Making Sense of Haematology:

Haemolytic Anaemia & Sickle Cell Disease

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Listening • Learning • Leading

Aims and Objectives

- Understand what is haemolysis
- Understand why and how haemolysis can occur
- Consider clinical features of haemolysis and diagnostic tests
- Know more about sickle cell disease

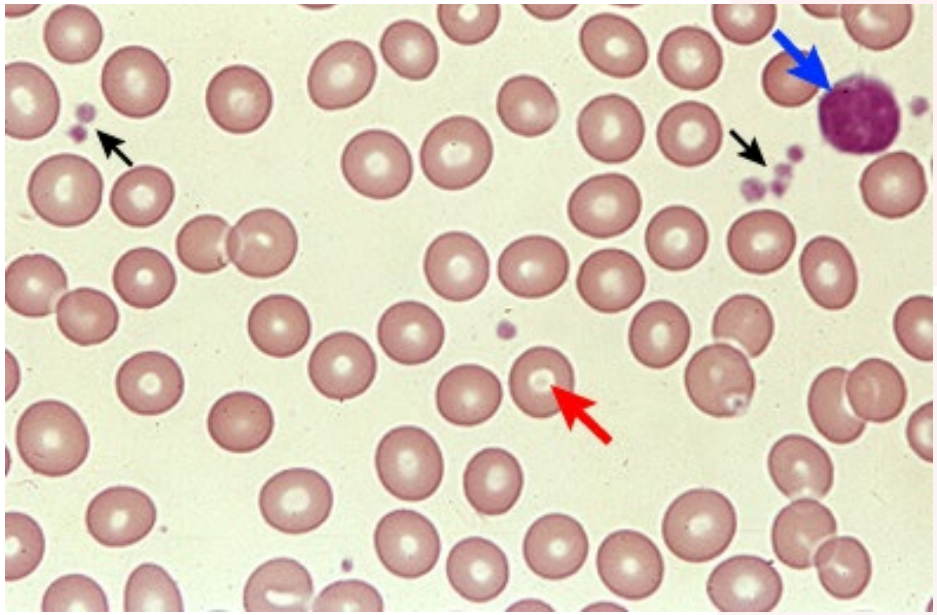
Red blood cells

- Usually, red cells are:
  1. Made in the bone marrow
  2. Circulate in the blood stream

- Question: What is the normal life span of a red blood cell?
  - 5 days
  - 20 days
  - 55 days
  - 120 days
  - 205 days

Haemolytic anaemia

- Red blood cell (RBC)
  - lifespan = @120 days



www.uptodate.com

Courtesy of Carola von Kapff, SH (ASCP).

Haemolytic anaemia

- Haemolysis
  - shortened RBC survival due to RBC destruction
- Haemolytic anaemia
  - anaemia due to shortened RBC survival

Question

- Which of these is **not** a feature of active haemolysis?
  - Anaemia
  - Elevated Lactate Dehydrogenase
  - Elevated Haptoglobin
  - Hyperbilirubinaemia
  - Reticulocytosis

Features of haemolytic anaemia

- Anaemia
  - Often normo- or macrocytic
- Reticulocytosis
  - Evidence of bone marrow response
- Raised bilirubin
  - Increased release of unconjugated bilirubin
- Raised lactate dehydrogenase
  - Non-specific
- Reduced haptoglobin
  - Free haemoglobin binds to haptoglobin

Causes of haemolytic anaemia

- **Intrinsic** abnormality
  - Abnormal membrane
  - Abnormal enzyme
  - Abnormal haemoglobin

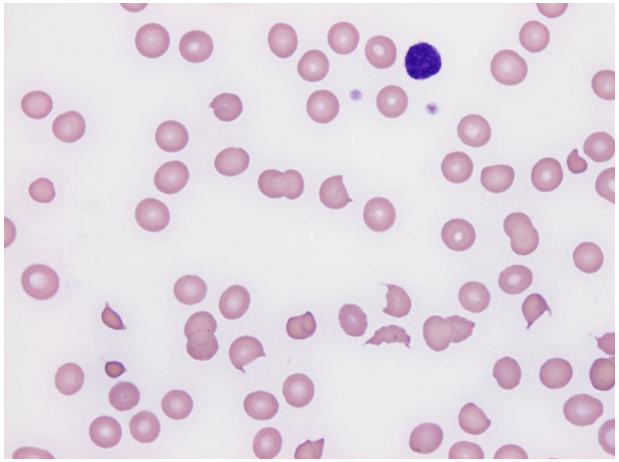
- **Extrinsic** forces acting on a normal red cells

Intrinsic abnormality

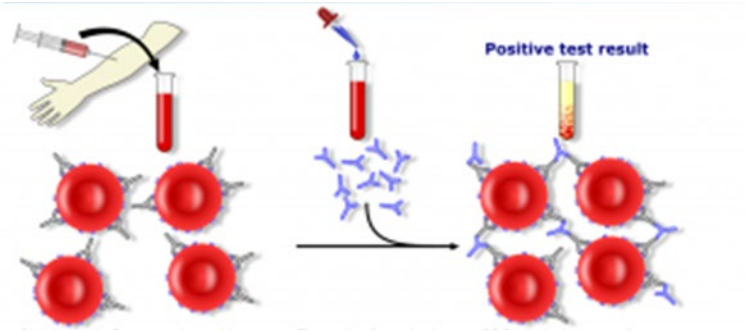
- Abnormal membrane
  - *Hereditary Spherocytosis (HS)*
- Abnormal enzyme
  - *Glucose 6 Phosphate Dehydrogenase (G6PD)*
- Abnormal haemoglobin (Hb)
  - *Sickle Cell Disease*
  - *Unstable Hb*

Extrinsic forces acting on a normal red cells

- **Microangiopathic Haemolytic Anaemia**
  - Intravascular RBC fragmentation



- **Autoimmune Haemolysis**
  - RBC coated with immunoglobulin or complement removed by reticuloendothelial system

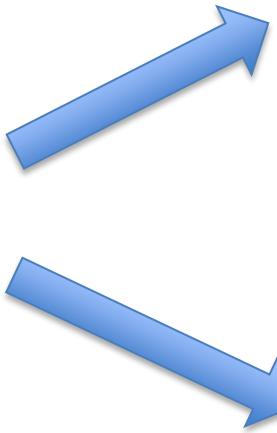


https://emedicine.medscape.com/article/1731264-overview

Approach to Haemolytic Anaemia

Patient with features of haemolysis:

