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Disclosures

- No financial disclosures
- No conflict of interest
Objectives of this talk

- Understand the genetics and prevalence of Sickle Cell Disease
- Pathophysiology of Sickle Cell Disease
- Clinical manifestations of Sickle Cell Disease
- Management of Sickle cell Disease complications
- Disease modifying agents in Sickle Cell disease
- Newer therapeutics in Sickle cell disease
Sickle Cell Disease

- Sickle Cell disease (SCD) is the commonest inherited hematological disorder
- Approximately 100,000 individuals affected by SCD in USA
- SCD gene prevalence is seen in African, Asian, South American, Indian and Mediterranean ethnicities
- In USA, African American and Latino American shown to have the gene prevalence
- SCD occurs among about 1 out of every 365 Black or African-American births.
- 1 in 385 births in AA has SCD (HbSS, HbS/Beta thal or HbSC)
- 1 in 13 has AA has Sickle cell trait*
- 1 in 6173 births has HbSC

*Resource: CDC
Distribution of Sickle Gene - World wide
There were approximately 5,100 people with SCD living in California in 2004-2008:

- 14% younger than 6 years
- 25% 6-17 years
- 22% 18-29 years
- 28% 30-50 years
- 11% 51 years and older

There were 486 babies born with SCD in California in 2004-2008:

- 89% were Black, African-American
- 8% were Hispanic, Hispanic-American
- 5% were Other

Resource: CDC
Total number of patients with SCD in FY2019 = 87

**Patient by Gender**

- Male: 46%
- Female: 54%

**Race/Ethnicity**

- Black/Not Hispanic: 5%
- Black/Hispanic: 5%
- White/Not Hispanic: 3%
- White/Hispanic: 3%
- Asian/Not Hispanic: 2%
- Other/Not Hispanic: 1%
- Other/Hispanic: 7%

- Total Black: 80%

SCD in Valley Children’s Hospital - 2019
## Sickle Cell Disease spectrum at Valley Children’s Hospital over the past 5 years

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>NUMBER (n)</th>
<th>% Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hb SS Disease</td>
<td>71</td>
<td>52.59%</td>
</tr>
<tr>
<td>Hb SC Disease</td>
<td>44</td>
<td>32.59%</td>
</tr>
<tr>
<td>HbS/B+ (Sickle Beta+ Thalassemia)</td>
<td>6</td>
<td>4.44%</td>
</tr>
<tr>
<td>HbS/B0 (Sickle Beta 0 Thalassemia)</td>
<td>3</td>
<td>2.22%</td>
</tr>
<tr>
<td>HbS/Hb E Disease</td>
<td>6</td>
<td>4.44%</td>
</tr>
<tr>
<td>HbS/Hb D Los Angeles</td>
<td>2</td>
<td>1.48%</td>
</tr>
<tr>
<td>HbS/Hb D Disease</td>
<td>1</td>
<td>0.74%</td>
</tr>
<tr>
<td>HbS/Hb Riyadh Disease</td>
<td>1</td>
<td>0.74%</td>
</tr>
<tr>
<td>HbS/Hb N Baltimore</td>
<td>1</td>
<td>0.74%</td>
</tr>
</tbody>
</table>
HbS is produced by a point mutation in \textit{HBB} in which the codon \textit{GAG} is replaced by \textit{GTG}.

This results in the replacement of hydrophilic amino acid \texttt{glutamic acid} with the hydrophobic amino acid \texttt{valine} at the sixth position (\(\beta 6\text{Glu} \rightarrow \text{Val}\)).

HbC is produced by a point mutation in HBB (\(\beta 6\text{Glu} \rightarrow \text{Lys}\))
Haplotypes of Sickle Cell Disease

Malarial resistance in Sickle cell disease

Sickle cell trait, HbSS and HbSC individuals have shown resistance to Malaria

This reduction is hypothesized to be due to the interference in the red cell membrane breakdown in the late schizont phase and release of merozoites into the peripheral circulation.

