# SICKLE CELL DISEASE IN ADULTS

**Background / Pathophysiology**

1. Inherited autosomal blood disorder.[1]
2. In United States, affects mostly individuals of African descent.[2]
3. Disorder caused by single amino acid substitution, valine for glutamic acid, in sixth position of the beta globin chain of hemoglobin…called hemoglobin S.[1]
4. When erythrocytes become deoxygenated, hemoglobin S becomes distorted and rigid; results in occlusion of blood vessels and hemolysis.[1]
    - Homozygous: HbSS - most severe. [3,4]
    - Combined heterozygosity: HbS/HbC - intermediate severity. [3,4]
    - Benign heterozygosity: HbS/HbA - Trait, Sickle cell-B thalassemia: HbS[3]
    - Hb S/beta zero thalassemia similar to Hb SS; Hb S/beta plus thalassemia typically more moderate than Hb SS- variability of symptoms for individuals with similar genotypes.
    - All genotypes considered sickle cell disease; sickle cell anemia refers to specific HgSS genotype. [3,4]
    - Sickle Cell Trait benign under usual conditions and not sickling syndrome. [1,3]
5. Severity of clinical manifestations varies greatly from asymptomatic patient to severely ill patient; can trend over time.

**General Information**

1. Number of individuals with sickle cell disease unknown. National estimates, when adjusted for early mortality, about 104,000-138,000. [2]
2. Improving survival rates of sickle cell disease is goal shared by those caring for increased numbers of adult patients.
3. Few adult sickle cell randomized controlled studies exist.
4. High level evidence lacking for acute and chronic complications treatment and prevention recommendations. [5]

**Diagnostics**

1. **Recommended History[1]**
    - Many adults in United States already have diagnosis on presentation due to mandatory testing in newborns.
    - At initial visit, obtain demographic information, active medical problems and history, surgical history, medication lists, previous hospitalizations and a ***complete review of pain crises*.**
    - Review social history: identify family support, occupation, tobacco, alcohol and illicit drug use and safe sex practices.
2. **Physical Examination:**
    - Routine physical exams, appropriate to age and co-morbid conditions, performed approximately every two to six months depending on the phenotype and active problems.[4]

3. **Labs:**
    - Recommended initial labs: CBC, reticulocyte count, urinalysis, pulse oximetry with each visit.
    - Comprehensive blood chemistries at least yearly.
    - Other labs for co-morbid conditions.
    - Chronic hemolysis leads to chronic anemia, increased reticulocyte count, unconjugated hyperbilirubinemia, elevated serum LDH, and low serum haptoglobin, elevated neutrophils and platelets.[1,4]
    - Erythrocytes in SCD destroyed randomly, with mean life span of 17 days.[4]
    - Leukocytosis common, which may indicate infection or vaso-occlusion.[6]
    - In acute pain crisis or acute chest syndrome, consider ordering CBC, reticulocyte count, UA, Urine culture, CXR, PRN blood cultures and ABG.[6]

**Acute Complications:**

1. **Acute chest syndrome:**
    - Defined by occurrence of chest symptoms, new pulmonary infiltrate on chest radiograph, and occasionally fever.[7]
    - Begin broad spectrum empiric antibiotics including coverage for community acquired pneumonia plus atypical organisms[8,9]
    - Fluid hydration, Oral or IV well accepted practice, but no clear evidence of efficacy or best choice of fluid. Avoid overhydration.[8,9]
    - Transfusion if hypoxemic
    - Exchange transfusion recommended if hypoxemia persists with possible hyperviscosity or evidence of iron overload, [3,9] but more studies needed to compare with simple transfusions.[10]
    - Urgent consultation with hematologist or pulmonologist advised for improved survival.[3]
    - Hydroxyurea should be considered for adults with severe or recurrent acute chest syndrome or symptomatic anemia (SOR:C)[3,22]

2. **Acute Pain crisis:**
    - Pain may be precipitated by stressful events, including infection, weather change, dehydration, menses, alcohol use etc.
    - In many cases, precipitating cause is unknown.[11]
    - Episodes defined as at least for 4 hours, but can last anywhere from 2 days to 1 week.
    - Pain usually affects back, legs, knees, arms, chest and abdomen
    - Treatment includes opioid analgesics, adequate hydration, rest, and cognitive and behavioral therapies[9]
    - Choice of analgesic and dosage based on severity and chronicity of pain.[6]
    - Outpatient treatment for mild pain: acetaminophen +/-codeine, NSAIDs.[6]
    - Opioid analgesics can be used in patients with moderate to severe pain.[6]
    - Severe pain may require emergent care or hospitalization.
        - Treat with parenteral opioids: morphine, hydromorphone (Dilaudid), or levorphanol (Levo-Dromoran).[6]

- Pain management decision: admit for inpatient treatment or treat as outpatient.[6]
- Reassess ongoing pain severity, sedation, and respiratory status.[6]

**Acute blood transfusions**

1. Transfusion may be indicated if symptoms directly attributable to anemia.
2. Transfusion not indicated for uncomplicated painful episode.
3. No target Hg value, but should be no higher than 10 to 11 g/dL.[5]

