Sickle cell disease management

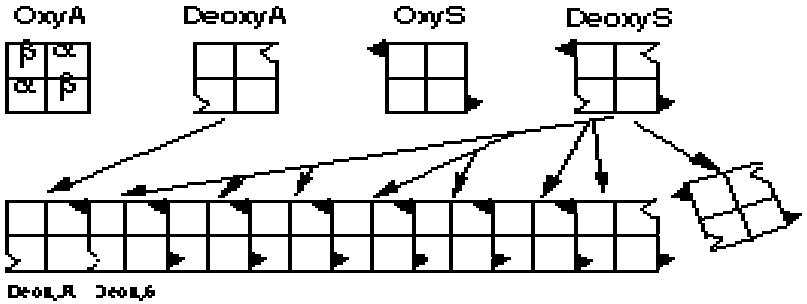
Mike Richards

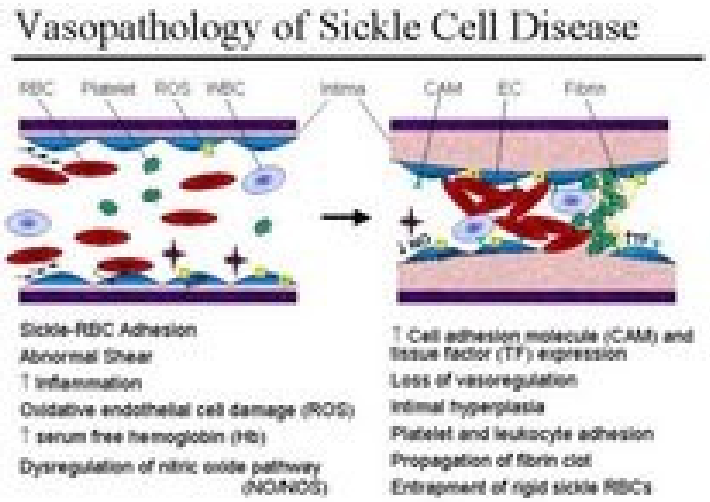
Paediatric Haematologist

Sickle cell anaemia

- Most common genetic condition in UK
  - Incidence 1:2000
- Autosomal recessive disorder
- Hydrophilic amino acid glutamic acid replaced with the hydrophobic amino acid valine at the sixth position of β–globin haemoglobin chain
- In 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

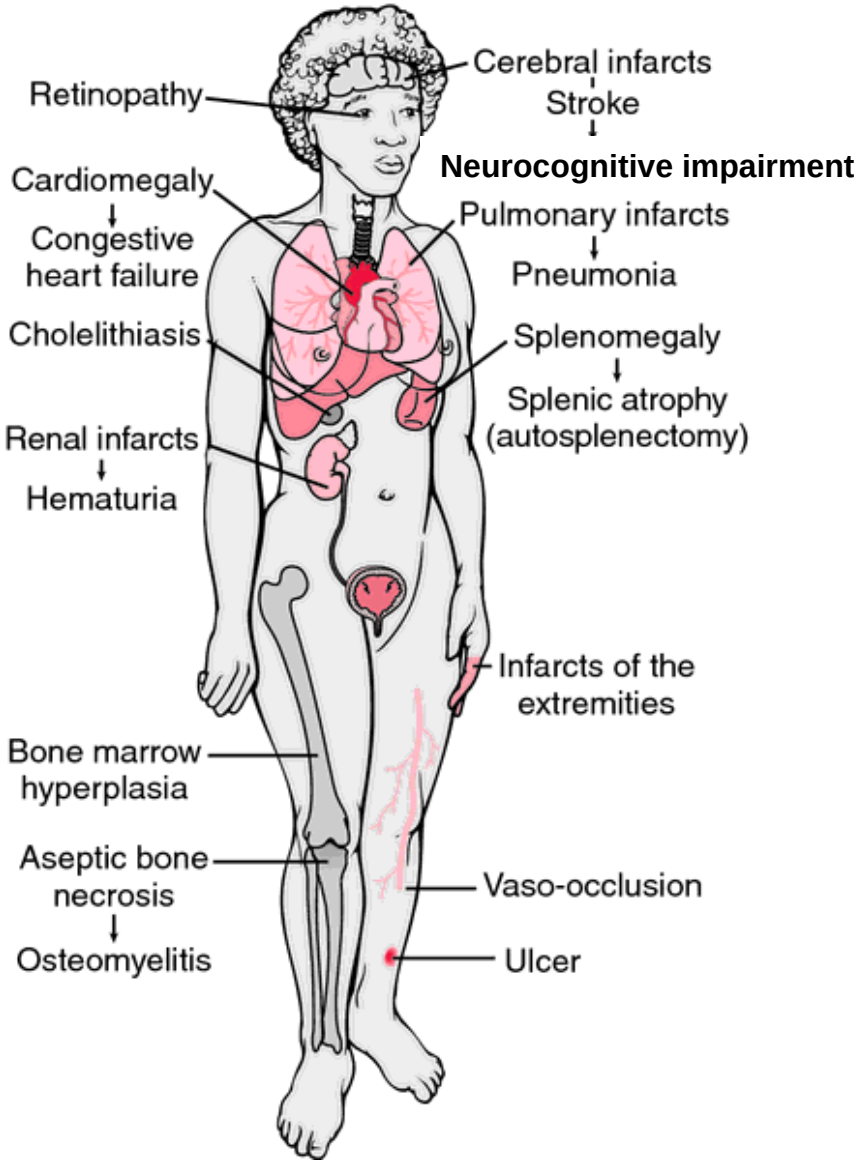




Sickling disorders

- HbSS
- HbSC
  - Increased risk of retinopathy and avascular necrosis of hip
- HbS trait/β^0-thalassaemia trait compound heterozygous state
- HbS trait/β^+-thalassaemia trait compound heterozygous state
- HbS/D^{Punjab}
- HbS/O^{Arab}

