ADULT TREATMENT GUIDELINE
Sickle Cell Disease

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Revised:

I. Definition, Assessment, and Diagnosis

a. **Definition**: Sickle Cell Disease is
   i. the most common hemoglobinopathy in the United States.
   ii. An Autosomal Recessive disorder involving abnormal hemoglobin
   iii. Hemoglobin S (the hemoglobin that sickle cell patients have) differs from normal hemoglobin (Hb A) because of a substitution of valine for glutamic acid in the 6^{th} position in the β-globin gene.
   iv. Causes an abnormal "sickled" shape of red blood cells
   v. Results in vaso-occlusive phenomena and hemolysis
   vi. A spectrum of diseases
      1. Sickle cell trait (Hb AS)
      2. Sickle cell anemia (Hb SS)
      3. Hemoglobin SC disease
      4. Sickle cell/Alpha Thalassemia
      5. Sickle cell/Beta Thalassemia (HbS-β-thalassemia)

b. **Assessment**
   i. **Sickle Cell Anemia**
      1. Periods of relatively good health with intermittent periods of crisis
      2. Chronic anemia (hemoglobin of 6-9g/dL) appears between 3-6 months of age, when Hemoglobin F falls to low levels.
      3. Turnover of red blood cells is 5-10 days, COMPARED TO THE NORMAL 120 DAYS.
      4. Common Complications:
         a. Bacterial infections, particularly pneumococcus.
            i. Adults with sickle cell disease are often functionally asplenic, and therefore more susceptible to infection with encapsulated organisms.
         b. Urinary tract infections and pyelonephritis
         c. Osteomyelitis
         d. Renal impairment
         e. Jaundice
         f. Cholelithiasis
         g. High output cardiac failure
         h. Left ventricular hypertrophy

i. Cardiomegaly
j. Stroke
k. Liver failure
l. Pulmonary infection (**ACUTE CHEST SYNDROME**)
    i. Common serious condition associated with the disease
    ii. Occurs in 40% of patients with this disease
    iii. Symptoms
        1. Pleuritic chest pain
        2. Fever
        3. Cough
        4. Lung infiltrates on CXR
        5. Hypoxia
    iv. Etiology
        1. Infection
        2. Infarction
        3. Pulmonary sequestration
        4. Fat embolization from bone marrow
    v. Treatment (See II.b.vii)
m. Splenic Sequestration
    i. Caused by intra-splenic trapping of red blood cells
    ii. Causes an acute drop in hemoglobin
        1. At least 2g/dl drop from steady-state levels
        2. Markedly elevated reticulocyte count
        3. Acutely enlarging spleen
        4. Recurrence rate is high
    iii. Treatment (See II.b.viii)

ii. **Sickle Cell Crisis**
1. Often preceeded by infection
2. Hemolysis
3. Viscosity
4. Hypoxia
5. Dehydration
6. Acidosis
7. Pain
    a. Long bones
    b. Abdomen
    c. Back
    d. Chest

iii. **Hb SC disease**
1. Less morbidity than patients with HbSS disease
2. Subject to crises in pregnancy (often diagnosed at this time)
    a. Increased incidence of spontaneous abortion and preeclampsia
3. Crises may be accompanied by marked sequestration of a large volume of red blood cells in the spleen, with a dramatic fall in hematocrit.

a. Can see mild thrombocytopenia

iv. **Thalassemias**

1. Alpha-thalassemia minor
    a. Mild microcytic anemia
    b. results when there is a deletion of two of the four copies of the four α-globin genes
    c. Patients with alpha-thalassemia and Hb SS have a less severe disease than those with Hb SS alone.
2. Beta-thalassemia minor
    a. Mild, usually asymptomatic anemia
    b. Often occurs with Hb S
        i. No normal β-globin chains are produced
        ii. No Hb A is produced
        iii. Called Sickle Cell β-thalassemia
            1. Similar symptoms to Hb SS disease, but milder
            2. Good quality of life and lifespan

c. Diagnosis

i. Diagnosis of all hemoglobinopathies is by hemoglobin electrophoresis
ii. Newborn screening is automatic now, but only since 1988
iii. All at-risk ethnic groups should be screened in pregnancy
iv. Sickledex and other solubility tests are inadequate in differentiating between some of the genotypes

