Clinical Commissioning Policy; Rituximab and eculizumab for the prevention and management of delayed haemolytic transfusion reactions and hyperhaemolysis in patients with haemoglobinopathies [URN 1821] [200602P]

Commissioning position

Summary

Rituximab and eculizumab is recommended to be available as a treatment option through routine commissioning for delayed haemolytic transfusion reactions and hyperhaemolysis in patients with haemoglobinopathies within the criteria set out in this document.

Executive summary

Equality statement

Promoting equality and addressing health inequalities are at the heart of NHS England's values. Throughout the development of the policies and processes cited in this document, we have:

- Given due regard to the need to eliminate discrimination, harassment and victimisation, to advance equality of opportunity, and to foster good relations between people who share a relevant protected characteristic (as cited under the Equality Act 2010) and those who do not share it; and
- Given regard to the need to reduce inequalities between patients in access to, and outcomes from healthcare services and to ensure services are provided in an integrated way where this might reduce health inequalities

Plain language summary

About delayed haemolytic transfusion reactions

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

Some patients will also go on to develop HH; 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 (blood count) drops further to below the pre-transfusion baseline haemoglobin (Hb). Once a patient has experienced HH, they are at risk of recurrence in subsequent transfusions, even if several years later.

About current treatments

Current treatments consist of supportive care with products to stimulate new red cell production (erythropoietin) and treatments such as steroids and intravenous immunoglobulin (IVIg) to reduce the immune system breaking down red blood cells. Steroids and IVIg are also used to prevent future DHTR/HH in patients at high risk of recurrence because of a previous history of this complication where there is a need for further transfusions.

About the new treatment

The new treatments use rituximab and eculizumab. Rituximab is a drug that acts on the body's immune system and decreases DHTR by reducing the production of proteins that attack the red blood cells (alloantibodies). Eculizumab is a drug that reduces the activation of complement, a key part of activating the immune response involved in the red blood cell destruction.

Rituximab has been used both to prevent the occurrence of DHTR in high risk patients and to manage severe ongoing DHTR/HH and eculizumab has been used to manage severe ongoing DHTR/ HH in patients at high risk of death and organ damage. Neither medicine is licenced for this intervention and will be used 'off label'.

What we have decided

NHS England has carefully reviewed the evidence to treat DHTR and HH in patients with haemoglobinopathies with rituximab and eculizumab. We have concluded that there is enough evidence to make the treatment available at this time.

Rituximab will be commissioned for adult and post-pubescent patients whilst eculizumab will be commissioned for patients of all ages in line with licensing restrictions of the drug (detailed in the links below) and as outlined within this policy to treat DHTR and HH patients.

https://www.medicines.org.uk/emc/product/362/smpc
https://www.medicines.org.uk/emc/product/8878/smpc

Further information can also be found at;

https://bnf.nice.org.uk/drug/eculizumab.html
https://bnf.nice.org.uk/drug/rituximab.html
https://bnfc.nice.org.uk/drug/rituximab.html

Committee discussion

The Clinical Panel considered that the evidence base was very low but were supportive of a routine commissioning position as a preventative treatment for a high risk, life threatening condition. Clinical Panel stipulated robust clear data collection must be completed once the policy is published to further determine efficacy. See the committee papers (link) for full details of the evidence.

The condition

DHTR and HH are rare, life threatening complications of blood transfusion associated with red cell alloantibody formation and activation of complement. DHTR is defined as a significant drop in haemoglobin (Hb) in the absence of an alternative cause within 21 days of transfusion associated with one or more additional clinical criteria and with the exclusion of an alternative cause. These criteria are:

- new red cell alloantibody (or antibodies)
- haemoglobinuria
- Hb level that decreases more rapidly than expected post transfusion
- relative reticulocytopenia or reticulocytosis from baseline
- significant rise in lactate dehydrogenase (LDH) from baseline.