Clinical presentations of vaso-occlusion



Specific organ damage in sickle cell disease

Kidney

- Glomerular hyperfiltration, hyposthenuria, asymptomatic microalbuminuria
- Focal segmental glomerulosclerosis
- End-stage renal disease occurs in up to 30% of adults
- At a mean age of 13 months 23% of infants were unable to concentrate urine with controlled fluid deprivation

Specific organ damage in sickle cell disease

Lungs

- 90% of adults with sickle cell disease have abnormal lung function
- Children have demonstrated a progressive decline in lung volumes with early lower airway obstruction, restriction, and airway hyper-reactivity

Specific organ damage in sickle cell disease

Brain

- Cerebro-vascular events such as overt strokes occur in 24% cases by the age of 45 years
- Silent cerebral infarcts, high-signal MRI abnormalities in the absence of overt neurological signs detectable in 20% - 35% of children
- Silent cerebral infarcts in 13% cases at a median age of 13.7 months

Specific organ damage in sickle cell disease

Spleen

- 88% of young children had decreased or absent splenic uptake
- Associated increased risk of overwhelming encapsulated organism infection

Sickle cell prognosis

- Modern life expectancy of patient with homozygous sickle cell disease in Europe/North America is 53-60 years

- Potential risk factors for adverse outcomes

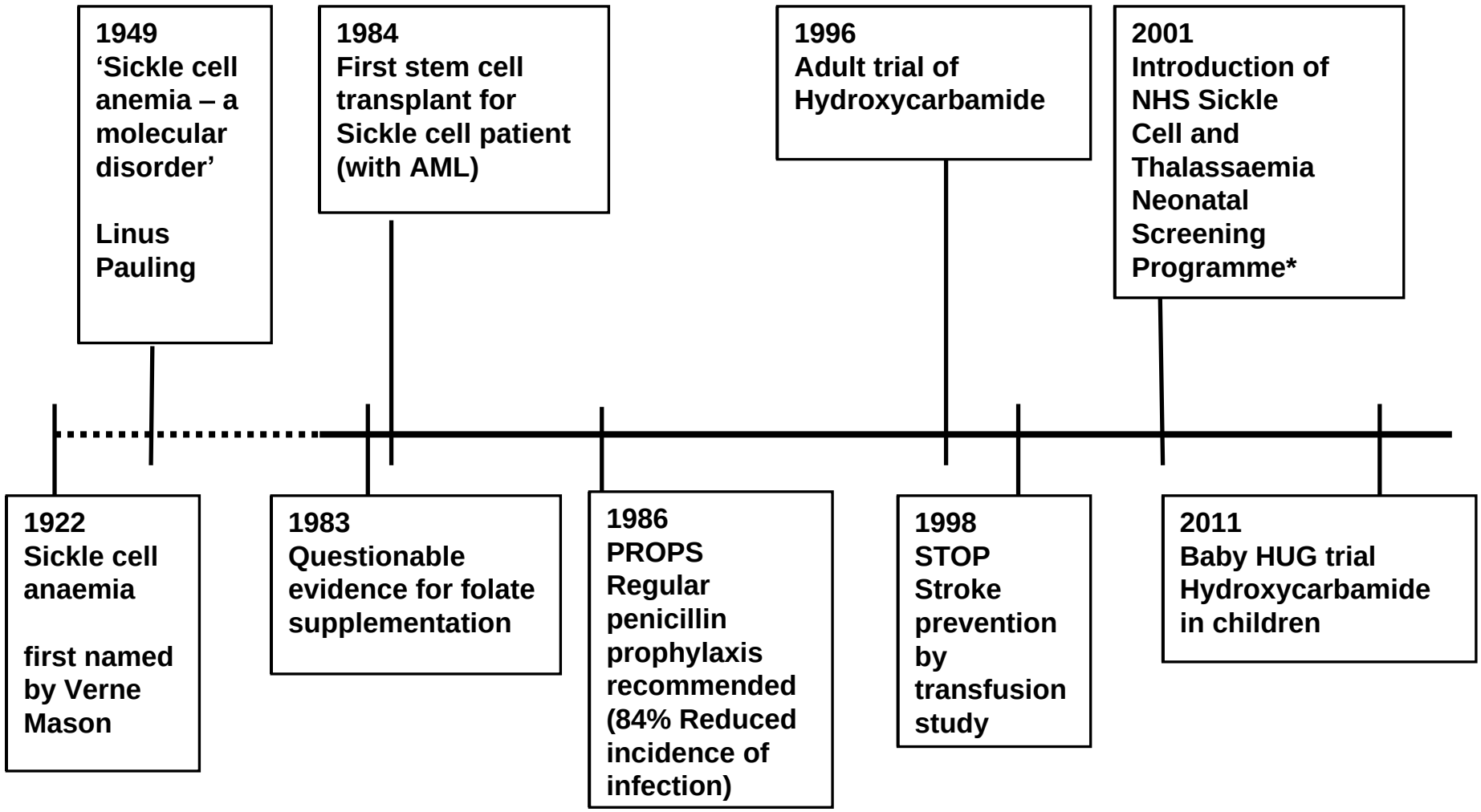
  (not validated in recent studies)

