Caring for patients with haemoglobinopathies who refuse transfusion

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Contents of Talk

- Sickle cell disease
  - Benefits of transfusion
  - Indications for transfusion
  - Reasons for difficulties giving blood transfusions
  - Adults refusing transfusion
  - Management
    - Discussions
    - Hydroxyurea
    - Erythropoietin
    - Blood substitutes
    - Others
  - Parental objections to transfusion in children
- Thalassaemia
  - Specific issues

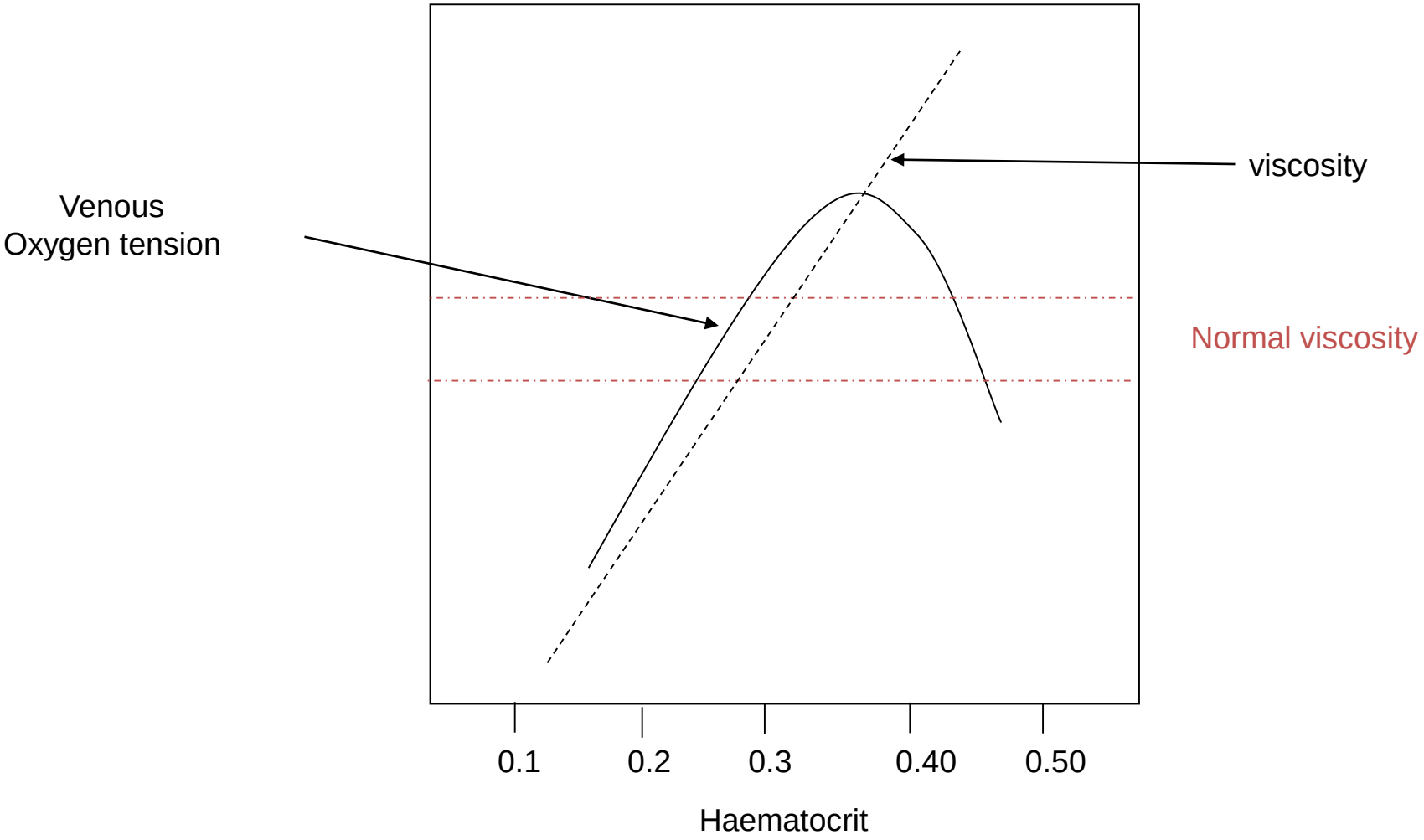
Role of Blood Transfusion in Sickle Cell Disease