Sickle Cell Disease Spectrum

- Homozygous Sickle Cell Disease (HbSS)
- Sickle – Hemoglobin C disease (HbSC)
- Sickle- Beta Thalassemia (HbS/ Beta Thal)
- Sickle Cell Trait (HbSA)- Not considered disease (but recent data shows some evidence of mild disease pathology)
- Severity (HbSS >/= HbS/Beta Thal> HbSC> HbSA)
Sickle Cell Disease genetics

- **If both parents have Sickle cell trait (SCT):**
  - 50% chance (or 1 in 2) that any of their children will have SCT
  - 25% chance (or 1 in 4) that any of their children will have SCD
  - 25% chance (or 1 in 4) that any of their children will not have SCD or SCT
Sickle Hemoglobin (HbS)
Pathophysiology of Sickle Cell disease

- HbS polymerizes makes the red cells become stiff, sticky and sickle shaped
- The deformed cells block blood flow, causes pain, organ damage and stroke
- It also causes hemolysis of abnormal red cells leading to loss of NO and complications like Pulmonary HTN, priapism and cutaneous ulcers
Modifiers of severity of Sickle Cell disease

- Depends on Haplotype (Bantu/ CAR more severe)
- Haplotype Arab- Indian less severe
- Presence of Hemoglobin F
- Co-existent α- thalassemia mutation
- Geographical factors
- Patient related factors
- Socio-economic factors
Pathophysiology of Sickle Cell Disease

- Oxygenated erythrocyte containing HbS
- Deoxygenated erythrocyte with polymerisation of HbS
- Dehydrated, sickled erythrocyte
- Occlusion of postcapillary venules (vaso-occlusion)
- Repolarisation
- Free radicals, causing tissue damage
- Vascularopathy and endothelial dysfunction
- Acute pain
  - Acute chest syndrome
  - Hyposplenism
  - Osteonecrosis
  - Nephropathy
- Infarction
- Haemolysis
- Free plasma haemoglobin, inactivating NO and generating reactive oxygen species
- Pulmonary hypertension
- Priapism
- Leg ulcers
- Cerebrovascular disease
- Increased expression of VCAM-1 and other adhesion molecules
- Hypercoagulability

Rees et al, Lancet, 2010
Pathophysiology of Sickle Cell disease

**Vaso-occlusive symptoms**
- pain
- avascular necrosis
- organ damage
- stroke

**Hemolytic symptoms**
- Pulmonary HTN
- priapism
- and cutaneous ulcers
Sickle cell disease symptoms

- Typically start around 4-5 months of age
  - When fetal hemoglobin switches to adult hemoglobin
  - Many complications are acute or chronic
  - Consists of pain crisis, acute chest syndrome, overt or silent stroke, priapism, deep vein thrombosis, cutaneous ulcerations, pulmonary HTN, osteonecrosis
## Symptoms of SCD

<table>
<thead>
<tr>
<th>Cardiothoracic System</th>
<th>Nervous System</th>
<th>Reticuloendothelial System</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chronic restrictive lung disease</td>
<td>Hemorrhagic stroke (brain)</td>
<td>Splenic sequestration</td>
</tr>
<tr>
<td>Left ventricular diastolic disease</td>
<td>Venous sinus thrombosis</td>
<td>Functional hypersplenism</td>
</tr>
<tr>
<td>Pulmonary hypertension</td>
<td>Silent cerebral infarction (brain)</td>
<td>Avascular necrosis</td>
</tr>
<tr>
<td>Acute chest syndrome</td>
<td>Chronic pain</td>
<td>Anemia</td>
</tr>
<tr>
<td>Dysrhythmias</td>
<td>Cognitive impairment</td>
<td>Hemolysis</td>
</tr>
<tr>
<td>Sudden death</td>
<td>Orbital infarction (eye)</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Musculoskeletal System</th>
<th>Urogenital System</th>
<th>Gastrointestinal System</th>
</tr>
</thead>
<tbody>
<tr>
<td>Avascular necrosis</td>
<td>Papillary necrosis</td>
<td>Cholelithiasis</td>
</tr>
<tr>
<td></td>
<td>Proteinuria</td>
<td>Cholangiopathy</td>
</tr>
<tr>
<td></td>
<td>Renal failure</td>
<td>Hepatopathy</td>
</tr>
<tr>
<td></td>
<td>Hematuria</td>
<td>Mesenteric vaso-occlusion</td>
</tr>
<tr>
<td></td>
<td>Nocturnal enuresis</td>
<td></td>
</tr>
<tr>
<td>Leg ulceration (skin)</td>
<td>Priapism</td>
<td></td>
</tr>
</tbody>
</table>

Rees et al, Lancet, 2010
Clinical symptoms in infants
Vaso-occlusive complications