  - lower Hb
  - lower HbF
  - higher white cell count
  - early dactylitis

Aims of sickle-cell modulating therapy

- Reduce the frequency of vaso-occlusive crises
- Slow or halt long term organ damage

Potted history of sickle cell management



Hydroxycarbamide

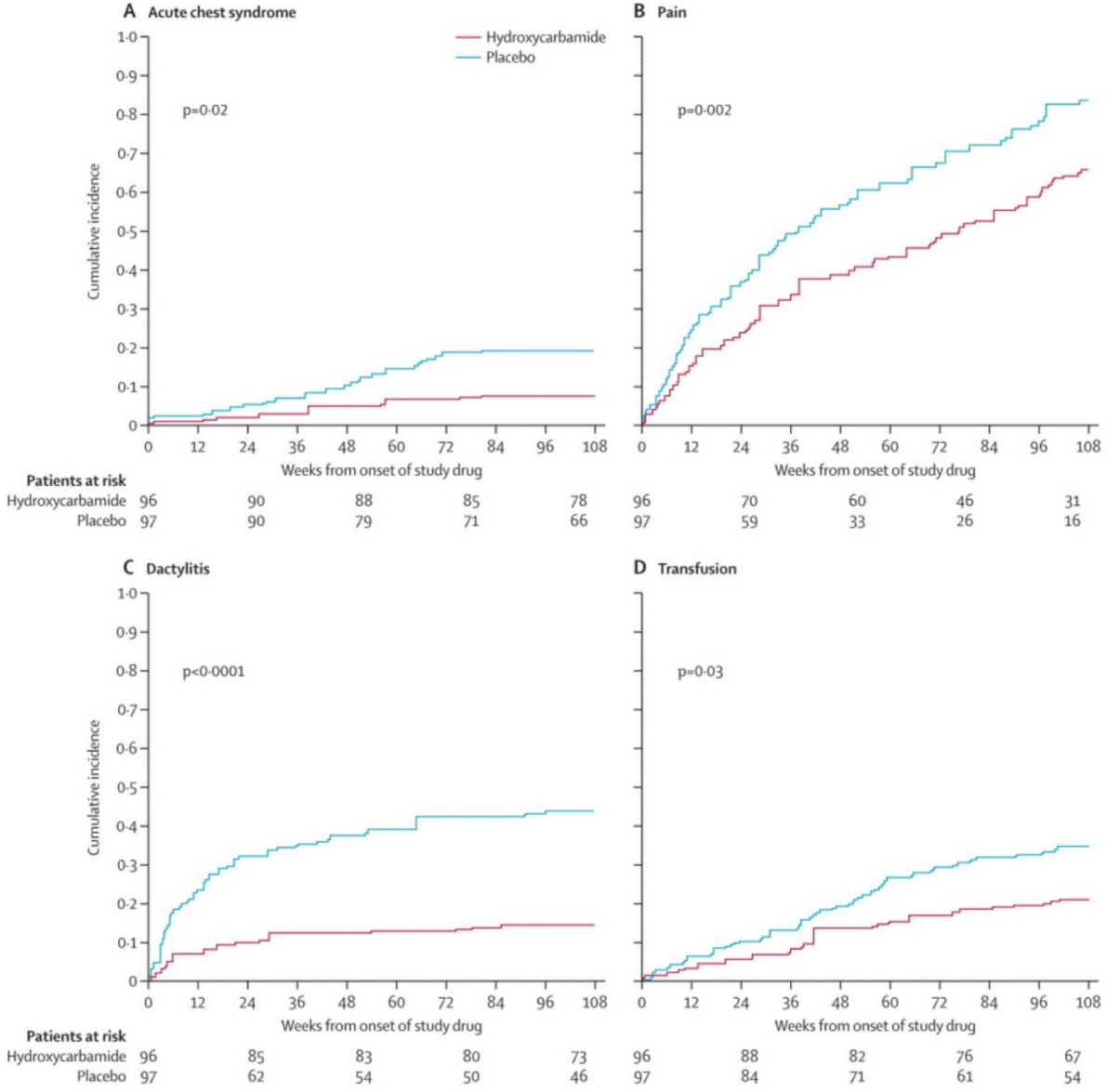
- Antineoplastic drug that inhibits ribonucleotide reductase in DNA synthesis used in myeloproliferative disorders
- Hydroxycarbamide induced marrow suppression leads to
  - proliferation of RBC precursors containing HbF
  - haemoglobin content is increased
  - increased sickle RBC hydration
  - reduction 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

