Adult SCD Complications and Treatments
Shift and Paradigm

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November 2012

Case presentation 1

32 yo AA F; Hgb SS

Hx:

- CVA w transient hemiparesis -16 yo
- Recurrent ACS/Pneumonia
- Pulm HTN –O_2 dependent-
- Osteomyelitis
- Chronic pain
- Poor compliance with HU
- AIHA; Goiter
- 5 – 7 ED visits; 1 - 3 admissions/yr.
- Delay completing Master degree due to illness and cognitive disorder

1 sibling w HgbSβ^0thal

2 siblings Hgb AS; No HLA transplant match

Case presentation 1

6 yrs later- Now

30 yo AA F; Hgb SS

Hx:

- CVA w transient hemiparesis -16 yo
- Recurrent ACS/Pneumonia
- Pulm HTN –O_2 dependent
- Osteomyelitis
- AIHA; Goiter
- Chronic pain
- Poor compliance with HU
- 5 – 7 ED visits; 1-3 admissions/yr.
- Delay completing Master degree due to illness and cognitive disorder

1 sibling w HgbSβ^0thal

2 siblings Hgb AS; No HLA match

36 yo AA F; Hgb SS

Hx:

- CVA w transient hemiparesis Recurrent ACS/Pneumonia
- Pulm HTN –O_2 dependent
- Osteomyelitis
- AIHA
- Goiter
- Chronic pain
- Poor compliance with HU
- 4 – 6 ED visits; 1-2 admissions/yr
- Unable to complete Master degree
- Cholecystectomy
- Severe obstructive sleep apnea
- Headache; Chiari I malformation

Case presentation 2

22yo AA M; Hgb Sβ^0thal

Hx:

- Priapism during childhool
- Scoliosis
- GERD
- Condyloma
- Smoker
- < 1 ED visits/yr;
- No admissions since 10 yo.
- Completed college in NYC
- UNC employee

1 sibling w Hgb SS

2 siblings Hgb AS

Case presentation 2

6 yrs later

23yo AA M; Hgb Sβ^0thal

Hx:

- Priapism during childhood
- Scoliosis
- GERD
- Condyloma
- Smoker
- < 1 ED visits/yr;
- No admissions since 10 yo.
- Completed college in NYC
- UNC employee

1 sibling w Hgb SS

2 siblings Hgb AS

29yo AA M; Hgb Sβ^0thal

Hx:

- Priapism
- Scoliosis
- GERD
- Condyloma
- Smoker
- 2.2009 Multiple ICH/SAH due to basilar /supraclinoid aneurysms
- Cortical blindness; Memory loss
- Unable to tolerate exchange Tx
- 4.2011 6/6 Allo nonmyeloablative SCT
  - Thrombocytopenia –ITP-
  - Vitreal hemorrhage
  - Headches
- Getting independent living & job training

Case presentation 3

45yo AA M; Hgb SC

Hx:

- Bilateral retinopathy and L eye bleed
- R hip and L shoulder AVN;
- S/P R hip replacement 2005
- GERD
- Sleep apnea
- Hypertension
- Diabetes Mellitus
- Employee as office manager. Longer episodes of missing work due to hospitalizations.
- 5 – 7 ED visits; 1-4 admissions/yr

1 sibling w Hgb SC; 1 sibling w Hgb AS

Case presentation 3

45yo AA M; Hgb SC

Hx:

- Bilateral retinopathy and L eye bleed
- R hip and L shoulder AVN;
- S/P R hip replacement 2005
- GERD
- Sleep apnea
- Diabetes Mellitus
- Employee as office manager. Longer episodes of missing work due to hospitalizations.
- 5 – 7 ED visits; 1-4 admissions/yr

1 sibling w Hgb SC; 1 sibling w Hgb AS

6 yrs later

51yo AA M; Hgb SC

Hx:

- Bilateral retinopathy and L eye bleed
- Bilateral hip and L shoulder AVN;
- S/P R hip replacement 2005 /L hip replacement 2008 complicated with hardware infection
- Depression
- GERD
- Sleep apnea
- Hypertension
- Diabetes Mellitus Now insulin dep
- Now on disability due to worsening illness.
- 5 – 8 ED visits; 3-6 admissions/yr

Sickle Cell Syndromes

Sickle Cell Anemia (Hgb SS)

Double -heterozygous states

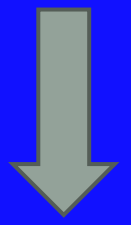
- Sickle β thalassemia (Hgb $S\beta^+$ thal & Hgb $S\beta^0$ thal)
- SC disease
- SD disease

