Complex systems management in paediatric haematology – A case of severe anaemia in sickle cell disease

Mike Richards

Consultant Paediatric Haematologist

Leeds Children's Hospital

Case history AB

- 11 yrs old female
- 2018 Nigerian family moved to Leeds from Canada

- HbSS (Homozygous sickle cell disease)
- Episodes of pain at home

- Admission with sickle chest crisis
  - Hb 43g/l Reticulocytes 11%, top up red cell transfusion led to clinical improvement

- Ongoing out patient review
  - Compliant with penicillin V and folic acid
  - Initial reluctance to use hydroxycarbamide then started treatment

- Family requested referral to stem cell transplant team

Sickle cell disease

- Most common genetic condition worldwide and probably UK

  Autosomal recessive disorder

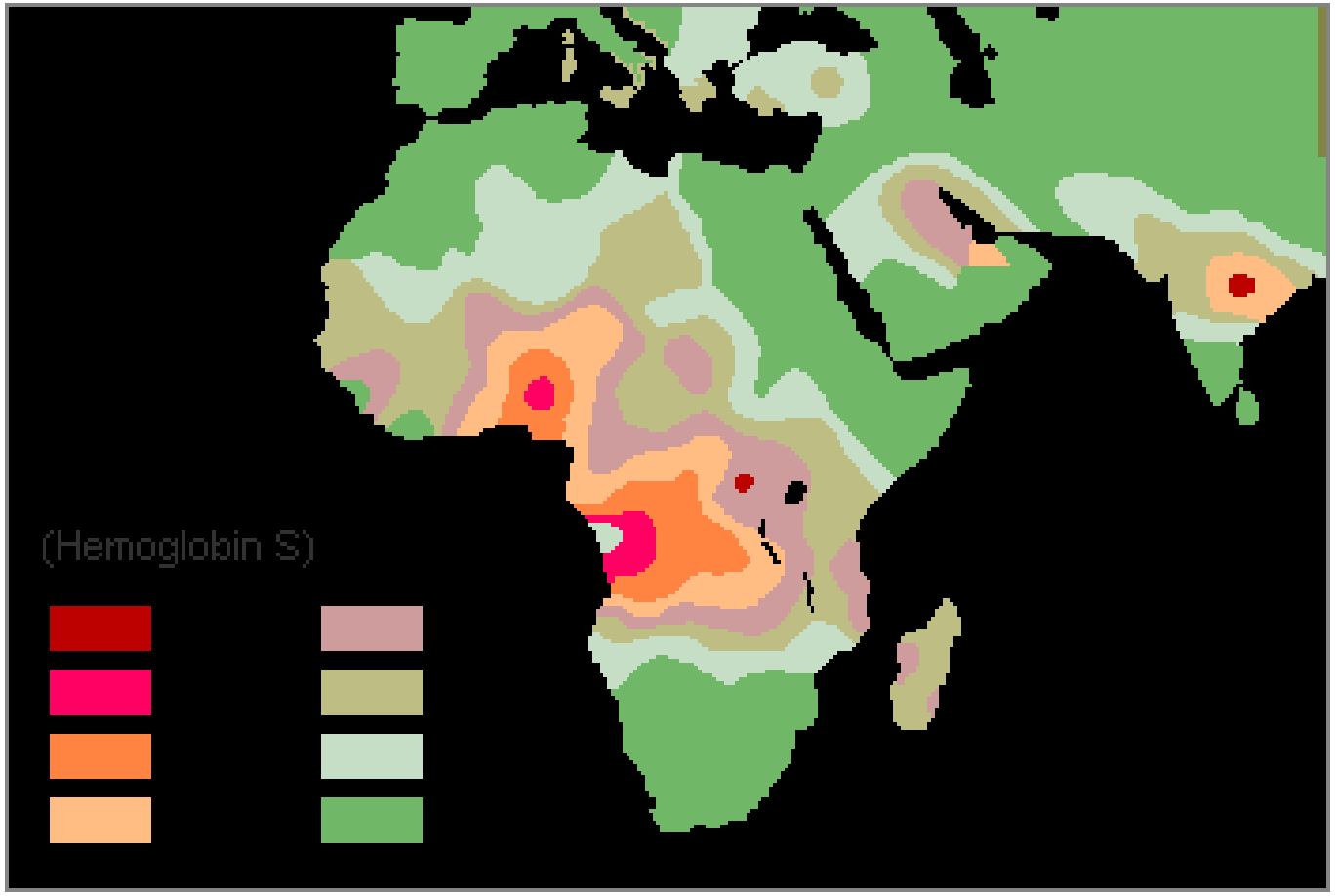
  Incidence 1:2000 in UK

  Estimated 300,000 affected infants born annually world-wide projected to rise to 400,000 by 2050

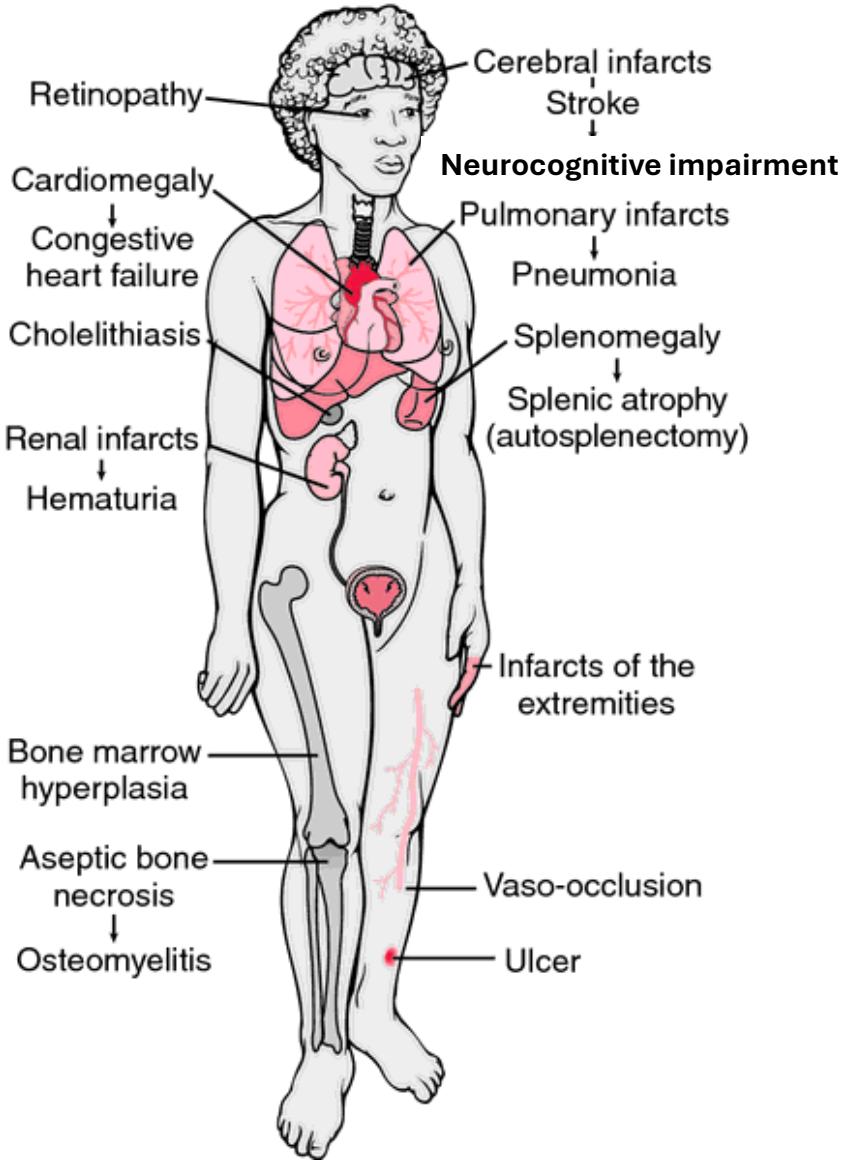
  African, Mediterranean, Middle East, Asian and Indian populations