Low Hb
Raised LDH
Low Haptoglobin
Raised Indirect bilirubin
Raised Reticulocytes



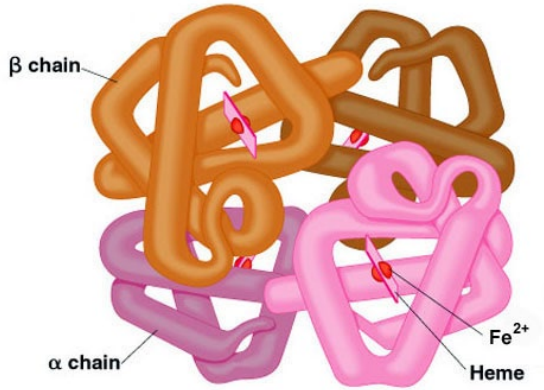
Patient with history of recent transfusion needs to be investigated and managed for haemolytic transfusion reaction

Arrange further tests to investigate cause. To include:

- Blood Film
- Coagulation Studies
- Direct Anti-globulin Test (DAT)
- Haemoglobin Electrophoresis
- Biochemistry

Haemoglobin Electrophoresis

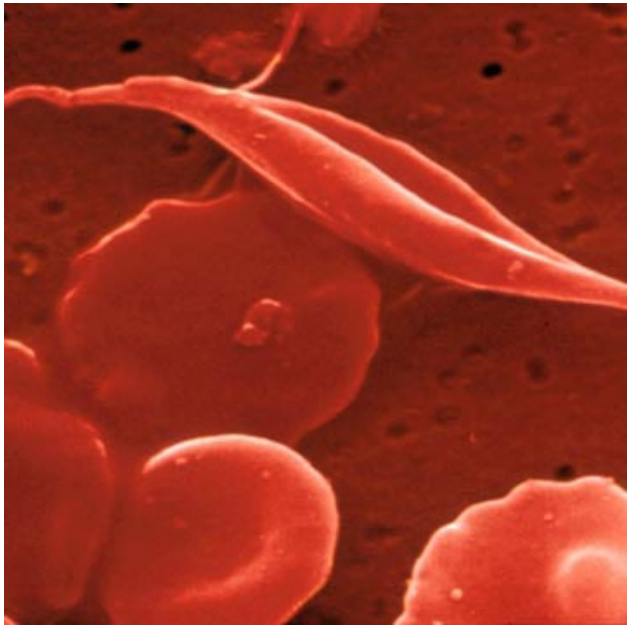
- Separates different haemoglobins based on weight and charge

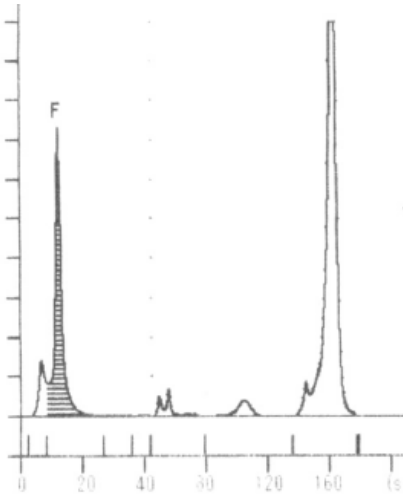


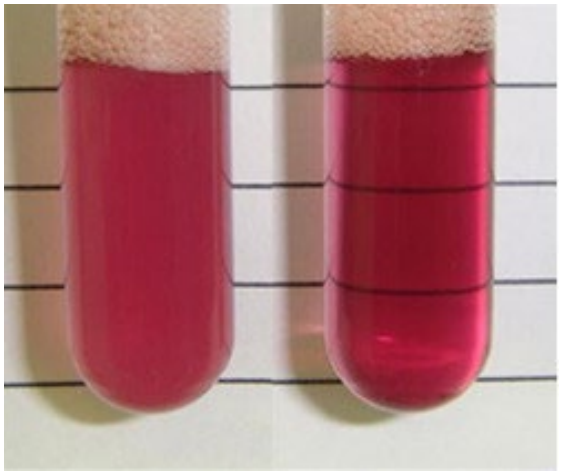
- Usual adult haemoglobin profile:

	Structure	Stage	Normal Adult level
Hb A	$\alpha_2\beta_2$	Adult	96-98%
Hb A_2	$\alpha_2\delta_2$	Adult	1.5-3%
Hb F	$\alpha_2\gamma_2$	Fetus/Adult	0.5-0.8%

