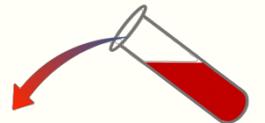


Sickle Cell Anemia

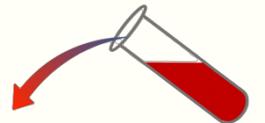
Thomas Harrington, MD
University of Miami/Jackson Medical Center
Miami, FL

tharring@miami.edu



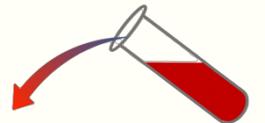
Disclosures

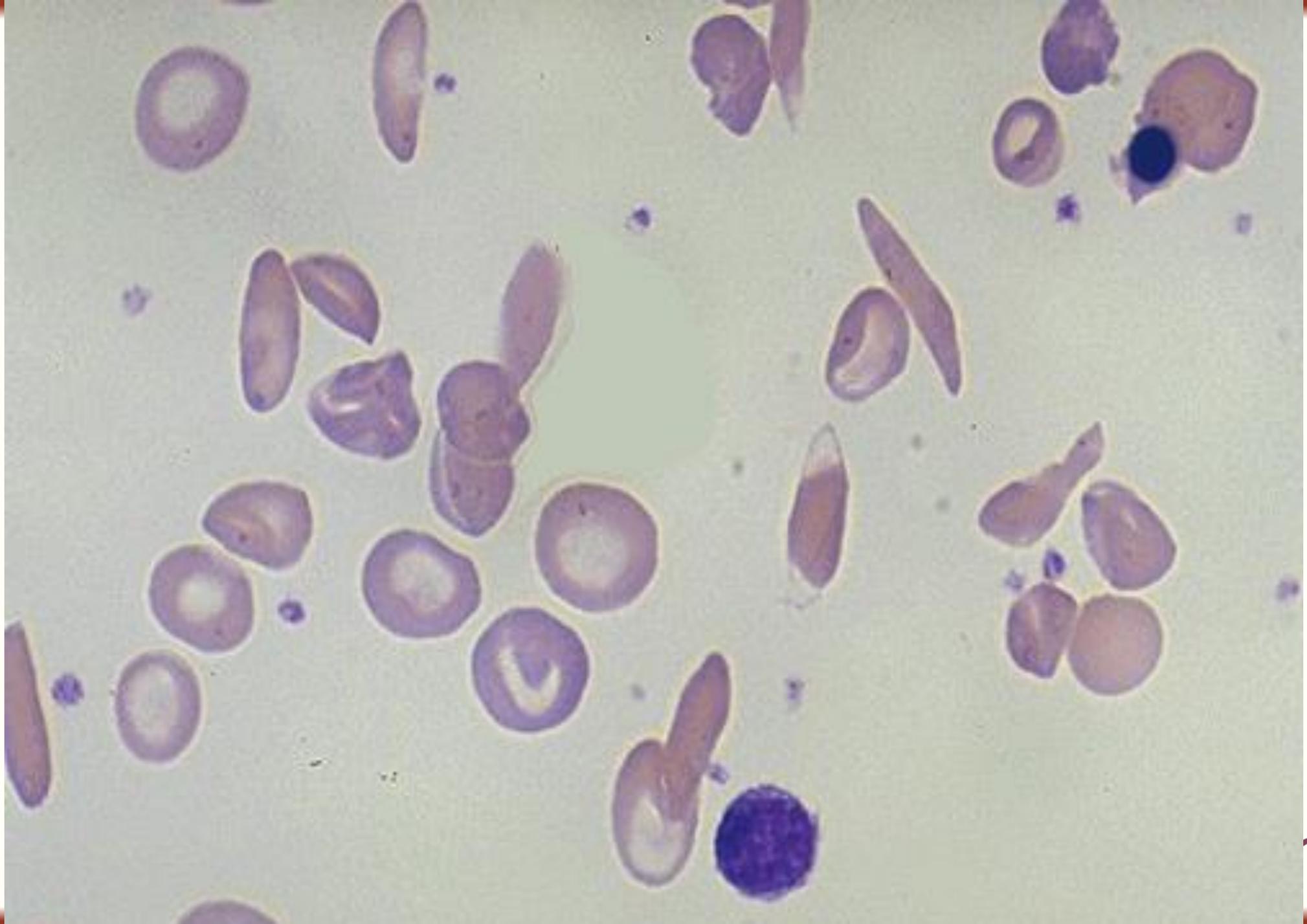
➤ None



Topics to Cover

- Origin
- Pathophysiology
- Clinical manifestations acute and chronic
- Therapeutic interventions
- Future prospects

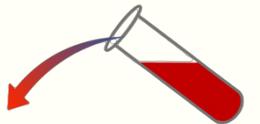
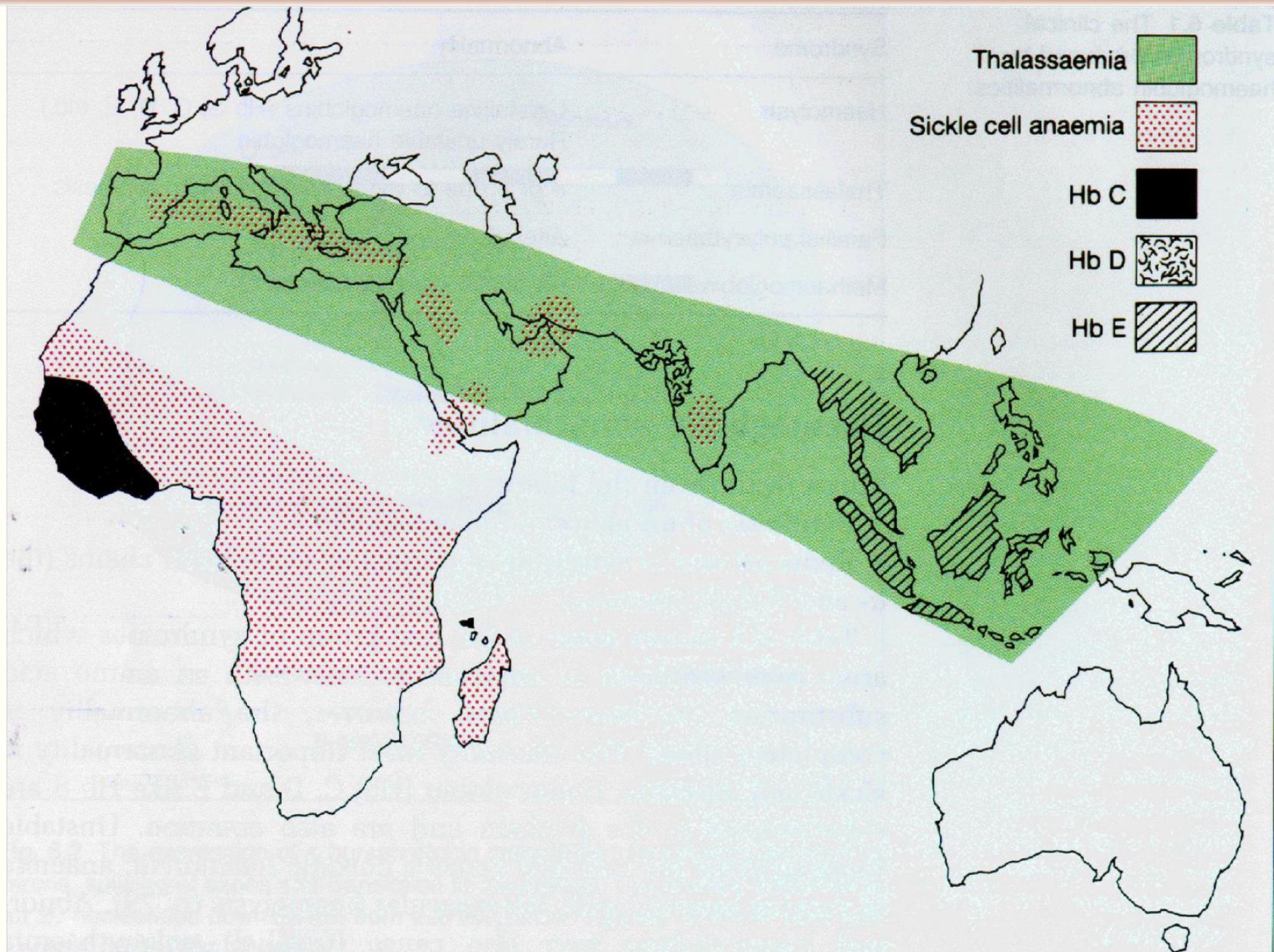




RED CELL DISORDERS COMMON IN HIGH MALARIA ZONES

- RBC disorders G6PD deficiency, **Duffy (-)**, etc.
- HEMOGLOBIN DISORDERS
 - Heterozygous (trait) have survival advantage**
 - Hemoglobin S has variants by locale (Africa, India, Middle East, Central and So. America by forced migration) and C (mainly West Africa)
- Thalassemic Disorders
 - Alpha and Beta thalassemia
 - Hemoglobin E (Far East and Asia) - hybrid