Others Hgb S related hemoglobinophaties

- Hgb SO_{arab}
- SHPFH

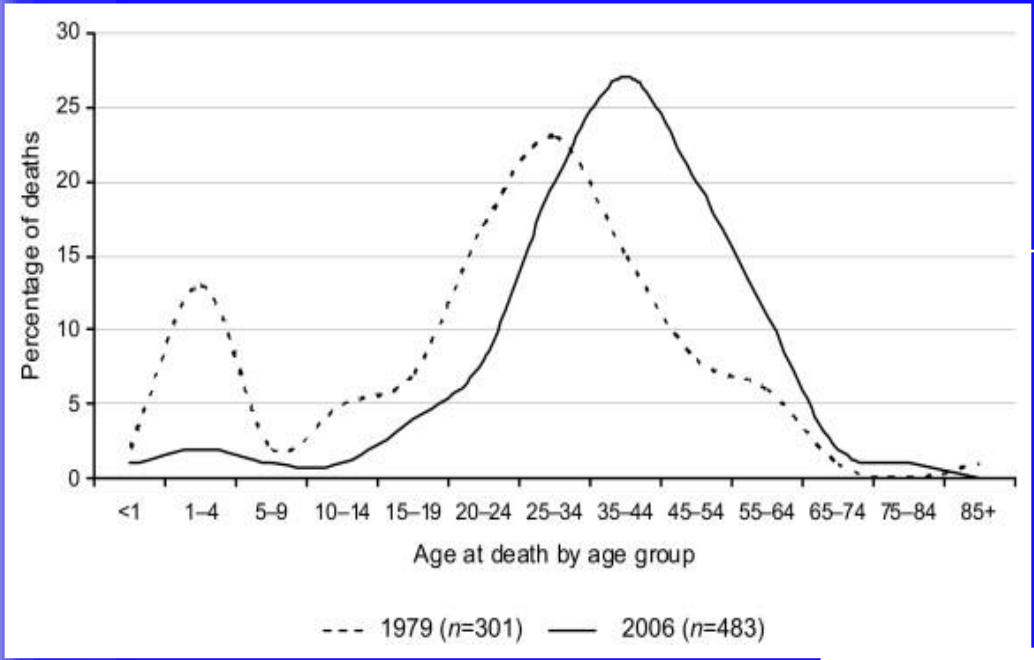
Shift

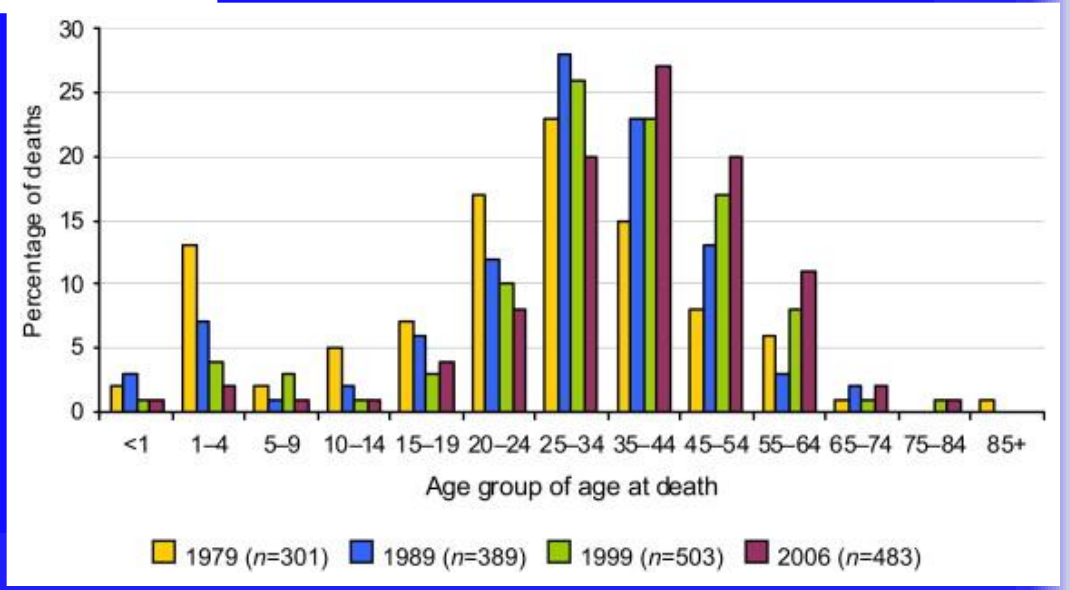
Pediatric



Adult Disease

Age at death for SCD in 1979, 1989, 1999 and 2006





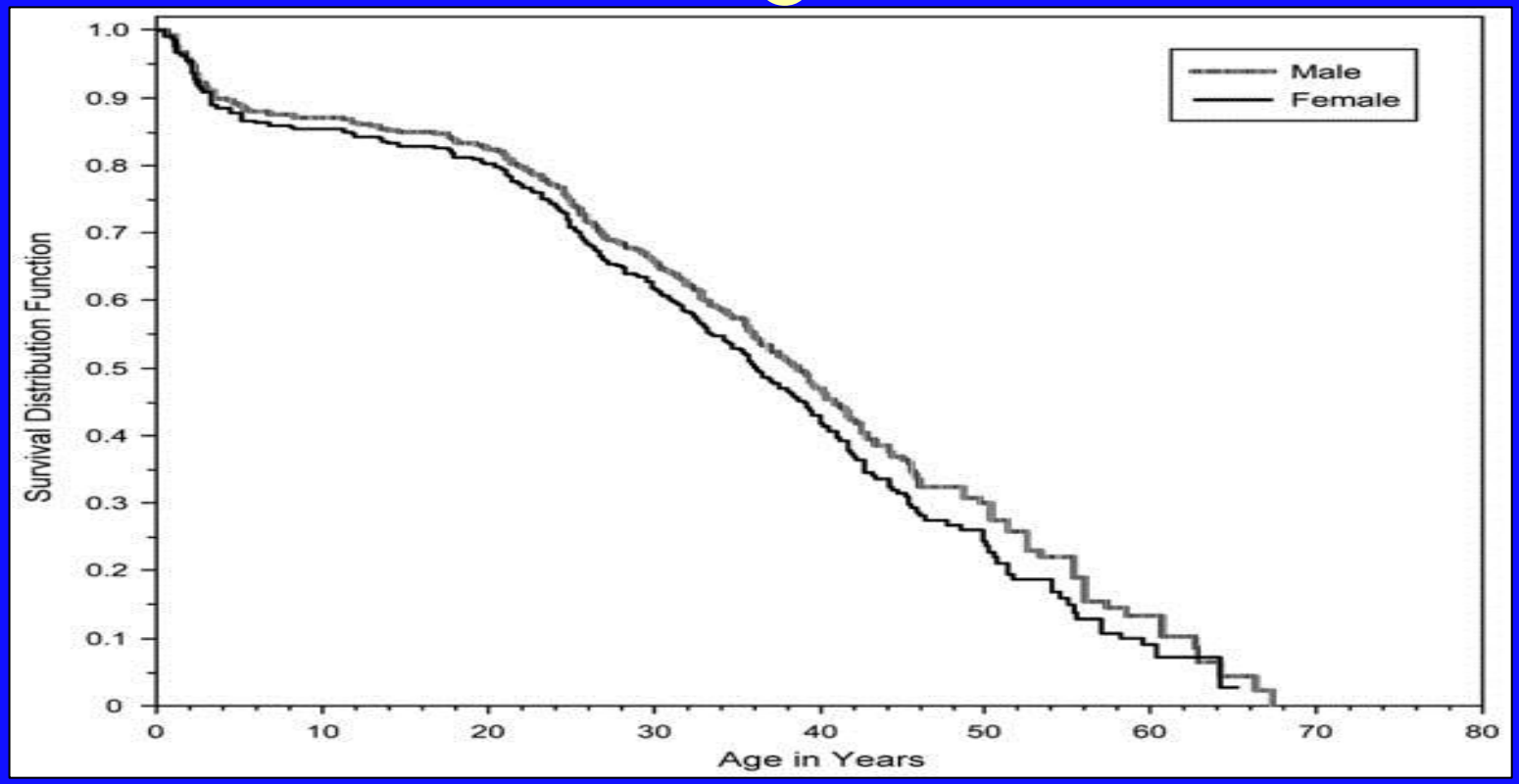
Hassell, K. Am J Prev Med 2010; 38:S512-S521

Improvements in SCD Care

- Early case identification by neonatal screening -all 50 states-.
- Prevention of pneumococcal sepsis through prophylactic antibiotics and vaccination.
- Improvement on longevity and QoL by Hydroxyurea therapy
- Primary and secondary stroke prevention
  - **11%** of patients with SCD experience at least one clinical stroke episode by the age of 20 years. **24%** by age 45.
  - Up to 35% have silent strokes.