Haemolytic Anaemia: Sickle Cell Disease

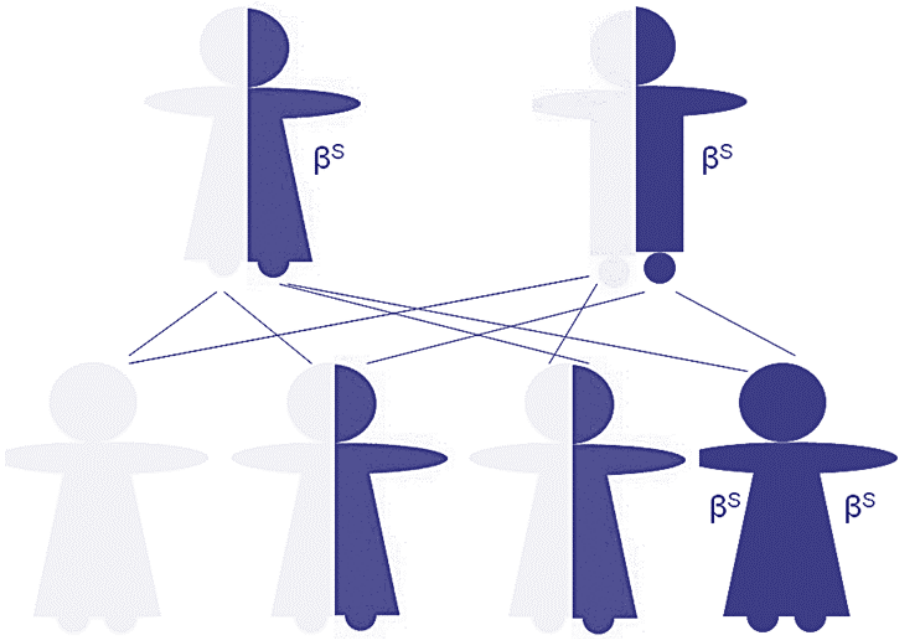


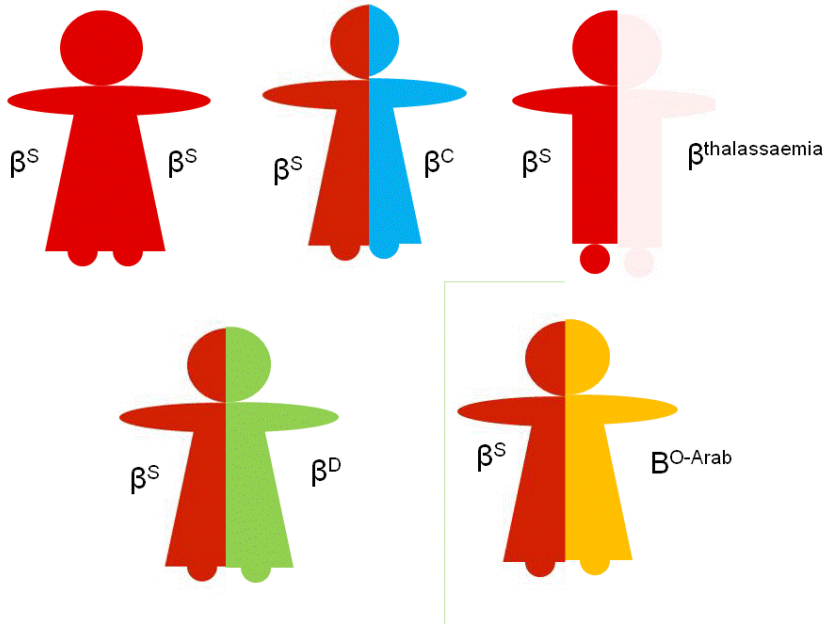




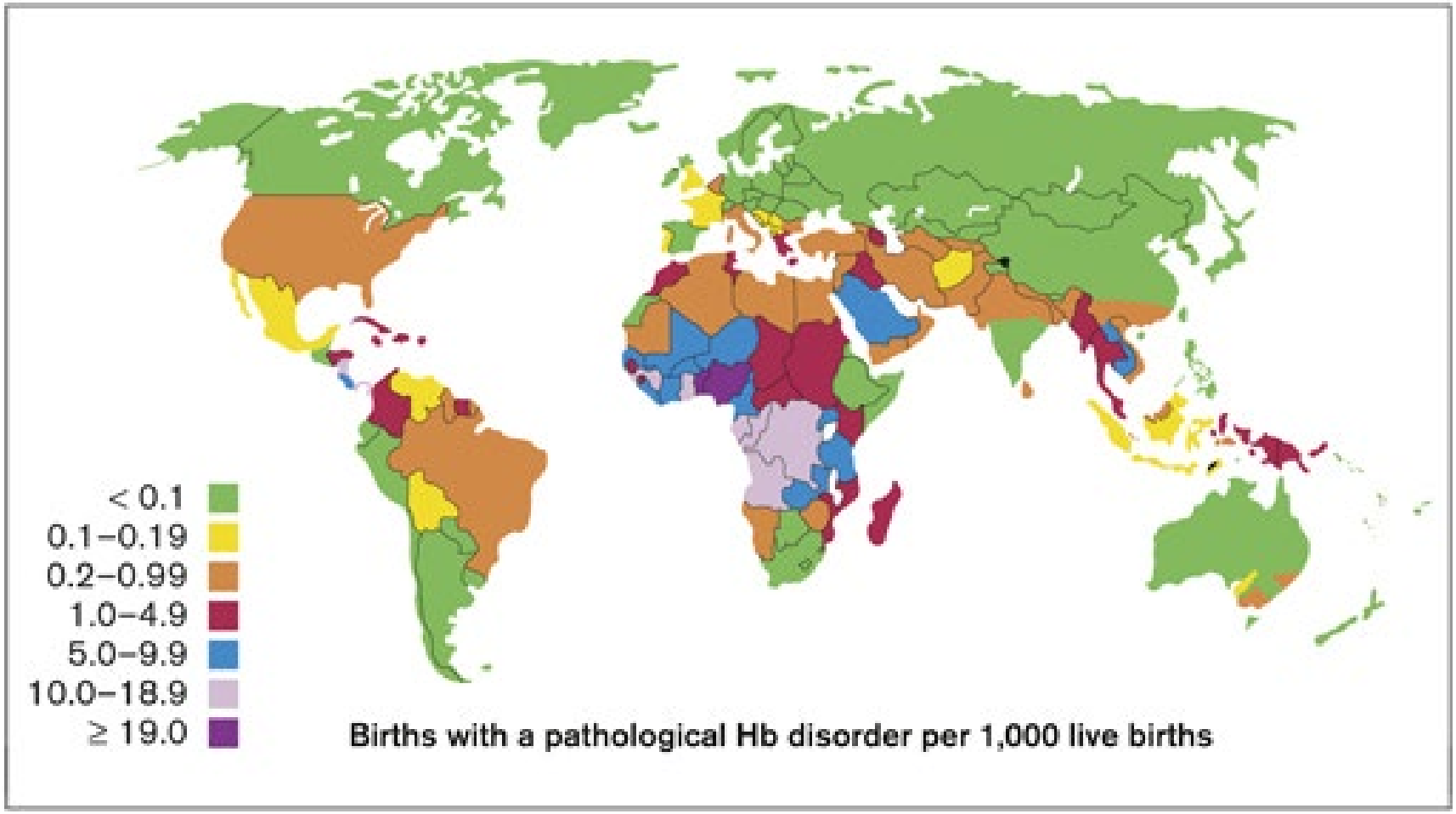
What is sickle cell disease?

- Genetic condition due to inheritance of the β^S gene from both parents **<u>or</u>** β^S with another clinically significant variant



