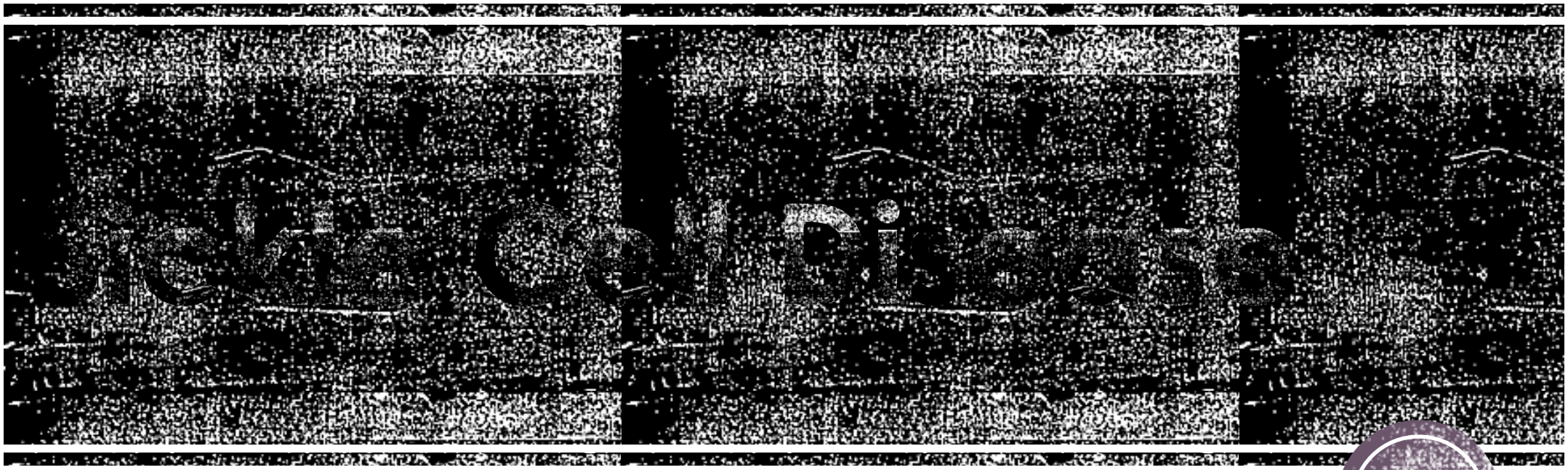

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Valley Children's HEALTHCARE

Disclosures

- No financial disclosures
- No conflict of interest

Valley Children's HEALTHCARE

Objectives of this talk

- Understand the genetics and prevalence of Sickle Cell Disease
- Pathophysiology of Sickle Cell Disease
- Clinical manifestations of Sickle Cell Disease
- Management of Sickle cell Disease complications
- Disease modifying agents in Sickle Cell disease
- Newer therapeutics in Sickle cell disease

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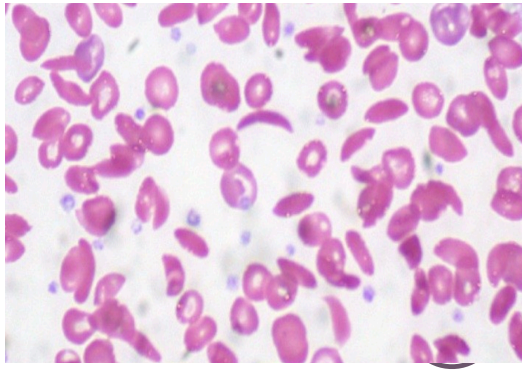
Sickle Cell Disease

- Sickle Cell disease (SCD) is the commonest inherited hematological disorder
- Approximately 100,000 individuals affected by SCD in USA
- SCD gene prevalence is seen in African, Asian, South American, Indian and Mediterranean ethnicities
- In USA, African American and Latino American shown to have the gene prevalence
- SCD occurs among about 1 out of every 365 Black or African-American births.
- 1 in 385 births in AA has SCD (HbSS, HbS/Beta thal or HbSC)
- 1 in 13 has AA has Sickle cell trait*
- 1 in 6173 births has HbSC



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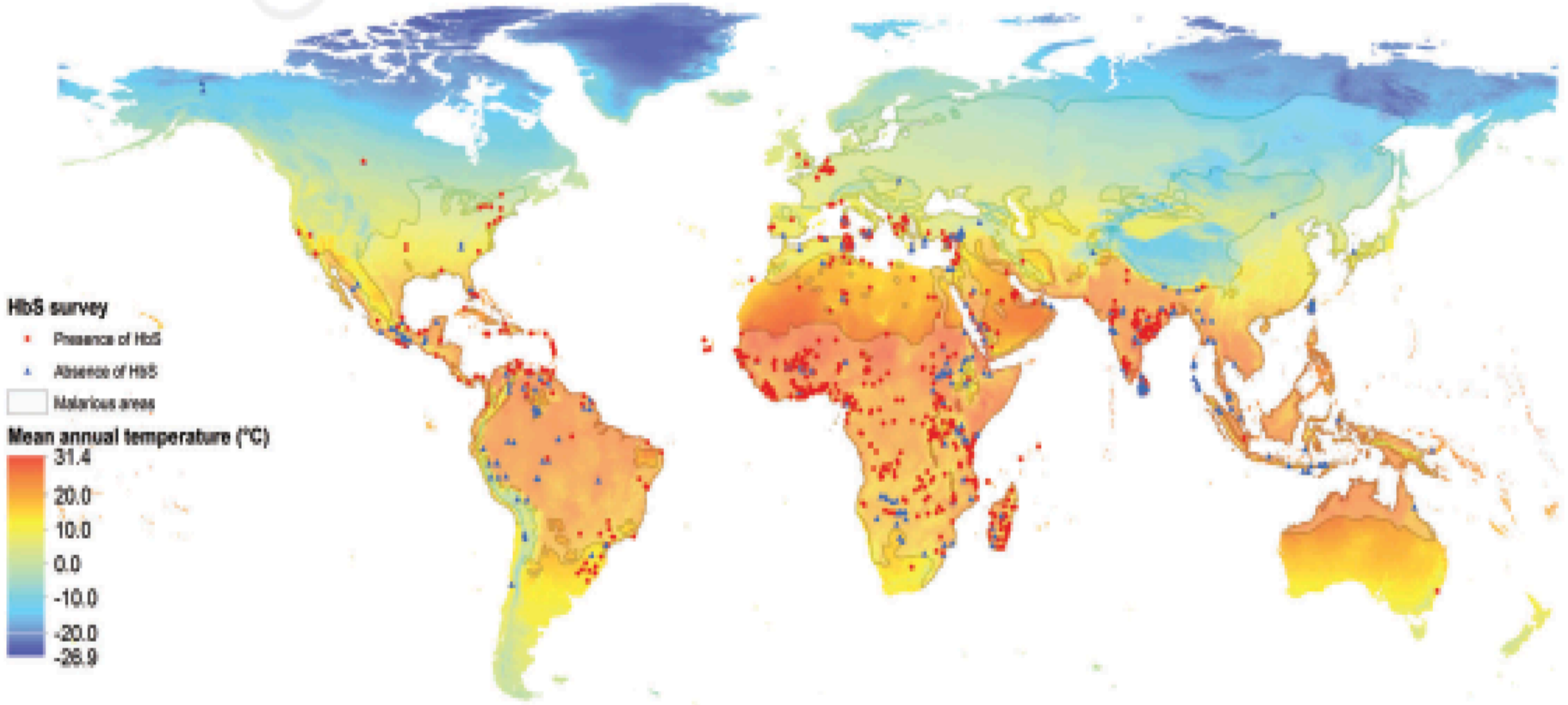
CDC

*Resource: CDC

Distribution of Sickle Gene- World wide



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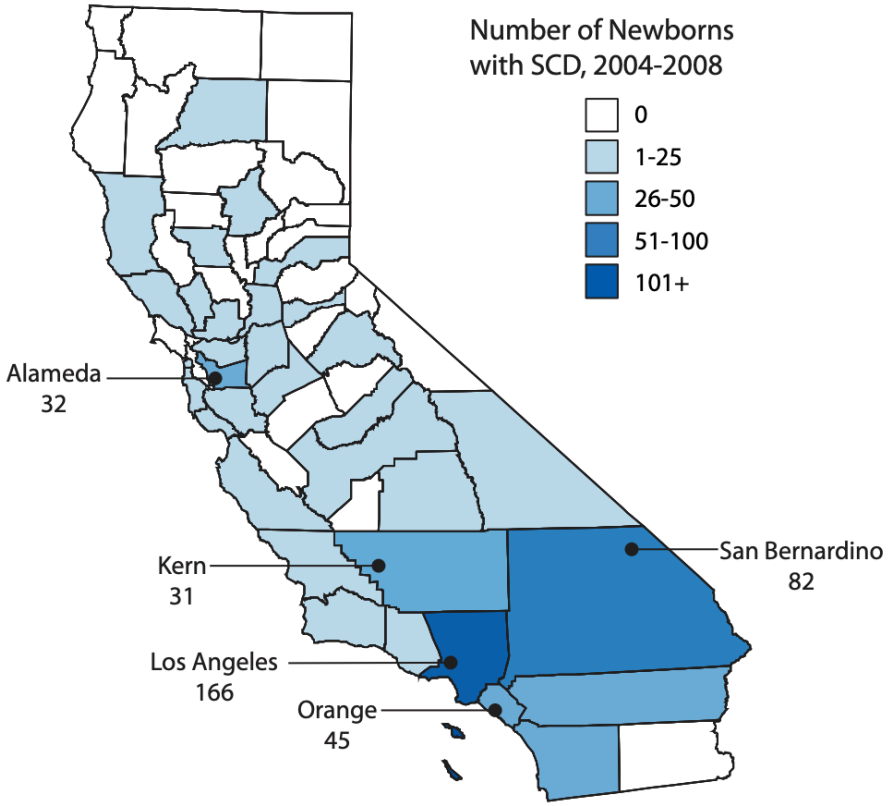
haematologica | 2015; 100(9)

Distribution of SCD in California



There were approximately 5,100 people with SCD living in California in 2004-2008:

- 14% younger than 6 years
- 25% 6-17 years
- 22% 18-29 years
- 28% 30-50 years
- 11% 51 years and older

There were 486 babies born with SCD in California in 2004-2008:

- 89% were Black, African-American
- 8% were Hispanic, Hispanic-American
- 5% were Other

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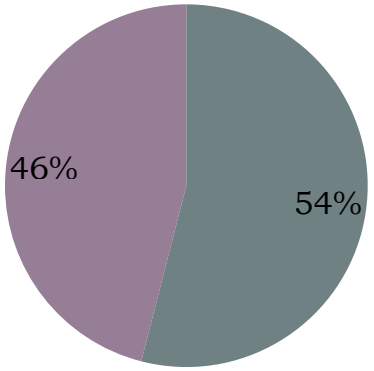
Resource: CDC

SCD in Valley Children's Hospital - 2019

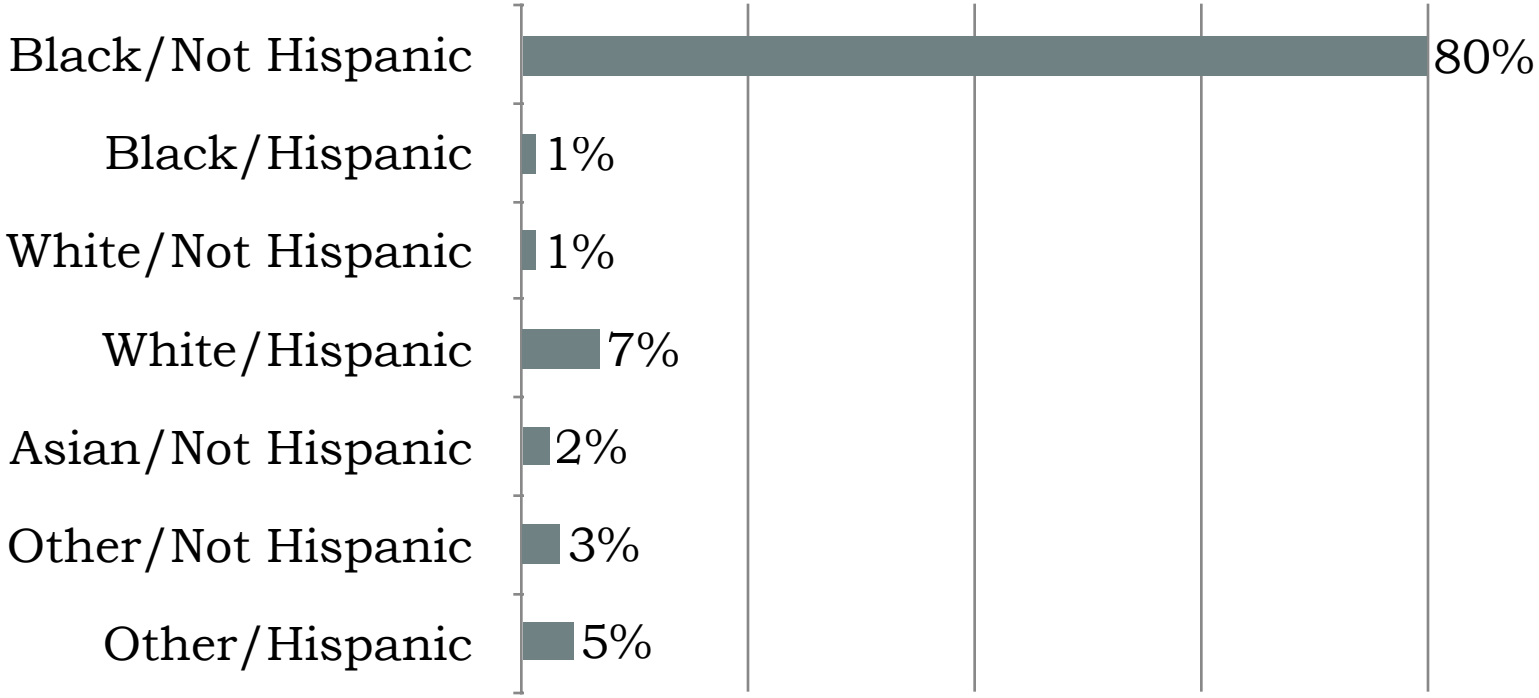
Patient by Gender



Male
Female

Total number of patients with SCD in FY2019= 87

Race/Ethnicity



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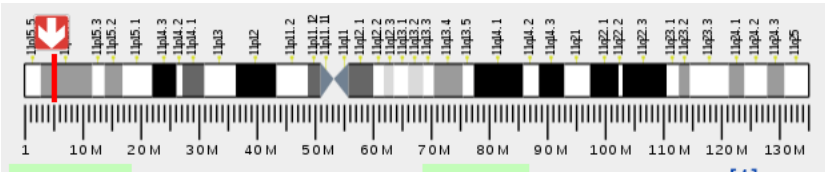
Sickle Cell Disease spectrum at Valley Children's Hospital over the past 5 years

Diagnosis	NUMBER (n)	% Total
Hb SS Disease	71	52.59%
Hb SC Disease	44	32.59%
HbS/B+ (Sickle Beta+ Thalassemia)	6	4.44%
HbS/B0 (Sickle Beta 0 Thalassemia)	3	2.22%
HbS/Hb E Disease	6	4.44%
HbS/Hb D Los Angeles	2	1.48%
HbS/Hb D Disease	1	0.74%
HbS/Hb Riyadh Disease	1	0.74%
HbS/Hb N Baltimore	1	0.74%

Genetics of Sickle cell disease

HBB gene: Chr 11p15.4



HbS is produced by a point mutation in *HBB* in which the codon GAG is replaced by GTG.

