Management of Sickle Cell Disease: What to do when there is no Evidence Base

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Objectives

- Describe the pathophysiology of vaso-occlusive (VOC) crises in sickle cell disease
- Recognize the clinical presentation of VOC
- Apply guideline based care to adults with SCD

Case JP

- 23 yr old male with hgb SS disease.
- Presents reporting typical VOC type pain in arms and legs.
- Last hospitalization was 2 weeks ago
- Medications:
  - Hydromorphone 4 mg every 4-6 hours PRN
  - Folic acid 1 mg a day
- He is talking to his mom when you walk in the room when he sees you he curls into a ball and starts to complain of 8/10 pain

Sickle Cell Anemia

JOHNS HOPKINS MEDICINE

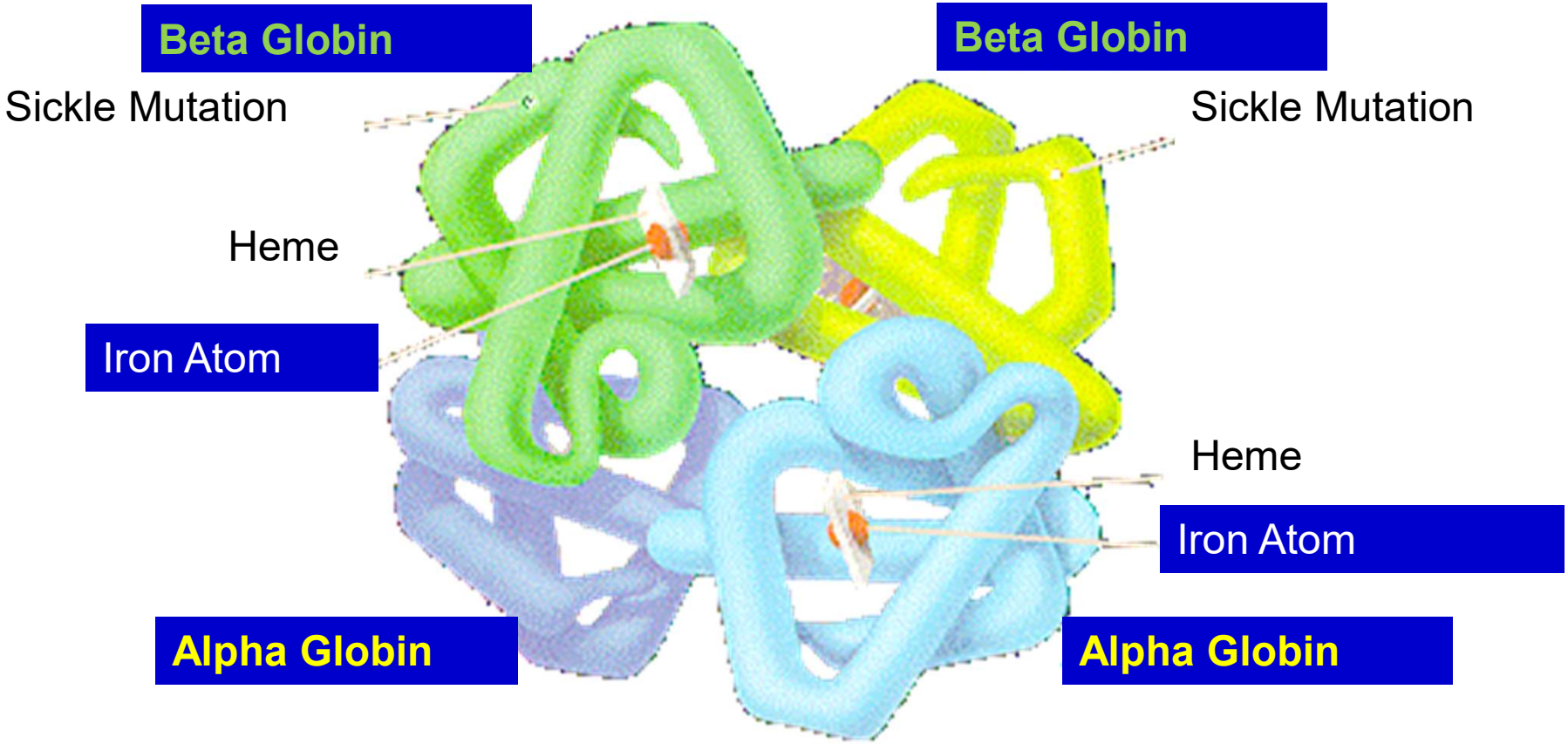
- Single base substitution of valine for a glutamine at the sixth amino acid of the gene encoding for the hemoglobin β chain.
- Affects approximately 100,000 Americans
- Compared to the general population decreases life expectancy by 25-30 years
- One distinct origin 7300 years ago
- Survival advantage under selective pressure of Falciparum malaria

Am J Hum Genet. 2018 Apr 5;102(4):547-556.

