NHLBI Guidelines Ward Hagar, MD

- **Access to Care**
- **Sickle Cell Disease in Central California**
- Cayenne Wellness Center and Sickle Cell Disease & Awareness
- May 19th, 2020

Disclosures

Consulting Research Funding	Agios Bluebird bio GBT Novartis BSL Bering Pfizer
Research Funding	ApoPharma Silarus Sangamo Forma

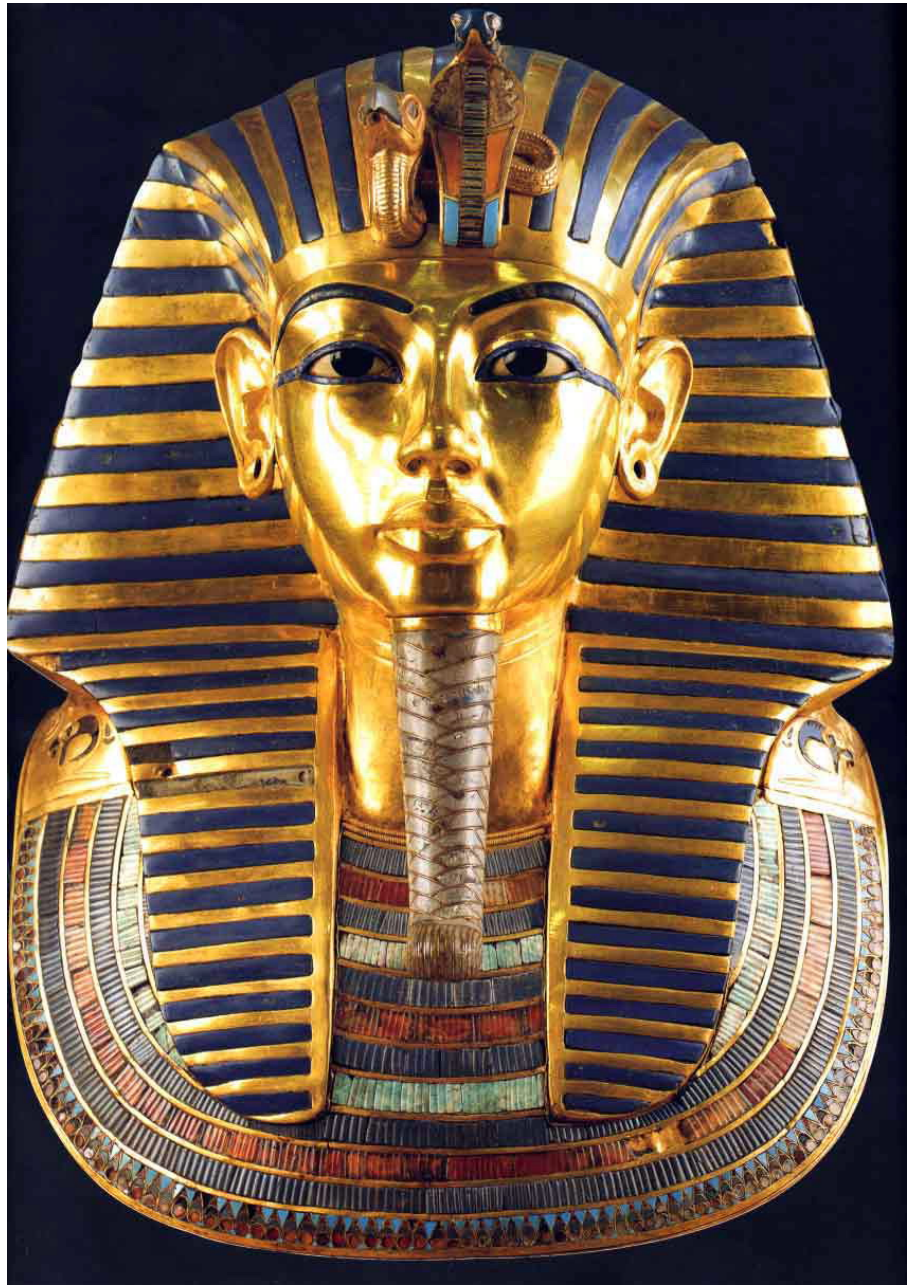
Thirty minutes to…

- Discuss why guidelines are needed
- Discuss NHLBI guidelines
- Discuss Problems with Guidelines

Why are Guidelines Needed?

Sickle Cell Is a Rare Disease
(in the US)

Only about 100,000 persons in a nation of
309,000,000 (0.032%)



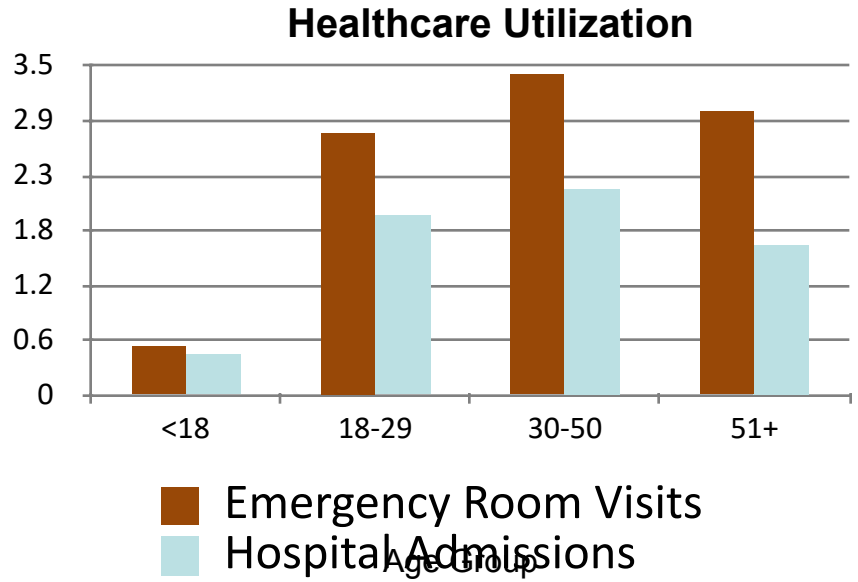
Sickle Cell Has Become a Chronic Disease

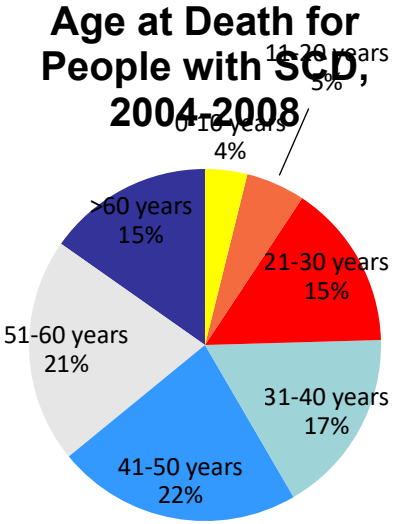
The care of the adult with sickle cell disease is the care of end organs.

Even without pains, sickle cells are constantly sickling

Transition from Pediatric to Adult Care

- Adults with SCD 18 – 30 years had highest inpatient and ED use and 30 day rates of return to hospital post-discharge
- Death and hospitalization rate increased when patients are not transferred to adult providers





Brousseau et al. *JAMA*. 2010;303:1288-94
Quinn et al. *Blood* 2010;115:3447-52
Centers for Disease Control and Prevention (CDC.gov)

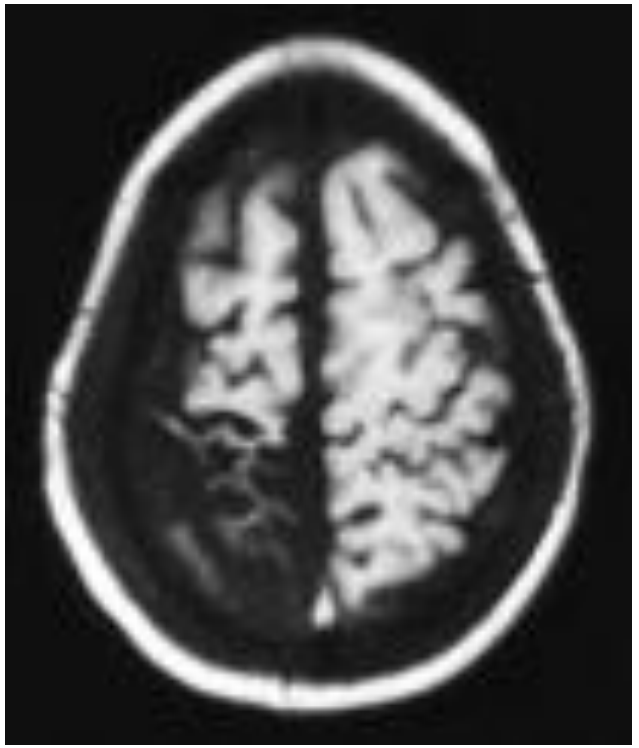
Vasa Recta: Area of hypoxia, acidosis, and hypertonicity

Microradioangiograph of a pyramid from (A) a normal kidney (72 yr.); (B) a sickle-cell-hæmoglobin-C-disease kidney (5 yr.); and (C) a homozygote sickle-cell-anæmia kidney (3 yr.).