BABY-HUG

Winfred C Wang *et al*
Lancet 2011

- Randomised controlled double blinded trial
- Inclusion criteria
  - sickle cell disease of all severity
  - age 9 – 18 months
  - 193 subjects randomised
- Hydroxycarbamide (20 mg/kg/day fixed dose) or placebo for two years
- Treatment group comparisons were by intention-to-treat analysis

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



Results – organ function

- Secondary measures of spleen, kidney, and central nervous system function suggested benefit, but these results were not significant
- Significant increased total haemoglobin and foetal haemoglobin and lower WBC counts
- No excess or novel toxicities
- Poorly characterised toxicities – leukaemogenesis and impaired fertility

Indications for Hydroxycarbamide use in UK

Main

- ≥ 3 admissions for painful episodes in previous 12 months
- > 1 admission with painful crisis in previous 12 months & symptomatic in community
- Two or more episodes of acute chest syndrome in the last 2 years, or one episode requiring ventilatory support

Other

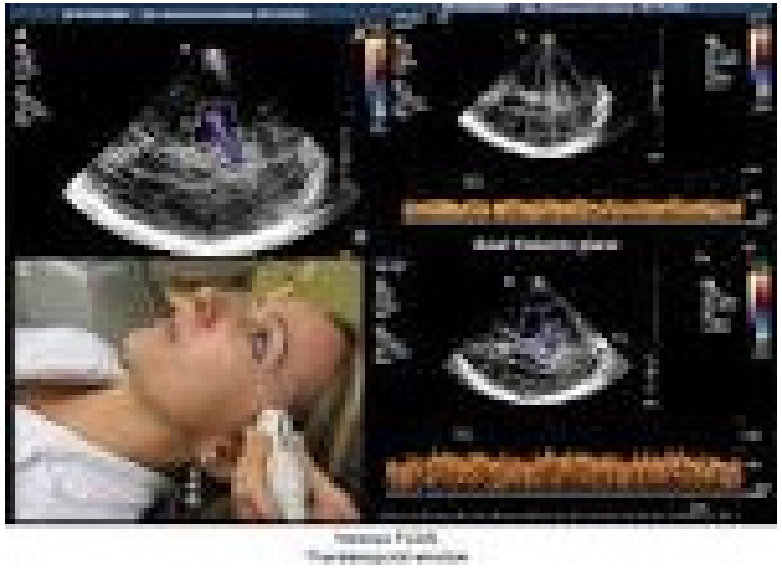
- Chronic symptomatic anaemia
- Priapism
- Nephropathy
- Pulmonary hypertension

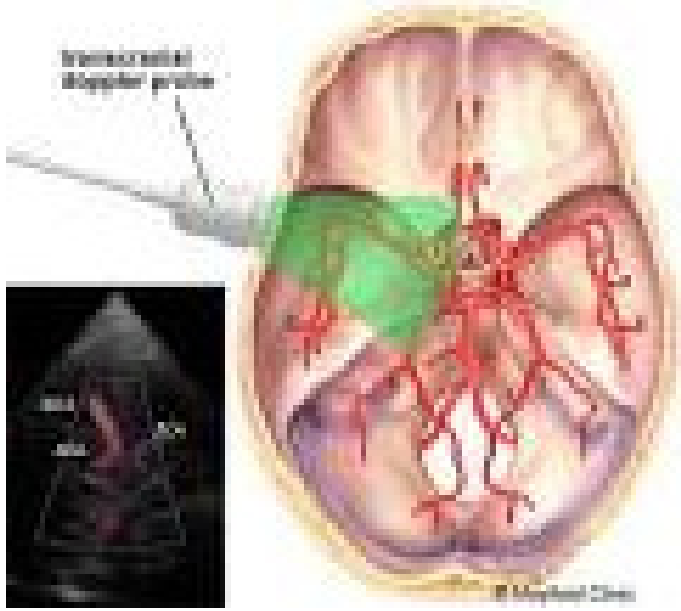
But should we use more liberally? Probably yes

Prophylactic red cell transfusions for prevention of sickle stroke

- STOP study (Stroke Prevention Trial in Sickle Cell Anemia) Adams *et al* 1998
- Prophylactic red-cell transfusions in children identified by transcranial Doppler ultrasonography as at high risk for stroke
- Incidence of stroke decreased from 10% per annum to <1% per annum
- But risks of chronic transfusions
  - Iron loading
  - Alloantibody formation
  - Infection
  - Hospital attendance

Transcranial Doppler Probe





Can you stop the transfusions?

- STOP 2 study (Optimizing Primary Stroke Prevention in Sickle Cell Anemia) Adams *et al* 2005
- Inclusion criteria: Patients on prophylactic transfusions for >30 months for high risk TCD who had reduced blood flow velocity to normal
- Randomised to continue transfusions or discontinue
- 41 children stopped transfusion

  High-risk Doppler results developed in 14 and stroke in 2 others within a mean (±SD) of 4.5 ± 2.6 months of the last transfusion
- 38 children continued transfusion