- All complications originate from red cells containing HbS
- In theory all complications can be prevented or treated by appropriate transfusion
  - Correction of anaemia
  - Reduction or dilution in number of red cells able to cause vaso-occlusion
  - Suppression of HbS synthesis
- Little good clinical evidence on how to use blood transfusions except in secondary stroke prevention
- No evidence except in sickle cell anaemia (HbSS)
- Very low haemoglobin levels tolerated in sickle cell disease but associated with increased risks

Simple and Exchange Transfusion in SCD

- Choice of simple or exchange transfusion determined primarily by
  - Pretransfusion Hb and HbS% in person receiving transfusion
  - Target Hb post-transfusion
  - Target HbS% post-transfusion
- No intrinsic value to exchange transfusion in sickle cell disease
  - no evidence that removal of plasma or other blood components is of benefit
- Exchange rarely or never appropriate in someone with very low haemoglobin (<5g/dl)
- Exchange usually necessary if starting haemoglobin >9g/dl and need to reduce percentage HbS

Blood Viscosity in HbSS



Relationship between whole blood viscosity, haematocrit and venous oxygen tension in whole blood in HbSS (adapted from Jan et al, 1982)

Indications for Acute Blood Transfusion in SCD

- Acute anaemia
  - Parvovirus B19 infection
  - Acute splenic sequestration
  - Acute hepatic sequestration
  - Need for transfusion determined by symptoms
  - Particular caution if evidence of cerebrovascular disease
  - Transfusion usually appropriate if Hb<5g/dl
  - Typically transfused to steady-state Hb, but ideally avoid need for repeat transfusion

Indications for Acute Blood Transfusion in SCD

- Acute chest syndrome
  - New pulmonary shadowing on X ray of someone with SCD
  - Typically accompanied by pain, fever, falling Hb
  - Trend towards treatment with early simple transfusion
    - Typically aim to increase Hb to 9-10g/dl and reduce HbS%
  - Exchange transfusion may be necessary
    - high Hb e.g. HbSC disease
    - Rapid deterioration suggesting need for HbS<30%
    - Evidence of underlying cerebrovascular disease
- Acute neurological symptoms
- Multiple organ failure
  - Target HbS<30%
- Preoperatively

Preopertaive Blood Transfusion

- Target HbS <30% generally accepted for high risk surgery
  - Cardiovascular surgery
  - Neurosurgery
  - Prolonged anaesthesia (expected >4 hours)
- For moderate and low risk surgery
  - Need for transfusion assessed on individual basis
  - No benefit of exchange transfusion over simple transfusion for standard patients
  - Probable benefit of simple transfusion to target Hb of 10g/dl if Hb<9g/dl shown in TAPS study
    - No transfusion: 13/33 had serious complications
    - With transfusion: 5/34 had serious complications (P=0.023)