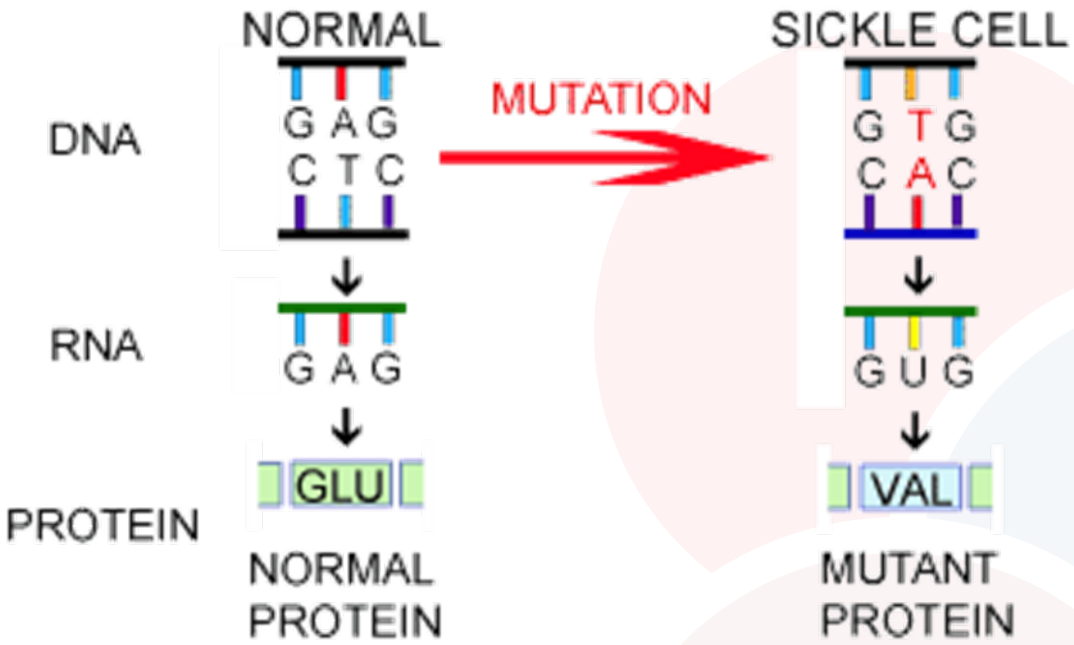


Global distribution of pathological Hb disorders, 1996



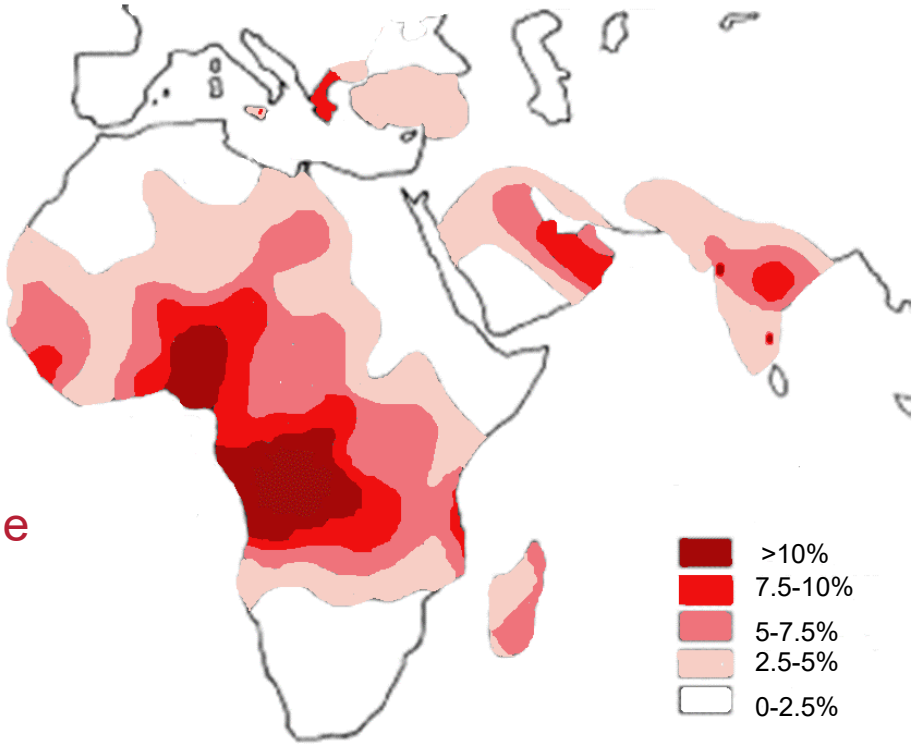
http://www.ironhealthalliance.com/disease-states/sickle-cell-disease/epidemiology-and-pathophysiology.jsp

How did haemoglobin S happen?



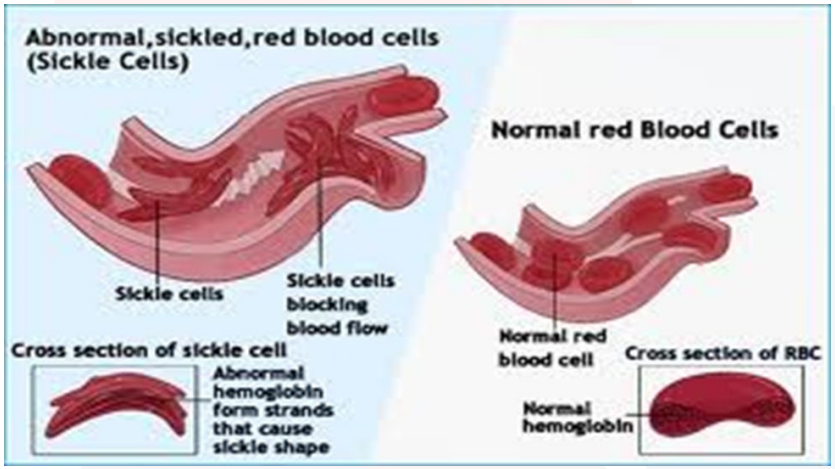
Where did this happen?

