HEMATOLOGY AND MEDICAL ONCOLOGY

BEST PRACTICES COURSE

9 – Sickling Disorders

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Disclosures

Disclosures of Financial Relationships with Relevant Commercial Interests

- Research Support – Pfizer, Novartis, Global blood Therapeutics
- Consulting – Novartis
- Advisory Board/Consulting – Global blood Therapeutics

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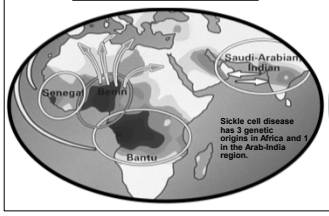
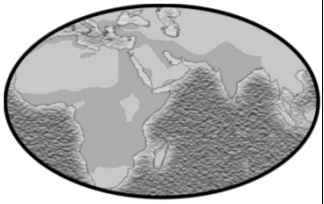
Epidemiology:

- Affects 1 in 365 African Americans
- World-wide: 300,000 births per year
  25 million people affected

Distribution of Hb S Mutation



Distribution of Malaria



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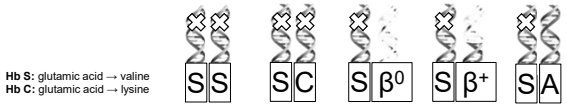
Sickle Cell Genotypes



Hgb (g/dL)	**6 – 10**	**9 – 12**	**6 – 10**	**9 – 12**	**11 – 15**
Retic (%)	**5 – 20%**	**5 – 10%**	**5 – 20%**	**5 – 10%**	**1 – 2%**
MCV (fL)	**> 80**	**> 80**	**< 80**	**< 80**	**80 – 100**
HPLC	**HbS**: 90% **Hb A**: 0%	**Hb S**: 50% **Hb C**: 50%	**Hb S**: 90% **Hb A**: 0%	**Hb S**: 75% **Hb A**: 25%	**Hb S**: 40% **Hb A**: 60%
Clinical Complications	**Severe:** Hemolytic & Vaso-occlusive	**Mild:** Vaso-occlusive	**Severe:** Hemolytic & Vaso-occlusive	**Mild:** Vaso-occlusive	Renal & Thrombotic

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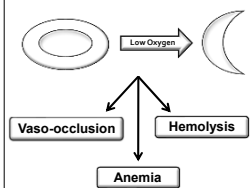
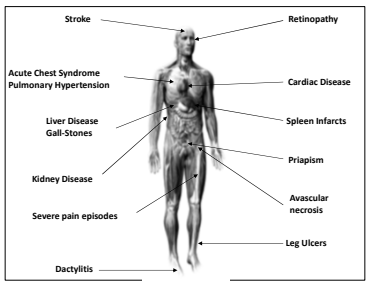
Background





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Endophenotypes

Hemolysis-
Endothelial Dysfunction

Higher
Hemolytic Rate

Pulmonary Hypertension
Kidney Disease
Leg Ulceration
Priapism
Stroke

Viscosity-
Vaso-occlusion

Lower
Hemolytic Rate

Pain crisis
Acute Chest Syndrome
Osteonecrosis

Kato et al. Blood Review 2007

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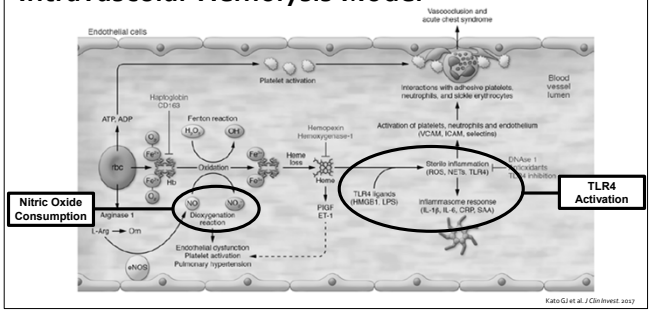
Intravascular Hemolysis Model



Kato GJ et al. *J Clin Invest.* 2017

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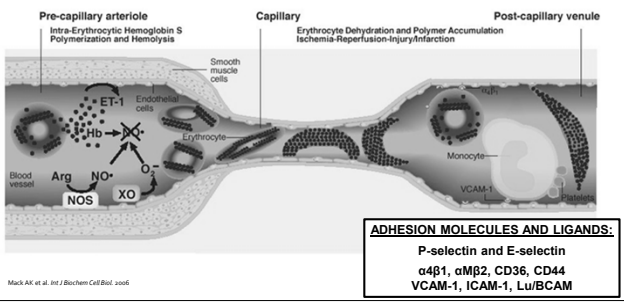
Vaso-Occlusive Model



Mack AK et al. *Int J Biochem Cell Biol.* 2006

ADHESION MOLECULES AND LIGANDS:

P-selectin and E-selectin

α4β1, αMβ2, CD36, CD44
VCAM-1, ICAM-1, Lu/BCAM

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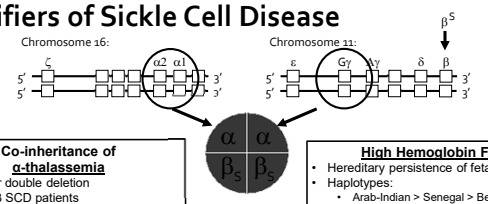
Modifiers of Sickle Cell Disease



Co-inheritance of α-thalassemia

- Single or double deletion
  - ~1/3 SCD patients
- Lowers RBC density and MCHC
  - Higher Hb/Lower hemolytic markers
- Protective from some SCD complications
  - Kidney disease
  - Leg ulcers
  - Cardiopulmonary
- **Not protective for VOC**

High Hemoglobin F%

- Hereditary persistence of fetal Hb
- Haplotypes:
  - Arab-Indian > Senegal > Benin > Bantu
- *BCL11A* rs1427407
  - Normally inhibits γ-globin
  - ~1/3 SCD patients
  - Target of gene therapy
- CSSCD: ↑ Hb F%: ↓ VOC and mortality
- Hb F > 10%: less stroke, AVN
- **Hb F > 20%: less VOC**

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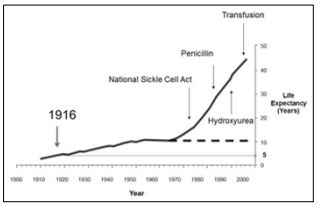
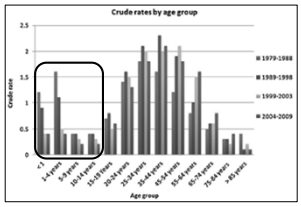
Morbidity & Mortality

≥ 95% of children with SCD survive into adulthood in high-income countries[1-3]



Wailoo K et al, NEJM 2017



Hamideh D et al, Pediatr Blood Cancer 2013

1. Telfer P et al, Haematologica 2007; 2. Quinn CT et al, Blood 2010; 3. Couque N et al, Br J Haematol 2016

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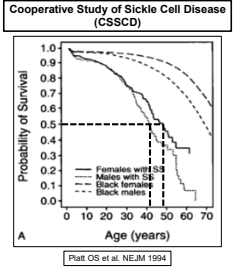
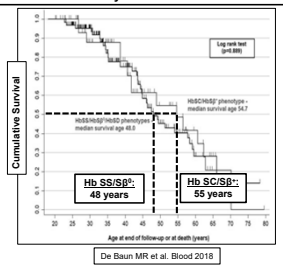
Median Survival

Cooperative Study of Sickle Cell Disease (CSSCD)



Platt OS et al. NEJM 1994

Contemporary estimates (high-income countries): 38 – 67 years in Hb SS[1-4]



De Baun MR et al. Blood 2018

1. Lanzkron S et al, Public Health Reports 2013; 2. Elmariah H et al, Am J Hematol 2014; 3. Gardner K et al, Blood 2016

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Predictors for Early Mortality

	CSSCD[1]	MSH[2]	USC[3]	NIH[4]	Brazil[5]	UK[6]	Meta-Analysis[7]
Frequent VOC		X		X	X	X	
Acute Chest Syndrome	X	X	X		X		
Stroke			X		X		
High TRJV				X			X
Kidney Disease	X		X	X		X	

VOC = vaso-occlusive crises
TRJV = tricuspid regurgitant jet velocity

1. Platt OS et al. NEJM 1994; 2. Powars DR et al. Medicine 2005; 3. Steinberg MH et al. JAMA 2003; 4. Darbari DS et al. PLOS One 2015; 5. Castro Lobo et al. Hematol Transfus Cell Ther 2018; 6. Gardner K et al. Blood 2016; 7. Madrid P et al. Haematologica 2017

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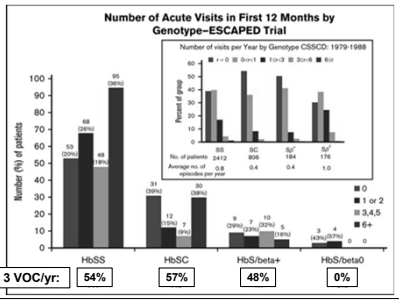
Predicting Risk for VOC



≥ 3 VOC/yr:	54%	57%	48%	0%

VOC Risk Factors:
- Lower Hb F%
- Nocturnal hypoxia
- Low vitamin D
- Higher hematocrit
- High WBC