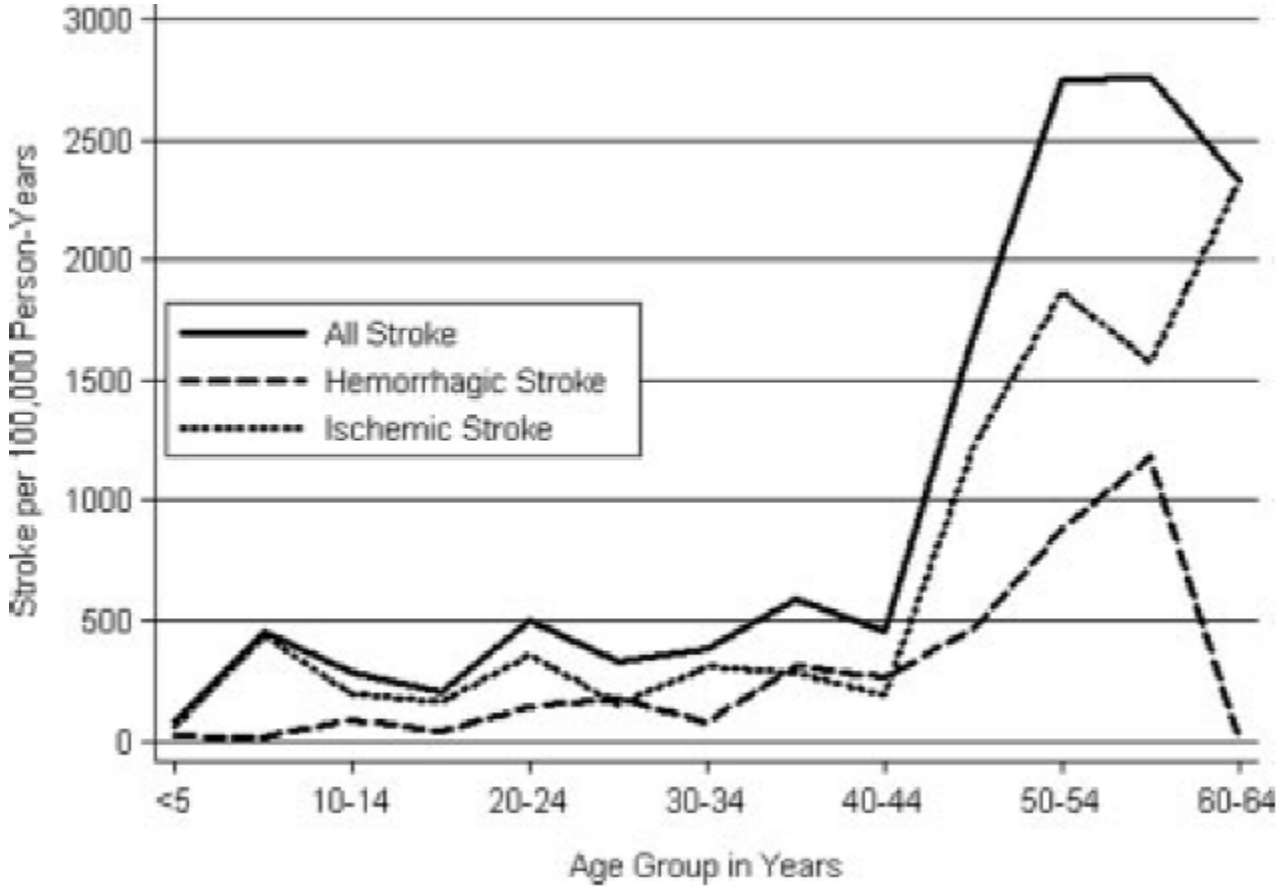
Renal concentrating power limited to 400 to 450 mOsmole (normal is 1200 mOsm)
Unaffected by transfusions after age 10
Loses of the 14% of juxta-medullary nephrons, leaving short cortical nephrons intact so not much effect on glomerular filtration rate
Loss of acidfications if from collecting duct dysfunction

Overt Neurologic Disease

- HbSS: Cumulative Risk
  - 20 years : 11%
  - 30 years: 15%
  - 45 years: 24%
- HbSC: Cumulative Risk
  - 20 years: 2%
  - 30 years: 4%
  - 45 years: 10%