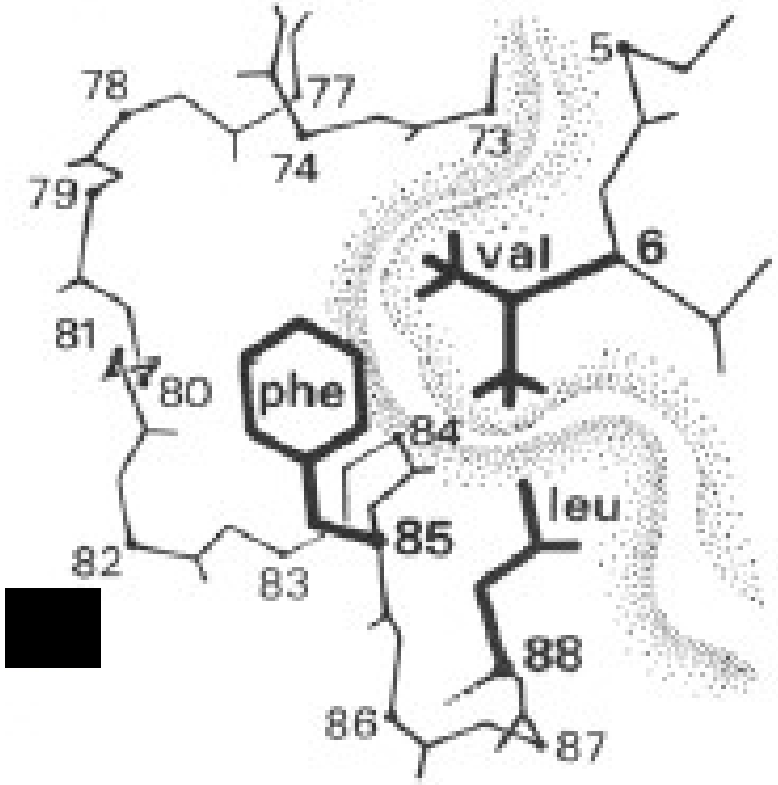
A Molecule to Breath With

JOHNS HOPKINS MEDICINE

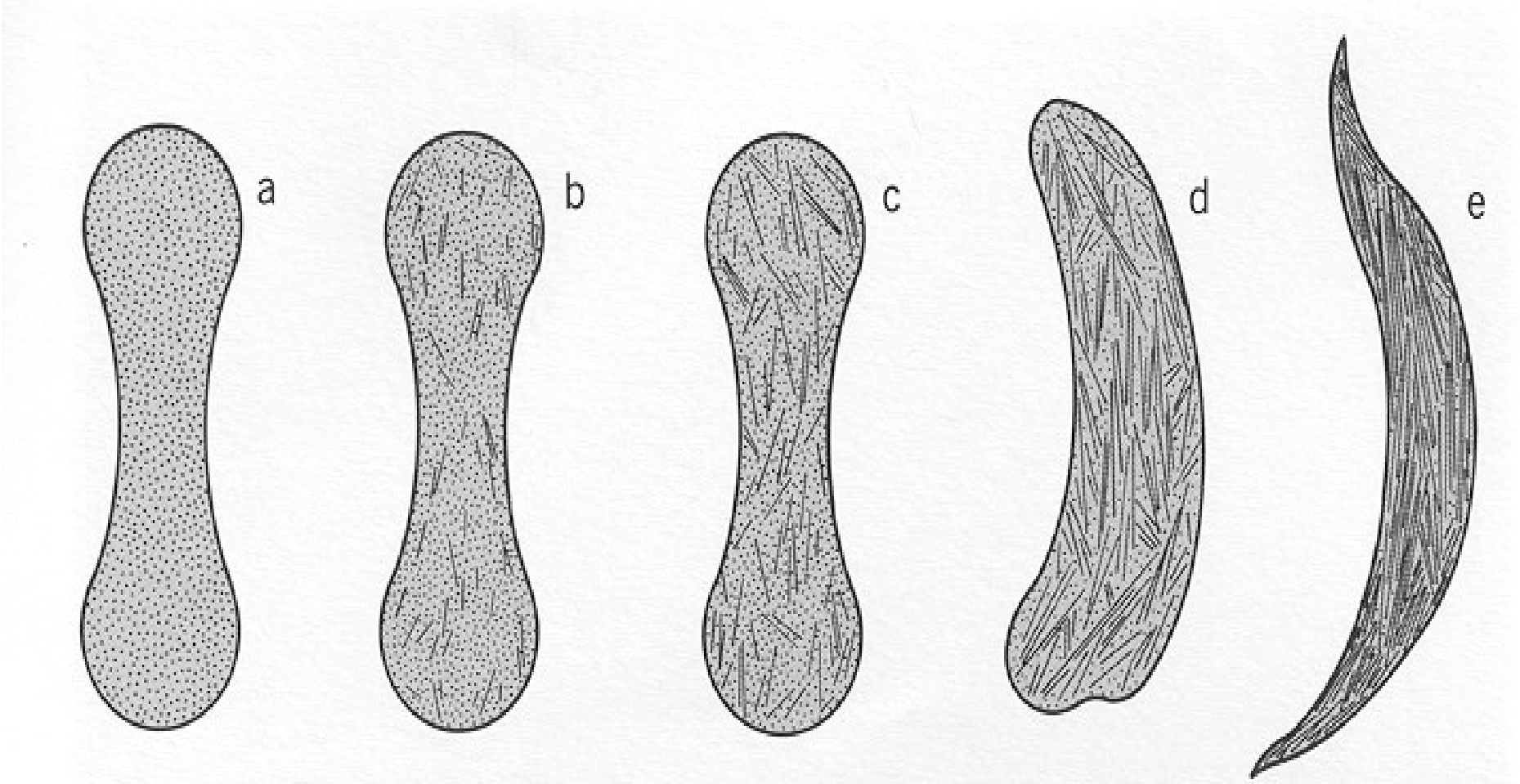
Hemoglobin



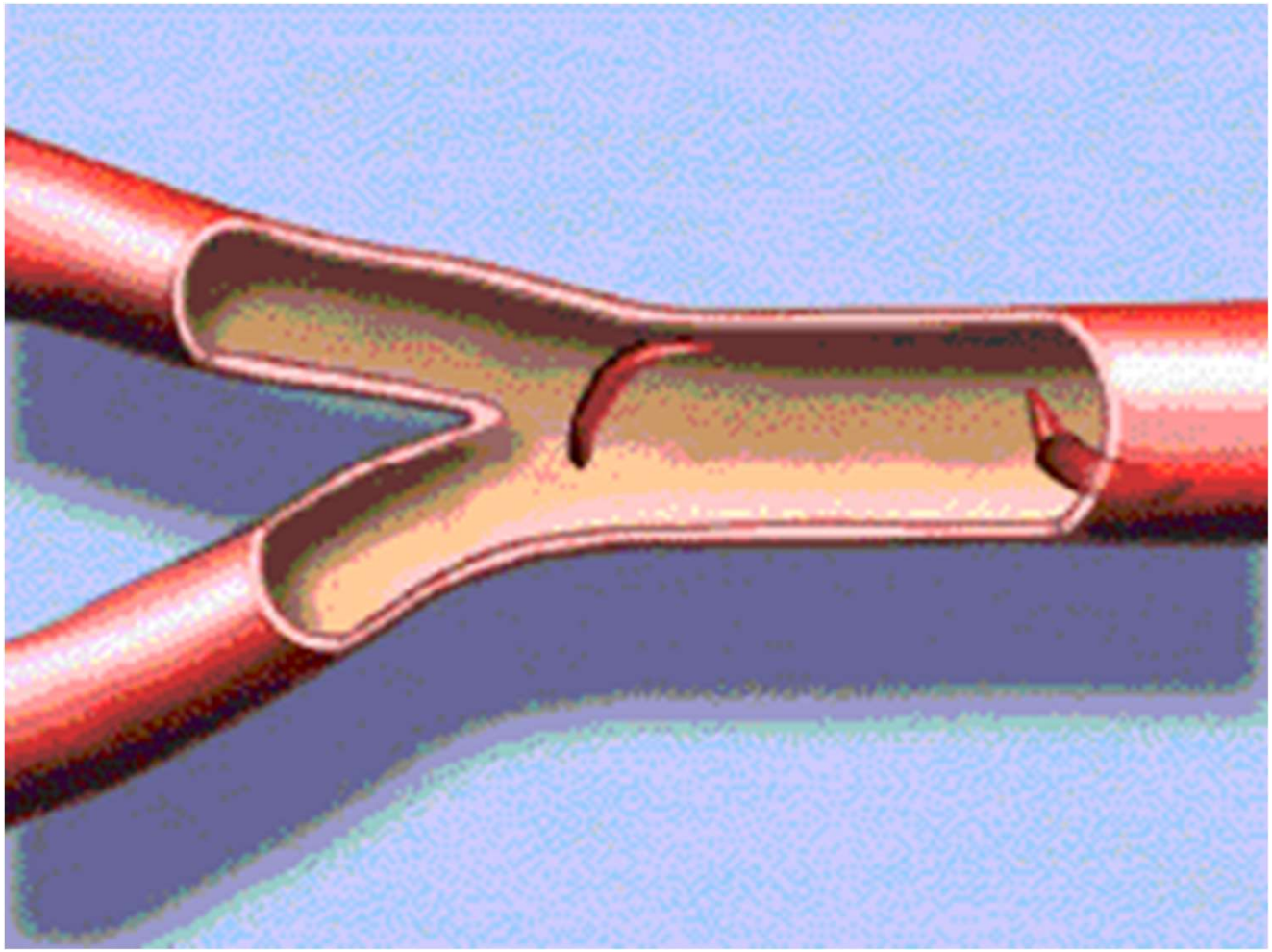
Hydrophobic pocket for 6β Val



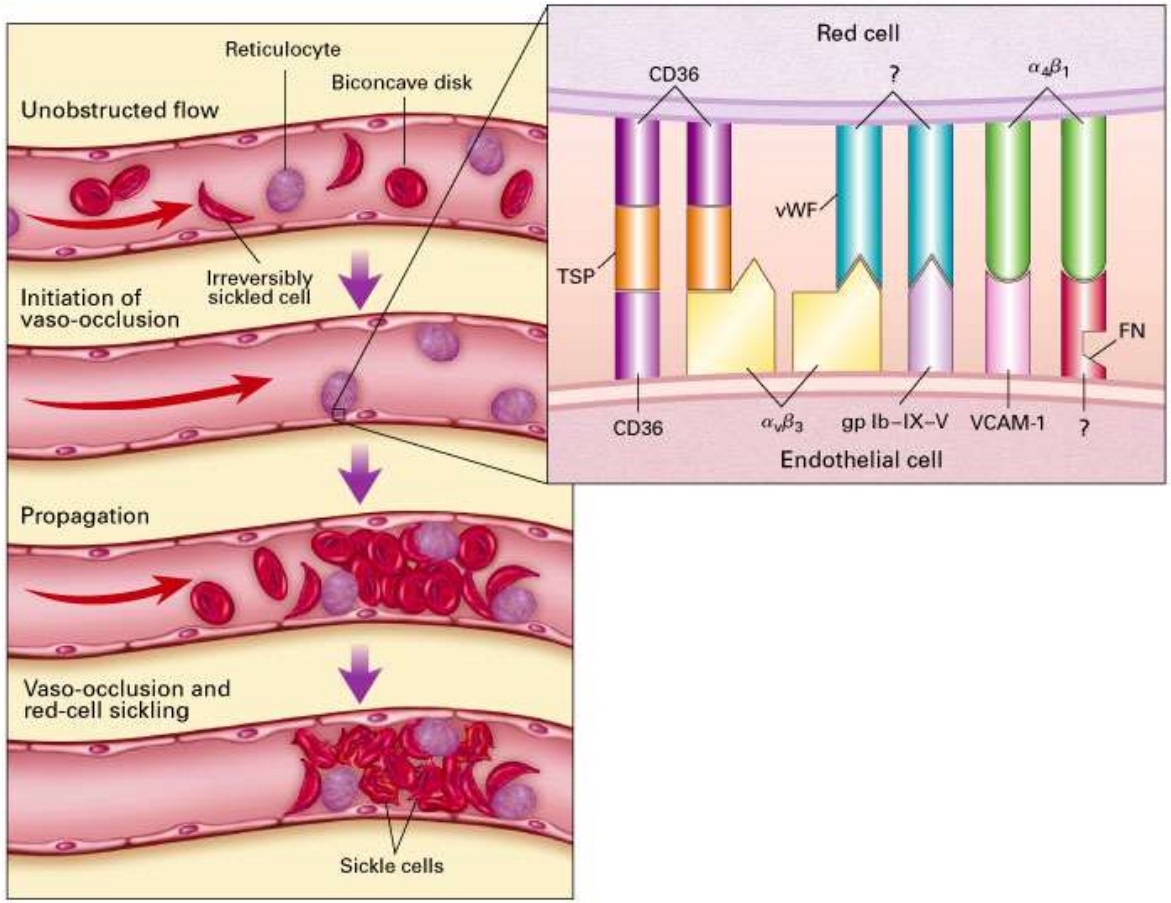
Intracellular polymer content results in RIGIDTY, changes in cell shape, and membrane distortion



Two consequences of polymerization: Vaso-occlusion



Cellular Adhesion



Red cell adhesion receptors:
- CD36 -binds thrombospondin
- integrin $_4$ß$_1$ -binds fibronectin & VCAM-1

Endothelial cell receptors:
- CD36
- integrin $_v$ß$_3$
- Complex of glycoproteins Ib, IX, and V -binds von Willebrand factor (vWF)
- VCAM-1

Hebbel, NEJM, 2000

https://accesspediatrics.mhmedical.com/content.aspx?bookid=1443&Sectionid=79850736#1114880087

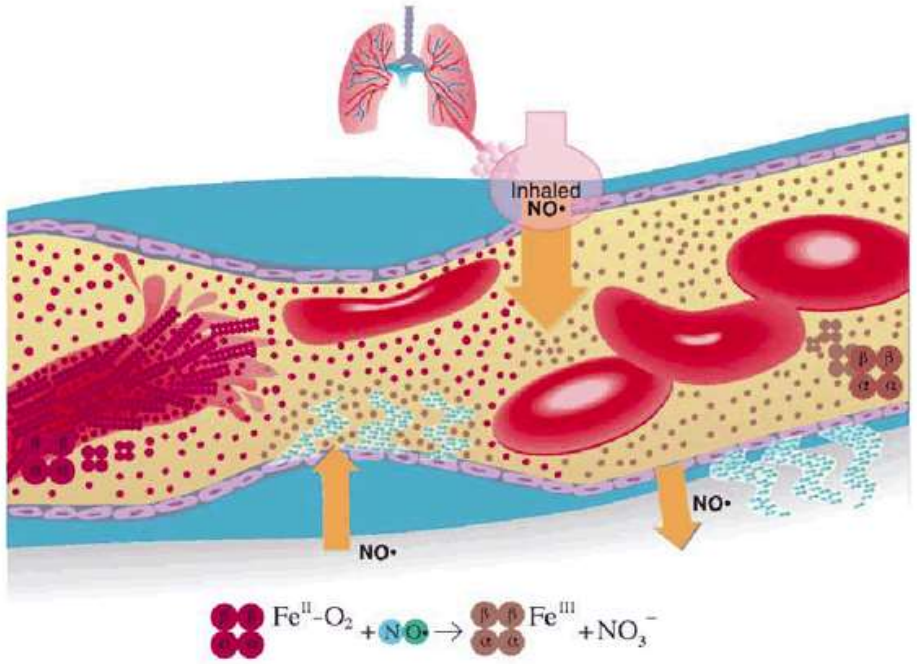
Second Consequence of Polymerization: Free Hemoglobin

- 30% of hemolysis occurs in vascular space ⟶ releasing free hemoglobin