Platt OS et al, NEJM 1991
Lanzkron S et al, Blood Adv 2018

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Exacerbation of Anemia

Etiology	Diagnostic Clues	Therapy
Aplastic Crisis	• Very low Retic count • Parvovirus IgM or PCR	• IVIG • Simple transfusion
Hyperhemolysis 1) Delayed hemolytic transfusion reaction 2) Nonimmune mediated	1) Transfusion 2 – 14 days prior, positive direct antiglobulin test, alloantibodies, low Retic count 2) Elevated hemolysis markers (Indirect bilirubin, AST, Retic)	1) Steroids, IVIG 2) Exchange transfusion
Hepatic Sequestration	• Hepatomegaly • Elevated ALT	• Simple vs. Exchange transfusion
Splenic Sequestration	• Splenomegaly • Hb SC or Sβ⁺-thalassemia • Thrombocytopenia	• Simple vs. Exchange transfusion

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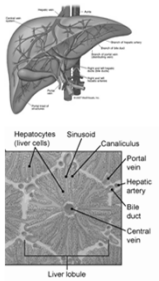
Sickle Hepatopathy

Acute hepatic crisis
- Vaso-occlusion in hepatic vasculature
- ALT ~100-300s; Normal direct bilirubin & Pt/Ptt
- Self-limited

Intrahepatic cholestasis
- Advanced hepatocyte ischemia
- ↑ Direct bilirubin & ≥ 50% of total bilirubin
- Abnormal Pt/Ptt
- Renal dysfunction
- ~90% fatality without exchange transfusion



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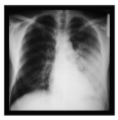
Acute Chest Syndrome



Definition: **Fever (T ≥ 38.5°C)** + **New Lung Infiltrate**
Hypoxia (↓O_2sat >2%)
Chest Pain
Cough, Wheezing, Tachypnea

Epidemiology:[1,2]
- 2nd most common cause of hospitalization
- Leading cause of death
- ½ of patients initially admitted for VOC
- Symptoms arise ~2.5 days after admission

1. Platt OS et al. NEJM 1994
2. Castro O et al. Blood 1994

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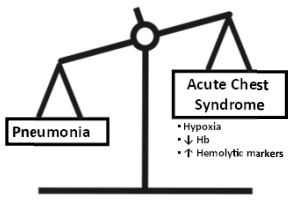
Acute Chest Syndrome

National Acute Chest Syndrome Study Group	
Etiology	**Proportion**
Infection	**30%**
• Chlamydia pneumoniae	• 7%
• Mycoplasma pneumoniae	• 7%
• Virus	• 6%
• Legionella	• 1%
• Other infection	• 9%
Fat Embolism	**9%**
Infarction	**16%**
Unknown	**46%**



Vichinsky EP et al. NEJM 2000

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Acute Chest Syndrome

Prevention
Aggressive incentive spirometery • 10 breaths q2 hours
Avoid oversedation or excessive hydration
Immunizations: • S. pneumonia • H. influenzae • Influenza
SCD-specific Therapies: • Hydroxyurea • L-glutamine

Treatment	
Supplemental O_2	Minimum ≥ 92% Ideal ≥ 95%
Adequate pain control	
Empiric antibiotics	Cephalosporin + macrolide 4th generation quinolone
VTE Prophylaxis	Unfractionated Heparin LMWH
Bronchodilators	Wheezing or Asthma history
RBC transfusion	Simple – mild/moderate Exchange – severe

Glucocorticoids
- Not standard management
- May ↓ hospital duration in children
- Risk of rebound VOC

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Acute Chest Syndrome

Indications for RBC transfusion

Physical Exam:
- Unstable Vitals: Tachypnea, Tachycardia, Hypotension
- Worsening hypoxia (O_2sat < 92%)
- Altered mentation

Laboratory:
- PaO_2 < 70mmHgb
- Hb drop > 2 g/dL
- Evidence of other organ dysfunction (kidney, liver, CNS)

Radiographic
- Multilobe involvement

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Rapidly Progressive Acute Chest Syndrome

1) Respiratory Compromise

2) Multiorgan Failure: Liver failure (75%)
Acute kidney injury (69%)
CNS/mental status changes (44%)

- ~20% of acute chest syndrome events in adults
- Acute drop in platelets
  - 10% decline or < 200k → 5 to 7-fold greater risk[1,2]
- Prompt exchange transfusion therapy

1. Vichinsky E et al, NEJM 2000; 2. Alhandalous C et al, AJH 2015

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Acute Chest Syndrome: Summary

50% develop during hospitalization for VOC
- Vigilant for hypoxia, worsening hemolysis, drop in platelets

Treatment: Supplemental oxygen (goal O_2sat ≥ 95%)
Empiric antibiotics (cover atypical pathogens)

Common transfusion triggers:
Unstable vital signs
O_2sat < 92%
Drop in Hb > 2g/dL from baseline
Multi-lobe infiltrates

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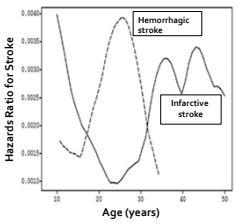
Stroke



