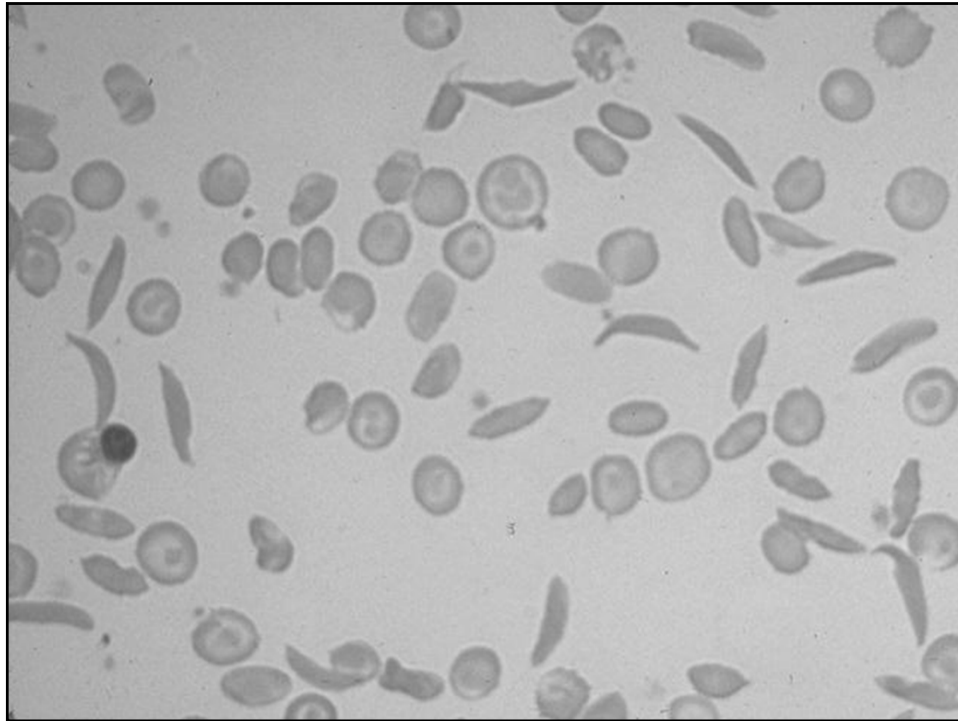


Sickle Cell Disease

Payal Desai, MD
Assistant Professor
Director of Sickle Cell Research
Division of Hematology
The Ohio State University Wexner Medical Center

Introduction/Diagnosis



Electrophoretic patterns in Common Hemoglobinopathies

<u>Condition</u>	<u>Hb A</u>	<u>Hb S</u>	<u>Hb C</u>	<u>Hb F</u>	<u>Hb A2</u>
Normal	95-98	0	0	<1	<3.5
Beta thal minor	90-95	0	0	1-3	>3.5
Sickle cell trait	50-60	35-45	0	<2	<3.5
Sickle-beta (+) thal	5-30	65-90	0	2-10	>3.5
Sickle-beta (0) thal	0	80-92	0	2-15	>3.5
Sickle-Hb C disease	0	45-50	45-50	1-8	<3.5
Sickle cell anemia	0	85-95	0	2-15	<3.5

Pathophysiology

Sickle Cell Anemia Pathophysiology

Sickle cell anemia (SCA) is the classical example of a genetic (or molecular) disorder

Beta chain of Hemoglobin A

.....GAG.....
..... β^6 Glu.....

Beta chain of Hemoglobin S

.....GTG.....
..... β^6 Val.....

Genetics

- **Haplotypes of Sickle Cell Disease:**



Gabriel, A. & Przybylski, J. (2010) Sickle-cell anemia: A Look at Global Haplotype Distribution. *Nature Education* 3(3):2

Sickle Cell Anemia Pathophysiology

- **Manifestations of SCD are driven by 2 major processes:**
 - **Vaso-occlusion with ischemia-reperfusion injury**
 - **Hemolytic anemia**

Pathophysiology

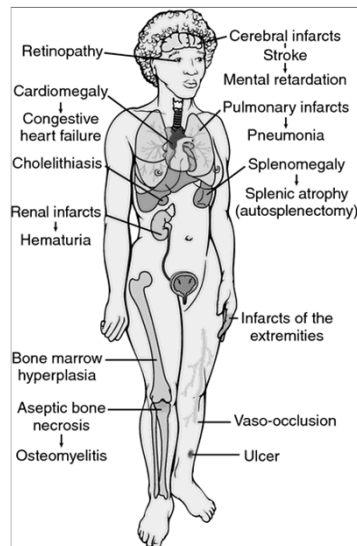
- **Polymerization of deoxygenated HbS – primary event in pathogenesis of SCD**
- **Rate and extent of polymer formation in sickle RBC depends on several variables:**
 - **The cell's degree of deoxygenation**
 - **The intracellular hemoglobin concentration**
 - **The presence or absence of hemoglobin F**

Sickle Cell Anemia Pathophysiology

- **Not just RBCs:**
 - **Platelet Activation**
 - **Endothelial Activation**
 - **Neutrophil Transmigration**

Clinical Complications & Therapy

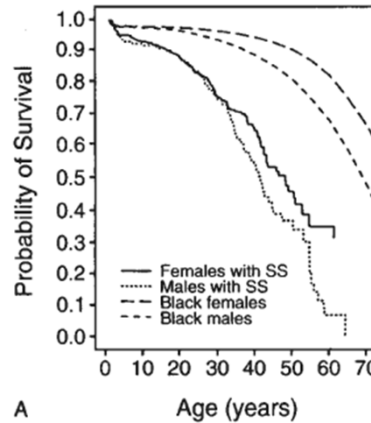
Complications of SCD



Konotey-Ahulu FID. The Sickle Cell Disease. Clinical Manifestations Including the "Sickle Crisis". *Arch Intern Med.* 1974;133(4):611-619.