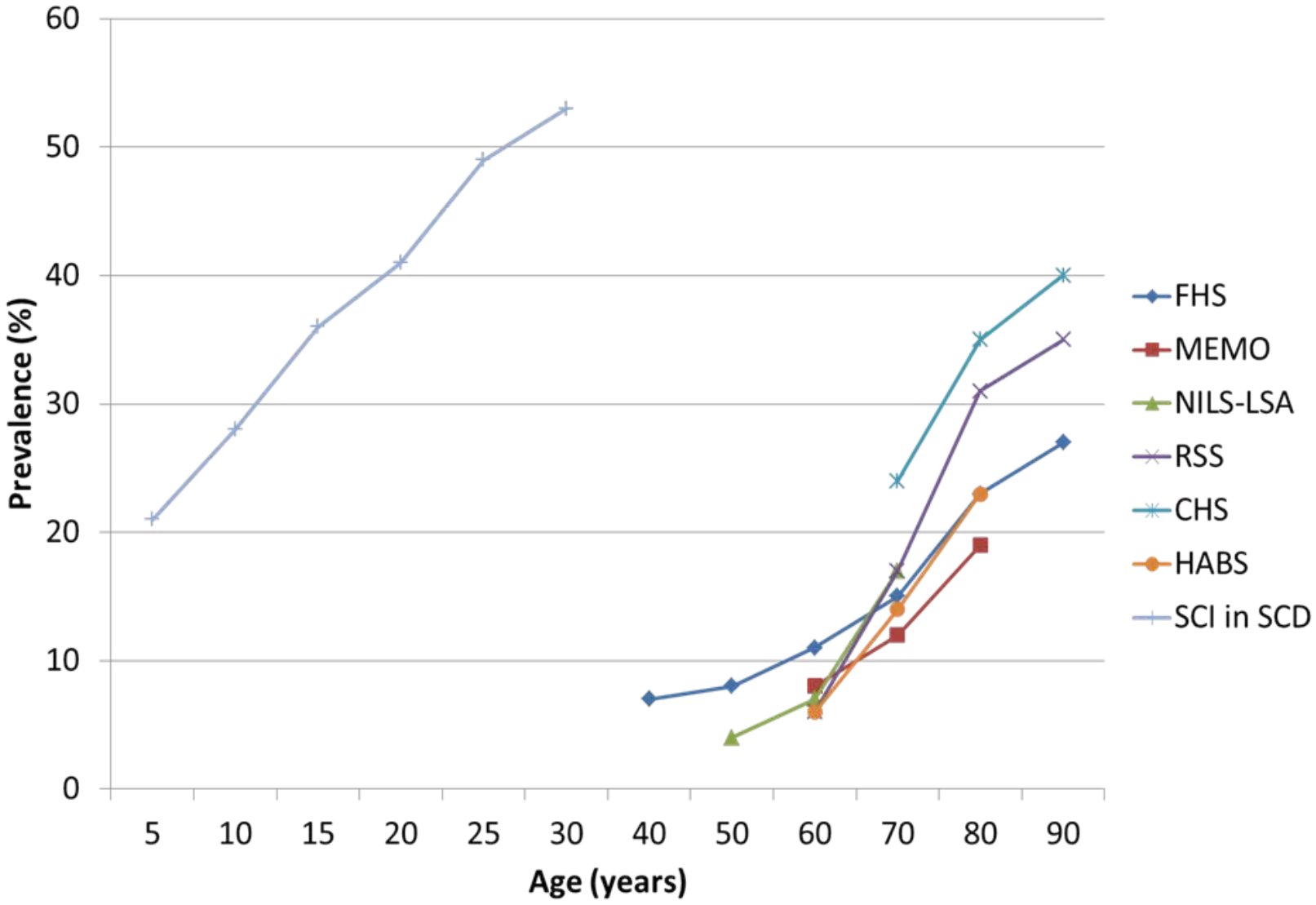


Overt Stroke Risk increases with Age

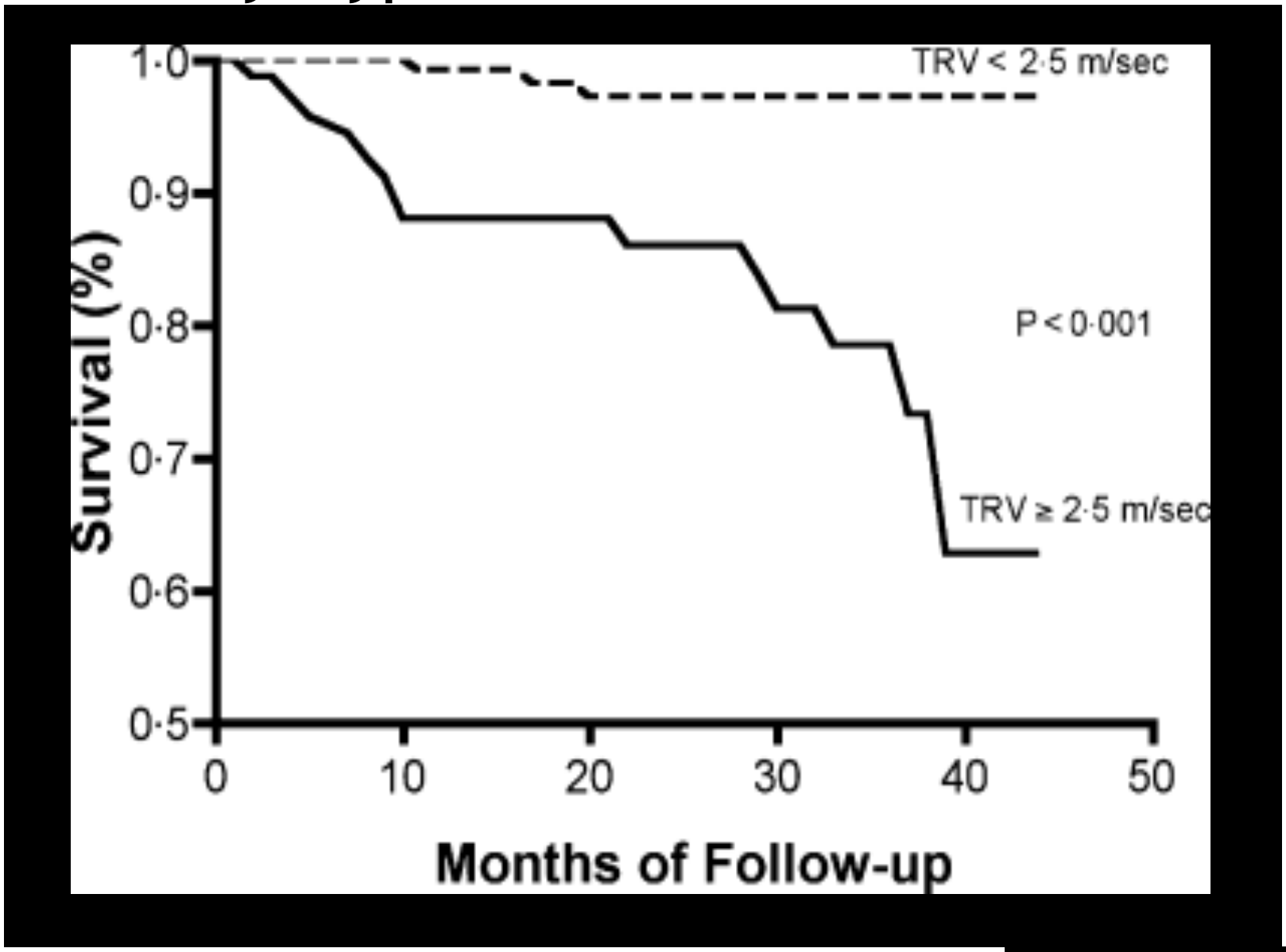


Strouse, et al, American Journal of Hematology, 2009

SCI in Normal Adults Vs. SCD



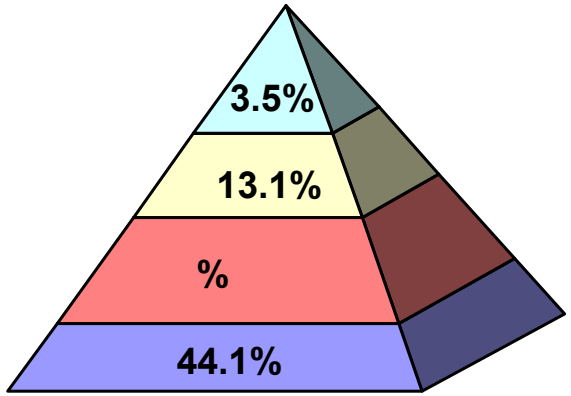
Pulmonary Hypertension



B JH 2005; 129: 449

Conclusions for PiSCES

- Pain is the rule rather than the exception, a chronic condition, under-recognized and undertreated
- Crisis doesn’t mean the same to patients and providers
- Utilization of health facilities is exception rather than a rule



Survival Related to Pain Rates

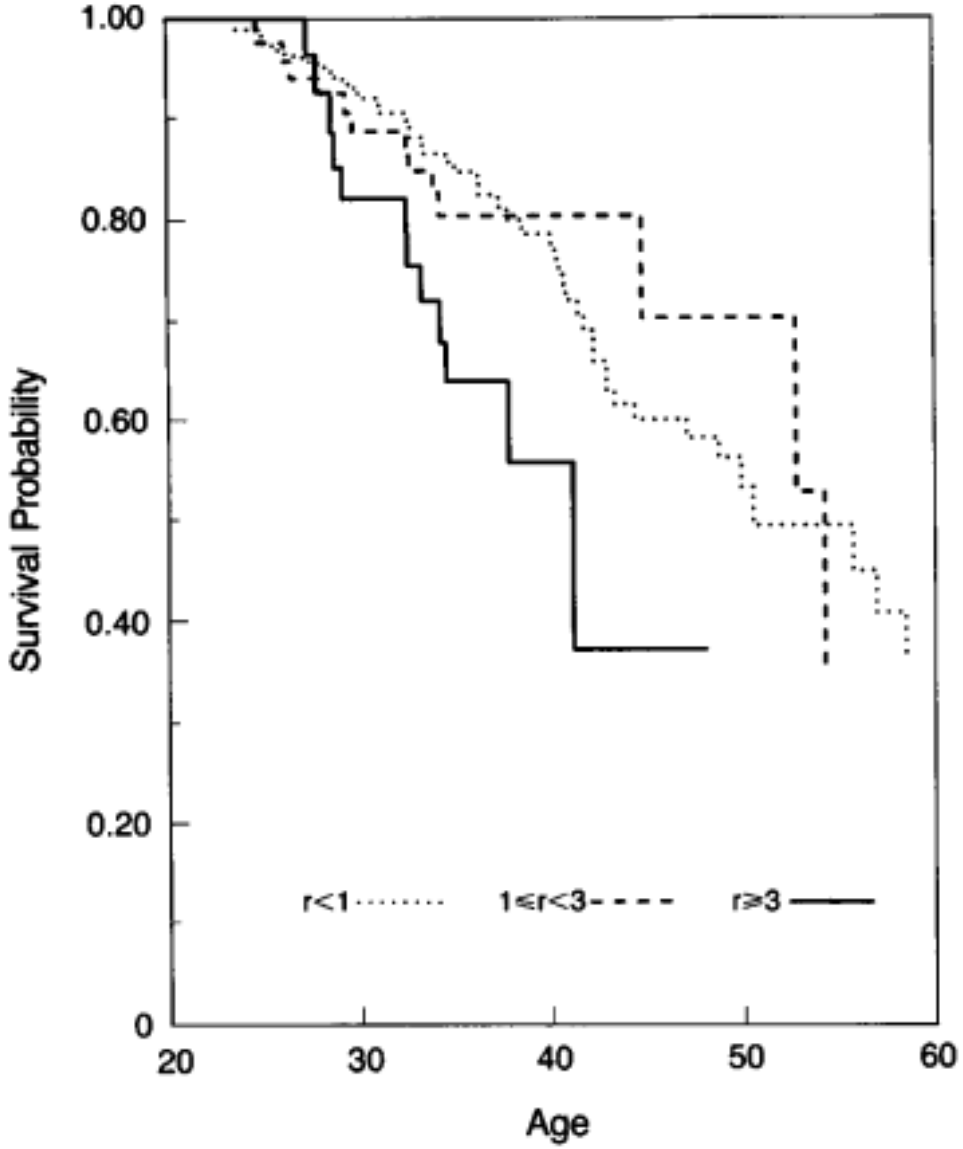
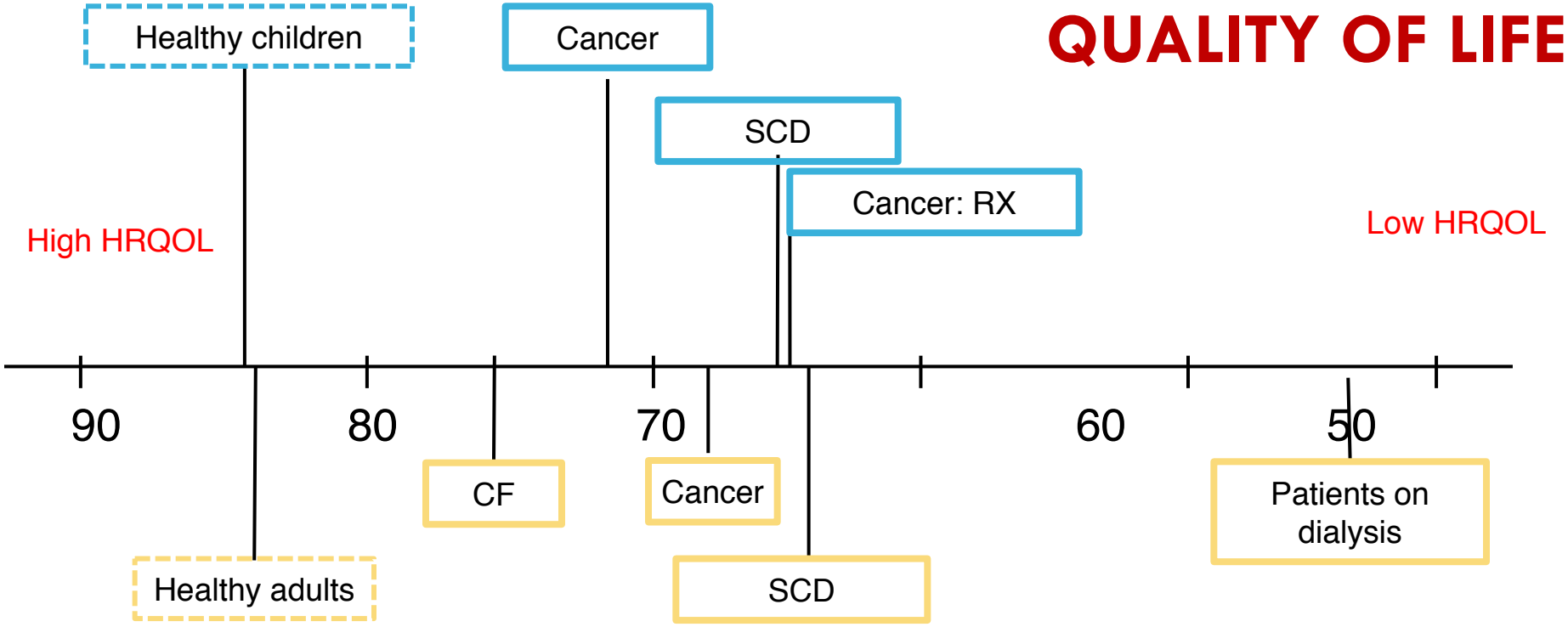