Early Mortality in Adults with SCD

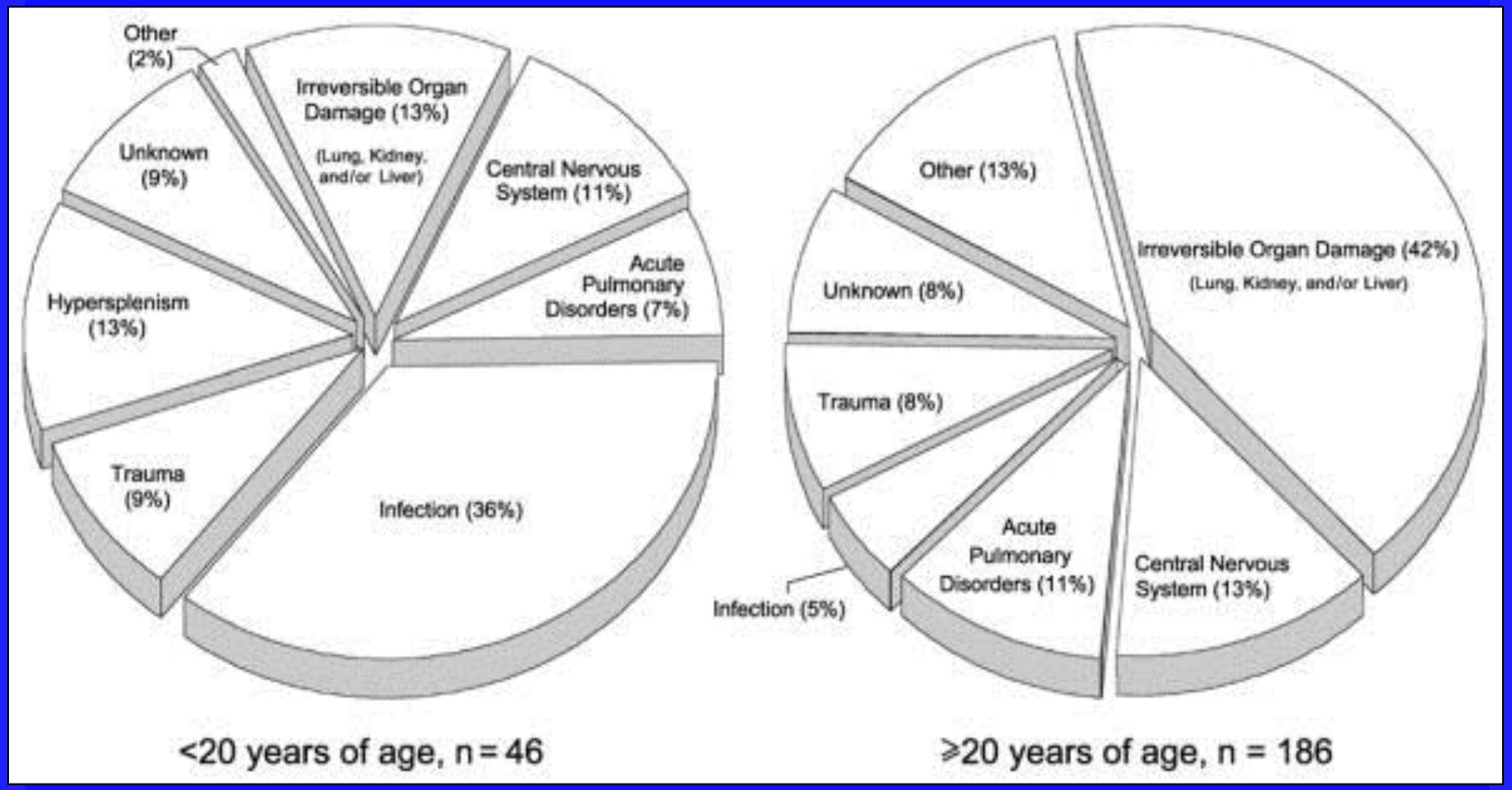
Outcome of Sickle Cell Anemia: A 4-Decade Observational Study of 1056 Patients.