This results in the replacement of hydrophilic amino acid glutamic acid with the hydrophobic amino acid valine at the sixth position (β6Glu→Val).

HbC is produced by a point mutation in HBB (β6Glu→Lys)

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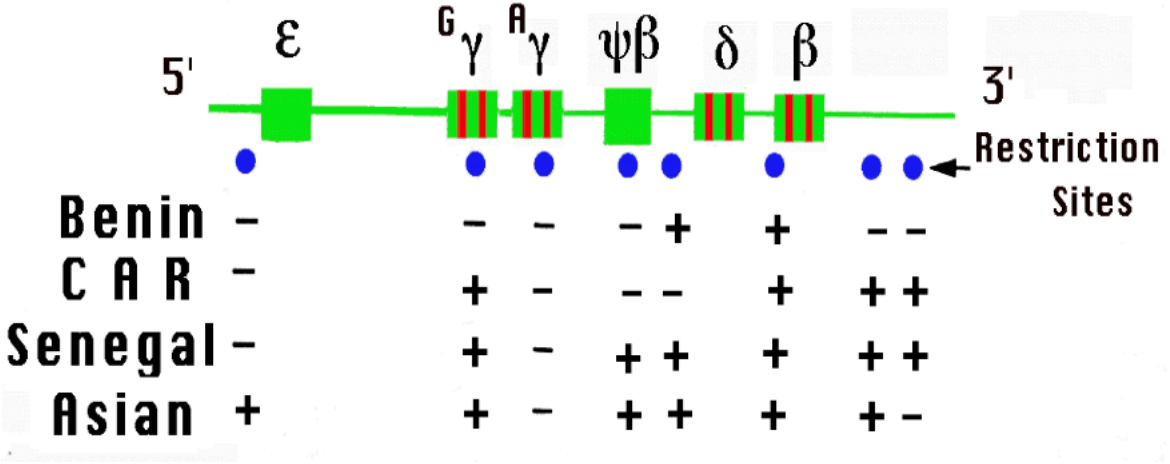
Haplotypes of Sickle Cell Disease



Powars et al, Am. J. Dis. Child. 147:1197-1202.

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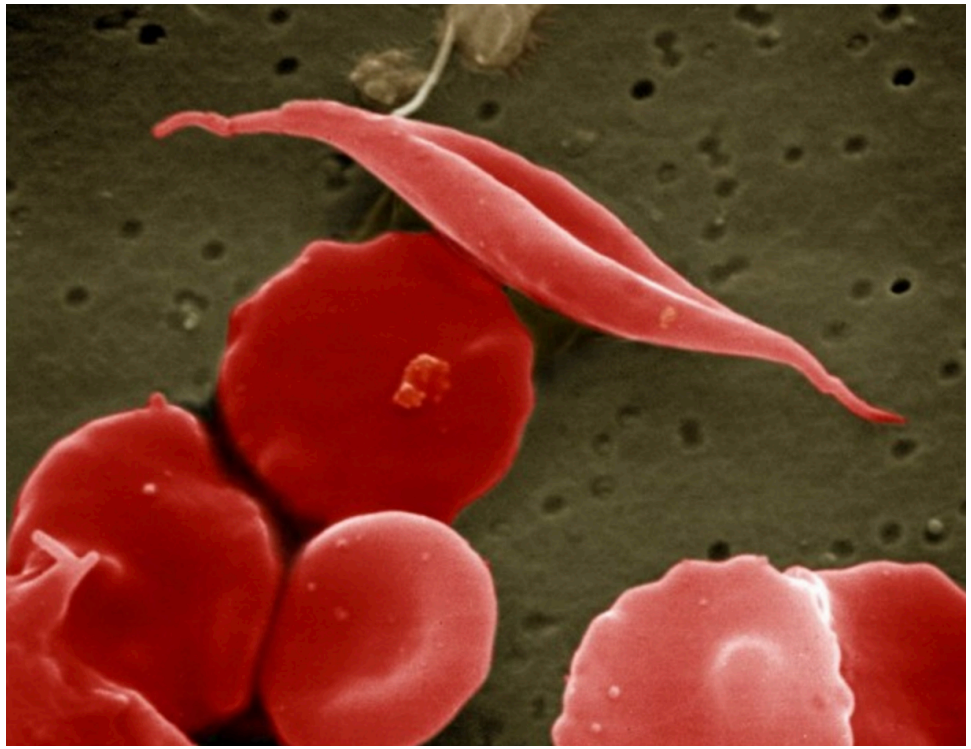
Malarial resistance in Sickle cell disease



Sickle cell trait, HbSS and HbSC individuals have shown resistance to Malaria

This reduction is hypothesized to be due to the interference in the red cell membrane breakdown in the late schizont phase and release of merozoites into the peripheral circulation

Blood. 1986;67(4):997-1001.

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Sickle Cell Disease Spectrum

- **Homozygous Sickle Cell Disease (HbSS)**
- **Sickle – Hemoglobin C disease (HbSC)**
- **Sickle- Beta Thalassemia (HbS/ Beta Thal)**
- **Sickle Cell Trait (HbSA)- Not considered disease (but recent data shows some evidence of mild disease pathology)**
- **Severity (HbSS >/= HbS/Beta Thal> HbSC> HbSA)**

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Sickle Cell Disease genetics

- **If both parents have Sickle cell trait (SCT):**
  - 50% chance (or 1 in 2) that any of their children will have SCT
  - 25% chance (or 1 in 4) that any of their children will have SCD
  - 25% chance (or 1 in 4) that any of their children will not have SCD or SCT

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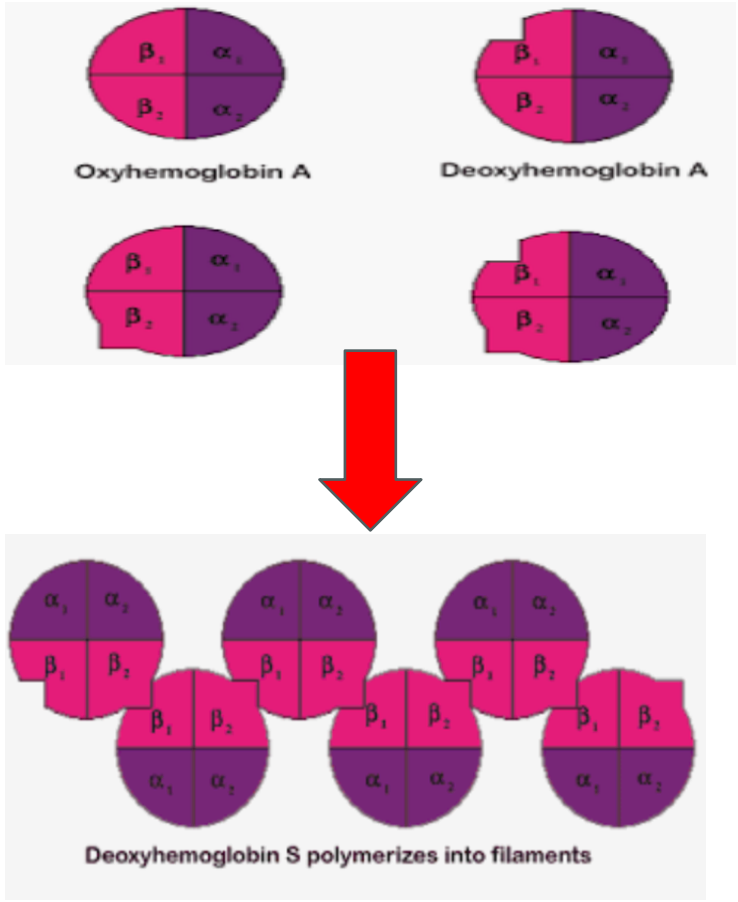
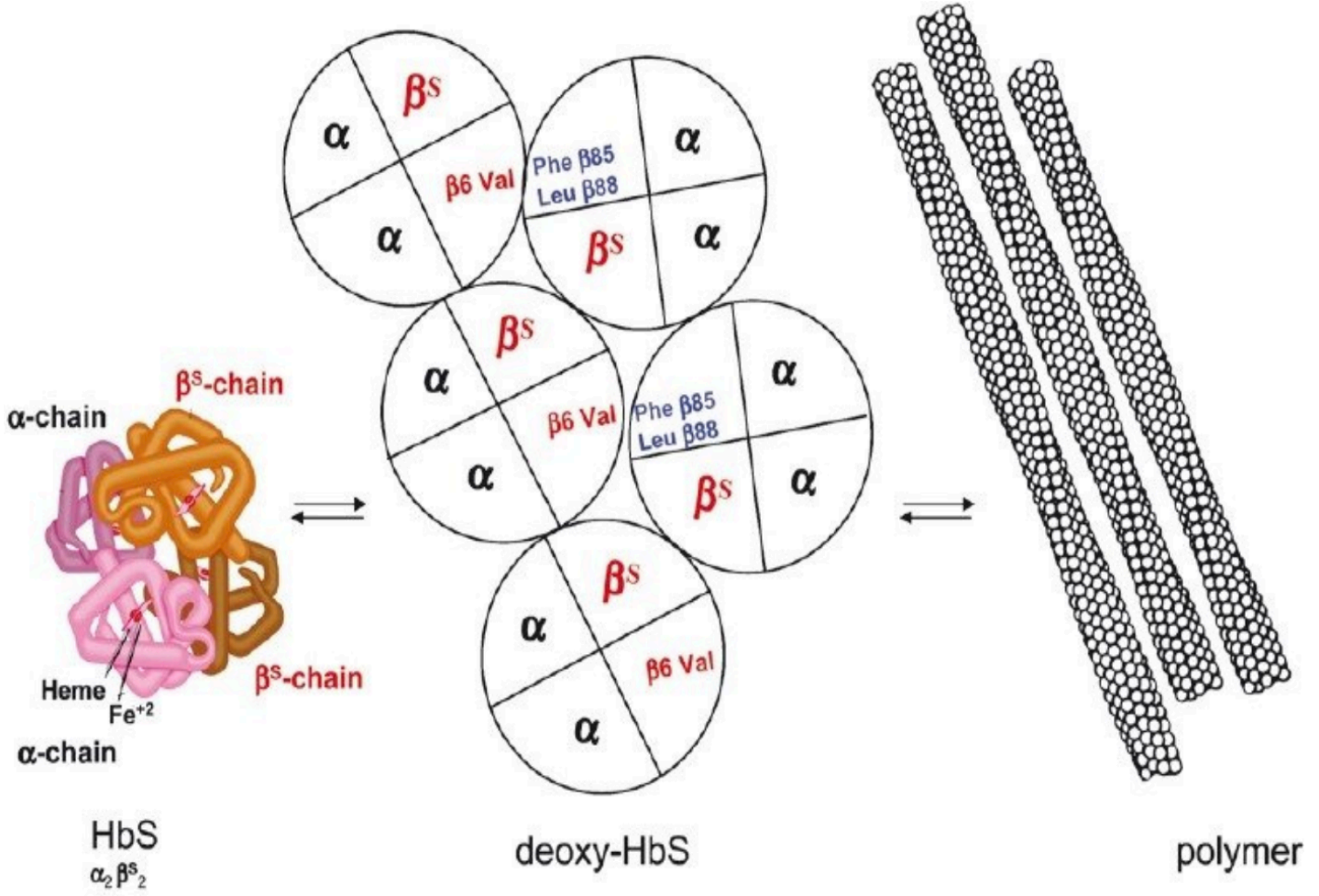
Sickle Hemoglobin (HbS)





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The Indian Journal of Medical Research 134(4):532-7

Pathophysiology of Sickle Cell disease

- HbS polymerizes makes the red cells become stiff, sticky and sickle shaped
- The deformed cells block blood flow, causes pain, organ damage and stroke
- It also causes hemolysis of abnormal red cells leading to loss of NO and complications like Pulmonary HTN, priapism and cutaneous ulcers

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Modifiers of severity of Sickle Cell disease

- Depends on Haplotype (Bantu/ CAR more severe)
- Haplotype Arab- Indian less severe
- Presence of Hemoglobin F
- Co-existent α- thalassemia mutation
- Geographical factors
- Patient related factors
- Socio-economic factors