Figure 3. Survival of Patients with Sickle Cell Anemia (≥20 Years Old at Entry) Who Had Different Pain Rates.
r denotes the number of episodes of pain per patient-year.

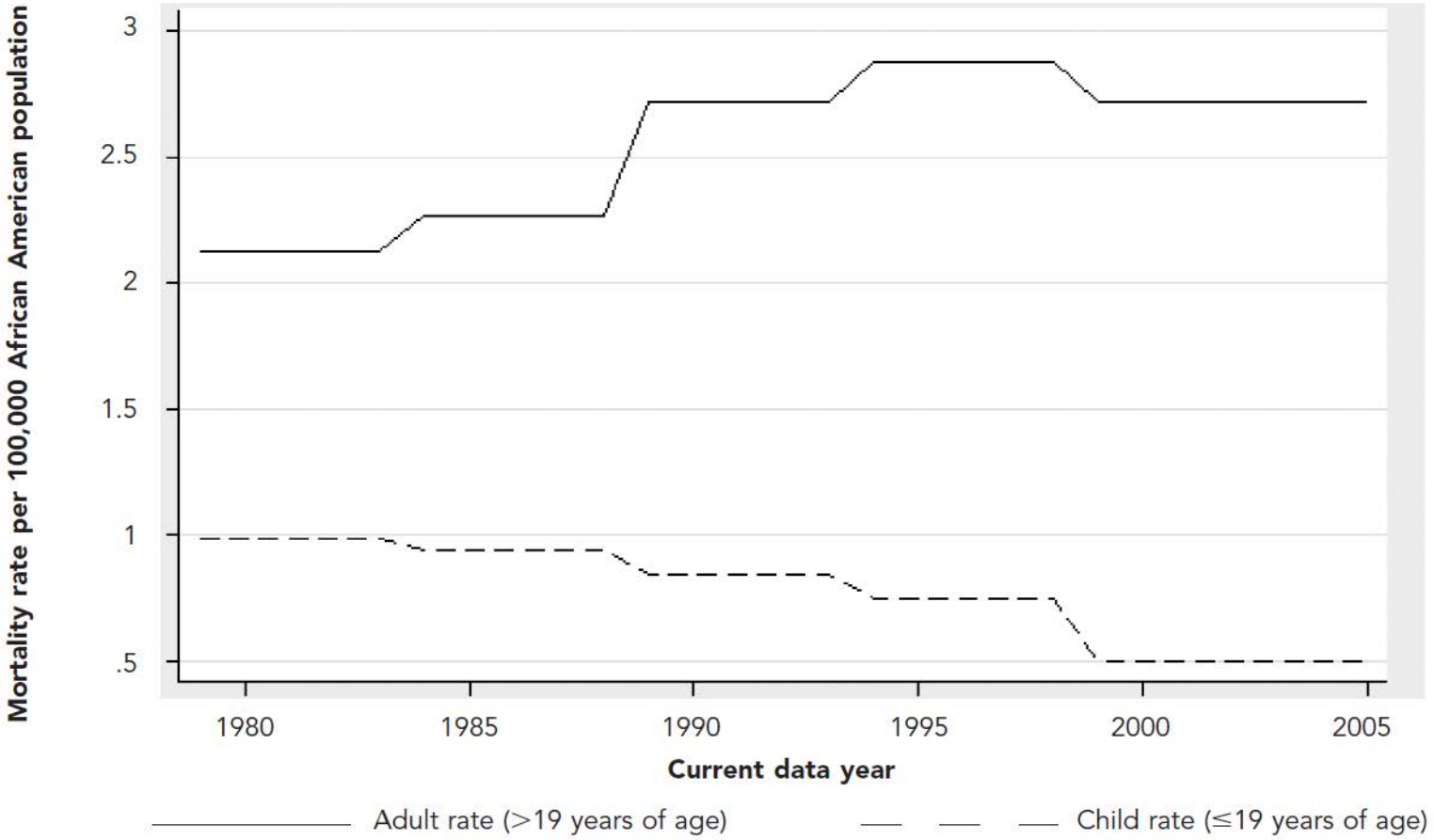
Platt, NEJM, 1991

QUALITY OF LIFE



	SCD N = 308	**Hemo-Dialysis** N = 1000	**Cystic Fibrosis** N = 223
Bodily Pain	47.4	60.4	82.2
General Health	39.2	50.0	43.4
Vitality	42.7	46.5	58.4
Social Function	63.5	66.0	80.4
Role-emotional	57.8	58.2	77.0