Some patients will develop post transfusion HH. This can occur in the presence or absence of a new alloantibody. This is considered the most severe type of DHTR whereby the transfusion triggers destruction of the patient's own red cells in addition to the transfused red cells and most likely to lead to increased mortality. In this situation, Hb decreases below the pre-transfusion baseline Hb. Once a patient has experienced HH, they are at risk of recurrence with subsequent

transfusions, even if several years later. The mechanisms of HH are not completely understood but include the presence of alloantibodies leading to red cell destruction by phagocytosis and complement mediated haemolysis. This complement mediated haemolysis can also occur in the absence of red cell alloantibodies.

Patients are at high risk of DHTR/HH if they have a history of multiple or life threatening DHTR or have multiple red cell alloantibodies. DHTR/HH is more common in patients with haemoglobinopathies (Sickle Cell Disease (SCD) and Thalassaemia) than in other patient groups. This may be explained by high rates of transfusions, transfusions performed in times of acute illness and a mismatch between blood groups of the donor and recipient.

Due to the rarity, life threatening nature of the condition and immediate need for treatment, it is more difficult to set up randomised controlled trials or comparator studies and the evidence base is limited to individual case studies.

Current treatments

Management of established DHTR/HH: Current first line treatment for established DHTR/HH in England consists of supportive care (fluids, pain relief) with erythropoietin and haematinic replacement to improve new red cell production. Treatments such as steroids and intravenous immunoglobulin (IVIg) are also used to reduce the immune system breaking down red cells. These drugs are not always effective and haemolysis may continue despite treatment.

Prevention of DHTR/HH: Some patients are at high risk of DHTR/HH because of previous history of this complication and a need for further transfusion therapy. In this situation, steroids and IVIg are used to prevent future DHTR/HH.

Proposed treatments

Intervention

Rituximab is a drug that acts on the body's immune system by depleting B cells. It decreases DHTR by reducing the production of alloantibodies and by preventing the antibody mediated red blood cell destruction. Therefore, it is also useful in preventing further delayed haemolytic transfusion reactions. Rituximab is licensed for the treatment of non-Hodgkin's Lymphoma, chronic lymphocytic leukaemia and rheumatoid arthritis; it is unlicensed for the treatment of DHTR/HH.

Eculizumab is a drug that has been shown to significantly reduce the activation of complement, which is a key mechanism involved in the immune response causing red blood cell destruction and there is evidence of its efficacy in other conditions with marked complement activation. Eculizumab led to rapid resolution of HH in a case report (Chonat 2018). Eculizumab is licensed for the treatment of Paroxysmal nocturnal haemoglobinuria and atypical haemolytic uremic syndrome; it is unlicensed for the treatment of DHTR/HH.

A recent paper recommended rituximab as first line treatment for prevention of DHTR and eculizumab as second line treatment for management of DHTR/HH (Pirenne et al 2018).

Treatment of DHTR/HH – IVIg and steroids with supporting treatment are the usual first line treatment. This policy recommends eculizumab for all ages as a second line treatment for the management of DHTR/HH in patients where first line treatment has failed to prevent rapid haemolysis. Rituximab is recommended as third line treatment for adult and post pubescent patients.

Prevention of DHTR/HH in patients requiring elective blood transfusion - IVIg and steroids are first line preventative treatment. Where this has previously failed, this policy proposes the use of rituximab for adult and post-pubescent patients only, as a second line treatment instead of using IVIg and steroid therapy for the prevention of DHTR/HH in patients requiring elective blood transfusion.

Epidemiology and needs assessment

In the UK, there is a national mandated reporting system where all transfusion reactions are reported to the 'Serious Hazard of Transfusion (SHOT) database, run by the National Blood Transfusion Service. In 2018, there were 28 cases of DHTR reported to SHOT (SHOT 2019). Five of these cases were associated with HH, three of whom had SCD, the other two had T-cell lymphoma and Rosai-Dorfman Syndrome and both non-SCD patients died. These were the first non-haemoglobinopathy patients reported to SHOT with HH. There were no paediatric cases of DHTR reported in 2018. However, there was one reported in 2017 from a total of 23 cases of DHTR reported to SHOT in 2017, of which six were HH in patients with SCD (SHOT 2018).

There have been five known cases of eculizumab being used in the UK to treat HH in the last two years. It is expected that there will be under 10 patients per year who will require eculizumab and under five patients that will need rituximab per year (expert clinical opinion from the Policy Working Group).