Sickle Cell

Most common inherited disorder in USA

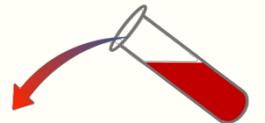
-100,000 Americans

1 in 500 African- American (8-10% trait)

1 in 1500 – 36,000 Hispanic-American

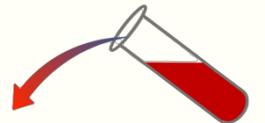
Trait is 25% in parts of Africa, India and Haiti

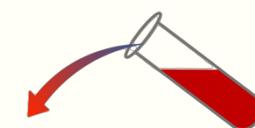
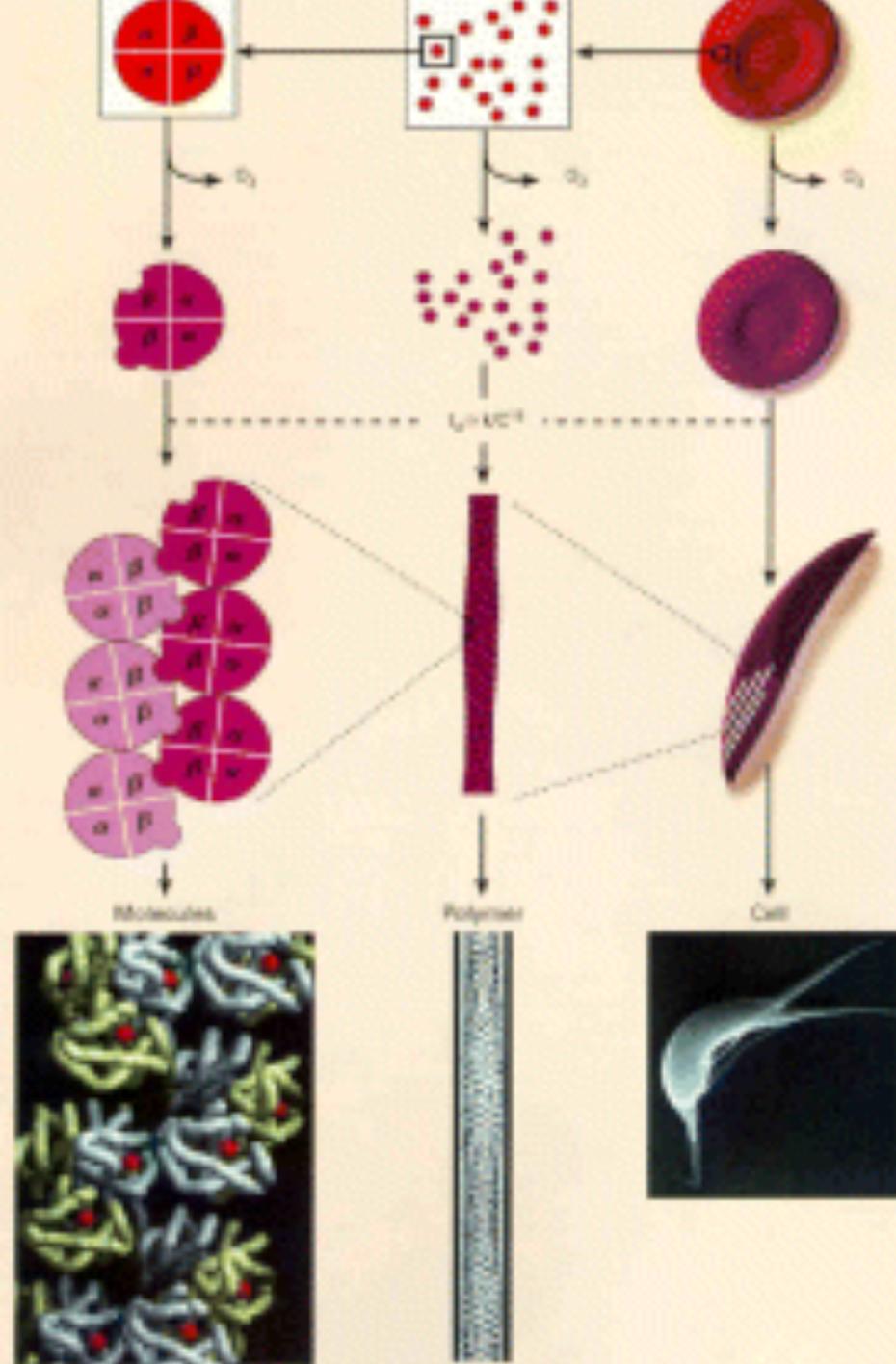
*Regions like the Caribbean, Brazil and South Florida with high rates of mixed ancestry, have more widely dispersed trait, also high incidence of disease in those of predominately African ancestry.



Sickle Cell

- Genetic defect (beta globin gene - glu6val)
clinical course affected by remaining genetic make-up - vascular, immune, etc.
 - Homozygous SS
 - Compound Heterozygous
 - SC (glu6lys) and Sbthal+ and Sbthal 0 and others
- Modifiers are innumerable
 - Fetal hgb - several known variants
 - Alpha-thal trait - up to 30% in sickle-prone populations
 - Inflammatory and immune response genes

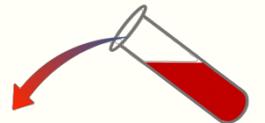


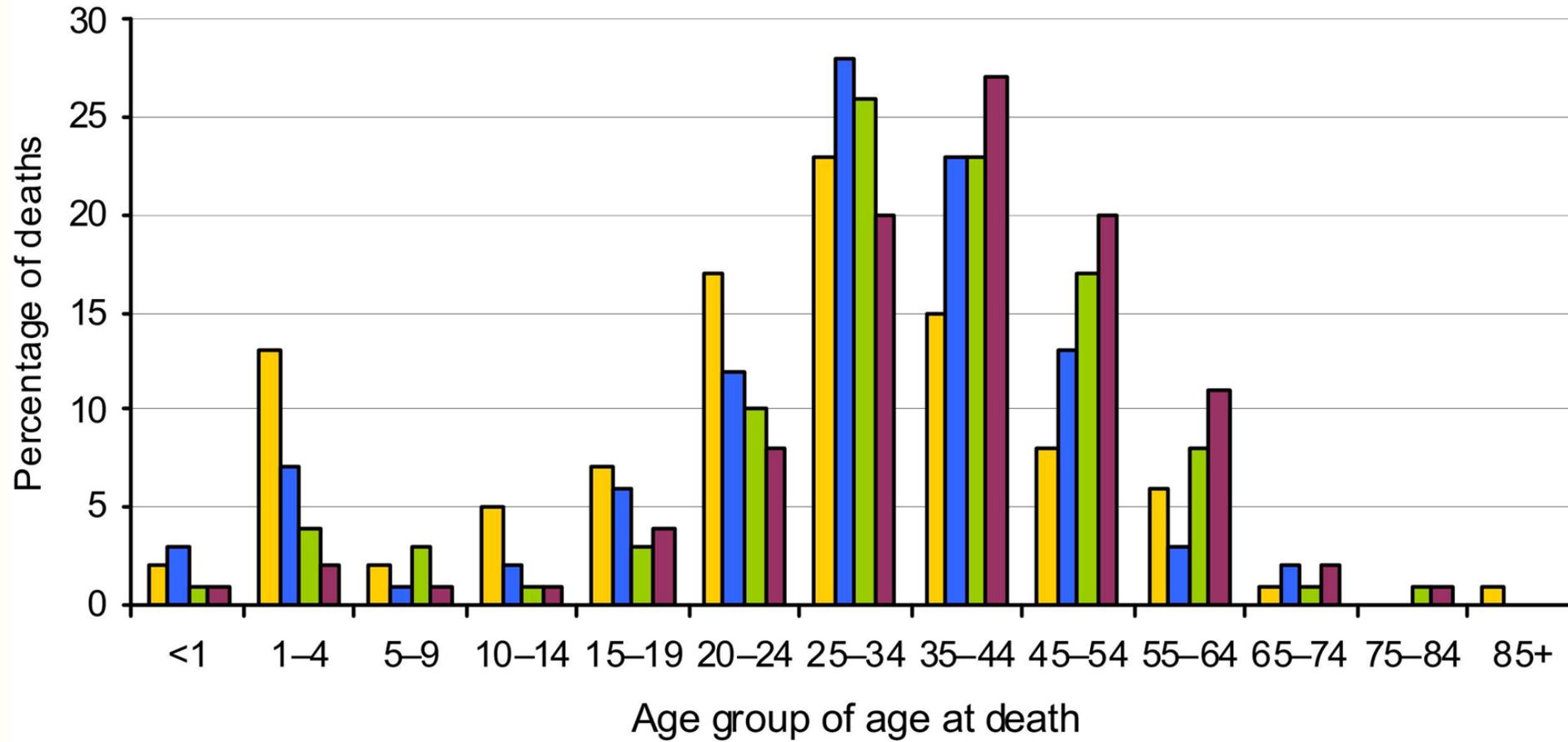


Improvements in Early Mortality

Childhood interventions preventing early mortality and morbidity

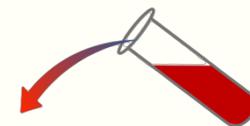
- Penicillin prophylaxis prevents early pneumococcal sepsis
- TCD to assess stroke risk >> primary transfusion regimen
- Hydroxyurea found to be safe and effective (BabyHUG study)
- Universal newborn screening – though many born in high-risk countries had no screening or born in US but unaware of their results