Mortality in Sickle Cell Disease

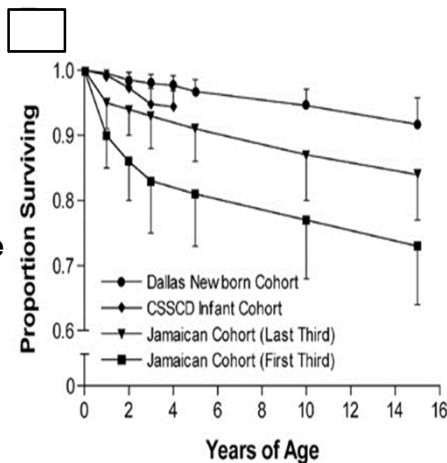
- Childhood mortality rates in SCD
 - In 1973 – median survival of 14.3 years
 - CSSCD ~ 85% SS children and adolescents with survived to age 20
 - In 2004 survival analysis of SS and S β^0 subjects SCD-related survival 93.6% by age 18



Diggs LM. Anatomic lesions in sickle cell disease. Sickle cell disease: diagnosis, management, education and research. St. Louis: C.V. Mosby, 1973:189-229
 Leikin SL, Gallagher D, Kinney TR, Sloane D, Klug P, Rida W. Mortality in children and adolescents with sickle cell disease. Pediatrics 1989;84:500-508
 Platt et al. Mortality In Sickle Cell Disease – Life Expectancy and Risk Factors for Early Death. N Engl J Med 1994; 330:1639-1644
 Quinn C T et al. Survival of Children with Sickle Cell Disease. Blood 2004;103:4023-4027

Mortality in Sickle Cell Disease

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Cardiovascular Complications of SCD

Acute Complications

- Acute Chest Syndrome
- Pulmonary Embolism
- Ventricular Arrhythmias
- Myocardial Ischemia
- Risk of Sudden Death

Chronic Complications

- Cardiomyopathy
- Pulmonary Hypertension

Acute Chest Syndrome *Definition*

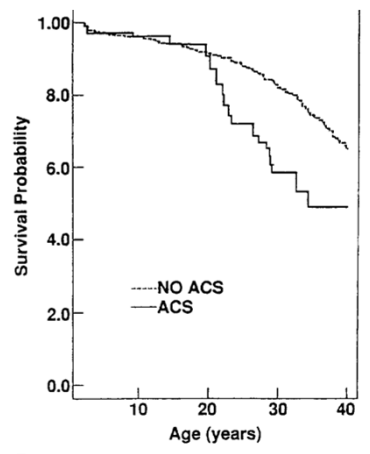
- Charache suggested this name in 1979 for what he felt was a poorly understood process
- A new pulmonary infiltrate in a clinically ill patient with sickle cell disease
- Fever, cough, chest pain, tachypnea, wheezing, rales on exam

Acute Chest Syndrome - Clinical Presentation

- Frequency of ACS is dependent on genotype and baseline hemoglobin level
- Young children (2 – 4 yrs): fever, cough, wheezing and rarely have pain
- Adults: Often afebrile, SOB, and with severe pain
- X-ray findings: upper lobe in children; multilobe/lower lobe in adults
- Children < blood transfusions than adults
- Hospitalization is ~ 5.4 days in children vs ~ 9 days in adults

Acute Chest Syndrome - Mortality

- Patients with higher ACS rate have higher rate of mortality than those with low ACS rate
- Increased rate of mortality may contribute to decline in ACS rate with age



Castro, et al., Blood, 1994

Acute Chest Syndrome Treatment

- **Broad spectrum antibiotics – cephalosporin + macrolide**
- **Bronchodilator, incentive spirometry ± chest PT**
- **RBC transfusion (Simple vs Exchange)**
 - **Phenotypically matched RBC**
- **Experimental treatments**
 - **Steroids**
 - **Inhaled nitric oxide**

Acute Chest Syndrome Prevention

- **Hydroxyurea – known to decrease the frequency of acute chest syndrome**
- **Incentive Spirometry**
- **Gentle Hydration**

Sickle cell disease and venous thromboembolism

- All patients require prophylaxis unless there is a contraindication
- Pulmonary Embolism: 0.44% vs 0.12% in nml AA popuation
- DVT: 2 fold increase in hospitalized patients compared to Hb AA patients
- Cerberal Vein Thrombosis:
Complicated with stroke as well but reported at 5-10% of patient with SCD