Evidence summary

NHS England has concluded that there is sufficient evidence to support a policy for the routine commissioning of rituximab and eculizumab for delayed haemolytic transfusion reactions and hyperhaemolysis in patients with haemoglobinopathies.

The evidence review focussed on seven publications of individual case studies (Boonyasampant et al 2015, Cattoni et al 2013, Chonat et al 2018, Hannema et al 2010, Noizat-Pirenne et al 2007, Pirenne et al 2018 and Uhlmann et al 2014) and three case series (Noizat-Pirenne et al 2015, Pirenne et al 2018 and Vagace et al 2016). In the case series by Noizat-Pirenne et al 2015, five patients of the eight included were relevant to this review. In the case series by Pirenne et al 2018, two patients of the three included were relevant to this review, one in the prevention section and one in the treatment with rituximab section. In the case series by Vagace et al 2016 only one patient was relevant to the review and is included in the treatment with eculizumab section.

The outcome of the review in the prevention of DHTR/HH using rituximab was not definitive. Due to the rarity of the conditions and corresponding limited evidence base, a decision was taken to include indirect evidence where patients did not meet the precise inclusion criteria. None of the included patients fully met the PICO as they were transfused with matched blood and there was no evidence of prior DHTR/HH, despite pre-transfusion treatment with IVIg and steroids.

Two case studies (Cattoni et al 2013 and Noizat-Pirenne et al 2007) and two case series (Noizat-Pirenne et al 2015 and Pirenne et al 2018) with a total of eight patients suggested a mixed response as, although all patients survived, four of the eight patients experienced a haemolytic reaction. Within the relevant paper by Noizat-Pirenne et al 2015, it is possible the treatment reduced the severity of three mild DHTR/HH reactions, but this was not explicit. One patient in the same publication suffered mild vaso-occlusive complications and haemoglobinuria.

Only one publication detailed acute facility utilisation beyond the expected elective stay, where length of stay was extended by approximately seven days post reaction (Cattoni et al 2013). Three included studies indicated that none of the seven patients formed new alloantibodies at least three months following the initial intervention (Noizat-Pirenne et al 2007, Noizat-Pirenne et al 2015 and Pirenne et al 2018). One patient was reported as requiring a further blood transfusion following a haemolytic transfusion reaction (Cattoni et al 2013).

The study methodologies, including their small size, relatively short follow-up and lack of relevant comparators makes it difficult to draw conclusions about the benefits and risks of rituximab treatment compared with no rituximab treatment.

There was very limited evidence available on the clinical effectiveness of eculizumab as a second line treatment for patients experiencing DHTR/HH as only one individual case study was identified in the evidence review (Vagace et al 2016). This patient did not fully meet the PICO criteria as they had a DHTR/HH reaction more than 28 days after their initial transfusion, so the evidence presented is indirect. Detail around the relationship between hyperhaemolysis and drug administration was unclear, and the patient received final treatment with a splenectomy which also necessitated further blood transfusion prior to surgery. Information was not available on total length of stay or how splenic sequestration affected the length of time admitted. The patient survived.

The publication reports that the patient developed several clinically significant alloantibodies though at what point during their inpatient episode this was identified was not clear (ibid). One patient included in the review of rituximab as treatment was treated with the drug as a second line treatment and eculizumab as a third line treatment (Chonat et al 2018). The patient experienced pain altered mental status and developed pulmonary oedema. Eculizumab was initiated as a third line treatment approximately two days after the initiation of rituximab after which the patient began to improve.

