Subspecialty Needs of Patients with Sickle Cell Disease

Lauren Beck, APRN-CNP

Akron Children's Hospital

Disclosures

- I have no relevant financial relationships to disclose.

Objectives

- Identify common cytopenias
- Define appropriate criteria for referral for bleeds and clots
- **Recognize subspecialty needs of patients with sickle cell disease**
- Appraise alternative consultation process to improve patient outcomes
- Implement pathways to allow for successful transition

Review of Sickle Cell Disease

- Point mutation in HBB gene substitutes glutamic acid for valine → creates Hemoglobin S
- **Most common inherited blood disorder**
- Deoxygenated HgbS molecules polymerize and change the shape of the red blood cell
- Altered RBC shape impairs blood flow

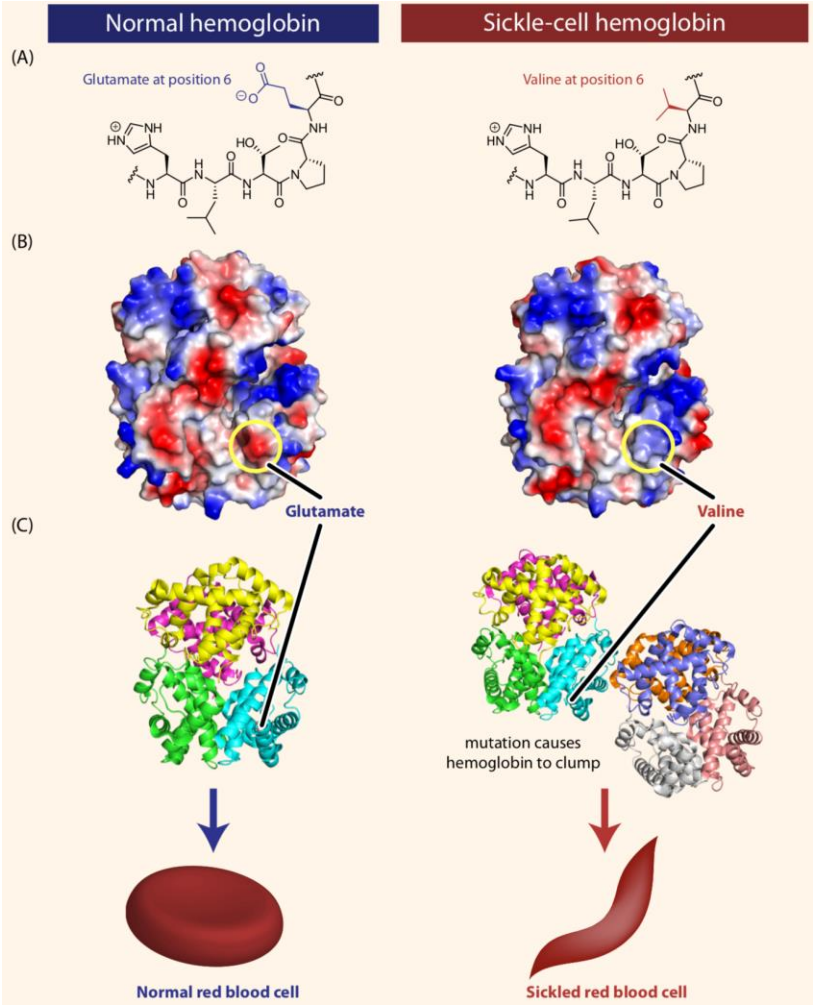
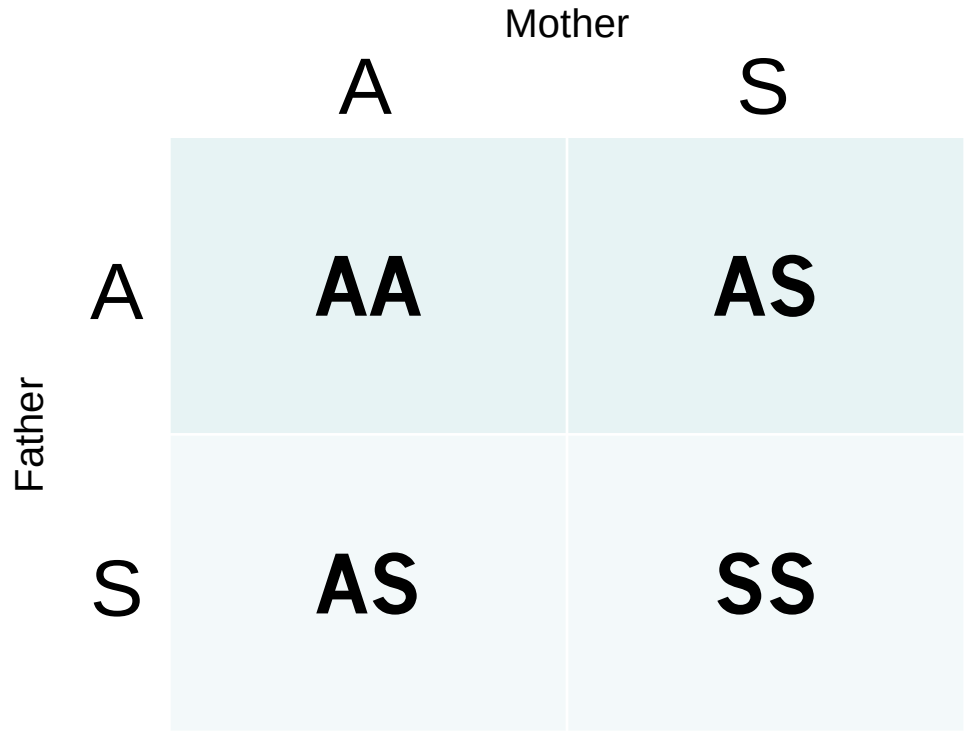


Image: LabXchange

Akron Children's Hospital

Inheritance Pattern for HgbSS



AA = Normal adult hemoglobin

AS = Sickle cell trait

SS = Hemoglobin SS disease

Different Types of Sickle Cell Disease

- Hemoglobin SS — Sickle cell anemia
- Hemoglobin SC
- Hemoglobin S/beta-0 thalassemia — Sickle cell anemia
- Hemoglobin S/beta+ thalassemia
- Hemoglobin SD
- Hemoglobin SE
- Hemoglobin S/Variant