■ 1979 (n=301)
 ■ 1989 (n=389)
 ■ 1999 (n=503)
 ■ 2006 (n=483)

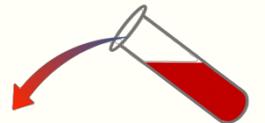
Hassell, AJPM VOLUME 38, ISSUE 4, SUPPLEMENT , S512-S521, APRIL 01, 2010

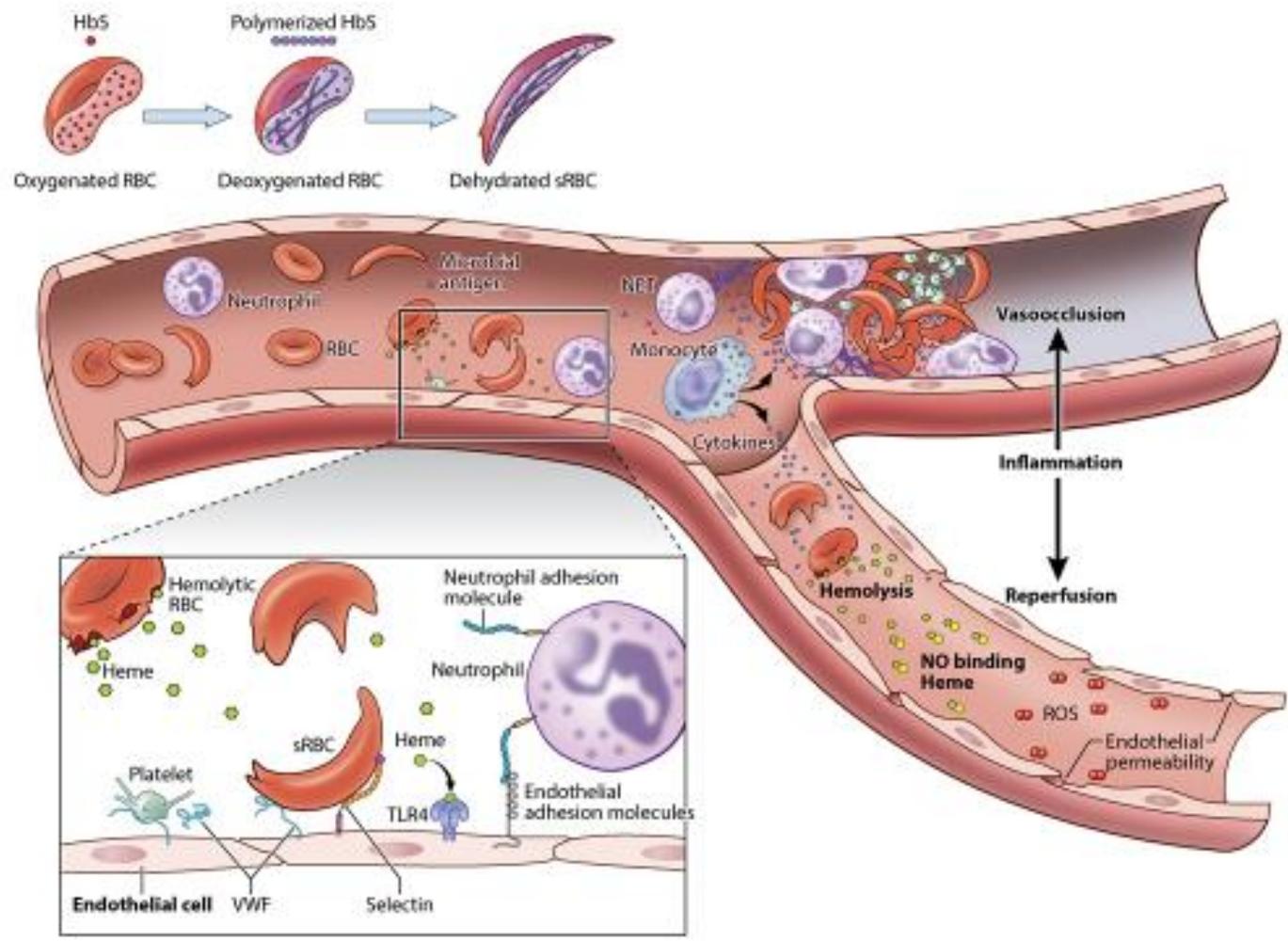


SICKLE CELL IS A VASCULAR DISEASE

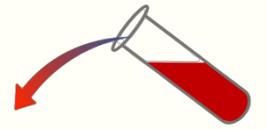
- Damage to endothelial cells (EC) with increased adherence
- Upregulated inflammation and oxidation
- Impaired vasodilation
- Prothrombotic - high FVIII and thrombin generation and low protein S (likely bound to free RBC membranes)

- Circulating ECs, platelet and RBC microparticles
- Neutrophil activation - NETosis



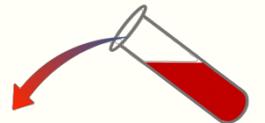


Williams TN, Thien SL. 2016. *Annu. Rev. Genom. Hum. Genet.* 19:113-47



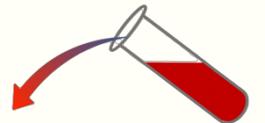
Impaired Nitric Oxide Vasodilation

- Free hemoglobin
 - Binds and clears nitric oxide (NO)
- Lysed RBC release arginases that consume arginine, the substrate of nitric oxide synthesis i.e. lowering NO production

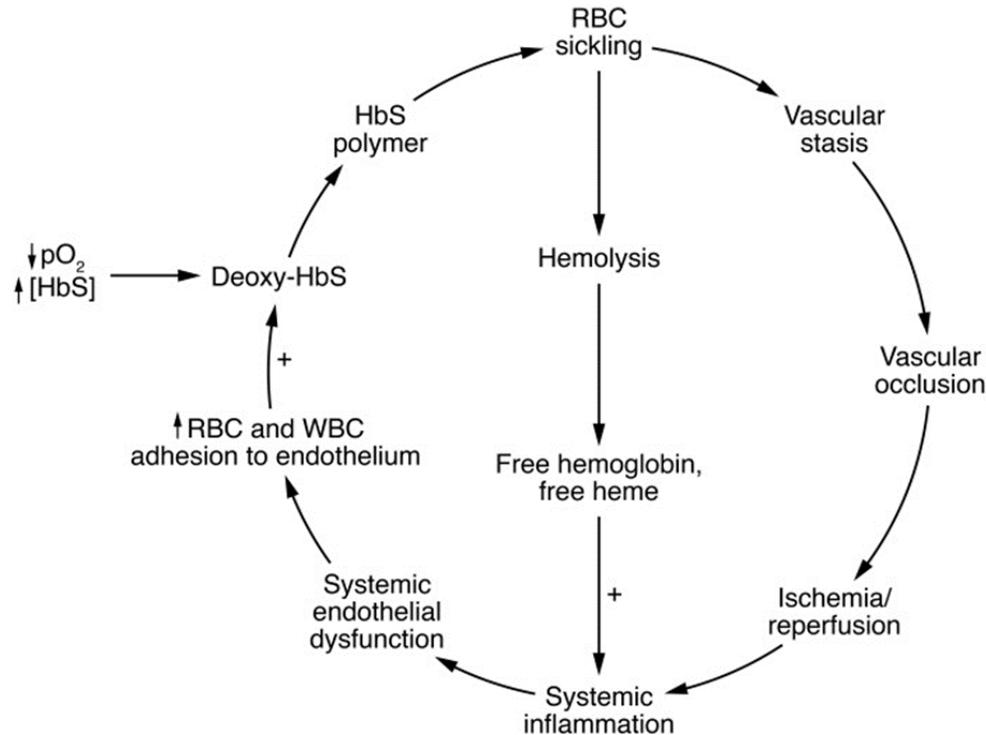


Activated Endothelial Cells

- Increased expression of activation molecules (and neutrophils)
 - P-Selectin
 - Tissue factor
 - VCAM
 - ICAM
 - PECAM
 - Alpha-4 beta-1 integrin
 - Neutrophil extracellular traps - NETs
 - others

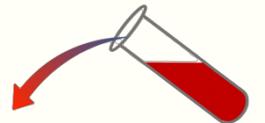


Vicious Cycle of Ischemia Reperfusion



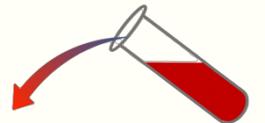
- Direct vascular injury
- Altered endothelial membranes
- Inflammation (WBC, platelets)
- Vasoconstriction
- Impaired vasodilation
- Ischemia/reperfusion

Hebbel, Belcher, Vercelotti, J Clin Invest. 2020 Mar 2; 130(3): 1062–1072.