Sickle cell disease and venous thromboembolism

Table 1 Factors influencing development of VTE in SCD patients		SS
Traditional risk factors	SCD-related factors	
<ul style="list-style-type: none"> • Central venous catheters (CVCs) for poor venous access, transfusion therapy <ul style="list-style-type: none"> • Totally implantable CVCs (port) • Partially implantable CVCs (tunneled and nontunneled lines) • Frequent hospitalization for pain and complications • Surgery <ul style="list-style-type: none"> • Orthopedic surgery (hip, shoulder avascular necrosis) • Cholecystectomy • Pregnancy 	<ul style="list-style-type: none"> • Increased prevalence of thrombophilic defects <ul style="list-style-type: none"> • Anti-phospholipid antibodies • Protein C/S deficiency • Genotype (SS/Sβ⁰ vs. SC/Sβ⁺) • Splenectomy <ul style="list-style-type: none"> • Surgical • Functional asplenia? 	<ul style="list-style-type: none"> • 1% • S • D

D-Dimer in SCD

- Nml < 50ng/ml
- 35 normal subjects: Mean D-dimer 79 +/- 25 ng/ml
- SCD steady state: Elevated in 23/25 subjects -> 566 +/- 739 ng/ml
- SCD painful crisis: 21/21 subjects -> 1,038 +/- 1,010 ng/ml

Francis RB Jr. Haemostasis. 1989;19(2):105-11.

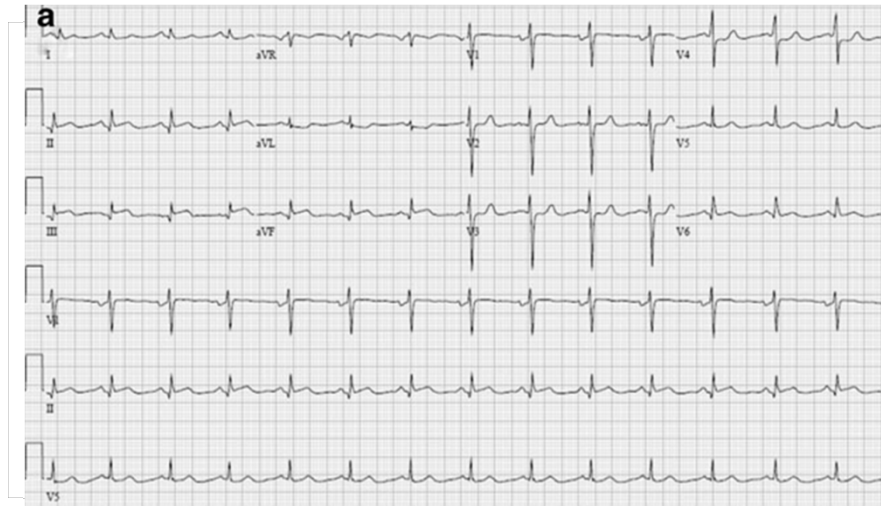
Elevated fibrin D-dimer fragment in sickle cell anemia: evidence for activation of coagulation during the steady state as well as in painful crisis.

Myocardial Infarction in Absence of Epicardial CAD

- 34 y/o AAF with SCD presents to the ED with atypical chest pain
 - On Hydroxyurea
 - Hx of TIA
- 10-20% of autopsies in SCD have shown myocardial infarctions (Martin CCR *et al.* J Nat Med Assoc 1995)

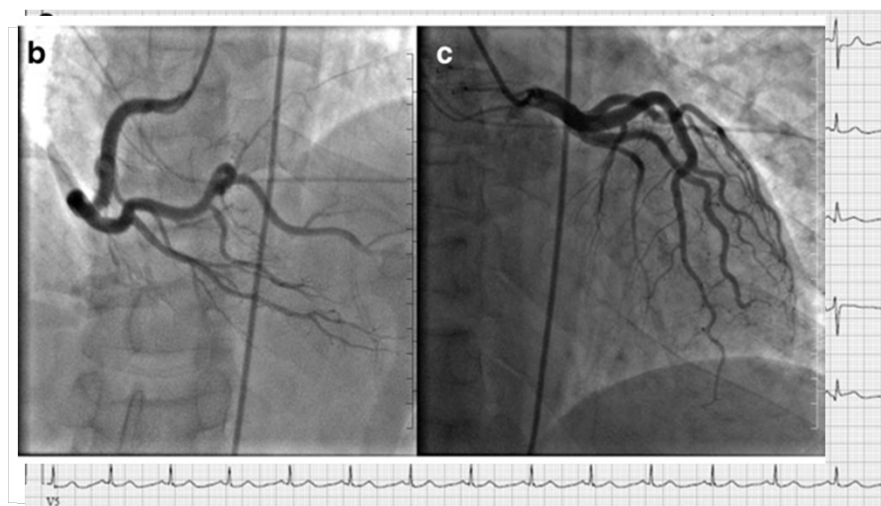
Assanasen C *et al.* J Ped Hem Onc 2003.