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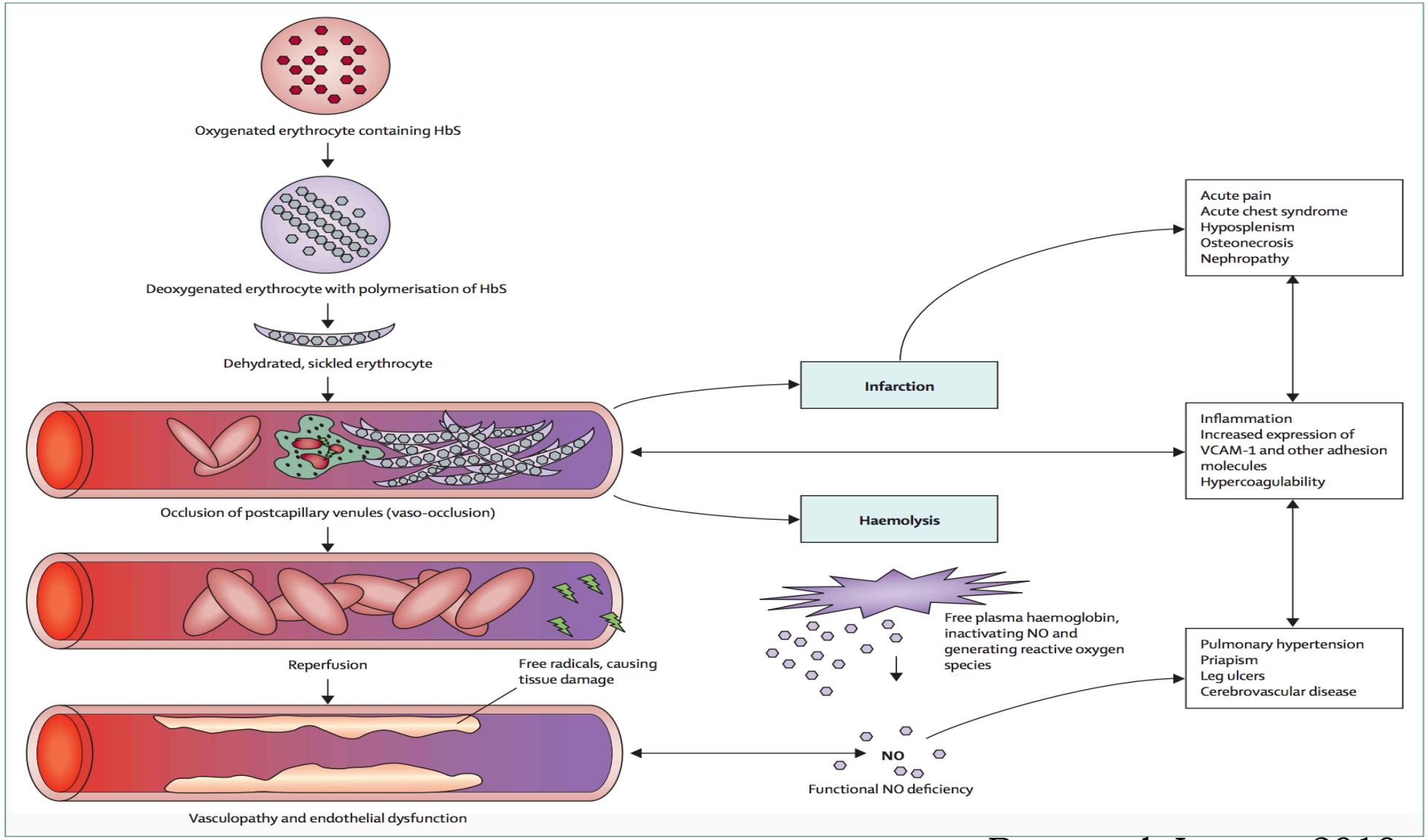
Pathophysiology of Sickle Cell Disease



Rees et al, Lancet, 2010

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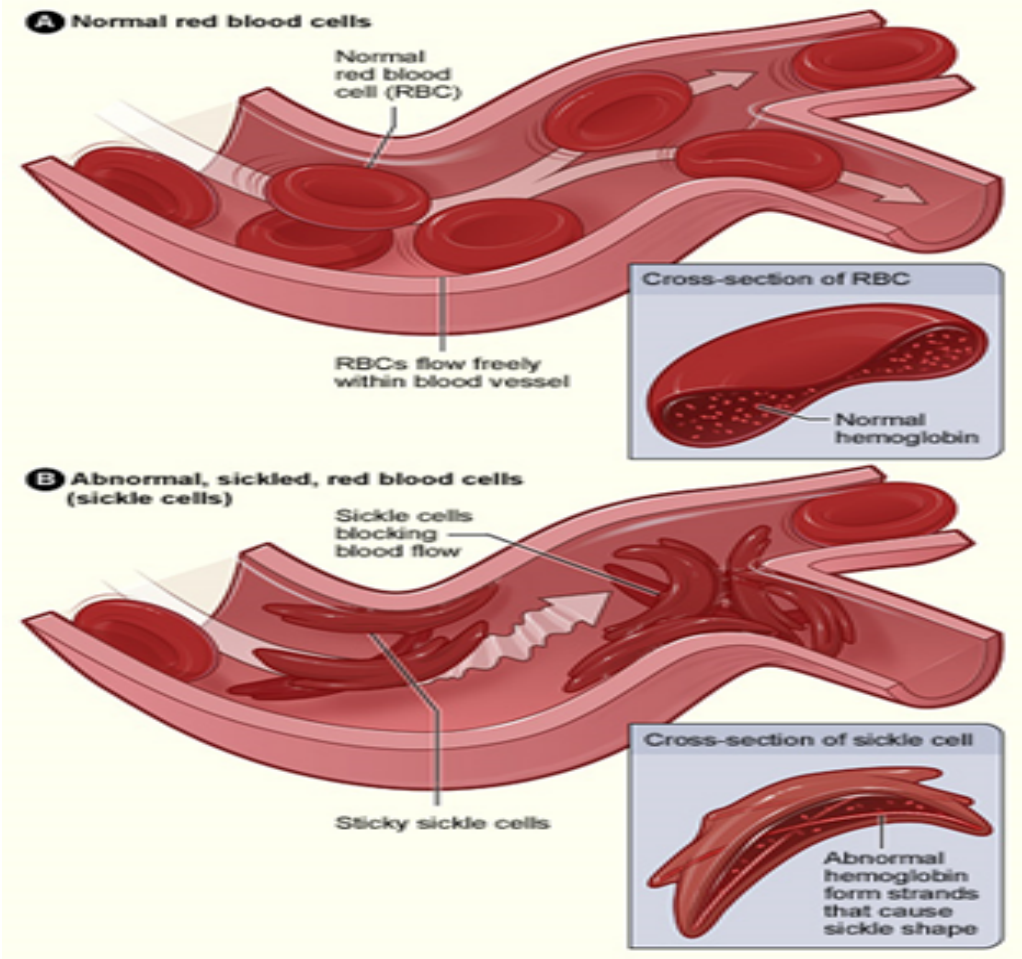
Pathophysiology of Sickle Cell disease

Vaso-occlusive symptoms

pain, avascular necrosis, organ damage and stroke

Hemolytic symptoms

Pulmonary HTN, priapism and cutaneous ulcers



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Sickle cell disease symptoms

- **Typically start around 4- 5 months of age**
  - When fetal hemoglobin switches to adult hemoglobin
  - Many complications are acute or chronic
  - Consists of pain crisis, acute chest syndrome, overt or silent stroke, priapism, deep vein thrombosis, cutaneous ulcerations, pulmonary HTN, osteonecrosis

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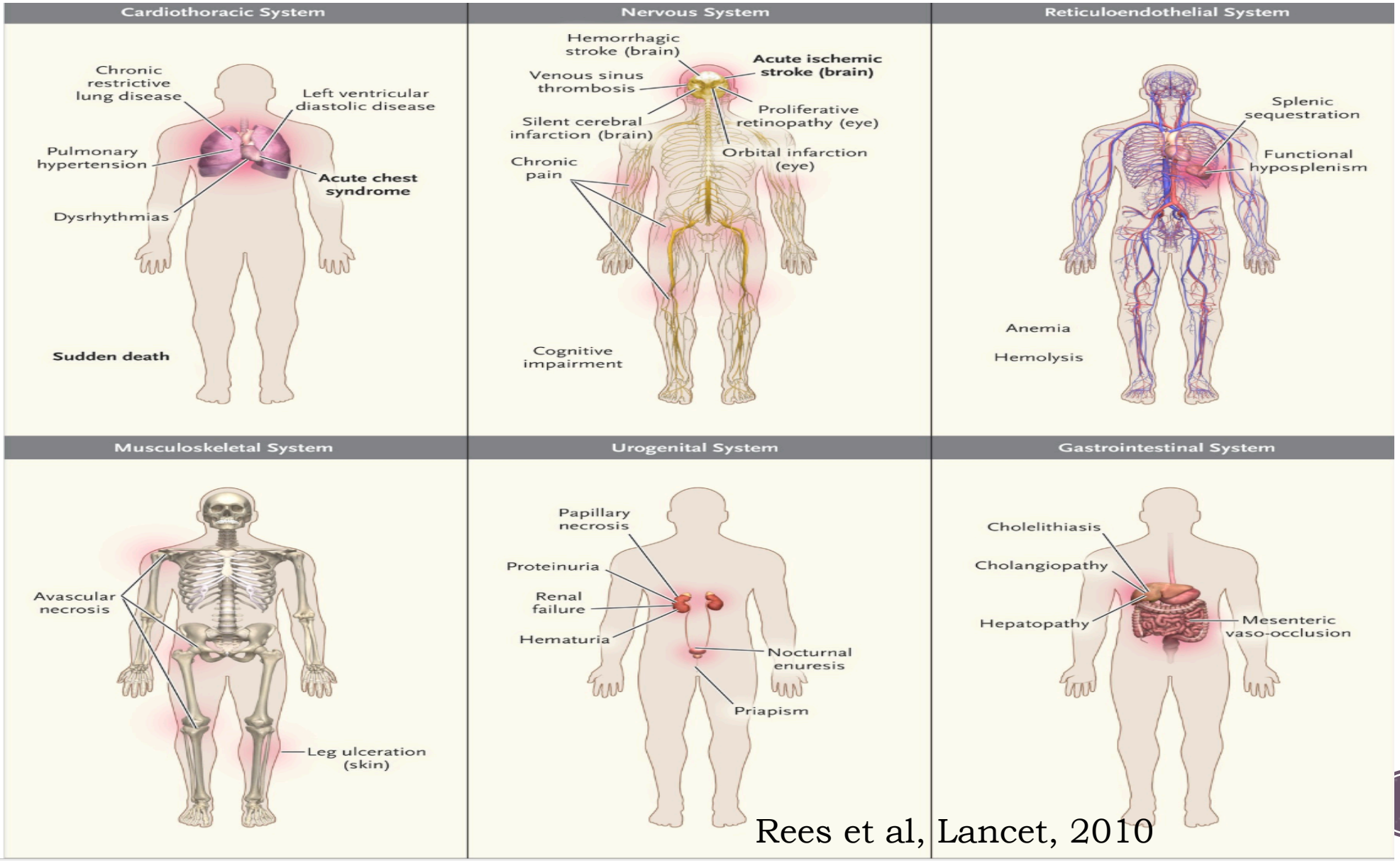
Symptoms of SCD



Rees et al, Lancet, 2010

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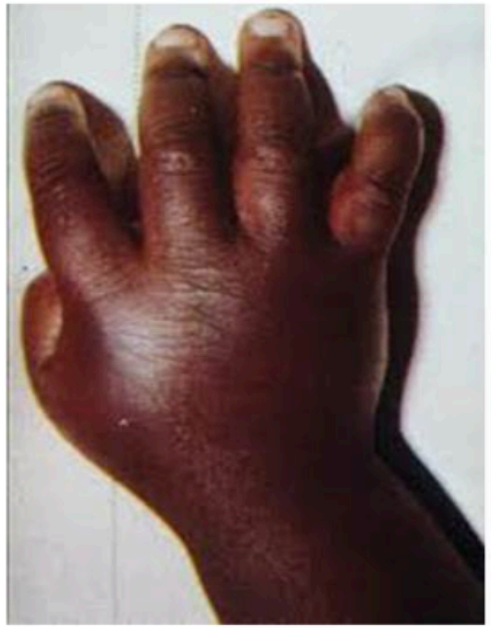
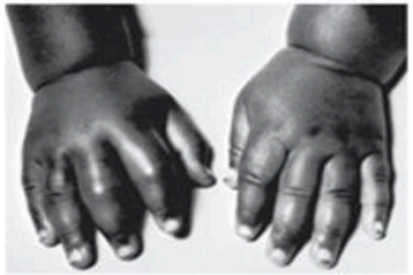
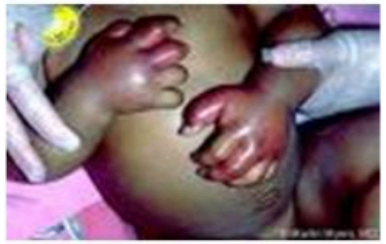
Clinical symptoms in infants







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Vaso-occlusive complications

- **Pain crisis-** the commonest symptoms, more pain episodes, associated with severe disease
- **Acute chest syndrome-** Fever, infiltrate in CXR and hypoxemia
- **Stroke**- Overt and Silent Stroke