Distribution of the sickle-cell trait

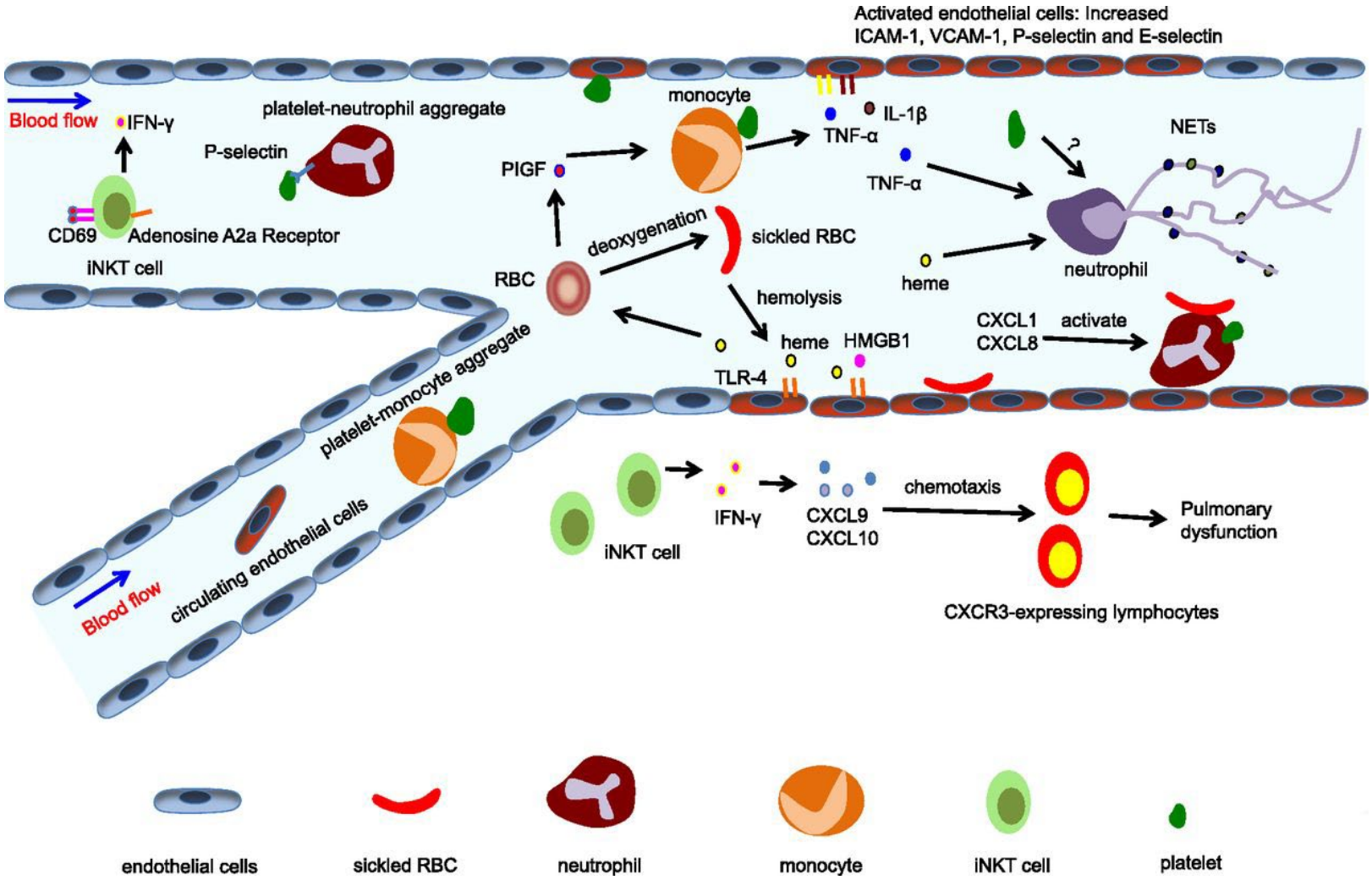


Clinical Impact

- Formation of crescent shaped cells (initially reversible)
- Haemolytic anaemia
- Chronic organ damage



Inflammation in SCD. SCD has been recognized as a chronic inflammatory disease.