There was very limited evidence on the clinical effectiveness of rituximab as a third line treatment in patients experiencing DHTR/HH. Due to variation in treatment course, it was not possible to draw definitive conclusions about the efficacy of rituximab as a treatment. All five patients treated with rituximab at any point in their care survived (Boonyasampant et al 2015, Chonat et al 2018, Hannema et al 2010, Pirenne et al 2018 and Uhlmann et al 2014). Of the two patients treated with corticosteroids, IVIg, eculizumab and rituximab, there is a possibility that treatment combination reduced the impact of DHTR/HH although this was not explicit in the publications (Boonyasampant et al 2015 and Chonat et al 2018). Acute heath events were noted in three patients. One patient experienced pain altered mental status and development of pulmonary oedema. Eculizumab was initiated as a third line treatment approximately two days after initiation of rituximab, after which the patient's condition improved (Chonat et al 2018). One patient with DHTR experienced congestive heart failure and was treated with rituximab (Uhlmann et al 2014). However, the patient's heart failure continued to worsen, and they were eventually treated with IVIg but no further rituximab and no eculizumab. One patient experienced a severe reaction to rituximab and had further complications resulting in a splenectomy (Hannema et al 2010). Information from several papers was not available on total length of stay or how complications experienced affected the length of time admitted (Boonyasampant et al. 2015, Chonat et al 2018, Hannema et al 2010, Pirenne et al 2018 and Uhlmann et al 2014). Two patients were reported as not having evidence of further alloantibody formation (Chonat et al 2018 and Hannema et al 2010). All patients described required further blood transfusion (Boonyasampant et al. 2015, Chonat et al 2018, Hannema et al 2010, Pirenne et al 2018 and Uhlmann et al 2014).

The study methodologies, including their small size, relatively short follow-up and lack of relevant comparators makes it difficult to draw conclusions about the benefits and risks of rituximab treatment compared with no rituximab treatment. The results highlight the need for additional research studies in this area.

With regard to safety, only one publication detailed the safety impact of rituximab compared to IVIg and steroids where a patient experienced a short-term allergy to rituximab following treatment (Hannema et al 2010). No evidence of safety of eculizumab as a treatment was identified.

No subgroups that may benefit from use of eculizumab or rituximab were identified.

No evidence was found on the cost-effectiveness of any of the interventions during the evidence review.

Implementation

Eligibility criteria

Due to the urgent nature with which the condition can occur, NHS England will commission treatment from any acute hospital. However, it is expected that all cases and treatment planning should be discussed with the Specialist Haemoglobinopathy Team (SHT) and/or the appropriate Haemoglobinopathy Co-ordinating Centre (HCC).

All cases will be required to seek approval (ideally before administering treatment) from the appropriate Haemoglobinopathy Co-ordinating Centre (HCC).

Provider organisations must register all patients using prior approval software and ensure monitoring arrangements are in place to demonstrate compliance against the criteria as outlined. All cases **must** be referred to the National Haemoglobinopathy Panel (NHP) for retrospective discussion of indications and outcomes.

In the non-emergency situation, patients with previous DHTR/HH despite pre-transfusion treatment with IVIg's and steroids who need elective transfusion therapy should be referred to the HCC MDT for discussion/approval and also (if time allows) to the NHP prior to treatment being given. As with the above, all cases must then be referred to the NHP for retrospective discussion of indications and outcomes. Provider organisations must register all patients using prior approval software and ensure monitoring arrangements are in place to demonstrate compliance against the criteria as outlined.

Prevention of DHTR/HH

Rituximab should be considered as second line treatment, given instead of IVIg and steroid for the prevention of DHTR/HH in adults and post-pubescent patients requiring elective blood transfusion who have:

- had DHTR/HH previously despite pre-transfusion treatment with IVIg and steroids OR
- multiple red cell alloantibodies where compatible blood is not available.

Management of DHTR/HH

- 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/m^2 given 7-14 days apart.
  - MANAGEMENT: 2 doses of 375mg/m^2 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.
- Eculizumab in paediatric patients based on weight: patients <10kg = 300mg, 10-40kg = 600mg; >40kg adult dose of 900mg dose. A maximum of two doses are commissioned and no further doses/ courses permitted.

Stopping Criteria

Eculizumab

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

- A complete response in line with the five defining criteria (page 7).
- 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.
- For rituximab, pre-pubescent paediatric patients

There is no well-controlled data for either drug when used in pregnancy. In both instances, this would be a risk benefit judgement balancing the clear and present danger to the mother with the unknown but theoretical risk of complement inhibition or B-cell depletion in the baby.