  No adverse events

Stem cell transplant

The British Paediatric Haematology Forum Recommendations

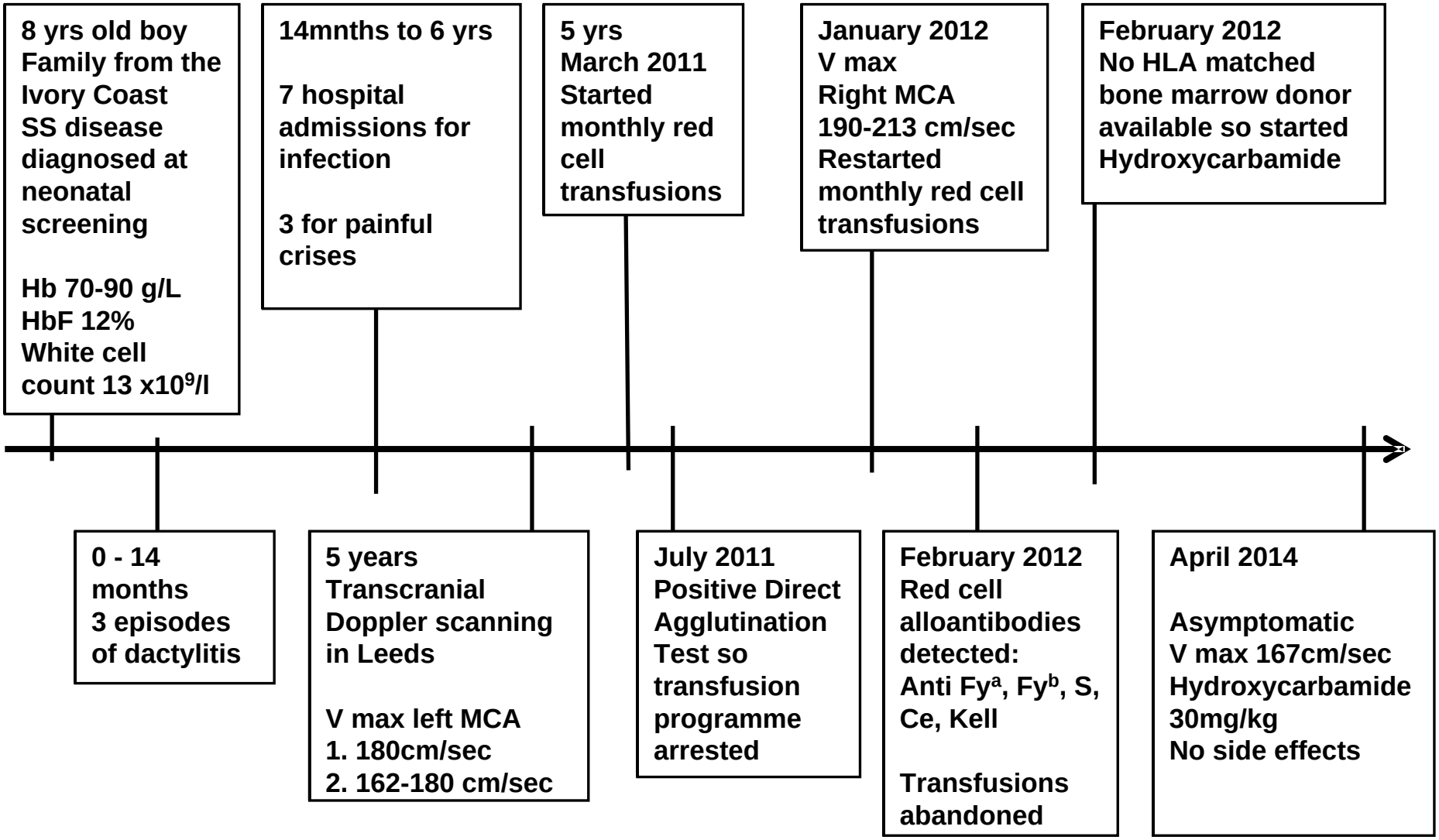
Indications

- <17 years with HLA-identical sibling and informed consent
- One or more of these SCD-related complications:
  - CNS disease
  - Recurrent acute chest syndrome
  - Stage I/II chronic sickle lung disease
  - Recurrent, severe, debilitating pain (>3 hospital admissions/year in 3-4 years)
  - Problems relating to future care – to be decided on case-by-case basis

