VASOOCCLUSIVE PAIN CRISIS IN SICKLE CELL DISEASE

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Objectives

- Describe the clinical presentation of a vasooclusive pain crisis in sickle cell disease.
- List treatment modalities for vasooclusive pain crisis.

Definitions

- Sickle Cell Disease (SCD)[1,2]
  - An inherited (genetic) disorder where both genes encoding for hemoglobin production are mutant, producing red blood cells that are abnormally shaped
  - Abnormal shape = sickle (crescent)
  - Results in RBC hemolysis (anemia) and multiple organ complications

- Vasooclusive Pain Crisis[1,2] (AKA Acute painful episode)
  - Hallmark clinical presentation of SCD
  - An episode of acute pain caused tissue hypoxia (infarction) from sickled RBC obstructing capillary blood flow
  - Most commonly involves the bones, liver, spleen, brain, lungs, and genitals
  - Unpredictable, abrupt onset
  - Can recur unpredictably throughout a patient's lifetime
  - Intensity ranges from mild to severe & debilitating
  - Lasts hours to several days

Definitions, cont'd

- Precipitating Factors to vasooclusive crises:[1]
  - Infection
  - Extremes in temperature / weather
  - Dehydration
  - Stress

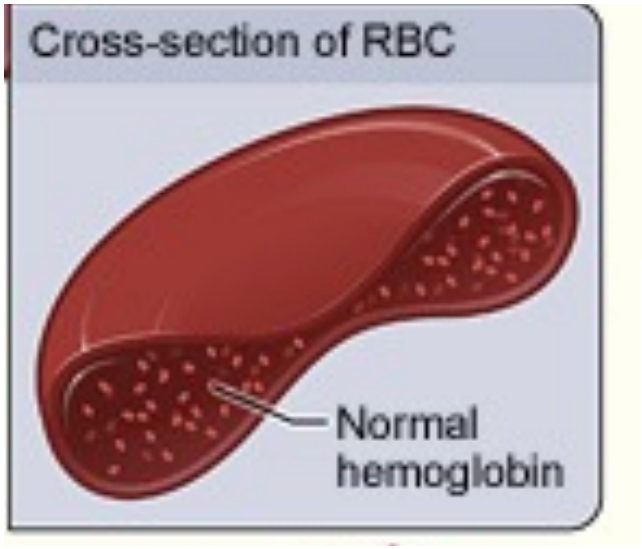
Epidemiology

- Prevalence of SCD[1,3]
  - 90,000 – 1000,000 people in the US
  - Most common in people with African heritage
  - Occurs in 1 in 500 African American births
  - Medial survival rates:
    - Age 72 (males)
    - Age 78 (females)

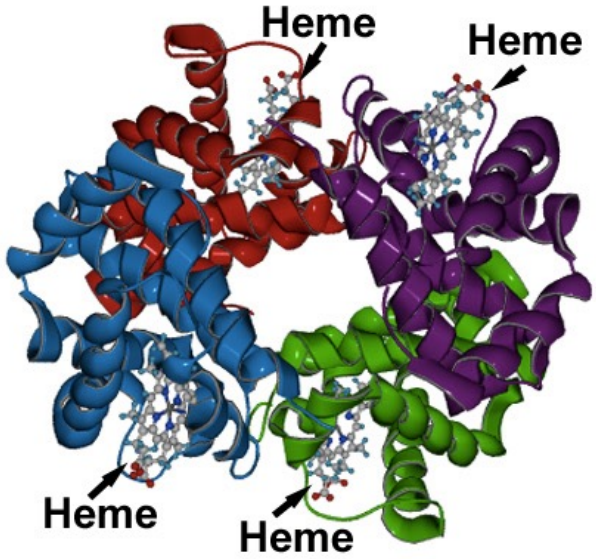
- Vasooclusive Crises[1,2]
  - Most common reason SCD patients will come to the hospital
  - Almost all patients w/ SCD will have recurrent episodes of acute pain
  - Frequency increases as patients enter early adulthood; peaks between 19-39[4]
  - One of the risk factors for early death in adults w/ SCD