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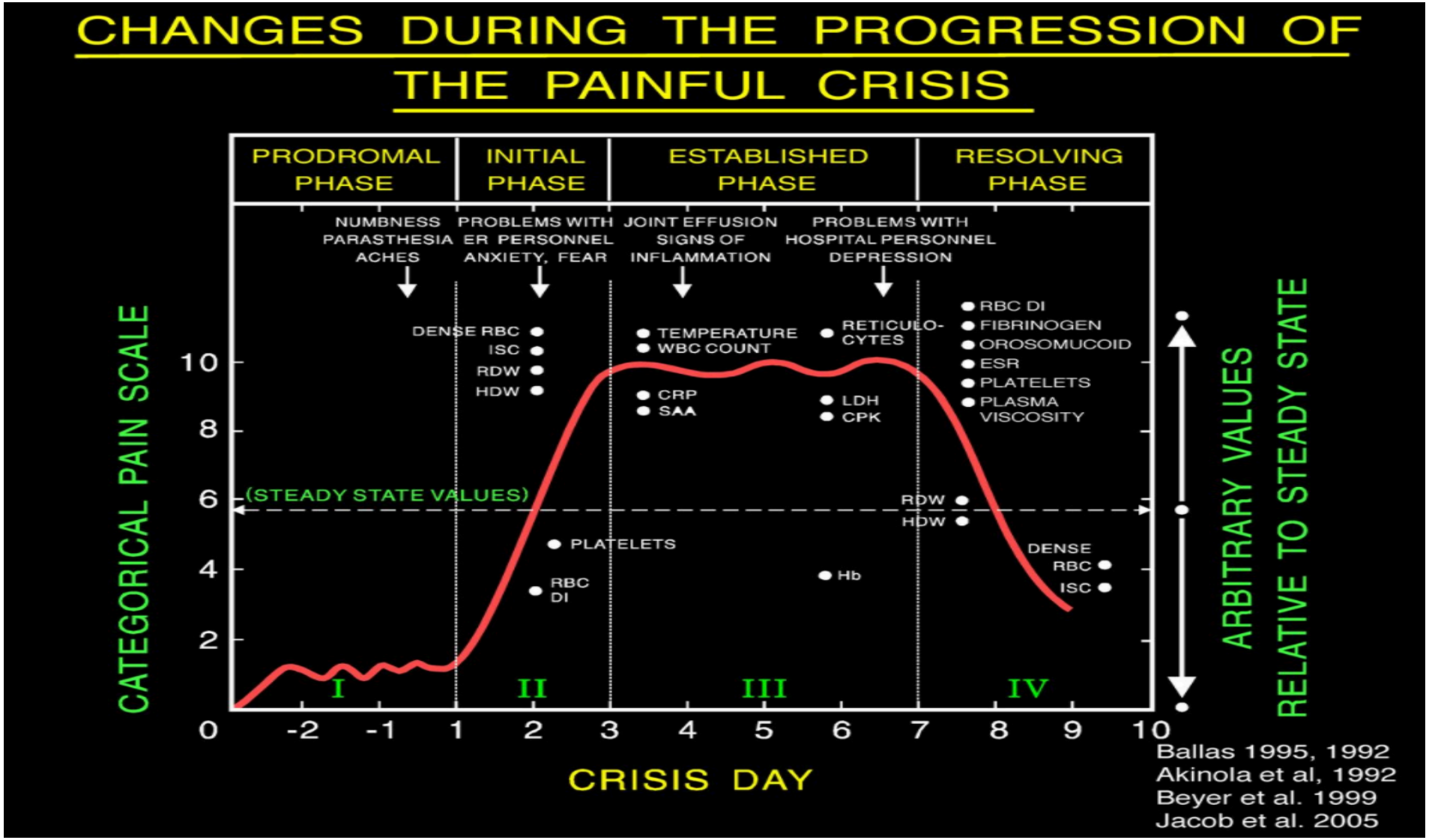

Ballas et al, Hemoglobin, 1995

Pain crisis of SCD

- Acute pain associated with occlusion of blood vessels to the bones
- Associated with low Hemoglobin F
- Triggered by hypoxia, temperature changes, high altitude
- Oral NSAIDs (Tylenol, Ibuprofen)
- Oral Opiods, followed by IV Opiodes
- Oral Hydration
- If admitted IV hydration
- Hydroxyurea reduces the pain episodes

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Splenic sequestration in SCD

- Sequestration of red cells in the spleen
- Vaso-occlusion of the venules of spleen with red cells
- Rapid enlargement of the spleen
- Fall in hemoglobin and anemia
- Circulatory shock
  - Treatment includes PRBC transfusion
  - Slow transfusion is preferred

Hemolytic complications of SCD

- Pulmonary Hypertension- Manifests as hypoxia, right to left shunt and increased TR Jet velocity on Echocardiography
- Cutaneous leg ulceration- In older age group
- Priapism- In Teenagers

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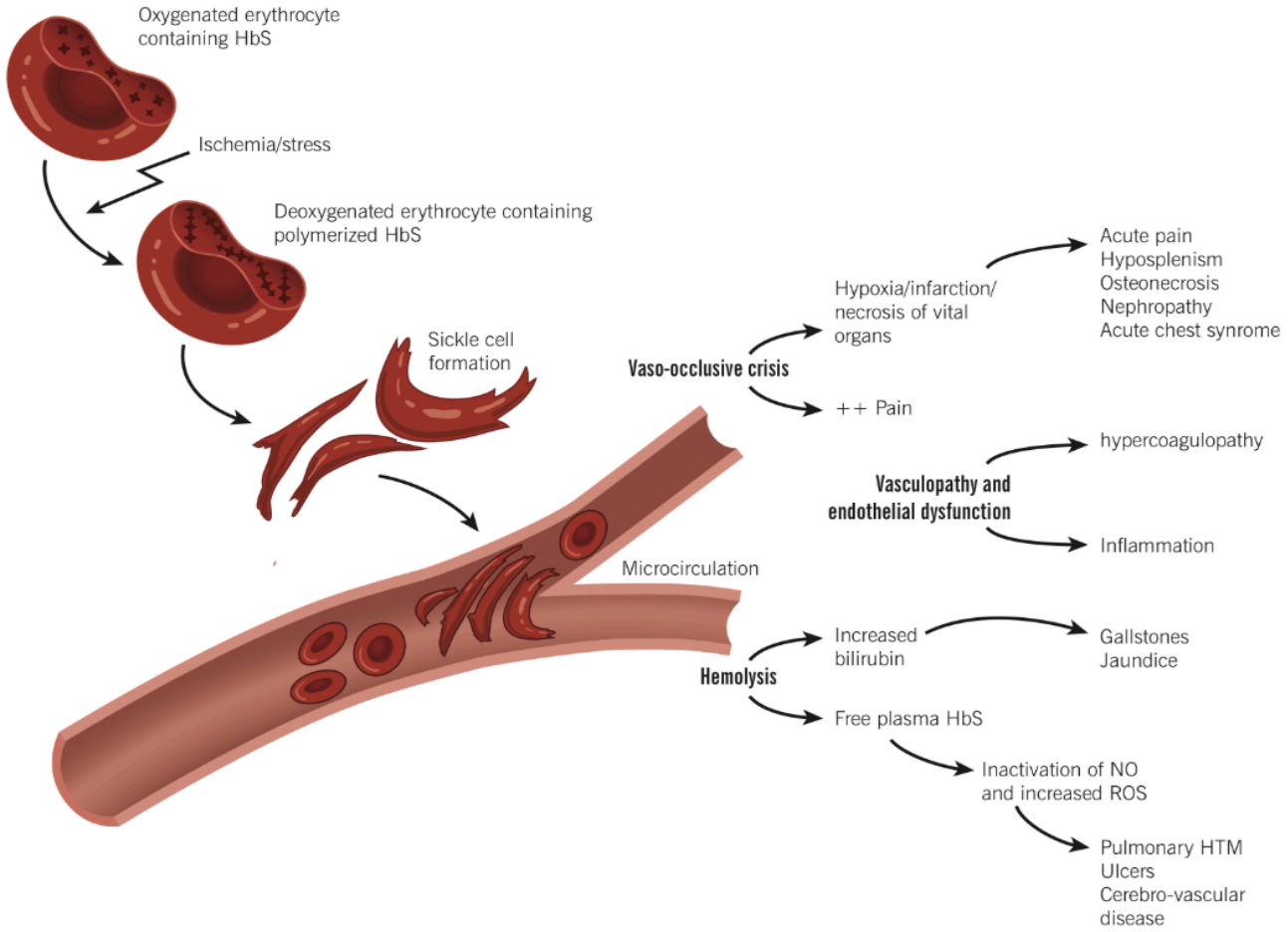
Hemolytic crisis in sickle cell disease

- Anemia
- Hyperbilirubinemia
- Reticulocytosis
- Increased LDH



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Aplastic crisis in Sickle Cell disease

- Anemia
- Reticulocytopenia
- No splenomegaly
- Maybe triggered by viral infection

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Fever in SCD

- Infections are more common in SCD children
- Reduced splenic function, defects in complement pathway, micronutrient deficiency, tissue ischemia
- S Pneumoniae, H influenza, and non-Typhi Salmonella species in developed countries
- Substantial improvements in prognosis have followed the introduction of penicillin prophylaxis
- Immunization with conjugate vaccines directed against S pneumoniae and H influenzae type b and Meningococcal required

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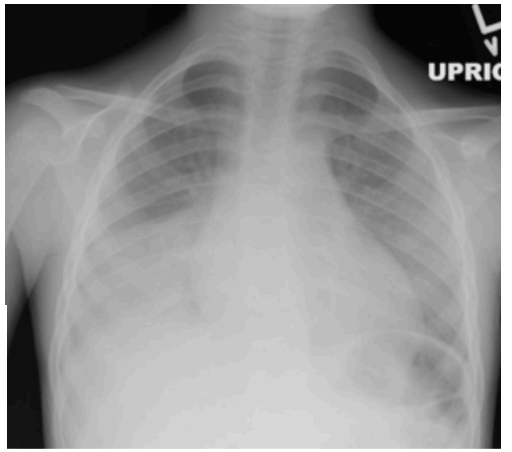
Acute chest syndrome in SCD

- Fever
- Respiratory symptoms- Cough, chest pain breathing difficulty, dyspnea or hypoxia
- New infiltrate on Chest X Ray
- Etiology include: Pulmonary infarction, fat embolism, hypoventilation, pul edema, infection
- Treatment: Blood cultures, CXR
- IVF (restricted), Antibiotics,
- Incentive spirometry
- Co-existent asthma worsens ACS



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Stroke in SCD

- SCD one of the commonest cause of stroke in children
- The vasculopathy seems to start in infancy, with a first-stroke incidence of 1·02 per 100 patient-years between the ages of 2 years and 5 years
- 11% of patients with sickle-cell disease have had a stroke by the age of 20 years
- Treated by blood transfusion: Simple or exchange transfusion, Goal HbS <30%
- Trials have looked into Hydroxyurea in SCD patients with stroke
- HU is found to be non-inferior to transfusion in a subset of patients with increased TCD velocities (Twitch trial)

TCD With Transfusions Changing to Hydroxyurea (TWiTCH): a multicentre, randomised controlled trial

Ware et al, Lancet: 2016

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Kidney in Sickle cell disease

- Renal damage inevitable in Sickle cell disease
- Glomerular hyperfiltration
- Papillary necrosis- Hematuria
- Microalbuminuria > Macroalbuminuria
- Nephrotic syndrome
- End- Stage renal disease
- Role of Hydroxyurea and ACE inhibitors

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Priapism in SCD

- Painful prolonged erection in teenagers
- Upto 35% of the patients with SCD gets affected
- May result in penile fibrosis and permanent damage
- IVF, transfusion useful in reducing or preventing episodes
- Alpha adrenergic agonist like pseudoephedrine and phenylephrine is useful
- Shunt surgery in severe cases
- Role of P-Selectin Inhibitor in trials

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Hemolysis in Sickle Cell Disease

Anemia

Jaundice

Gall bladder stones

Hemoglobin in urine

Urobilinogen in urine

Increased bilirubin (Indirect)

Increased LDH

Increase Reticulocyte

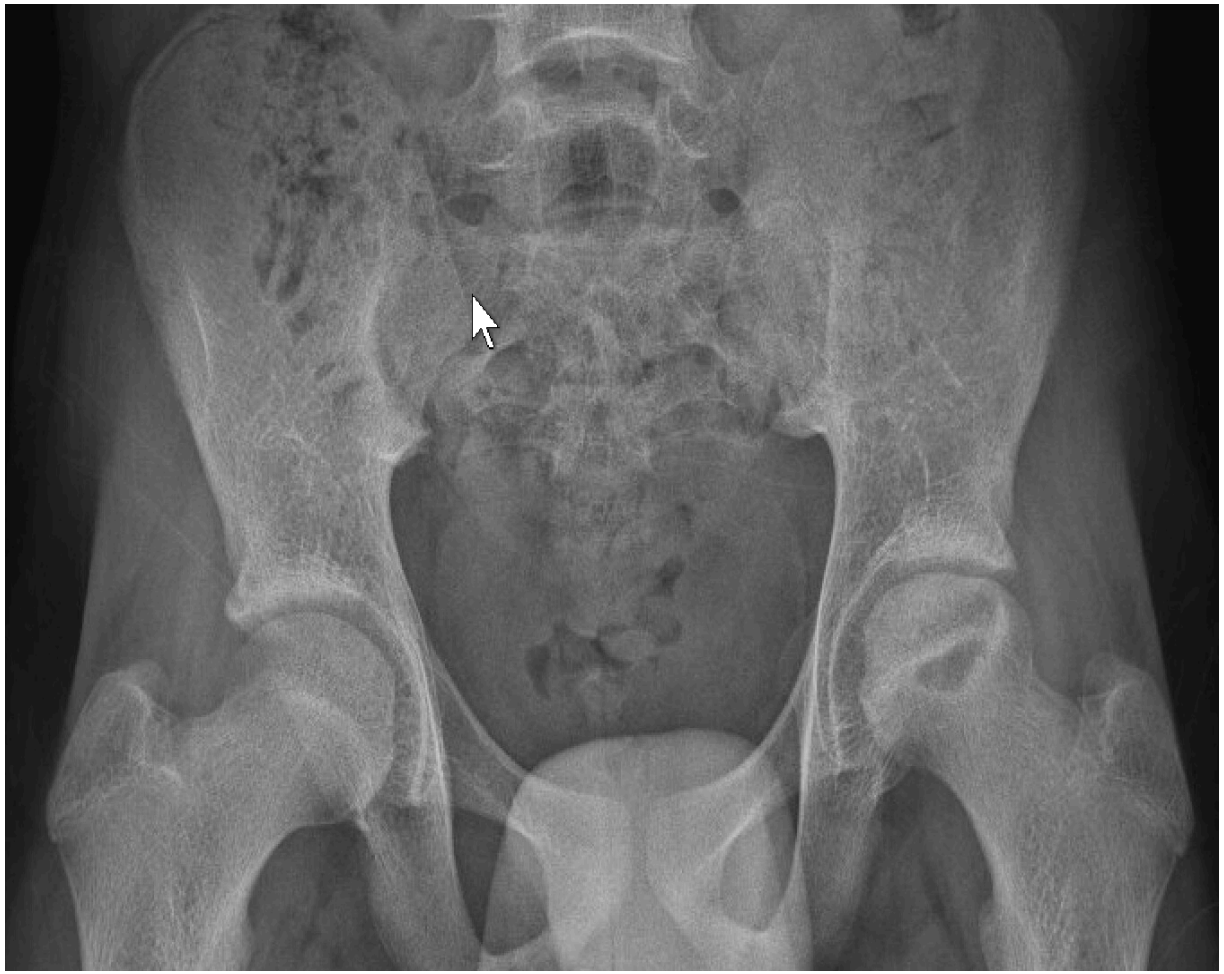
Liver complication in Sickle cell disease