Myocardial Infarction in Absence of Epicardial CAD



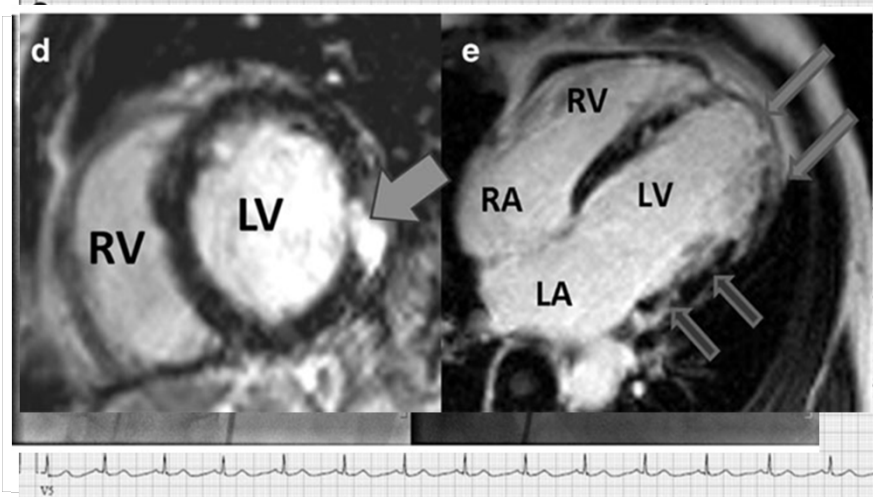
Assanasen C *et al.* J Ped Hem Onc 2003.

Myocardial Infarction in Absence of Epicardial CAD



Assanasen C *et al.* J Ped Hem Onc 2003.

Myocardial Infarction in Absence of Epicardial CAD



Assanasen C et al. J Ped Hem Onc 2003.

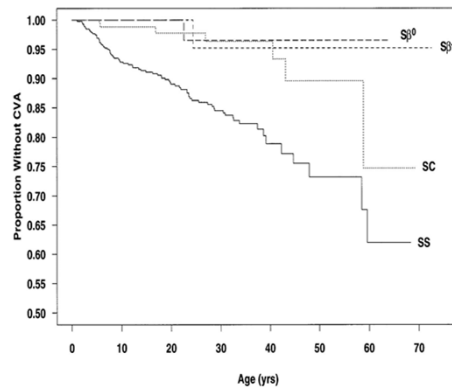
Acute Multi Organ Failure

- Acute development of severe dysfunction of at least 2/3 major organs during crises: Neurologic, lung, liver, and kidney
- Reason for obtaining renal ** and hepatic enzymes
- Requires aggressive treatment with antibiotics and exchange transfusion (to be decided in conjunction hematology)

** baseline renal enzymes low in SCD due to hyposthenuria

Acute Stroke

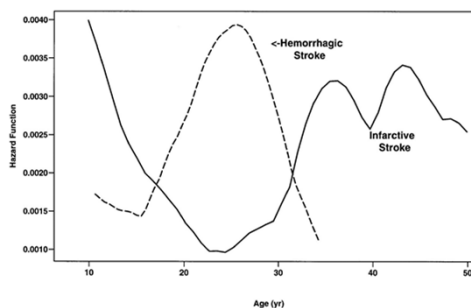
- 24% of patients with clinically overt stroke by age of 45
- MRI and cognitive testing suggest subtle abnormalities frequent
- Exchange transfusion (preventative)
- Role of
 - tPA
 - ASA
 - Plavix



Ohene-Frempong K et al. Blood 1998;91:288-294

Acute Stroke

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- MRI and cognitive testing suggest subtle abnormalities frequent
- Exchange transfusion (preventative)
- Role of
 - tPA
 - ASA
 - Plavix



Ohene-Frempong K et al. Blood 1998;91:288-294

Priapism

- **Sustained penile erection**
- **May correlate with hemolysis due to importance of nitric oxide**
- **Treatment may be local urologic, drainage, or use of vasodilators such as sildenafil**
- **Hydrea and exchange transfusion effect unclear and not effective as acute rx**

Alloimmunization

- **Alloimmunization is a serious and common complication of transfusion therapy in SCD**
- **Refers to the development of new clinically important antibody following exposure to foreign red cell antigens**
- **Frequency in SCD is higher than in other chronically transfused populations**

Sickle Cell HTR Syndrome

- Manifestations of an acute or delayed HTR
- Symptoms suggestive of a sickle cell pain crisis that develop or are intensified during the HTR
- Can have marked reticulocytopenia or reticulocytosis based on antibody
- Development of a more severe anemia after transfusion than was present before (*bystander immune cytotoxicity*)
- Subsequent transfusions may further exacerbate the anemia, and may become life-threatening

Adapted from Petz et al. Transfusion, April '97

Sickle Cell HTR Syndrome - Management

- Limit RBC transfusion to only when clearly needed
- Judicious pRBC transfusion
- Employ phenotypically matched RBC
- Treatment of transfusion reaction
 - steroids, intravenous immunoglobulin, EPO
 - ? Rituximab – to decrease risk of transfusion reaction in alloimmunized patients

Pain in Sickle Cell Disease

Robert Taylor, MD
Associate Professor – Clinical
Department of Neurology
The Ohio State University Wexner Medical Center