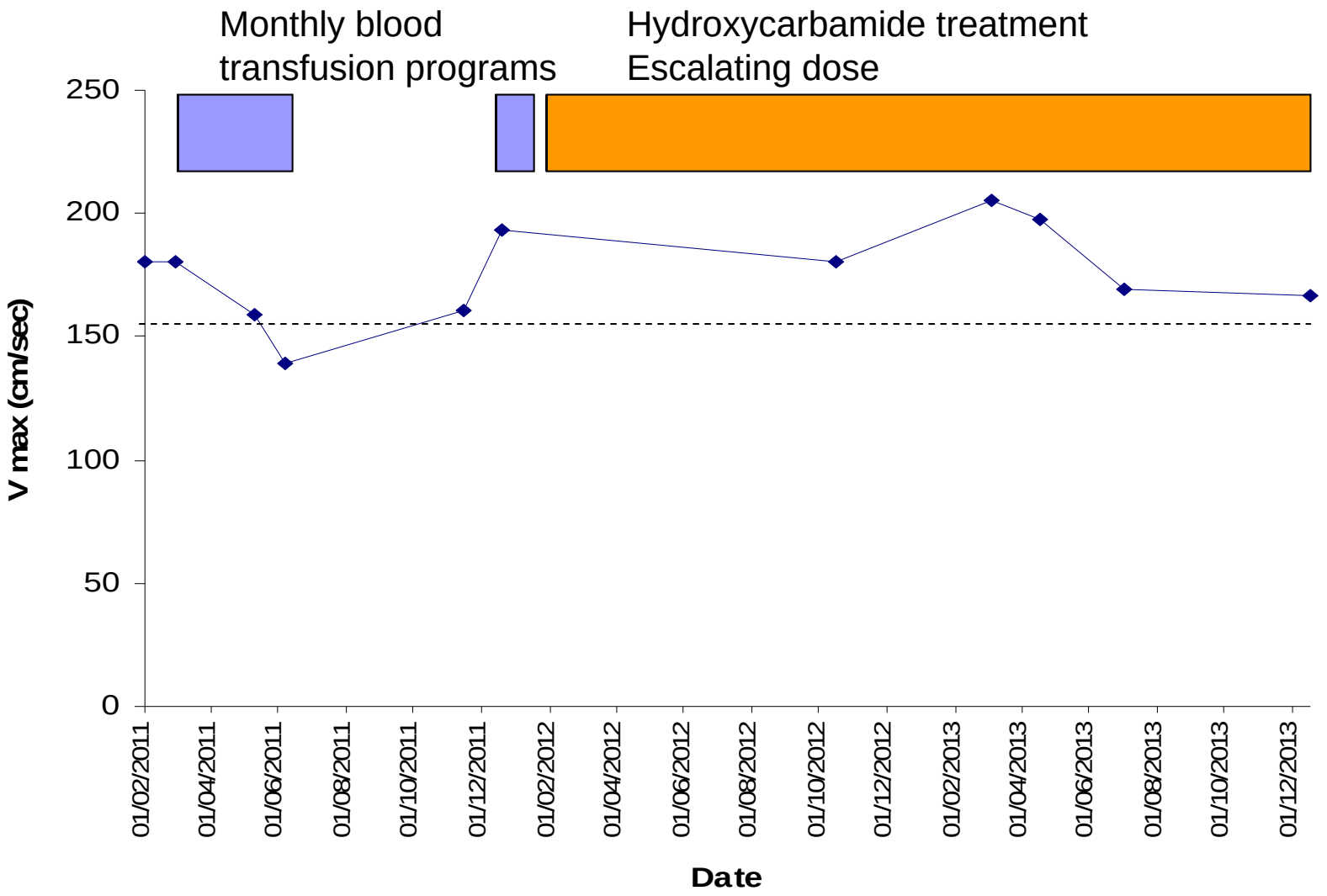
Exclusions

- Donor with a major haemoglobinopathy
- One or more of the following:
  - Karnofsky performance <70%
  - Portal fibrosis (moderate or severe)
  - Renal failure (GFR <30%)
  - Major intellectual impairment
  - Stage III or IV chronic sickle lung disease
  - Cardiomyopathy
  - HIV infection

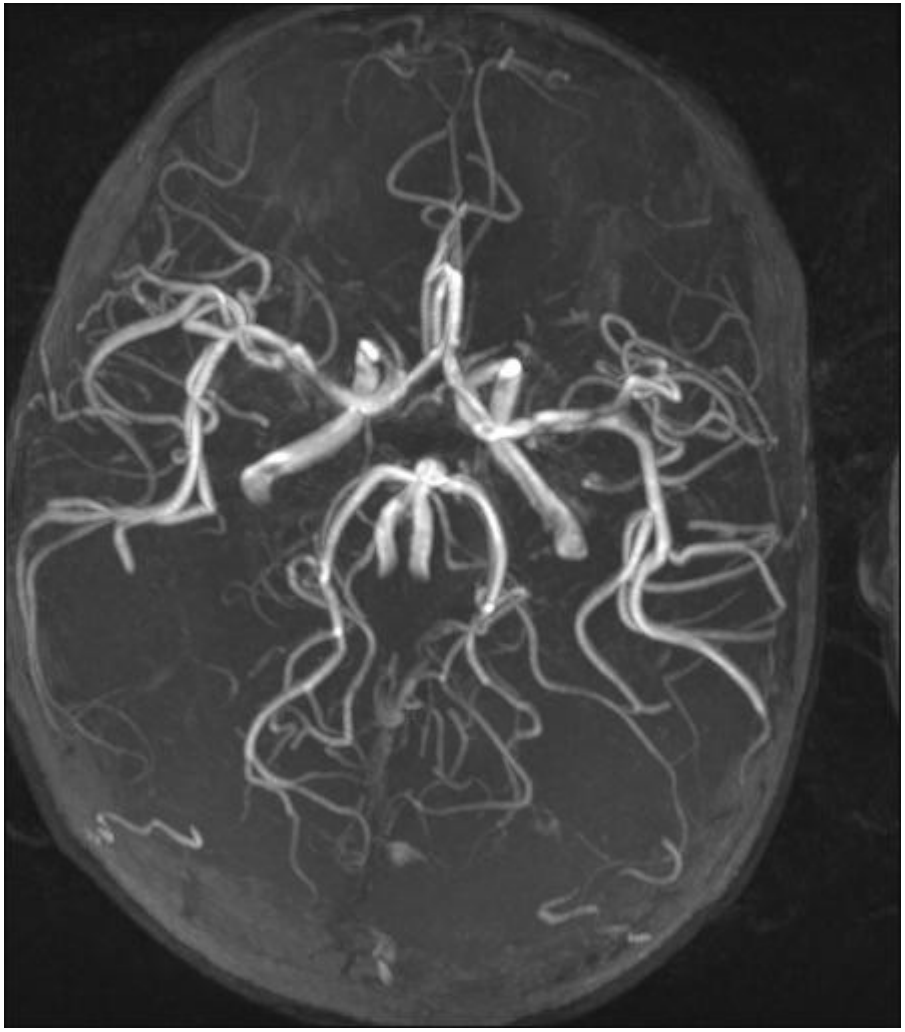
The clinical course of a patient with sickle cell disease