- **Pain crisis** - the commonest symptoms, more pain episodes, associated with severe disease
- **Acute chest syndrome** - Fever, infiltrate in CXR and hypoxemia
- **Stroke** - Overt and Silent Stroke
CHANGES DURING THE PROGRESSION OF THE PAINFUL CRISIS

<table>
<thead>
<tr>
<th>PRODROMAL PHASE</th>
<th>INITIAL PHASE</th>
<th>ESTABLISHED PHASE</th>
<th>RESOLVING PHASE</th>
</tr>
</thead>
<tbody>
<tr>
<td>NUMBNESS</td>
<td>PROBLEMS WITH PERSONNEL</td>
<td>JOINT EFFUSION</td>
<td>PROBLEMS WITH HOSPITAL PERSONNEL</td>
</tr>
<tr>
<td>PARAESTHESIA</td>
<td>ANXIETY, FEAR</td>
<td>SIGNS OF INFLAMMATION</td>
<td>DEPRESSION</td>
</tr>
<tr>
<td>ACHES</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

CATEGORICAL PAIN SCALE

(STEADY STATE VALUES)

CRISIS DAY

ARBITRARY VALUES RELATIVE TO STEADY STATE

Ballas et al, Hemoglobin, 1995
Pain crisis of SCD

- Acute pain associated with occlusion of blood vessels to the bones
- Associated with low Hemoglobin F
- Triggered by hypoxia, temperature changes, high altitude
- Oral NSAIDs (Tylenol, Ibuprofen)
- Oral Opiods, followed by IV Opiodes
- Oral Hydration
- If admitted IV hydration
- Hydroxyurea reduces the pain episodes
Splenic sequestration in SCD

- Sequestration of red cells in the spleen
- Vaso-occlusion of the venules of spleen with red cells
- Rapid enlargement of the spleen
- Fall in hemoglobin and anemia
- Circulatory shock
  - Treatment includes PRBC transfusion
  - Slow transfusion is preferred
Hemolytic complications of SCD

- Pulmonary Hypertension- Manifests as hypoxia, right to left shunt and increased TR Jet velocity on Echocardiography
- Cutaneous leg ulceration- In older age group
- Priapism- In Teenagers
Hemolytic crisis in sickle cell disease

- Anemia
- Hyperbilirubinemia
- Reticulocytosis
- Increased LDH
Aplastic crisis in Sickle Cell disease

- Anemia
- Reticulocytopenia
- No splenomegaly
- Maybe triggered by viral infection
Fever in SCD

- Infections are more common in SCD children
- Reduced splenic function, defects in complement pathway, micronutrient deficiency, tissue ischemia
- S Pneumoniae, H influenza, and non-Typhi Salmonella species in developed countries
- Substantial improvements in prognosis have followed the introduction of penicillin prophylaxis
- Immunization with conjugate vaccines directed against S pneumoniae and H influenzae type b and Meningococcal required
Acute chest syndrome in SCD

- Fever
- Respiratory symptoms- Cough, chest pain breathing difficulty, dyspnea or hypoxia
- New infiltrate on Chest X Ray
- Etiology include: Pulmonary infarction, fat embolism, hypoventilation, pulmonary edema, infection
- Treatment: Blood cultures, CXR
- IVF (restricted), Antibiotics,
- Incentive spirometry
- Co-existent asthma worsens ACS
Stroke in SCD

- SCD one of the commonest cause of stroke in children
- The vasculopathy seems to start in infancy, with a first-stroke incidence of 1·02 per 100 patient-years between the ages of 2 years and 5 years
- 11% of patients with sickle-cell disease have had a stroke by the age of 20 years
- Treated by blood transfusion: Simple or exchange transfusion, Goal HbS <30%
- Trials have looked into Hydroxyurea in SCD patients with stroke
- HU is found to be non-inferior to transfusion in a subset of patients with increased TCD velocities (Twitch trial)

TCD With Transfusions Changing to Hydroxyurea (TWiTCH): a multicentre, randomised controlled trial

Ware et al, Lancet: 2016
Kidney in Sickle cell disease

- Renal damage inevitable in Sickle cell disease
- Glomerular hyperfiltration
- Papillary necrosis- Hematuria
- Microalbuminuria > Macroalbuminuria
- Nephrotic syndrome
- End- Stage renal disease
- Role of Hydroxyurea and ACE inhibitors
Priapism in SCD