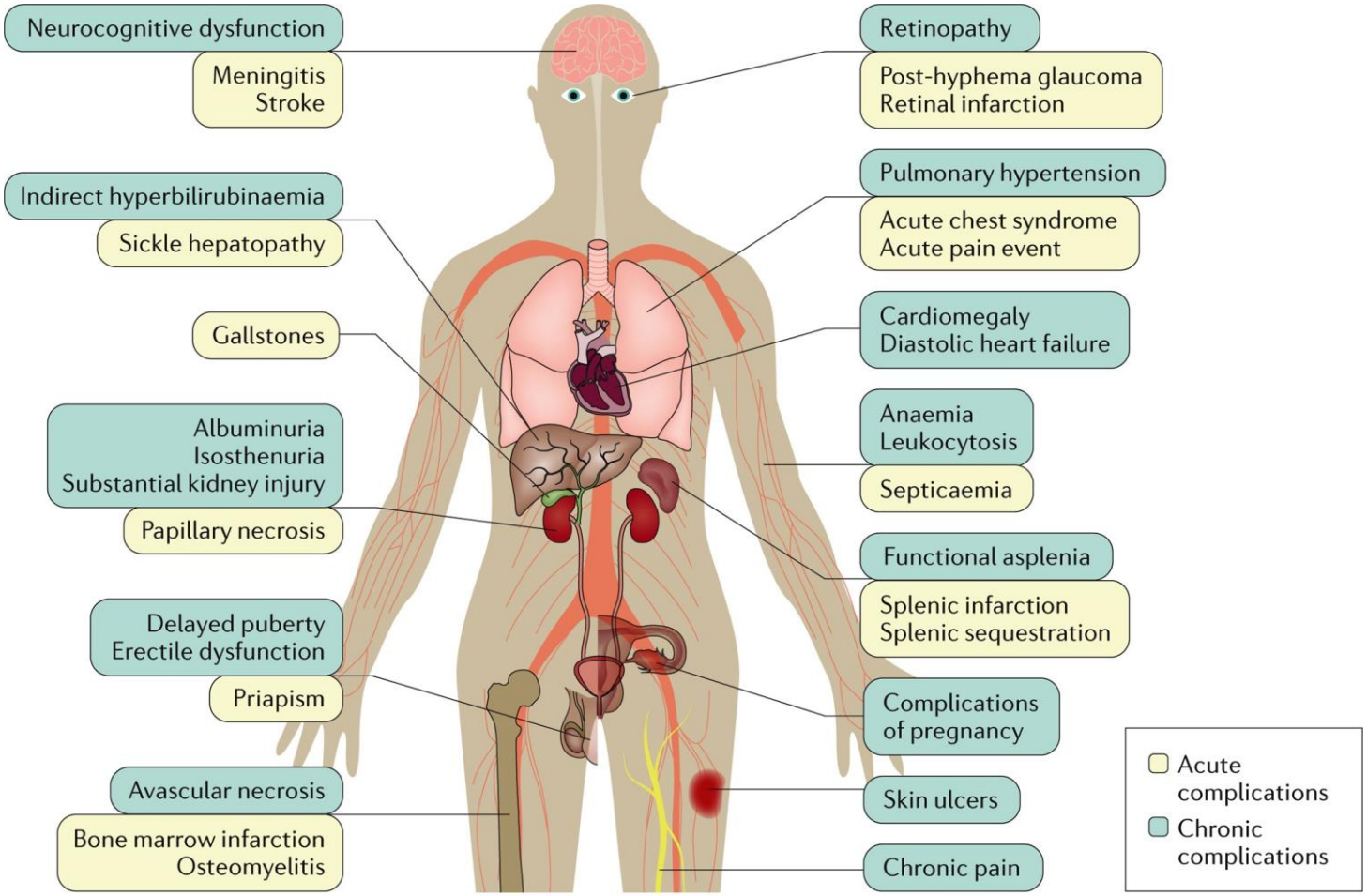
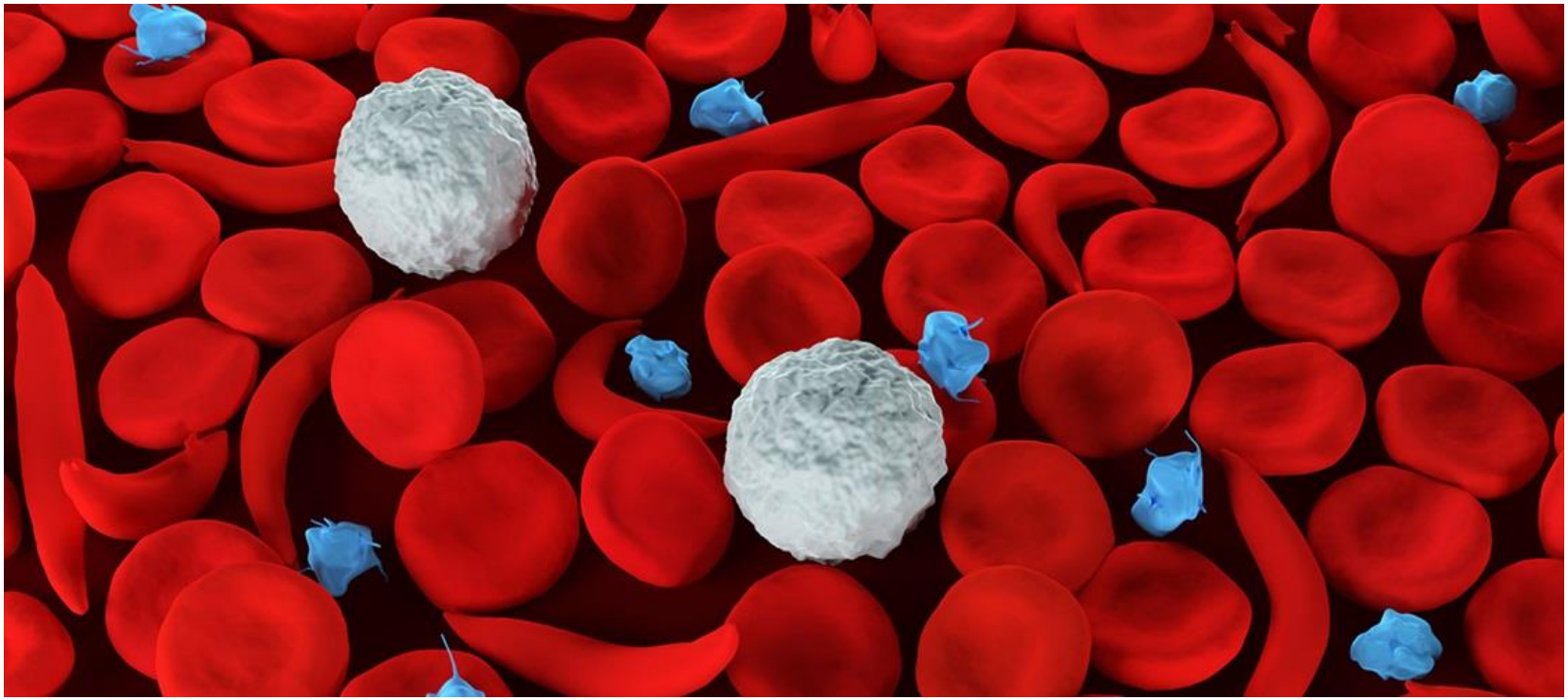