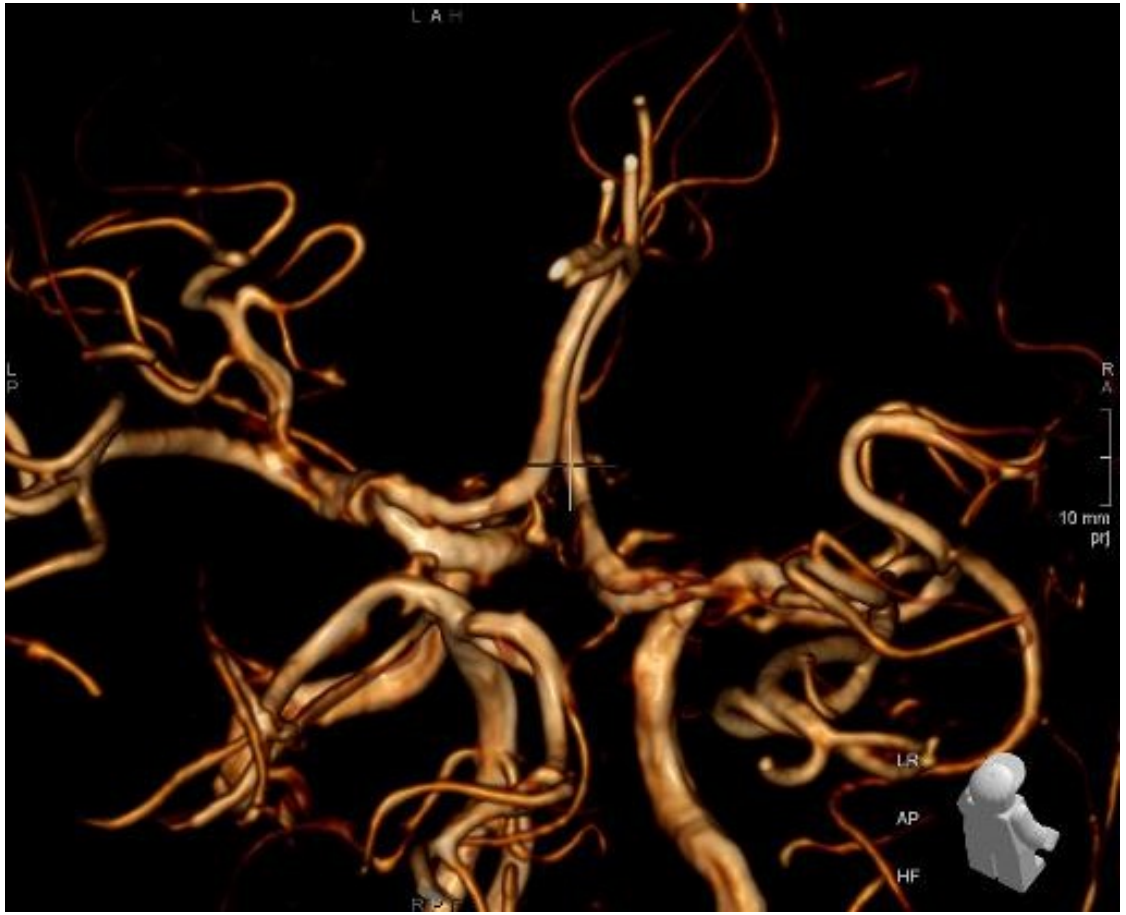
Maximum velocity of cerebral blood flow and interventions