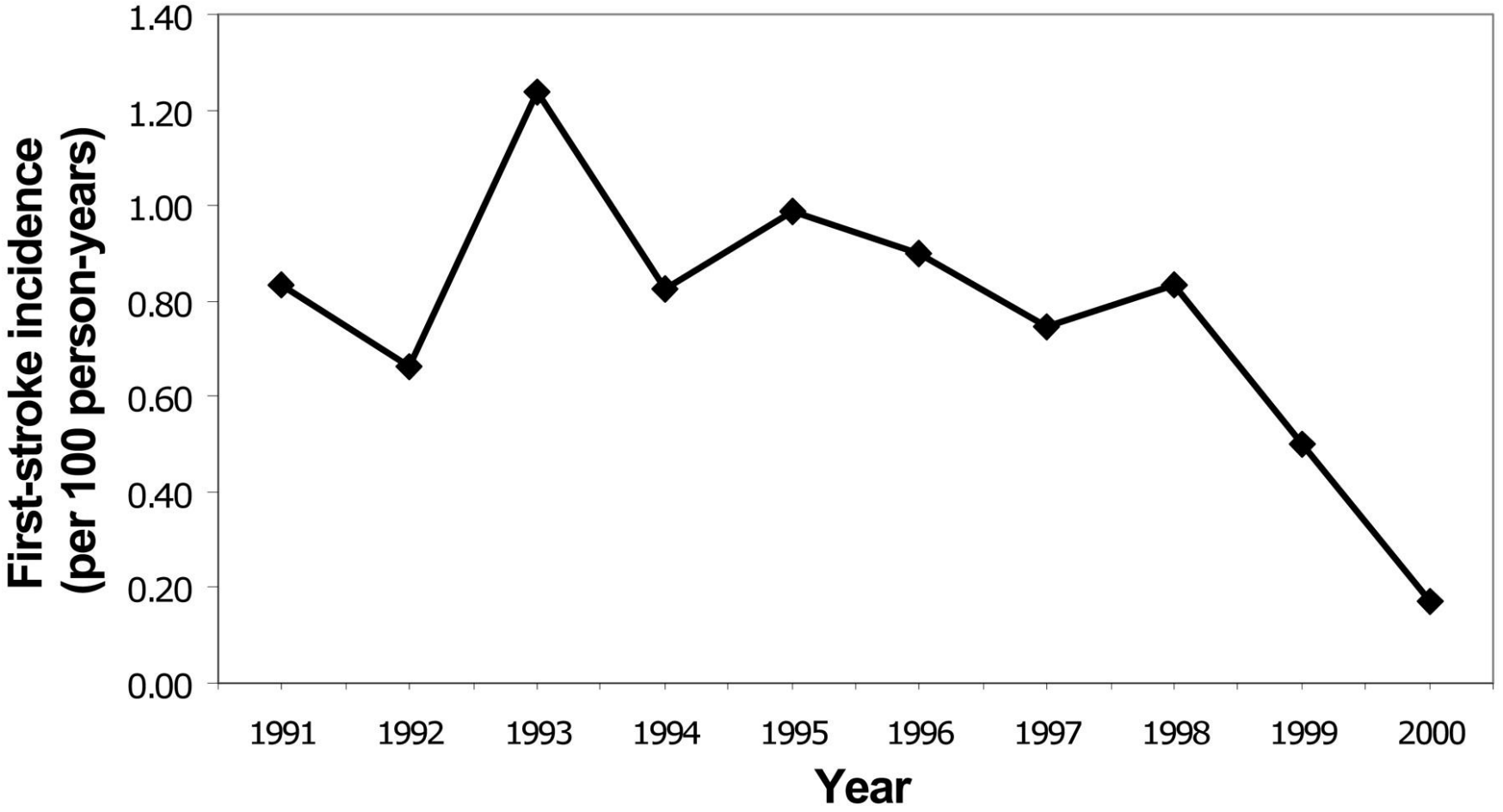
Indications for Acute Blood Transfusion in SCD

- There is no good evidence for the use of acute blood transfusions for the following acute complications
  - Acute pain
  - Osteomyelitis
- Controversial indications
  - Priapism
    - No good evidence and case reports suggest lack of efficacy and possible increased neurological complications for partial exchange transfusions
    - Possible benefit from full automated exchange
    - Possibly necessary as preoperative preparation
  - Pregnancy
  - Leg ulcers
  - Prior to intravenous contrast media

Indications for Regular Blood Transfusions in SCD

- Established role in primary and secondary stroke prevention
- Possible role in
  - Recurrent episodes of acute chest syndrome not responding to hydroxyurea
  - Recurrent episodes of acute pain not responding to hydroxyurea
  - Significant or progressive organ damage
    - Chronic sickle lung
    - Pulmonary hypertension
    - Progressive hepatic damage
    - Progressive renal failure
  - Avascular joint necrosis
  - Leg ulcers
  - Frequent episodes of acute pain in pregnancy
  - Recurrent splenic sequestration in young children

Incidence rates of first stroke in Californian children with SCD



Fullerton, H. J. et al. Blood 2004;104:336-339

Reasons for difficulties giving blood transfusions in SCD

- Safe supply of blood is not available
  - Majority of patients in the world do not have adequate access to safe blood for transfusion
  - Only 20-50% transfusion requirements are met by current donation rates across Africa
  - Increased risks of infection transmission and alloimmunization
- Alloantibodies making it very difficult to find compatible blood
  - Multiple alloantibodies
  - Antibodies against very common antigens
    - Anti-U antibodies
- Difficult venous access
- Refusal by patient or parents/guardians

