



ICT 2023

28th International
Congress on Thrombosis

Thrombosis in Hemoglobinopathies The different faces of thrombosis

Ana Parente Freixo



Declaration of Conflict Of Interest

I have no potential conflict of interest to report



ICT 2023

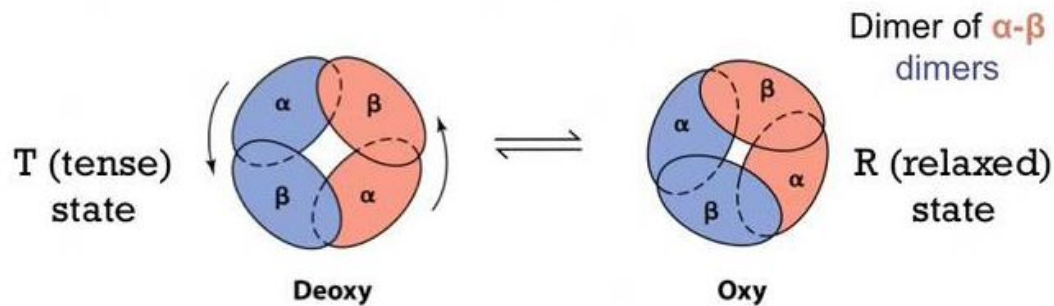
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VTE in Sickle Cell Disease
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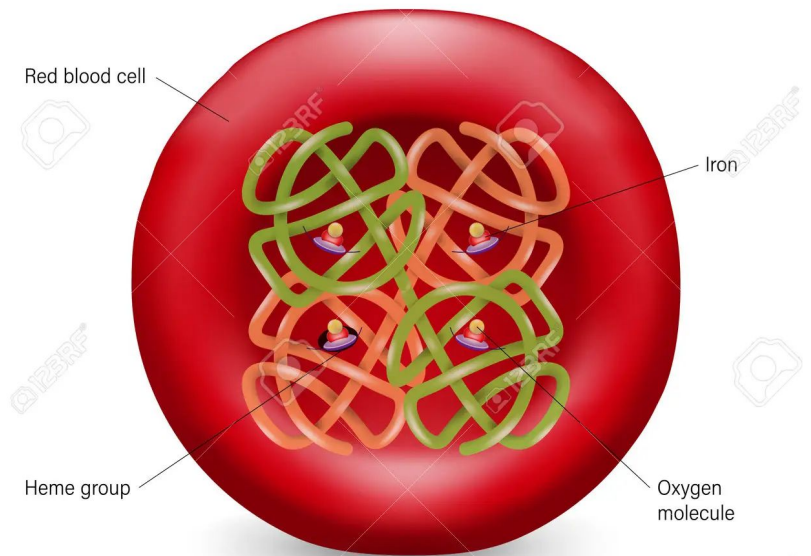
Hemoglobin structure and function

- Hemoglobin (Hb) is the oxygen-carrying protein
- Hemoglobin is a tetramer, with a molecular mass of ~64kDa, consisting of 2 pairs of globin chains
- Normal adult Hb (HbA) has 2 α -globins and 2 β -globins($\alpha_2\beta_2$)
- Hemoglobin enables RBCs to deliver oxygen to tissues by its reversible binding of oxygen.



Conformational changes in HbA

Hemoglobin



Hemoglobin disorders: classification

Mutations in the β or α gene leading to quantitative or qualitative changes.