Biology

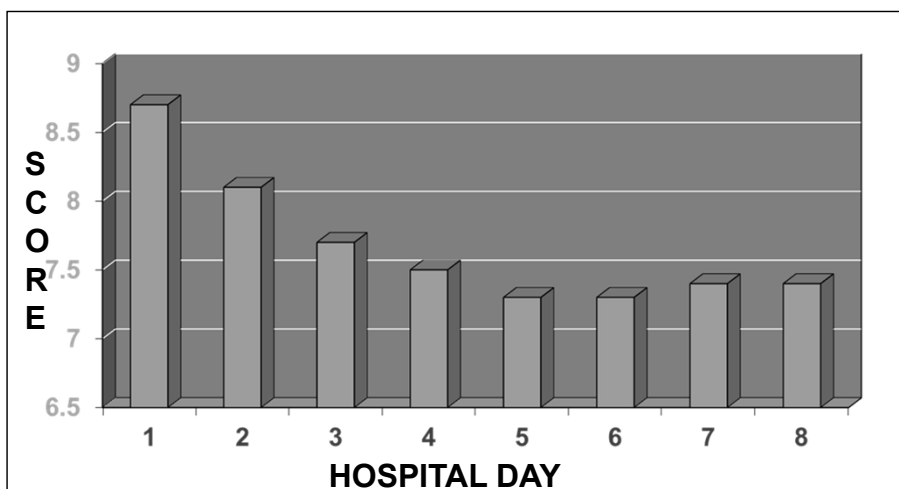
- **Types of Pain in Sickle Cell Disease**
 - » **Acute Pain**
 - » **Chronic Pain**
 - » **Neuropathic Pain**
 - » **Mixed Pain**

Courtesy of Dr. Samir Ballas

Biology

- **Acute Vaso-occlusive Crises**
 - Degree of polymer formation/cellular damage
 - Interacting with other factors in the cells environment (endothelial cells and leukocytes)
 - Neutrophil transmigration
 - Dehydrated dense sickle cells contribute to anemia and hemolysis

Pain Intensity Scores During Hospitalization for Acute Painful Episodes in 1998-2002



Ballas & Lusardi, Am J Hematol 2005, Courtesy of Dr. Samir Ballas

Sickle Cell Pain - Progressive Disease

←————→

Episodic

Chronic

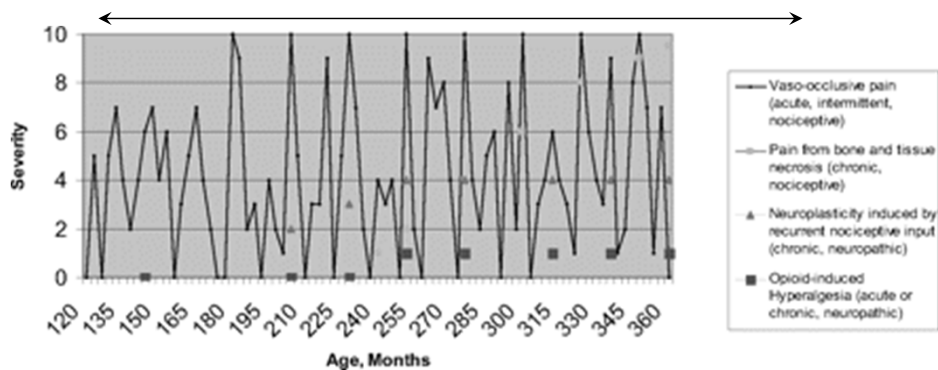
Relapsing

Remitting

Progressive

Smith et al. *ASH Education Book*
December 4, 2010 vol. 2010 no. 1 409-415

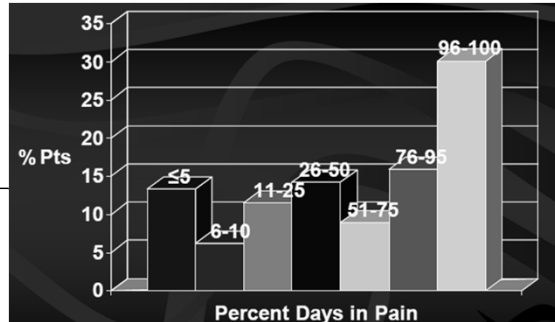
Sickle Cell Pain - Progressive Disease



Smith et al. *ASH Education Book*
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Sickle Cell Pain – PICES STUDY

- 29,839 submitted diaries
- 141 pts. (62%) submitted
- >70% of diaries
- Pain on 16,586 diaries (55.6%)
- Crisis on 4,429 diaries (14.8%)



- 30% of subjects had pain nearly every day
- 13% with no pain

Smith et al. *ASH Education Book*
December 4, 2010 vol. 2010 no. 1 409-415

Neuropathic Pain

- Neuroplasticity and Remodeling:
 - Anatomical brain changes in the surrounding glia (astrocytes and microglia)
 - Altered neuronal phenotype
- Sensations of pain in the absence of an experimental stimulus and/or by demonstrating abnormal (hyperalgesic) pain responses from standardized pain stimuli

Hansson et al. *Pain* 129:256-259

Neuropathic Pain/Mixed

- Transplanted patients ages 16 to 45 years with severe SCD who achieved cure showed that they still had pain after transplantation, which lasted for months
- Study showed SCD patients choose descriptors commonly used to describe neuropathic nociceptive pain to describe their SCD pain
 - Burning
 - Tingling
 - Shooting
 - Lancinating
 - Numbness
 - Paroxysmal

Courtesy of Dr. Sameer Ballas, Bennett MI et al. *Pain* 127(3):199–203
Hsieh MM, et al. *N Engl J Med* 361(24):2309–2317.