Ohene-Frempong K et al, Blood 1998

Lifetime risk:[1] **30%** overt stroke
44% silent infarctions

Primary prevention: STOP Study[2] **(2 – 16 years)**

Transcranial Doppler Velocity > 200 cm/s → Chronic RBC transfusions reduce stroke risk by 92%

Secondary prevention:
- Untreated, 50% have repeat stroke within 2 years [3]
- Chronic RBC transfusions reduces risk

Goal: Hb 10g/dL & Hb S < 30%

1. WY Wong et al, Hematol Oncol Clin N Am 2005; 2. Adams RJ et al, Blood 2004; 3. Powars DR et al, Am J Med 1978

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Stroke: Acute Management

Initial Evaluation: CT of Head, MRI/MRV

Negative →
- Seizure
- Hemiplegic migraine
- TIA
- Post Reversible Encephalopathy Syndrome
- Central sinus venous thrombosis

Positive →
- **Exchange transfusion**
  - Hb 10g/dL
  - Hb S < 30%
- **Maintain O_2 sat ≥ 95%**
- **Adequate blood pressure control**

Role of thrombolytics (tPA)
- Not considered standard of care
- Risk of hemorrhagic stroke
- Retrospective claims database study[1]
  Intracranial hemorrhage (p = 0.45)
  - SCD: 4.9%
  - Non-SCD: 3.2%
- Used in a case-by-case situation

1. Adams RJ et al. Stroke 2017

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Cardiovascular Disease

~26% of deaths in SCD adults attributed to cardiac disease[1]

Biomarkers	Mortality Risk Increase
TRJV > 2.5 m/s[2]	10-fold
Elevated NT-pro BNP[3]	5-fold
Low E/A ratio[4]	3.5-fold

TRJV = tricuspid regurgitant jet velocity

Pulmonary Hypertension[5]
- Present in ~10% of SCD patients
  - TRJV 2.5 – 2.9 m/s → 25 – 39% have mPAP ≥ 25 mmHg
  - TRJV ≥ 3.0 m/s → ~66% have mPAP ≥ 25 mmHg
- Associated with chronic intravascular hemolysis

Heart Failure w/ Preserved Ejection Fraction (HFpEF)/Diastolic Dysfunction[4,5]
- Present in ~20% of SCD patients
- Chronic effects of anemia, ischemia, reperfusion injury may result in diffuse myocardial fibrosis

1. Fitzhugh CD et al, Am J hematol 2009; 2. Gladwin MT et al, NEJM 2004; 3. Machado RF et al, JAMA 2006; 4. Sachdev V et al, J Am Coll Cardiol 2007; 5. Gladwin MET, ASH Education Program 2017

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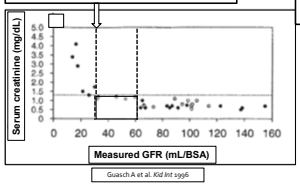
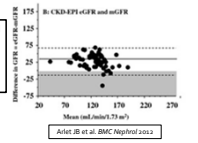
Kidney Function

Serum creatinine rose to standard definitions of abnormal after measured GFR < 30 mL/min/BSA



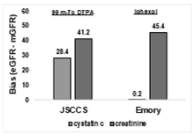
Guasch A et al. *Kid Int* 1996

Serum Creatinine-based CKD-EPI eGFR
- Lowest bias and greatest precision of serum creatinine-based formulas in SCD adults



Arlet JB et al. *BMC Nephrol* 2012

Cystatin C-based CKD-EPI eGFR



Asrani M et al. *Blood Cells Mol Dis* 2015
Yee MEM et al. *Am J Hematol* 2017

- Abnormal tubular secretion of creatinine into urine
- High cardiac output from anemia
- Serum creatinine levels affected by muscle mass

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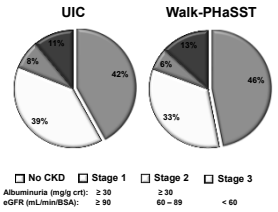
Kidney Disease

Serum creatinine ≥ 1.5 mg/dL → **Time to dialysis/kidney transplant or death averages 3.3 years**[1]



Albuminuria
- Early biomarker for kidney disease
- Associated with degree of hemolysis
- Predicts rapid eGFR decline[2]
- Measure annually
  - If abnormal, check q3 months
- BP < 130/80 mmHg
- Avoid chronic NSAIDs
- ASH Guidelines[3]: Consider ACE-i/ARB
  - Conditional with very low evidence

1. Powars DR et al. Ann Intern Med 1991; 2. Niss O et al. Blood Adv 2019; 3. Liem R et al. Blood Adv 2019

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Priapism

Chronic NO Depletion ⟹ **Down-regulation of Phosphodiesterase 5** ⊥

Stimulus ⟹ **cGMP Accumulation in Corpus Smooth Muscle** ⟹ **PRIAPISM**

Prevalence of 5 – 35% among adolescents and young men
- Mean age at first attack = 15 years
- Average duration 125 minutes