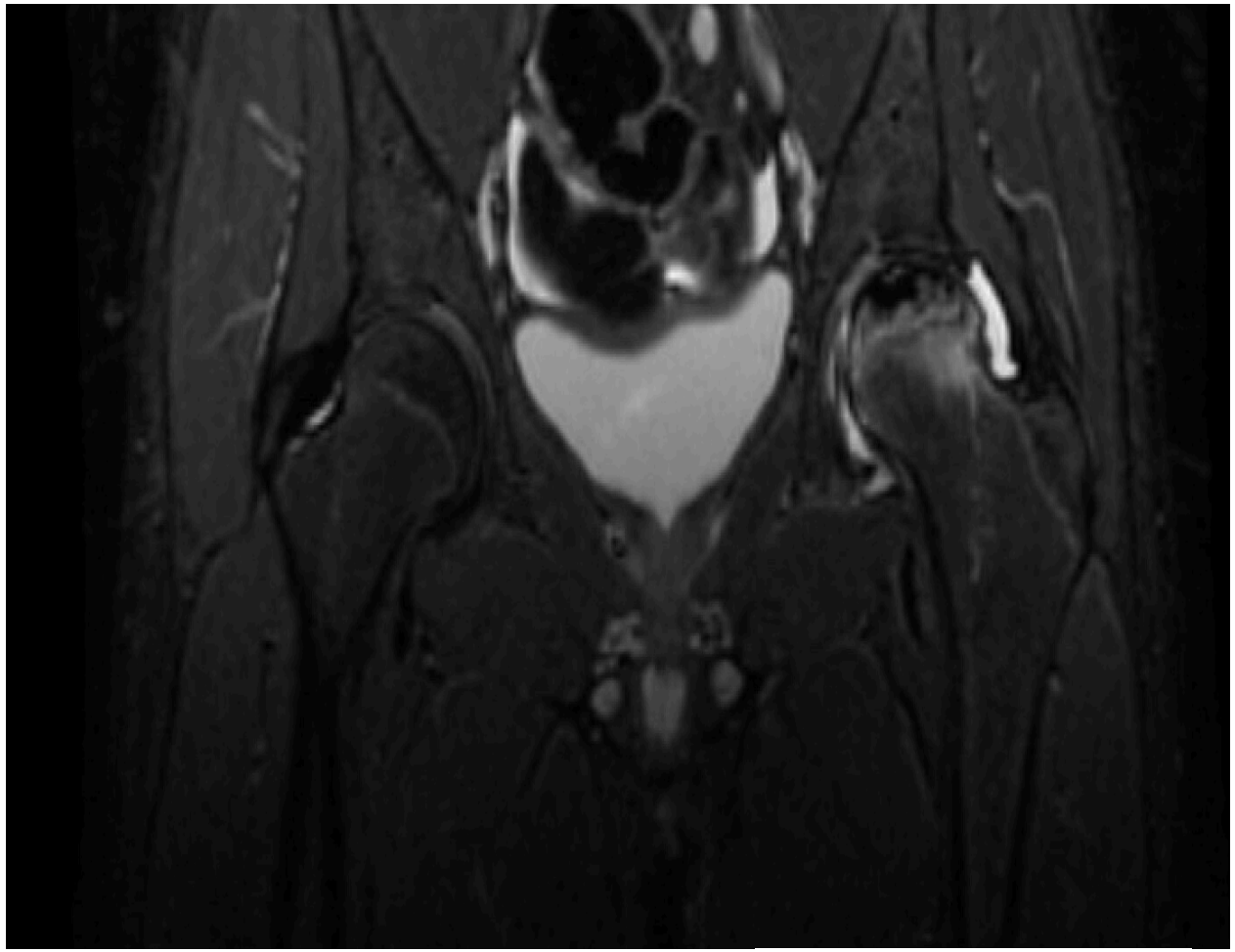
- **Acute sickle cell hepatic crisis :** Fever, pain, jaundice and enlarged liver
  - Rx: Supportive care

- **Acute hepatic sequestration:** Acute pain, enlarged liver and anemia
  - Rx: Supportive care and exchange transfusion

- **Acute intrahepatic cholestasis:** Fever, Right upper quadrant pain, progression to liver failure
  - Rx: Supportive care, exchange transfusion and correction of clotting problems (severe progressive condition)

Osteonecrosis in SCD





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Annual screening Program in SCD

- Transcranial Doppler US
- CXR and PFTs
- Echo and EKG
- Vision Screen to r/o proliferative retinopathy and other ocular complications
- Urine analysis
- Renal and Liver function
- Bone health, r/o avascular complications
- Pregnancy screen on HU
- Vit D status
- Neurocognitive testing

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New born screening for Sickle Cell Disease

- 47 states, the District of Columbia,

  Puerto Rico, and the Virgin Islands currently provide universal neonatal screening for SCD

Disorder	Approximate Percentage of US Patients With SCD	Neonatal Screening Results	Hemoglobin Separation by Age 6 Weeks	Serial CBC and Reticulocyte Counts	Hematologic Studies by Age 2 Years MCV†	HbA_2‡ (percent)	HbF (percent)
HbSS	65	FS	FS	Hemolysis and anemia By age 6-12 mo	Normal or increased §	<3.6§	<25
HbSC	25	FSC	FSC	Mild or no anemia by age 2 y	Normal or decreased	NA‖	<15
Sβ+-thalassemia	8	FSA or FS	FSA	Mild or no anemia by age 2 y	Normal or decreased	>3.6	<25
Sβ°-thalassemia	2	FS	FS	Hemolysis and anemia	Decreased	>3.6	<25

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Treatment and Curative therapies in Sickle cell Disease

- Bindu K Sathi, MD

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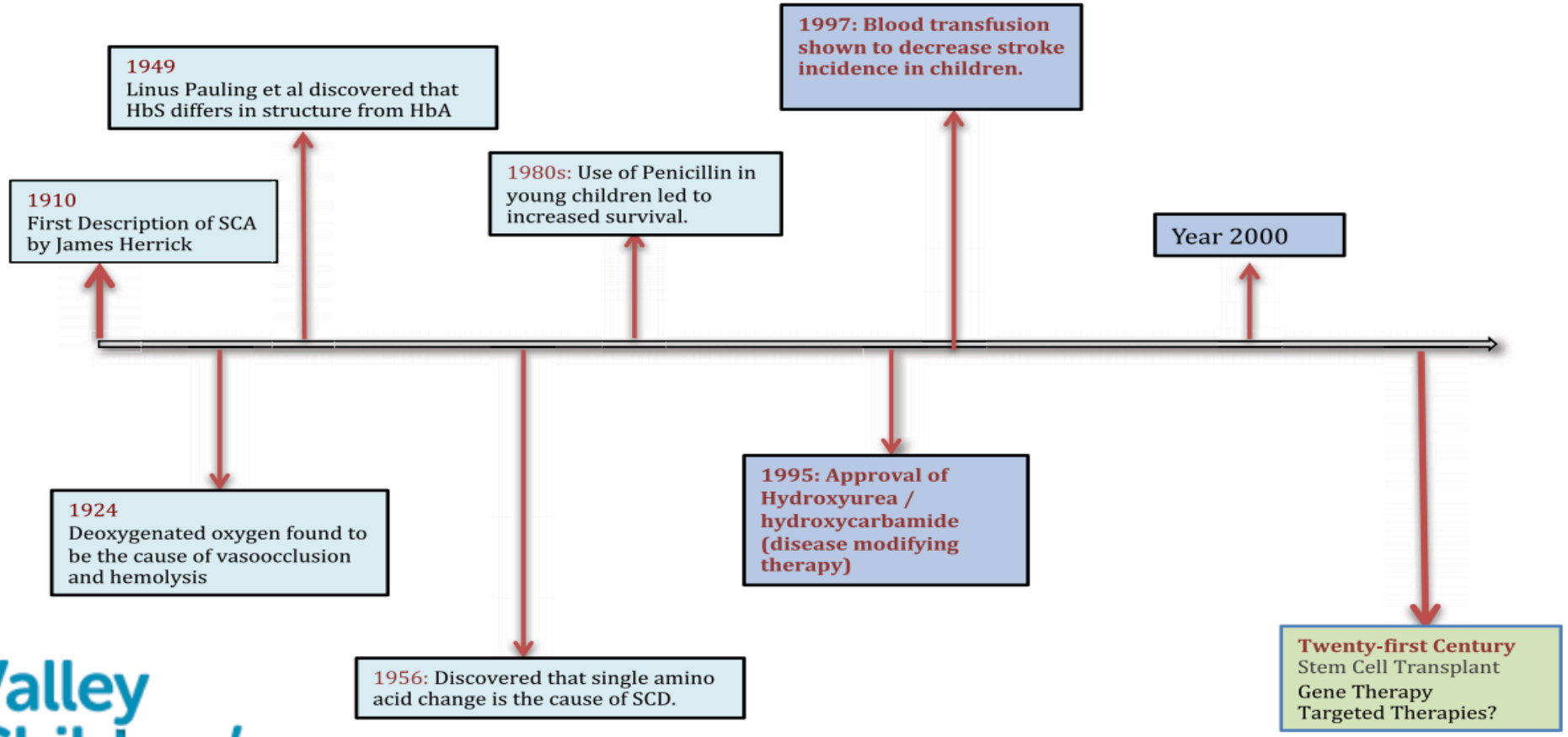
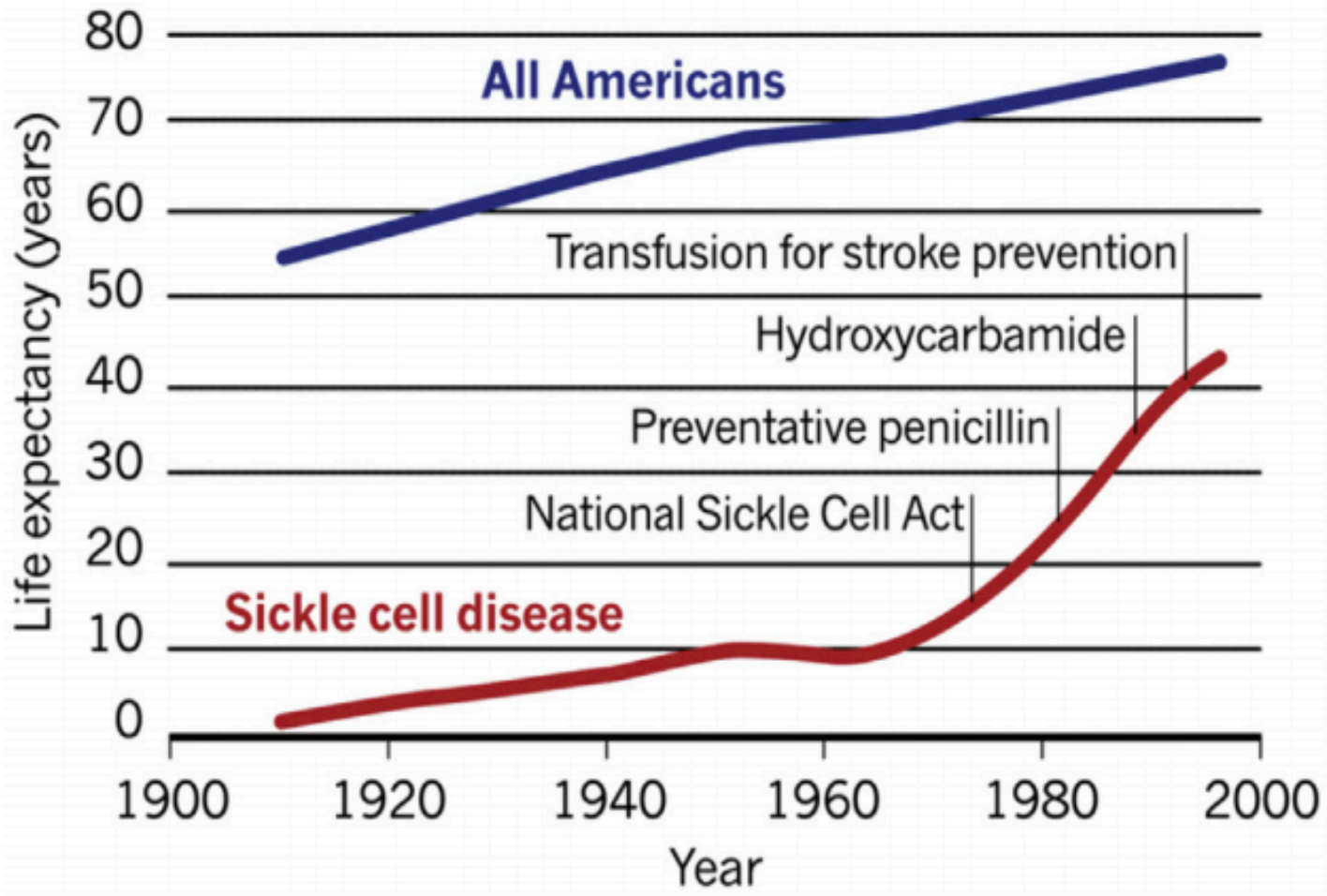
Time line of advances made in Sickle Cell Disease