Median age of death: 37 years

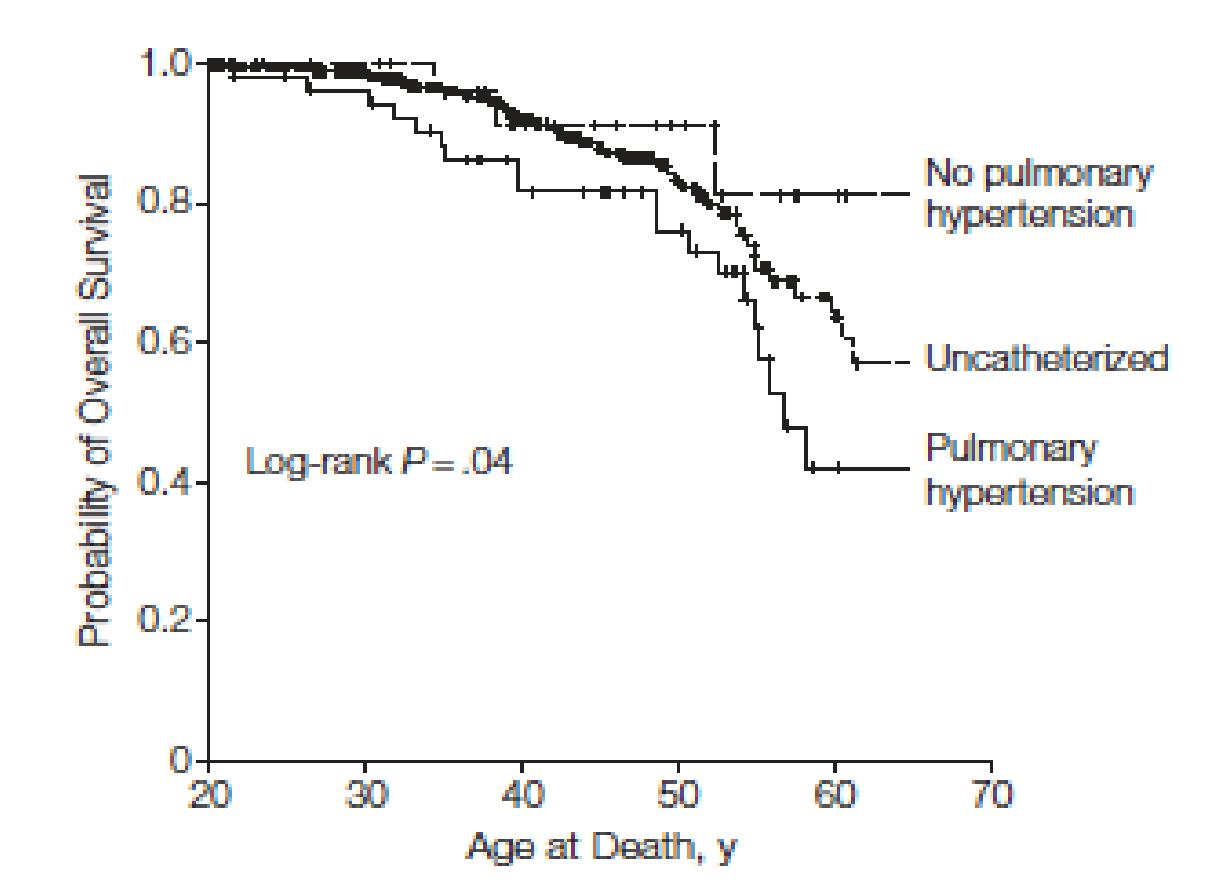
Powars, D et al Medicine. 84(6):363-376, 2005.

Causes of Mortality



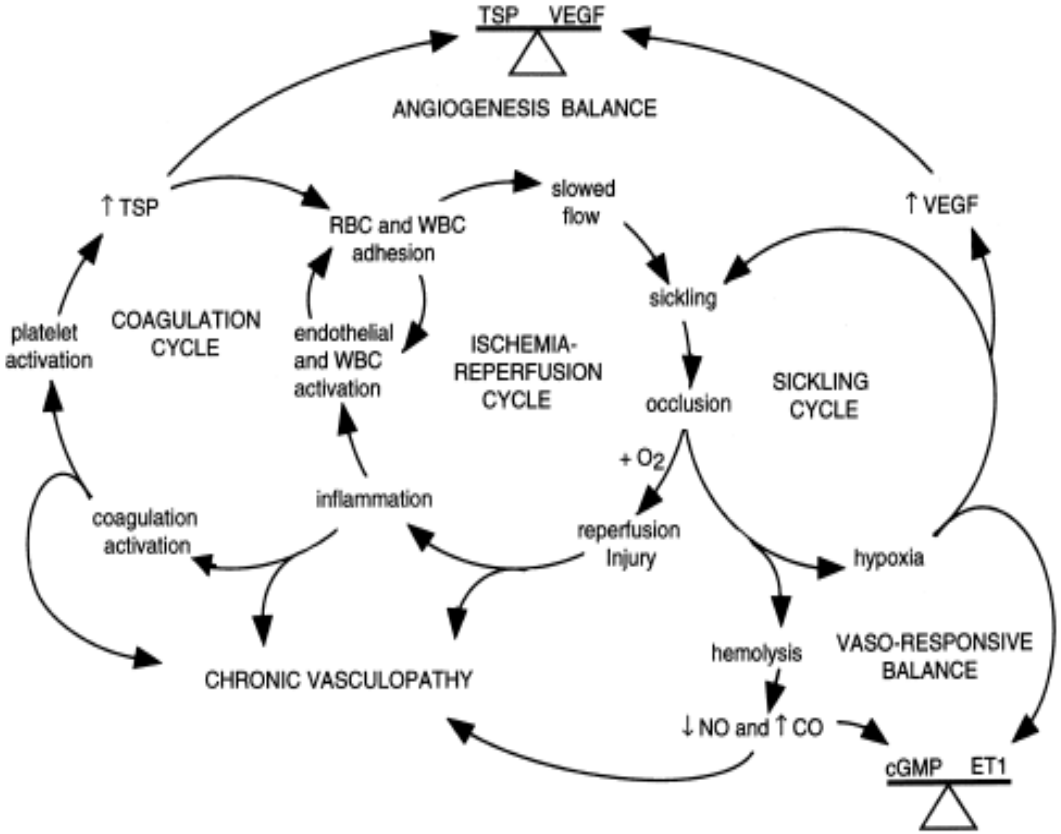
Powars, D et al Medicine. 84(6):363-376, 2005.

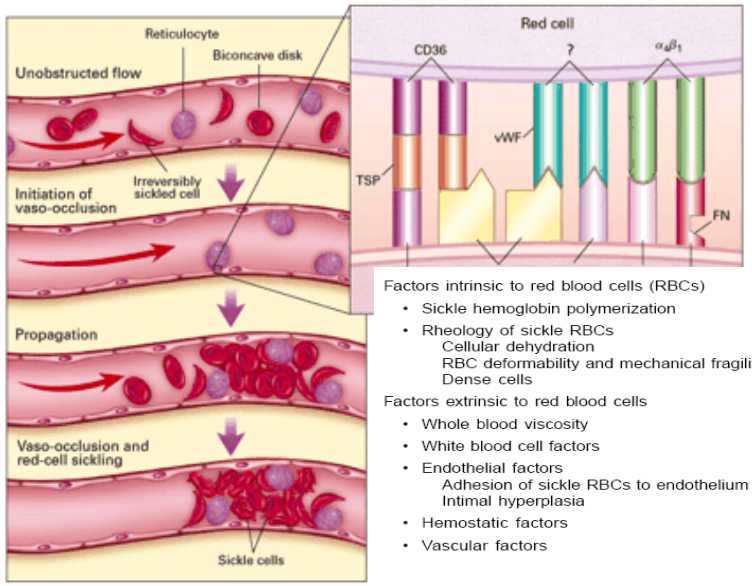
Mortality in Adults with SCD: Pulmonary Hypertension as a Risk Factor



