South Thames Sickle Cell & Thalassaemia Network

Guideline for the management of post transfusion hyperhaemolysis in patients with Sickle Cell Disease

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Nov 2014	Department of Health Clinical Guidelines for Immunoglobulin Use for this indication has changed from grey to blue
September 2020	NHSE Commissioning guidelines on use of Eculizumab/Rituximab in delayed Haemolytic Transfusion Reaction/Hyperhaemolysis in Haemoglobinopathy patients

STSTN Clinical Guidelines Writing Group

All guidelines have been peer-reviewed and agreed to be published by the relevant lead consultants in the network.

Summary

Delayed haemolytic transfusion reaction (DHTR) and Hyperhaemolysis are a well-recognised but rare complication of blood transfusion in patients with sickle cell disease (SCD).

DHTR is characterised by a significant drop in haemoglobin (Hb) within 21 days of transfusion in the absence of an alternative cause. Some patients can additionally develop post transfusion hyperhaemolysis, where both recipient and transfused red cells are destroyed, leading to a haemoglobin (Hb) level lower than that pre-transfusion. It may lead to severe life threatening anaemia.

This Guideline describes the management of this complication, including the use of immunoglobulin which is a blue indication according to the Department of Health Clinical Guidelines for Immunoglobulin Use, and of Eculizumab/Rituximab.

Main recommendations:

1) IVIg and IV methylprednisolone should be considered for patients with SCD who present with evidence of severe haemolysis *following* a blood transfusion, in addition to optimal supportive treatment.

2) Patients who continue to haemolyse briskly despite first line treatment with IVIg and Methylprednisolone or who develop multi-organ failure should be considered for Eculizumab therapy

3) Rituximab should be considered for patients presenting with post transfusion hyperhaemolysis who require further transfusion due to worsening anaemia

4) In patients with a past history of post transfusion hyperhaemolysis who require transfusion (planned elective or acute), this can be attempted with further IVIg and methylprednisolone cover, discuss cases with a consultant haematologist experienced in the management of sickle cell disease.

5) Rituximab can be given to cover essential blood transfusion in patients who require transfusion (planned elective or acute),who have previously haemolysed *despite* the pre administration of IVIgs and methylprednisolone.

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BACKGROUND

Blood transfusion is an important treatment in the management of patients with sickle cell disease (SCD), however about one third of transfused SCD patients develop antibodies to red cell antigens, becoming allo-immunised, and around 10% develop the most serious consequence of this allo-immunisation which is a delayed haemolytic transfusion reaction (DHTR). Allo-immune DHTR is usually characterised by an extravascular haemolytic process without frank haemoglobinuria, which is associated with preferential destruction of the transfused haemoglobin A (HbA) and a corresponding increase in the patient's haemoglobin S (HbS%), a new alloantibody is usually detected.

In SCD patients presenting with DHTR, the patient's haemoglobin level may fall *below* the pre-transfusion baseline, suggesting destruction of patient's own RBCs as well as transfused RBCs (so called 'bystander haemolysis'). The differential diagnoses for this presentation includes a coincidental severe sickle episode with brisk haemolysis; as well as other causes of haemolysis such as G6PD crisis; bleeding; and post transfusion hyperhaemolysis – this is a particularly severe form of DHTR which can occur in the absence or presence of a demonstrable antibody mediated allo-immune reaction.

Hyperhaemolysis is characterised by rapid intravascular haemolysis with haemoglobinuria and usually occurs 4-14 days after the initial transfusion, although it can be as late as 21 days after transfusion. It may be associated with a fever, pain typical of sickle cell, and occasionally may also be associated with multi organ dysfunction and lead to death. The direct antiglobulin test (DAT) may be either negative or positive and new red cell allo-antibodies are not usually identified, but may be present and there may be a reticulocytopenia.

The pathogenesis of hyperhaemolysis remains unclear but appears complex, including bystander haemolysis whereby there is 'immune' haemolysis of cells negative for the antigen against which an antibody response is directed. Activated macrophage destruction and reticulocytopenia are likely secondary to immune destruction.

Hyperhaemolysis can recur in patients following blood transfusions several months or years after the initial episode.

DIAGNOSIS

Hyperhaemolysis should be considered in any patient with SCD who presents with increasing haemolysis after a blood transfusion. It typically presents 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, report sickle cell pain in any part of their body including abdominal pain, they may additionally have hepatomegaly or hepatic discomfort.

INVESTIGATIONS:

FBC: worsening anaemia – Hb typically falls below the pre-transfusion level.

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

Other markers of Haemolysis: Raised Bilirubin
Raised LDH

Direct Antiglobulin Test (DAT): Usually negative but can be positive, transfusion laboratory should send for an eluate if DAT is positive.

Group and screen: New allo-antibodies may be found but are usually absent.

Haemoglobin S%: this should be sent on initial presentation and repeated after 24 hours if HbA is present, how often this test is repeated thereafter will be determined by the haematology consultant/paediatric sickle consultant managing the case, although daily HbS levels until the diagnosis is established are ideal.

Historical alloantibodies: check with transfusion laboratory, who can liaise with previous Trusts the patient has been managed in and the Sp-ICE system for previously detected antibodies to ensure the transfused units did not contain corresponding antigens.

Urine HPLC: if available, can be useful in demonstrating presence of HbA in urine as well as HbS

Extended Red cell phenotype/genotype: if an extended red cell phenotype has previously not been sent then consider sending a red cell genotype

TREATMENT

- Admit all SCD patients in whom DHTR and or Hyperhaemolysis is suspected
- Commence standard supportive management including analgesia, hydration, antibiotics and oxygen therapy as required.

- Minimise phlebotomy and consider using paediatric specimen collection bottles for all tests.