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, long term prophylactic penicillin (Penicillin V) or erythromycin (if penicillin allergic) is required, although long term penicillin treatment may already be part of haemoglobinopathy treatment. Patients receiving eculizumab should be vaccinated with Meningitis ACWY and Meningitis B.

Patient Pathway

Figure 1: Pathway for management of DHTR/HH in patients with haemoglobinopathies

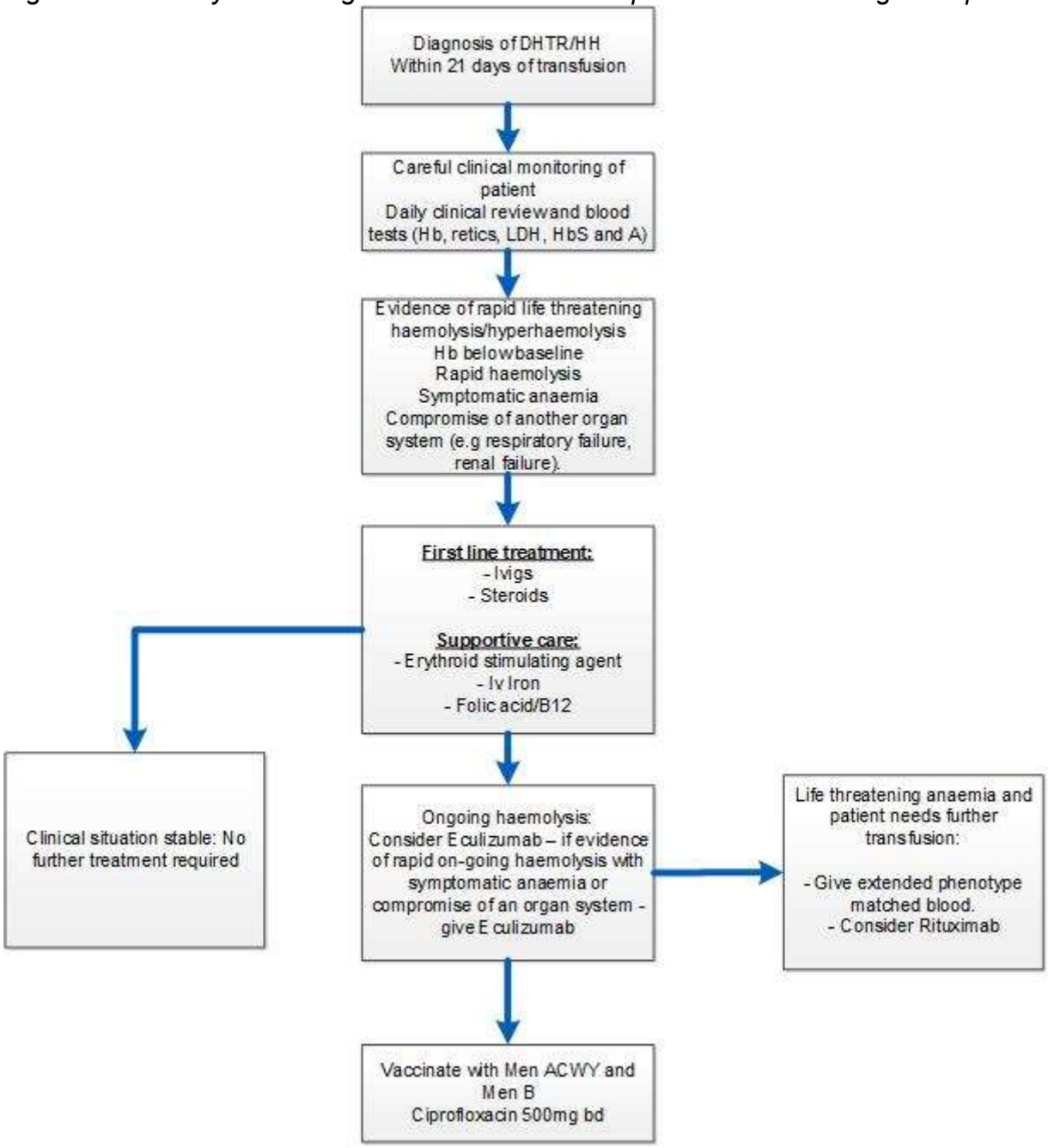
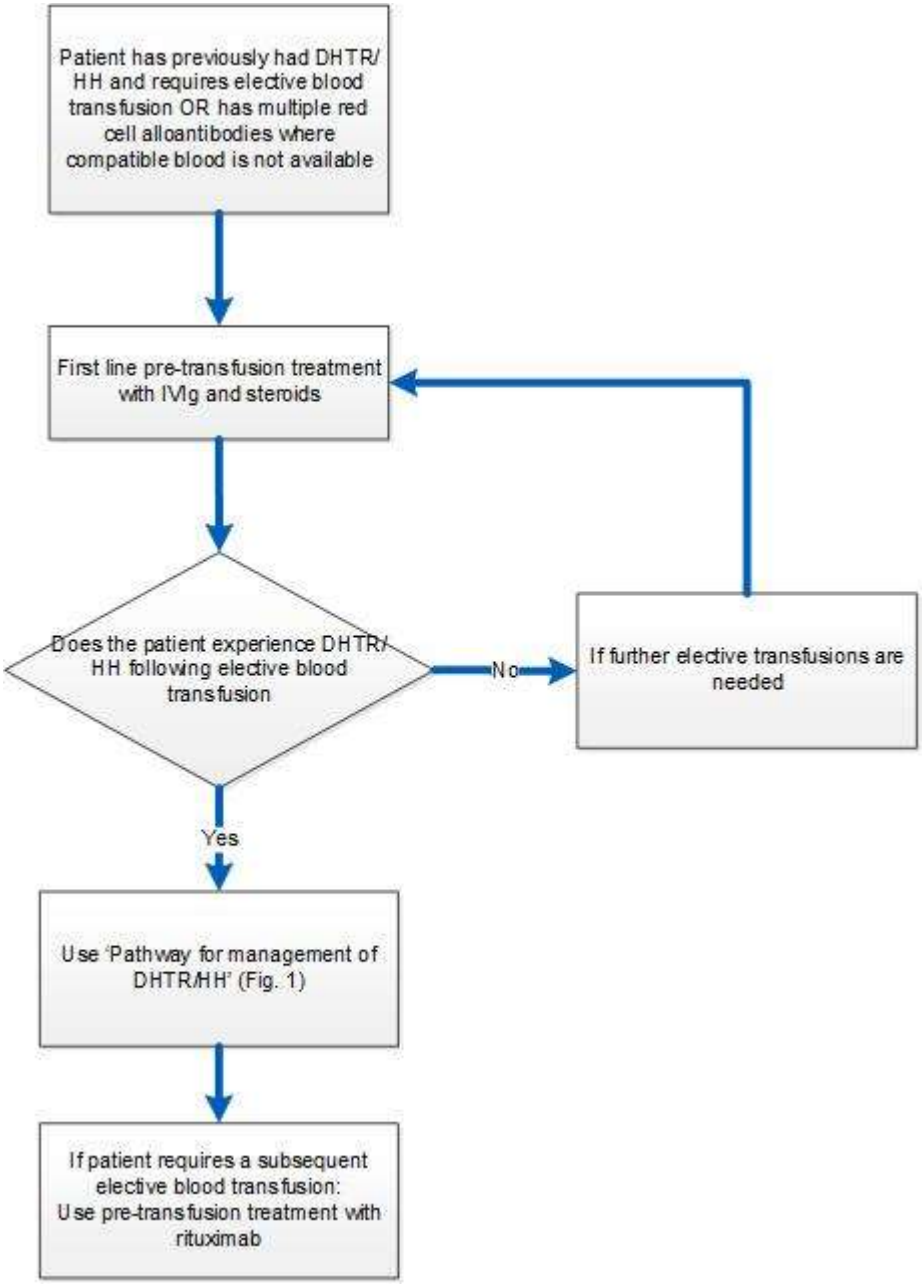


Figure 2: Pathway for prevention of DHTR/HH in patients with haemoglobinopathies



Governance Arrangements

See service specifications:

NHS England (2019). NHS Standard Contract for Specialist Haemoglobinopathy Services: Specialist Haemoglobinopathy Teams and Haemoglobinopathy Coordinating Centres specifications are available from: https://www.england.nhs.uk/publication/specialist-haemoglobinopathy-services-specialist-haemoglobinopathy-teams/

Any provider organisation treating patients with this intervention will be required to assure itself that the internal governance arrangements have been completed before the medicine is prescribed. These arrangements may be through the Provider's Drugs and Therapeutics committee (or similar) and NHS England may ask for assurance of this process.