Gladwin,M et al NEJM. 2004 26;350(9):886-95

An Endothelial Disease





Factors intrinsic to red blood cells (RBCs)

- Sickle hemoglobin polymerization
- Rheology of sickle RBCs
  - Cellular dehydration
  - RBC deformability and mechanical fragility
  - Dense cells

Factors extrinsic to red blood cells

- Whole blood viscosity
- White blood cell factors
- Endothelial factors
  - Adhesion of sickle RBCs to endothelium
  - Intimal hyperplasia
- Hemostatic factors
- Vascular factors

Hebbel, R et al. Microcirculation 11: 1290151, 2004

The Ages of Sickle Cell Disease

- Childhood - Infections, Strokes
- "Golden Years" - 12-20
- Young Adulthood - 20-40 Acute events
- Older Adulthood - >40 Organ failure/End organ damage

Clinical Manifestations of SCD

Vaso-occlusive = Painful episode/crisis:

Most common episodes, hallmark of the patient with SCD

- Measure of disease severity; correlate with early death in adult patients.
- Predisposing factors: Hypoxia, dehydration, vasospasm, infections, menstruation, acute temperature changes, Acidosis, anxiety/depression and physical exhaustion.

Hemolytic:

- Acute and rapid RBC destruction; Rare frequency
- Clinical findings: malaise, pallor, icterus and jaundice
- Labs: falling Hct and elevated reticulocytes count, LDH and bilirrubin. Hemoglobinuria.
- Associated with concurrent G6PD deficiency, sepsis or malaria.
- If chronic: associated with bilirubin stones and biliary obstruction

Clinical Manifestations of SCD

Aplastic:

- **Decreased RBC production in the bone marrow added to the usual RBC peripheral destruction.**
- **Clinical findings: Increased weakness. Falling Hgb and RBC volume with decrease reticulocytes.**
- **Usually associated with infection -Parvovirus B 19**
- **Extensive marrow necrosis. May be 2ry to folic acid deficiency**

Sequestration:

- Massive pooling of RBC by the spleen or liver with significant fall of Hgb and Hct.
- More frequent in infants and small children
- **Clinical findings**: Variable symptoms from weakness to shock, abdominal pain, painful splenomegaly.
- Falling Hgb and RBC volume; Thrombocytopenia.
- May occur in adults with splenomegaly (Hgb SC or $S\beta^+$ thal)

Other Clinical Manifestations

Constitutional:

Defective host defenses in sickle cell disease

- Opsonophagocytic defect (altered complement pathway)
- Functional (anatomical asplenia)
- Depressed granulocyte bacterial kill.
- Increase risk for infection
  - Pneumoccocus and Salmonella.
- Delayed growth and development
- Absence of splenic function after year **3-4.**

Other Clinical Manifestations

Pulmonary /lungs

- Infection
- Fat embolism
- Acute chest / ARDS
- Thrombosis
- Pulmonary infarcts
- Pulmonary Hypertension

Cardiac dysfunction

- Ventricular enlargement = compensatory mech of volume overload
- Systolic ejection murmur due to hyperdinamic state
- Right heart failure due to recurrent pulmonary HTN and infarcts
- Myocarditis associated with iron overload.
- Pericarditis associated with renal failure/sepsis

Other Clinical Manifestations

Genito-urinary:

- Functional: papillectomy (isosthenuria and hematuria)
- Glomerulonephritis (tubular Ag, post strep infections)
- Renal tubular dysfunction
- Pyelonephritis (Kidney infections)
- Interstitial nephritis
- Priapism

Hepatobiliary:

- Hepatic sequestration
- Biliary tract disease (cholelithiasis, cholecystitis)
- Cirrhosis
- Hepatitis
- Hepatic infarcts

Musculoskeletal

- Arthritis - tap joints
- Osteomyelitis (Salmonella, Staph)
- Bony infarcts - fish mouth vertebrae
- Aseptic/Avascular necrosis (any joint)
- Dactylitis (hand- food Syndrome)

Other Clinical Manifestations

Ocular:

-Central retinal artery occlusion

- Retinal arteriolar occlusion
- Neovascularization (Sea fans)
- Retinal detachment/infarcts
- Vitreous hemorrhage
- Anterior chamber ischemia

CNS:

- Cerebral infarcts with increased risk of recurrence (67% in children)
- Subarachnoid and intracerebral hemorrhage
- Fat embolization

Skin

-Legs ulcers

Common Symptoms/Complications

- Anemia
  - Hyperhemolysis
  - Aplastic episodes
  - Acute splenic sequestrations
- Vaso-occlusive Episodes (Tissue damage and Hypoxia)
- Pain syndromes (Bone, joints, muscle, chest)
  - Acute pain episodes
  - Acute multiorgan failure
  - Chronic / Neuropathic pain

Ballas et al Am. J. Hematol. 85:6–13, 2010

Common Symptoms/Complications

- Asthma/Reactive Airway Disease
- Infections: Pneumonia, Osteomyelitis
- Priapism
- Leg Ulcers
- Pulmonary Hypertension
- Kidney and liver Failure
- Transfusion related complications
  - Hyperviscocity
  - Immune hemolysis
  - Transfusional Iron overload

Treatment of Common Symptoms
Anemia

- Determine the patient's baseline Hgb / Hct / Retic
- Address changes from baseline
  - Increase: Dehydration Hyperviscocity
  - Decrease: Hemolysis Aplastic Episode Bleeding
- Iron therapy only for Iron deficiency (Ferritin and transferin)
- "Aplastic episode is a medical emergency" –Parvo-
- Transfusion:
  - Single or chronic

Treatment of Common Symptoms
Anemia and Pain

- Erythropoietin used in specific situations
  - Inability to transfuse –Poor access, Allo-inmunization
  - Renal Insufficiency - Especially if Low Reticulocyte count and in conjunction with Hydroxyurea –
  - Aplastic episode in conjunction with transfusion support
  - Worsening /severe anemia due to hemolysis or bleeding.