Management
- Self-help: moderate exercise, oral hydration, hot compresses
- Stuttering priapism (< 3 hours):
  - α-adrenergic agonists, hormonal analogues, smooth muscle regulators
- **Ischemic Priapism (≥ 4 hours)** – concern for compartment syndrome
  - Cavernous aspiration ± Irrigation

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Transfusion Therapy

NIH Expert Panel Report 2014

Evidence Based Recommendations

Indication	Strength
Symptomatic, severe Acute Chest Syndrome	Strong
Acute splenic sequestration + severe anemia	Strong
Stroke (Acute or Chronic)	Moderate

Additional Consensus-Based Recommendations

Indication	Method of Transfusion
Hepatic sequestration	Exchange or simple
Intrahepatic cholestasis	Exchange or simple
Multisystem organ failure	Exchange or simple
Aplastic crisis	Simple
Symptomatic anemia	Simple

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Pre-operative Transfusion

- 25 – 30% risk of SCD patients have post-operative complications
- RBC transfusions improve oxygen delivery and lower risk of vaso-occlusion

TAPS Study
- Randomized Hb SS/Sβ^0–thal patients
  - Transfusion (**goal Hb 10g/dL**) or no transfusion
  - Low-risk: Adenoidectomy, Herniorrhapy
  - Moderate-risk: Cholecystectomy, Joint replacement

OR 3.8 for adverse events in no-transfusion arm

* Consider exchange transfusion for high risk surgeries (intracranial, cardiothoracic)

Howard J et al. Lancet 2013

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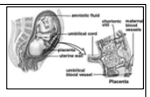
Pregnancy



- Cardiopulmonary stressors (↑ cardiac output, plasma volume)
- Increased adhesion and coagulation proteins
- Reduction of endothelial NO synthase
- Maternal anemia

Maternal and Fetal Risks
• Miscarriage
• Placental abruption
• Pre-eclampsia
• Pre-term labor
• ↑ VOC, Acute chest syndrome
• Low birth weight

1. Koshy M et al. NEJM 1988
2. Malinowski AK et al. Blood 2015

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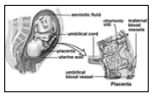
Pregnancy



Randomized study in Hb SS[1]
- Emergent (Hb >6 g/dL) vs. Prophylactic transfusion (Hb ~10g/dL)
- No reduction in OB complications or fetal birth weight
- Significant reduction in VOC

Meta-analysis (12 studies/1291 SCD patients)[2]
Prophylactic transfusions:
- Reduced maternal/neonatal mortality
- Reduced VOC and acute pulmonary events

* Consider transfusions if pregnancy complicated by ↑ VOC, severe anemia, pre-eclampsia[3]

1. Koshy M et al. NEJM 1988; 2. Malinowski AK et al. Blood 2015; 3. NIH Guidelines 2004

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Transfusion Therapy

Red Blood Cell Alloimmunization
- Rh and K ~2/3 of RBC Antibodies
- Incidence[1]: **ABO/D** match → **18 – 76%**
  Full Rh/K match → **5 – 15%**
  Extended RBC match → **7%**

Disparate RBC antigens between donors (European ancestry) vs. SCD patients (African ancestry)[2]

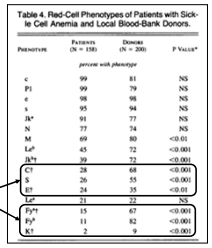

Table 4. Red-Cell Phenotypes of Patients with Sickle Cell Anemia and Local Blood-Bank Donors.

Phenotype	Patients (N = 150)	Donors (N = 200)	P Value*
	percent with phenotype		
c	99	81	NS
P_1	99	79	NS
e	98	98	NS
s	95	94	NS
Jk^a	91	77	NS
N	77	74	NS
M	69	80	<0.01
Le^b	45	72	<0.001
Jk^{a+}	39	72	<0.001
C^+	28	68	<0.001
S	26	55	<0.001
E^+	24	35	<0.01
Le^a	21	22	NS
Fy^{a+}	15	67	<0.001
Fy^b	11	82	<0.001
K^+	2	9	<0.001

1. Chou ST et al. ASH Education Book 2013; 2. Vichinsky E et al, NEJM 1990

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Transfusion Therapy

Delayed Hemolytic Transfusion Reaction
- **2 to 14 days** post-transfusion
- ~5% of transfused SCD patients experience DHTR[1]
- Can lead to **Hyperhemolysis + low Retic count**

Milder cases:[2] Corticosteroids + IVIG

Severe cases: Corticosteroids + IVIG
Judicious RBC transfusions (extended-match)
Limited data for Rituximab, Erythropoietin