- Painful prolonged erection in teenagers
- Upto 35% of the patients with SCD gets affected
- May result in penile fibrosis and permanent damage
- IVF, transfusion useful in reducing or preventing episodes
- Alpha adrenergic agonist like pseudoephedrine and phenylephrine is useful
- Shunt surgery in severe cases
- Role of P-Selectin Inhibitor in trials
Hemolysis in Sickle Cell Disease

- Anemia
- Jaundice
- Gall bladder stones

- Hemoglobin in urine
- Urobilinogen in urine
- Increased bilirubin (Indirect)
- Increased LDH
- Increase Reticulocyte
Liver complication in Sickle cell disease

- **Acute sickle cell hepatic crisis**: Fever, pain, jaundice and enlarged liver
  - Rx: Supportive care

- **Acute hepatic sequestration**: Acute pain, enlarged liver and anemia
  - Rx: Supportive care and exchange transfusion

- **Acute intrahepatic cholestasis**: Fever, Right upper quadrant pain, progression to liver failure
  - Rx: Supportive care, exchange transfusion and correction of clotting problems (severe progressive condition)
Osteonecrosis in SCD
Annual screening Program in SCD

- Transcranial Doppler US
- CXR and PFTs
- Echo and EKG
- Vision Screen to r/o proliferative retinopathy and other ocular complications
- Urine analysis
- Renal and Liver function
- Bone health, r/o avascular complications
- Pregnancy screen on HU
- Vit D status
- Neurocognitive testing
New born screening for Sickle Cell Disease

- 47 states, the District of Columbia, Puerto Rico, and the Virgin Islands currently provide universal neonatal screening for SCD

<table>
<thead>
<tr>
<th>Disorder Percentage of</th>
<th>Approximate Screening US Patients With SCD</th>
<th>Neonatal Separation by Results</th>
<th>Hemoglobin Age 6 Weeks</th>
<th>Serial CBC and Reticulocyte Counts</th>
<th>Hematologic Studies by Age 2 Years</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>MCV+ (percent) HbA₂ (percent) HbF (percent)</td>
</tr>
<tr>
<td>HbSS</td>
<td>65</td>
<td>FS</td>
<td>FS</td>
<td>Hemolysis and anemia By age 6-12 mo</td>
<td>Normal or increased § &lt;3.6§ &lt;25</td>
</tr>
<tr>
<td>HbsC</td>
<td>25</td>
<td>FSC</td>
<td>FSC</td>
<td>Mild or no anemia by age 2 y</td>
<td>Normal or decreased NA § &lt;5&lt;15</td>
</tr>
<tr>
<td>Sβ+-thalassemia</td>
<td>8</td>
<td>FSA or FS</td>
<td>FSA</td>
<td>Mild or no anemia by age 2 y</td>
<td>Normal or decreased &gt;3.6 &lt;25</td>
</tr>
<tr>
<td>Sβ-+-thalassemia</td>
<td>2</td>
<td>FS</td>
<td>FS</td>
<td>Hemolysis and anemia</td>
<td>Decreased &gt;3.6 &lt;25</td>
</tr>
</tbody>
</table>
Treatment and Curative therapies in Sickle cell Disease

- Bindu K Sathi, MD
Time line of advances made in Sickle Cell Disease

1910: First Description of SCA by James Herrick

1924: Deoxygenated oxygen found to be the cause of vasooclusion and hemolysis

1949: Linus Pauling et al. discovered that HbS differs in structure from HbA

1956: Discovered that single amino acid change is the cause of SCD.

1980s: Use of Penicillin in young children led to increased survival.

1995: Approval of Hydroxyurea / hydroxycarbamide (disease modifying therapy)

1997: Blood transfusion shown to decrease stroke incidence in children.

Year 2000

Twenty-first Century
Stem Cell Transplant
Gene Therapy
Targeted Therapies?

Thein et al, Pathology, 2017
Improvement in life expectancy in SCD

Thein et al, Pathology, 2017
Treatment of SCD

- Transfusion therapy
- Hydroxyurea
- Immunization
- Nutrition assessment
- Target organ assessment
  - Cognition assessment
  - Bone assessment
  - Kidney, Lung, Heart assessment
- Cognition assessment

Standard of care
Treatment team for SCD

- Trained Hematologist
- RN, trained in SCD
- Psychologist
- Social Worker
- Comprehensive Health care coordinators
- School nurses
- Community Physicians
# Indications for transfusion in SCD