Addiction vs Pseudo-addiction vs Tolerance

- **Addiction**
 - Loss of control over use of a drug
 - Compulsive use of the drug
 - Continued use despite harming the person or others
- **Pseudo-addiction**
 - May mimic addiction behavior
 - Return over and over to MD seeking more pain relief
 - Watching the clock for the next dosage
 - Key is what is driving their behavior
 - Inadequate pain control
- **Tolerance**
 - Loss of Efficacy over Time
 - Generally due to worsening disease

Psychosocial and Environmental Processes

- Range of interpersonal and social processes
 - Affect interpretation of environmental experiences
 - Response to Stress
 - Risk Resiliency/Coping
 - Neuroendocrine and immune responses to stress
 - Impact of how individuals interpret and respond to the environment including progression of disease
 - Catastrophizing
 - Depression
 - Distrust of the Medical Community

Health Behaviors

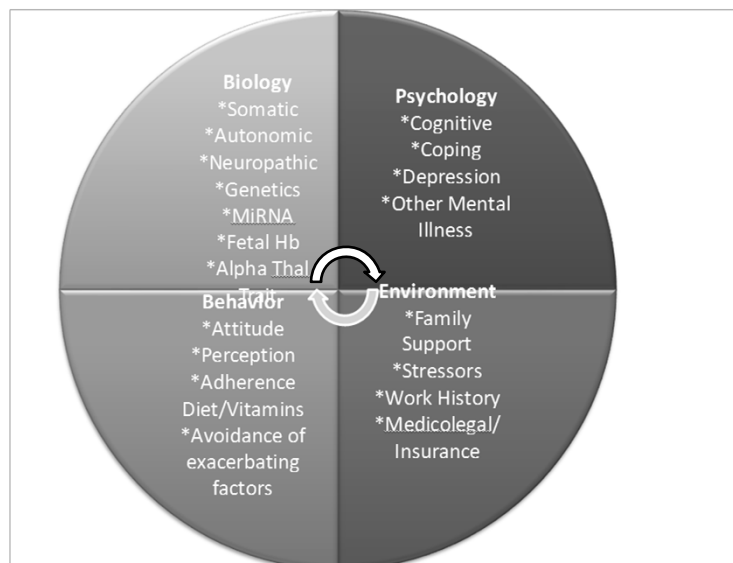
- 1st Study
 - No significant relationship between temperature and the occurrence of painful episodes
 - Higher wind speeds during the preceding 24 h were associated with the onset of pain
- 2nd Study – MSH – direct associations between other climate conditions and SCD pain
 - Exacerbated SCD pain during seasonably colder temperatures, but not during days with lower barometric pressure
 - Colder seasons were significantly associated with greater pain intensity

Nolan VG, et al. *Br J Haematology* 143:433–438, Charache S, et al. *N Engl J Med*.1995;332:1317-1322

Health Behavior

- **Role of Sleep: Nocturnal Hypoxemia and OSA**
- **Vitamin D Deficiency**
- **Menstrual Cycle Pain**
- **Medication Compliance:**
 - **Retrospective claims in North Carolina Medicaid program (6/1999 – 8/2008)**
 - **35% of 312 subjects adherent with Hydroxyurea**
 - **Adherence associated with**
 - **↓ in both all-cause and SCD-related inpatient and emergency room visits & costs, and SCD-related total costs**
 - **↑ in HU cost and all-cause office visit costs**
- **Other anecdotal behaviors**
 - **Exercise – moderate**
 - **Hydration – due to hyposthenuria**

Multi-factorial Model



Payal Desai, MD
Assistant Professor
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Our approach to treatment: Biology

- **Hydroxyurea**
 - ↓ frequency of painful episodes, acute chest syndrome, blood transfusions and hospitalization
 - May ↑ survival in patients with severe disease
- **Decitabine**
 - May be beneficial for patients intolerant or refractory to HU
- **Penicillin**
- **Folic acid**
- **Transplant**
- **Other Experimental Therapies**

Charache et al, NEJM, 1995; Steinberg et al, JAMA, 2003; Steinberg et al, 2010; Voskaridou et al, Blood, 2010; Sauntharajah et al, BJH, 2008

A Word About Transfusions

Three types

- Simple (ie Top Up)
- Partial
- Exchange

Factors deciding type

- Baseline Hemoglobin
- Pre Transfusion Hb S %
- Goal Hb S % Post Transfusion
- Alloimmunization/Patient History

A Word About Transfusions

Three types

7

Don't routinely transfuse patients with sickle cell disease (SCD) for chronic anemia or uncomplicated pain crisis without an appropriate clinical indication.