1. Talano JA et al. Pediatrics 2003; de Montalembert M et al. Haematologica 2011

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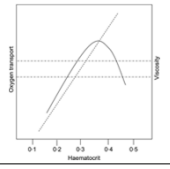
Transfusion Therapy

Iron Overload
- 1 unit pRBC = 200 – 250mg of iron
- **Liver**, pancreas, heart vulnerable to iron overload
- Ferritin > 2,500 ng/mL : 78% specificity for liver iron 7 mg/g[1]
- Chelation: Subq/IV: Deferoxamine
  Oral: Deferasirox or Deferiprone

Hyperviscosity
- Avoid acute simple transfusion > 10 g/dL



1. Karam LB et al. Pediatr Blood Cancer 2008; 2. Jan K et al. Transfusion 1982

34

Transfusion Summary

- **Indications for transfusion**
  - Severe acute chest syndrome, stroke, splenic sequestration
  - Pre-operative
  - Pregnancy with complications
- **ABO/Full Rh/Kell minimum typing**
- **Delayed hemolytic transfusion reaction**
  - 2-14 days post-transfusion
  - Steroids + IVIG

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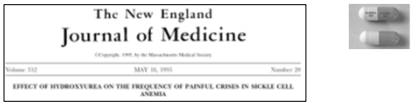
Hydroxyurea


The New England Journal of Medicine
EFFECT OF HYDROXYUREA ON THE FREQUENCY OF PAINFUL CRISES IN SICKLE CELL ANEMIA

Multicenter Study of Hydroxyurea (MSH) in Sickle Cell Anemia
- 299 Hb SS/Sβ^0-thal adults with ≥ 3 VOC/year
- Start 15 mg/kg, titrate up 5 mg/kg q12 weeks if no myelosuppression

Clinical Complication	HU	Placebo	p-value
VOC Episode	1.0/year	2.4/year	< 0.001
Acute Chest Syndrome	25 patients	51 patients	< 0.001
Transfusions	336 U	586 U	0.004

*** FDA-Approved for adults in 6/1998, children in 12/2017.**

Charache S et al. NEJM 1995

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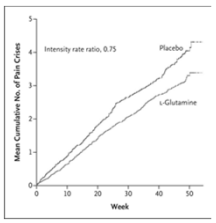
L-Glutamine

- Essential amino acid necessary for NAD production
- ↑ NAD redox ratio, ↓ Endothelial adhesion in sickle RBC
- 253 Hb SS/Sβ⁰-thal, Age ≥ 5 years, ≥ 2 VOC/year
- Randomized (2:1) to L-glutamine vs. placebo
  - 0.3 mg/kg given for 48 weeks
  - Stratified by HU use (~2/3 on HU in each group)



Placebo: 4 VOC/yr
L-glutamine: 3 VOC/yr

*** FDA-Approved in 7/2017**

Niihara Y et al. NEJM 2018

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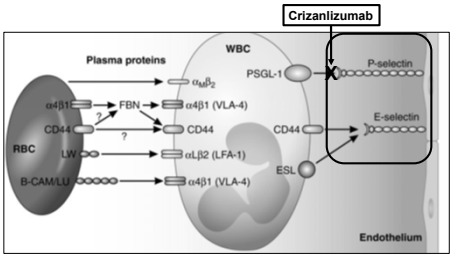
Selectin Mediates Vaso-Occlusion

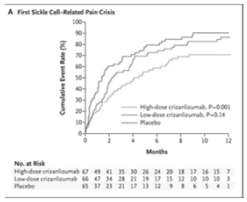


Telen MJ. Blood 2016

38

Crizanlizumab

- 198 SCD patients (all genotypes), Age 16 - 65 years, 2 -10 VOC/year
- Randomized (1:1:1) low (2.5mg/kg), high (5 mg/kg) dose or placebo
  - 52 week study
  - ~2/3 on HU in each group



Placebo: 3 VOC/yr
Crizanlizumab 2.5mg/kg: 2 VOC/yr
Crizanlizumab 5mg/kg: 1.6 VOC/yr

*** FDA-Approved in 11/2019**

Ataga KI et al. NEJM 2017

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FDA-Approved Therapies to Reduce VOC

Hydroxyurea[1]

Outcome	HU	Placebo	p-value
VOC	1.0 events	2.4 events	< 0.001
Acute Chest Syndrome	25%	51%	< 0.001

L-glutamine[2]

Outcome	L-glutamine	Placebo	p-value
VOC	3.0 events	4.0 events	0.005
Acute chest syndrome	8.6%	23.1%	0.003

Crizanlizumab[3]

Outcome	Crizanlizumab	Placebo	p-value
VOC	1.6 events	3 events	0.005
Hospital days	4.0 days	6.9 days	0.02