Factors That Increase Sickling

- Deoxygenated hemoglobin S polymerizes
 - Hypoxia
 - Acidosis
 - Increased 2,3 BPG reduces O₂ affinity
- Higher intracellular hemoglobin concentration
 - RBC dehydration (increases intracellular Hgb concentration)
 - Loss of intracellular water/cations from RBC membrane damage

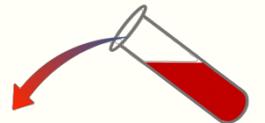


Hemoglobin SC

- Milder anemia due to lower hemolytic rate
- Form less typical sickle-shape, but still causes marked membrane damage leading to vascular injury/inflammation
- Higher rate of retinopathy than SS- eye exams essential
- May be mistakenly labeled “TRAIT” only, delaying care

- Higher hemoglobin associated with bone infarcts/necrosis

- Higher rate of marrow fat embolism



Sickle Cell Trait

- Generally benign with similar lifespan to unaffected people
- Several problems can be seen
 - Hyposthenuria due to ischemic injury in renal medulla where hyperosmolar gradient can cause sickling
 - Renal papillary necrosis
 - Priapism
- **Sickling occasionally experienced at high altitude or hypoxic/acidotic conditions such as anaerobic exercise/stress (athletes/boot camp)**
- Higher risk of DVT
- Renal Medullary Carcinoma is highly lethal and mainly in S trait characterized by the loss of SMARCB1, a tumor suppressor gene, probably from repeated hypoxic injury and repair



ER Management

- Rapid evaluation and treatment
- Familiarity with Sickle Cell problems
 - Pain
 - Infections
 - Other complications
- Smooth transition once admitted
- Trust – both patients and providers –listen to the patient!

- They are NOT “drug-seekers”
- Addiction is relatively RARE but tolerance occurs



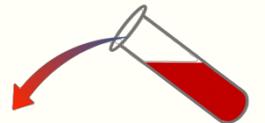
Psychological effects

- Depression is very common due to: HRQOL often very poor
 - Unpredictable pain and other complications
 - Fatigue from anemia and poor sleep
 - Loss of function from bone damage, stroke, vision loss
- Distrust of “care givers” who doubt their symptoms or judge them differently from other medical conditions
- Isolation - perceived or self-imposed
- Stigmatized
- Guilt due to effects on family and friends



Acute Vascular Events

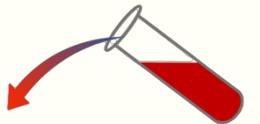
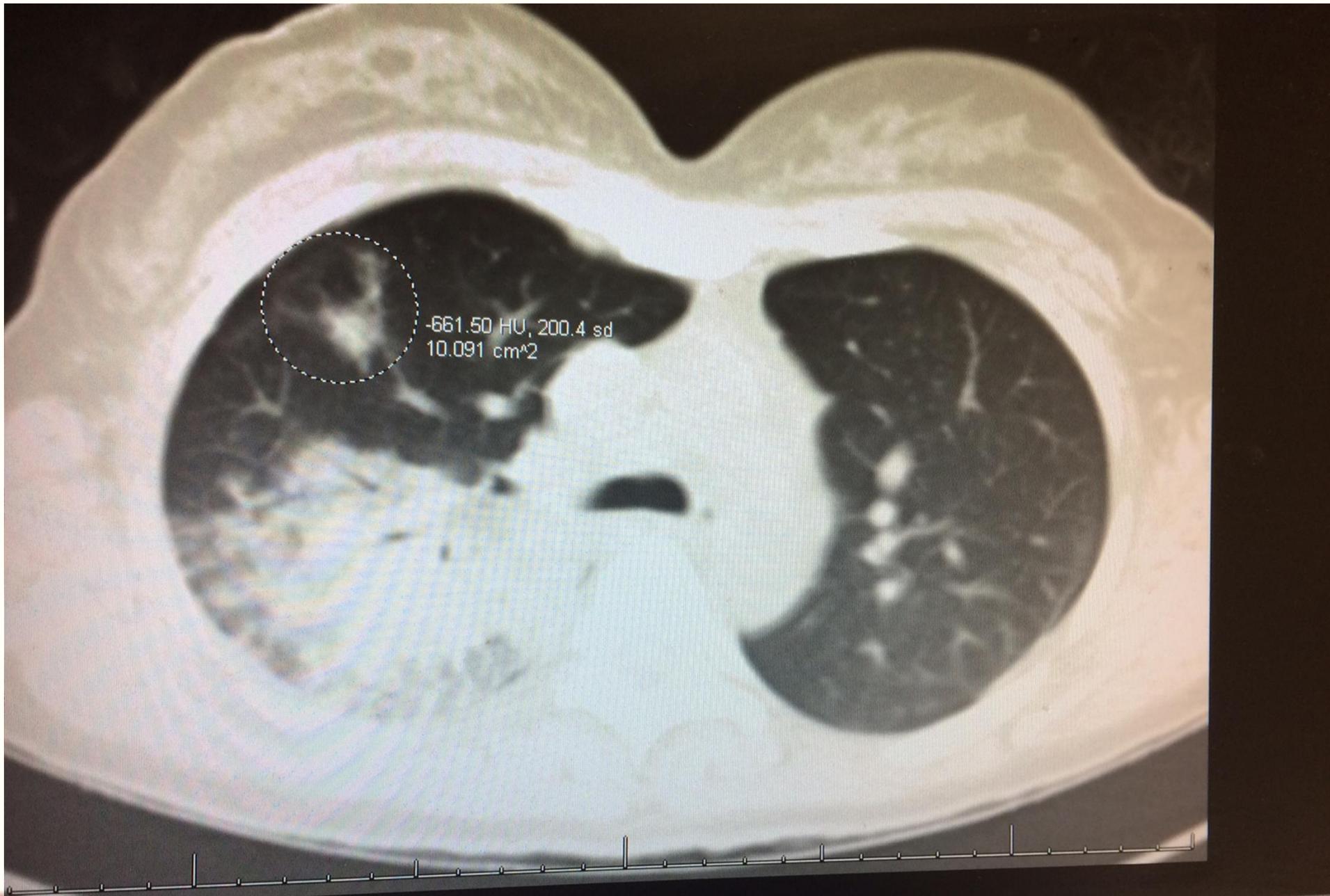
- Bone (marrow) ischemia -“crises”
- Acute chest syndrome*
- Stroke*
- Multi-organ failure syndrome*
- Priapism
- Acute hemolytic episode due to hypoxia, infection, etc.