Pathophysiology

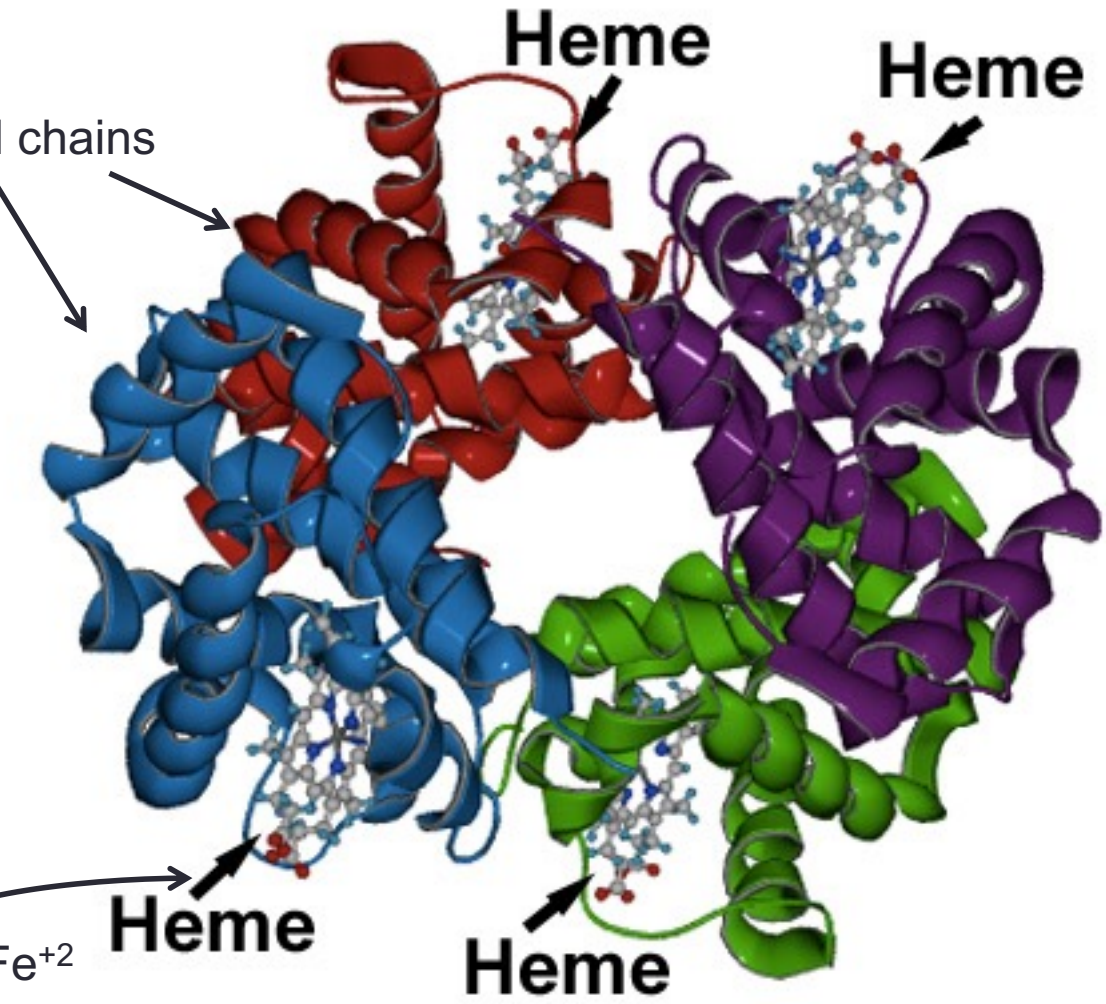
Red blood cell



Hemoglobin Molecule
(carries Oxygen)



http://wizznotes.com/biology/transport/blood-cells



Hemoglobin molecule:

4 AA chains
4 heme molecules

(can carry total of 4 molec. of O2)

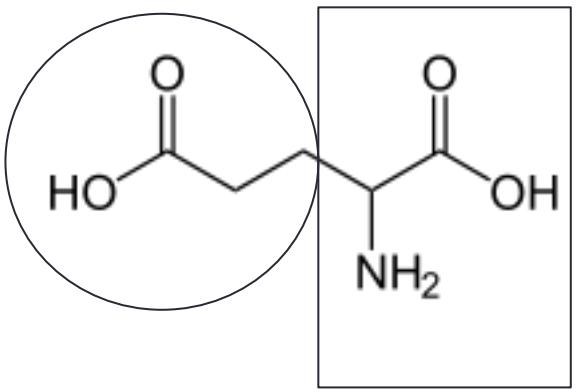
Contains Fe^{+2} at center, which carries oxygen

http://www.chemistry.wustl.edu/~edudev/LabTutorials/Hemoglobin/MetalComplexinBlood.html