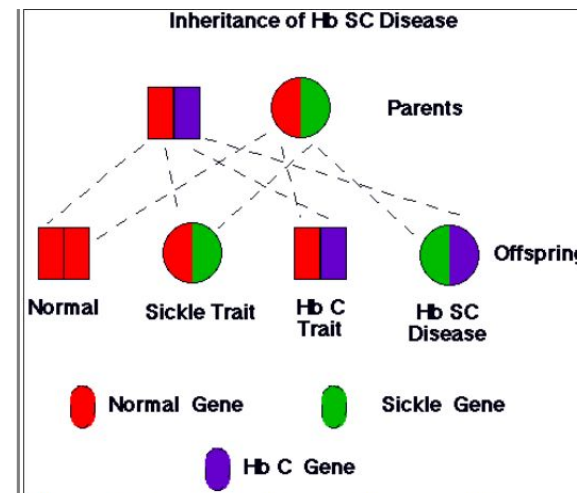
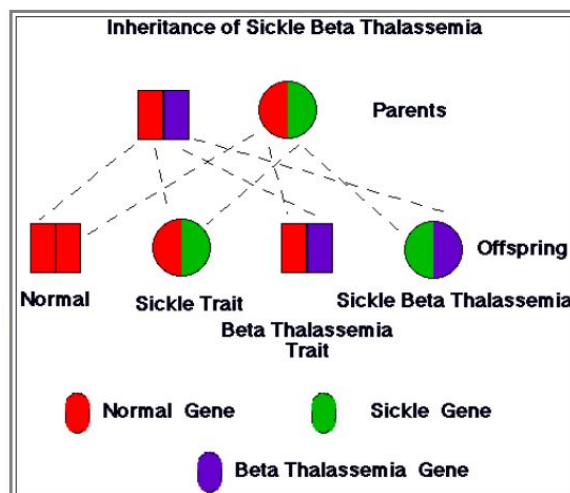
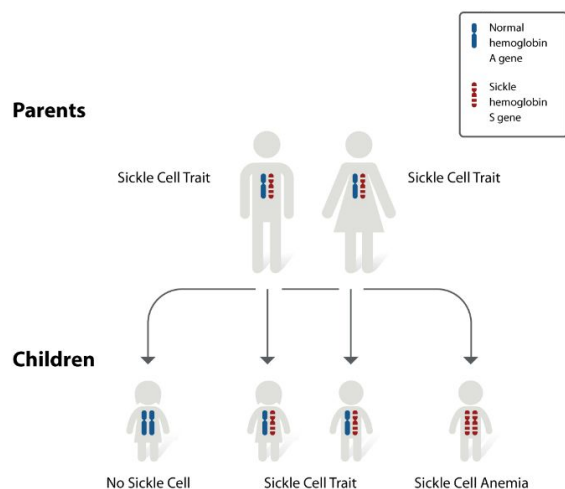
Quantitative - Thalassemias beta and alpha

Qualitative

- (1) decreased solubility or altered physical/chemical properties (eg, **sickle hemoglobin [HbS]**)
- (2) instability (eg, Hb Köln)
- (3) altered oxygen affinity (eg, HbM-Saskatoon)
- (4) altered maintenance of the oxidation state of the heme-coordinated iron (eg, HbM-Iwate).

Sickle Hemoglobin (HbS)

- In 1949, Pauling and his team, using electrophoresis techniques, found that hemoglobin from sickle shaped red cell had abnormal electrophoretic movement in comparison with other Hb when deoxygenated.
- The sickle cell gene is inherited in an autosomal codominant fashion. That is, heterozygous inheritance does not cause disease - **sickle cell trait**.
- Homozygous inheritance (**HbSS**) or compound heterozygous inheritance with another mutant b-globin gene results in disease (**HbSC**, **HbSb⁰**, **HbSb⁺**,...).

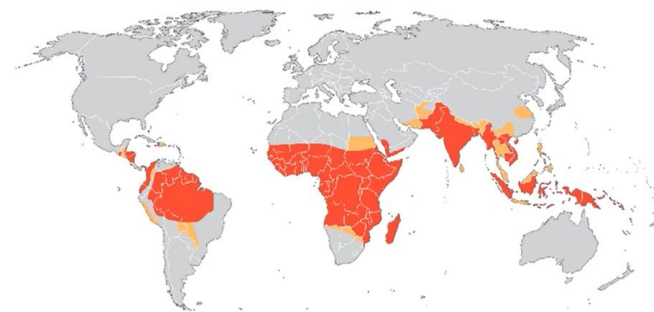


Sickle cell Disease - Epidemiology

- 7% of the world population are carriers and that 300,000–400,000 affected children are born every year. The majority of these (approximately 250,000) have sickle cell disease.
- Heterozygous inheritance of HbS offers a degree of protection from severe malaria infection.
- The majority of individuals with SCD are born in Africa , but also Nigeria, India and Democratic Republic of Congo.
- Migration is changing the sickle cell disease landscape.