Reasons for objecting to blood transfusion

- Fear of risks, side-effects, complications
- Religious beliefs
  - Jehovah's Witnesses
    - 7.5 million worldwide
    - Approximately 140 000 in UK
- Other strongly held beliefs
  - Increasingly common
- Impaired capacity to take decisions
  - Psychiatric illness
  - Delirium
  - Dementia
  - Cognitive impairment

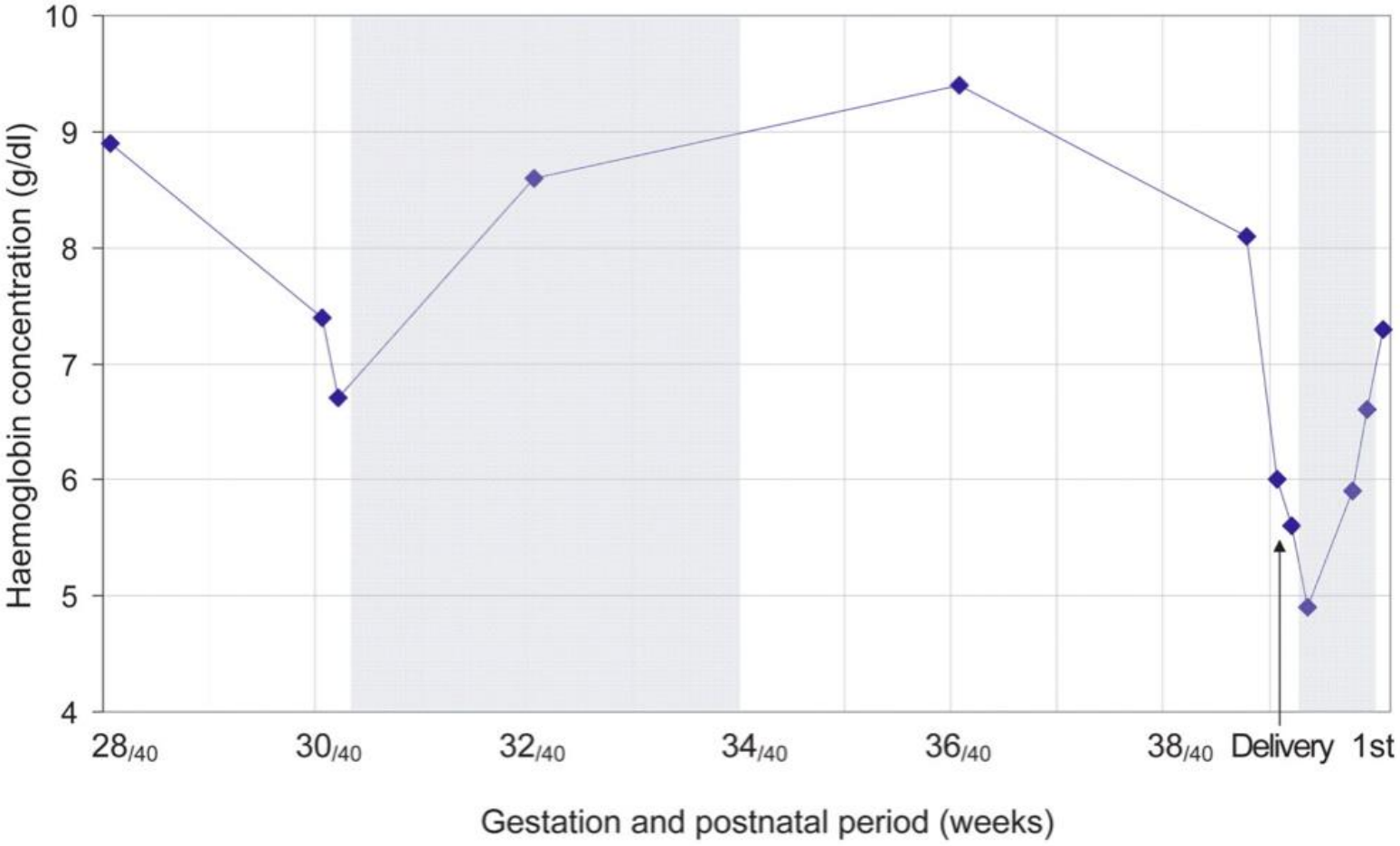
Adult patients refusing blood transfusion