Pathophysiology

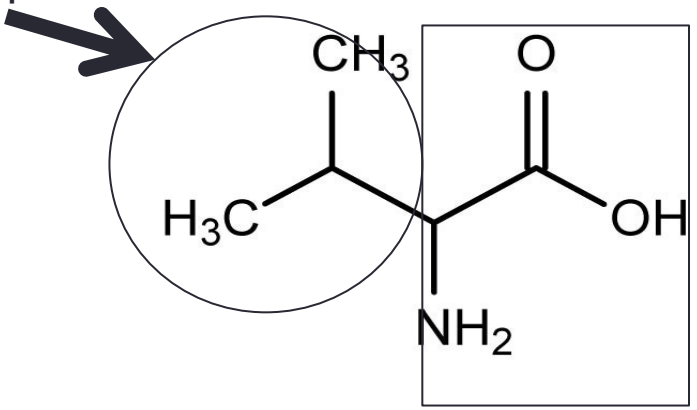
- Amino Acid chains in Hemoglobin differ by 1 amino acid

Normal Hbg



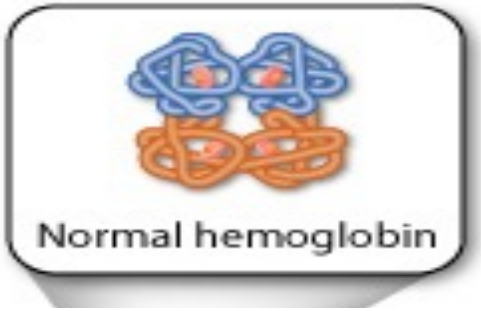
Hb in SCD

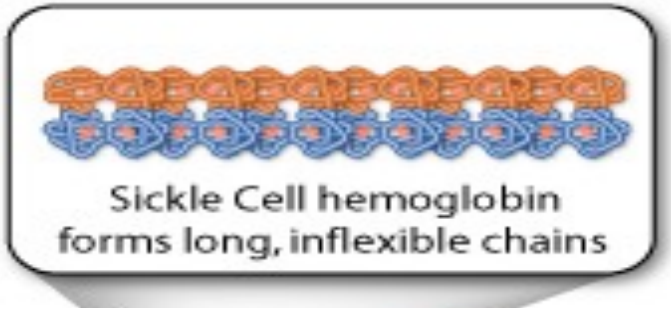
Makes more hydrophobic

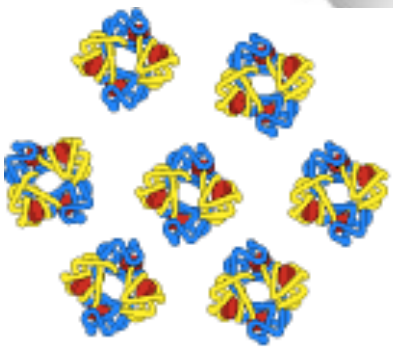


Pathophysiology

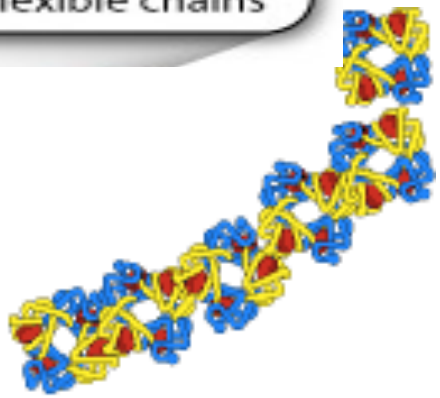
	Normal RBC	Sickled RBC
Hemoglobin Type	HbA	HbS
Solubility when oxygenated	(same)	(same)
Solubility when deoxygenated	---	Reduced (more hydrophobic) -mutant AA chains will cross-link together, forming long chains → polymerization → forms viscous, thick, semi-solid gel that protrudes into RBC membrane → RBC shape becomes distorted
Shape	Bio-concave ("doughnut w/o a hole")	Normal when oxygenated Sickle (crescent) when deoxygenated -But over time, becomes irreversibly sickled due to permanent damage to the cell membrane (phospholipids become permanently rearranged)
Deformability	High Can easily squeeze through capillaries	Low / non-flexible Can clog capillaries (capillary sludging)