Thein et al, Pathology, 2017

Improvement in life expectancy in SCD



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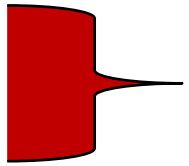
Thein et al, Pathology, 2017

Treatment of SCD

- Transfusion therapy
- Hydroxyurea



Standard of care

- Immunization
- Nutrition assessment
- Target organ assessment
  - Cognition assessment
  - Bone assessment
  - Kidney, Lung, Heart assessment
- Cognition assessment

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Treatment team for SCD

- Trained Hematologist
- RN, trained in SCD
- Psychologist
- Social Worker
- Comprehensive Health care coordinators
- School nurses
- Community Physicians

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Indications for transfusion in SCD

Indications where primary goal of transfusion is to correct acute anaemia	GRADE evaluation	Type of transfusion*
Aplastic crisis	1B	Simple (top up)
Acute splenic sequestration	1B	Simple
Acute hepatic sequestration	1B	Simple
Delayed haemolytic transfusion reaction (transfusion should be avoided unless the anaemia is severe or life-threatening)	1C	Simple
Indications where primary goal of transfusion is to reduce HbS concentration in relation to HbA	**GRADE evaluation**	**Type of transfusion***
ACS	1B	Simple or exchange†
Acute stroke or other neurological deficit (e.g. TIA)	1B	Exchange
Acute multi-organ failure	1C	Exchange
Mesenteric/girdle syndrome	1C	Exchange
Severe sepsis	2C	Exchange
Acute intrahepatic cholestasis	1C	Exchange
Primary stroke prevention	1A	Simple or exchange
Prevention of silent cerebral infarct recurrence	1A	Simple or exchange
Secondary stroke prevention	1B	Simple or exchange
Surgery		
• SS patients – elective low or medium risk surgery	1A	Simple or exchange
• SC patients – elective low or medium risk surgery	1C	Exchange
• All sickle genotypes – elective high risk surgery	1C	Exchange
• Emergency surgery	1D	Individual considerations‡
Pregnancy		
• Sickle complications (e.g. painful crises, ACS, stroke)	1B	Simple or exchange
• Severe anaemia	1C	Simple
• High obstetric, medical or fetal risk	1C	Simple or exchange
Recurrent ACS§	2C	Simple or exchange
Recurrent painful crises§	2C	Simple or exchange

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British Journal of Haematology, 2017, 176, 192–209

Transfusion therapy in Sickle Cell disease

The ASH guideline panel recommends prophylactic **red cell antigen matching for Rh (C, E or C/c, E/e) and K antigens** over only ABO/RhD matching for patients with SCD (all genotypes) receiving transfusions

Extended red cell antigen matching (Jka /Jkb , Fya /Fyb , S/s) may provide further protection from alloimmunization

blood advances

American Society of Hematology 2020 guidelines for sickle cell disease: transfusion support

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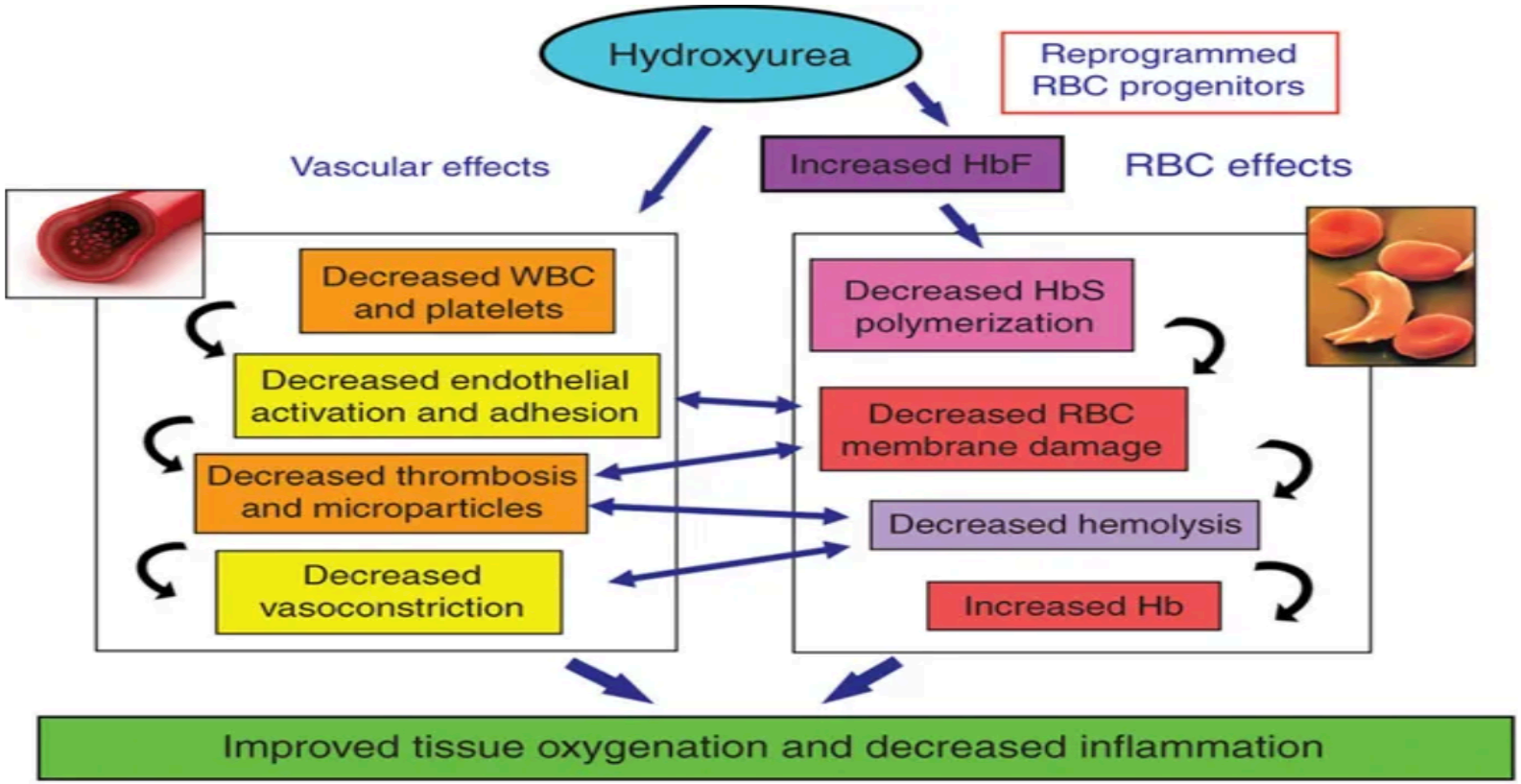
Hydroxycarbamide (hydroxyurea) in Sickle cell disease



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Pediatric Research **volume 75**, pages196–204(2014)

Recommendations for the start of HU

- In adults and children with HbSS/Sb0 who have 3 or more sickle cell-associated moderate to severe pain crisis in a 12-month period, treat with hydroxycarbamide (1A)
- In infants with SS/Sb0 aged 9–42 months, offer hydroxycarbamide regardless of clinical severity to reduce sickle cell complications (pain, dactylitis, acute chest syndrome (ACS), anaemia (1A)
- In children aged >42 months, adolescents and adults with SS/Sb0 , offer treatment with hydroxycarbamide in view of the impact on reduction of mortality (1B)
- In adults and children with SS/Sb0 who have sickle cell pain that interferes with daily activities and quality of life, treat with hydroxycarbamide (1C)
- In adults and children with SS/Sb0 and a history of severe and/or recurrent ACS treat with hydroxycarbamide (1A)
- The benefits of hydroxycarbamide should be discussed with all parents of children, adolescents and adults with SS/Sb0 to enable informed joint decision-making. There should be on-going discussion between provider and patient (1B)

NIH guidelines, 2014; JAMA. 2014;312(10):1033-1048.

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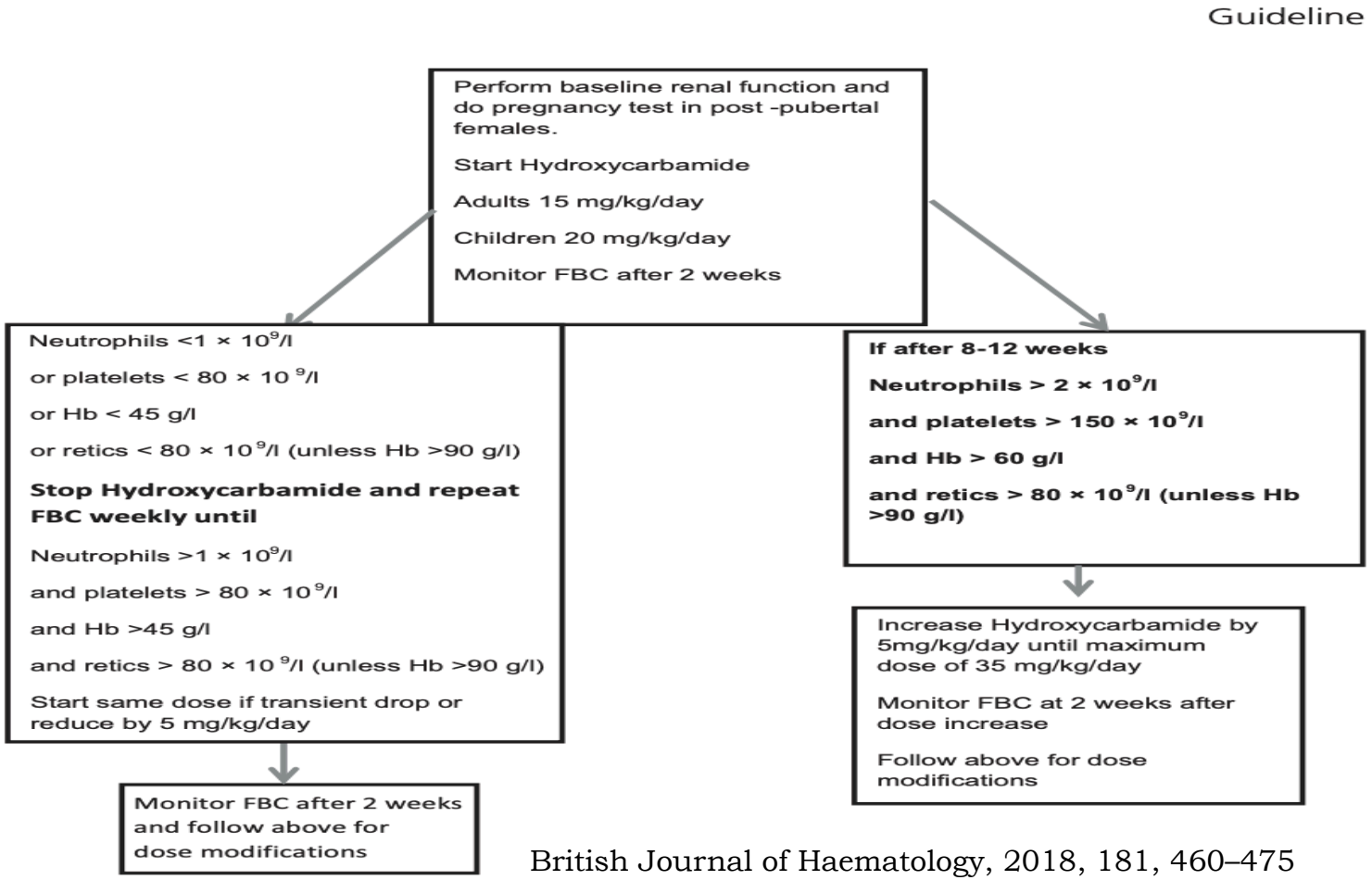
Modifications for HU therapy



British Journal of Haematology, 2018, 181, 460–475

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Concerns with HU therapy

- Leukemiogenesis (Not proven--- 25 years worth of data!)
- Normal growth and development
- Fertility
  - Female fertility is preserved
  - Spermatogenesis affected (affects on sperm count, motility and morphology
- Concern for teratogenicity (Need to stop HU prior to pregnancy)

British Journal of Haematology, 2018, 181, 460–475

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Penicillin Treatment in SCD

1. Administer oral penicillin prophylaxis (125 mg for age <3 years and 250 mg for age ≥3 years) twice daily until age 5 in all children with HbSS.
   (Strong Recommendation, Moderate-Quality Evidence)

2. Discontinue prophylactic penicillin in children with HbSS at age 5 unless they have had a splenectomy or invasive pneumococcal infection. When discontinuing penicillin prophylaxis at age 5, it is important to assure that the child has completed the recommended pneumococcal vaccination series, and if not, complete the series immediately.
   (Weak Recommendation, Moderate-Quality Evidence)

3. Consider withholding penicillin prophylaxis from children with HbSC disease and HbSβ^+-thalassemia unless they have had a splenectomy
   (Weak Recommendation, Low-Quality Evidence)

NIH guidelines, 2014; JAMA. 2014;312(10):1033-1048.

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Immunization protocol in SCD

All individuals should be immunized as recommended by the ACIP. The most up-to-date schedule should be followed, as changes can be made up to four times per year. Consult the immunization schedule at: http://www.cdc.gov/vaccines/schedules. The following immunizations are of special importance or unique to people with SCD as recommended by the ACIP. These recommendations may also change periodically, and the above ACIP recommendations should be consulted for confirmation.