- Pain Management
  - Believe and treat the Pain
    - Narcotics
    - Hydration
    - Adjuvant therapy (NSAIDS, Stress management,
  - Treatment of predisposing cause if known

Treatment of Common Symptoms

Immune system compromise

- Treat infections aggressively with a low threshold for antibiotics
- Flu vaccine yearly
- Pneumonia vaccine Q 5 -10 yrs
- Hepatitis B vaccine
- Prophylactic penicillin:
  - Routinely prescribed for children with SCD.
  - Not indicated in adult with SCD.

Treatment of Common Symptoms

Priapism

- Medical emergency
  - Hydration
  - Ice packs
  - Surgical detumescence –Aspiration-
  - Transfusion
  - Pain control
- Hydroxyurea
- Urology referral
  - Casodex
  - Viagra

Treatment of Common Symptoms
Lower extremity ulcer

- Rest
- Wet to dry saline dressing
- Antibiotics as necessary
- Unna boot
- Moisturize the skin around the ulcer
- Wound clinic referral
- Skin grafts

Hydroxurea use may be associated with new and worsening painful ulcers

Acute Chest Syndrome (ACS)

1st cause of death in adults with SCD

Clinical diagnosis: Hypoxemia, SOB, chest pain, +/- pulmonary infiltrates-ARDS-.

All patients with chest/lung symptoms must be considered for ACS

Evaluation: Blood gas, Chest X ray, cultures, CBC, type and hold

Administer Oxygen if PO2 < 70 mmHg or O_2 sat < 92 % RA.

IV antibiotics (Mycoplasma frequent in children)

VQ scan / EKG / thoracocentesis if clinically indicated

Treatment: Transfusion or exchange transfusion

The Toll of Sickle Cell Disease

Years of pain and suffering

Loss of function of main organs (brain, lungs, liver, kidneys, heart, spleen)

Difficulty in maintaining social functioning

- 60% do not enter the work force
- Difficulty in maintaining job

High medical costs-average $26,000/year

Shortened life span

Paradigm

SCD Patient

vs.

Person with SCD

Health Maintenance and SCD

- Often overlooked in sickle cell patients
- Recommended health screenings as for the general population
  - Gynecologic exam
  - Breast exam / Mammogram
  - Colonoscopy
  - Prostate exam and PSA
  - Yearly and age specific vaccines
    - Flu Pneumonia Hepatitis B Herpes
  - Obesity
  - Screeennig for:
    - Hypercholesteronemia
    - Depression and other mental illness
    - Pulmonary Hypertension

Women and Pregnancy

- Pregnancy Complications:
  - Worsening Anemia and painful Episodes
  - Infection, including urinary tract and lungs
  - Gallbladder problems including gallstones
  - Heart enlargement and heart failure from anemia
  - Miscarriage and spontaneous abortions
- Fetus Complications and increased risks:
  - Intrauterine growth restriction (poor fetal growth)
  - Preterm birth (before 37 weeks of pregnancy)
  - Low birth-weight (less than 5.5 pounds)
  - Stillbirth and newborn death

Women and Pregnancy

Pregnancy Management

- Pregnant women with SCD should be managed by a multidisciplinary team with experience of high risk pregnancies.

- Offered pre-conceptual partner screening and appropriate genetic counseling.

- Painful crises are the most common complication thus each obstetric unit should have a clear management protocol for this and other complications.

APPROACHES TO THERAPY

- Chemical inhibition of hemoglobin S polymerization
  - Hydroxyurea, 5-azacytidine.
- Reduction of the intracellular hemoglobin concentration
  - Mg Clortrimazole
- Gene Therapy
  - Transgenic mice
- Bone Marrow Transplant

Hydroxyurea (HU)

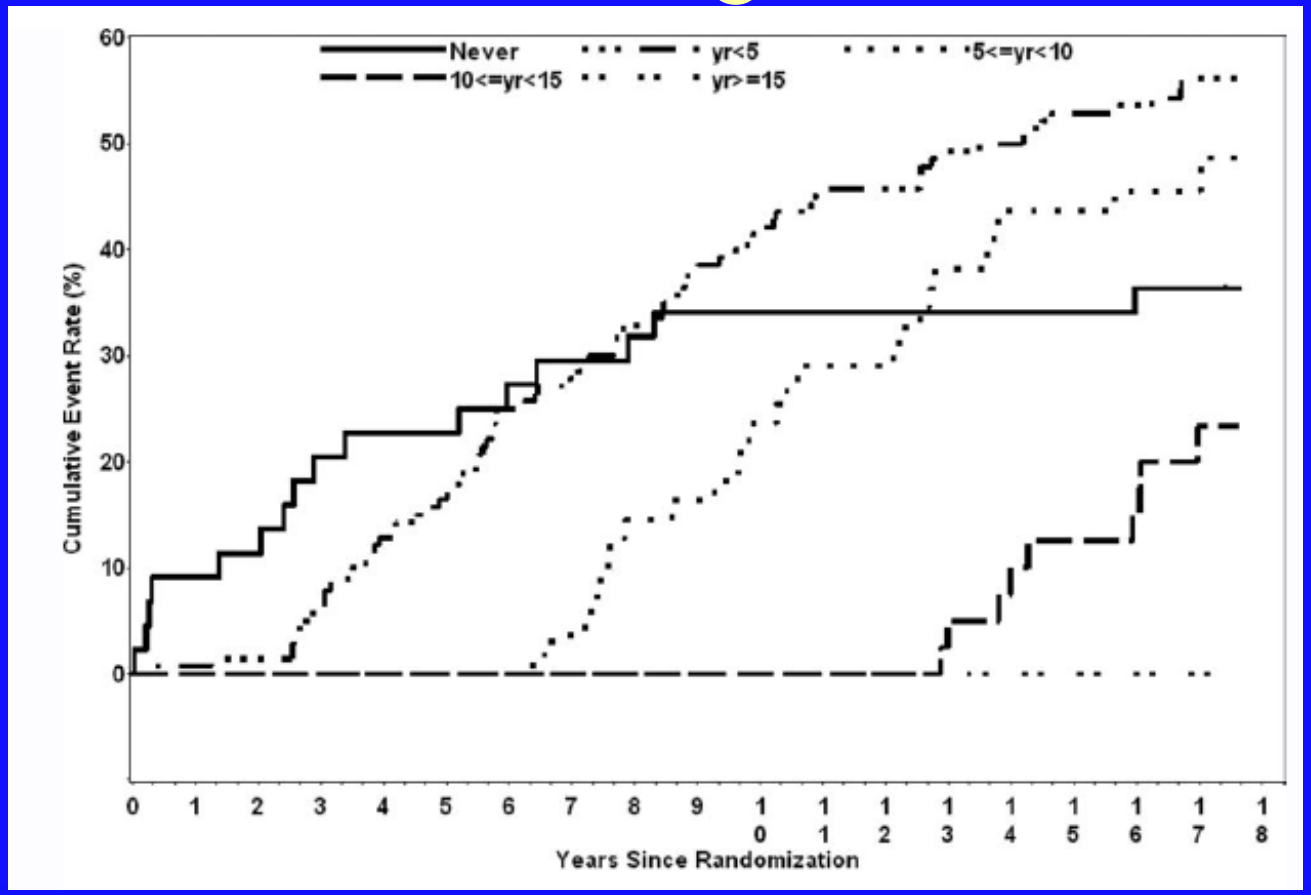
- Only FDA approved drug to treat some of the complications of SCD
- HU reduced by nearly half:
  - Frequency of hospitalizations;
  - Incidence of both first vaso-occlusive crisis (3.0 vs. 1.5 months):
  - Time to the second crisis (8.8 vs. 4.6 months)