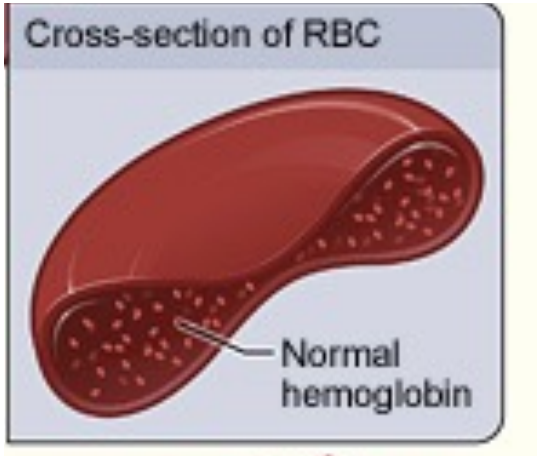


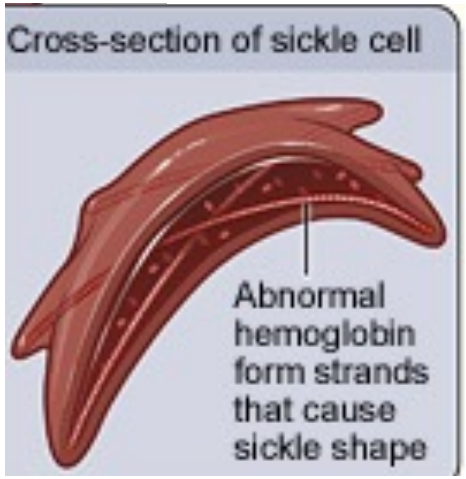


NORMAL
HEMOGLOBIN



CLUMPED
HEMOGLOBIN





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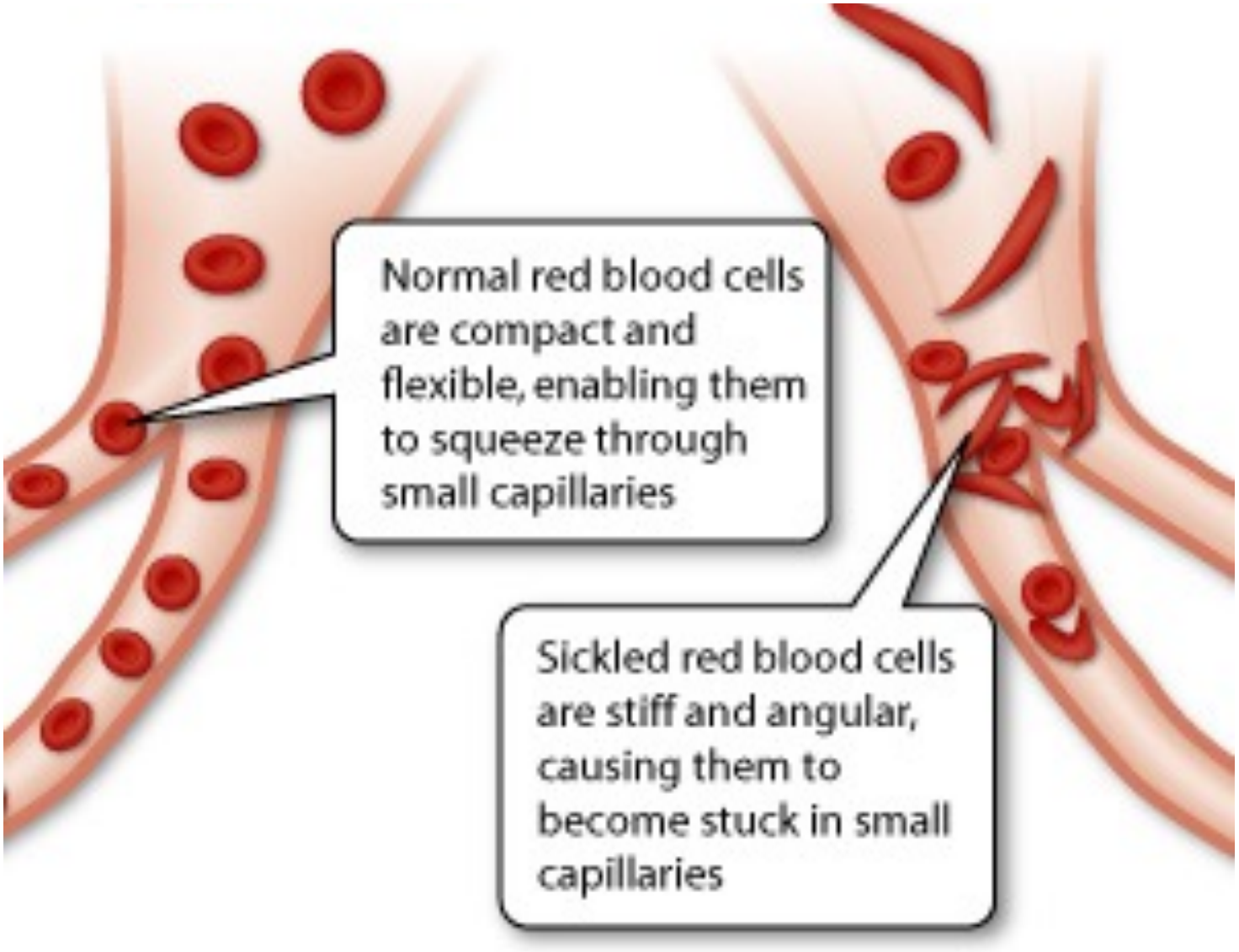
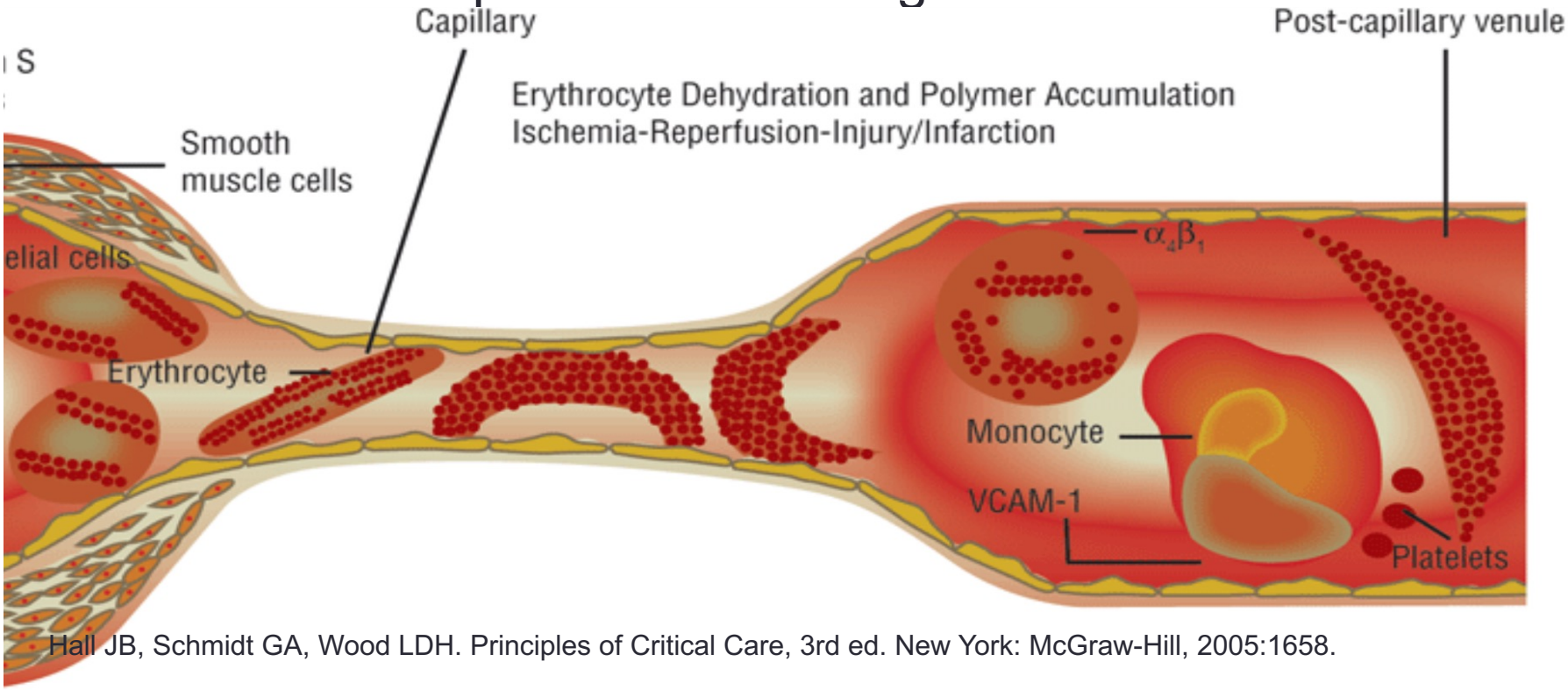
http://learn.genetics.utah.edu/units/disorders/whataregd/sicklecell/images/sicklecell.jpg



http://learn.genetics.utah.edu/units/disorders/whataregd/sicklecell/images/sicklecell.jpg

Pathophysiology

- HbS makes RBC sickled as it is deoxygenated in the capillary bed → sludging → local tissue hypoxia → pain
- The sickling is reversible at first, but ultimately becomes irreversible from permanent damage to RBC membrane