- Nigeria current estimated under 5 yrs mortality 49% (95% CI 24-70)
- UK <1% infants die
- Life expectancy in the USA is shortened by over 2 decades

Percentage population with HbS allele



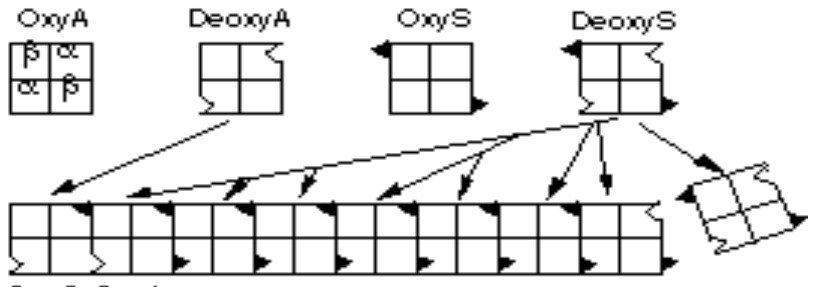
Clinical presentations of vaso-occlusion

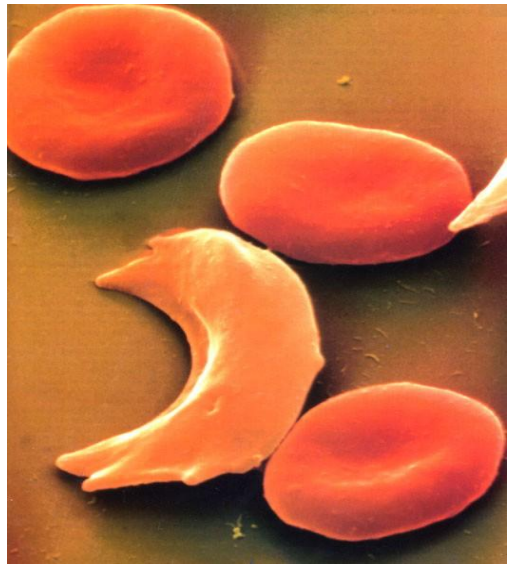


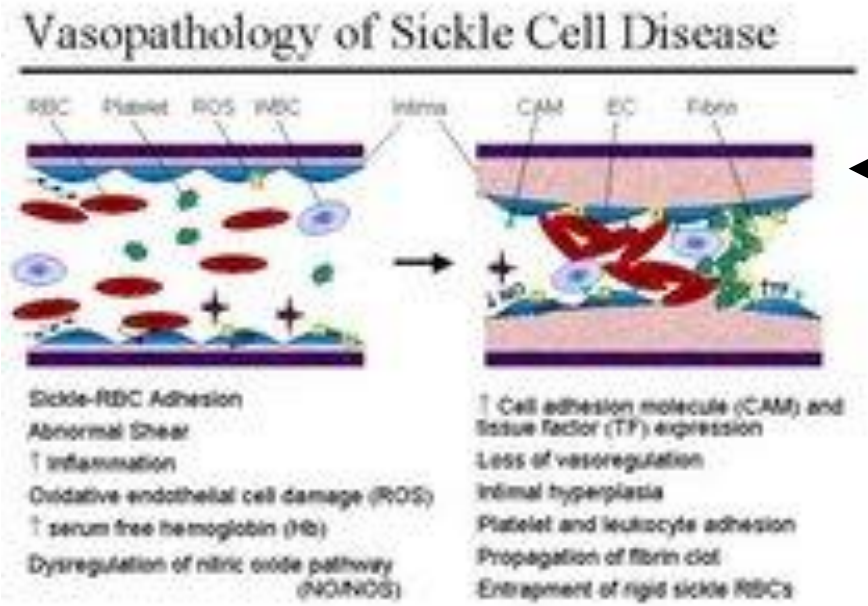
Genetic basis

- The replacement of Adenine by Thymine at the 17th nucleotide of the gene for the beta chain of haemoglobin changes the codon GAG to GTG
- Hydrophilic amino acid glutamic acid replaced with the hydrophobic amino acid valine at the sixth position of β–globin haemoglobin chain
- Low-oxygen conditions the change in amino acid structure promotes the non-covalent polymerisation of haemoglobin
- Distortion of red blood cells into a sickle shape and decreases their elasticity