Sickle Cell
Distribution

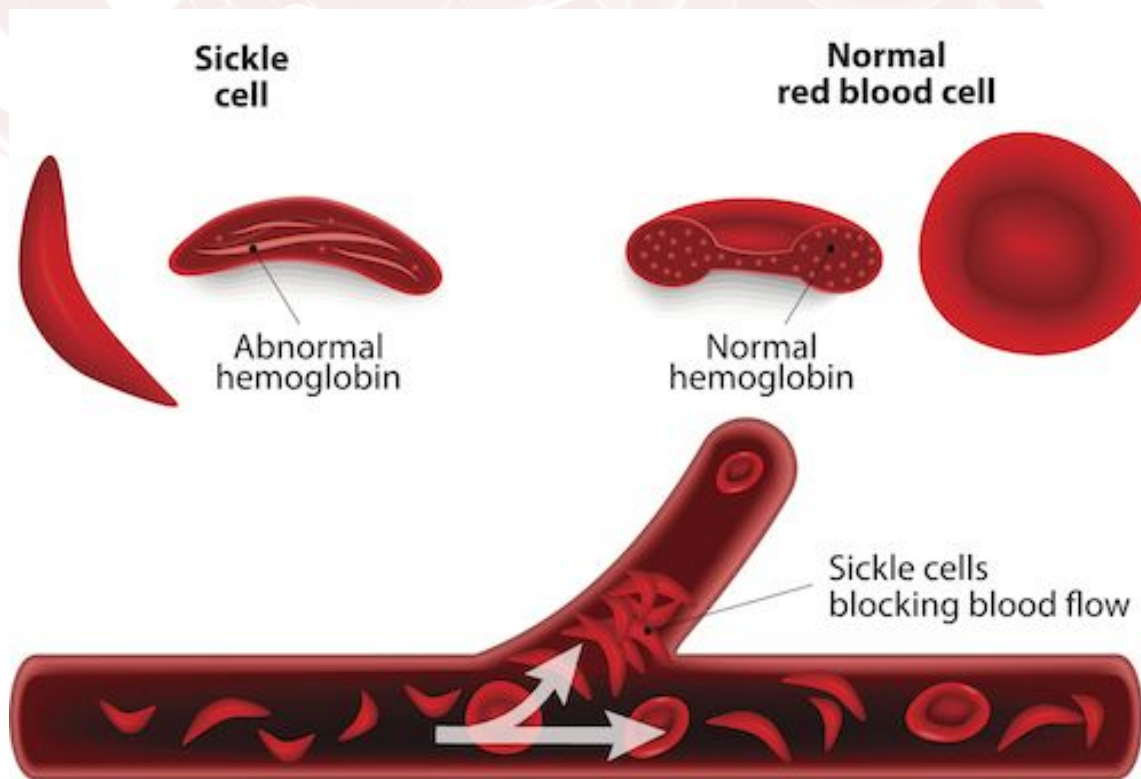
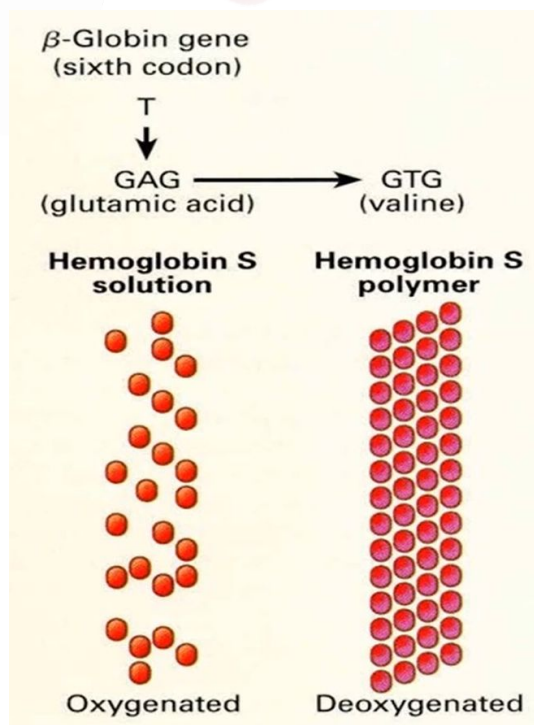


Malaria
Distribution

Irene Roberts, Mariane de Montalembert. Sickle cell disease as a paradigm of immigration hematology: new challenges for hematologists in Europe. Vol. 92 No. 7 (2007): July, 2007

Sickle Disease pathophysiology

- Intraerythrocytic polymerization of deoxyhemoglobin S (hypoxia, dehydration, and acidosis) into the unique sickle shape leading to anemia and vaso-occlusion.



A lot more than just sickling ...