II. Management

a. Responding to Call Center Calls

i. Determine whether or not the patient needs to go to the ED for further work up.
    1. Is patient unconscious/unarousable?
    2. Is patient vomiting and unable to hold down any medications?
    3. Has the patient lost vision?
    4. Does the patient have stroke symptoms? (slurred speech, inability to move one side of the body, etc)?
    5. Is patient febrile (>100.4 F)?
    6. Has the patient had a painful erection for more than 2 hours?
    7. If the main complaint is pain, has the patient:
        a. tried hot bath/shower?
        b. Tried increasing PO pain med (including NSAID)?
        c. Drank as much water as possible?
ii. If talking to another provider:
    1. Refer to the sections below to walk them through various treatment scenarios, if the physician is comfortable treating the patient.

b. In the ED:

i. Tease out the History of Present Illness.
   1. Pain location, duration, severity. "Is this your normal pain?"
   2. Meds taken in last 24 hours?
   3. Normal pain medication regimen when in crisis?
   4. Medication compliance
   5. Venous Access?
   6. Last admission? Last clinic visit? Last transfusion? Primary Care provider?
   7. Number of crises per year? Number of ED visits per year?
   8. Vaccination Hx (influenza, pneumococcal, HBV, H.flu)
   9. Stroke symptoms?
   10. Acute chest syndrome?
   11. Avascular necrosis?
   12. Renal disease?
   13. Liver disease?
   14. Vision history?
   15. Skin ulcers?
   16. Priapism?

ii. Administer IV bolus dose of opiate (5mg morphine or 1mg dilaudid, for example)

iii. If still in pain 15 minutes, bolus again. Repeat until pain controlled, then schedule that cumulative dose every 4 hours.

iv. Start 1 liter normal saline (or D5-1/2normal saline with 20meq of K+)

v. Check following labs:
   1. CBC, BMP(with Ca, Phos, Mg), HPLC, ferritin, LFTs, Reticulocyte analysis
   2. **IF** the patient has fever ***and*** leukocytosis:
      a. Blood, urine, sputum, wound cultures and CXR

c. In the hospital:

i. Continue home dose of folate, hydroxyurea and/or Exjade, as well as other meds (tri-cyclic's, antiepileptics, SSRIS, diabetic meds, and anti-hypertensives, etc) **unless contra-indicated**.

ii. **IF** patient's hemoglobin is less than 5g/dl **OR** level has dropped by 2g/dl below patient's baseline, **THEN** consider transfusion.
   1. TRANSFUSION MANAGEMENT:
      a. In patients hospitalized for pain episodes and other events, the Hb concentration may fall well below the admission value. If the patient is stable and the reticulocyte count high (>20 percent or >250,000/µL), transfusions can be deferred

b. **Avoid transfusion if at all possible!**
c. If HbS% is less than 40%, NO TRANSFUSION IS NEEDED.
d. The rational of transfusion is to reduce HbS%
e. Leukocyte-reduced blood preferred
f. NO ROLE in routine chronic transfusion in adults to prevent stroke
g. Only transfuse to patient's baseline hemoglobin (NOT 10g/dl)
h. NO role for prophylactic transfusion in PREGNANCY
i. Hemoglobin >10g/dl associated with increased morbidity secondary to hyperviscosity
j. The antigenic phenotype of the red cells (at least ABO, Rh, Kell, Duffy, Kidd, Lewis, Lutheran, P, and MNS groups) should be determined in all patients older than 6 months of age. A permanent record of the phenotyping should be maintained in the blood bank to optimize matching, and *a copy of the record should be given to the patient or family*.
k. All patients with a history of prior transfusion should be screened for the presence of alloantibodies.

iii. If patient has a history of stroke, and/or is having Acute Chest Syndrome, and/or is iron overloaded and anemic, then consider Exchange Transfusion.
1. <u>EXCHANGE TRANSFUSIONS:</u>
a. In the setting of iron overload, stroke, multi-organ failure, acute chest syndrome and priapism.
b. Purpose: to remove sickle cells and replace them with normal red blood cells without increasing whole blood viscosity or chronic iron burden.
c. Goal: to get the Hemoglobin S% under 30%.
d. Exchange transfusions do NOT hasten the resolution of a pain crisis

iv. Control pain.
1. Consider PCA administration of opiates. Reassess often.
2. Consider SCHEDULED administration of IV short-acting opiate, with prn IV opiate for breakthrough.
3. Recommend AVOIDING PRN administration of IV pain meds
4. If renal function **not** impaired, consider one time dose of 30mg IV ketorolac (toradol), which can work synergistically with opiates for pain control (Beware gastritis and GI bleeding).
5. Transition to oral pain medication WHILE STILL ON IV OPIATES. Beware of relapsed pain.
6. **DO NOT USE DEMEROL**
a. Not recommended for first line treatment of acute pain in sickle cell disease because of CNS toxicity related to its metabolite, normeperidine
b. Medication has long ½ life and is a cerebral irritant

c. Should not be used for more than 48 hours, nor at doses more than 600mg in 24 hours
d. Contraindicated in patients with renal impairment