- Capacity of protective hemoglobin-scavenging mechanisms (i.e. haptoglobin) overwhelmed
- Levels of cell-free hemoglobin increase in the plasma
- Results in consumption of nitric oxide and clinical sequelae

Nitric Oxide - Role in Vascular Homeostasis

NO:

- Decreases PAP
- Inhibits platelet aggregation
- Down regulates adhesion molecule expression
- Causes vasodilitation



Nature Medicine **8**, 1383 - 1389 (2002)

Epidemiology of Sickle Cell Disease Pain

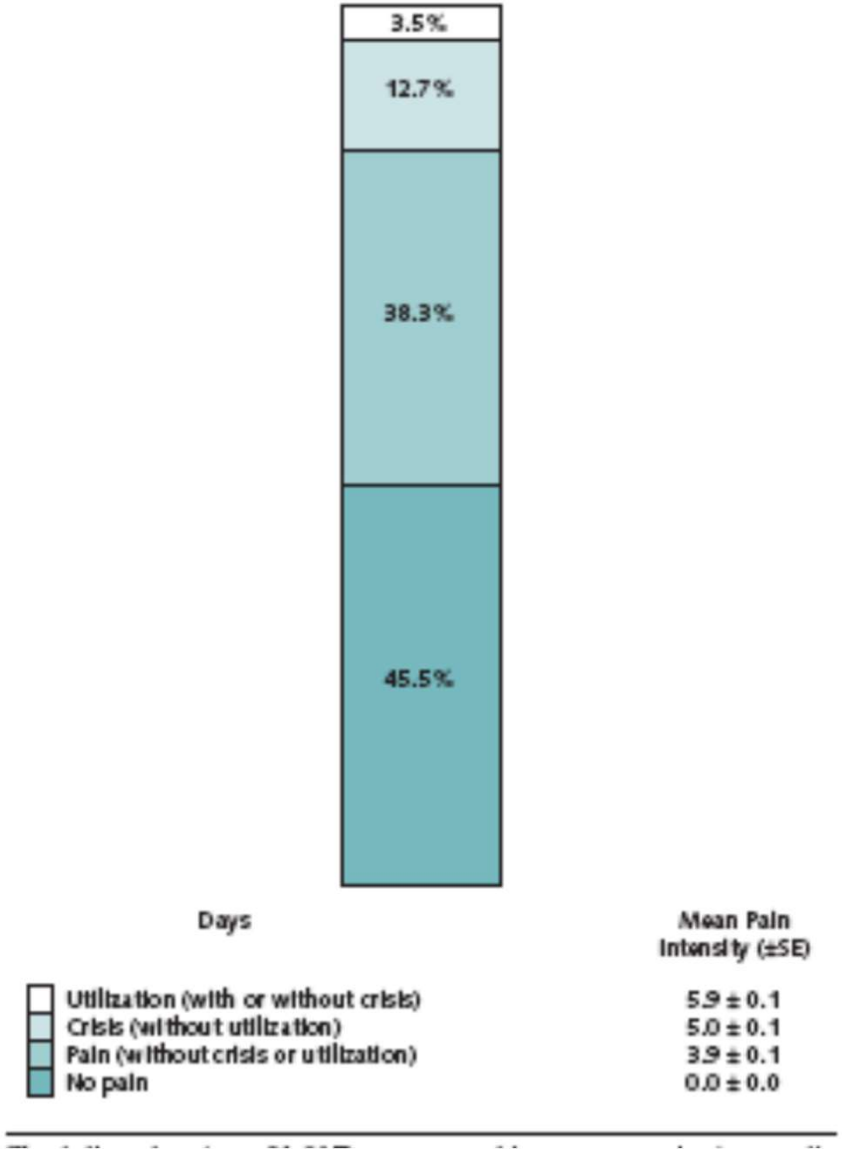
- Pain drives the majority of SCD patient interactions with the healthcare system
- Generally speaking, there are two types of SCD pain:
  1. The vaso-occlusive crisis (VOC) – also known as a “sickle cell crisis”; an attack of acute pain that is the “hallmark symptom” of the disease
  2. Chronic Pain – Due to accumulation of organ/tissue damage over time…may also be due to chronic levels of vaso-occlusion