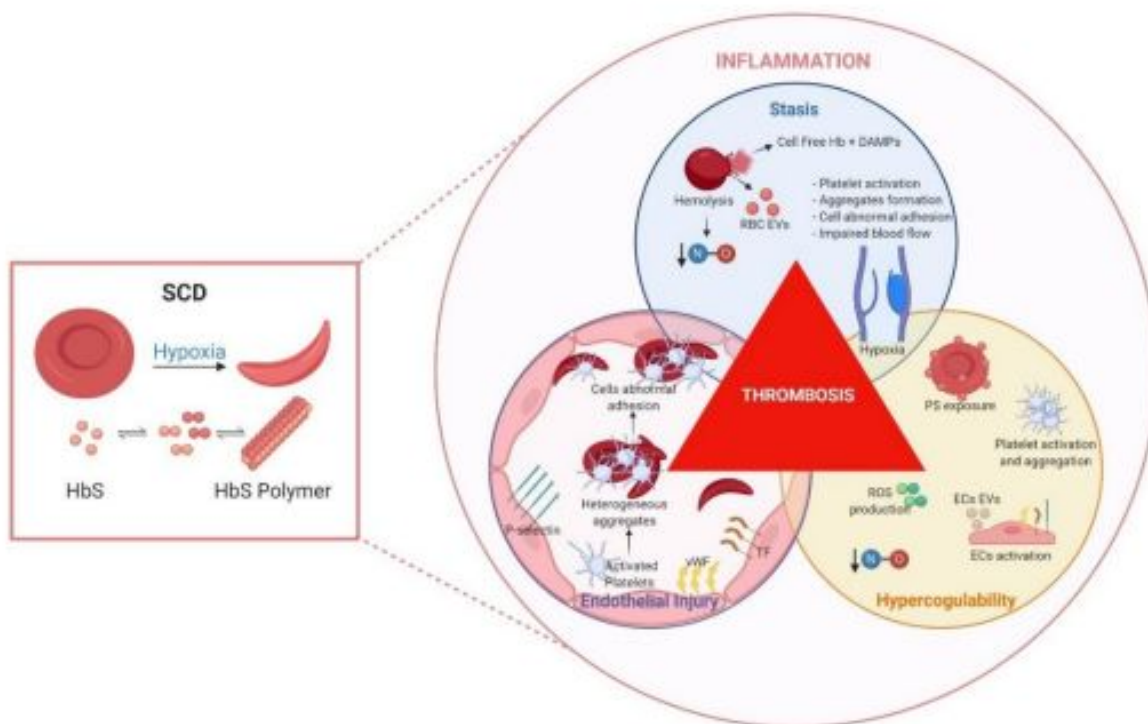


Table 1. Hemostatic alterations in patients with SCD

Increased levels	Decreased levels
Platelet activation	Factor V
Platelet aggregation	Factor XII
Phosphatidylserine-rich platelets and red blood cells	Factor IX
Thrombin-antithrombin complexes	Protein C
Prothrombin fragment F 1.2	Protein S
Plasmin-antiplasmin complexes	
Fibrinogen and fibrin-fibrinogen complex	
Fibrinopeptide A	
D-dimer	
Plasminogen activator inhibitor	

Adapted from De Franceschi et al.⁴⁷

Ted Wun and Ann Brunson. Sickle cell disease: an inherited thrombophilia. *Hematology Am Soc Hematol Educ Program*. 2016 Dec 2; 2016(1): 640–647.



Venous Thromboembolism in Sickle Cell Disease

- 25% of adults with SCD are at risk for developing VTE - a prevalence found in other high-risk thrombophilias like Protein C and S deficiency.
- The incidence of VTE in adults with sickle cell disease is high, with up to 12% of patients experiencing an event before the age of 40 years.
- VTE is associated with increased mortality in adults with SCD, regardless of the type of VTE (i.e. catheter or non-catheter related, PE, DVT).

Rakhi P. Naik, Michael B. Streiff, and Sophie Lanzkron. Sickle cell disease and venous thromboembolism: what the anticoagulation expert needs to know. J Thromb Thrombolysis. 2013 Apr; 35(3): 352–358.
Foluso Joy Ogunsile, Rakhi Naik & Sophie Lanzkron. Overcoming challenges of venous thromboembolism in sickle cell disease treatment. Expert Review of Hematology. 10.1080/17474086.2019.1583554
Ann Brunson, M.S, Theresa Keegan, Ph.D., M.S., Anjee Mahajan, M.D., Richard White, M.D., Ted Wun, M.D High Incidence of Venous Thromboembolism Recurrence in Patients with Sickle Cell Disease. Am J Hematol. 2019 August ; 94(8): 862–870.

