.48% Mild
- 17.81% Moderate
- 17.81% Severe
- 3.42% Critical
- 5.48% Asymptomatic

**Symptom Resolution**
- 73.29% Yes
- 11.64% No
- 14.38% Asymptomatic

**Patient Death**
- 89.73% No
- 9.59% Yes
- 0.68% Unknown

**Number of Patient Deaths**
- 14

**Patients with Renal Failure**
- 6

**Required Dialysis**
- Yes: 44.17%
- No: 33.33%
- Unknown: 22.49%

**Recovered Renal Function**
- Yes: 16.67%
- No: 50%
- Unknown: 33.33%

Source: https://covidsicklecell.org/updates-data/
Covid Precautions

• Sickle Cell is a Potentially High Risk Condition
  • Concerns about lungs
  • Concerns about clotting
• Fewer Cases in our area
• Follow current social distancing
• Still go to ED if:
  • Breathing issues
  • Possible brain issues
  • Severe pain that can’t be home managed
• If you are admitted with Covid, call your sickle cell provider