- In UK, legally able to refuse life-saving treatment if at least 18 years old
- Need to ensure patient has capacity to take decision
  - Formal assessment by psychiatrist
- Consult with hospital legal advisers
- Hospital may appeal to high court if decision likely to result in death of long-term morbidity if there is time
- Potential involvement of Jehovah's Witness Hospital Liaison committees
- In urgent situations requirement to respect patient's wishes

Acute Management

- Optimise medical treatment
  - Oxygen
- Start erythropoietin
  - Typically high doses used
    - For exampe 100 -200 IU/kg 2-3 times per week
- Intravenous iron usually started with erythropoietin
  - Accompanying erythropoietin injection
- Consider hydroxyurea if not already taking it
  - Further boost to haemoglobin
  - Reduction in sickling complications
  - Caution to avoid myelosuppression
    - 10-20mg/kg depending on reticulocyte count

Erythropoietin and iron in pregnancy



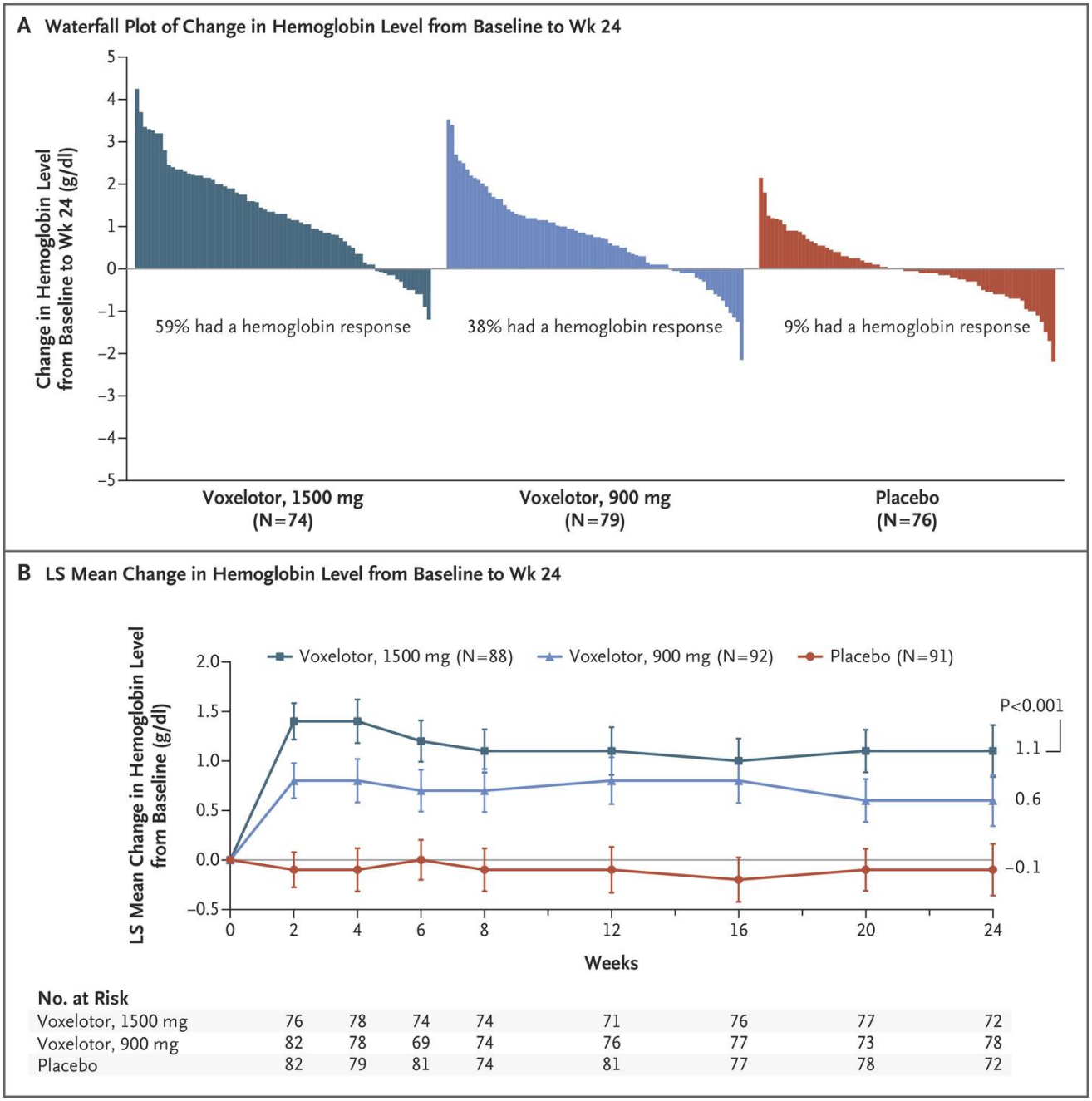
Tan et al. J Obstet Gynaecol 2007, 27, 82-3.

