Summary
Hyperhaemolysis is a well-recognized but rare complication of blood transfusion in patients with sickle cell disease (SCD).

This Guideline describes the management of this complication, including the use of immunoglobulin, which is a ‘blue’ indication according to the Clinical Guidelines for Immunoglobulin use.

Background
Hyperhaemolysis is characterised by rapid haemolysis following a blood transfusion, and the post-transfusion haemoglobin (Hb) will often be lower than the pre-transfusion Hb, implying the destruction of recipient as well as donor red cells. It may be associated with a fever and with pain typical of sickle cell disease. The direct antiglobulin test (DAT) is often negative and no new red cell allo-antibodies are identified. There may be a reticulocytopenia.

Additional transfusion has been associated with increasing haemolysis and worsening anaemia, and should be avoided if possible. The haemolysis can be treated with intravenous immunoglobulins (IVIg) and IV Methylprednisolone.

In cases where there is very rapid haemolysis and critical anaemia, additional transfusion will be required and this should be preceded by IVIg and IV Methylprednisolone. Erythropoietin, iron replacement, B12 and folate replacement should also be considered. Hyperhaemolysis can recur following blood transfusions several months or years after the initial episode, and patients should be retreated with IVIg and Methylprednisolone prior to future transfusion.

Patient Groups
1) IVIg and IV Methylprednisolone should be considered in patients with SCD who present with evidence of severe haemolysis following a blood transfusion.

2) Patients with SCD and hyperhaemolysis who continue to haemolyse despite initial treatment and have worsening anaemia may need a further transfusion. This should be preceded by IVIg and IV Methylprednisolone.

3) Patients with SCD and a history of hyperhaemolysis are at risk of recurrence and if transfusion is necessary should be pre-treated with IVIg and IV Methylprednisolone.
**Diagnosis**

Hyperhaemolysis should be considered in any patient with SCD who presents with increasing haemolysis after a blood transfusion. It typically presents at 1 week post-transfusion, but may occur sooner than this if the patient is re-challenged with transfusion. Clinical features: Increasing jaundice, dark urine (‘coca-cola’ coloured), anaemia. They may also have a fever, back, leg or abdominal pain, hepatomegaly or hepatic discomfort.

Differential diagnosis is a delayed haemolytic transfusion reaction due to new allo-antibodies and blood must be sent to the transfusion laboratory for the investigation of new allo-antibodies.

**Investigations:**

FBC: Worsening anaemia – Hb may often fall to below the pre-transfusion level

Haemolysis: raised bilirubin, raised LDH

Reticulocytes: may be raised (in keeping with haemolysis) or decreased, due to suppression of red cell production

Group and antibody screen

Direct Antiglobulin Test (DAT): May be positive if hyperhaemolysis is associated with a new allo-antibody, but may be negative.

Haemoglobin electrophoresis: A rapid increase in %HbS indicates haemolysis of transfused blood

Ferritin, B12 and Folate levels: May aid in decisions about replacement

**Treatment**

Discuss with Haematology Consultant (Contact the on-call Consultant if out-of-hours)

Prescribe Folic acid 5mg.

Primary treatment is with immunosuppression: IV Methylprednisolone and IVIg

Consider treatment with erythropoietin and IV iron replacement

Consider B12 replacement.

Blood transfusion should only be given after discussion with the Haematology Consultant. Blood transfusion may be necessary if clinically indicated (profound symptomatic anaemia)

Phenotyped blood should be given (CDE and Kell matched).

**Dosage - consult local formularies and BNF to confirm current dosing recommendations**

Intravenous immunoglobulin (IVIg) – Adult and paediatric dose (Unlicensed indication)

1g/kg once daily for 2 days (total dose = 2g/kg)

Administration, ordering and preparation as per local guidance

**Methylprednisolone**

Adults: 500mg IV for 2 days

Paediatrics 10mg/kg IV for 2 days (maximum dose 500mg)

Review dose after 2 days.
**Erythropoietin**  
Adults: NeoRecormon® 300units/kg subcutaneously once daily for 5 days followed by 300units/kg once daily on alternate days (i.e. 3 times per week) (Ref 2: Guy’s and St.Thomas’ guidelines for the management of hyperhaemolysis)

Paediatrics: recombinant EPO – Consult spc and published information (Ref 3)

**Ferritin, B12 and Folate**  
If ferritin <100µg/l - Prescribe IV iron as per local protocol  
If ferritin >100µg/l - Prescribe oral iron

If B12 <200 ng/l or active B12 <70 pmol/L - prescribe Hydroxycobalamin 1mg IM 3 times a week for 2 weeks

Folate: Folic acid 5mg once daily

**Management of refractory cases:**  
For patients with ongoing haemolysis refractory to treatment as outlined above, monoclonal antibody treatments may be considered after specialist discussion and advice.

**Monitoring of treatment:**  
Haemoglobin:  
Target is return of haemoglobin to baseline.  
Stop EPO if haemoglobin returns to baseline or if lack of response after full treatment dose.

**Monitoring of this Guideline**  
Use of IVIg for this indication will be monitored via the DH Immunoglobulin Demand Management Programme Database.

**References**  
2. Summary tables - Page 20
3. Guidelines for the management of hyperhaemolysis in patients with Sickle Cell Disease, including the use of intravenous immunoglobulins (IVIg) – Guys and St.Thomas’ NHS Foundation Trust
7. Talano JM, Hillery CA, Gottschall JL, Baylerian DM, Scott JP. Delayed haemolytic Transfusion


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NOTE
This guideline is not intended to be construed or to serve as a standard of care. Standards of care are determined on the basis of all clinical data available for an individual case and are subject to change as scientific knowledge and technology advance and patterns of care evolve. Adherence to guideline recommendations will not ensure a successful outcome in every case, nor should they be construed as including all proper methods of care or excluding other acceptable methods of care aimed at the same results. The ultimate judgement must be made by the appropriate healthcare professional(s) responsible for clinical decisions regarding a particular clinical procedure or treatment plan. This judgement should only be arrived at following discussion of the options with the patient, covering the diagnostic and treatment choices available. It is advised, however, that significant departures from the national guideline or any local guidelines derived from it should be fully documented in the patient’s case notes at the time the relevant decision is taken.