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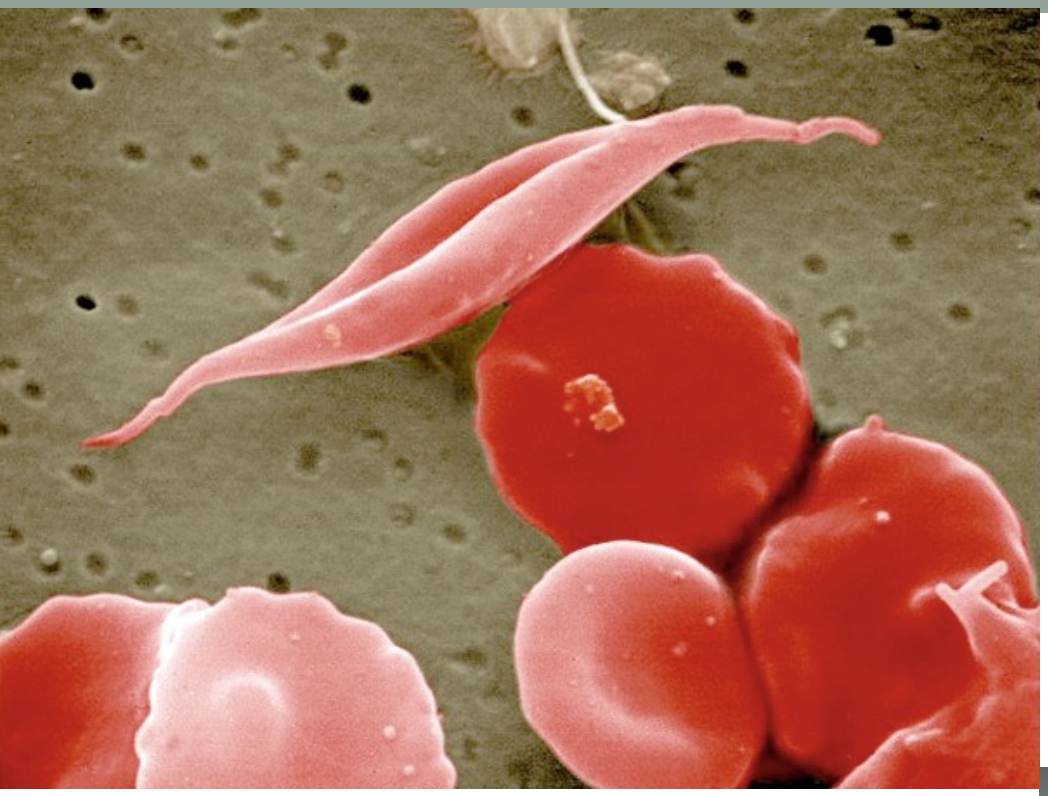
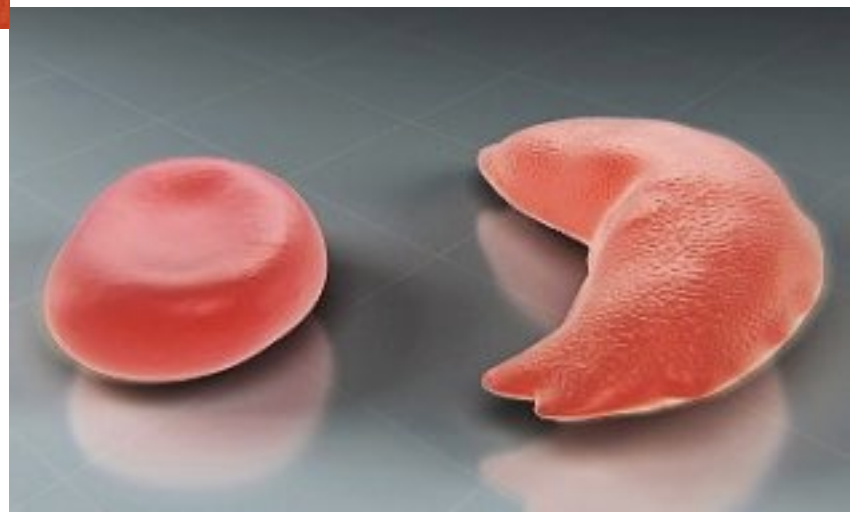
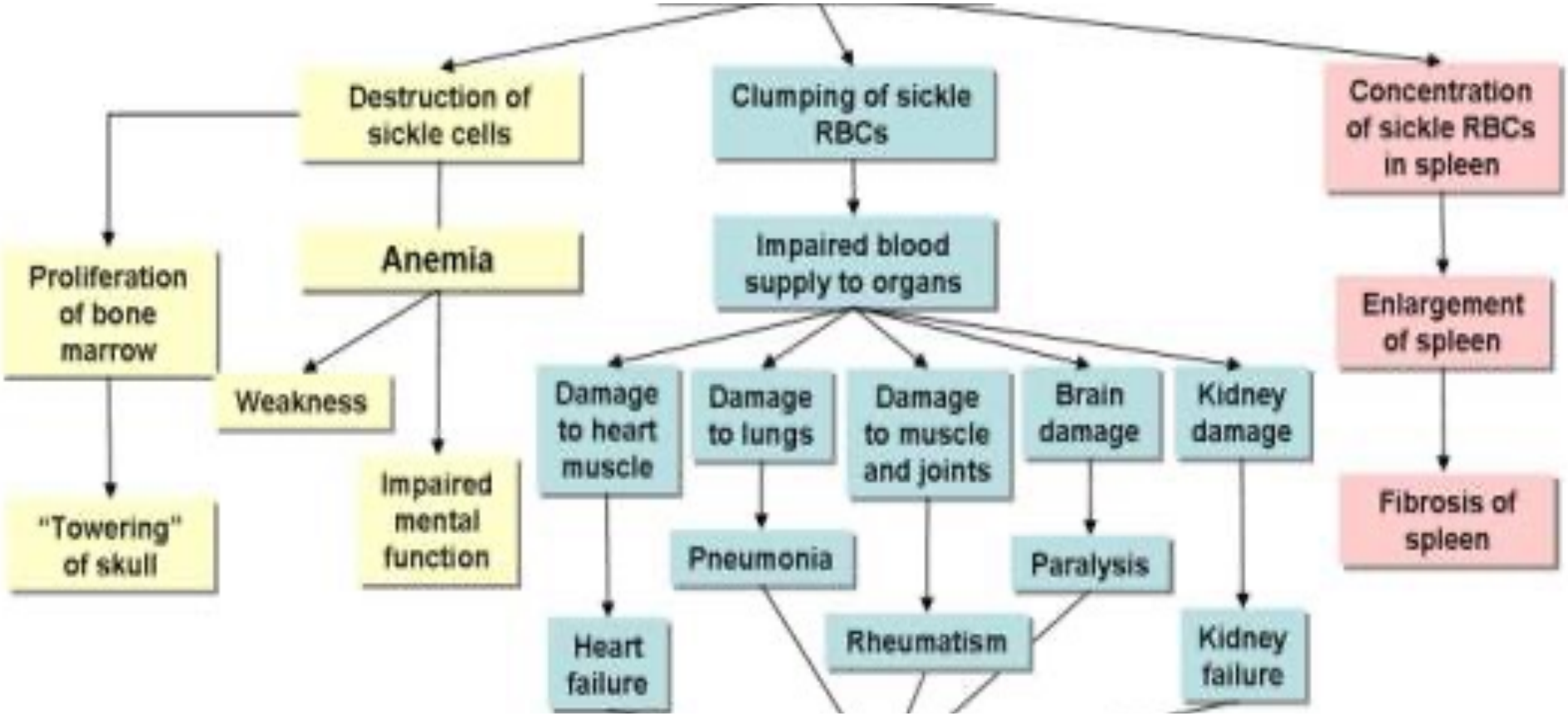