- Fewer patients treated with HU had chest syndrome (25 vs. 51); or underwent transfusions (48 vs. 73).

Steinberg, De Castro et al. Am. J. Hematol. 85:403–408, 2010

Adult Survival in the Hydroxyurea Era

Long term HU use associated with decreased mortality and increased survival.



Steinberg, De Castro et al. Am. J. Hematol. 85:403–408, 2010

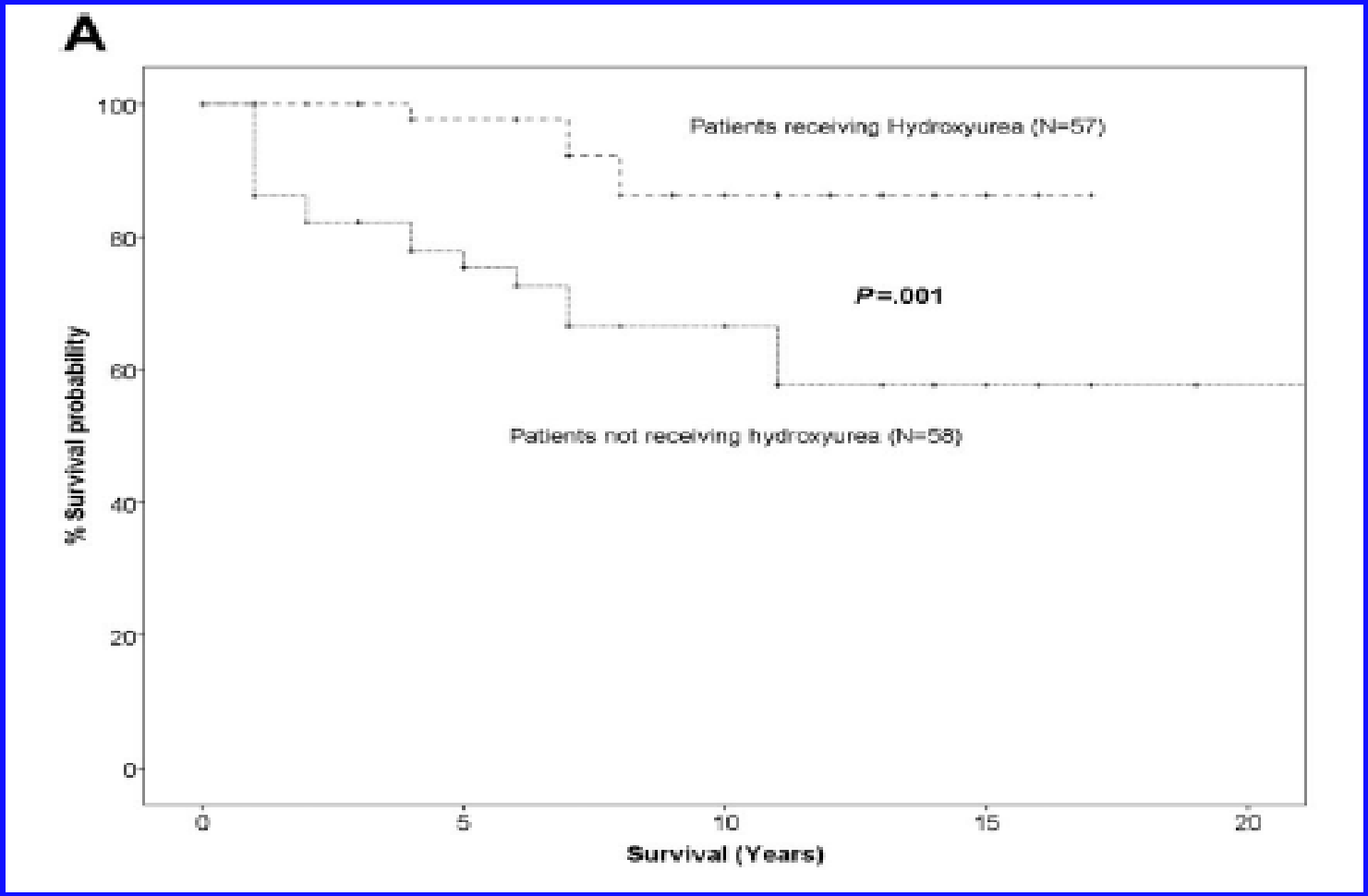
Baseline	HU (n = 131) Median	HU (n = 131) SD	Non-HU (n = 199) Median	Non-HU (n = 199) SD	P
Age, y	33.0	11.2	35.0	12.8	.506
Follow-up, y	8.0	4.7	5.0	6.0	.009
Blood units/y	0	5.86	0	2.83	.004
Hospital admissions/y	1.00	2.95	0	1.18	.000

Cause of death	HU patients (13/131 = 9.9%)	Non-HU patients (49/199 = 24.6%)
Liver dysfunction	1	10
Pulmonary hypertension	8	8
Stroke	3	10
Sudden death	3	5
Vasoocclusion crisis	1	6
Acute chest syndrome	1	5
Sepsis	1	1
Heart failure	2	2
Intervention	1	2

HU patients did better despite worse baseline disease.