7. DO NOT USE MORPHINE IN PATIENTS WITH RENAL IMPAIRMENT
8. Don't forget adjuvants (neurontin and/or tricyclic antidepressants, SSRIs for neuropathic pain, NSAIDS for bone pain/inflammation, acetaminophen, etc)
9. While on opiates for pain control, the patient MUST be on SCHEDULED docusate and senna to promote regular bowel movements and combat constipation caused by narcotics.

v. Treat all infections aggressively. Consider ID consult
vi. Stroke? Consult Neurology
vii. Pneumonia = Acute Chest Syndrome
1. Treatment
a. Supplemental Oxygen
b. Transfusion
c. Antibiotics (Erythromycin, cephalosporin)
d. Pain control
e. Incentive Spirometry
f. Bronchodilators

viii. Splenic Sequestration:
1. Treatment
a. Observation
b. Chronic transfusion
c. Splenectomy

ix. Priapism? Treat pain and consult Urology
x. Loss of Vision? Consult Ophthalmology
xi. Coordinate discharge with patient's primary care provider. Patient needs to be seen in the clinic within **2 weeks** of discharge.
xii. Many of these patients have a PAIN CONTRACT with a specific physician and DO NOT NEED PO PAIN MEDICATIONS at time of discharge.

d. In the Ambulatory setting:
i. NO ROLE for prophylactic antibiotic after age 5
ii. Daily folic acid of 1mg/day
iii. Routine visit every 3 months with blood counts
iv. Monthly visits may be necessary if patient is on chronic opiates
v. Hemoglobin electrophoresis at baseline, when not in crisis
vi. Yearly 2D Echo after age 15
vii. Yearly ophthalmological exam (rule out proliferative retinopathy)
viii. Yearly gynecological exam, with contraceptive counseling, if on hydroxyurea.
ix. Biannual BMP and urinalysis to monitor kidney function

x. Vaccines:
    1. Yearly influenza vaccine
    2. Srep. Pneumoniae every 5 years
    3. H.Influenza at least once
    4. N. Meningitides every 2 years
    5. HBV vaccine
    6. HPV vaccine before age 26

xi. Recommend SMOKING CESSATION

xii. Encourage proper nutrition

xiii. Avoid extremes in temperature, heavy physical exertion, stress and dehydration.

xiv. <u>Important Medications:</u>
    1. <u>Hydroxyurea</u>:
        a. Indications:
            i. Acute chest syndrome
            ii. 3 or more painful crises per year that interfere with daily activities
            iii. Males and Females should avoid conception while on hydroxyurea due to teratogenicity
        b. Mechanism of Action: increases concentration of Hb F in blood, thereby improving the oxygen-carrying capacity of RBCs.
        c. Initial dose is 15mg/kg/day
        d. Monitor CBC every 2 weeks after starting.
            i. If blood counts stay in an acceptable range, dose may be increased by 5mg/kg/day every 12 weeks until the maximum tolerated dose or 35mg/kg/day is reached.
                1. Acceptable counts:
                    a. Neutrophils >2,500
                    b. Platelets >95K
                    c. Hemoglobin >5.3g/dl
            ii. If blood counts are in the toxic range, treatment is discontinued until counts recover, then started back at reduced dose (reduce dose by 2.5mg/kg/day from the dose associated with hematologic toxicity.
                1. Toxic Counts:
                    a. Neutrophils <2,000
                    b. Platelets <80K
                    c. Hemoglobin <4.5g/dl
        e. MCV and %Hb F should increase. If they don't, consider noncompliance or drug failure.
            i. Cautiously increase to a maximum dose of 35mg/kg/day, while monitoring blood counts
            ii. After a trial period of 6-12 months with no increase in Hgb F or MCV, and no decrease in the amount of hospitalizations, <u>consider discontinuing the medication</u>.

2. Exjade (Deferasirox):
    a. Indications
        i. Iron overload (Ferritin >1000)
    b. Contraindications
        i. Poor performance status
        ii. Poor renal function (creatinine more than 2 times upper limit of normal)
        iii. Advanced malignancy
        iv. Platelets less than 50K
        v. High risk MDS
    c. Dosing
        i. Start at 20mg/kg/day
        ii. Take on an empty stomach, 30 minutes before eating
        iii. Dissolve tablets in water or juice and drink immediately

III. References

a. NIH Publication No 02-2117 "The Management of Sickle Cell Disease, 4th Edition", revised 5/28/02