- **Primary treatment** is with intravenous methylprednisolone and intravenous immunoglobulin (IVIg):
    - **IVIg**: Adult and paediatric dose (Blue indication on National Prescribing Guidance = medium priority): 1g/kg once daily for 2 days (total dose = 2g/kg). The administration and choice of preparation should be as per local Trust guidance. Round the dose to nearest vial size (5g, 10g and 20g vials available).
    - **Methylprednisolone:**
        - Adults: 500mg IV for 2 days.
        - Paediatrics: 10mg/kg IV methylprednisolone for 2 days (maximum dose 500mg per dose).
        - The dose should be reviewed after 2 days and tailing considered

- Start erythropoietin (EPO) in the absence of contraindications for patients with significant anaemia (<20g/l below their normal baseline or <70g/l). Prescribe NeoRecormon 300 iu/kg once daily for 5 days, then 300 iu/kg once daily on alternate days (i.e. 3 times per week).

- EPO requires adequate haematinics to work properly. For adults, in the absence of contraindications, prescribe folic acid 5mg, hydroxycobalamin 1mg IM 3 times a week for 2 weeks, and give IV iron if not iron overloaded (ferritin <500µg/L) prescribe IV Ferinject® (Ferric carboxymaltose).

- Ferinject® dosage for patients who weight <60Kg at a stat dose of 500mg, if they weight >60Kg give 1g Ferrinject®,

- **Blood transfusion** may be necessary if clinically indicated (profound symptomatic anaemia), but should only be given after discussion with a consultant haematologist experienced in the management of sickle cell disease.
    - Phenotyped blood should be given (CcDEe and Kell matched), which should also be antigen negative for any previously identified allo-antibodies and HbS negative, in some cases NHSBT will provide extended phenotype matched units.

- **Eculizumab**: reduces the activation of complement, a key mechanism involved in the immune response resulting in red blood cell destruction during hyperhaemolysis. A single dose should be *considered in patients of all ages who continue to haemolyse briskly with symptomatic anaemia or compromise of another organ* (e.g. renal failure, respiratory failure) *despite first line treatment with IVIg.* A second dose may be considered 7 days later if there is evidence of efficacy of treatment but ongoing haemolysis.
    - The adult dose is 900mg as an IV infusion over 45 minutes (patients <10Kg = 300mg, 10-40Kg= 600mg, >40kg adult dose of 900mg dose).

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- Please see summary of product characteristics for paediatric dosing.

All patients who have received Eculizumab:

1. Should be advised to use effective contraception for 6 months post administration
2. Should be tested retrospectively for latent TB, hepatitis B, and Hepatitis C and receive appropriate prophylaxis/treatment if indicated.
3. Should be counselled about the risk of severe infections and receive meningoccal and pneumococcal vaccination at the earliest opportunity if not already/in date.
4. ***Administration should be reported and discussed at local, regional and national MDM (National Haemoglobinopathy Panel) with a view to ratification.***

- **Rituximab:** reduces the production of alloantibodies and prevents antibody mediated red cell destruction**.** Rituximab should be considered third line treatment for adult and post-pubescent patients when all criteria for giving eculizumab has been met and there is a need for ongoing blood transfusion therapy.
  Doses: 2 doses of 375mg/m2 to a maximum of 4 doses given 7 days apart, depending on response and the need for further blood transfusions.
  Please follow your Trust's Standard protocols including virology screening and counselling regarding infections. Administration shouldbe discussed at the network MDM

Monitoring response to treatment

Daily (at least initially): Hb, reticulocytes, bilirubin, LDH and creatinine
Every 48hours: DAT and group and crossmatch to allow urgent transfusion if required.
Consider HbS and A quantitation pre and post each transfusion episode, and daily at presentation.

Aim of management

Return of haemoglobin to baseline and haemolysis to steady state.
Review and consider stopping erythropoietin once haemoglobin returns to baseline or if lack of response after full treatment dose.

All patients managed with hyperhaemolysis should be encouraged to consider/commence Hydroxycarbamide if not already on this medication before discharge.

Follow up and future transfusion management

ALL cases of post transfusion hyperhaemolysis must be reported to SHOT

All suspected cases of hyperhaemolysis should be discussed with the transfusion biomedical scientist who should add a comment to the patient record on their local laboratory system as well as on Sp-ICE.

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All patients who have had hyperhaemolysis should have this documented in their clinical records and any patient hand held records. If you issue an antibody card at your Trust this must be updated.

Future Transfusion management/prevention of DHTR:
For patients who have had a previous episode of hyperhaemolysis, consideration should be given to pre-treatment with IVIg and Methyprednisolone for future/elective transfusions**.**

Patients who haemolyse despite IVIg and Methyprednisolone pre-treatment
Rituximab should be considered as second line treatment and given instead of IVIg and steroid, for the prevention of DHTR/HH in adults and post-pubescent patients who experience a second episode of DHTR/HH despite pre-treatment with IVIg and Steroids and are requiring an elective blood transfusion.
Dose: 375mg/m^2 weekly for 2 doses given 1-2 weeks apart. Standard Trust protocols including virology screening and counselling regarding infections must be followed. Administration should be discussed at the network MDM

Monitoring of this guideline
Use of IVIg for this indication will be monitored via the DH Immunoglobulin Demand Management Programme Database and though the Network M&M meetings.

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References

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NHSE Specialist Commissioning Guidelines for the prevention and treatment of Delayed Haemolytic Transfusion Reaction and Hyperhaemolysis in Haemoglobinopathy patients, 24 September 2020.

Eculizumab Summary of Product Characteristics

Rituximab Summary of Product Characteristics

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South Thames Sickle Cell & Thalassaemia Network

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