<table>
<thead>
<tr>
<th>Indications where primary goal of transfusion is to correct acute anaemia</th>
<th>GRADE evaluation</th>
<th>Type of transfusion*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aplastic crisis</td>
<td>1B</td>
<td>Simple (top up)</td>
</tr>
<tr>
<td>Acute splenic sequestration</td>
<td>1B</td>
<td>Simple</td>
</tr>
<tr>
<td>Acute hepatic sequestration</td>
<td>1B</td>
<td>Simple</td>
</tr>
<tr>
<td>Delayed haemolytic transfusion reaction (transfusion should be avoided unless the anaemia is severe or life-threatening)</td>
<td>1C</td>
<td>Simple</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Indications where primary goal of transfusion is to reduce HbS concentration in relation to HbA</th>
<th>GRADE evaluation</th>
<th>Type of transfusion*</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACS</td>
<td>1B</td>
<td>Simple or exchange</td>
</tr>
<tr>
<td>Acute stroke or other neurological deficit (e.g. TIA)</td>
<td>1B</td>
<td>Exchange</td>
</tr>
<tr>
<td>Acute multi-organ failure</td>
<td>1C</td>
<td>Exchange</td>
</tr>
<tr>
<td>Mesenteric/girdle syndrome</td>
<td>1C</td>
<td>Exchange</td>
</tr>
<tr>
<td>Severe sepsis</td>
<td>2C</td>
<td>Exchange</td>
</tr>
<tr>
<td>Acute intrahepatic cholestasis</td>
<td>1C</td>
<td>Exchange</td>
</tr>
<tr>
<td>Primary stroke prevention</td>
<td>1A</td>
<td>Simple or exchange</td>
</tr>
<tr>
<td>Prevention of silent cerebral infarct recurrence</td>
<td>1A</td>
<td>Simple or exchange</td>
</tr>
<tr>
<td>Secondary stroke prevention</td>
<td>1B</td>
<td>Simple</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Surgery</th>
</tr>
</thead>
<tbody>
<tr>
<td>• SS patients – elective low or medium risk surgery</td>
</tr>
<tr>
<td>• SC patients – elective low or medium risk surgery</td>
</tr>
<tr>
<td>• All sickle genotypes – elective high risk surgery</td>
</tr>
<tr>
<td>• Emergency surgery</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Pregnancy</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Sickle complications (e.g. painful crises, ACS, stroke)</td>
</tr>
<tr>
<td>• Severe anaemia</td>
</tr>
<tr>
<td>• High obstetric, medical or fetal risk</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Recurrent ACS*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Recurrent painful crises*</td>
</tr>
<tr>
<td>2C</td>
</tr>
<tr>
<td>2C</td>
</tr>
</tbody>
</table>
Transfusion therapy in Sickle Cell disease

The ASH guideline panel recommends prophylactic **red cell antigen matching for Rh (C, E or C/c, E/e) and K antigens** over only ABO/RhD matching for patients with SCD (all genotypes) receiving transfusions.

**Extended red cell antigen matching (Jka /Jkb , Fya /Fyb , S/s)** may provide further protection from alloimmunization.
Hydroxycarbamide (hydroxyurea) in Sickle cell disease
Recommendations for the start of HU

• In adults and children with HbSS/Sb0 who have 3 or more sickle cell-associated moderate to severe pain crisis in a 12-month period, treat with hydroxycarbamide (1A)

• In infants with SS/Sb0 aged 9–42 months, offer hydroxycarbamide regardless of clinical severity to reduce sickle cell complications (pain, dactylitis, acute chest syndrome (ACS), anaemia (1A)

• In children aged >42 months, adolescents and adults with SS/Sb0, offer treatment with hydroxycarbamide in view of the impact on reduction of mortality (1B)

• In adults and children with SS/Sb0 who have sickle cell pain that interferes with daily activities and quality of life, treat with hydroxycarbamide (1C)

• In adults and children with SS/Sb0 and a history of severe and/or recurrent ACS treat with hydroxycarbamide (1A)

• The benefits of hydroxycarbamide should be discussed with all parents of children, adolescents and adults with SS/Sb0 to enable informed joint decision-making. There should be on-going discussion between provider and patient (1B)

Modifications for HU therapy

Guideline

**Perform baseline renal function and do pregnancy test in post-pubertal females.**

- Start Hydroxycarbamide
- Adults 15 mg/kg/day
- Children 20 mg/kg/day
- Monitor FBC after 2 weeks