Image: Nature Reviews

Akron Children's Hospital

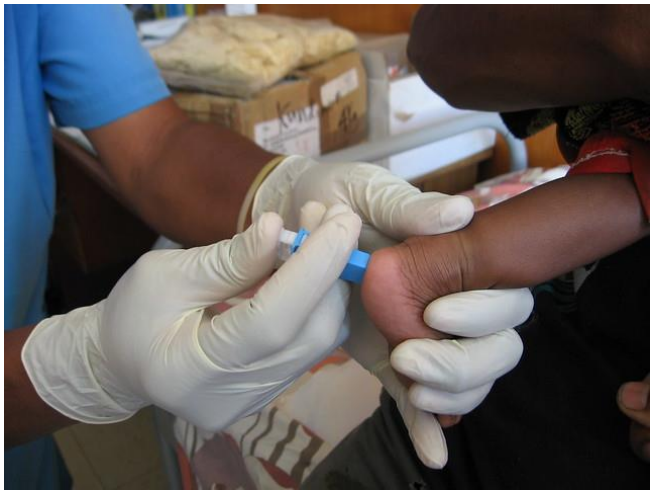


Why might you be seeing a patient with sickle cell disease?

Image: Johns Hopkins Medicine

Primary Care

- Newborn screen results indicating sickle cell disease
  - **FS** → Hgb SS vs. S/beta-0 thalassemia disease
  - **FSA** → Hgb S/beta+ thalassemia disease
  - **FSC** → Hgb SC disease
  - **FSV** → Hgb SD, SE, S/Lepore, etc.
- Prescribe prophylactic penicillin 125mg PO BID
- Sick visits WITHOUT fever or sickle cell pain



Emergency Department

(and potentially ICU)

- **Fever/sepsis**
  - Functional asplenia + complement deficiency = increased risk for invasive bacterial infection
  - Blood culture & cefepime for fever ≥101°F
- **Acute chest syndrome**
  - Leading cause of death (~25%)
  - Diagnostic criteria:
    - At least 1 of the following: fever, chest pain, hypoxia, respiratory distress (e.g., tachypnea, cough, wheezing, rales, retractions)
    - AND a new infiltrate on CXR
- **Splenic sequestration**
  - Impaired splenic function by 1 year old
  - Reduction in hgb by ≥2g/dl
  - Transfuse blood SLOWLY
  - 67% recurrence rate
- **Stroke**
  - Ischemic strokes more common in children with SCD
  - Children with Hgb SS have a 4% risk of stroke
- **Priapism**
  - ≥4 hours is a medical emergency
  - May result in impotence

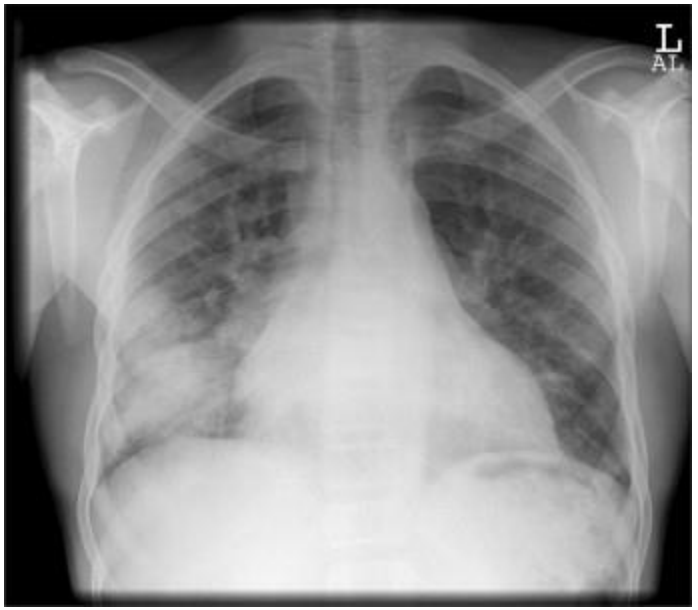


Image: ScienceDirect

Emergency Department cont.

- **PAIN CRISIS** (acute vaso-occlusive crisis)
  - Diagnosis of exclusion
  - Requires rapid assessment & administration of analgesia, *ideally within 1 hour*
  - Treatment is multimodal: opioids, NSAIDs, acetaminophen, heat (NO ICE), hydration, massage, physical therapy, incentive spirometry, expressive therapy, alternative therapies
  - More frequent VOCs associated with higher morbidity & mortality

Image: Rethink Sickle Cell Disease

Table 1 Comparing number of deaths due to opioid pain relievers of non–sickle cell disease patients with the number of deaths due to opioid pain relievers of sickle cell disease patients from 1999 to 2013 in the United States

Year	Non-SCD Patients Who Died Due to OPR	SCD Patients Who Died Due to OPR
1999	4,022	8
2000	4,393	7
2001	5,521	7
2002	7,450	6
2003	8,513	4
2004	9,856	1
2005	10,922	6
2006	13,717	6
2007	14,401	7
2008	14,795	5
2009	15,594	3
2010	16,641	10
2011	16,907	10
2012	16,002	5
2013	16,225	10
Totals	**174,959**	**95**

OPR = Opioid Pain Reliever; SCD = Sickle Cell Disease.

Reference: Multiple Cause of Death Data, 1999-2013. CDC WONDER Online Database. 2015. Available at http://wonder.cdc.gov/mcd.html .

Adolescent Medicine

- Hormonal contraceptives may decrease menstrual blood flow, leading to higher hemoglobin levels
- Regular use of contraception can decrease the health risks associated with an unintended pregnancy in women with SCD

- *No restrictions or concerns for use in women with SCD*: Progestin-only contraceptives (pills, injections, and implants), levonorgestrel IUDs, and barrier methods
- *May be used in women with SCD if the benefits outweigh the risks*: combined hormonal contraceptives (pills, patches, rings)

Audiology

- **Sensorineural hearing loss**
  - More common in patients with Hgb SS disease
  - Affects children & adults
- Hearing loss is also an adverse effect of chelation therapy
  - Dose-limiting