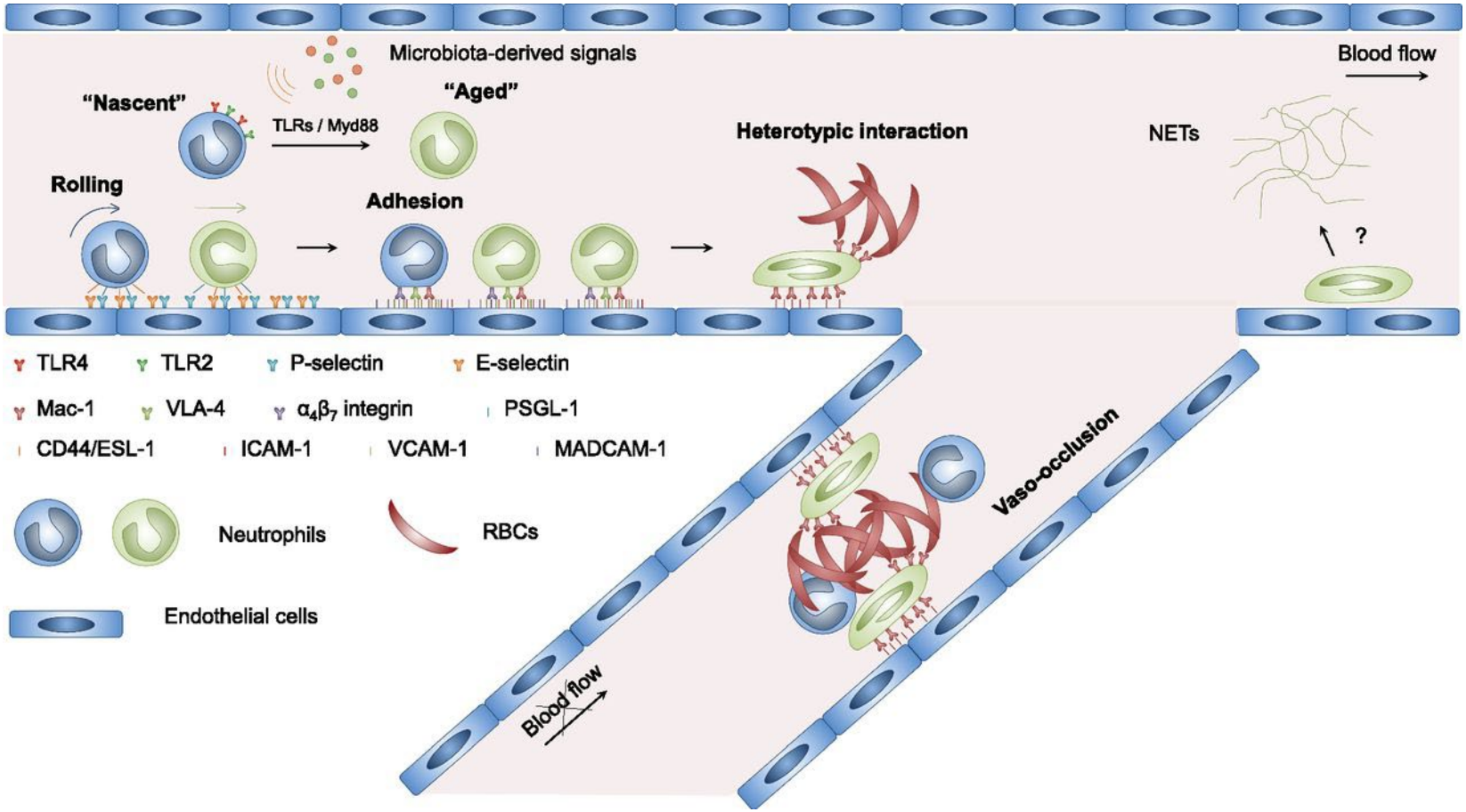


Dachuan Zhang et al. Blood 2016;127:801-809

Clinical Impact

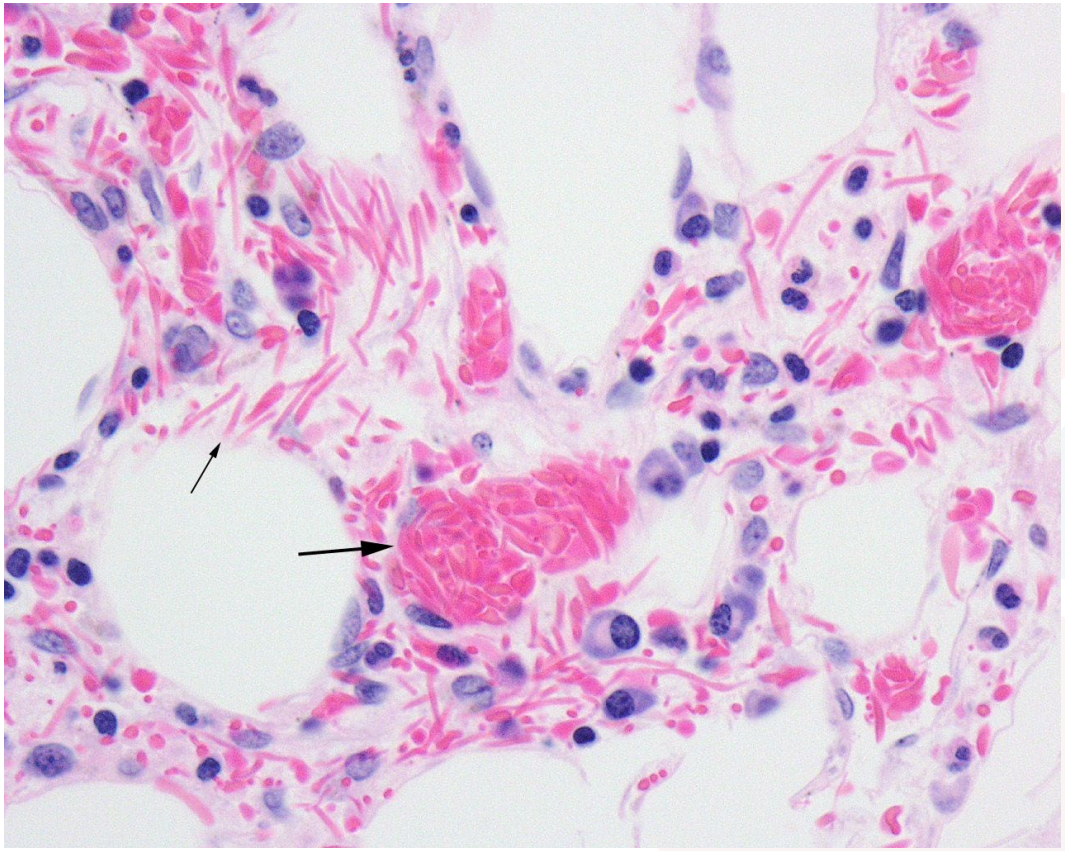
- Damage to red cell membrane
- Oxidation of intracellular contents
- Interaction of RBC with:
  - Endothelial cells
  - Neutrophils
- Reduced blood flow:
  - Increased polymerisation
  - Vascular obstruction
  - Infarction
  - **PAINFUL CRISES**

Multicellular and multistep model of sickle cell vaso-occlusion.



Dachuan Zhang et al. Blood 2016;127:801-809

Vascular Obstruction



ASH Imagebank

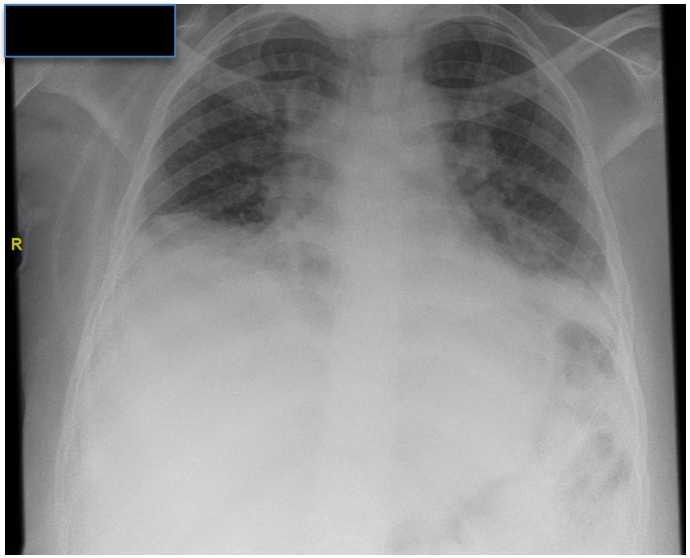
Acute presentation – vaso-occlusion

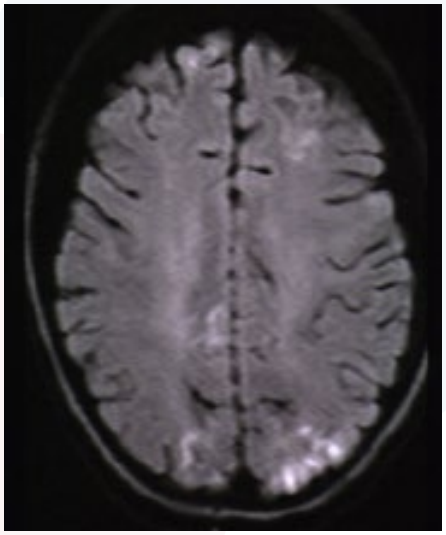
- Which of these is unlikely to form routine management of an acute sickle cell crisis?
  - Analgesia with opioid-based analgesia
  - Blood transfusion
  - Heat packs
  - Fluid hydration
  - Monitoring of oxygen saturations

Acute vaso-occlusive crisis

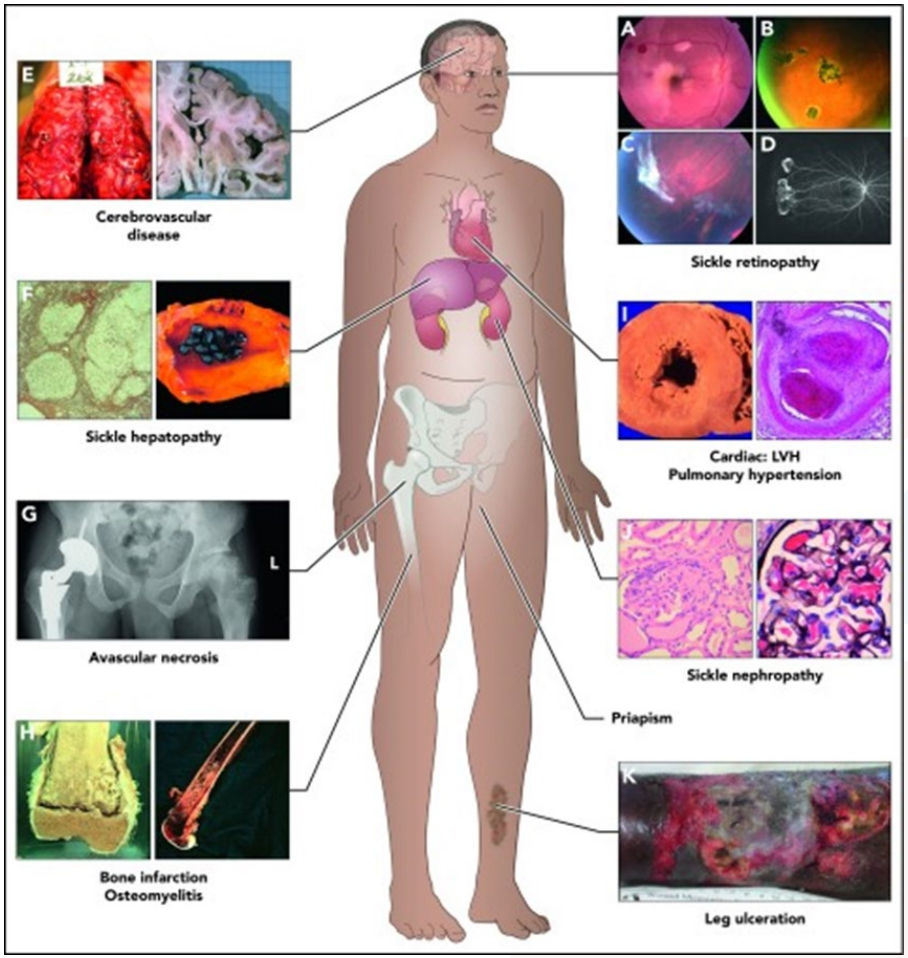
- Analgesia
  - Within 30 minutes of arrival and ongoing reassessment
  - Opioid + Anti-inflammatory
- Heat Packs
  - Important to maintain warmth and avoid cold – trigger
- Fluid hydration
  - Dehydration recognised trigger
- Oxygen
  - Hypoxia can drive further polymerisation, but hypoxia also a feature of acute chest crisis