**If after 8-12 weeks**

- Neutrophils > 2 x 10^9/l
- and platelets > 150 x 10^9/l
- and Hb > 60 g/l
- and retics > 80 x 10^9/l (unless Hb > 90 g/l)
- Increase Hydroxycarbamide by 5mg/kg/day until maximum dose of 35 mg/kg/day
- Monitor FBC at 2 weeks after dose increase
- Follow above for dose modifications

**Neutrophils < 1 x 10^9/l**

- or platelets < 80 x 10^9/l
- or Hb < 45 g/l
- or retics < 80 x 10^9/l (unless Hb > 90 g/l)

Stop Hydroxycarbamide and repeat FBC weekly until

- Neutrophils > 1 x 10^9/l
- and platelets > 80 x 10^9/l
- and Hb > 45 g/l
- and retics > 80 x 10^9/l (unless Hb > 90 g/l)
- Start same dose if transient drop or reduce by 5 mg/kg/day

Monitor FBC after 2 weeks and follow above for dose modifications
Concerns with HU therapy

- Leukemiogenesis (Not proven--- 25 years worth of data!)
- Normal growth and development
- Fertility
  - Female fertility is preserved
  - Spermatogenesis affected (affects on sperm count, motility and morphology
- Concern for teratogenicity (Need to stop HU prior to pregnancy)
Penicillin Treatment in SCD

1. Administer oral penicillin prophylaxis (125 mg for age <3 years and 250 mg for age ≥3 years) twice daily until age 5 in all children with HbSS.
   (Strong Recommendation, Moderate-Quality Evidence)

2. Discontinue prophylactic penicillin in children with HbSS at age 5 unless they have had a splenectomy or invasive pneumococcal infection. When discontinuing penicillin prophylaxis at age 5, it is important to assure that the child has completed the recommended pneumococcal vaccination series, and if not, complete the series immediately.
   (Weak Recommendation, Moderate-Quality Evidence)

3. Consider withholding penicillin prophylaxis from children with HbSC disease and HbSβ+-thalassemia unless they have had a splenectomy
   (Weak Recommendation, Low-Quality Evidence)

All individuals should be immunized as recommended by the ACIP. The most up-to-date schedule should be followed, as changes can be made up to four times per year. Consult the immunization schedule at: http://www.cdc.gov/vaccines/schedules. The following immunizations are of special importance or unique to people with SCD as recommended by the ACIP. These recommendations may also change periodically, and the above ACIP recommendations should be consulted for confirmation.

- **Pneumococcal (PCV13) vaccine—Children**
  - Children aged 6 to 18 years with functional or anatomic asplenia should receive one dose of PCV13.

- **Pneumococcal vaccine-naive Adults**
  - Adults aged ≥19 years with functional or anatomic asplenia who have not previously received PCV13 or PPSV23 should receive
    - One dose of PCV13 first, followed by a dose of PPSV23 at least 8 weeks later.
    - Subsequent doses of PPSV23 should follow current PPSV23 recommendations for adults at high risk.
  - A second PPSV23 dose is recommended 5 years after the first PPSV23 dose for persons aged 19–64 years with functional or anatomic asplenia.
  - Additionally, those who received PPSV23 before age 65 years for any indication should receive another dose of the vaccine at age 65 years, or later if at least 5 years have elapsed since their previous PPSV23 dose.

- **Previous vaccination with PPSV23—Adults**
  - Adults aged ≥19 years with functional or anatomic asplenia who previously have received ≥1 dose of PPSV23 should
    - Be given a PCV13 dose ≥1 year after the last PPSV23 dose was received.
  - For those who require additional doses of PPSV23, the first such dose should be given no sooner than 8 weeks after PCV13 and at least 5 years after the most recent dose of PPSV23.

- **Hib**
  - One dose of Hib vaccine for people aged >5 years who have SCD if they have not previously received Hib vaccine

- **Meningococcal vaccine**
  - Vaccinate infants at high risk (including those with SCD) at 2, 4, and 6 months of age, and again at 12 through 15 months with this vaccine, which is generically known as HibMenCY.
  - Persons aged 9 months through 55 years at increased risk for meningococcal disease (e.g., adults with anatomic or functional asplenia or persistent complement component deficiencies) should receive MenACWY.
  - Children aged 2 months to 6 years should receive an additional dose of MenACWY 3 years after primary immunization; boosters should be repeated every 5 years thereafter.
  - Children ≥7 years of age should receive an additional dose of MenACWY 5 years after primary immunization; boosters should be repeated every 5 years thereafter.
CDC recommendation in SCD