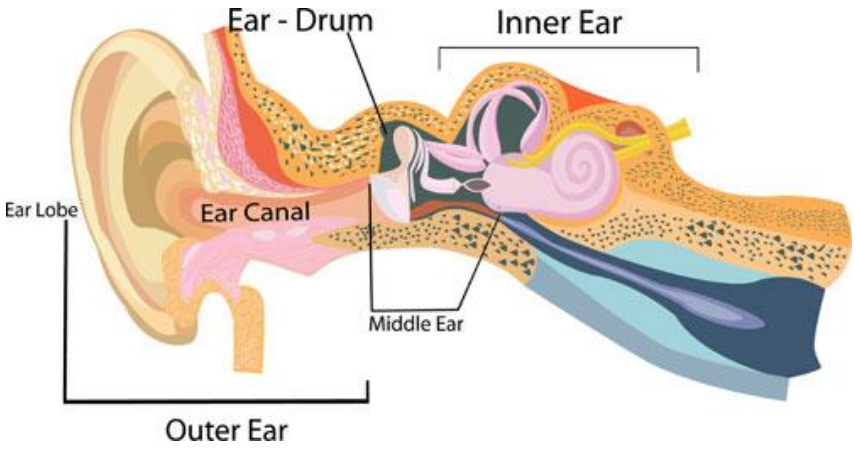


Image: Centers for Disease Control

Cardiology

- Top 2 Cardiac Complications: (1) Pulmonary Hypertension, (2) LV Hypertrophy & Diastolic Dysfunction
  - Due to chronic hemolytic anemia with high cardiac output and high pulmonary blood flow
  - Obtain annual echocardiogram to quantify TRV (tricuspid regurgitation velocity) and rule out pulmonary hypertension
- Other: chronic hypertension, RV dysfunction, myocardial dysfunction, cardiac iron overload, dysrhythmia, sudden death

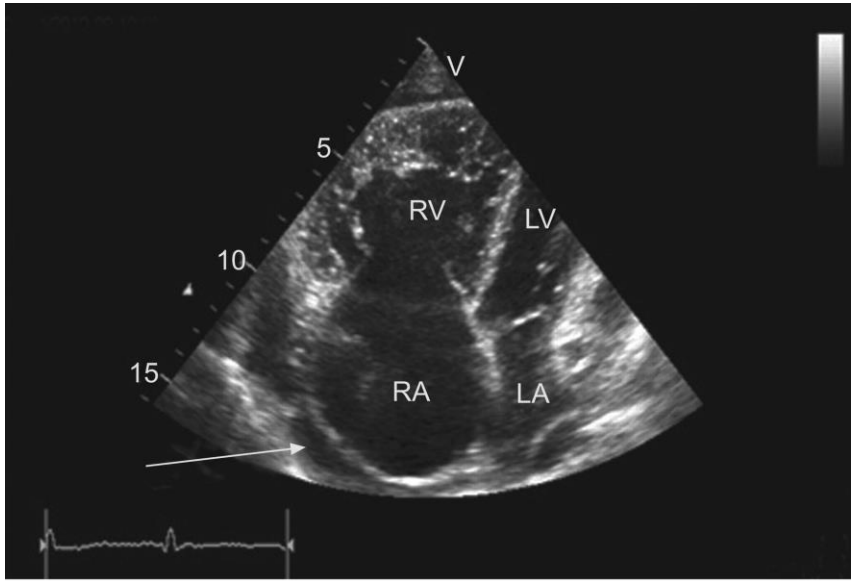


Image: European Respiratory Review

Dentistry

- Patients with SCD have increased risk of:
  - Dental caries
  - Delayed eruption
  - Dental hypoplasia
  - Mucosal pallor
  - Radiographic changes
  - Toothaches, related to hypoxia of dental pulp
- Contact hematology before patient needs to undergo a dental procedure with general anesthesia or deep sedation

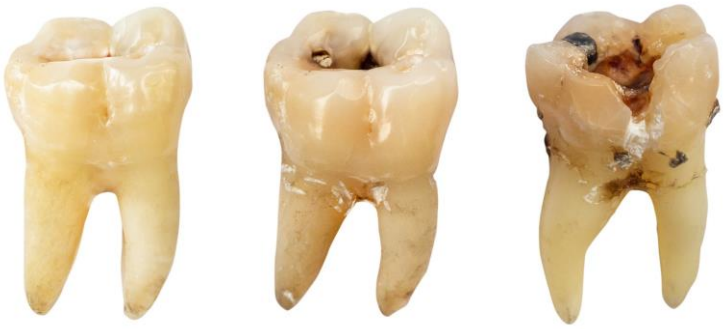


Image: Northampton Pediatric Dentistry

Dermatology

- **Leg Ulcers**
  - More common in older males
  - More common around the ankles
  - Triggers: trauma, infection, severe anemia
  - Contribute to chronic pain, osteomyelitis
- Initial standard therapy: debridement, wet to dry dressings, topical agents
- Treat with systemic or local antibiotics if wound culture is positive for infection
- Potential side effects of hydroxyurea: eczema (~13%), hair thinning/loss (<10%), leg ulcers (<10%)

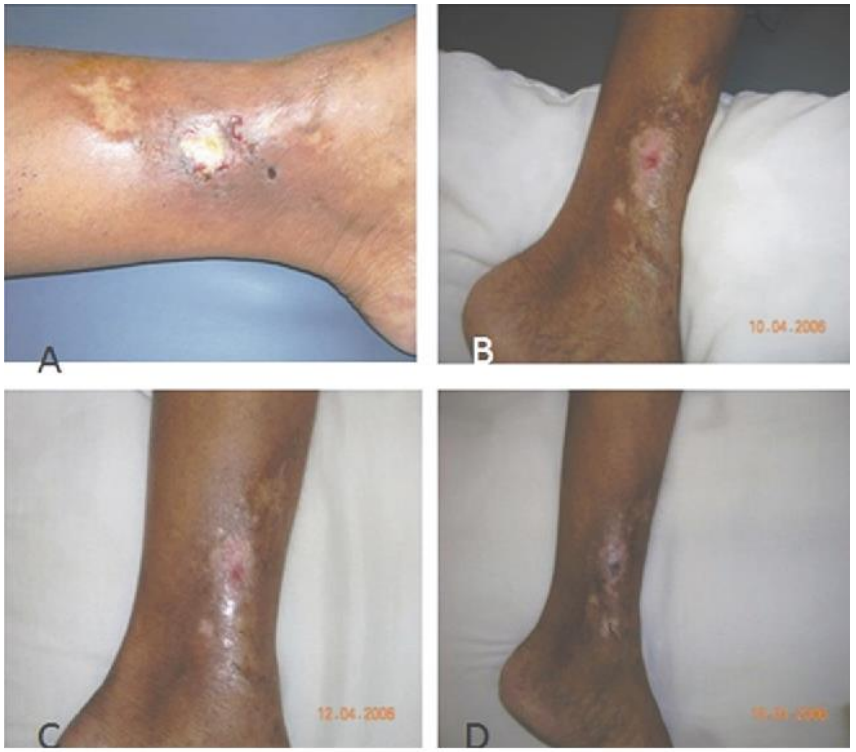


Image: Semantic Scholar

Endocrinology

- Delayed growth & puberty due to chronic anemia
- Patients with SCD may develop:
  - Vitamin D deficiency (84.7%)
  - Insulin resistance (11.5%)
  - Growth hormone deficiency (3.8%)
  - Hypothyroidism (3.8%)
  - Hypogonadism (1.9%)
- Endocrine dysfunction common in patients with SCD who have iron overload due to frequent blood transfusions (>8 per year)
- Hemoglobin A1C is not accurate