US Mortality Rates for Adults and Children 1979-2005

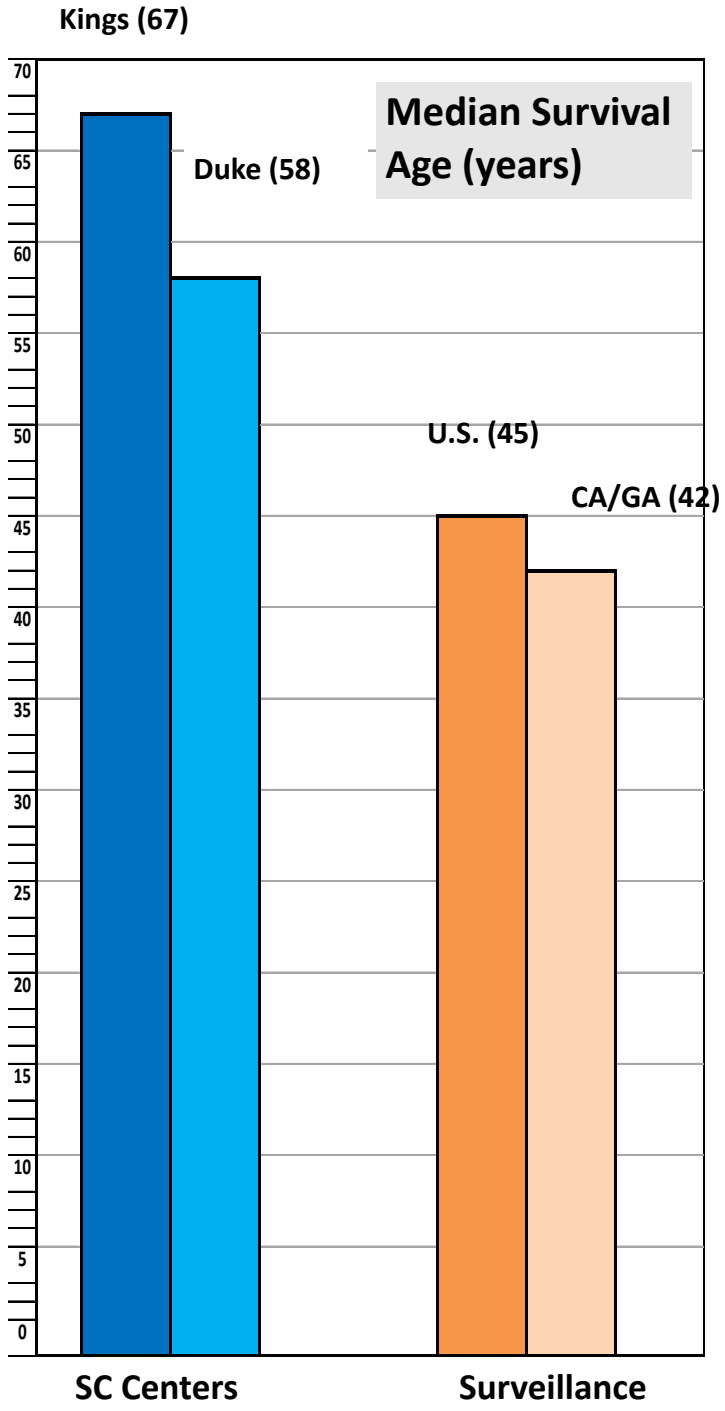


Lanzkrom, Public Health Reports, 2013

Survival Disparity in Adult Sickle Cell Disease: Sickle Cell Centers vs. Regional Surveillance

Years	Median Survival (years)	Dx	Location	N Pts	Author
Regional Surveillance:					
1978-1988	45 *42M 48 F*	SS only	United States	2,920	Platt/CSSCD study 1994
2004-2008	43	all SCD	California, Georgia	12,143	Paulukonis 2016
Comprehensive Sickle Cell Centers:					
2002-2014	58	SS , SBO	Duke Univ. +	449	Elmariah 2014
2004-2013	67	SS, SBO	King's College U.K.	450	Gardner 2016

- Nationally, survival data has not improved in last 25 years.
- Survival patients in sickle cell centers markedly improved.
- disparity in survival based on prevention/treatment of complications in adults.



What are Guidelines?

- The IOM (2011) defined clinical practice guidelines as "statements that include recommendations intended to optimize patient care that are informed by a systematic review of evidence and an assessment of the benefits and harms of alternative care options.“
- Provides framework for standards of care
- Helps the doctor know what to do

National Heart Lung and Blood Institute of the National Institutes of Health

- 2009 – 2014
- 161 pages
- Dozens of co-chairs, members, reviewers, methodologists, and subject matter experts
- Extensive reviews of what is published
- Expert working groups
- Preliminary drafts, editing, and revisions

https://www.nhlbi.nih.gov/health-topics/evidence-based-management-sickle-cell-disease

Reviewed by the major organizations

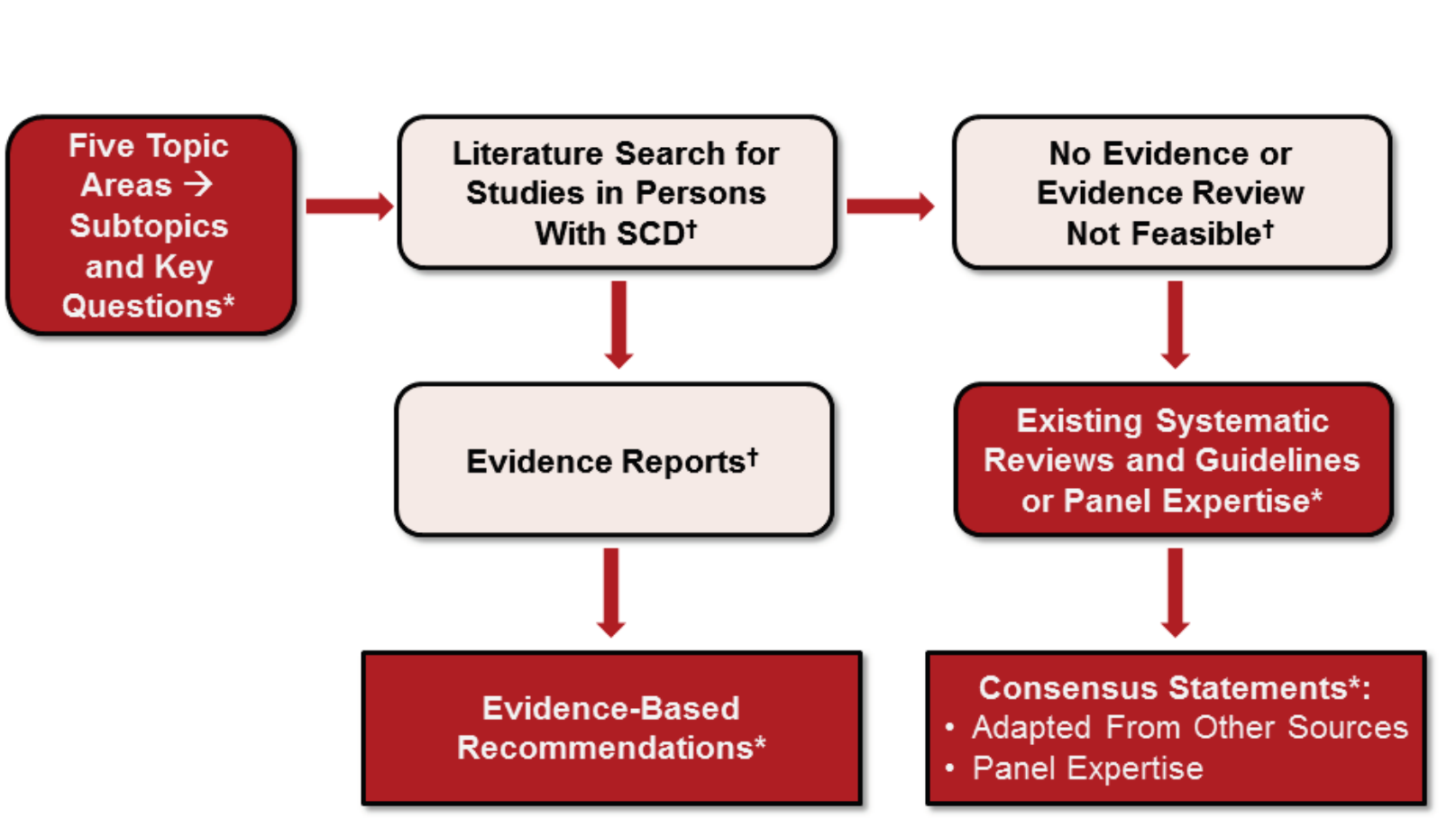
- Academy of Emergency Medicine (AAEM)
- American Academy of Pediatrics (AAP)
- American Academy of Physician Assistants (AAPA)
- American Osteopathic Association (AOA)
- American Society of Hematology (ASH)
- American Society of Pediatric Hematology/Oncology (ASPHO)
- International Association of Sickle Cell Nurses and Physician Assistants (IASCNAPA)
- National Black Nurses Association (NBNA)
- National Initiative for Children's Health Quality (NICHQ)
- National Medical Association (NMA)
- Sickle Cell Disease Association of America (SCDAA)

Framework of Guidelines

Ask Key Question

- **KQ2. In asymptomatic individuals with SCD, what is the effect of screening for renal disease, by measuring serum creatinine and urine albumin and protein, on mortality and the development of end-stage renal disease (ESRD)?**
- Made recommendation
- Listed strength of recommendation
  - Research quality of data, how definite, when and who it applies to.

Review what was known



Make recommendations

- Screen all individuals with SCD, beginning by age 10, for proteinuria. If the result is negative, repeat screening annually. If the result is positive, perform a first morning void urine albumin-creatinine ratio and if abnormal, consult with or refer to a renal specialist.

