Hyperhaemolysis in adults and children with sickle cell disease

What is hyperhaemolysis?

Delayed haemolytic transfusion reactions (DHTR) including hyperhaemolysis (HH) are rare, life-threatening blood transfusion complications. DHTR is defined as a significant drop in haemoglobin with no alternative cause identified, within 21 days of the transfusion.

Some patients will develop hyperhaemolysis; the most severe form of DHTR, where the transfusion reaction triggers destruction of the patient's own red cells in addition to the new transfused red cells. **The patient's haemoglobin drops further to below the pre-transfusion baseline haemoglobin.** Once a patient has experienced hyperhaemolysis, they are at risk of recurrence in subsequent transfusions, even if several years later.

Generally, patients with hyperhaemolysis are treated with IVIg and steroids. If the haemolysis control is suboptimal, Eculizumab (monoclonal antibody against C5) can be used to prevent ongoing activation of the complement cascade. Further transfusions should be avoided if at all possible, but if the patient has required Eculizumab and requires a transfusion, Rituximab should be given beforehand.

- All cases should be discussed acutely with local Specialist Haemoglobinopathy Team (SHT)/Haemoglobinopathy Coordinating Centre (HCC). For Thames Valley and Wessex hospitals, the OUH is the HCC.
    - OUH Switch board: 0300 304 7777
    - 9-5 Mon-Fri: Paediatric haematology: Dr Amrana Qureshi; Adult haematology Dr Wale Atoyebi/Dr Noemi Roy
    - Out of hours: Paediatric or adult haematologist on call.

Patients should be cared for on a haematology ward where staff are familiar with managing monoclonal antibodies and severe anaemia. *Also note* that this protocol contains both adult and paediatric drug dosing. Where the drug dose is different, this is clearly stipulated.

Clinical Picture

Patients most commonly present soon after a recent acute admission with a sickle complication or crisis. Hyperhaemolysis should be considered when the patient presents within 21 days of a blood transfusion. Symptoms include sickle cell vaso-occlusive type pain, fevers, and haemoglobinuria is a characteristic feature.

Initial Investigations

• FBC and reticulocytes • U&E • LFT • CRP • LDH • Coagulation screen including fibrinogen • Haptoglobin • Group and save and DAT. Please send 3 EDTA bottles to the transfusion lab for additional testing	• Ferritin, iron studies, B12/folate • Haemoglobinopathy screen (HPLC) to determine blood HbS and HbA levels • Urine HPLC for urinary HbS and HbA levels • HepB serology incl. hepatitis B core antibody and surface antigen test • Urine dipstick and microscopy – to differentiate between haematuria and haemoglobinuria.

Characteristic laboratory features of hyperhaemolysis:

- The post-transfusion Haemoglobin is lower than pre-transfusion Haemoglobin
- The reticulocyte count is often lower than usual (high in DHTR)
- Elevated ferritin (correlates with disease activity)
- The DAT is often negative
- New alloantibodies can be present but this is often delayed
- HbA falls in blood (might require serial measurements)
- HbS and HbA are present in serial HPLC analysis of urine
- Further transfusions may exacerbate haemolysis

First line treatment: IVIg and steroids

- During working hours, discuss with a red cell consultant/on call haematologist. Discuss with paediatric haematologist if the patient is paediatric.
- Out of hours, discuss with on call haematologist. They may choose to contact a red cell consultant.
- Avoid transfusion if possible, but do not withhold if life threatening anaemia is present.
- X-match 6 units immediately (30ml/kg if paediatric) so blood is on site if needed (there may be a delay if the patient has a positive antibody screen). Do not administer without discussion with a haematologist.
- **IVIg and steroids should be given ASAP.**
    - Intravenous immunoglobulin (IVIg) - 1g/kg once daily for 2 days or 0.4g/kg/day for 5 days (total dose = 2g/kg)
        - As per NHSE policy prior approval is not required for this indication. Link here: PSS9-Immunoglobulin-Commissioning-Guidance-CQUIN-1920.pdf (england.nhs.uk),
    - Methylprednisolone:
        - *Adult dose:* 500mg to 1g IV once daily for 2 days. Review dose after 2 days.
        - *Paediatric dose:* 10-30mg/kg up to a max of 500mg.