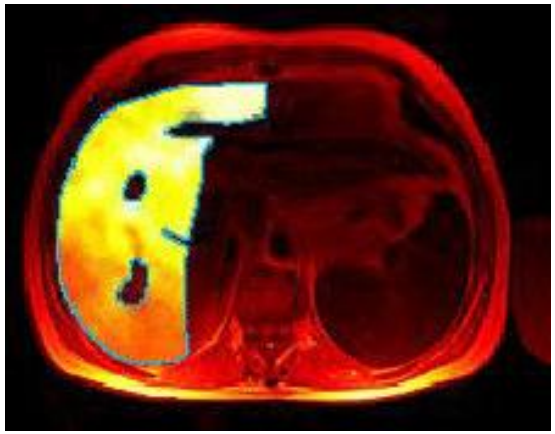


Image: ResearchGate

Gastroenterology

- Gallbladder Disease: cholelithiasis, cholecystitis
- Liver Disease: acute infarction, acute sickle hepatic crisis, intrahepatic cholestasis, hepatitis, iron overload
- Rare: pancreatitis, ischemic bowel, peptic ulcer disease

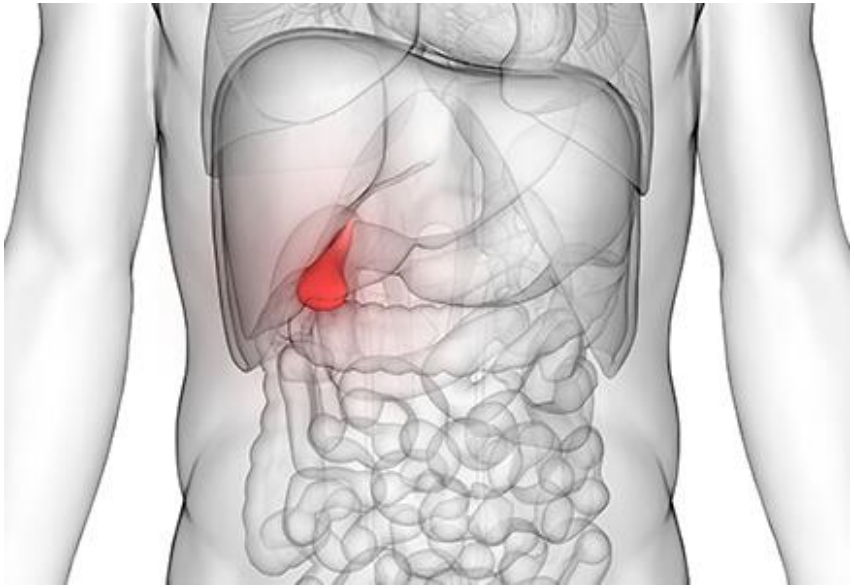


Image: Indiana Hemophilia & Thrombosis Center

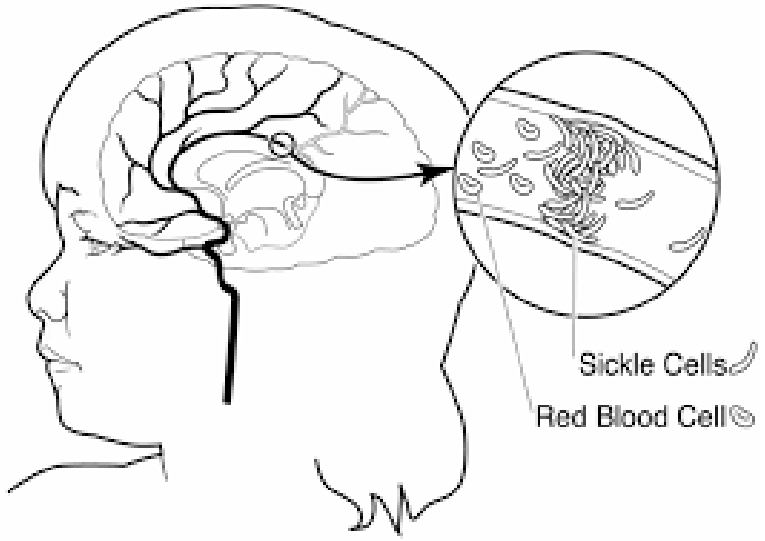
Nephrology

- 16-18% of overall mortality in patients with SCD is related to sickle cell nephropathy
  - Patients with SCD are 2-3x more likely to develop ARF or CKD than other patients
  - Risk Factors: Male, advanced age, diabetes, hypertension, chronic heart disease, dyslipidemia, hx of blood transfusions
- #1 Complication: **Hyposthenuria** (inability to concentrate urine)
- Increased risk for **renal medullary carcinoma**
  - Hematuria & flank pain
- Refer to Nephrology for: elevated BUN/Cr, elevated urine microalbumin, hypertension, renal papillary necrosis (painless hematuria)

Image: Nephrology Associates of Upland and Pomona

Neurology/Neurosurgery

- Reasons for referral:
  - overt *ischemic*/hemorrhagic stroke
  - silent stroke
  - TIA
  - moyamoya disease
  - posterior reversible encephalopathy syndrome (PRES)
  - cerebral fat embolism
  - cerebral venous sinus thrombosis
  - epilepsy
  - headaches/migraines



- Refer to **NeuroDevelopmental Science Center** for neurocognitive testing
  - Patients with SCD may have decreased cognitive thinking and poor school performance due to silent stroke

Signs of Stroke

facial droop, one-sided weakness, speech difficulty, altered gait, confusion, numbness & tingling, vision changes, headache

Image: Nationwide Children's Hospital

Ophthalmology

- **Sickle Cell Retinopathy**
  - Occurs in up to 50% of patients with SCD
  - Can ultimately cause retinal detachment and vision loss
  - May require laser therapy or surgery
- **Increased IOP**
- Dilated eye exam annually