1. Charache S et al, NEJM 1995; 2. Niihara et al., NEJM 2018; 3. Ataga KI et al, NEJM 2017

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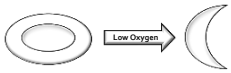
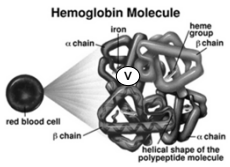
Deoxygenation Leads to Hb S Polymerization





Voxelotor:
Small molecule that binds Hb stabilizing it in the oxygenated state

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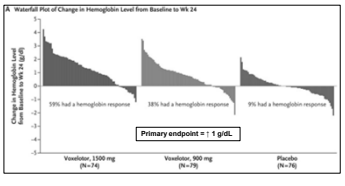
VOXELOTOR

- 274 SCD patients (all genotypes), Age 12 - 65 years
- Randomized (1:1:1) low (900mg), high (1500mg) dose or placebo
  - 1º endpoint assessed week 24
  - ~2/3 on HU in each group



Placebo: Δ -0.1 g/dL
Voxelotor 900mg: Δ +0.6 g/dL
Voxelotor 1500mg: Δ +1.1 g/dL

*** FDA-Approved in 11/2019**

Vichinsky et al. NEJM 2019

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Curative Therapies: Allogeneic HSCT*

1,000 SCD recipients from HLA-matched, sibling donors (1986 – 2013)[1]
- **Median age 9 years** (range: 1 – 54 years) & **87% myeloablative**
- At 5 years: **91% cure rate**
  15% acute GVHD, 14% chronic GVHD

Nonmyeloablative & SCD adults:[2] **87 – 92% stable engraftment**
0% acute or chronic GVHD

Haploidentical HSCT:[2]
- ~15% of eligible patients have HLA-matched sibling
- **Post-Cy:** **57 – 100% stable engraftment**
  0 – 25% aGVHD, 0 – 13% cGVHD

* Most common indications include stroke, recurrent VOC or acute chest syndrome despite HU therapy

1. Gluckman E et al, Blood 2017; 2. Saraf SL et al. J Clin Med 2019

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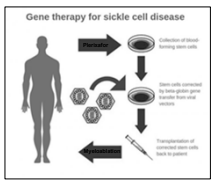
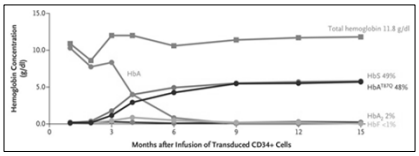
Gene Therapy





6 gene therapy studies currently enrolling SCD patients on clinicaltrials.gov
- 4 targeting γ-globin/Hb F
- 2 targeting β-globin/Hb A

Ribeil JA et al. NEJM 2017

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Therapy Summary

Hydroxyurea, L-Glutamine, Crizanlizumab → Reduce VOC
- L-glutamine & crizanlizumab improve VOC even in those on hydroxyrea

Voxelotor → Improves Hgb concentration

Curative Approaches
- Allogeneic hematopoietic stem cell transplantation
  - Nonmyeloablative approaches well tolerated in adults
  - Haploidentical approaches increase donor pool
- Gene therapy
  - Uses autologous cells
  - Challenges –CD34 dose, transfection efficiency, myeloablative regimen, cost

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THANK YOU & QUESTIONS

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Question 1

A 21 year old man with Hb SS sickle cell disease presents for a vaso-occlusive pain episode. Upon admission, he is started on IV hydration and patient controlled analgesia with adequate pain relief.

On the 2nd day of hospitalization, he develops worsening chest pain, a new pulmonary infiltrate on chest x-ray, and worsening hemolysis (LDH increases 2-fold, Hb drops by 2.4 g/dL from admission values).

His vital signs are as follows: T 38.3, P 85, RR 18, BP 124/80, and O_2 saturation 91%.

Which of the following are NOT indicated for his initial management:

1. Supplemental O_2
2. Continued PCA for pain relief
3. Dexamethasone 4mg IV q12 hours
4. Red blood cell transfusion
5. Initiating antibiotics

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Question 1: Acute chest syndrome

1. Supplemental O_2: Maintain oxygen at least ≥ 92% (> 95% preferred)
2. Adequate pain management is essential
3. Dexamethasone: Risk of rebound VOC, questionable benefit in children that are critically ill, but not considered standard management in adults
4. Red blood cell transfusion: Simple or exchange could be given
5. Initiating antibiotics: Infection is most common identifiable cause of acute chest syndrome. Ensure that atypical bacteria are covered.

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Question 2

A 32 year old woman with Hb SS SCD presents to a follow up clinic visit doing well and without increased VOC frequency/intensity. She informs you that she is 12 weeks pregnant. She had 1 prior pregnancy that went to term and was not complicated by increased VOC or pre-eclampsia. Her blood pressure and renal function are stable and Hb = 7.3 g/dL.