List strength of recommendation

(Consensus–Panel Expertise)

What's Covered

Chapter 2: Health Maintenance for People With Sickle Cell Disease

- Prevention of Invasive Pneumococcal Infection
- Screening for Renal Disease
- Screening for Pulmonary Hypertension
- Electrocardiogram Screening
- Screening for Hypertension
- Screening for Retinopathy
- Screening for Risk of Stroke Using Neuroimaging
- Screening for Pulmonary Disease
- Reproductive Counseling
- Contraception
- Clinical Preventive Services
- Immunization

Chapter 4: Managing Chronic Complications of Sickle Cell Disease

- Chronic Pain
- Avascular Necrosis
- Leg Ulcers
- Pulmonary Hypertension
- Renal Complications
- Stuttering/Recurrent Priapism
- Ophthalmologic Complication

What's Not Covered

- Voxelotor (Oxbryta) – Approved 11/2019
  - Affects Oxygen Affinity
  - 274 patients studied
- Crizanlizumab (Adakveo) – Approved 11/2019
  - Affects cells sticking to blood vessels
  - 198 patients studied
- L-glutamine (Endari) – Approved 7/2017
  - ? Likely increases nitric oxide
  - 230 patients studied

Bone Marrow Transplants

Genetic Therapies

Any study since 2014

ASH Guidelines 2019-2020

Example of Change:
Renal Screening after 2014

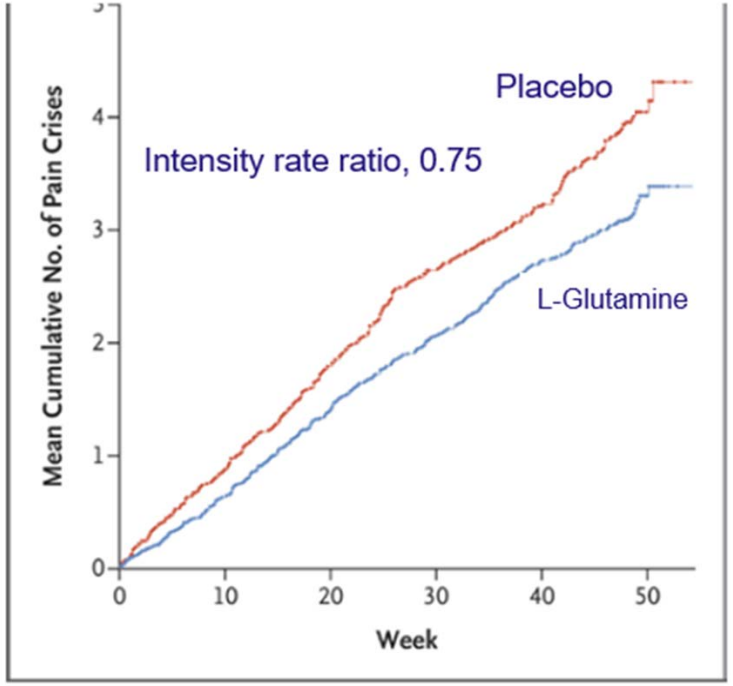
Quarterly UA (albuminuria, albuminuria/creatinine ratio)

Serum creatinine (Serum creatinine does not↑ abn GFR
> .7 mg/dL in children > 1 mg/dL in adults Δ 0.3 mg/dL

Cystatin-C better than creatinine

A Phase 3 Trial of L-Glutamine in SCD

Glutamine is a Precursor of NADH and Decreases Oxidative Stress in sRBC



25% reduction in number of pain crises (3.0 vs 4.0; P 0.005)

30% lower hospitalization rates (2.0 vs 3.0; P 0.005)

Reduced number of episodes of acute chest syndrome (ACS; ~8% vs 23% P 0.003)

Y. Niihara et al, 2018. NEJM

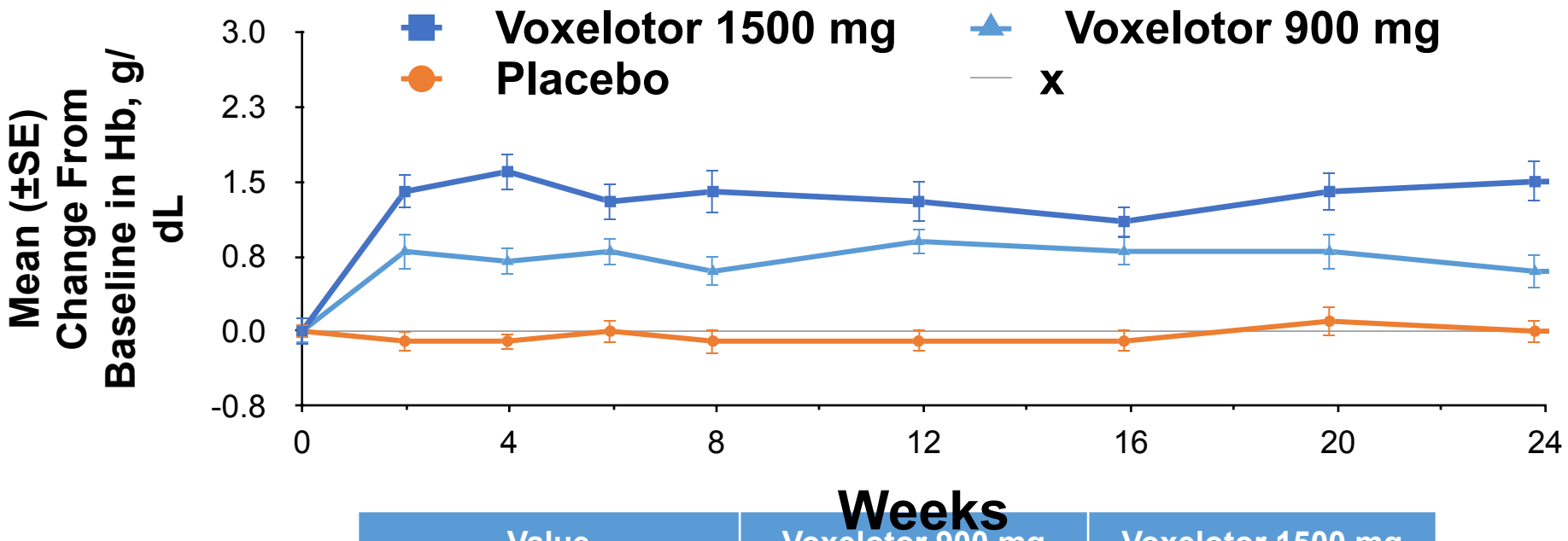
Primary End Point - Annual Rate of SCPC
SUSTAIN Study Monthly Infusions in 3 Arms, One Year

Primary End Point	High-Dose SelG1 (N=67)	Low-Dose SelG1 (N=66)	Placebo (N=65)
Median rate of SCPC per year	1.63	2.01	2.98
Reduction vs. placebo	45.3%	32.6%	
P value	0.010	0.180	
Interquartile Range	(0.00 - 3.97)	(1.00 – 3.98)	(1.25 – 5.87)
Number of patients with SCPC rate of zero at end of study	24	12	11

Annual Rate of Days Hospitalized

	High-Dose SelG1 (N=67)	Low-Dose SelG1 (N=66)	Placebo (N=65)
Median rate per year	4.00	6.87	6.87
Reduction vs. placebo	41.8%	0.0%	
P value	0.450	0.837	
Interquartile Range	(0.00 – 25.72)	(0.00 – 18.00)	(0.00 – 28.30)

Voxelotor Demonstrates a Rapid, Robust and Sustained Improvement in Anemia at Target Hemoglobin Occupancy



Value	Voxelotor 900 mg	Voxelotor 1500 mg
% Hb occupancy[a] (C_{min})	13.8% (46.5)	25.3% (32.8)

[a]Hb occupancy geometric mean (%CV) = calculated % of RBC Hb bound by voxelotor

What's known about new Sickle Cell medications

Medication	VOC	Hospital	Hemoglobin	Hemolysis	Transfusions	Acute Chest	Organ
Hydroxyurea	↓(44%)	↓(58%)	↑	↓	↓(36%)	↓(54%)	↑
L-glutamine	↓(25%)	↓(33%)	→	?	?	?	?
Crizanlizumab	↓(33%)	?	→	?	?	? (↑?)	?
Voxelotor	→	?	↑(51% > 1)	↓	?	?	?

Approved Medications for Sickle Cell Disease
Hydroxyurea – all patients with SS hemoglobin and no contraindication beginning at age 9 months
L-glutamine – any patient with recurrent VOCs and admissions after hydroxyurea
Crizanlizumab—patients with ongoing pains despite hydroxyurea or transfusions
Voxelotor—patients on transfusions who are accumulating iron despite chelation; patients with chronic symptomatic anemia despite hydroxyurea; patients with markers of ongoing hemolysis

Checklist:

Good Health Care

1.Work closely with your doctors – primary care and sickle cell specialist -- to develop your own unique care plan.