Epidemiology of Sickle Cell Disease Pain

- 232 patients age 16 years or older with sickle cell disease.
- Daily diary for up to 6 months
- Pain reported on 54.5% of 31,017 analyzed patient-days
- 29.3% of patients reported pain in greater than 95% of diary days
- Only 14.2% reported pain in 5% or fewer diary days

Ann Intern Med. 2008;148:94-101.

Figure. Breakdown of diary days.



Case Presentation

23 yr old male with Hgb SS disease

Labs 12/02

- WBC-8.8 #/cu mm
- Hgb- 10.8 g/dl
- HCT- 29%
- Plt- 286 K/Cu MM
- Retic 7.6%/ abs 229.8

Labs 8/25/03

- WBC- 4.6 #/cu mm
- Hgb 10.3 g/dl
- HCT 28%
- Plat 364 K/ Cu MM
- Retic 7.5%/Abs 210.1

Diagnosing a Painful Crises

- The following objective indicators can be reliably used in the diagnosis of acute SCD pain:
  - Lab work: None known
  - Radiographic findings: None known
  - Vital signs: None known
- No objective indicators that can be used to reliably indicate the presence of a vaso-occlusive crisis
- Patient's self-report = gold-standard by which a vaso-occlusive crisis is identified

Evidence Base for the Treatment of VOC

- There is none!
- Wang et al, expert panel process to identify quality indicators for children with SCD
- Children with SCD who present with an acute pain episode should receive a parenteral analgesic within 60 min of registration or 30 min of triage
- Initial pain assessment should be documented using an age-appropriate pain scale, and the assessment should be repeated within 30 min of the first dose of analgesic

Curr Opin Hematol. 2009 May;16(3):173-8
Pediatrics 2011 Sep;128(3):484-93.

What Is the Best Way to Treat the Pain?

- Benjamin et al.
  - Bronx Comprehensive Sickle Cell Center.
  - Used a specific assessment and treatment protocol in the setting of a day hospital,
    - pain was controlled in 90% of patients,
    - hospital admissions decreased by 40%
    - average length of stay for hospitalized patients decreased by 1.5 days.
  - Key- patients were assessed and started on treatment within 15-20 minutes of arrival
  - Patients were assessed at half hour intervals for pain, psychological distress, pain relief and adverse events.

Blood. 2000 Feb 15;95(4):1130-6.

Treating Acute SCD Pain

- Guidelines for the management of acute SCD pain promote the following principles:
  - Rapid clinical assessment
  - Recognize tolerance and dose appropriately
  - Aggressive management…typically involving opioids, often at high doses
  - Frequent re-assessment and re-administration of pain medicine if patient's pain not tolerable
  - Involve the patient (i.e. ask about medicines/doses that typically work, what was taken at home and how much, how quality of current pain compares to typical acute pain episodes)

http://www.nhlbi.nih.gov/health-pro/guidelines/sickle-cell-disease-guidelines/

Case

- JP gets admitted for VOC and is started on PCA and IVF at 200 cc/hr
- 24 hrs later on rounds see that nurse has been increasing oxygen to keep pulse ox >95%.
- Pt is on 5L by NC and pulse ox is 94% and c/o CP.
- Over next few hours increasing oxygen demand and Temp of 39^0
- CXR now with multilobar infiltrates
- Pt is put on 100% NRB

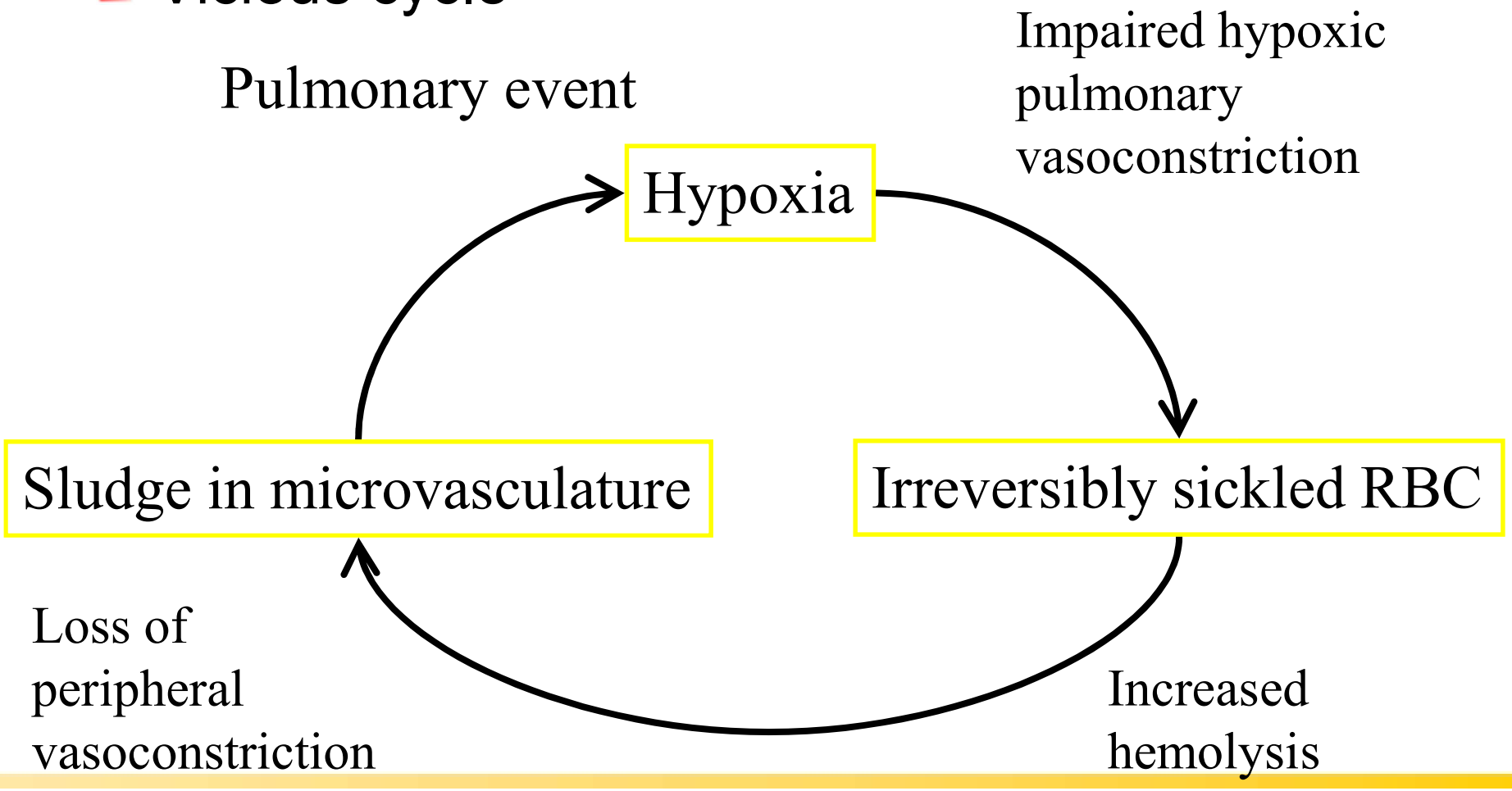
Acute Chest Syndrome

JOHNS HOPKINS MEDICINE

- The most common pulmonary complication
- Leading cause of death in patients with sickle cell disease.
- Clinical diagnosis defined as:
  - New consolidation on CXR
  - Fever
  - Chest pain