- Hand washing
- Food safety
- Do not eat raw or undercooked meat; use pasteurized products
- Bacteria – Salmonella is especially dangerous in SCD. Do not pet snake, lizards or turtle
Newer therapeutics in Sickle cell disease
Definitive and symptomatic treatment in sickle cell disease

Primary treatments
- HSCT gene therapy
- HbF inducers
- Antisickling agents

Secondary treatments
- Adhesion
  - IVIG
  - Propranolol
  - Rivipansel
  - Crizanlizumab
- Inflammation
  - Simvastatin
  - Zileuton
  - Regadenoson
- Thrombophilia
  - Antiplatelet agents
  - Rivaroxaban
  - Apixaban
- Oxidant stress
  - Glutamine
  - N-acetylcysteine
  - Omega-3 FA

Root cause:
- HbS mutation
- HbS polymerization

Downstream sequelae
<table>
<thead>
<tr>
<th>Target</th>
<th>Study drug</th>
<th>Mechanism of action</th>
<th>ClinicalTrials.gov Identifier</th>
<th>Status (phase)</th>
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<tbody>
<tr>
<td>Oxidative injury</td>
<td>Glutamine</td>
<td>Increases NADPH</td>
<td>NCT01179217</td>
<td>Completed (3)</td>
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<tr>
<td></td>
<td>NAC</td>
<td>Increases glutathione</td>
<td>NCT01849016</td>
<td>Completed (3)</td>
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<td></td>
<td>Omega-3 FA</td>
<td>Antioxidant</td>
<td>NCT02947100</td>
<td>Ongoing (1, 2)</td>
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<td>α-Lipoic acid</td>
<td>Increases glutathione</td>
<td>NCT02604368</td>
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<td>Acetyl-L-carnitine</td>
<td>Decreases lipid peroxidation</td>
<td>NCT01054768</td>
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<tr>
<td>Adhesion</td>
<td>Crizanlizumab</td>
<td>Monoclonal antibody against P-selectin</td>
<td>NCT01895361</td>
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<td>Rivarense</td>
<td>Pan-selectin inhibition</td>
<td>NCT02187003</td>
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<td></td>
<td>IVIG</td>
<td>Inhibits leukocyte activation/adhesion</td>
<td>NCT01757418</td>
<td>Ongoing (1, 2)</td>
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<td>Heparin</td>
<td>Inhibitor of P-selectin</td>
<td>NCT02096993</td>
<td>Ongoing (2)</td>
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<td></td>
<td>Propranolol</td>
<td>Inhibits RBC adhesion to endothelium</td>
<td>NCT02012777</td>
<td>Terminated (1)</td>
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<tr>
<td>Hemoglobin F induction</td>
<td>Decitabine</td>
<td>Demethylation/activation of γ-globin gene</td>
<td>NCT01685515</td>
<td>Ongoing (1)</td>
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<td>Pormalidomide</td>
<td>Histone deacetylase inhibition</td>
<td>NCT01522547</td>
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<td>Dimethylbutyrate</td>
<td>Histone deacetylase inhibition</td>
<td>NCT01322269</td>
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<tr>
<td>Other antisickling agents</td>
<td>Aes-103</td>
<td>Shifts Oxy-Hb</td>
<td>NCT01597401</td>
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<td>GBT440</td>
<td>Dissociation curve to left</td>
<td>NCT03036813</td>
<td>Ongoing (3)</td>
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<td>INC8059872</td>
<td>Hypomethylating agent, increases HbF</td>
<td>NCT03132324</td>
<td>Ongoing (1)</td>
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<td>Panobinostat</td>
<td>Histone deacetylase inhibitor, increases HbF</td>
<td>NCT01245179</td>
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<td>Senicapoc</td>
<td>Inhibits cell dehydration</td>
<td>NCT00040677</td>
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<td>Sanguinolite</td>
<td>Carbon monoxide releasing/oxygen transfer agent</td>
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<td>Ongoing (2)</td>
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<td>SCD-101</td>
<td>Antisickling agent, unknown mechanism</td>
<td>NCT02380079</td>
<td>Ongoing (1b)</td>
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<td>Antiplatelet therapy</td>
<td>Prasugrel</td>
<td>Inhibition of platelet activation (ADP receptor blockade)</td>
<td>NCT01794000</td>
<td>Terminated (3)</td>
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<td>Ticagrelor</td>
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<td>NCT02482298</td>
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<td>Eptifibatide</td>
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<td>NCT00834899</td>
<td>Terminated (1, 2)</td>
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<td>Anti-inflammatory agents</td>
<td>Simvastatin</td>
<td>Activates endothelial NO synthase</td>
<td>NCT01702246</td>
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<td>Zileuton</td>
<td>Inhibition of leukotrienes</td>
<td>NCT01136941</td>
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<td>Regadenoson</td>
<td>Agonist of adenosine receptor</td>
<td>NCT01788631</td>
<td>Ongoing (2)</td>
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<tr>
<td>Vascular tone</td>
<td>Magnesium</td>
<td>Improves vascular tone</td>
<td>NCT01197417</td>
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<td>L-arginine</td>
<td>Substrate for NO</td>
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<td>Ongoing (1, 2)</td>
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<td>Anticoagulant mechanism</td>
<td>Rivaroxaban</td>
<td>Inhibition of coagulation cascade (exact mechanism being studied)</td>
<td>NCT02072668</td>
<td>Ongoing (2)</td>
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<tr>
<td></td>
<td>Apixaban</td>
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<td>NCT02179177</td>
<td>Ongoing (2)</td>
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</table>
Crizanlizumab for the Prevention of Pain Crises in Sickle Cell Disease