Sickle haemoglobin polymerisation







Treatment - prophylaxis

- Keep warm
- Keep well hydrated
- Penicillin
- Immunisations
- Folic acid
- Immediate access to emergency treatment
- Multidisciplinary team support
  - Social work
  - Psychology
  - School

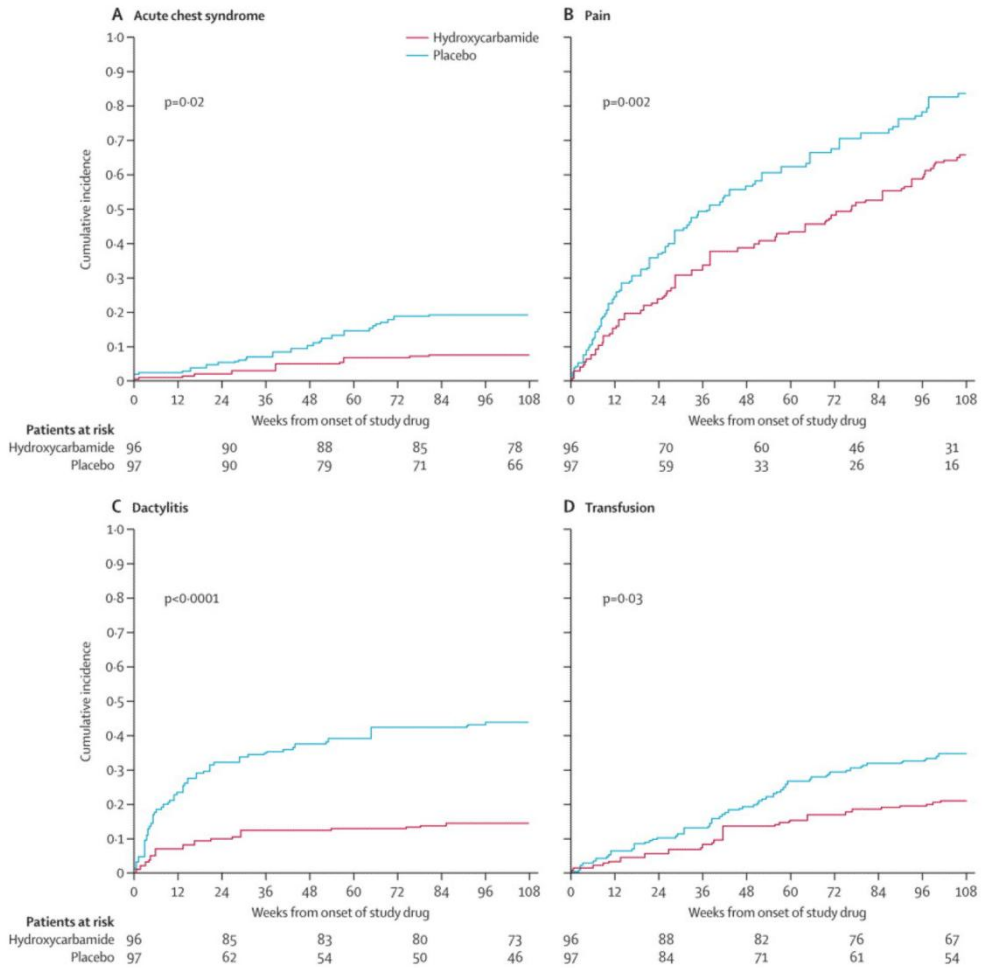
Hydroxycarbamide

- Antineoplastic drug that inhibits ribonucleotide reductase in DNA synthesis used in myeloproliferative disorders