Acute Complications





Chronic Complications



Thein SW, Howard J How I treat the older adult with sickle cell disease Blood. 2018 Oct 25; 132(17): 1750–1760.

Why do people with sickle cell disease die?

Cause of death	Deaths < age 20y	Deaths > age 20y
Infection	36%	5%
'Hypersplenism'	13%	
Irreversible organ damage*	13%	42%
CNS events	11%	13%
Trauma	9%	8%
Unknown	9%	8%
Acute pulmonary events	7%	11%
Other	2%	13%

*Lung, kidney, liver

Data from Los Angeles, 1959-2005

Powars (2005) Medicine, 84, 363

Treatment

- Folic acid
- Manage hyposplenism risk
  - Vaccination, penicillin prophylaxis
- Hydroxycarbamide
- Blood transfusion
  - Acute management
  - Long term prophylaxis
- New Therapies
  - Crizanlizumab
- Curative Therapies
  - Bone Marrow Transplant
  - Gene Therapy

Hydroxycarbamide

- Routinely offered to HbSS and HbS/B^0thal children by 9 months

- Benefits:
  - Reduced VOC incidence
  - Reduced ACS incidence
  - Reduced need for transfusion
  - Long term disease modification

When is transfusion indicated?

- Certain specific indications circumstances
  - Stroke treatment and prevention
  - Acute chest syndrome
  - Planned surgery
  - Some pregnant women
  - Symptomatic anaemia (consider if <20g/l fall from baseline)

  - NOT for Rx of uncomplicated painful crises or routine use

Complications of Transfusion

- Iron overload
- Transfusion reactions
- Red cell antibody production

Novel Therapies

- Crizanlizumab
  - NICE licence 2021
  - P-selectin inhibitor
- Bone Marrow Transplant
  - Sibling transplant available on NHS for eligible adults
  - Standard of care for children with matched sibling

National screening for sickle cell disease & Thalassaemia

- Antenatal screening of all pregnant women
  - Identify women with clinically significant conditions
  - Partner testing if indicated (at risk pregnancy)
  - Offer option of pre-natal diagnosis to at risk couples

UK neonatal screening

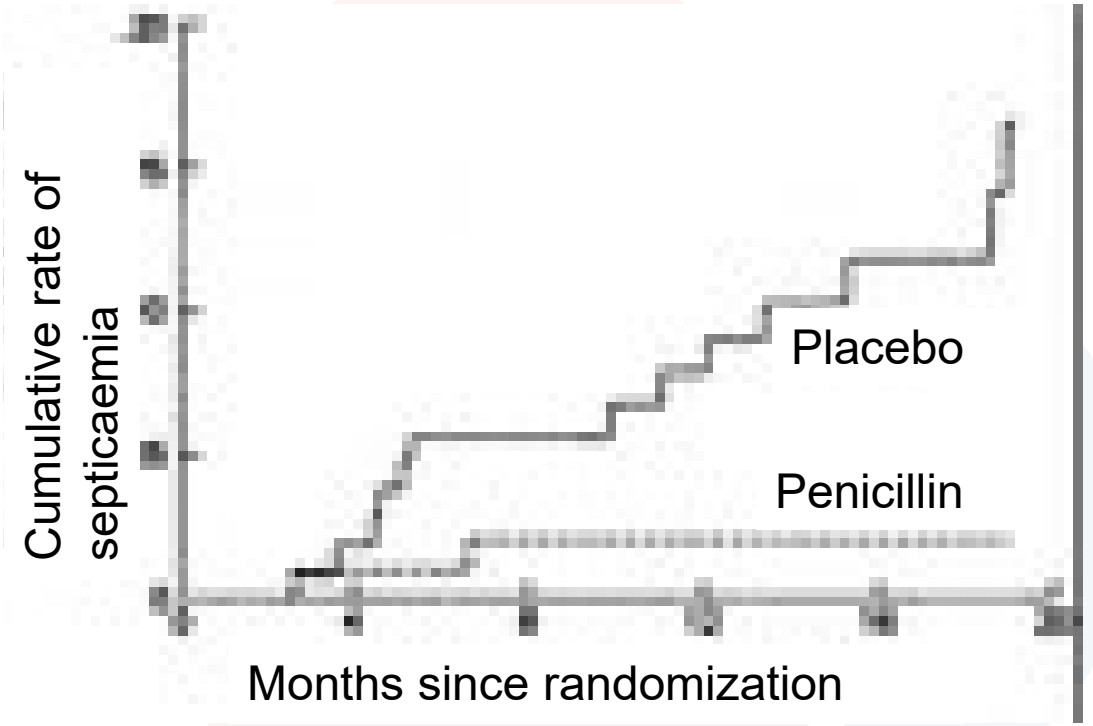
- Newborn blood spot screening
- All babies, regardless of ethnic background on day 5
- Confirmatory samples

Outcome following neonatal screening

- Education
  - Parental assessment for spleen size
  - Precipitant avoidance
- Prophylaxis
  - Penicillin
  - Additional vaccinations
  - Folic acid
  - TCD screening