**Chronic complications:[1]**

1. CNS: ischemic stroke most common in older adults; hemorrhagic stroke in third decade of life
2. Eyes: proliferative or nonproliferative retinopathy.
3. Lungs: increased incidence of asthma; 1/3 of adult patients will develop pulmonary hypertension.
4. Heart: systolic and diastolic flow murmurs common. Diastolic left ventricular dysfunction independent risk factor for death. Cardiac autonomic dysfunctional so common and may contribute to sudden death.
5. Gastrointestinal: acute and chronic cholecystitis, cholestasis, and viral hepatitis. Patients with symptomatic cholelithiasis: refer for possible cholecystectomy.
6. Renal: renal glomerular disease, renal failure, hematuria, proteinuria.[12]
7. Blood: anemia, leukocytosis, reticulocytosis, iron overload, functional asplenia
8. Bone: osteomyelitis (most commonly salmonella, then staphylococcus) avascular necrosis of the hips, bone marrow infarction, orbital compression syndrome.
9. Skin: leg ulcers
10. Psych: depression, suicidal ideation and suicidal attempts.[13,14,15]

**Treatment**

1. Hydroxyurea [5,16]
    - Should be considered for adults and older adolescents with three or more painful vaso-occlusive episodes per year (SOR:A)[3]
    - If used, often under-dosed : needs proper supervision/follow-up
    - Effective therapy associated with potentially severe complications.
    - Initial dose 15mg/kg/day; titrate by 5mg/kg/day q12 weeks until maximum dose of 35mg/kg/day or highest tolerated dose without toxicity.
    - Increases Hemoglobin F, leukocyte count, and platelet count.
    - Short term side effects: leukopenia, thrombocytopenia, anemia and decreased reticulocyte count.
    - Men - decreased sperm production.
    - Long-term: hyperpigmentation of skin and birth defects in offspring.
    - No clear evidence of increased leukemia or cancer in SCD patients.
    - In severely affected adults, continuous use over 2 years appears effective and safe
    - In 17.5 year follow-up from initial randomized trials, long-term hydroxyurea exposure reported to decrease mortality and improve preservation of end-organs[17]
    - Cutaneous vasculitic toxicities, including vasculitic ulceration and gangrene, reported in patients with myeloproliferative disorders receiving hydroxyurea, mostly in patients also receiving interferon therapy.[18]

**Chronic blood transfusions**

1. Exchange transfusions can be used for prolonged refractory and recurrent vaso-occlusive crises; goal is reducing Hb S level to below 20%[1]
2. Avoid total iron overload over time.
3. Regular blood transfusions show significant decrease in stroke risk; may revert to former risk status if discontinued.[19]
4. Hematopoietic stem cell transplantation (HSCT) – best used before irreversible end-organ damage occurs.
    - Considered more effective in younger patients; experimental in older patients
    - Best in HLA matched sibling donors with normal or sickle cell trait
    - Allogeneic hematopoietic stem-cell transplant reportedly successful in patients with severe sickle cell disease.[19]

**Health Maintenance:**

1. USPSTF guidelines recommend age and gender appropriate periodic health screening.
2. Annual screening examination after age 10 by ophthalmologist for retinopathy, increased intraocular pressure, and refraction errors (SOR:C)[3,23]
3. Immunization:
    - pneumococcal vaccine every five years for functional asplenia (SOR:B)[3,20]
    - influenza vaccines annually (SOR:C)[3,20]
    - one dose of Haemophilus Influenzae type B (HIB)[20]
    - Meningococcal Vaccine (SOR:C)[3,20]
    - other appropriate vaccines for age[20]
4. Renal function assessment and urinalysis for microalbumin and proteinuria (SOR:C)[3,5]
5. ACE inhibitors or Angiotensin Receptor Blockers for patients with significant proteinuria.[5,21]
6. Priapism may be prevented with alpha/beta adrenergic agonists, and gonadotropin releasing hormone.[21]
7. Perform Transthoracic Doppler Ultrasound for pulmonary hypertension screening; no consensus on frequency of assessment or target age group.[22]
8. Family planning and contraceptive counseling.[23]
9. Adequate B12 and B6 to avoid endothelial damage.
10. Little evidence for folate, but Folic Acid 1mg/day often used,[24]

**Chronic Pain – related to vascular damage**

1. Opioid addiction believed less than 1% in this population[25]
2. Avoid using only opioids – always combine with acetaminophen or NSAID (avoid NSAID's in patients with renal disease), adjuvants: [1,6,25,26]
    - Adjuvants used as pain modifying adjuncts to opiates such as muscle relaxants, antidepressants, anti-seizure medications, topical agents, and atypical antipsychotics, especially for neuropathic pain.
    - Tylenol or NSAID's recommended to amplify direct or nociceptive pain suppressive properties of opiates.
3. Long-acting opioids can be used chronically, with short-acting for breakthrough pain.[25]
4. Opioids chosen based on prior history and current assessment.[25]

5. Avoid Hyperalgesia Syndrome[27]
    - Hyperalgesia Syndrome thought to originate from metabolite of morphine that increases central sensitivity to pain.
    - Decreasing dosage or changing to different class or combination of opioids/adjuvants may help.
    - Observe for chronic pain-enhancing conditions including length and severity of daily pain which is often underreported.[27]

**Pregnancy[28]**

1. Pregnant sickle cell disease patients face serious fetal and maternal complications.
2. Fetal complications: intrauterine growth restriction, low birth weight, fetal death.
3. Rate of spontaneous abortion may be as high as 25%.
4. Serial ultrasonography to assess fetal growth in second and third trimester.
5. Maternal complications: Increase morbidity.
    - Infections common, including urinary tract infections and pulmonary infections.
    - Increased incidence of pregnancy induced hypertension.
6. Once pregnancy established, hydroxyurea discontinued, and 1g/day folic acid administered (0.4g/day when trying to conceive).

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