Which of the following are NOT indicated for her initial management:

1. Prenatal vitamins + folic acid supplement
2. Referral to high-risk obstetrics service
3. Genetic counseling
4. Red blood cell transfusion

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Question 2: Pregnancy & SCD

1. Prenatal vitamins + folic acid supplements
2. Referral to high-risk obstetrics service
3. Genetic counseling to discuss risk of child
4. Red blood cell transfusion – The role of prophylactic pRBC transfusions in an uncomplicated pregnancy is unclear. In a randomized study of transfusion to maintain > 6 g/dL vs. 10 g/dL, no differences in OB complications or fetal birth weight but a reduction in VOC frequency were observed in the higher Hb arm. This patient had no complications with prior pregnancy and is doing well at this time.

   If the patient was having more VOC, signs of pre-eclampsia, or had prior complications during her pregnancy, would strongly consider prophylactic RBC transfusions.

   The patient should be referred to high-risk OB, start prenatal vitamins + folic acid due to high demands, and monitored closely (q4weeks).

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Question 3

A 25 year old man with Hb Sβ^0-thal SCD presents with L arm and leg weakness for the past day. MRI imaging demonstrates an acute stroke without hemorrhagic conversion. His Hb = 7.8 g/dL and you contact the hospital's Blood Bank to arrange an emergent transfusion.

Which of the following are the goal parameters for transfusion in the setting of an acute stroke?:

1. Hb 10g/dL, Hb S < 50%
2. Hb 10g/dL, Hb S < 30%
3. Hb 12 g/dL, Hb S < 50%
4. Hb 12 g/dL, Hb S < 30%
5. No exchange required, just simple transfusion to Hb 10g/dL

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Question 3

1. Hb 10g/dL, Hb S < 50%
2. Hb 10g/dL, Hb S < 30%: This should be your initial goal. In the first two years after the initial event, the risk of another stroke is 50% and this can be substantially reduced by continuing to maintain these transfusion parameters. A hemoglobin of > 11g/dL is not recommended in the acute transfusion setting due to the risk of hyperviscosity. A simple transfusion is used pre-operatively, but will not improve blood flow rheology rapidly enough for acute situations such as stroke or severe acute chest syndrome.
3. Hb 12 g/dL, Hb S < 50%
4. Hb 12 g/dL, Hb S < 30%
5. No exchange required, just simple transfusion to Hb 10g/dL

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Question 4

A 20 year old woman with Hb SS SCD presents for a consultation to help with her management. She had dactylitis and several VOC as a young child that had improved until the past 12 months. At that time she enrolled in college and has had 4 VOC in the past year requiring hospitalization.

Which of the following therapies could be offered to this patient to reduce the frequency of VOC?:

1. Hydroxyurea
2. L-glutamine
3. Crizanlizumab
4. Voxelotor
5. Options 1 – 3
6. Any of the above

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Question 4: FDA-approved therapies for SCD

Hydroxyurea

Outcome	HU	Placebo	p-value
VOC	1.0 events	2.4 events	< 0.001
Acute Chest Syndrome	25%	51%	< 0.001

L-glutamine

Outcome	L-glutamine	Placebo	p-value
VOC	3.0 events	4.0 events	0.005
Acute chest syndrome	8.6%	23.1%	0.003

Crizanlizumab

Outcome	Crizanlizumab	Placebo	p-value
VOC	1.6 events	3 events	0.005
Hospital days	4.0 days	6.9 days	0.02

Voxelotor

Outcome	Voxelotor	Placebo	p-value
Increase Hb > 1g/dL	51%	7%	< 0.001

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Question 5

A 25 year old man with Hb SC SCD presents to the emergency room with a painful erection that has been ongoing for 4 hours. He tried pseudophedrine and taking a cold shower without improvement.

Which of the following therapies should be immediately provided to treat this patient?

1. Aspiration and Irrigation of the corpora cavernosa
2. Exchange transfusion
3. Bicalutamide
4. IV hydration and clinical surveillance
5. Cavernosal artery embolization

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Question 5: Ischemic Priapism

1. Aspiration and Irrigation of the corpora cavernosa – Priapism lasting 4 or more hours requires emergent aspiration + irrigation. An α-agonist, such as phenylephrine, is often used with the irrigation improvement is observed in > 80% of cases.
2. Exchange transfusion –There are case reports of ASPEN (**A**ssociation of **S**CD, **P**riapism, **E**xchange transfusion and **N**eurologic events) syndrome, characterized by neurologic complications, occurring after treating priapism with exchange transfusion. Believed that vasoactive substances released after priapism detumescence leads to cerebral ischemia with symptoms ranging from headaches to seizure or obtundation.
3. Bicalutamide – Preventative measure for future priapism episodes.
4. IV hydration and clinical surveillance – Not recommended for ischemic priapism.
5. Cavernosal artery embolization – Can be used for stuttering priapism but 50% risk of erectile dysfunction.

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