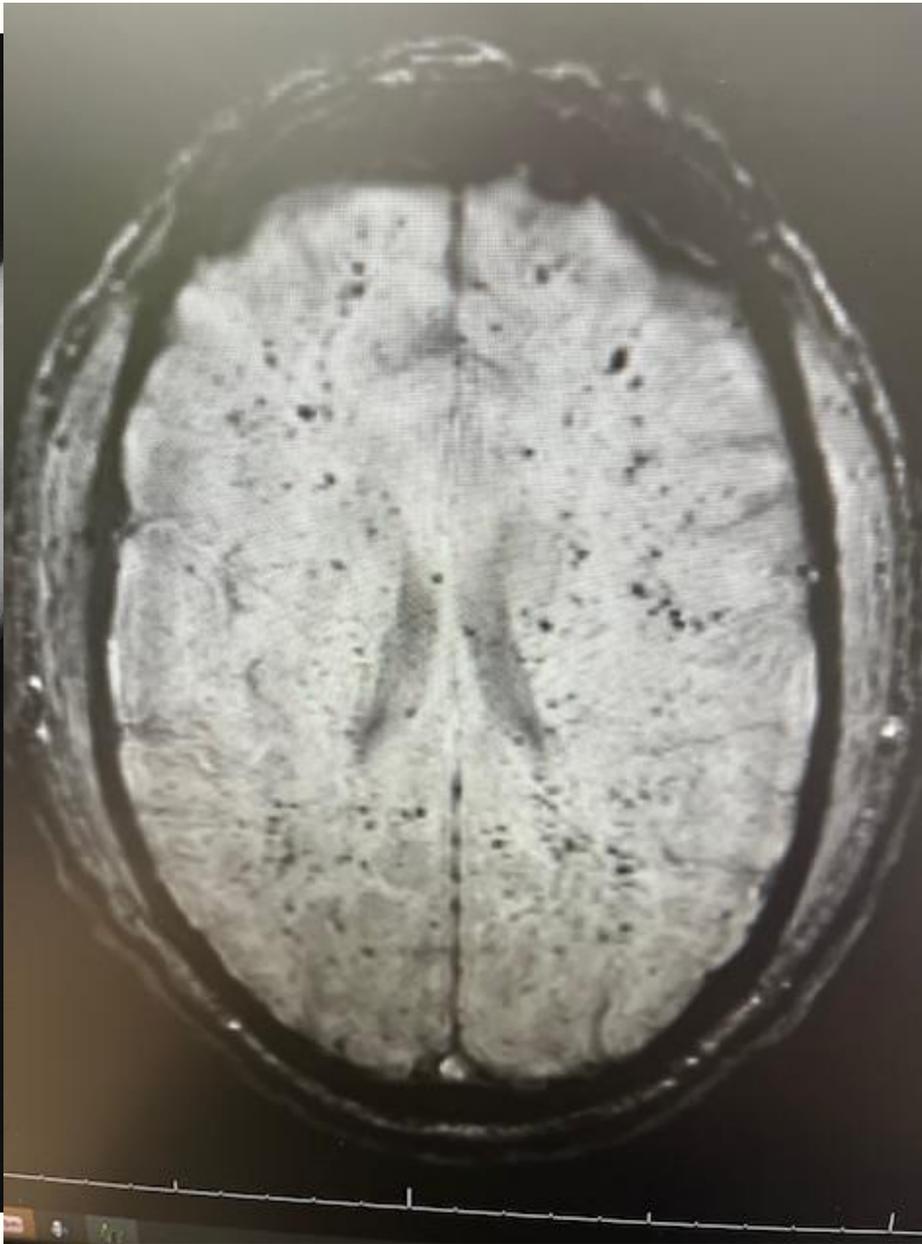
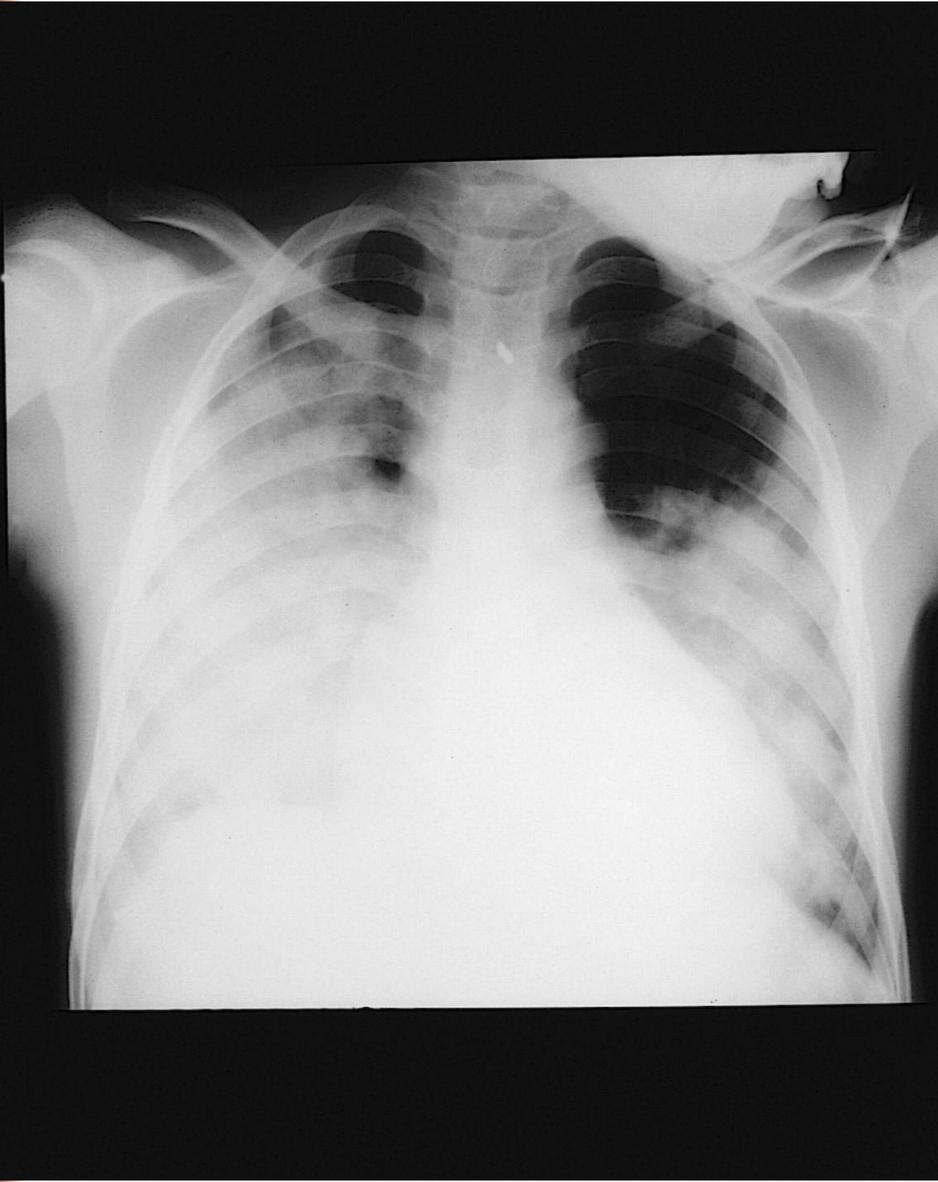


ACUTE CHEST SYNDROME

- MOST COMMON CAUSE OF DEATH
- Mostly pneumonia in children but also adults
 - Chlamydia, mycoplasma, pneumococcus, viral, etc.
- Lung infarcts, rib infarcts and thrombi are increasingly common in adults, though infection is still the most common cause
- **Bone marrow fat embolus from infarcts of the large marrow-containing bones – typically follows severe bone pain, is multilobar and often with AMS/neurologic symptoms, may be rapidly fatal**
- **Can be result of Parvo-B19 causing acute marrow necrosis**

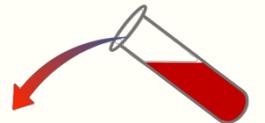






Marrow fat embolism Syndrome

- Often presents with no respiratory signs
- Excruciating pain
- Progressing to severe multilobar pneumonia in 12-48 hours
- CNS symptoms from AMS to coma
- Treat with RBCX and PLEX and steroids should be considered.



OTHER ACUTE VASCULAR COMPLICATIONS

- Stroke is usually ischemic, though adults may also have bleeds. These may be from prior CVAs that lead to Moya Moya vasculopathy
- Acute retinal hemorrhage (SC>SS) ischemia or detachment
- Ischemic (“low flow”) Priapism – very painful and may cause impotence if inadequately managed
 - Etilefrine α 1 agonist intracavernous injection in ER
 - Surgical shunt – Winter procedure
 - Prophylaxis – pseudoephedrine, terbutaline, sildenafil and anti-androgens



Renal Complications

- Isosthenuria – concentration defect caused by ischemia of medullary kidney is universal, even seen in Sickle trait
- Progressive renal damage usually starts with proteinuria
- Renal papillary necrosis – acute ischemic necrosis presents as significant hematuria and typically quite painful
- *Medullary carcinoma of the kidney seen mainly in trait and is highly aggressive, lethal cancer. Probably associated with ischemic injury



Transfusion Indications

- ***Check the patient/vitals - Daily labs should be avoided**
They can be difficult and disrupt sleep as often lead to unnecessary transfusions (iron overload, alloimmunization)
- Simple transfusion of **one unit** is often effective
(recommended guideline)
- Regular **transfusion protocol** after stroke (esp. children)
 - May also be appropriate for:
 - **Severe pulmonary hypertension**
 - non-healing **malleolar ulcers**
 - **recurrent ACS or VOCs** unresponsive to Hydrea, etc
 - Also as primary prophylaxis in children with high TCD speeds in MCA



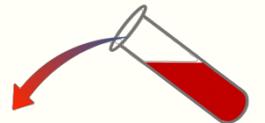
Exchange Transfusion

- Acute Indications:
 - Severe acute chest syndrome (ACS) – severe respiratory distress
 - Stroke
 - Multi-organ failure – may result from ACS or Fat Embolism
- Dialysis-type access
- Chronic indications
 - May be used for iron-overloaded patients and transfusion indication. Including chronic recurring VOC/ACS.