Voskaridou et al. Blood. 2010;115:2354-2363

Effect of HU on Overall Survival



Voskaridou et al. Blood. 2010;115:2354-2363

Hydroxyurea (HU)

- Underutilized in adolescents and adults due to both provider and patient concerns

HuMA Score meaning	Summed HuMA Score	N (%)
100% Adherence	0	15 (16.7)
Good Adherence	1	34 (37.8)
Poor Adherence	2	28 (31.1)
Non Adherence	3 or 4	13 (14.4)

De Castro, L et al manuscript in preparation

Other therapeutic Interventions

Hydroxyurea (HU):

- Only FDA approved drug to treat some of the complications of SCD
- HU reduced by nearly half:
  - Frequency of hospitalizations;
  - Incidence of both first vaso-occlusive crisis (3.0 vs. 1.5 months):
  - Time to the second crisis (8.8 vs. 4.6 months)
- Fewer patients treated with HU had chest syndrome (25 vs. 51); or underwent transfusions (48 vs. 73).
- Long term HU use associated with decreased mortality and increased survival.

Other Therapeutic Modalities

- Penicillin prophylaxis in children.
- Vaccination: Pneumovax, Menactra, Hepatitis B and H Flu
- Folic Acid
- Iron chelation:
  - For treatment of Iron Overload due to frequent transfusions.
  - Desferrioxamine (Desferal) SQ
  - Deferipone (Exjade) Oral

Treatment Intensification with Chronic Transfusion

Stroke prevention:

- Most common indication for chronic transfusion :
- Primary prevention (STOP trial)
  - ~ 10% of SS and $S\beta^0$thal children have abnormal TCD findings.
  - Among those with abnormal TCD cannot differentiate who would get a stroke and who would not.
- 2ry prevention -recurrences-.

- Transfusional iron overload, viral illnesses and alloinmunization remain a major adverse outcome of chronic transfusion.

Other therapeutic modalities

Bone marrow transplant

- Experimental therapy.
- Potential cure
- Mini transplant project: BMT on individuals with HLA matched siblings. Goal of chimerism –trait-.
- Costly
- High mortality and procedure associated risks

Gene therapy

- Experimental therapy.
- Potential cure
- Goal: change of genetic makeup.
- Not currently available

Life Expectancy and Quality of Life

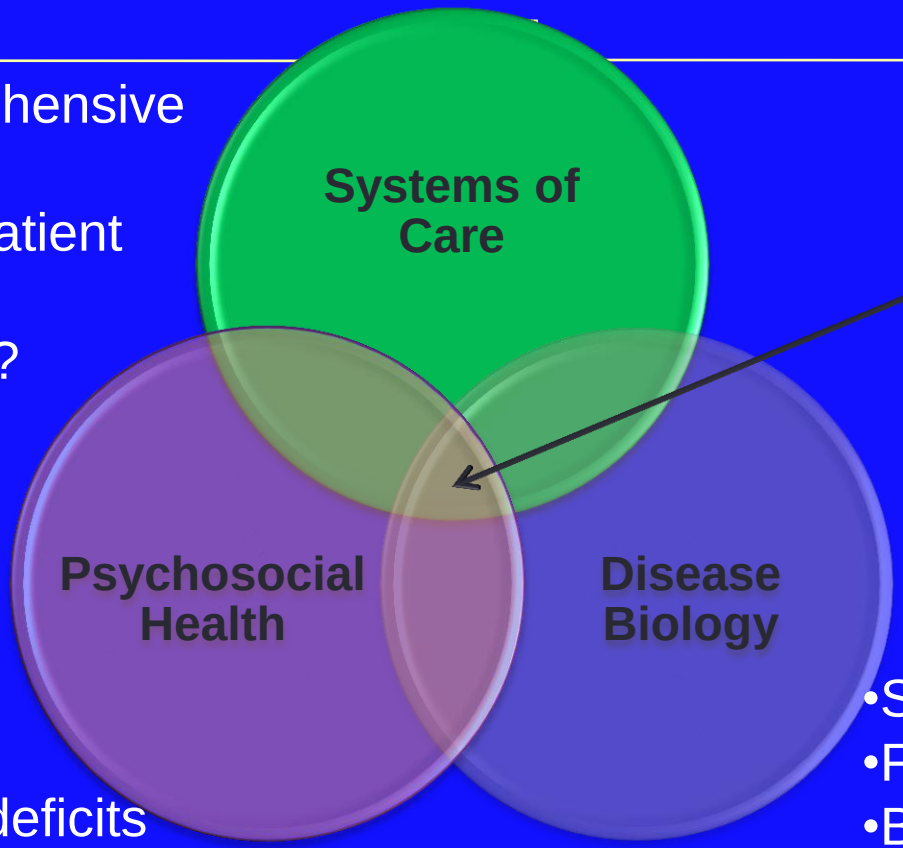
Life expectancy remains in the 5th or 6th decade.

- Duke cohort of >400 adult patients, mean age of death <46 yrs – stable over last decade-.
- By age 40, **48%** of surviving patients have documented irreversible organ damage.
- **37 %** (38/142) found to have depression, which was associated with higher healthcare utilization.
- Illness chronicity, combined with frequent hospitalizations for pain and other medical management, contribute significantly to impaired psychosocial functioning, altered intra- and interpersonal relationships, and reduced QoL

De Castro et al manuscript in preparation

Adults with SCD: Disease Biology Compounded by Systems of Care and Psychosocial Health

- Access to comprehensive care
- Outpatient vs. inpatient management
- Hydroxyurea Use?



Patients with Worst phenotype

- Chronic pain
- Depression
- Neurocognitive deficits
- Stroke
- Unemployment (80%)
- Sexual Dysfunction

- Sickle cell type
- Fetal hemoglobin
- Beta globin haplotype
- Hemolysis & Vasocclusion
- Age related illness

What Can we Offer Patients with SCD

- Compassionate, comprehensive medical care
  - Acute and chronic pain management
  - Longitudinal and comprehensive health care and psychosocial support
- Drugs that reduce sickling and complications:
  - Hydroxyurea and Iron Chelation
- Bone marrow transplantation
- Future developments (Basic, clinical and translational **research**)
  - Gene therapy
  - Combination drug therapy
- Advocacy and Education