Acute Management

- Synthetic blood substitutes
  - Bovine haemoglobin
    - Pegylated carboxyhaemoglobin (Sanguinate)
      - Orphan drug designation in USA for SCD
      - FDA-approved emergency access for profound anaemia
      - Accepted by some Jehovah's Witnesses
      - Phase II trial in SCD in USA to treat acute vaso-occlusive pain
    - Polymerised bovine haemoglobin (HBOC-201, Hemopure)
      - Anecdotal reports of use in Jehovah's Witnesses with SCD
      - Three patients with acute chest syndrome treated and survived
        - » All three had severe anaemia – Hb<4g/dl
        - » 20 units HBOC-201 given

Acute Management

- Perfluorocarbons
  - Liquids with high gas solubility and potential to deliver oxygen in vivo
  - Need high concentrations of inhaled oxygen to deliver adequate oxygen to tissues
  - None commercially available now because of limited efficacy and toxicity
- Voxelotor
  - Limited ability to increase Hb in SCD over 7 or more days
  - Unclear if oxygen delivery is improved
- Induced coma to minimise oxygen demands
  - Anecdotal reports



Vichinsky at al, NEJM 2019

Acute management in adults

- Identify potential problem at an early stage
- Discuss with patient and clarify wishes
- Formal assessment of mental capacity if decision likely to result in death or disability
- Discuss with hospital legal advisers
- Optimise oxygenation and medical care
- Start erythropoietin and intravenous iron at an early stage
  - Investigate possibility of acellular haemoglobin-based oxygen carriers

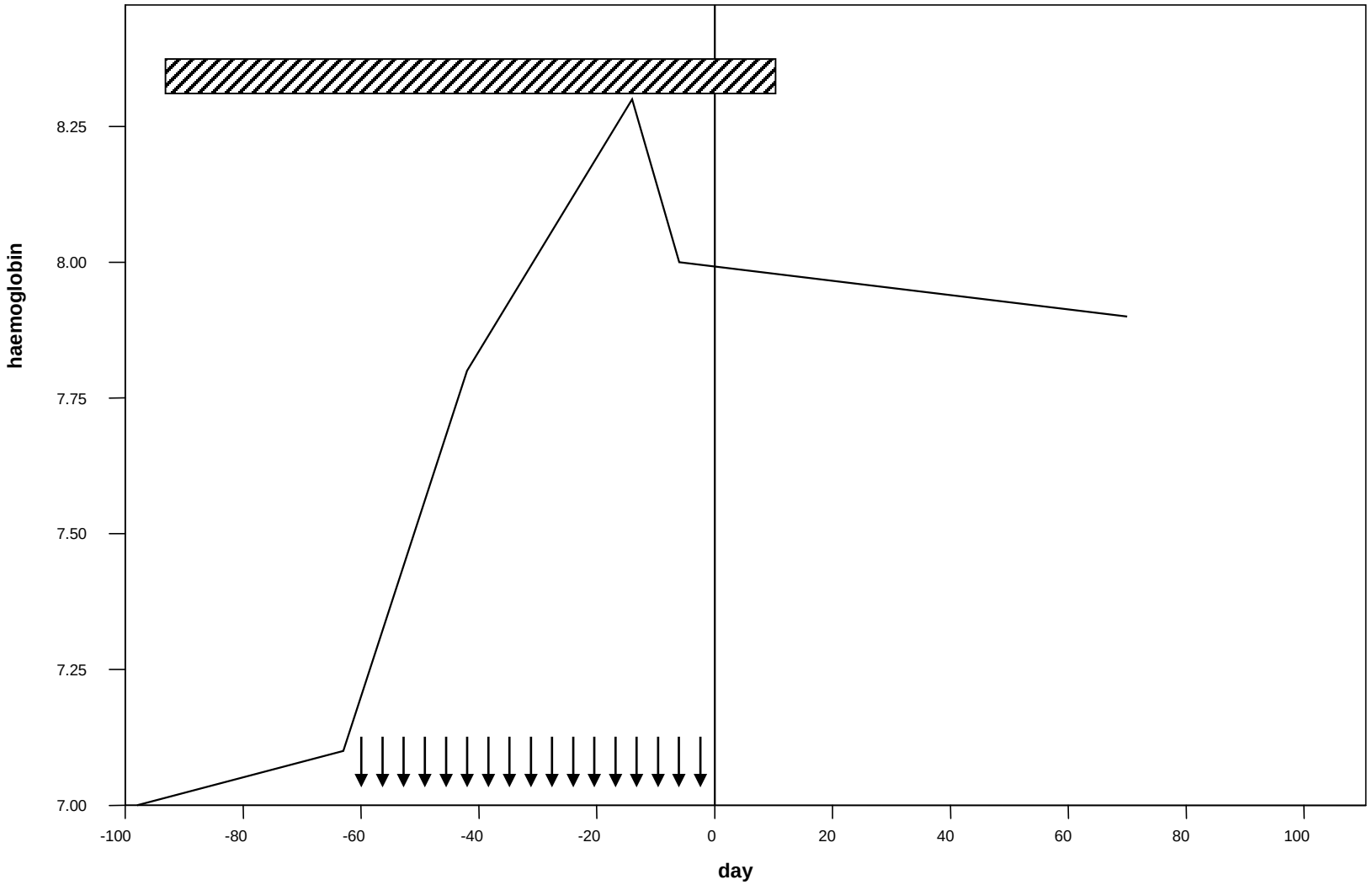
Management of anaemia in children whose parents object to blood transfusion