Patients with SCD are especially vulnerable to potential harms from unnecessary red blood cell transfusion. In particular, they experience an increased risk of alloimmunization to minor blood group antigens and a high risk of iron overload from repeated transfusions. Patients with the most severe genotypes of SCD with baseline hemoglobin (Hb) values in the 7-10 g/dL range can usually tolerate further temporary reductions in Hb without developing symptoms of anemia. Many patients with SCD receive intravenous fluids to improve hydration when hospitalized for management of pain crisis, which may contribute to a decrease in Hb by 1-2 g/dL. Routine administration of red cells in this setting should be avoided. Moreover, there is no evidence that transfusion reduces pain due to vaso-occlusive crises. For a discussion of when transfusion is indicated in SCD, readers are referred to recent evidence-based guidelines from the National Heart, Lung, and Blood Institute (NHLBI) (see reference below).

Our approach to treatment: Indications for Transfusion

Acute

- Stroke/CNS Deficit
- Acute Chest Syndrome
- Multiorgan Failure/Sepsis
- Preoperative (moderate to high risk surgery, consider for mild)
- Acute hepatic/splenic sequestration
- SYMPTOMATIC anemia
- Myocardial Infarction

Chronic

- Primary or secondary stroke prevention
- Prevention of progression of end organ damage
- Prevention of recurrent pain
- Prevention of stuttering priapism

Incidence of Adverse Events in the Observation and Transfusion Groups per 100 Person-Years

Adverse Event	Sample Size	At Least 1 Adverse Event	Total Adverse Events	At-Risk Time	Adverse Events/ 100 Person-Yr	Incidence Rate Ratio (95% CI) ^a	P Value
	<i>no. of participants</i>		<i>no.</i>	<i>person-yr</i>			
Vaso-occlusive pain						0.41 (0.20–0.75)	0.004
Observation group	97	56	295	289	102.21		
Transfusion group	99	32	126	304	41.58		
Acute chest syndrome						0.13 (0.04–0.28)	<0.001
Observation group	97	24	41	289	14.35		
Transfusion group	99	5	5	304	1.81		
Priapism [†]						0.13 (0.03–0.55)	0.02
Observation group	52	7	10	158	6.65		
Transfusion group	59	1	1	178	0.84		
Symptomatic avascular necrosis of the hip						0.22 (0.05–0.85)	0.02
Observation group	97	6	6	289	2.25		
Transfusion group	99	1	1	304	0.49		
Headache						0.78 (0.39–1.57)	0.40
Observation group	97	30	93	289	32.34		
Transfusion group	99	24	76	304	25.15		
Blood-transfusion reaction						5.33 (1.67–23.52)	0.05
Observation group	31 [‡]	1	1	90	1.66		
Transfusion group	90 [§]	15	24	277	8.85		
Ferritin >1500 ng/ml						14.42 (5.41–875.17)	<0.001
Observation group	31 [‡]	3	33	90	37.07		
Transfusion group	90 [§]	76	1479	277	534.70		

^a The incidence ratio was calculated as the rate of adverse events per 100 person-years in the transfusion group divided by the rate of adverse events per 100 person-years in the observation group. The 95% confidence intervals were calculated with the use of the bootstrap method with 10,000 replications.

[†] This event was documented in male participants only.

[‡] A total of 31 participants who were randomly assigned to observation received one or more transfusions.

[§] A total of 9 participants who declined transfusions were excluded from this analysis.

DeBaun MR et al. N Engl J Med 2014;371:699-710.

Treatment of Pain

Robert Taylor, MD
Associate Professor – Clinical
Department of Neurology
The Ohio State University Wexner Medical Center

Dosing opioids in patients with SCD

- Little data available
- “Serum concentrations of of meperidine in patients with sickle cell crisis” Ann Emerg Med 1986;15:433-438
 - Patients received meperidine 100 mg IM
 - Blood levels obtained at 15-30 min intervals for 2 hrs
 - Peak levels (at about 30 minutes):
 - Controls: 0.72 +/- 0.32 mcg/ml
 - SCD: 0.32 +/- 0.08 mcg/ml ($P < 0.01$)
- So a given dose of IV opioid is likely about half to a third as potent for a patient with SCD as for a control

PCA vs Bolus Dosing

- **Minimizes Nursing “Fatigue”**
- **Prevents under-treatment due to fear that patients may become addicted**
- **Decreases risk of negative patient and nurse interaction**
- **PCA leads to empowerment of the patient**
- **PCA allows for “stacking” of doses**
- **PCA provides more consistent and effective pain management**

Study 1 – Gonzalez et al 1991

- **Randomized Study in the ED**
- **45 patient w/ SCD**
- **PCA vs Intermittent Boluses of Morphine**
- **PCA groups had a significantly shorter elapsed time between onset of pain and treatment**
- **No significant difference in total morphine administered, pain intensity, verbal pain scale, vital signs, or level of alertness.**
- **The ED discharge rate and side effects did not differ**

Study 2 – van Beers et al 2007

- 25 crisis in 19 patients
- PCA group with markedly lower mean and cumulative morphine use
- Mean daily scores were comparable (~5/10)
- PCA group with less nausea and constipation
- Shorter duration of hospital admission of 3 days in PCA group, but not statistically significant

Treatment of Acute Pain Proposed Strategy

Our approach to treatment: Biology

- **Treatment of aggravating factors**
 - **Sleep Apnea/Nocturnal Hypoxemia**
 - **Oral Contraceptives**
 - **Vitamin D Replacement**
 - **Neuropathic Pain Therapy**
- **Non-opioid interventions**
 - **Relaxation**
 - **Music Therapy**
 - **Heat Pads**
 - **Neuropathy assessment**
 - **Antidepressant**
- **Opioid interventions**