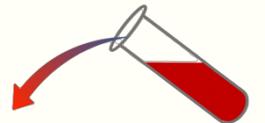
Chelation

- Major problem - compliance with therapies is generally poor (this often starts in childhood post-CVA)
 - Deferoxamine - parenteral SQ/IV slow daily infusion - Oto and ocular toxicity
 - Deferasirox (Exjade/Jadenu) oral – GI and renal toxicity
 - Deferiprone – marrow toxicity (esp ANC)



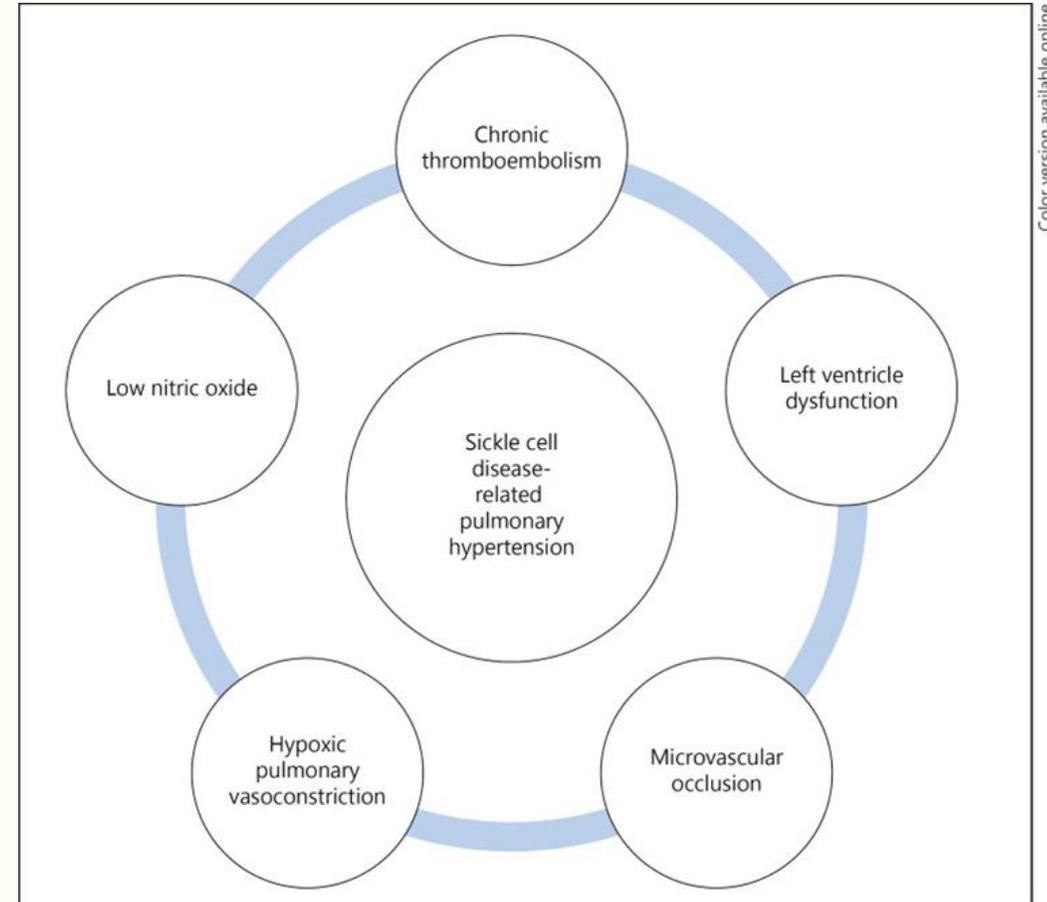
Chronic Vascular Events

- Pulmonary hypertension
- Avascular necrosis (esp. hip and shoulder)
- Retinopathy (SC>>SS)
- Lower extremity **malleolar ulcers** (can occur with **Hydrea** use)
- Renal dysfunction – proteinuria to ESRD
- Cardiac and CNS ischemia (silent strokes are common)

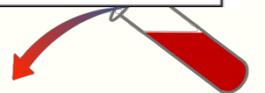


PULMONARY HYPERTENSION

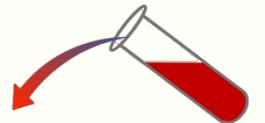
- Serious (often silent) complication but DOE is usual
- Screening echo (ideally confirmed with RHC)
- Multifactorial (both pre and post-capillary factors)
 - Vessel hypertrophy and fibrosis, thrombosis
 - Recurrent infarcts and pneumonia
 - Loss of vasodilator, nitric oxide
- Transfusion and Hydreia generally 1st line
- Sildenafil therapy has been disappointing
- ET1 antagonist
- Prostacyclin
 - N Engl J Med. 2011 Jul 7;365(1):44-53
 - European Respiratory Journal 2012 39: 112-118;
 - Pulse (Basel). 2021 Sep 23;9(3-4):57-63



Color version available online

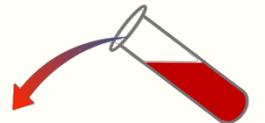


AVASCULAR NECROSIS (AVN)



RETINOPATHY

- Hydroxyurea resulting in high HgbF levels decreases incidence and progression of retinopathy
- Proliferative retinopathy typically treated with **laser** photocoagulation and may respond to VEGF inhibitors
- Retinal detachment may require more invasive measures



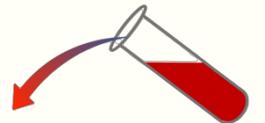
**Chronic, painful and relapsing –
aggressive wound care,
transfusion and possibly
voxelator**



CHRONIC GENITOURINARY COMPLICATIONS

- Hyposthenuria – intramedullary sickling
- Hematuria and renal papillary necrosis
- Type IV RTA with hyperkalemia

- MYH9 and APOL1 genetic markers
- Proteinuria an early marker for future CKD



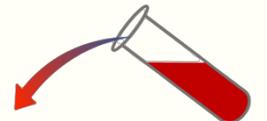
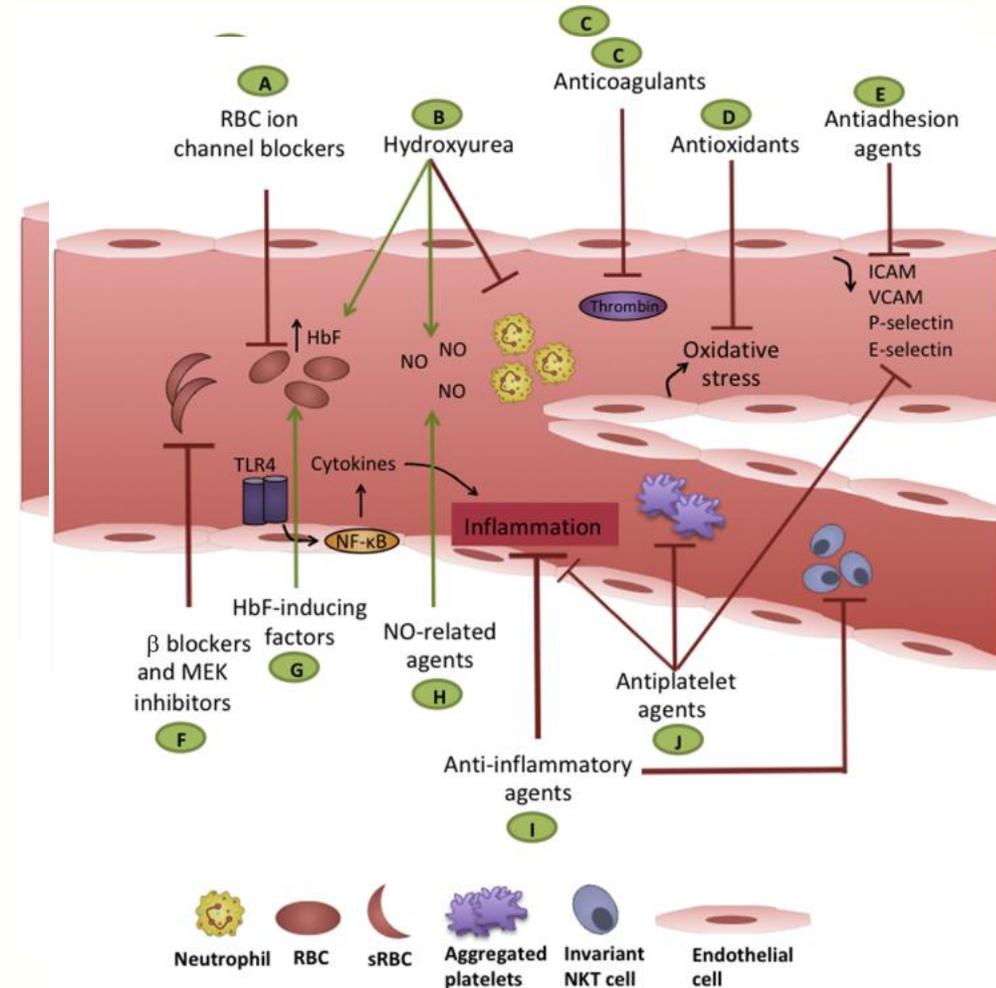
Therapeutic targets in sickle cell

- Fetal hemoglobin induction
- Antioxidants
- Blocking adhesion molecules
- Anti-inflammatory**
- Altering hemoglobin O2 affinity

Not effective so far

- NO inducers
- RBC ion channel blockers
- Anti-platelet agents and anticoagulants

Ansari and Gavins, Am J Pathol. 2019 Apr; 189(4): 706–718.