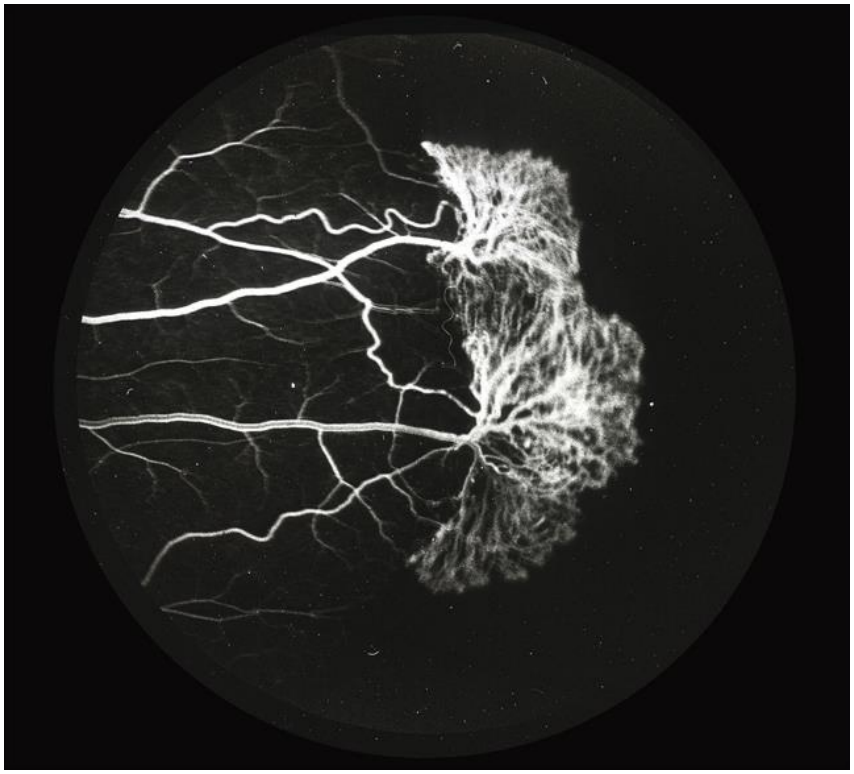


Image: The American Society of Retina Specialists

Orthopedics

- Bone infarction causes **severe bone pain** that characterizes many sickle cell crises
- **Avascular Necrosis (AVN)**
  - More common in sickle cell anemia
  - Damage is cumulative
  - May cause limb-length discrepancies, impaired mobility, permanent gait abnormalities
- **Infections**
  - **Osteomyelitis (OM)**
    - *Salmonella* (most common), *Staph aureus*
    - Symptoms mimic sickle cell pain crisis (painful swollen limb, limited ROM, fever)
    - Utilize imaging to diagnose (US, MRI)
  - **Septic Arthritis**
    - *Staph aureus* more common
    - Lower incidence overall (~3% in patients with Hgb SS)
    - Often associated with AVN or OM
  - Treatment includes antibiotics, surgical debridement, PT

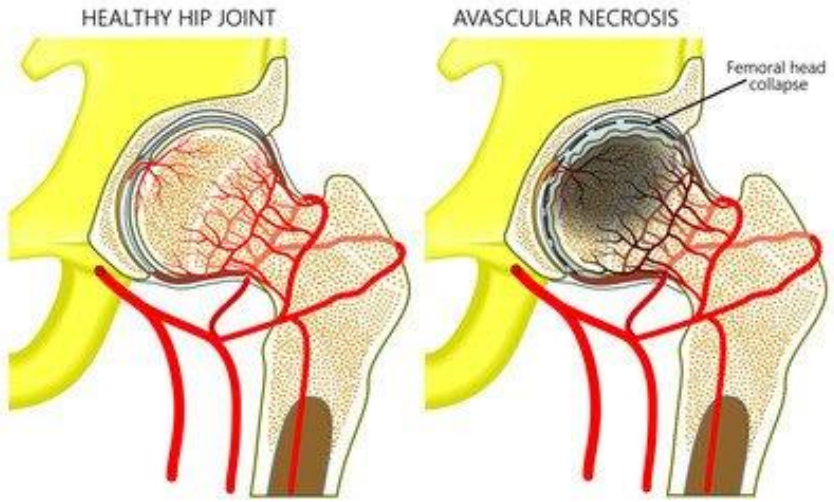


Image: Dr. Lox Sports & Regenerative Medicine Centers

Palliative Care

- Inpatient consults for PCAs for severe sickle cell pain crisis
- Management of **Chronic Pain**
  - SC pain → central sensitization, hyperalgesia, altered opioid metabolism (increased clearance)
  - Chronic pain contributes to mental health, mood changes, emotional disturbance, behavioral dysfunction
  - Patients with AVN often have chronic pain
  - ~30% of adults with sickle cell disease have daily pain

Image: Med One Group

Psychology

- Depression (~30%)
- Anxiety (~7%)
- Insomnia
- Loneliness/Isolation
- PTSD
- Socioeconomic Challenges
  - Multiple prescriptions may not be covered by insurance
  - Transportation to appointments with multiple specialists
  - Difficulty attending school or keeping a job due to frequent pain, hospital admissions, and appointments
  - Reduced opportunities for career advancement → decreased financial security

PHQ9P

PATIENT HEALTH QUESTIONNAIRE - 9

Comments:

Over the last 2 weeks, how often have you been bothered by any of the following problems?	Not at all	Several days	More than half the days	Nearly every day
1. Little interest or pleasure in doing things	0	1	2	3
2. Feeling down, depressed, or hopeless	0	1	2	3
3. Trouble falling or staying asleep, or sleeping too much	0	1	2	3
4. Feeling tired or having little energy	0	1	2	3
5. Poor appetite or overeating	0	1	2	3
6. Feeling bad about yourself — or that you are a failure or have let yourself or your family down	0	1	2	3
7. Trouble concentrating on things, such as reading the newspaper or watching television	0	1	2	3
8. Moving or speaking so slowly that other people could have noticed? Or the opposite — being so fidgety or restless that you have been moving around a lot more than usual	0	1	2	3
9. Thoughts that you would be better off dead or of hurting yourself in some way	0	1	2	3
	0 + ____ + ____ + ____ = Total Score: ____			

If you checked off any problems, how difficult have these problems made it for you to do your work, take care of things at home, or get along with other people?

Not difficult at all	Somewhat difficult	Very difficult	Extremely difficult
☐	☐	☐	☐

Developed by Drs. Robert L. Spitzer, Janet B. W. Williams, Kurt Kroenke and colleagues, with an educational grant from Pfizer Inc.