Acute Chest Syndrome

- Vicious cycle



ACS

- Atelectasis
  - Painful rib and vertebral infarctions,
- Pulmonary infection
  - Chlamydia/mycoplasma
- Macro and microvascular infarction
- Fat Embolism
- Pulmonary Edema

Acute Chest Syndrome

JOHNS HOPKINS MEDICINE

- 671 episodes of ACS in 538 patients treated at 30 centers
  - 3.3% mortality
  - 13% required mechanical ventilation
  - 72% received red cell transfusion
  - Cause found in 38%
    - Infection
      - Chlamydia/ mycoplasma
    - Fat Embolism

Vichinsky et al, NEJM 2000;342:1855-1865.

TABLE 3. OVERALL PREDICTORS OF PROLONGED HOSPITALIZATION, RESPIRATORY FAILURE, AND NEUROLOGIC COMPLICATIONS AMONG PATIENTS WITH THE ACUTE CHEST SYNDROME.*

	PERCENT REQUIRING MECHANICAL VENTILATION	ODDS RATIO (95% CI)§	P VALUE
Respiratory failure‡			
History of cardiac disease			
No	12	1.0	
Yes	44	6.7 (2.1–22.3)	0.002
No. of lobes involved on radiographic examination			
0 to 1	3	1.0	
2 to 3	11	2.2 (1.0–4.6)	0.04
≥4	54	9.0 (2.5–32.7)	<0.001
Platelet count at diagnosis			
0 to 199,000/mm³	23	1.0	
200,000 to 399,000/mm³	11	0.9 (0.37–2.1)	0.75
≥400,000/mm³	8	0.3 (0.10–0.96)	0.04

Transfusion

- Simple v. Exchange
- Indications

Simple Transfusion in SCD

- Giving several units of blood
- Improve dyspnea
- Severe fatigue
- Heart failure associated with an oxygen-carrying deficit
- Decrease percentage of Hb S containing cells.

Simple Transfusion in SCD

- Risks:
  - Excessive blood viscosity
    - the post-transfusion Hb level should not exceed 10 to 11 g/dL to prevent this
  - Alloimmunization
    - Occurs in up to 30% of adult patients who receive frequent transfusions;
    - Can cause delayed transfusion reaction or life threatening hyperhemolysis
  - Iron overload
  - Infection

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Blood Viscosity and Sickle Cell

- Blood viscosity increases with increasing hemoglobin level
- Elevated viscosity limits blood flow and oxygen transport
- Blood from a patient with sickle cell anemia has a significantly higher viscosity than normal blood at the same hemoglobin level

Blood Viscosity and Sickle Cell

- Deoxygenated sickle blood has 10-fold greater viscosity than oxygenated sickle blood at the same hemoglobin level
- Increased viscosity dramatically promotes the physiology of sickling.
  - Flow will be slowest in vessels of small radius (capillaries,arterioles and venules) and under lower pressures (venules)
- Deoxygenated sickle cells greatly increase the blood viscosity, slowing flow through the venules even more

Exchange Transfusion

- Replacement of sickle cells by normal cells can help prevent further vaso-occlusion
  - pre-existing vasoocclusion does not reverse
- Rapidly reduces the concentration of Hb S
- Can be used when simple transfusion would result in hyperviscosity or volume overload
- Red cell exchange rapidly decreases rate of hemolysis which decreases
  - damage to renal tubular cells
  - scavenging of nitric oxide by free hemoglobin released from sickle cells

Exchange Transfusion and SCD

- Risks:
  - Increase risk of alloimmunization because of increase exposure to blood products
  - For patients more than 20% below their usual hemoglobin, either a simple transfusion to increase the hemoglobin or a blood prime helps avoid vascular compromise
  - The greater number of units transfused confers a risk of citrate toxicity
    - treated with calcium
  - Requires large access device (Shiley)

NHLBI Guideline Recommendations for ACS

- In people with SCA, give simple blood transfusion (10 mL/kg red blood cells) to improve oxygen carrying capacity to people with symptomatic ACS whose hemoglobin concentration is >1.0 g/dL below baseline If baseline hemoglobin
- ***(Weak Recommendation, Low-Quality Evidence)***
- Perform urgent exchange transfusion when there is rapid progression of ACS as manifested by oxygen saturation below 90 percent despite supplemental oxygen, increasing respiratory distress, progressive pulmonary infiltrates, and/or decline in hemoglobin concentration despite simple transfusion ***(Strong Recommendation, Low-Quality Evidence)***

http://www.nhlbi.nih.gov/health-pro/guidelines/sickle-cell-disease-guidelines/

Transfusion Pitfalls

- Uncomplicated VOC not indication for transfusion
  - No data that transfusion decreases length of crises.
- No Hgb threshold where transfusion is indicated
  - Pt's in crises often will have decrease in Hgb below baseline this is not an indication to transfuse
    - If pt has adequate reticulocyte response and is not SOB would not transfuse

Closely monitor pulse ox, symptoms and daily CBC

Transfusion Pitfalls

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- Avoiding delayed transfusion reactions:
  - Ask patient if they were told about antibody or if there was ever a delay in getting them blood products
  - Give every patient phenotypically matched red cells (assuming you have a phenotype)
    - matched blood for at least the C, E, and Kell antigens
    - If a pt has not been transfused in 3 months make sure that blood bank gets/has a phenotype prior to transfusion