- Medical and legal obligation to provide best possible care to child (age<16 year old)
  - Problems when this does not coincide with the parents wishes
- In emergency, life-threatening situation
  - Start erythropoietin early if need for transfusion seems likely
  - Explain to parents and child, but consent not necessary
  - Possibly discuss with hospital solicitor and/or apply to court if time permits
  - Proceed with blood transfusion as clinically indicated
  - Cover blood and giving set during transfusion
  - If possible give sufficient blood to avoid the need for a second transfusion

Management of anaemia in children whose parents object to blood transfusion

- Preoperative transfusions
- Discuss with parents and child
- If high risk essential surgery requiring exchange transfusion
  - Discuss with hospital legal team and apply for court order if time
  - Exchange as required
- Moderate or low risk surgery
  - Advise transfusion is optimal preparation
  - Assess individualized risks of patient and surgery
    - Consider preoperative erythropoietin and hydroxyurea
- Consider risks of delaying surgery until patient is 18 years old and can consent to or refuse treatment

Hydroxyurea and EPO in Preoperative Management



Management of abnormal Transcranial Doppler velocities in children whose parents refuse transfusion

- Indication for long-term transfusions in children with abnormal TCDs but very difficult if parents/child refuse transfusion
- Possible options
  - Discuss with families
  - Assess severity of vasculopathy with MRI/MRA, cognitive testing
  - Consider hydroxyurea at maximum tolerated dose depending on severity of condition
    - Frequent re-evaluation for progressive vasculopathy
  - Apply for court order to give transfusions
    - But evidence in favour of transfusion not overwhelming
    - Very difficult to enforce in long term
  - Consideration of haematopoietic stem cell transplantation

Young adults <18 years old

- Teenagers age > 16 years and those with Gillick competence can agree to treatment, including transfusion, against their parents' wishes
- Cannot refuse life-saving treatment until age 18 years
  - Life-saving treatment given as required
  - Transfusion usually decided by Family Court if time permits
  - Possibility of delaying procedure requiring surgery until patient 18 years old if appropriate

Thalassaemia

- Overall situation similar to sickle cell disease
- Difficult starting regular transfusions in transfusion-dependent thalassaemia
  - Decided by Family/High Court
- Potential limited role for hydroxyurea, erythropoietin and luspatercept

Summary

- Identify potential problem at an early stage
- Discuss with patients and families
- Seek legal advice but try and avoid court order unless essential
- Respect adult wishes to avoid transfusion
- Provide optimal treatment to children, whilst trying to be sensitive to parents wishes