2. Build relationships with a hematologist and a team of **other specialists** so they are available for you when needed.

Healthy Lifestyle

1. Stay active.
2. Drink 8–10 glasses of water daily.
3. Follow a heart-healthy eating plan that includes limiting alcohol.
4. Aim for 7–8 hours of sleep a night.

Prevent Infections

✓ Children under 5 years old should take penicillin regularly.

✓ Adults and children should get scheduled vaccines, including flu shots.

✓ Wash hands often.

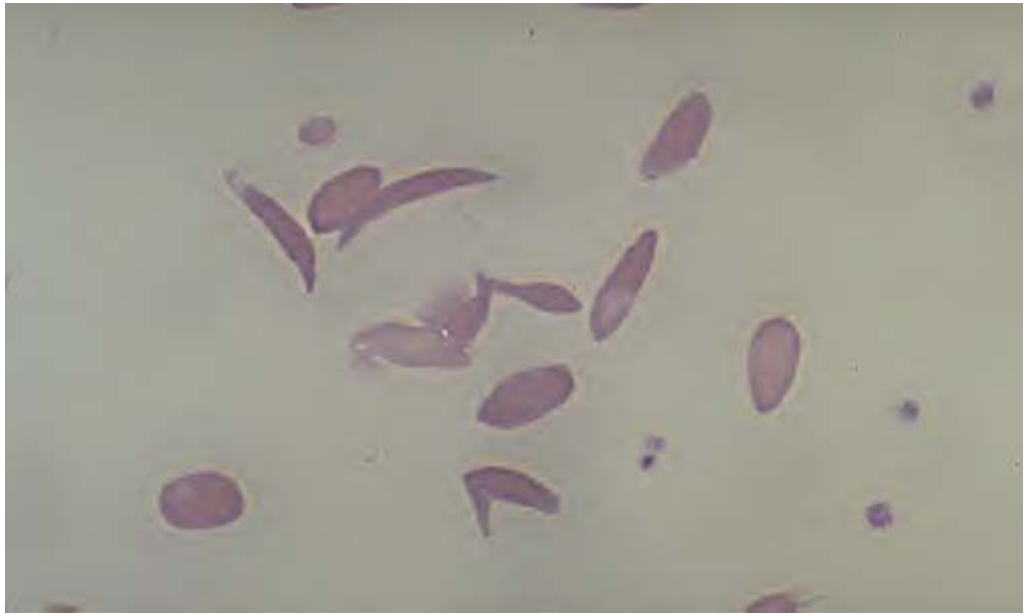
Topics to Discuss with Your Doctor

Pain Control

1. How has your pain been since your last visit?

2. What do you do to control pain?

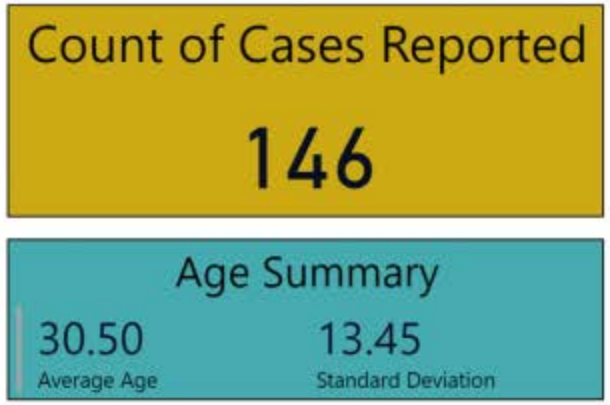
3. Have you been screened for any organ changes from sickle cell that are recommended in the guidelines?