- Hydroxycarbamide induced marrow suppression leads to
  - proliferation of RBC precursors containing HbF
  - haemoglobin content is increased
  - increased sickle RBC hydration
  - reduction of RBC adherence to endothelial cells
  - improved nitric oxide metabolism

- 1996 double-blinded placebo-controlled study in adults with severe sickle cell disease hydroxycarbamide substantially reduced
  - episodes of pain and acute chest syndrome
  - hospital admissions
  - transfusions

Cumulative probability curves of time to first event for acute chest syndrome, pain, dactylitis and transfusion.



AB 2022

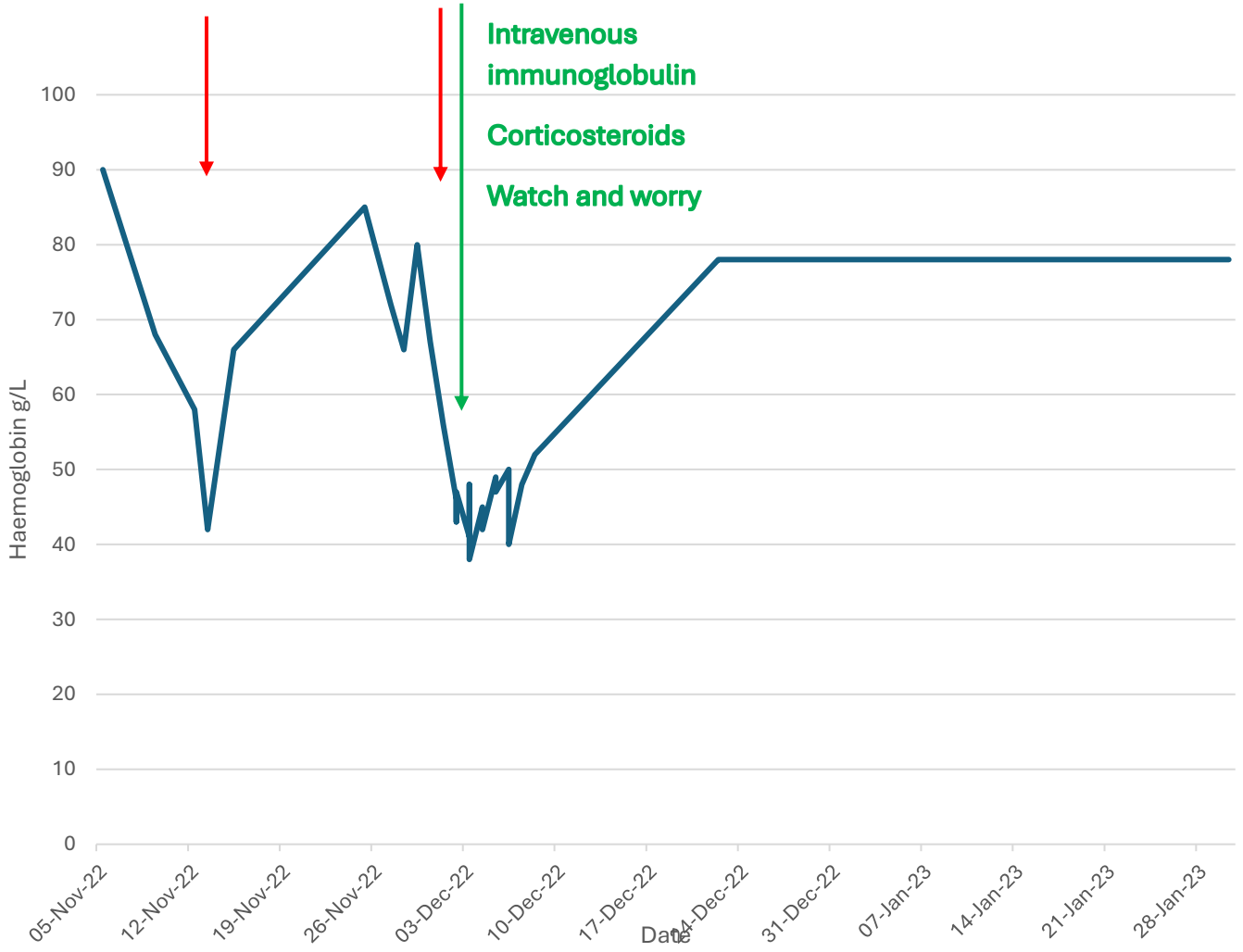
- Ongoing painful crises despite hydroxycarbamide
- Early November admission with leg pain
- Dizzy on standing
- Hb 42g/l Reticulocyte 12%
- Single red cell top up transfusion
- Discharged well