Hydroxyurea

- Increases fetal hemoglobin
- Decreases RBC – blood vessel adhesion*
- Less crises, less ACS, increased total hemoglobin and **prolongs life**
- **Precautions**
 - Bone marrow suppression, lowers retic count* and titrate to modest neutropenia*
 - Use effective birth control - theoretical mutagen though not associated with significant risk of malignancy in SS and is now given to babies



RECENTLY APPROVED MEDICAL THERAPY

- Crizanlizumab - P-selectin blocking MoAb

- N Engl J Med. 2017 Feb 2;376(5):429-439

- L-Glutamine (Endari) antioxidant amino acid

Voxelotor (Oxbryta) small molecule that increased Hgb O₂ affinity causing less hemolysis

***removed due to higher death rate in follow-up studies

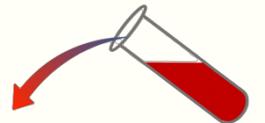
- Statins – small studies, but known to decrease inflammatory markers and NETs

- Blood. 2004;104:840–846 Minnesota
 - Haematologica. 2011 Apr;96(4):526-33. Campinas
 - Br J Haematol. 2017 May; 177(4): 620–629 Oakland
 - Pediatr Blood Cancer . 2013 Apr;60(4):550-7
 - Cytokine. 2019 Nov 25;127:154933



Some Current Studies

- Pyruvate kinase activators (boost ATP and lower 2,3 BPG)
 - Decitabine bound to THU – long-acting HgbF inducer
 - Rilzabrutinib BTK inhibitor and other drugs that target immune response to decrease NETosis/inflammatory state
-
- Hemopexin - binds and clears free hemoglobin



Crizanlizumab/Adakveo - Sustain Trial

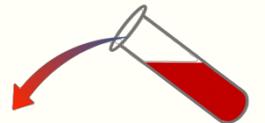
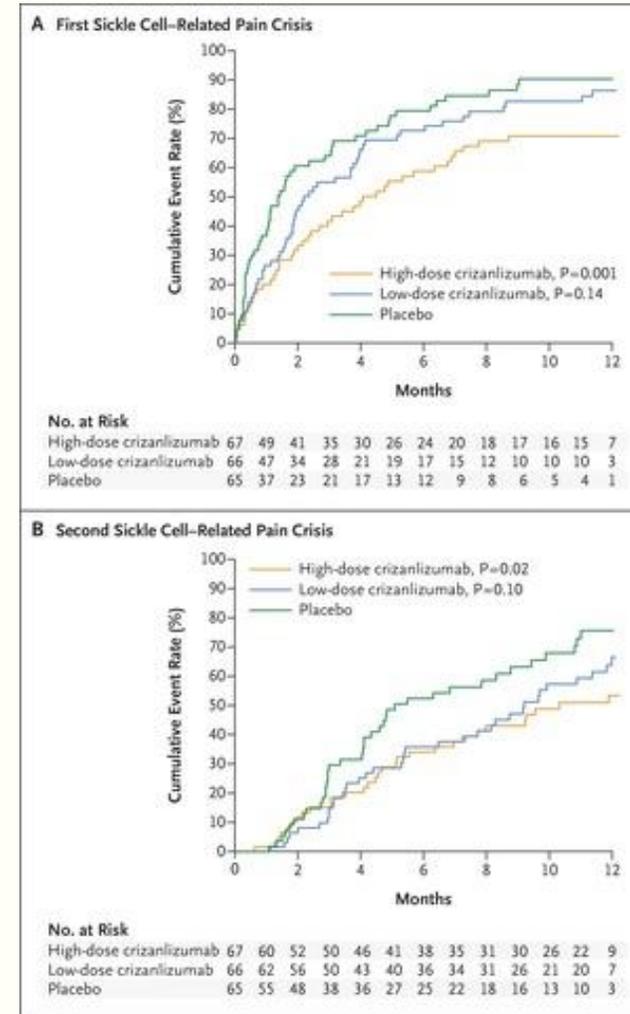
**P-selectin blocking MoAb given
monthly as prophylaxis, decreased VOC
by 45%**

N Engl J Med

2017; 376:429-439 Ataga, et al

- P-selectin found in storage granules of resting ECs and platelets
- Transferred to the cell membrane on activation of the cell inflammation
- Binds neutrophils and platelets inducing adhesion to sickle RBCs and vascular occlusion

**Rivipansel a pan-selectin blocker to be
tried for acute VOC management – but
results were negative**

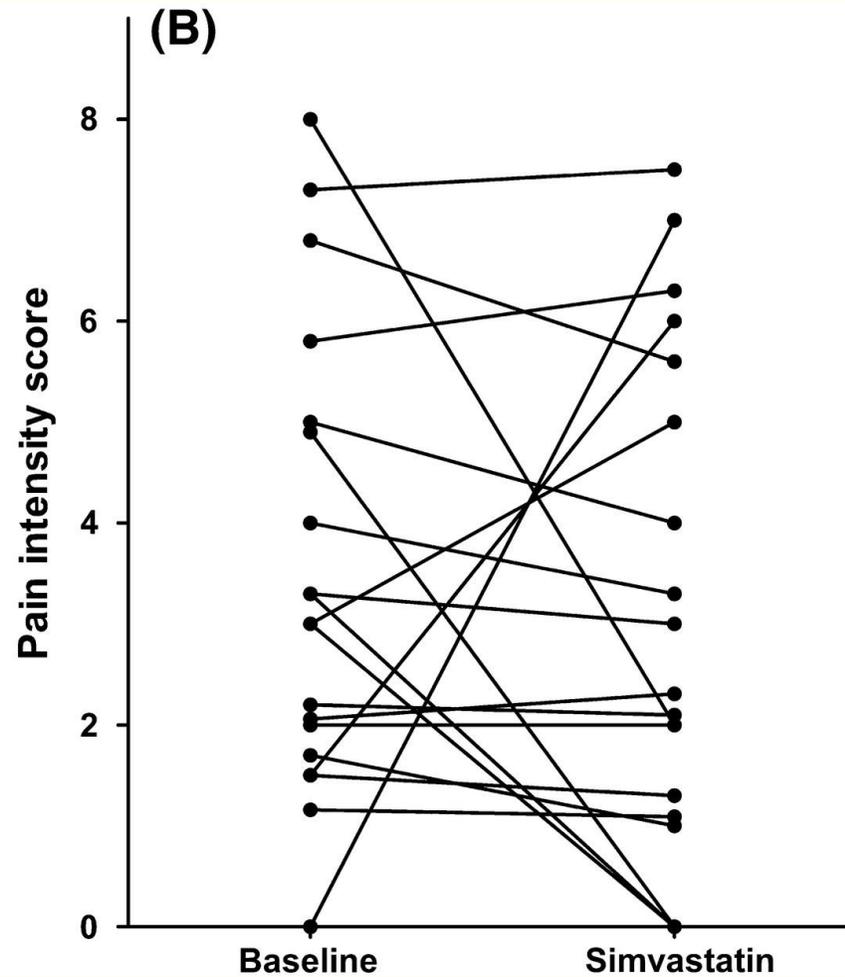
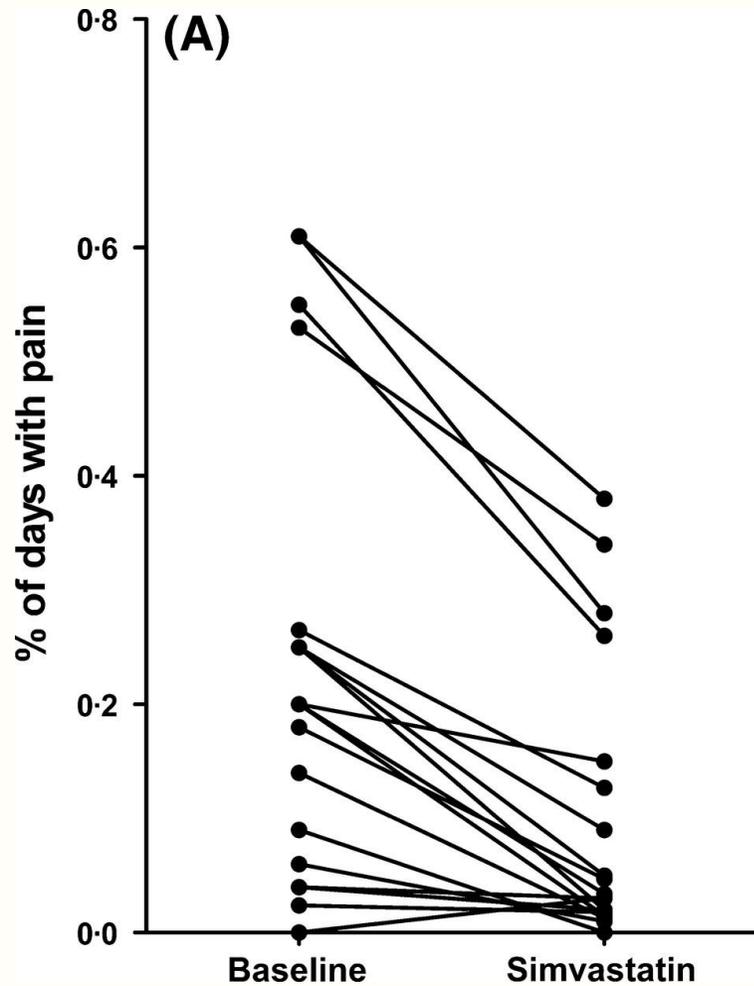