- **Pneumococcal (PCV13) vaccine—Children**
  - Children aged 6 to 18 years with functional or anatomic asplenia should receive one dose of PCV13.
- **Pneumococcal vaccine-naïve Adults**
  - Adults aged ≥19 years with functional or anatomic asplenia who have not previously received PCV13 or PPSV23 should receive
    - One dose of PCV13 first, followed by a dose of PPSV23 at least 8 weeks later.
    - Subsequent doses of PPSV23 should follow current PPSV23 recommendations for adults at high risk.
  - A second PPSV23 dose is recommended 5 years after the first PPSV23 dose for persons aged 19–64 years with functional or anatomic asplenia.
  - Additionally, those who received PPSV23 before age 65 years for any indication should receive another dose of the vaccine at age 65 years, or later if at least 5 years have elapsed since their previous PPSV23 dose.
- **Previous vaccination with PPSV23—Adults**
  - Adults aged ≥19 years with functional or anatomic asplenia who previously have received ≥1 dose of PPSV23 should
    - Be given a PCV13 dose ≥1 year after the last PPSV23 dose was received.
  - For those who require additional doses of PPSV23, the first such dose should be given no sooner than 8 weeks after PCV13 and at least 5 years after the most recent dose of PPSV23.
- **Hib**
  - One dose of Hib vaccine for people aged >5 years who have SCD if they have not previously received Hib vaccine
- **Meningococcal vaccine**
  - Vaccinate infants at high risk (including those with SCD) at 2, 4, and 6 months of age, and again at 12 through 15 months with this vaccine, which is generically known as HibMenCY.
  - Persons aged 9 months through 55 years at increased risk for meningococcal disease (e.g., adults with anatomic or functional asplenia or persistent complement component deficiencies) should receive MenACWY.
  - Children aged 2 months to 6 years should receive an additional dose of MenACWY 3 years after primary immunization; boosters should be repeated every 5 years thereafter.
  - Children ≥7 years of age should receive an additional dose of MenACWY 5 years after primary immunization; boosters should be repeated every 5 years thereafter.

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NIH guidelines, 2014; JAMA. 2014;312(10):1033-1048.

CDC recommendation in SCD

- Hand washing
- Food safety
- Do not eat raw or undercooked meat; use pasteurized products
- Bacteria – Salmonella is especially dangerous in SCD. Do not pet snake, lizards or turtle

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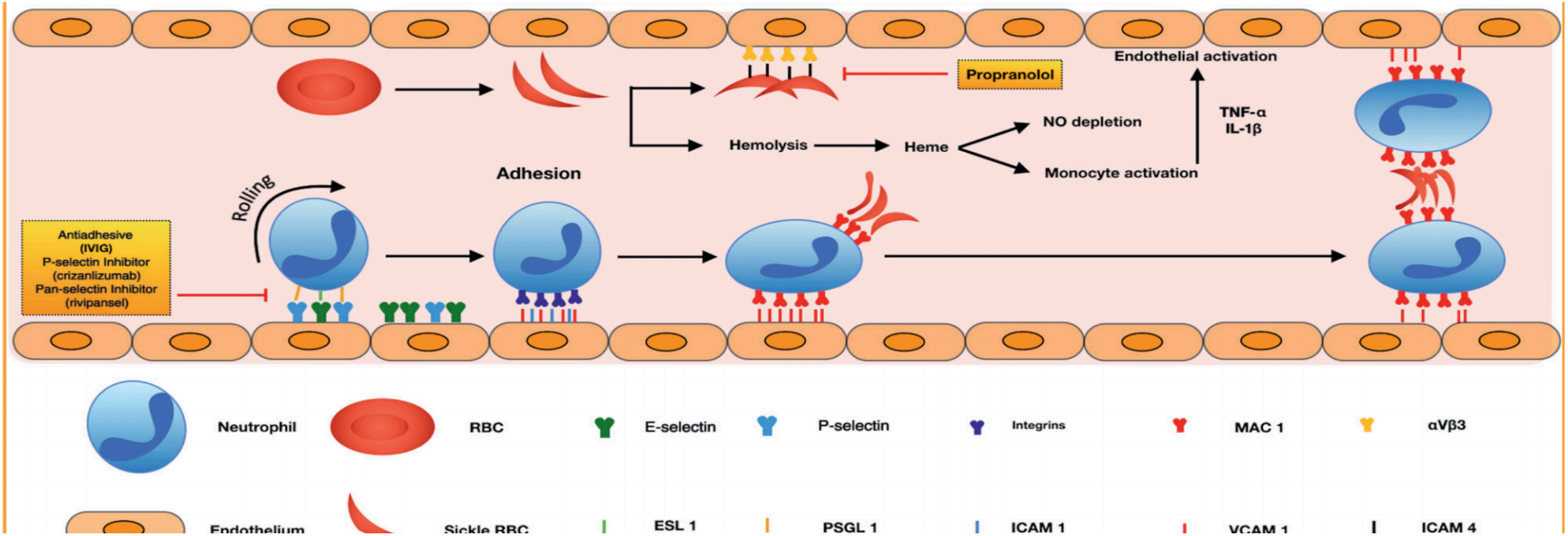
Newer therapeutics in Sickle cell disease



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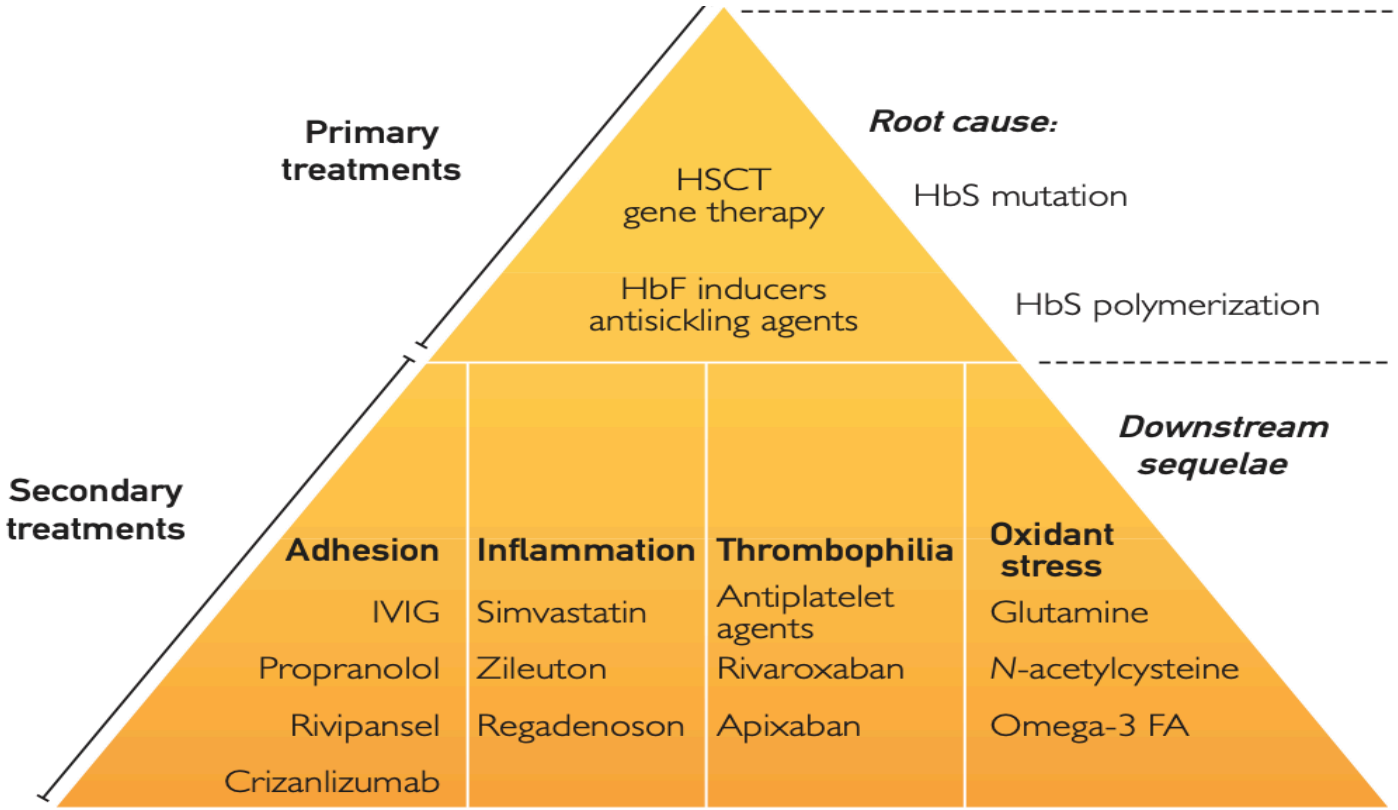
Mayo Clin Proc. ■ December 2018;93(12):1810-1824 ■ https://doi.org/10.1016/j.mayocp.2018.08.001
www.mayoclinicproceedings.org

Definitive and symptomatic treatment in sickle cell disease



Mayo Clin Proc. ■ December 2018;93(12):1810-1824 ■ https://doi.org/10.1016/j.mayocp.2018.08.001
www.mayoclinicproceedings.org

TABLE. Ongoing or Completed Drug Trials for Sickle Cell Disease

Target	Study drug	Mechanism of action	ClinicalTrials. gov Identifier	Status (phase)
Oxidative injury	Glutamine	Increases NADPH	NCT01179217	Completed (3)
	NAC	Increases glutathione	NCT01849016	Completed (3)
	Omega-3 FA	Antioxidant	NCT02947100	Ongoing (1, 2)
			NCT02604368	Ongoing (3)
	á-Lipoic acid	Increases glutathione	NCT01054768	Completed (2)
	Acetyl-L-carnitine	Decreases lipid peroxidation		
	Omega-3			
	Curcumin			
	Gum arabic			
Adhesion	Crizanlizumab	Monoclonal antibody against P-selectin	NCT01895361	Completed (2)
	Rivapansel	Pan-selectin inhibition	NCT02187003	Ongoing (3)
	IVIG	Inhibits leukocyte activation/adhesion	NCT01757418	Ongoing (1, 2)
	Heparin	Inhibitor of P-selectin	NCT02098993	Ongoing (2)
	Propranolol	Inhibits RBC adhesion to endothelium	NCT02012777	Terminated (1)
			NCT01077921	Completed (2)
Hemoglobin F induction	Decitabine	Demethylation/ activation of ã-globin gene	NCT01685515	Ongoing (1)
	Pomalidomide	Histone deacetylase inhibition	NCT01522547	Completed (1)
	Dimethylbutyrate	Histone deacetylase inhibition	NCT01322269	Completed (2)
Other antisickling agents	Aes-103	Shifts Oxy-Hb	NCT01597401	Completed (1)
	GBT440	dissociation curve to left	NCT03036813	Ongoing (3)
	INCB059872	Hypomethylating agent, increases HbF	NCT03132324	Ongoing (1)
	Panobinostat	Histone deacetylase inhibitor, increases HbF	NCT01245179	Ongoing (1)
	Senicapoc	Inhibits cell dehydration	NCT00040677	Completed (2)
			NCT00102791	Terminated (3)
	Sanguinate	Carbon monoxide releasing/oxygen transfer agent	NCT02411708	Ongoing (2)
	SCD-101	Antisickling agent, unknown mechanism	NCT02380079	Ongoing (1b)
Antiplatelet therapy	Prasugrel	Inhibition of platelet activation (ADP receptor blockade)	NCT01794000	Terminated (3)
	Ticagrelor		NCT02482298	Completed (2)
	Eptifibatide		NCT00834899	Terminated (1, 2)
Anti-inflammatory agents	Simvastatin	Activates endothelial NO synthase	NCT01702246	Completed (1)
	Zileuton	Inhibition of leukotrienes	NCT01136941	Completed (1)
	Regadenoson	Agonist of adenosine receptor	NCT01788631	Ongoing (2)
Vascular tone	Magnesium	Improves vascular tone	NCT01197417	Completed (2, 3)
	L-arginine	Substrate for NO	NCT02447874	Ongoing (1, 2)
Anticoagulant mechanism	Rivaroxaban	Inhibition of coagulation cascade	NCT02072668	Ongoing (2)
	Apixaban	(exact mechanism being studied)	NCT02179177	Ongoing (2)

Clinical trials in SCD

Mayo Clin Proc. ■ December 2018;93(12):1810-1824 ■ https://doi.org/10.1016/j.mayocp.2018.08.001
www.mayoclinicproceedings.org

FDA approved new therapies in SCD

ORIGINAL ARTICLE

Crizanlizumab for the Prevention of Pain Crises in Sickle Cell Disease

Kenneth I. Ataga, M.B., B.S., Abdullah Kutlar, M.D., Julie Kanter, M.D., Darla Liles, M.D., Rodolfo Cancado, M.D., Ph.D., João Friedrisch, M.D., Ph.D., Troy H. Guthrie, M.D., Jennifer Knight-Madden, M.B., B.S., Ph.D., Ofelia A. Alvarez, M.D., Victor R. Gordeuk, M.D., Sandra Gualandro, M.D., Ph.D., Marina P. Colella, M.D., Ph.D., et al.