http://blackdoctor.org/category/health-conditions/sickle-cell-anemia/
http://www.jhunewsletter.com/2012/10/04/half-matched-bone-marrow-alleviates-sickle-cell-disease-32042/

Consequences of Sickling

	Normal RBC	Sickled RBC
Life Span	100-120 days	10-20 days



http://www.icagen.com/media/images/rd_sicklecell.jpg

Clinical Presentation[1]

- Deep, throbbing pain
- Local tenderness
- Erythema
- Swelling
- Fever
- Leukocytosis
- Jaundice and increased transaminases if liver is involved
- Increased fibrinogen levels
- Decreased serum pH
- Decreased bicarbonate

Diagnosis[1]

- Screening for SCD occurs at birth
- Laboratory findings of SCD
  - Anemia / Low Hbg (7-10 g/dL)
    - Hct 20-30%
  - Increased reticulocytes (immature RBC)
    - Reticulocytosis (3-15%)
  - Increased platelets
  - Increased WBC
  - Blood smear showing sickled forms
  - Markers of hemolysis
    - Increased Lactate Dehydrogenase (from hemolyzed RBC's)
    - Decreased haptoglobin
      - Binds to hemoglobin released during hemolysis
      - Undetectable levels (>7) almost always associated w/ hemolysis

Diagnosis, cont'd

- The acute pain crisis itself more a diagnosis of exclusion
  - No diagnostic test
  - Pain w/o any other explanation
  - Needle aspiration may be needed to r/o osteomyelitis[1]
  - Abdominal studies may be needed to r/o other causes of abdominal pain[1]
  - Cultures to r/o infectious trigger or cause[1]
  - Chest XR to r/o pneumonia, acute chest syndrome