Magnetic Resonance Angiogram

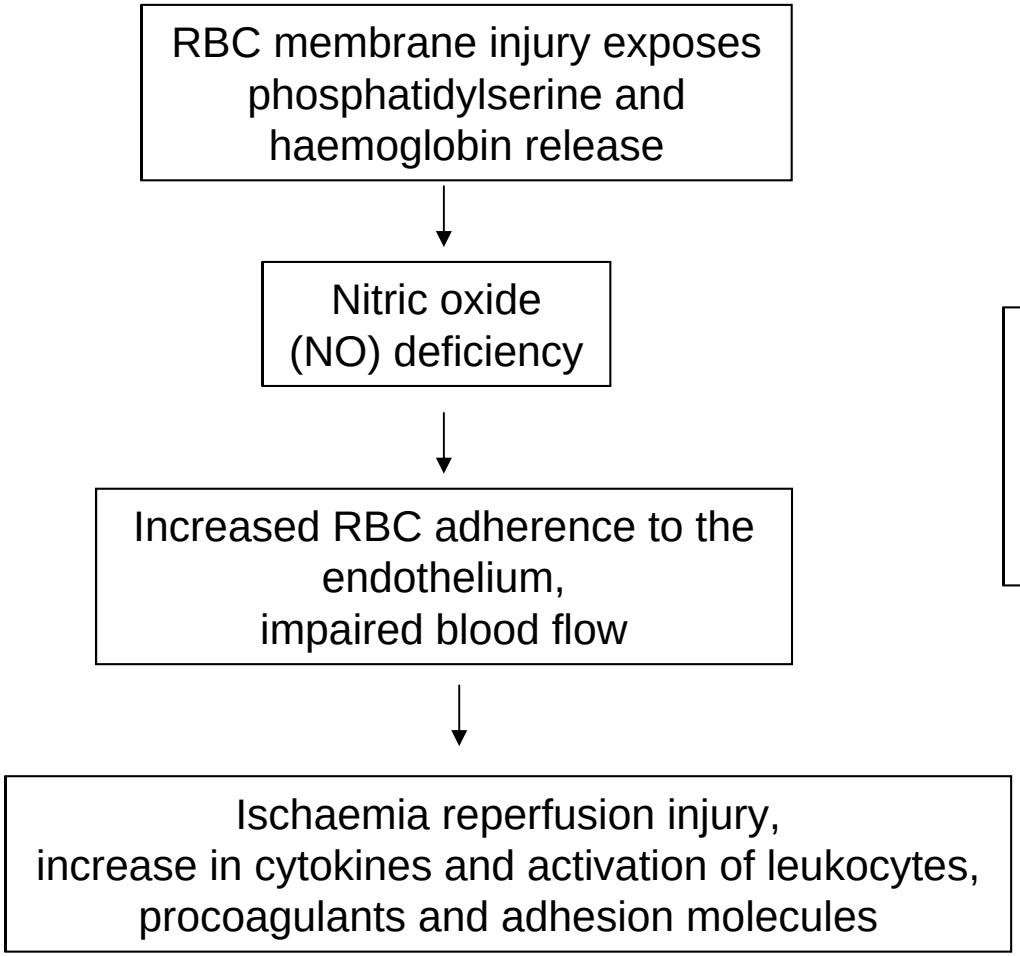


Magnetic Resonance Digital Subtraction Angiogram



Sickle Cell Disease
Potential novel therapies

Pathophysiology of sickle cell organ injury



Cytoprotective mediators such as antioxidants are depleted

Ineffective erythropoiesis partly secondary to functional iron deficiency caused by inadequate circulating transferrin

Sickle Cell Disease
Potential novel therapies

Inhibitors of cellular adhesion (phase 1 and 2 trials)

- GMI-1070, a pan-selectin inhibitor
- Heparin
- Eptifibatide, platelet antagonist
- Propanolol

Anti inflammatories (phase 1 trial)

- Regadenoson $A_{2A}R$ agonist that blocks iNKT cell activation
- Statins
- Zileuton 5-lipoxygenase inhibitor that decreases inflammation
- MP4CO A haemoglobin conjugated with polyethylene glycol and saturated with carbon monoxide

NO-arginine dysregulation (phase 1,2,3 trials)

- L-arginine Substrate of NO that increases NO synthesis
- Tetrahydrobiopterin (R-BH4) Essential cofactor for NO production
- Nitrite, niacin NO donor

Sickle Cell Disease
Potential novel therapies

Oxidative injury (phase 3 trials)

- Oral supplementation of glutamine in SCD

Iron metabolism and erythropoiesis (animal models)

- Transferrin injections
- Jak-2 inhibitors

Sickle cell management - summary

- Previously reactive care to crises
- Last decade exciting new advances to provide primary prevention strategies
- Still need new interventions to intervene in acute crisis
- Possible increasing roles for hydroxycarbamide and stem cell transplant

Haemolytic state

- Shortened half life of red cells
- Compensatory reticulocytosis
- Hyperbilirubinaemia
- Elevated LDH, reduced haptoglobin
- Functional deficiency of nitric oxide
  - Vascular endothelial damage

Potential complications

- Haemolytic state
  - Increased rate of haemolysis
    - Infection
  - Reduced rate of red cell production
    - Virus infection
    - Haematinic deficiency
  - Splenic pathology
    - Increased consumption
    - Reduced splenic function
  - Bile pigment gall stones

Potential complications

- Vaso-occlusive complications
  - Site specific
    - Limbs/skeleton
      - Pain, swelling, heat, bone infarction
      - Dactylitis in infants, stunted digit growth
    - Chest
      - Pain, hypoxia +/- secondary infection
    - Abdomen
      - Pain, ileus
    - CNS
      - Stroke/TIA
    - Priapism

Potential complications

- Vaso-occlusive complications
  - Splenic infarction
    - Overwhelming post splenctomy infection
    - Rationale for national newborn screening program
  - Splenic sequestration
    - Rapidly enlarging spleen
    - Life threatening anaemia
  - Hepatic sequestration
    - Rapidly enlarging liver
    - Liver dysfunction

Potential complications

- Vaso-occlusive complications
  - Ophthalmic
    - Proliferative retinopathy
    - Potential vitreous haemorrhage