Proposed General Strategy – Acute Crisis

- **All patients on PCA with escalation for 48-72 hrs**
 - **If opioid tolerant and known to OSUWMC**
 - **Start with known effective PCA dose**
 - **Interval 15 to 60 minutes**
 - **Add continuous infusion (CI) for first 48 hours (+/-)**
 - **If effective dose not known, start low, using 15 minute interval to define effective dose quickly**
- **Lower IV dosing as tolerated as pain improves**
- **Transition patients to PO dosing for D/C (taper?)**
- **Avoid IV pain medications if hospitalized in the last 7 days and no clinical complications**

Proposed General Strategy – Acute Crisis

- PCA with continuous infusion (CI) + demand dosing
 - Requires experienced staff with careful monitoring
 - Base initial dosing on ED dosage or 24 hr dosage from last hospitalization
- Opioid naïve patients – start at IV doses of
 - Morphine sulfate at 0.1 to 0.15 mg/kg (~6-12 mg)
 - Hydromorphone, 0.015 to 0.02 mg/kg (~1-2 mg)
 - PCA q 15 minutes or titrate prn dosing at bedside to determine effective dose
 - Effective dose should reduce pain to tolerable level for at least an hour
- If PCA use > 3 doses/hour, increase both CI & PCA

Proposed Strategy – Acute Pain Crisis

Weaning

- No weaning of opioid in the first 48 – 72 hours
 - May need to escalate
- Then wean off IV PCA opioid ~20% per day
- Decrease the dosage, do not increase the interval
- Transition to Oral Medications
 - Usually must replace IV with equianalgesic PO dose
 - Caution: cross-tapering may increase opioid use
 - Some patients can transition to po at discharge
 - Consider oral taper as outpatient

Proposed Strategy Reasons to Consider Discharge

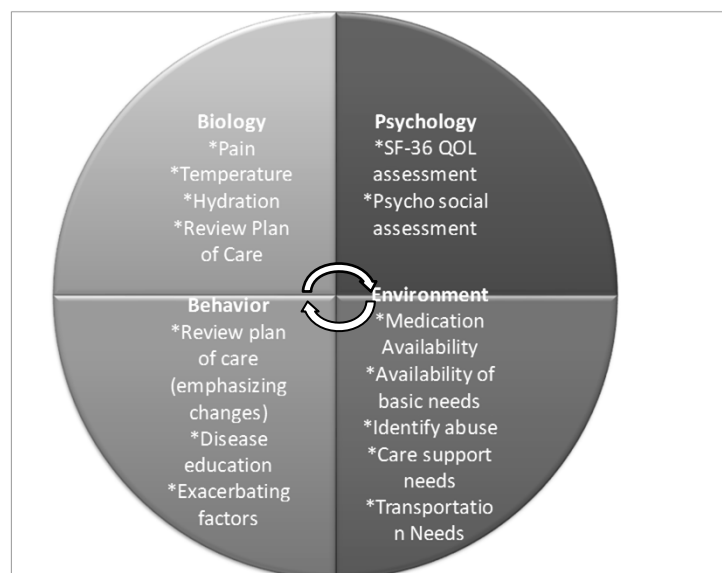
- **Resolution of crisis**
- **Patient ambulating and able to function at normal activity level**
- **Leaving the floor on IV pain medications without staff**

Payal Desai, MD
Assistant Professor
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Division of Hematology
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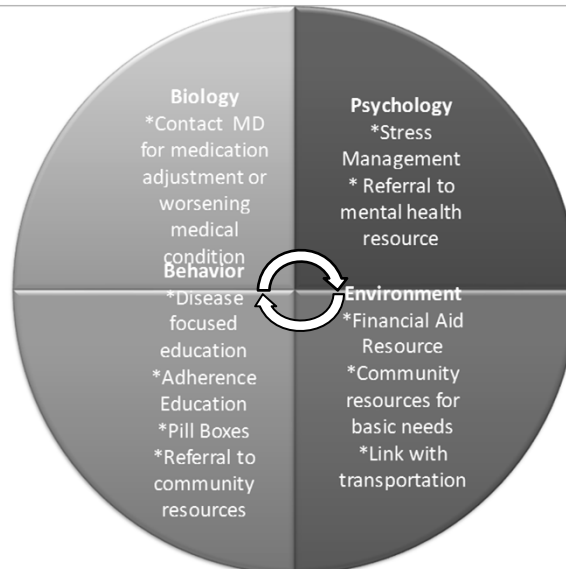
Our approach to treatment: Psychology/Environment

- **Inpatient/Outpatient Mental Health Services**
 - Inpatient mental health NP
 - Engagement with the chair/department of Psychiatry
 - Home Mental Health Visits and Connection with area centers
- **Home Visits for SCD**
 - A multidisplinary sickle cell team with social work, NP/CNS, and MD make visits
 - Evaluation/Intervention

Our approach to treatment: Psychology/Environment



Our approach to treatment: Psychology/Environment



Our approach to treatment: Behavior

- **Consistency**
- **Accountability**
- **Open Discussion**
- **Family/Support System Involvement**
- **Addiction Medicine**