- Given failure of hydroxycarbamide in controlling symptoms consideration of elective red transfusion programme – ideally exchange transfusion

- Readmitted with pain later that month

Hb 43 ->38, Reticulocytes 272->244 X10.9/L(14%) HbS% increased
LDH 1299IU/L (<246) DAGT Positive

Diagnosis Hyperhaemolysis



Hyperhaemolysis syndrome

- Severe form of delayed haemolytic transfusion reaction with destruction of donor and recipient red cells
- Recent transfusion past 7-10 days (up to 21 days)

- Post transfusion Hb < pre transfusion Hb
- Total bilirubin /LDH acutely elevated or identify plasma free Hb
- Absolute reticulocytopenia or drop in reticulocyte counts
- Drop in HbA%

- Involves activation of both classical and alternate complement cascades

Chou and Hendrickson

Systematic review

Blood 2024

- 51 patient study

- 31 sickle cell disease
- 12 thalassaemia

- Median nadir Hb 39g/l at median 10 days post transfusion
- 33% negative antibody screen
- 39% new antibody
- 46% negative DAGT

Treatments received

- Recombinant Erythropoietin
- Intravenous iron
- Steroids 1-4g/kg/day
- Immunoglobulin 0.4-1mg/kg/day for 3-5 days
- Eculizimab 900-1200 mg (>40kg) 600mg (10-40kg)
  - complement inhibitor
- Tocilizumab 8mg/kg/day up to 4 days
  - IL6 and macrophage inhibtor
- Rituximab 375mg/m2 2-4 doses over a month
  - anti CD20 antibody

Recommended treatments

- Intravenous Immunoglobulin and High dose steroids

then

- Eculizumab
- Rituximab for prevention of future alloimmunization
- Try to avoid red cell transfusion but challenging balance of risk

- UK National Haemoglobinopathy Panel reporting of hyperhaemolysis syndrome and Eculizimab use

- Preventative measures – more detailed Rhesus grouping possibly via genotype matching

Indications for red cell transfusions in sickle cell disease

Acute transfusion

- Acute anaemia
- Parvovirus B19 infection if causing anaemia (often accompanied by reticulocytopenia)
- Acute splenic or hepatic sequestration
- Acute chest syndrome – early top-up transfusion may avoid the need for exchange transfusion
- Stroke or acute neurological event
- Multi-organ failure
- Failure of conservative therapy
- Preparation for urgent significant surgery

An elective long-term transfusion programme

- Primary and secondary stroke prevention
  - Reduces risk of stroke from 10% to 1% in high risk patients
- Failure of hydroxycarbamide therapy
- Progressive organ failure

- Either regular top up transfusions with iron chelation

Or

- Automated or manual red cell exchange

AB update

- Underwent allogeneic stem cell transplant x2
  - 1 st sibling donor but graft rejection
  - 2 nd haploidentical donor – father with top up
  - Successful engraftment
  - NHSBT Barnsley Blood Centre Stem Cell and Immunotherapy Department was a vital partner
- 2 yrs post transplant relatively well
  - Ovarian failure
  - Difficulty concentrating in school
- Underwent red cell exchange coinciding with immunosuppression conditioning therapy for transplant – no resulting hyperhaemolysis