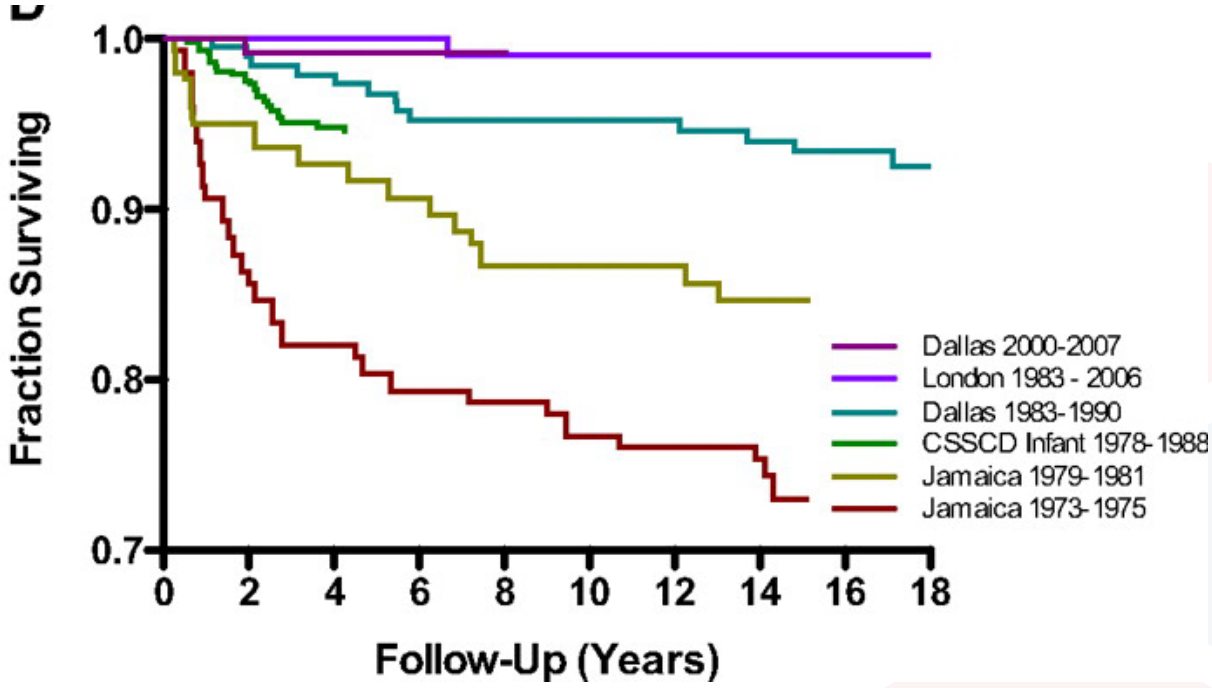
Daily oral penicillin

- Proven benefit in a double-blind randomized controlled trial
- Children with SS less than 5 y
- 84% reduction septicaemia 0.0025)
- 3 deaths in group, penicillin group



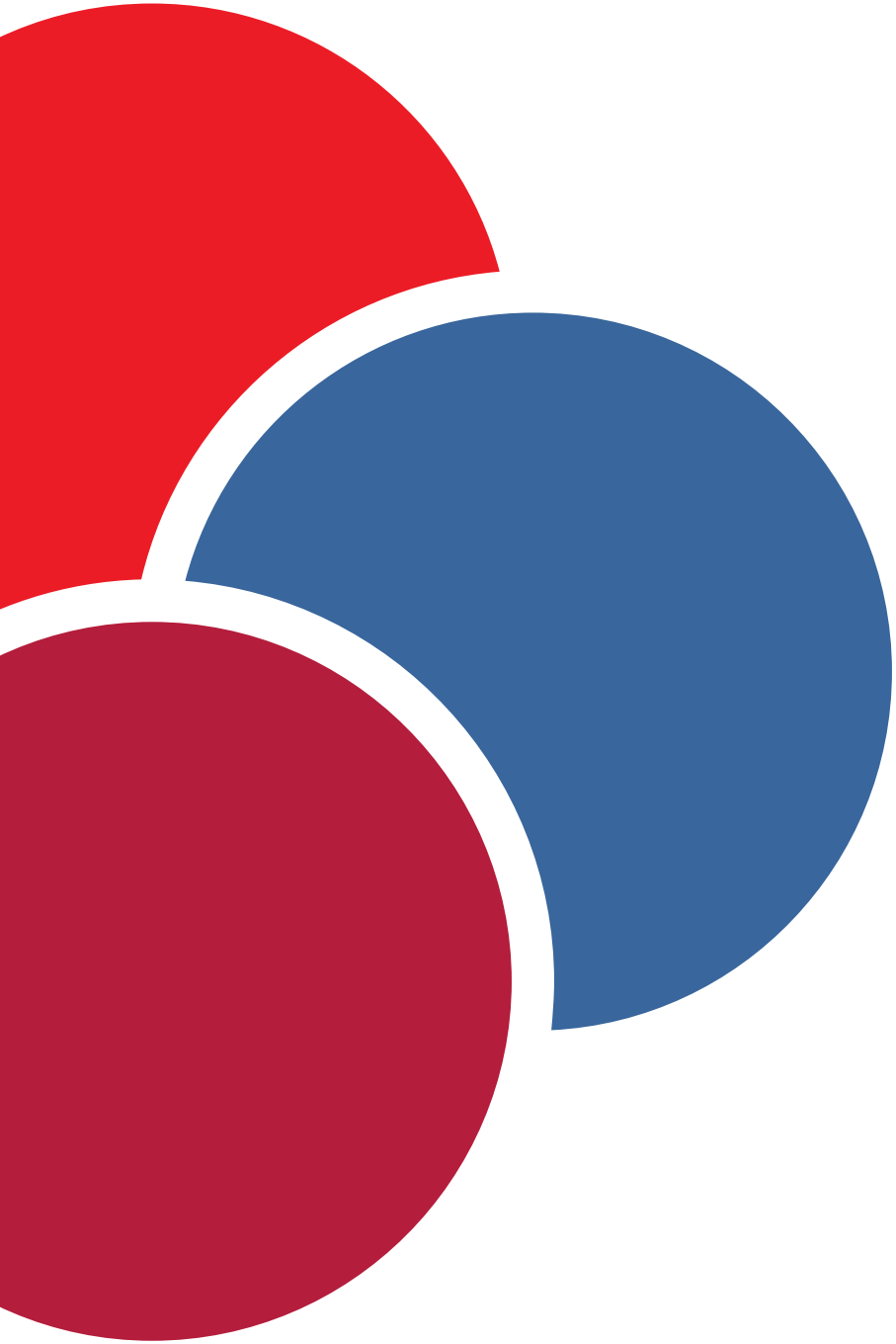
Gaston *et al*. (1986) N Eng J Med, 314, 1593

Cumulative effect of intervention



- Improving prognosis of SS and $S\beta^{0}$ thalassaemia over 30 years

Quinn, 2010, Blood, 115, 3447



The End

Questions?