Patient's name:	Date:

Image: Advancing Integrated Mental Health Solutions Center

Pulmonology

- SCD + **Asthma** = 2x higher risk of pain, acute chest syndrome, decreased lung function, & mortality
  - Asthma affects ~15-20% of African American children, similar in children with SCD
- SCD + **OSA** = 4x higher risk for nocturnal hypoxemia <85%
- **Acute Chest Syndrome** (ACS)
  - 2nd most common reason for hospital admission
  - Often develops during a hospitalization for another reason
  - Repeat episodes of ACS contributes to development of chronic lung disease (~3% of adults)
- PFTs not recommended as a screening tool for asymptomatic patients unless they have asthma

Image: Healthline

Surgery/IR

- Cholecystectomy
- Splenectomy
- Joint replacement
- Laser eye surgery
- Port placement
- Apheresis catheter placement
- Peripheral & neuraxial nerve block
- Dental surgery
- Increased risk for postop complications
  - Mainly: acute chest syndrome, pain crisis
  - Other: infection, stroke, AKI, thromboembolism, hypertension, heart failure

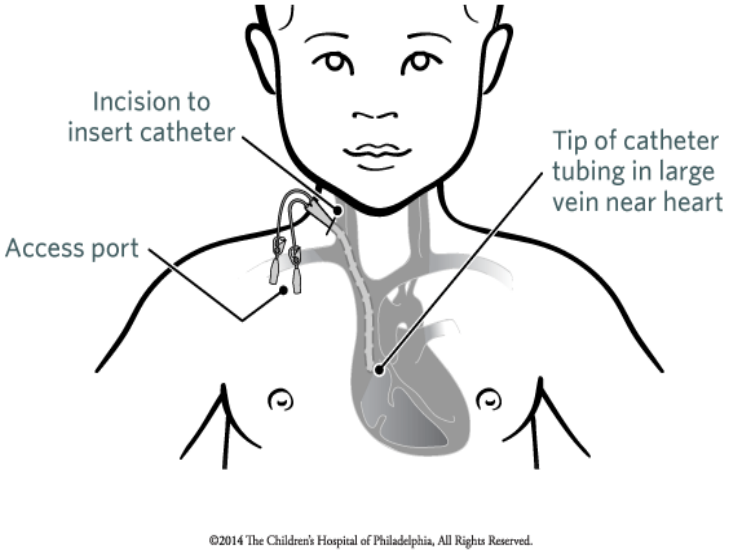


Image: Children's Hospital of Philadelphia

Urology

- **Priapism**
  - Prolonged, often painful erection that can lead to erectile dysfunction
    - May be persistent or stuttering
  - Males with SCA:
    - 13% experience by age 10, 50% by age 15, 90% by age 20
  - Precipitating factors: sleep, sexual activity, fever
  - >4 hours = MEDICAL EMERGENCY
  - Often a lack of awareness about this complication
  - Treatment/Prevention
    - Analgesia, hydration, exercise, voiding, warm baths
    - Pseudoephedrine, sildenafil
    - Drainage

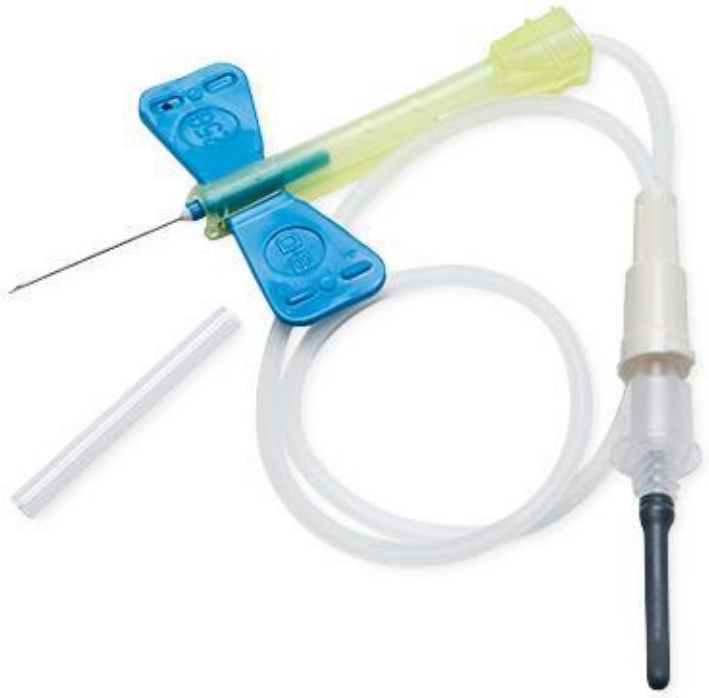
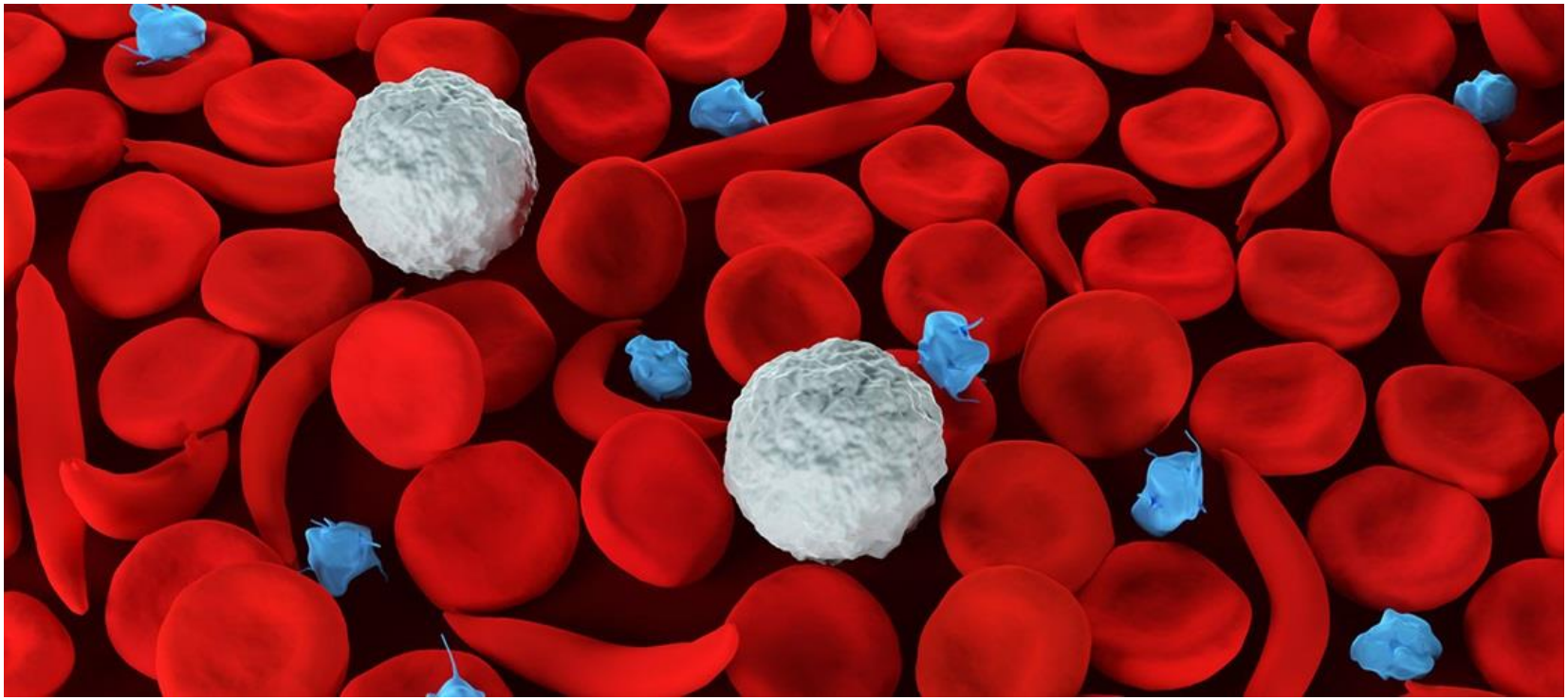


Image: Medline



What is the best way to prevent all these sickle cell complications?