Venous Thromboembolism in Sickle Cell Disease

- Multifactorial
- Risk factors that increase VTE risk in patients with SCD include:

<u>Tradiconal risk factors</u>	<u>SCD-related factors</u>
CVCs for poor venous access, transfusion therapy	Increased prevalence of <u>thrombophilic defects</u>
<ul style="list-style-type: none"> ○ <u>Totally implantable CVCs (port)</u> ○ <u>Partially implantable CVCs (tunneled and nontunneled lines)</u> 	<ul style="list-style-type: none"> ○ <u>Anti-phospholipid antibodies</u> ○ <u>Proteins S/C deficiency</u>
Frequent hospitalization (for pain and complications), specially >3 admissions/year	Genotype (SS/S · 0 vs SC/S · +)
<u>Surgery</u>	<u>Splenectomy</u>
<ul style="list-style-type: none"> ○ <u>Orthopedic surgery (hip, shoulder avascular necrosis)</u> ○ <u>Cholecystectomy</u> 	<ul style="list-style-type: none"> ○ <u>Surgical</u> ○ <u>Functional asplenia?</u>
Female sex (COC use, Pregnancy)	Elevated Tricuspid regurgitant jet velocity (greater than 2.5 m/s ²)
VTE venous thromboembolism, SCD sickle cell disease, CVC central venous catheter	

Rakhi P. Naik, Michael B. Streiff, and Sophie Lanzkron. Sickle cell disease and venous thromboembolism: what the anticoagulation expert needs to know. *J Thromb Thrombolysis*. 2013 Apr; 35(3): 352–358.

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Primary prevention of VTE in SCD

Modifying risk factors for VTE

SCD risk factors

- more difficult to modify
- Hydroxyurea and chronic transfusion - Reduction in arterial thrombotic events (i.e. stroke) but limited or no evidence for reducing the risk of VTE
- Daily pharmacologic prophylaxis (anticoagulant or antiplatelet) use in the outpatient setting is not recommend for asymptomatic individuals

Primary prevention of VTE in SCD

Modifying risk factors for VTE

Traditional risk factors

- Thromboprophylaxis during pregnancy should be considered
- Thromboprophylaxis during admission to hospital unless CI
- CVL placement: Use of peripheral venous access or ultrasound guided peripheral deep vein cannulation for apheresis, short term non-tunneled catheter placement in the jugular and subclavian
- Lifestyle modifications (i.e. obesity, smoking) and avoid the use of COC in women with SCD

Anticoagulation treatment of VTE in SCD

Type of anticoagulant therapy

- Warfarin, LMWH and DOACs (dabigatran, rivaroxaban and apixaban) equally effective in SCD
- DOACs may be associated with lower bleeding risk and better adherence
- When prescribing DOACs or LMWH cystatin C should be used to calculate GFR

Duration of anticoagulation

- Management of symptomatic VTE relies on general VTE guidelines management
- 3 (to 6 months) of anticoagulation therapy

Secondary prevention of VTE in SCD

Recurrence risk

- Retrospective studies show high recurrence rates around 30-40% at 5 years
- A provoked VTE in a patient with SCD may be associated with a much higher risk of recurrence than a provoked VTE event in the general population
- D-dimer level is commonly elevated in SCD and is not helpful in stratify recurrence

Bleeding risk

- Absolute percentage of of bleeding is higher in SCD than general population, leading some providers to classify individuals with SCD as moderate to high risk for bleeding

Take home messages

- **VTE occurs relatively frequently in adults living with SCD**
- **There is a thrombogenic environment in SCD resulting from multifactorial causes related to endothelial injury, venous stasis, and activated pro-coagulant activity.**
- **Patients often encounter traditional VTE risk factors such as frequent hospitalizations, surgeries, and central venous catheter line placements.**
- **Inpatient pharmacologic thromboprophylaxis should be considered for all adults with SCD who are hospitalized or undergoing surgery.**
- **In secondary prevention providers should consider extending the duration of therapeutic anticoagulation therapy for patients with SCD with an unprovoked VTE and those with a provoked VTE by a non-surgical risk factor like hospitalization for medical illness.**