A Phase 3 Trial of L-Glutamine in Sickle Cell Disease

Yutaka Niihara, M.D., M.P.H., Scott T. Miller, M.D., Julie Kanter, M.D., Sophie Lanzkron, M.D., M.H.S., Wally R. Smith, M.D., Lewis L. Hsu, M.D., Ph.D., Victor R. Gordeuk, M.D., Kusum Viswanathan, M.D., Sharada Sarnaik, M.D., Ifeyinwa Osunkwo, M.D., Edouard Guillaume, M.D., Swayam Sadanandan, M.D., et al., for the Investigators of the Phase 3 Trial of L-Glutamine in Sickle Cell Disease*

ORIGINAL ARTICLE

A Phase 3 Randomized Trial of Voxelotor in Sickle Cell Disease

Elliott Vichinsky, M.D., Carolyn C. Hoppe, M.D., Kenneth I. Ataga, M.D., Russell E. Ware, M.D., Ph.D., Videlis Nduba, M.B., Ch.B., M.P.H., Amal El-Beshlawy, M.D., Hoda Hassab, M.D., Maureen M. Achebe, M.D., M.P.H., Salam Alkindi, M.B., B.Ch., R. Clark Brown, M.D., Ph.D., David L. Diuguid, M.D., Paul Telfer, M.D., et al., for the HOPE Trial Investigators*

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The NEW ENGLAND JOURNAL of MEDICINE

Stem cell transplantation for Sickle cell disease

- Matched sibling HSCT
- Matched cord blood transplantation (good cell doses)
- Matched unrelated 8/8 transplantation

- Phase 1 clinical trial
  - Haploidentical transplantation
  - Mismatched unrelated

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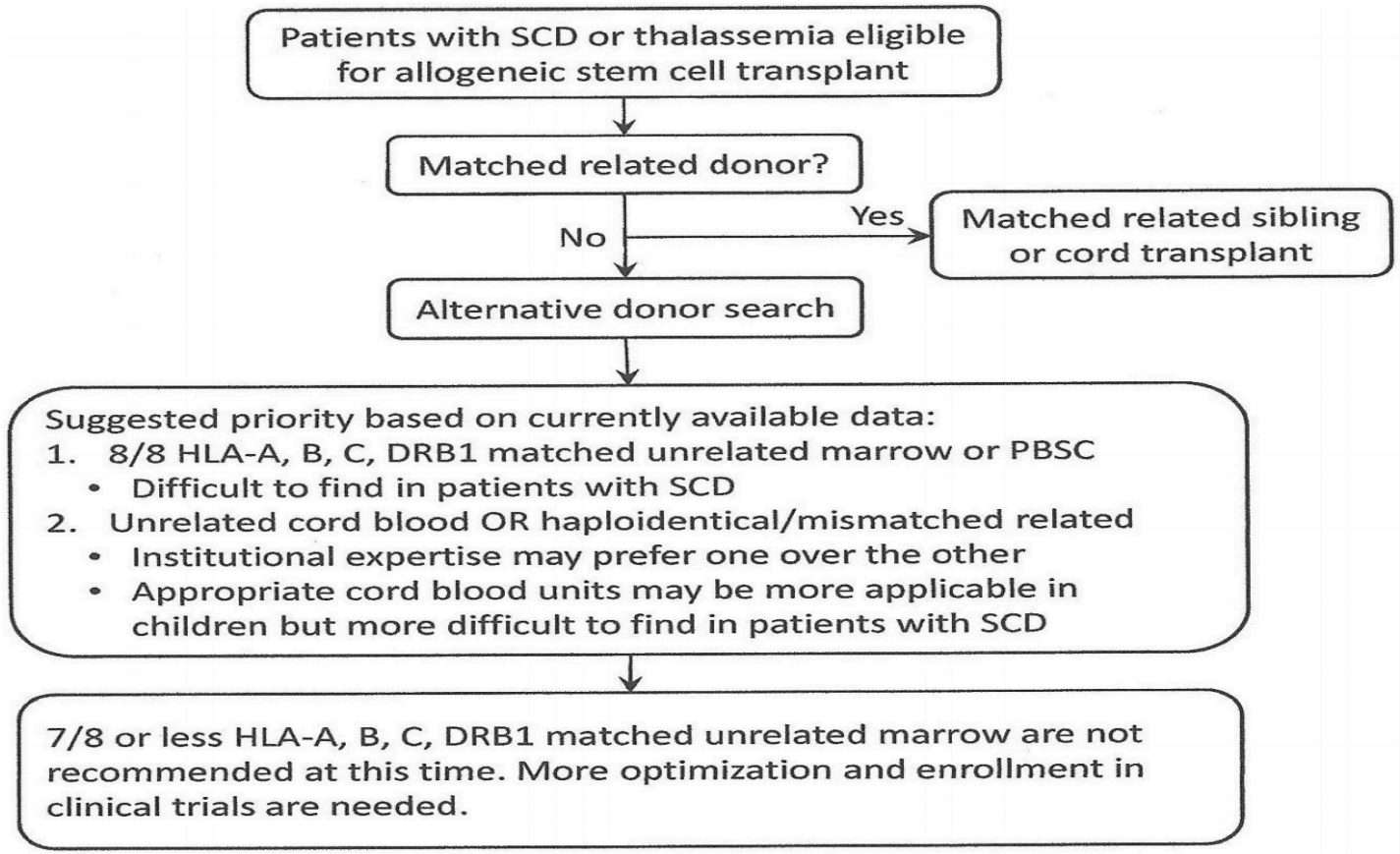
Adv Exp Med Biol. 2017 ; 1013: 123–153. doi:10.1007/978-1-4939-7299-9_5.

Transplantation algorithm for Sickle cell disease



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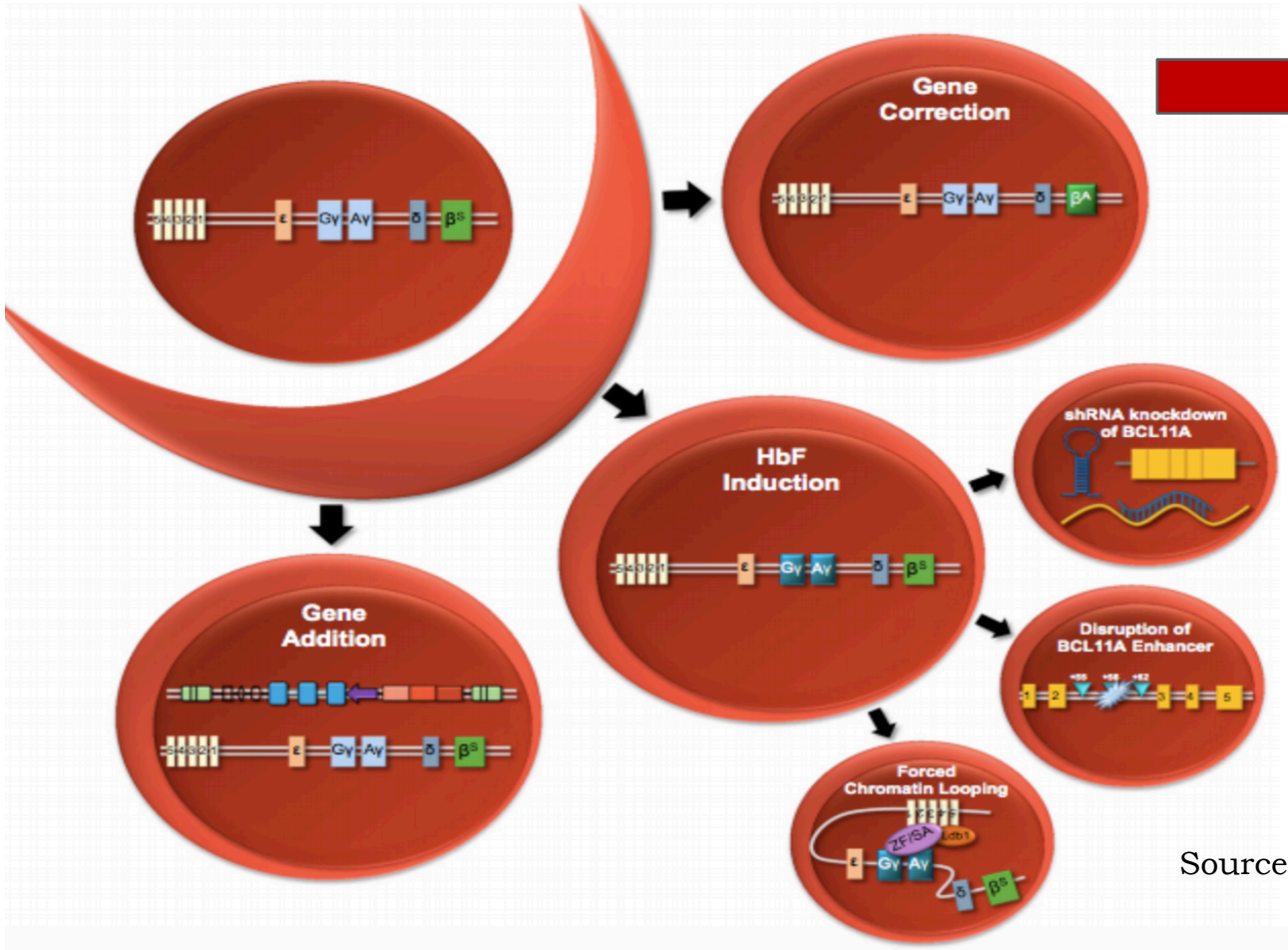
Adv Exp Med Biol. 2017 ; 1013: 123–153. doi:10.1007/978-1-4939-7299-9_5.

Gene therapy in Sickle cell disease



Complete correction of Mutated gene sequence

Induction of HbF

Source: American Society of Hematology

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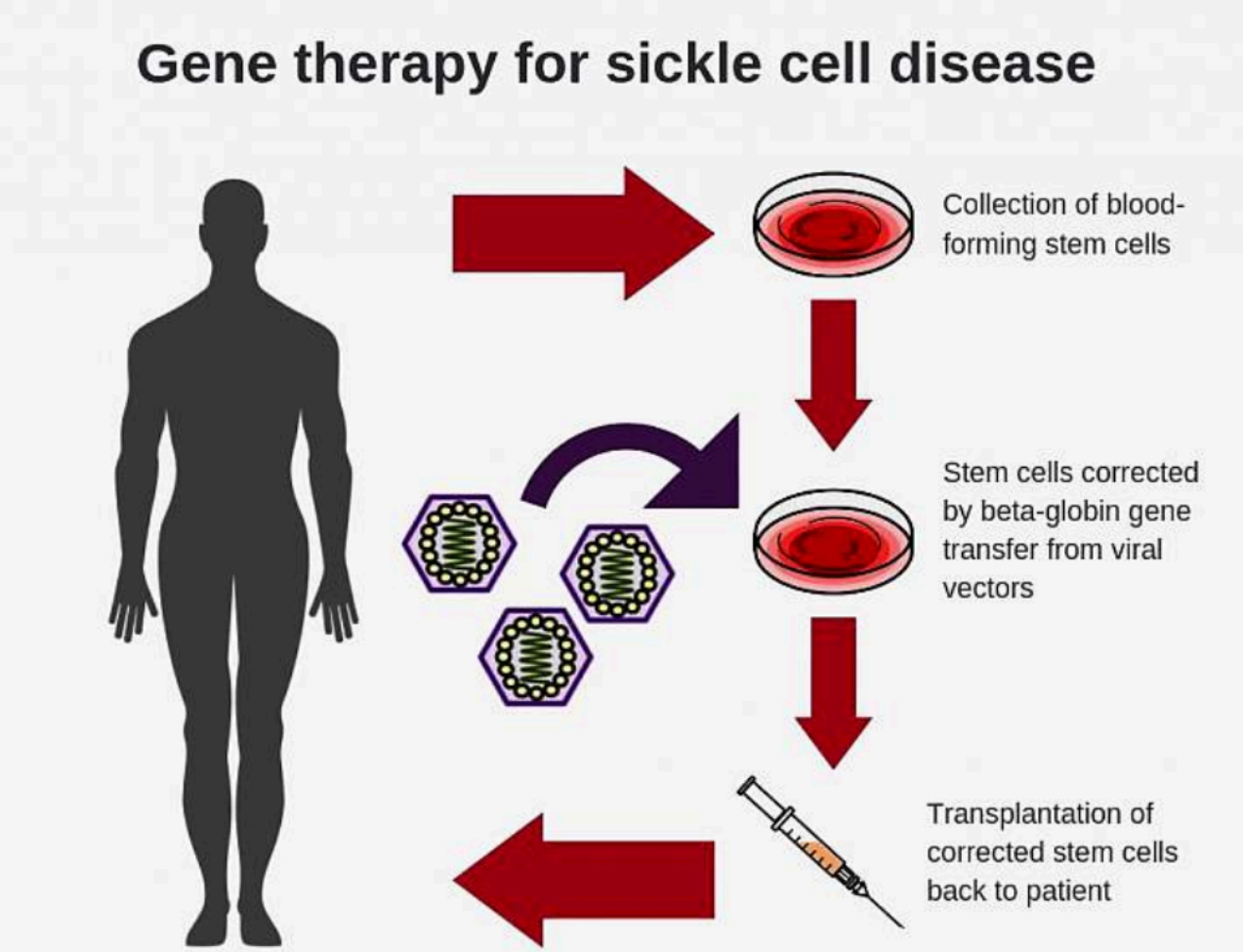
Schema



Source: NIH.gov

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Gene therapy in SCD

N Engl J Med. 2017 Mar 2;376(9):848-855. doi: 10.1056/NEJMoa1609677.

Gene Therapy in a Patient with Sickle Cell Disease.

- **Inclusion criteria for transplantation**
- Clinically-significant neurologic event: stroke or any central nervous system deficit lasting >24 hours.
- Abnormal head CT or brain MRI demonstrating previous stroke
- Administration of regular RBC transfusions for equal or longer than 1 year to prevent vaso- occlusive crises or other sickle cell disease complications or to maintain Hb >6.
- Pulmonary arterial hypertension with tricuspid regurgitant jet velocity > 2.5 m/sec within 1 year prior to enrollment
- At least one episode of acute chest syndrome that required hospitalization, within the 2 years prior to enrollment
- At least 2 acute sickle pain crises requiring hospitalization within the 2 years prior to enrollment
- Severe osteonecrosis
- History of acute dactylitis during childhood
- Recurrent priapism (2 or more episodes)

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FIRST PATIENT TO BE TREATED WITH CRISPR...

THE FIRST PATIENT TO BE TREATED WITH CRISPR

This year, CRISPR-CAs9 treatments for sickle cell disease were taken from the lab to clinical trials. In January 2019, CRISPR Therapeutics and Vertex Pharmaceuticals Incorporated reported that the US Food and Drug Administration (FDA) **had fast tracked CTX001**, an investigational, gene-edited stem cell therapy to treat patients with severe hemoglobinopathies such as sickle cell disease.

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Acknowledgements

- Pacific Sickle Cell research collaborative
- Heartland Sickle Cell Research Group
- Funding for State Department of Health and Senior Services

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Questions??

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