Our policies provide access on the basis that the prices of therapies will be at or below the prices and commercial terms submitted for consideration at the time evaluated. NHS England reserves the right to suspend or rescind policies where the supplier of an intervention is no

longer willing to supply the treatment to the NHS at or below this price and to review policies where the supplier is unable or unwilling to match price reductions in alternative therapies. Each provider organisation treating children with a medicine approved under this policy will be required to assure itself that the internal governance arrangements have been completed before the medicine is prescribed. These arrangements may be through the Provider's Drugs and Therapeutics Committee (or similar) and NHS England can ask for documented evidence that these processes are in place.

Provider organisations must register all patients using prior approval software and ensure monitoring arrangements are in place to demonstrate compliance against the criteria.

Mechanism for funding

The cost of implementing the clinical commissioning policy statement is driven by the costs of eculizumab and rituximab together with the cost of delivery. Drug costs have been derived using the lowest acquisition costs. The cost of delivering care reflects appropriate national prices, as stated within the National Tariff Payment System.

Rituximab and eculizumab will be commissioned and funded by NHS England specialised commissioning under existing arrangements for the provision of specialised haemoglobinopathy services. The rituximab biologic with the lowest acquisition costs should be used. This is likely to be a rituximab biosimilar.

Audit requirements

A prospective data collection process with an agreed dataset will be required to inform prescribing in the future. All cases of DHTR/HH in England will be reported to the NHP. The dataset will be completed by the NHP and the reporting provider. That dataset will include information on usage, indications and outcomes. Outcome measures will include mortality, NHS utilisation (e.g. ITU admission and length of stay), clinical complications (including side effects of eculizumab and rituximab) and prevention of post transfusion haemolysis 24 hours to 21 days following transfusion. The NHP will produce an annual report that will be used to inform future policy developments.

In the UK there is a national mandated reporting system whereby all transfusion reactions are reported to the SHOT database run by the National Blood Transfusion Service. Cases must continue to be reported to allow outcomes to be compared with those in patients with DHTR/HH who are not treated with these therapies or who do not have a haemoglobinopathy.

Policy review date

This document will be reviewed when information is received which indicates that the policy requires revision. If a review is needed due to a new evidence base, then a new Preliminary Policy Proposition needs to be submitted by contacting england.CET@nhs.net.

Our policies provide access on the basis that the prices of therapies will be at or below the prices and commercial terms submitted for consideration at the time evaluated. NHS England reserves the right to review policies where the supplier of an intervention is no longer willing to supply the treatment to the NHS at or below this price and to review policies where the supplier is unable or unwilling to match price reductions in alternative therapies.

Definitions

Haemoglobinopathy	A hereditary condition involving an abnormality in the structure of or amount of haemoglobin
Haemoglobin	A protein responsible for transporting oxygen in the blood
Haemolysis	The destruction of red blood cells
Reticulocyte	Immature red blood cells involved in the formation of red blood cells
Reticulocytopenia	An abnormal decrease of reticulocytes (immature red blood cells)
Reticulocytosis	A condition where there is an increase in reticulocytes (immature red blood cells).
Sickle Cell Disease	A group of inherited health conditions that affect the red blood cells and are associated with the production of abnormal haemoglobin
Alloantibodies	An antibody that occurs against foreign tissues from a person of the same species.
Lactate Dehydrogenase (LDH)	An enzyme involved in energy production found in almost all cells in the body and which increases during haemolysis
Haemoglobinuria	Presence of haemoglobin in the urine
Thalassaemia	An inherited blood disorder in which the body makes an abnormal form of haemoglobin due to the production of abnormal amounts of globin chains

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