- Laboratory values
  - Non-specific acute phase reactants can be elevated
    - CRP
    - LDH
  - Rabdomyolysis may be present
    - Elevated CK
      - Muscle ischemia from vasooclusion → releases muscle contents into circulation → elevated CK
      - Myoglobin also released → nephrotoxic

Goals of Therapy

- Relieve pain[2]
  - "Severe pain [in SCD acute pain crisis] should be considered a medical emergency that prompts timely and aggressive management."[2]
  - Treat aggressively
  - Tailor pain therapy to each patient
    - Consider medications and doses which provided relief during their previous episode
    - Consider medications they were taking at home for pain management
  - Reassess pain frequently
    - Before receiving medications
    - At the peak effect of the medication chosen
    - At frequent intervals
    - Relief could be defined as a reduction in intensity of at least 50-60%
    - Pain assessment tool
      - Choose one; none have been validated for sickle cell pain
  - Monitor for AE of pain medications
    - Opioids: Respiratory depression, sedation, itching, n/v, constipation
- Identify and treat precipitating factors when possible
  - Infx
  - Dehydration
  - Stress

Pharmacological Therapy

- IV Hydration
  - D5W + 1/2NS + 20 mEq KCl/L
  - Adjust for serum chemistry levels
  - Give at no more than 1.5 x maintenance requirement
    - Also consider fluids getting for other drug infusions
- IV Pain Medication
  - Should be started w/in 15-20 mins after arrival in ED[2]
  - Scheduled pain medication (avoid PRN only)[1]
  - Continuous infusion has advantage of less fluctuation in blood levels[1]
  - Use boluses or PCA for break-through pain[1]
- Blood transfusion if the pt also presents w/ anemia
  - Transfuse to maintain the Hbg level at pt's baseline

Pharmacological Therapy, cont'd

- Suggested pain medications[1,2]
- If on scheduled and pt experiences break-through pain:[1]
  - Give ¼ - ½ of the scheduled dose as a bolus q1-2 hrs
  - Assess the amt of rescue doses used in 8-12 hrs and readjust scheduled dose or infusion rate as needed

	mg/Dose	Continuous Infusion (mg/kg/hr)	PCA
Morphine	5-10 q2-4 hr	0.04-0.05 Titrate to effect	Basal: 0.01-0.03 mg/hr Demand: 0.01-0.03 mg/kg q6-10 mins 4-hr lock out: 0.4-0.6 mg/kg
Hydromorphone	1.5-2 q3-4 hr	0.004 Titrate to effect	Basal: 0.003-0.005 mg/kg/hr Demand: 0.03-0.05 mg/kg q6-10 mins 4-hr lock out: 0.06-0.08 mg/kg
Ketorolac	0.5 – 30 q6h **NO MORE THAN 5 DAYS		

Pharmacological Therapy, cont'd

- 3 Approaches to pain management suggested in guidelines:
  - One Approach = Aggressive Approach:
    - Give loading dose (ex: 5-10 mg morphine)
    - Reassess pain in 15-30 mins
    - If no relief, give bolus = ¼ - ½ of loading dose given
    - Reassess again in 15-30 mins
    - If no relief, repeat w/ another bolus
    - Once relief is achieved, maintain relief w/ around-the-clock / scheduled dosing
    - Set rescue dose at approx. ½ of maintenance dose for break-through pain
    - Adjust maintenance dose based on number of rescue doses needed

Pharmacological Therapy, cont'd

- Stimulant / Stool Softener
- Antihistamines for itching
- Antiemetics for n/v

Non-pharmacological Therapy

- Prevention[3]
  - Drink plenty of water
  - Avoid extremes in temperature
  - Avoid areas of low oxygen (mountain climbing, flying)
  - Avoid extremely strenuous exercise

- Hydroxyurea
  - Shown to significantly reduce frequency of acute pain episodes in SCD patients[1,2]
    - MSH Trial (Multicenter Study of Hydroxyurea in Sickle Cell Anemia)
  - FDA approved for this purpose
  - Indication: frequent painful episodes in SCD
  - Starting dose = 10-15 mg/kg QD (titrate up q8-12 weeks to max tolerated; max=35 mg/kg/day)
  - Takes 3-6 months for effect
  - MOA: induces production of fetal Hb (HbF); has antineoplastic activity (cytotoxic effect in the bone marrow)
  - AE: bone marrow suppression (blood counts must be monitored q2 weeks at first)

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