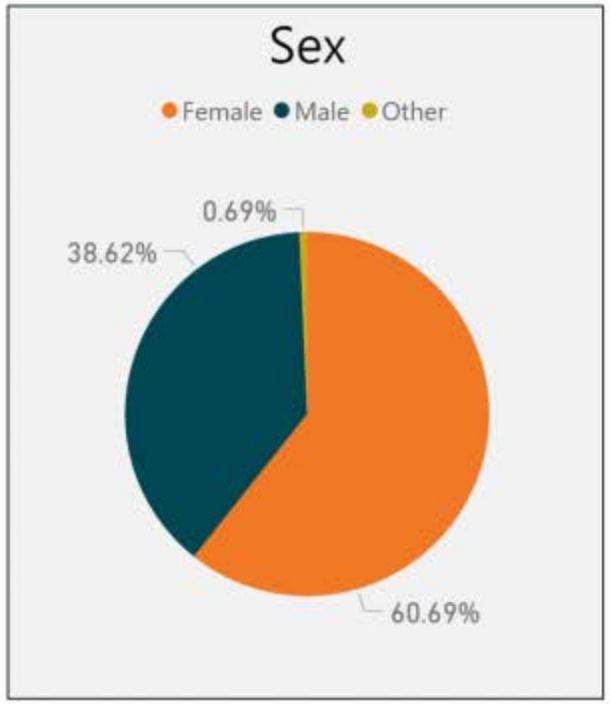


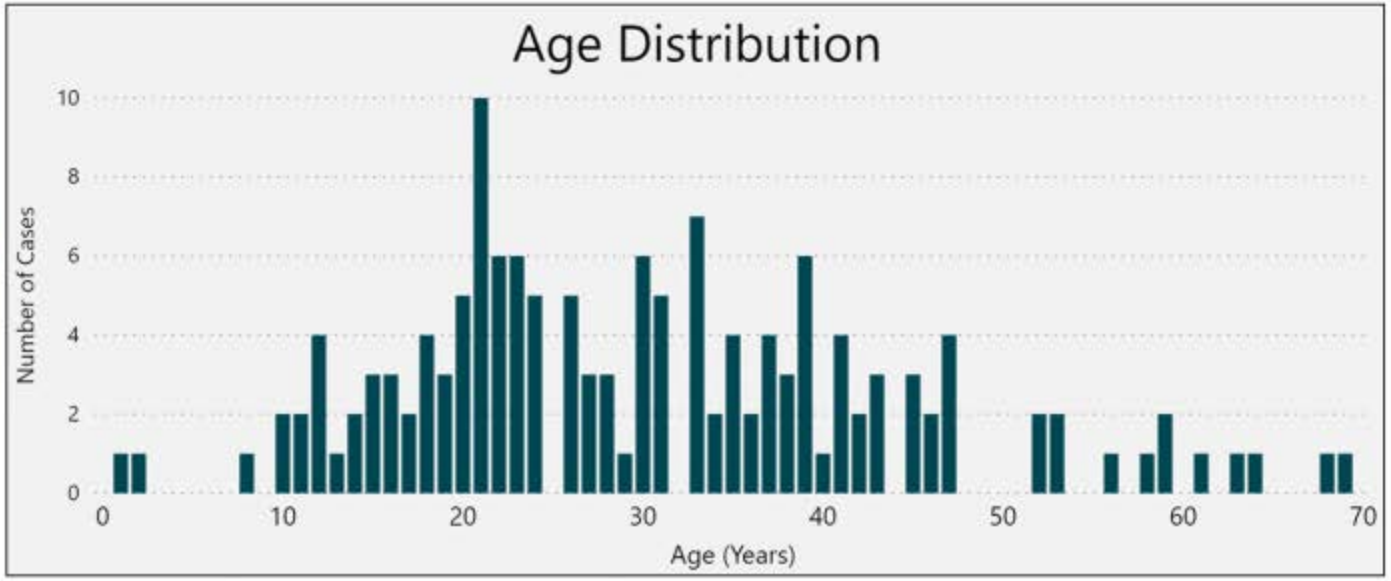
Thank You

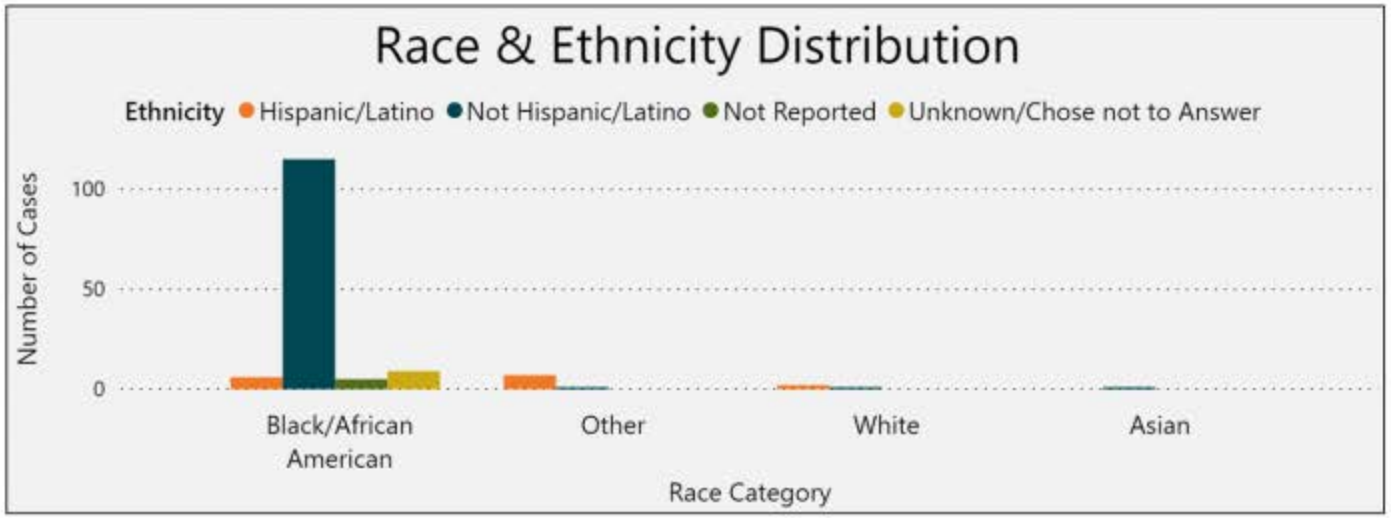
Covid-19 Update

Cases as of May 8, 2020









Source: https://covidsicklecell.org/updates-data/

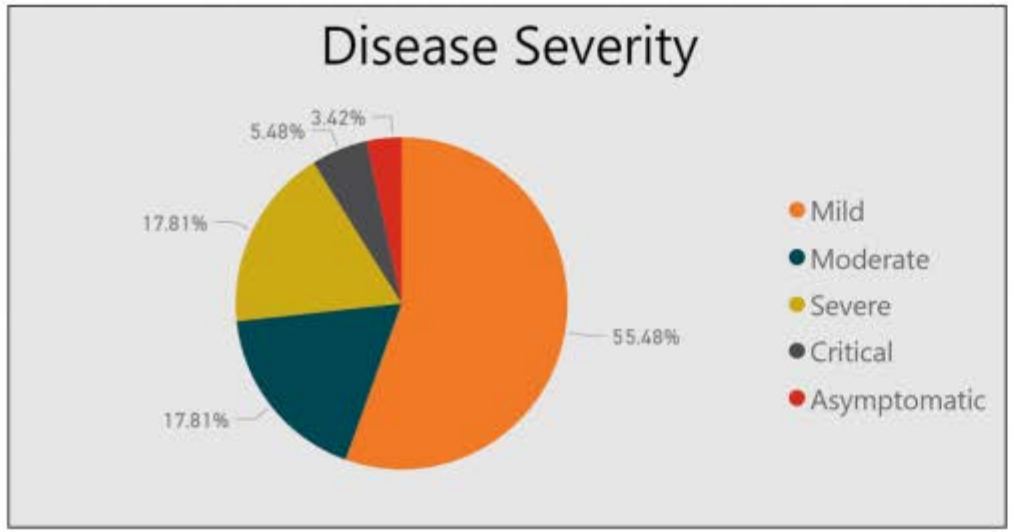
Case Locations in the World as of May 8, 2020

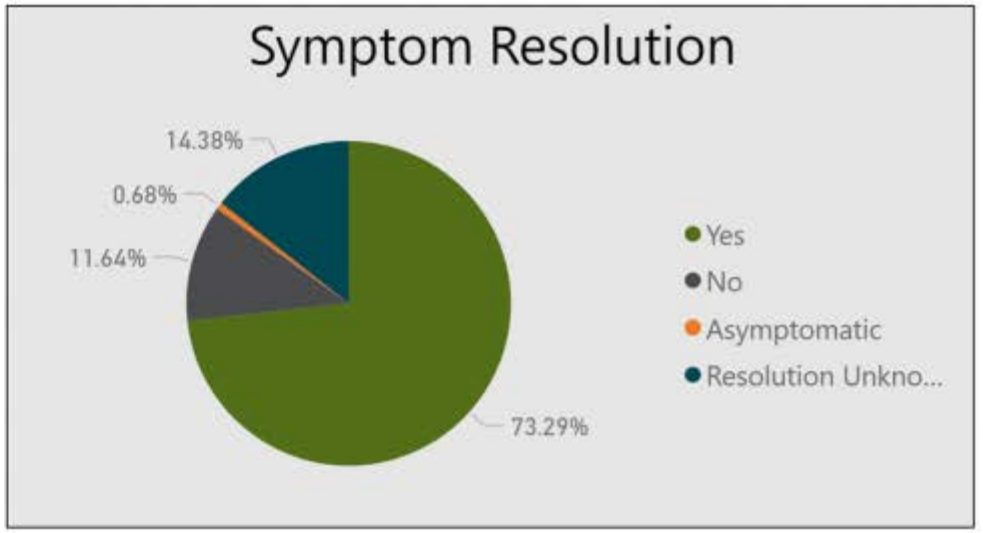
Source: https://covidsicklecell.org/updates-data/

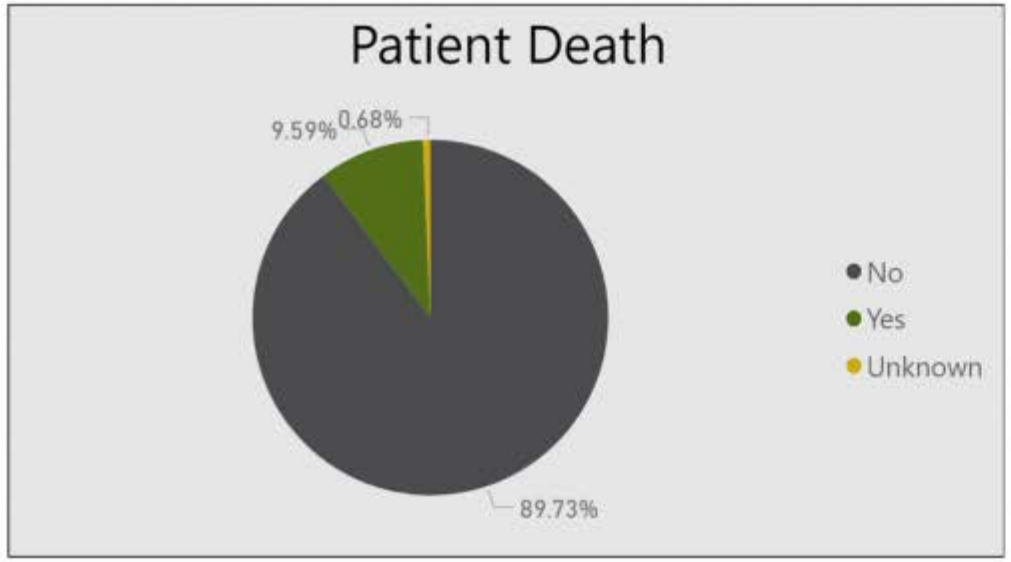
Case Locations in US as of May 8, 2020

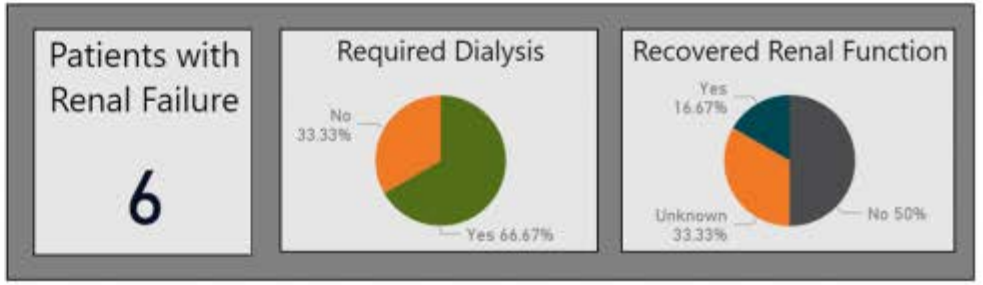
Source: https://covidsicklecell.org/updates-data/

Outcome of Know Cases as of May 8, 2020









Source: https://covidsicklecell.org/updates-data/

Covid Precautions

- Sickle Cell is a Potentially High Risk Condition
  - Concerns about lungs
  - Concerns about clotting
- Fewer Cases in our area
- Follow current social distancing
- Still go to ED if:
  - Breathing issues
  - Possible brain issues
  - Severe pain that can’t be home managed
- If you are admitted with Covid, call your sickle cell provider