A Phase 3 Trial of L-Glutamine in Sickle Cell Disease

A Phase 3 Randomized Trial of Voxelotor in Sickle Cell Disease
Stem cell transplantation for Sickle cell disease

- Matched sibling HSCT
- Matched cord blood transplantation (good cell doses)
- Matched unrelated 8/8 transplantation

- Phase 1 clinical trial
  - Haploidentical transplantation
  - Mismatched unrelated
Transplantation algorithm for Sickle cell disease

Patients with SCD or thalassemia eligible for allogeneic stem cell transplant

Matched related donor? 

No  

Alternative donor search

Yes  

Matched related sibling or cord transplant

Suggested priority based on currently available data:
1. 8/8 HLA-A, B, C, DRB1 matched unrelated marrow or PBSC
   - Difficult to find in patients with SCD
2. Unrelated cord blood OR haploidentical/mismatched related
   - Institutional expertise may prefer one over the other
   - Appropriate cord blood units may be more applicable in children but more difficult to find in patients with SCD

7/8 or less HLA-A, B, C, DRB1 matched unrelated marrow are not recommended at this time. More optimization and enrollment in clinical trials are needed.
Gene therapy in Sickle cell disease

Complete correction of Mutated gene sequence

Induction of HbF

Source: American Society of Hematology
Gene therapy for sickle cell disease

Collection of blood-forming stem cells

Stem cells corrected by beta-globin gene transfer from viral vectors

Transplantation of corrected stem cells back to patient

Source: NIH.gov
Gene therapy in SCD

Gene Therapy in a Patient with Sickle Cell Disease.

- **Inclusion criteria for transplantation**
  - Clinically-significant neurologic event: stroke or any central nervous system deficit lasting >24 hours.
  - Abnormal head CT or brain MRI demonstrating previous stroke.
  - Administration of regular RBC transfusions for equal or longer than 1 year to prevent vaso-occlusive crises or other sickle cell disease complications or to maintain Hb >6.
  - Pulmonary arterial hypertension with tricuspid regurgitant jet velocity > 2.5 m/sec within 1 year prior to enrollment.
  - At least one episode of acute chest syndrome that required hospitalization, within the 2 years prior to enrollment.
  - At least 2 acute sickle pain crises requiring hospitalization within the 2 years prior to enrollment.
  - Severe osteonecrosis.
  - History of acute dactylitis during childhood.
  - Recurrent priapism (2 or more episodes).
THE FIRST PATIENT TO BE TREATED WITH CRISPR

This year, CRISPR-Cas9 treatments for sickle cell disease were taken from the lab to clinical trials. In January 2019, CRISPR Therapeutics and Vertex Pharmaceuticals Incorporated reported that the US Food and Drug Administration (FDA) had fast tracked CTX001, an investigational, gene-edited stem cell therapy to treat patients with severe hemoglobinopathies such as sickle cell disease.
Acknowledgements

- Pacific Sickle Cell research collaborative
- Heartland Sickle Cell Research Group
- Funding for State Department of Health and Senior Services
Questions??