Image: Johns Hopkins Medicine

Hydroxyurea (Droxia, Hydrea, Siklos)


Mechanism of Action	• Antimetabolite chemotherapeutic agent • Increases RBC water content → less likely to become deformed & rigid • Alters RBC adhesion to endothelium (makes environment "less sticky") • Increases fetal hemoglobin levels (goal >20%)
Age Group	9 months & up
Dose	Start at 20mg/kg/day PO daily, advance as tolerated to optimal dosing of 35mg/kg/day
Available Forms	Liquid 100mg/ml, 200/300/400mg capsules (Droxia), 500mg capsules (Hydrea), 100/1000mg scored dissolving tablets (Siklos)
Monitoring	Labs every 4 weeks until optimal dosing reached, then every 3-4 months
Common Side Effects	• Bone marrow suppression, increased infection risk due to mild neutropenia (HU takes ANC out of inflammatory range) • GI upset • Headache • Rash
Special Considerations	• Wear gloves when handling liquid or pills, wash hands before & after • Clean up spills with a damp paper towel, dispose in a plastic bag • Protect your skin from the sun • Discontinue if pregnant (unknown if it causes fetal harm)

Image: WebMD, Cigna, CareFirst, Medunik USA

Hydroxyurea Benefits

- Safe and effective
- Prevents sickling through multiple mechanisms of action
- Well studied in children and adults
- Inexpensive
- Low side effect profile
- Most formulations can be stored at room temperature
- Widely available

Sickle Cell Trait

- Affects 1 in 13 Black newborns
- Risks: High altitude, increased atmospheric pressure (scuba diving), dehydration, high-intensity physical activity
  - Increased risk of sudden death during extreme physical exertion
- Potential Complications:
  - Exertional rhabdomyolysis
  - Renal papillary necrosis
  - Renal medullary carcinoma
  - Splenic infarction
  - Venous thromboembolism
  - Glaucoma post-hyphema

Image: Mike Drop Sports

Our Sickle Cell Team

- **Dr. Prasad Bodas**, Lead Hematologist
- **Lauren Beck**, Sickle Cell Nurse Practitioner
- **Bobbi Moser**, Sickle Cell Nurse
- **Alyssa Hatton**, MV Sickle Cell Nurse
- **Joseph Delagrange**, Sickle Cell Social Worker
- **LaTonya Lewis**, Program Director/Newborn Screen Counselor/Outreach Education Coordinator
- **Shari Harmon**, MV Clinical Coordinator
- **Laura Gerak**, Psychologist
- **Mallory Zehe**, Psychologist
- **Melinda Aylward**, School Teacher
- **Carla Lukens**, School Teacher
- **Vicki Vitale**, Dietician
- **JoEllen Weilnau**, Pharmacist
- **Madeline Frederick**, Genetics Counselor
- **Cynthia Laliberte**, Echo Services
- **Katherine Pritchard**, Physical Therapist
- **Jascelynn Romeo**, MV Physical Therapist
- **Amanda Wiseman**, Apheresis Nurse
- **Tori Thompson**, Apheresis Nurse

Questions?

LBeck2@akronchildrens.org

References

Acharya, S. (2015). Oral and dental considerations in management of sickle cell anemia. *International Journal of Clinical Pediatric Dentistry, 8*(2), 141-144. doi: 10.5005/jp-journals-10005-1301

Al Farii, H., Zhou, S., & Albers, A. (2020). Management of osteomyelitis in sickle cell disease: Review article. *The Journal of the American Academy of Orthopaedic Surgeons, 4*(9), e20.00002. doi: 10.5435/JAAOSGlobal-D-20-00002

Ebert, E.C., Nagar, M., & Hagspiel, K.D., (2010). Gastrointestinal and hepatic complications of sickle cell disease. *Clinical Gastroenterology and Hepatology, 8*(6), 483-489. doi: 10.1016/j.cgh.2010.02.016

Ferster, A., Tahriri, P., Vermylen, C., et al. (2001). Five years of experience with hydroxyurea in children and young adults with sickle cell disease. *Blood, 97*(11), 3628-32. doi: 10.1182/blood.v97.11.3628

Gladwin, M.T., & Sachdev, V. (2012). Cardiovascular abnormalities in sickle cell disease. *Journal of the American College of Cadiology, 59*(13). doi: 10.1016/j.jacc.2011.10.900

Khan, U., Kleess, L., Yeh, J., et al. (2014). Sickle cell trait: Not as benign as once thought. *Journal of Community Hospital Internal Medicine Perspectives*, *4*(5), 25418. doi: 10.3402/jchimp.v4.25418

Kiser, Z.M., Clark, K.A., Sumner, J.L., et al. (2019). Association between sensorineural hearing loss and homozygous sickle cell anemia: A meta-analysis. *Blood, 143*(1), 3453. doi: 10.1182/blood-2019-127740

Miller, A.C., & Gladwin, M.T. (2012). Pulmonary complications of sickle cell disease. *American Journal of Respiratory and Critical Care Medicine, 185*(11), 1154-1165. doi: 10.1164/rccm.201111-2082CI

Mitchell, B.L. (2018). Sickle cell trait and sudden death. *Sports Medicine Open Journal, 4*(19), 1-6. doi: 10.1186/s40798-018-0131-6

Msaouel, P. (2019). Renal medullary carcinoma. Retrieved from https://rarediseases.org/rare-diseases/renal-medullary-carcinoma/#:~:text=Renal%20medullary%20carcinoma%2C%20also%20known,of%20the%20red%20blood%20cells.

National Heart, Lung, and Blood Institute (2014, September). Evidence-based management of sickle cell disease: Expert panel report, 2014. Retrieved from: http://www.nhlbi.nih.gov/health-pro/guidelines/sickle-cell-disease-guidelines

Ruta, N.S., & Ballas, S.K. (2016). The opioid drug epidemic and sickle cell disease: Guilt by association. *Pain Medicine, 17*(10), 1793-1798. doi: 10.1093/pm/pnw074

Smiley, D., Dagogo-Jack, S., & Umpierrez, G. (2008). Therapy insight: Metabolic and endocrine disorders in sickle cell disease. *Nature Clinical Practice Endocrinology & Metabolism, 4*, 102-109. doi: 10.1038/ncpendmet0702

Tanabe, P., Spratling, R., Smith, D., et al. (2019). Understanding the complications of sickle cell disease. *American Journal of Nursing, 119*(6): 26–35. doi:10.1097/01.NAJ.0000559779.40570.2c