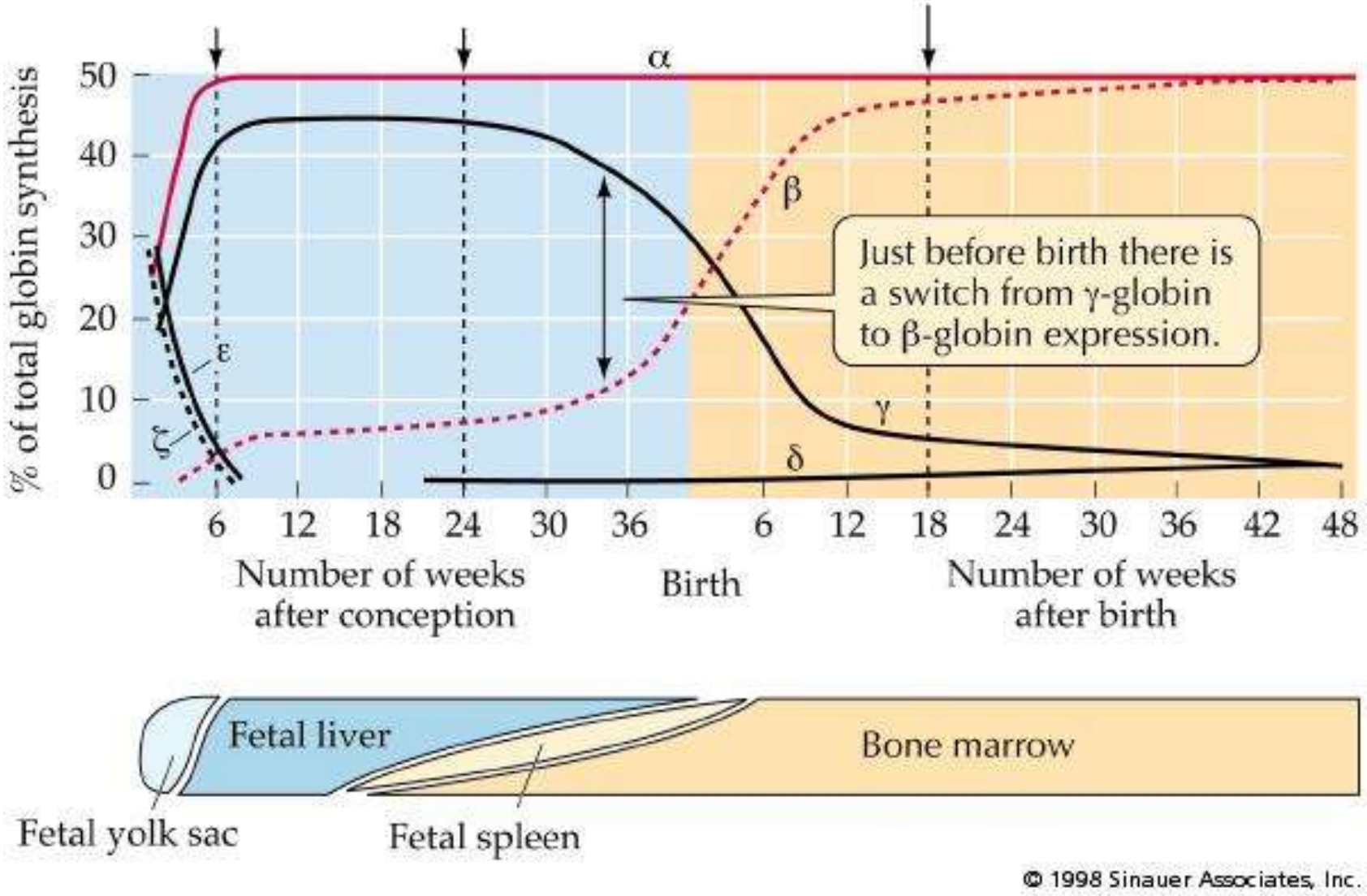
Patient Case

- JP undergoes emergent exchange transfusion
- Discharged and presents for routine PCP visit 2 weeks later accompanied by his mother.
- He is without pain
- He has not completed high school
- Mother would like to know what can be done to prevent another life threatening episode of ACS
- Mother is concerned that patient has been unable to complete GED. Patient and mother begin to argue over whether he is even trying

Current Medicine Cabinet

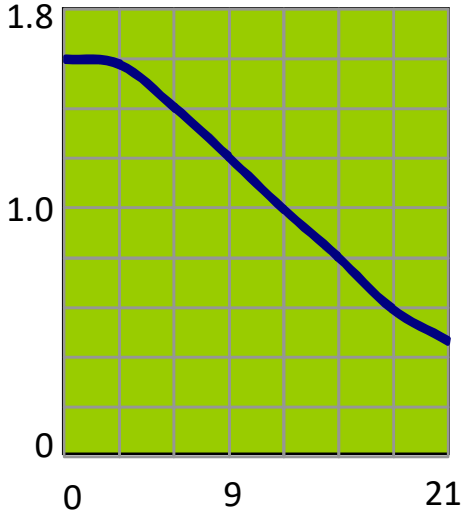
Lone bottles of hydroxyurea and L-glutamine