L-GLUTAMINE- ENDARI

- FDA approval 2017 though after only conference abstracts
Later published in NEJM N Engl J Med 2018; 379:226-235
- Purported benefit:
 - Anti-oxidant by reconstituting NADPH
 - Fewer hospital visit - 3 vs. 4 and shorter stays **in limited study**
 - High daily dose - 20-30g/d hindering compliance
 - Generally well tolerated though more GI side effects
 - ~\$40,000 yearly



Simvastatin



Br J Haematol. 2017 May; 177(4): 620-629



HSCT

- HLA-identical sibling or cord blood limited by lack of matched siblings, but also lack of referrals/HLA testing, etc.
 - Myeloablative (BU-CY + ATG, etc.)
 - Non-myeloablative (e.g. XRT/ATG/alemtuzumab Hsieh NEJM 361(24):2309)
- Unrelated donors form cord and marrow registries
 - Limited by fewer* matched donors for ethnic minorities

- Haploidentical SCT- may markedly expand donor options



FDA NEWS RELEASE

FDA Approves First Gene Therapies to Treat Patients with Sickle Cell Disease

December 08, 2023

- Exa-cel/Casgevy uses CRISPR/CAS9 to edit the binding site of BCL11A to promoter blocking HbF to adult hgb switch
- Lentiglobin/Lovo-Cel (Lyfgenia) inserts DNA fragment by **lentivirus** into beta chain that alter folding of Hb S and prevents polymerization, β A-T87Q an anti-sickling globin



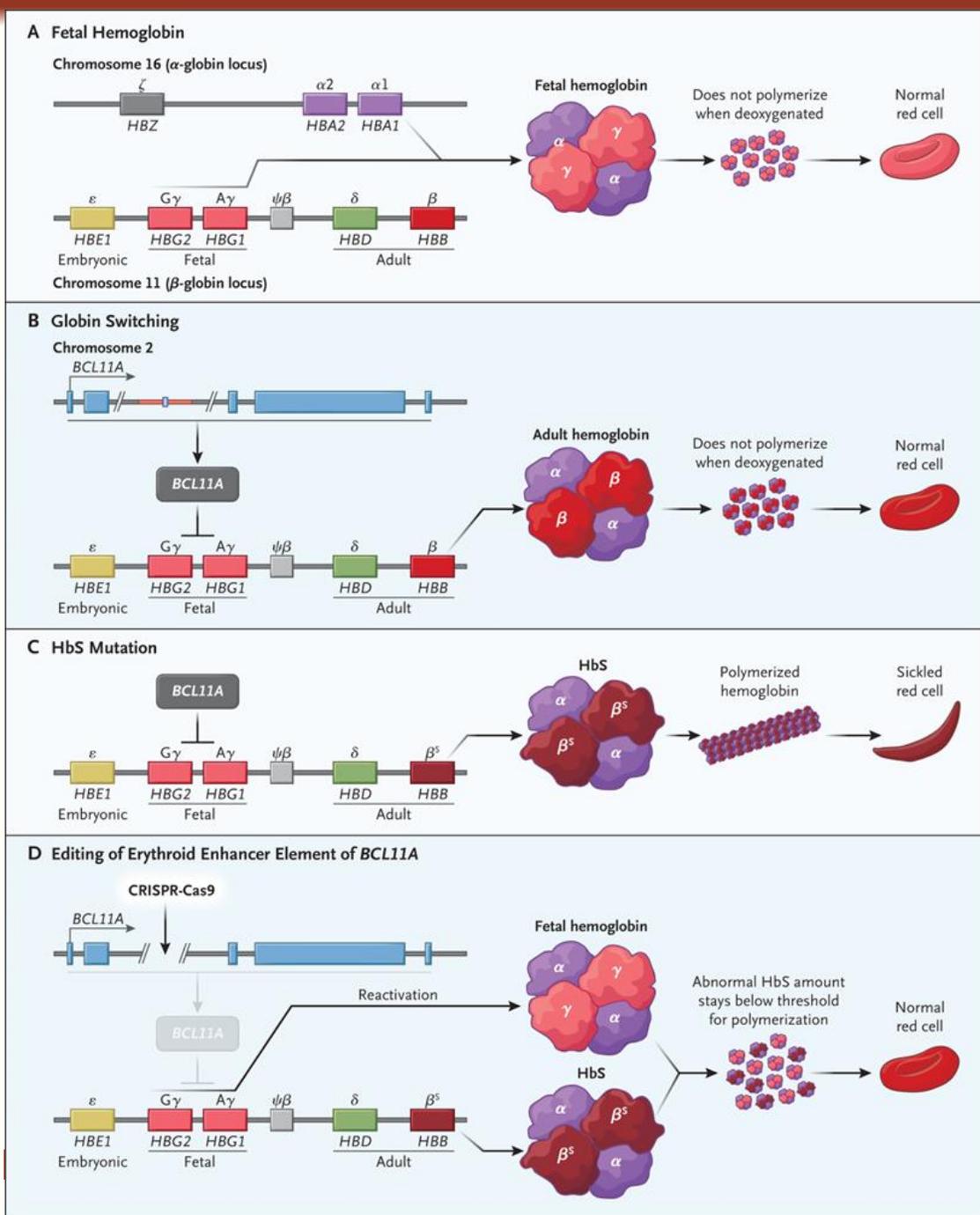
CRISPR-Cas9 Gene Editing for Sickle Cell Disease and β -Thalassemia

NEJM December 5, 2020

N Engl J Med 2024;390:1642-1645

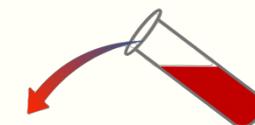
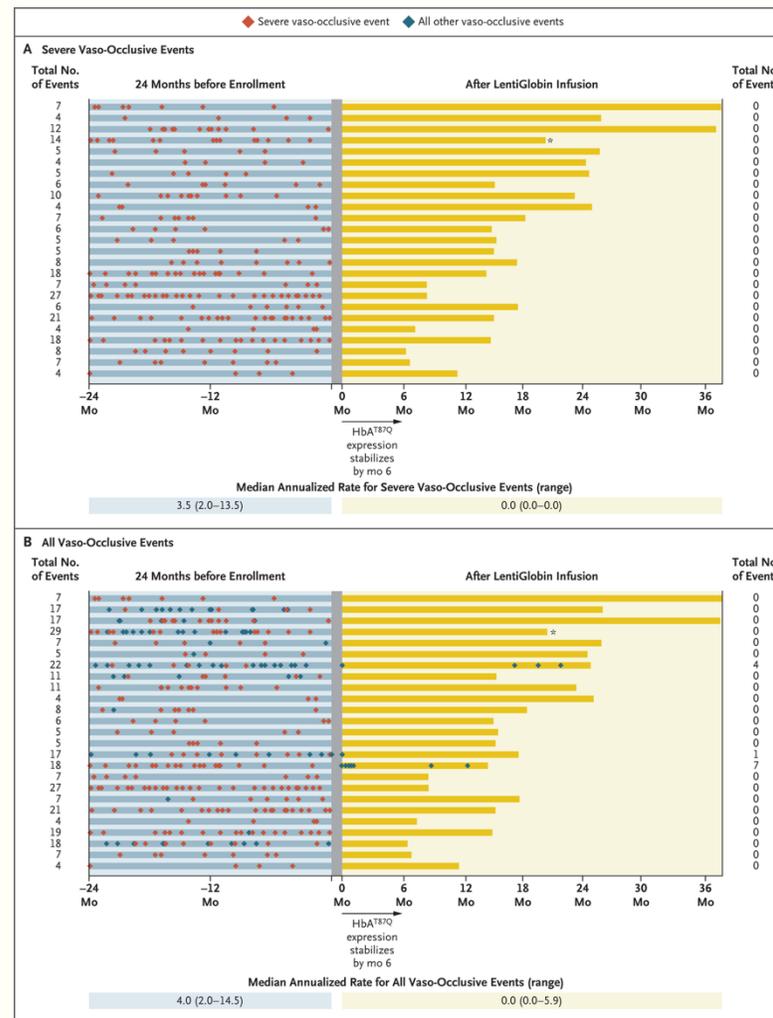
HematologyEducationOnline

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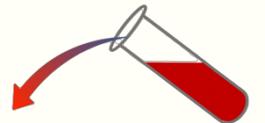
Lentiglobin/Lovocel Gene Addition/Bluebird Bio

Modified HbA_{T87Q} introduced ex vivo with lentiviral vector Alters tertiary structure that prevents sickling



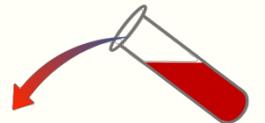
Potential Risks

- 2 cases of AML reported in 2021 out of 47 patients paused LovoCel, but studies suggested the cause was likely the conditioning regimen or prior undetected mutations unrelated to the gene therapy.



HIGH COST HAS LIMITED ACCESS TO GENE THERAPY

- \$2.2 million for Casgevy and \$3.1 mil. for Lyfgenia
- Current attempts to arrange 3rd party funding in US
- Recently approved on preliminary basis in UK with plan to evaluate effectiveness





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