Scottish Paediatric & Adult Haemoglobinopathy Network

Paediatric and Adult Guideline: Management of Hyperhaemolysis in patients with Sickle Cell Disease

Summary

Hyperhaemolysis is a well-recognised 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)
Alternative regimen is NeoRecormon 10-20,000 units sc 3 times a week (Ref 2)

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

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.

Management of refractory cases:
Eculizumab and Rituximab
There are case reports of successful outcomes using eculizumab and rituximab which are now recommended as a treatment option through routine commissioning within set criteria outlined by NHS England. Use in Scotland should ideally be discussed and agreed at a case discussion meeting and local approval sought as unlicensed.
(Ref 8)

Eculizumab
Second line treatment with eculizumab should be considered for patients of all ages when the rate of rapid haemolysis WITH symptomatic anaemia OR compromise of another organ system (e.g. respiratory failure, renal failure, neurological symptoms) continues despite first line treatment with IVIg and steroids.

Third line treatment with rituximab should be considered 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.

Dose:
Rituximab in adult and post-pubescent patients:
- PREVENTION: 2 doses of 375mg/m2 given 7-14 days apart.
- MANAGEMENT: 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.

Eculizumab in adult patients:
900mg IV ONCE and a second dose 7 days if there is evidence of efficacy of treatment but ongoing haemolysis. No further doses/ courses are permitted.

Stopping Criteria:
Eculizumab
One dose to be given initially and no further dose given if there is:
A complete response
No evidence of response.
An adverse event.

Rituximab
Following initial dose(s) no further doses given if there is:
No further transfusion is needed.
An adverse event of a severity such that the balance of risks and benefit do not support further use.

Contraindications
As per the summary of the product characteristics of both products.
Exclusions
- Patients who do not have a haemoglobinopathy.
- Patients previously treated without a response.

Monitoring
Principle long-term adverse effects of rituximab include neutropenia and hypogammaglobulinaemia from prolonged B-cell depletion. The product license for rituximab recommends regular measurement of blood neutrophils which would be part of ongoing monitoring.

Following eculizumab administration, ciprofloxacin 500mg bd should be administered for 8 weeks from the last dose, once completed long term prophylactic penicillin (Penicillin V) or erythromycin (if penicillin allergic) should continue. Patients receiving

eculizumab should be vaccinated with Meningitis ACWY and Meningitis B. (Ref 9)

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

References

1. Clinical guidelines for immunoglobulin use 2nd Edition Update Scotland (2011) Summary tables - Page 20

2. 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. tstn.co.uk/wp-content/uploads/2012/02/506_Guidelines-for-the-management-of-hyperhaemolysis-GSTT.pdf

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4. Cullis JO, Win N, Dudley JM, Kaye T. Post-transfusion hyperhaemolysis in a patient with Sickle Cell Disease: Use of Steroids and Intravenous Immunoglobulin to prevent further red cell destruction. (1995). Vox Sang. 69; 355-357

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7. Win N, New H, Lee E, De La Fuente J. Hyperhemolysis syndrome in sickle cell disease: case report (recurrent episode) and literature review. (2008) Transfusion. 48; 1231-1238

8. NHS England » Rituximab and eculizumab for the prevention and management of delayed haemolytic transfusion reactions and hyperhaemolysis in patients with haemoglobinopathies

9. Guidelines for the management of sickle cell disease in adults. West London HCC Clinical Guideline.

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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.