Supportive care

- Prescribe 5mg OD folic acid (*for patients under 1 year*, 2.5mg OD)
- Consider B12 replacement if <200pg/ml (IM Hydroxycobalamin 1mg 3 times a week for 2 weeks).
- Erythropoetin
    - Consider erythropoietin 300 IU/kg OD for 5 days then 3 x week.
- Iron supplementation
    - if ferritin <100, Parenteral iron e.g. Ferinject as per manufacturer/SPC
    - Oral ferrous sulphate if ferritin >100.
- FBC should be repeated 2-3 times daily initially and discuss results with a consultant.
- Consider midline insertion if venous access is poor

Start to organise acquisition of Eculizumab for second line treatment at the time of giving IVIg and steroids.

Second line treatment: Eculizumab

Treatment with Eculizumab should be considered if, despite IVIg and steroids, 24 hours later there is evidence of:

- ongoing or worsening haemolysis WITH symptomatic anaemia
- OR evidence of organ failure (renal failure, respiratory failure, neurological dysfunction).

Please complete a BLUETEQ form when prescribing Eculizumab. Prescribe on EPR or trust specific prescribing system (Not ARIA).

Dose:

- *Adults:* 900mg IV ONCE and a second dose 7 days later if there is evidence of efficacy of treatment but ongoing haemolysis.
- *Paediatrics:* based on weight: <10kg = 300mg, 10-40kg = 600mg, >40kg = adult dose of 900mg.

Eculizumab should only be given on ICU or a haematology/oncology ward (i.e. those familiar with administering monoclonal antibodies), not on outlying/general medical wards.

One dose to be given initially and no further dose should be given if there is:

- A complete response (stabilisation of Hb, resolution of haemoglobinuria, normalisation of LDH, recovery of reticulocytes).
- No evidence of response
- An adverse event

Possible adverse effects:

- Infusion reactions including anaphylaxis
- Most common side effects are headache, dizziness, nausea and pyrexia. Most headaches do not persist after the initial administration phase of Eculizumab.

Exclusions for Eculizumab:

- Patients who do not have sickle cell disease
- Patients previously treated without a response.
- There is no well-controlled data for either drug when used in pregnancy. In both instances, this would be a risk benefit judgement balancing risk of hyperhaemolysis to the mother with the unknown but theoretical risk of complement inhibition or B-cell depletion in the baby.

Vaccination:

- Treating centre to check vaccination status of Men B & Men ACWY with GP vaccination records while inpatient and receiving eculizumab
- If already vaccinated – no further action required. Document year of vaccination in patient's notes
- If not vaccinated or vaccination history unclear – treating centre to give 1st dose of Men B and Men ACWY vaccine as soon as reasonably practicable as an inpatient.

Include in discharge letter the date of the first dose and request GP to give 2nd dose of Men B vaccine 1 month later.
- Other vaccinations should also be up to date

Process of obtaining Eculizumab:

- This treatment can be given in any acute hospital, but should be discussed with the Specialist haemoglobinopathy team (SHT) / Haemoglobinopathy coordinating centre (HCC) first.
- All cases need approval from the appropriate SHT /HCC.
- All cases should be discussed at the National haemoglobinopathy panel (NHP). This will usually be retrospective in an emergency. The HCC might consider e-mail advice from the NHP.
- For Thames Valley and Wessex hospitals, the OUH is the HCC.
    - Switch board: 0300 304 7777.
    - 9-5 Mon-Fri: Paediatric haematology: Dr Amrana Qureshi; Adult haematology Dr Wale Atoyebi/Dr Noemi Roy
    - Out of hours: Paediatric haematologist on call; adult haematologist on call.
- DGH hospitals: Eculizumab can be ordered from directly from the manufacturer Alexion via your pharmacy purchasing team. There is also an out of hours service provided from Alexion (between 5pm-8am and all day on weekends/bank holidays). Delivery from Alexion should occur within a 5-12 hour time frame. If it is not possible to request directly from Alexion, contact the OUH pharmacy team via switchboard to discuss a wholesale purchase order.