Hemoglobin Production



Effects of HbF in SS disease

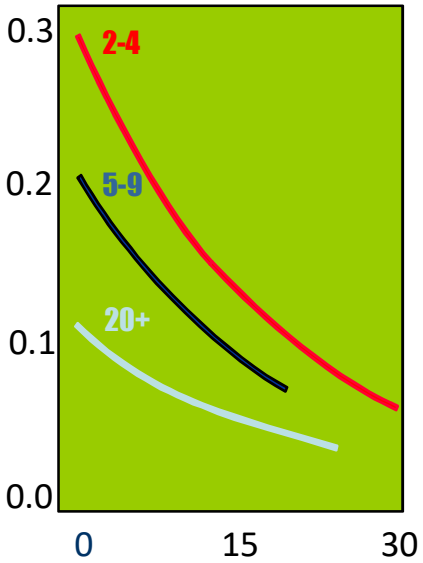
pain



rate/yr
av Hct
20-29yr

Platt, 1991

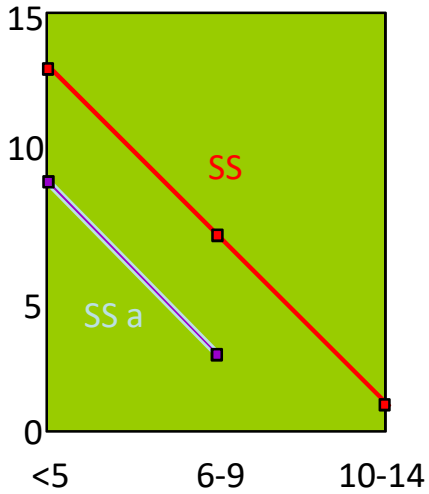
chest



rate/year

Castro, 1994

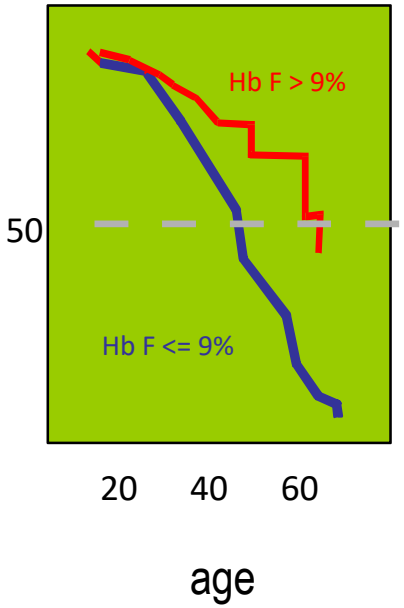
ulcer



new/100 pt-yr

Koshy, 1989

death



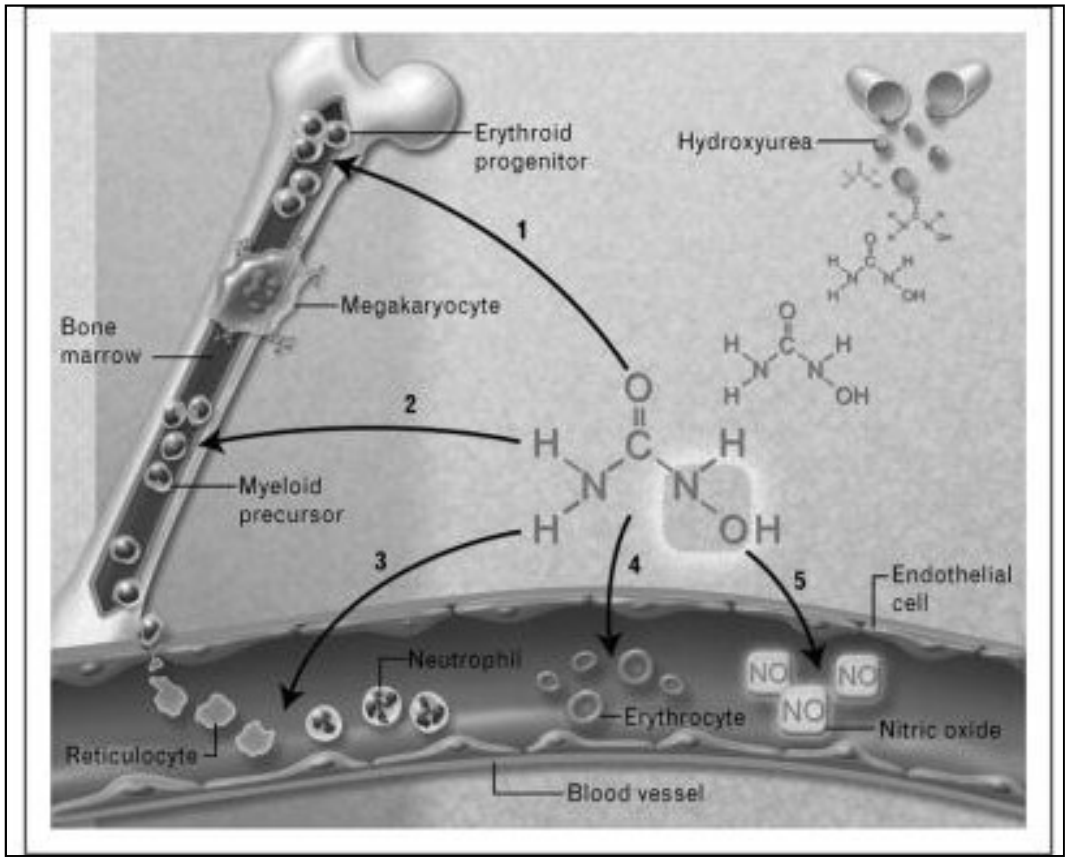
Platt, 1994

Multicenter Study of Hydroxyurea

- Double-blind, randomized
- Pt's with SS or Sβ^0thalassemia
- 299 patients with history of 3 or more crises/year
- Decrease in number of crises/yr (2.5 v. 4.5 $p < 0.001$)
- Decrease in ACS (25 v. 51 $p < 0.001$))
- Decrease in no. of patients undergoing transfusion (48 v. 73 ($p = 0.001$)

N Engl J Med. **1995** May 18;332(20):1317-22.

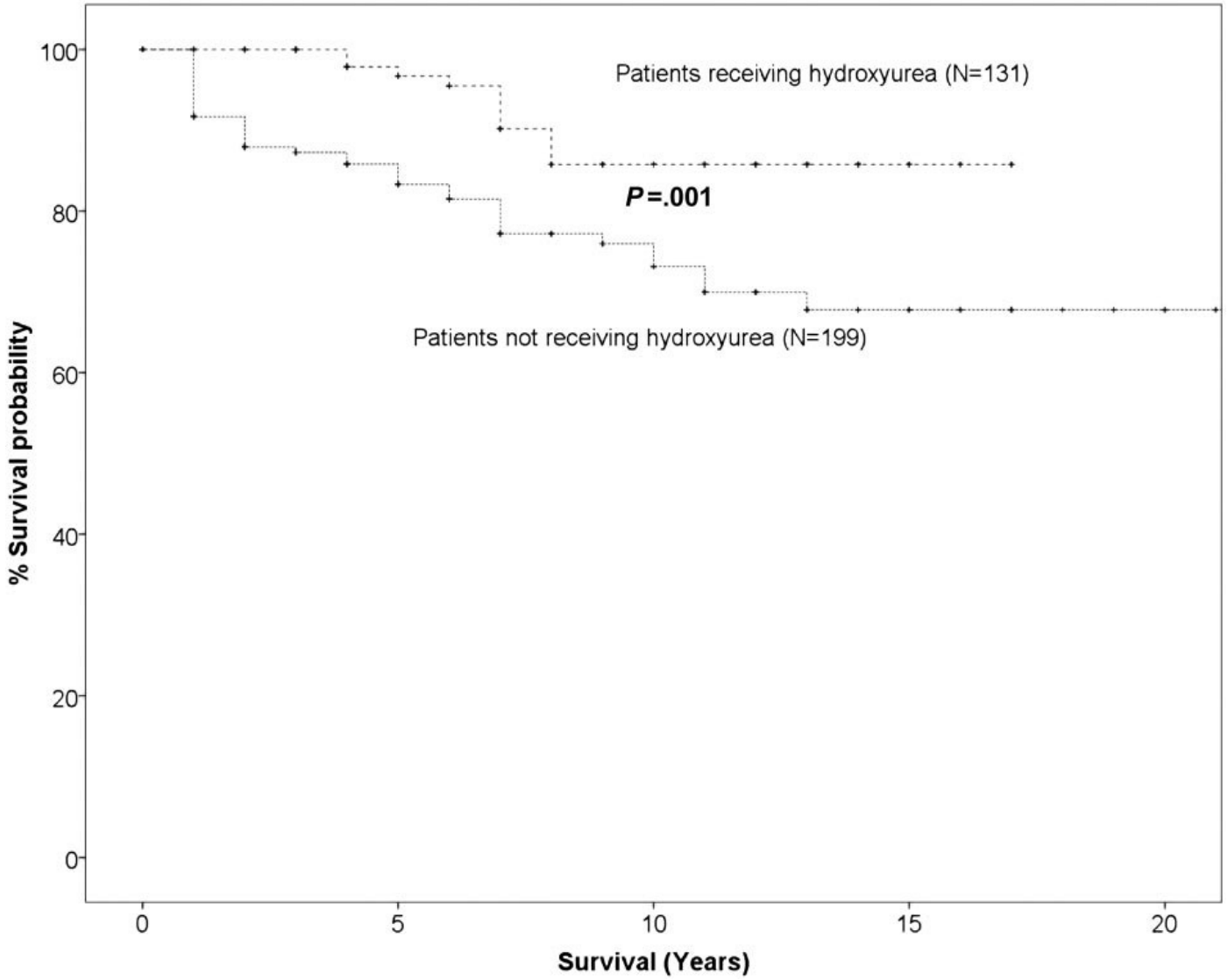
Hydroxyurea Benefits not Limited to Hb F Induction



- Improved erythrocyte morphology and deformability
- Lowering of circulating leukocyte and reticulocyte counts,
- Reduction in hemolysis
- Local release of nitric oxide

Current Opinion in Hematology
Issue: Volume 18(3), May 2011, p 158–165

Probability of 10- year overall survival in SCD HU v No HU



No patients developed malignancy

BLOOD, 25 MARCH 2010 VOLUME 115, NUMBER 12

Treat with Hydroxyurea

- In adults with sickle cell anemia
  - who have **3 or more SCD-associated moderate to severe pain events in a 12 month period**
  - who have **SCD-associated pain** that interferes with daily activities and quality of life
  - with a history of **severe and/or recurrent acute chest syndrome**
  - who have **severe symptomatic chronic anemia** that interferes with daily activities or quality of life

Common Mistakes with Hydroxyurea

- Not initiating therapy in eligible patients
  - hgb F levels are high
  - Patient concerns over toxicity
- Failing to titrate dose to MTD
  - Most studies with HU – dose titrated to MTD
- Too short a trial of drug
  - Patients/providers should anticipate that it will take 3-6 months to see an effect
  - Patients need to be reminded to be adherent
- Stopping HU during hospital admission
  - Only stop if counts are too low

Glutamine

- Mechanism of action in SCD is unknown
- Speculated to cause decreased susceptibility of sickle erythrocytes to oxidative damage (and hemolysis) so should have improved red cell survival
  - None of the clinical trial data show any improvements in hemoglobin or reticulocyte count: no appreciable decrease in hemolysis
- Oral administration of L-glutamine raises the NAD redox potential within sickle red blood cells

Blood. 2018 Jun 12

RCT of L-Glutamine

- 230 individuals with SCA (SS or S beta 0thal) and ≥2 painful events in the preceding year
- Randomized (2:1) to L-glutamine or placebo for 48 weeks
- Excluded if :
  - Recent transfusions
  - Renal insufficiency
  - Uncontrolled liver disease
  - Pregnancy or lactation