A maximum of two doses are commissioned and funded with no further doses/ courses permitted.

Third line treatment: Rituximab

Third line treatment with Rituximab should be considered for adult and post-pubescent patients when all criteria for giving Eculizumab have been met AND there is a need for ongoing blood transfusion therapy.

Dose: 2-4 doses of 375mg/m2 IV given weekly, depending on response and the need for further blood transfusions.

Following initial dose(s), no further doses given if:

- No further transfusions are needed.
- An adverse event of a severity such that, the balance of risks and benefit do not support further use.

Prescribe on EPR or trust specific prescribing system (Not ARIA)

Possible adverse effects:

- Severe cytokine release syndrome is characterised by severe dyspnoea, often accompanied by bronchospasm and hypoxia, in addition to fever, chills, rigors, urticaria, and angioedema.
- Hepatitis B reactivation – see pathway for treatment and management of HBV positive patient in references (Adult)

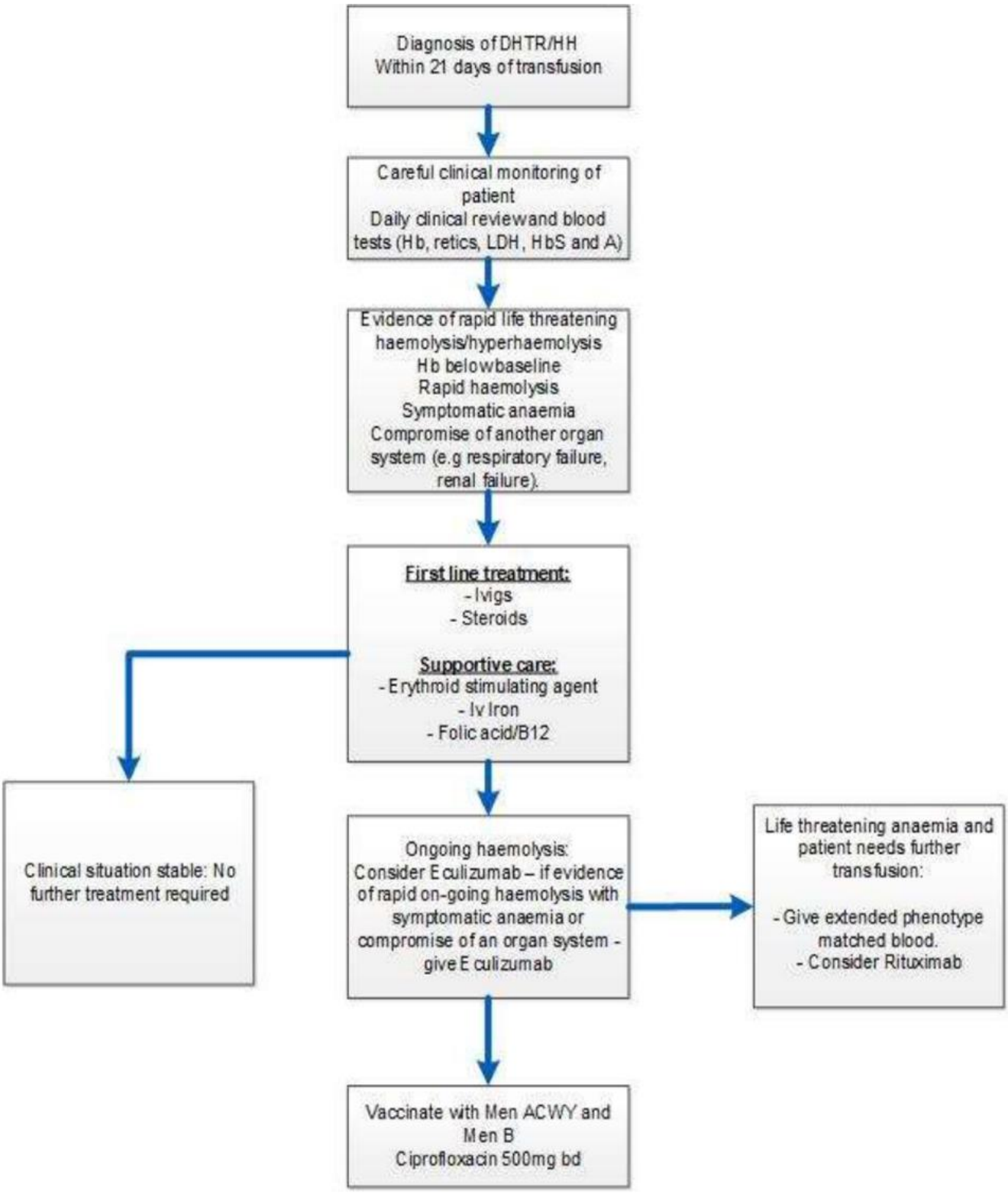
Exclusions for Rituximab:

- Patients who do not have a haemoglobinopathy
- Patients previously treated without a response
- Pre-pubescent paediatric patients

Flowchart from NICE Clinical commissioning policy 2020.

NB: the ciprofloxacin dose detailed below is the adult dose, use appropriate paediatric dose.

Figure 1: Treatment of patients with Hyperhaemolysis: NHS England Clinical commissioning policy 2020.



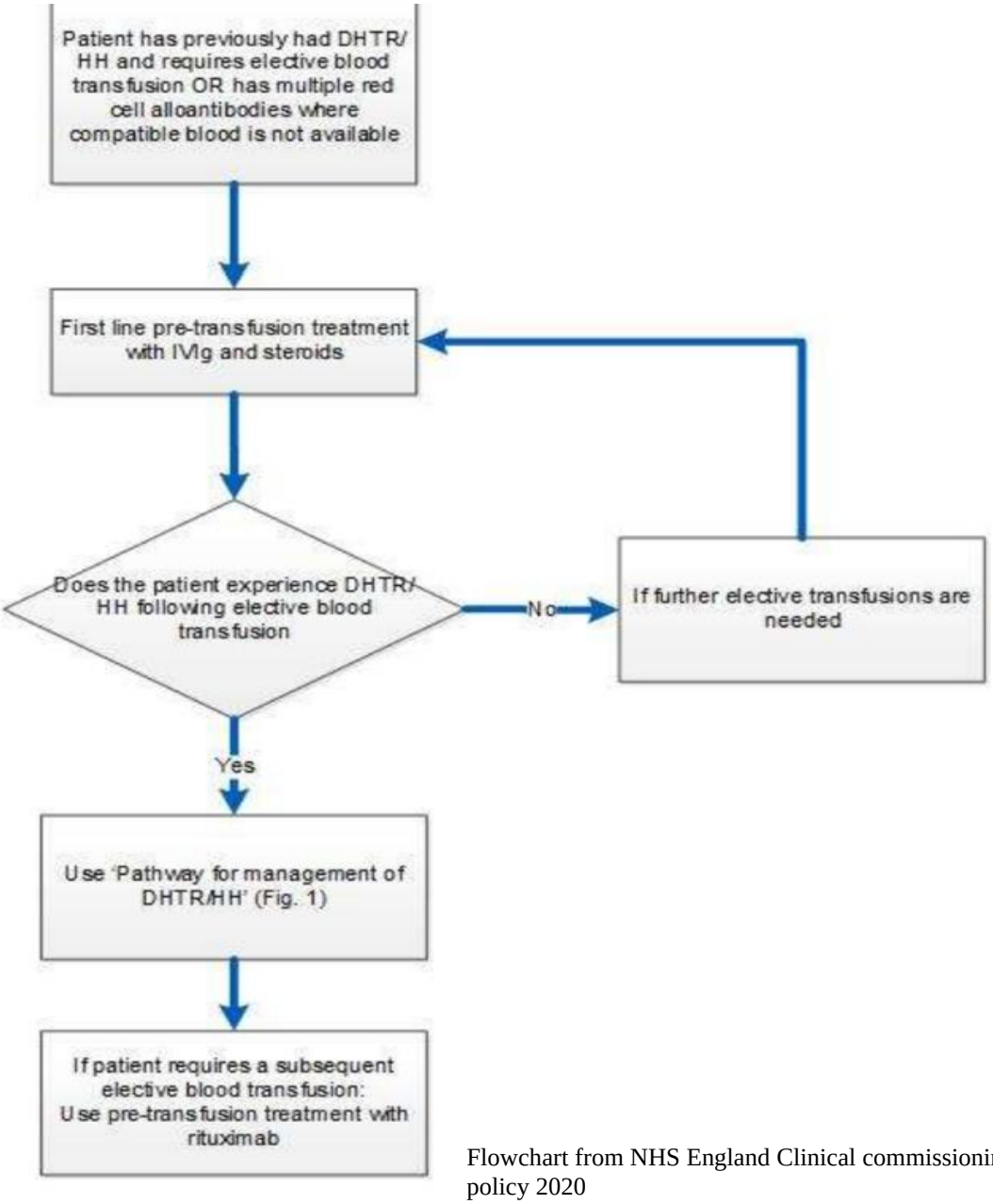
Subsequent transfusions:

Hyperhaemolysis can recur after subsequent transfusions, even many years later. Preventative treatment can be given to reduce the risk.

- If a patient with previous hyperhaemolysis needs an elective blood transfusion give IVIg and steroids prior to the transfusion at the doses stated above.
- If the patient has a recurrence of hyperhaemolysis/DHTR despite IVIg/steroids, treat as above.

When the patient needs subsequent transfusions, give rituximab INSTEAD of steroids/IVIg as a pre-transfusion treatment. Dose: 2 doses of Rituximab 375mg/m2 IV given 7-14 days apart.

Figure 2: Prevention of hyperhaemolysis in subsequent transfusions.



Flowchart from NHS England Clinical commissioning policy 2020

Ongoing monitoring:

Rituximab: Principal long-term adverse effects of rituximab include neutropenia and hypogammaglobulinaemia from prolonged B-cell depletion. The product license for Rituximab recommends regular FBC assessment, as it is associated with an immune-mediated neutropenia.

Eculizumab:

- Following Eculizumab administration, two weeks of Ciprofloxacin (*Adults:* 500mg BD; *Paediatrics:* 10mg/kg BD to a maximum of 500mg BD) should be administered followed by long term prophylactic penicillin (Penicillin V) or erythromycin (if penicillin allergic),
- Vaccination: see notes on page 4
    - Other immunisations should also be up to date.

Reporting Guidance:

1. All cases should be discussed with local SHT/HCC acutely
2. All cases should be referred at the national haemoglobinopathy panel for discussion.
3. All elective transfusions in patients with previous hyperhaemolysis should be discussed at the national haemoglobinopathy panel.
4. All cases should be reported to SHOT

References

OUH MMTC approval: March 2021

https://www.england.nhs.uk/wpcontent/uploads/2020/09/1821_Rituximab_Eculizumab_Clinical_Commissioning_Policy.pdf

http://nssg.oxford-haematology.org.uk/lymphoma/documents/lymphoma-clinical-resources/LPW-21-immunosuppression-and-hepatitis-b.pdf

Authors: Dr Asha Aggarwal (SpR); Dr Wale Atoyebi (Consultant adult haematologist); Dr Amrana Qureshi (Consultant paediatric haematologist); Julie Staves (Blood bank manager); Yuen Lim (Adult Haematology pharmacist); Stephen Amoah-Nyako (Paediatric haematology pharmacist); Sandy Hayes (lead adult nurse)

Review

Name	Revision	Date	Version	Review date
Dr Wale Atoyebi	New document		1.0	April 2023
Dr Magbor Akanni	Full Review	June 2024	2.0	June 2026