L-Glutamine: Result of Phase III Trial

JOHNS HOPKINS MEDICINE

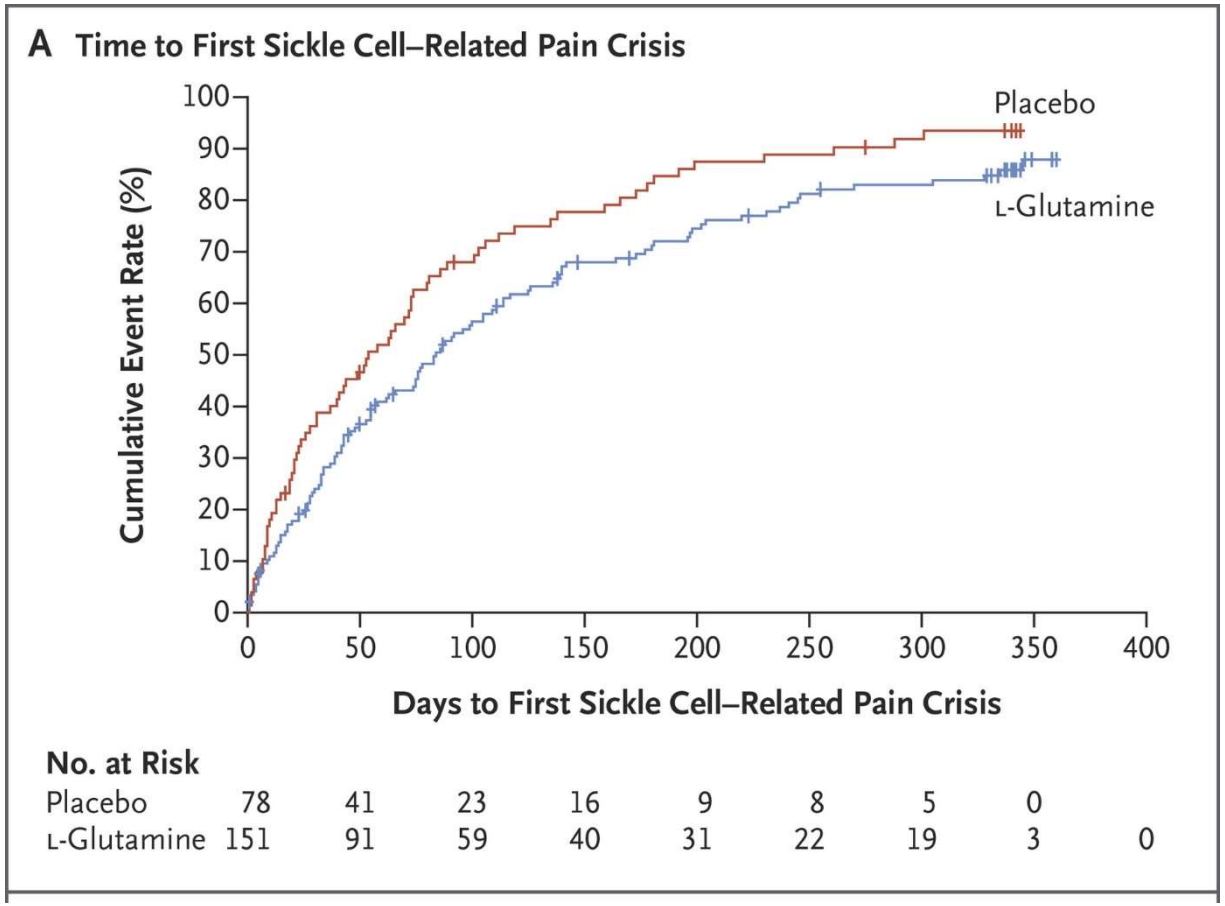
Table 2. End-Point and Additional Analyses.

Through Week 48	L-Glutamine (N=152)	Placebo (N=78)	P Value
Primary end point			
No. of pain crises			0.005*
Mean	3.2±2.24	3.9±2.54	
Median (range)	3 (0–15)	4 (0–15)	
Secondary end points			
No. of hospitalizations for sickle cell–related pain			0.005*
Mean	2.3±1.99	3.0±2.33	
Median (range)	2 (0–14)	3 (0–13)	
No. of emergency department visits for sickle cell–related pain			0.09*
Mean	1.1±1.49	1.5±2.29	
Median (range)	1 (0–12)	1 (0–15)	
Additional analyses			
Cumulative no. of days in hospital			0.02†
Mean	12.1±16.6	18.1± 27.4	
Median (range)	6.5 (0–94)	11 (0–187)	
Median no. of days to first pain crisis (95% CI)	84 (62–109)	54 (31–73)	0.02‡
Median no. of days to second pain crisis (95% CI)	212 (153–250)	133 (115–179)	0.03‡

Interpretation of the trial's results is complicated by high dropout rates (36% L-glutamine arm; 24% placebo arm)

N Engl J Med. 2018 Jul 19;379(3):226-235

Time to First Crisis



Side Effects

- Most common adverse events:
  - Constipation, nausea, vomiting, headache, abdominal pain
- In critically ill patients (not SCD) with multiorgan failure randomized to 0.35 g/kg of IV glutamine daily had higher mortality rates than those who did not receive it and this was seen in other multicenter trial of glutamine for critically ill patients
- L-glutamine supplementation should probably be avoided in SCA patients with hepatic or renal impairment, and should be stopped in those who develop hepatic, renal, or multiorgan failure

Blood. 2018 Jun 12

How I Use L-Glutamine

- Endari® is estimated to cost over $3,000/month for adults and $1,000/month for children
  - 20-times more expensive than hydroxyurea
- If hydroxyurea therapy is maximized and patient with SCA continues to have painful events would consider addition of of L-glutamine
- May consider it in those with SCA who can't tolerate hydroxyurea
- Without data on variant genotypes and cost of therapy have not recommended it to those individuals

Blood. 2018 Jun 12

JP

- Agrees to start hydroxyurea
- Your nurse calls to remind him to get labs 2 weeks after his visit but he doesn't show
- Patient returns with his mother for his 1 month follow-up and reports poor adherence to his hydroxyurea
- The patient says "he thought he was supposed to take the medication when he felt a crisis coming on"
- He was given 30 tablets of hydromorphone a week ago at his last ED visit and has run out and is requesting more
- He has had 4 visits for pain to the ED in the last month
- He and his mother begin to argue again

The Difficult Patient

- Samir Ballas identified the existence of a subset of sickle cell patients as “problem” or “difficult” patients:
  - suspicion of drug seeking behavior
  - overuse of health care facilities
  - dependence on opioid analgesics
  - evidence of antisocial personality disorder
- Patients attribute some of these problems to:
  - negative attitudes by some providers
  - improper pain management
  - delay in initiating analgesic therapy

The American Journal of Bioethics, 13(4): 3–10, 2013

Difficult Patient: Neuropsychological Dysfunction

- Cross sectional study of asymptomatic adults with sickle cell anemia and controls
- Mean WAIS-III performance IQ score of patients with SCA was significantly lower than that of controls (adjusted mean, 86.69 for patients with SCA vs 95.19 for controls p = .008)
- 33% performing more than 1 SD (<85) below the population mean
- Anemia was associated with poorer neurocognitive function in older patients
- Etiology unknown

JAMA. 2010 May 12;303(18):1823-31.

Difficult Patient and Opioid Misuse

- Clinician fears about contributing to addiction to opioids are a recognized barrier to the delivery of high quality pain management
- Studies have found the prevalence of substance abuse and addiction among SCD patients to be lower than, or at most the same as, that found in the general population
- Physicians and nurses both tend to greatly overestimate the prevalence of addiction in the SCD population
- These attitudes contribute to SCD patient reports that acute visits for their pain are often a dehumanizing experience

J Natl Med Assoc. 2009 Oct;101(10):1022-33.
J Pain. 2006 Jul;7(7):453-8.

“High Utilizers” or “Frequent Flyers”

- There is a known subset of the SCD population that contributes a disproportionate amount of ED utilization
- This high-utilizing subset does have a higher prevalence of substance abuse problems
- This high-utilizing subset also has been shown to have more severe disease requiring treatment

Clin J Pain. 2013 Apr;29(4):317-23.
Ann Emerg Med. 2009 May;53(5):587-93.

Coping Skills

Summary

- Little evidence base to drive strong recommendations in guidelines
- Strong evidence for the use of hydroxyurea
- Remember patients with SCD live with pain everyday
  - Reward good coping skills
  - Aggressive upfront pain management results in better outcomes