NHS England

# Evidence review: Prevention and Management of Delayed Haemolytic Transfusion Reactions and Hyperhaemolysis in patients of all ages with haemoglobinopathies

# NHS England

# Evidence review: Prevention and Management of Delayed Haemolytic Transfusion Reactions and Hyperhaemolysis in patients of all ages with haemoglobinopathies


First published: June 2020

Updated: Not applicable



Prepared by: Speciality Registrar Public Health England

## Contents

# 1 Introduction

**Indication and epidemiology**

- Delayed haemolytic transfusion reactions (DHTR) and Hyperhaemolysis (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 exclusion of alternative cause. These criteria are:
    - New red cell alloantibody (or antibodies)
    - Haemoglobinuria
    - HbA 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 hyperhaemolysis (HH). This can occur in the presence or absence of a new alloantibody. This is considered a severe type of delayed haemolytic transfusion reaction whereby the transfusion triggers destruction of the patient's own red cells in addition to the transfused red cells. In this situation, haemoglobin decreases below the pre-transfusion baseline haemoglobin. Once a patient has experienced HH, they are at risk of recurrence with subsequent transfusions, even if several years later. HH is the most severe form of DHTR/HH and most likely to lead to increased mortality.
- 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 transfusion, transfusions performed in times of acute illness and a mismatch between blood groups of the donor and recipient. 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.
- In the UK, there is a national mandated reporting system where all transfusion reactions are reported to the 'Serious Hazards of Transfusion (SHOT)' database run by the National Blood Transfusion Service. In 2017 there were 14 cases of DHTR reported to SHOT, 13 in patients with SCD and one in a patient with thalassaemia. Six cases were associated with hyperhaemolysis, of whom one died (due to complications of SCD). Eight cases were DHTR without hyperhaemolysis.
- Current first line treatment for established DHTR/HH consists of supportive care with erythropoietin and haematinic replacement to improve new red cell production and with treatments such as steroids and intravenous immunoglobulins (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 DHTR/HH because of a previous history of this complication and a need for further transfusion therapy.

**The intervention**

- Rituximab is a drug that acts on the body's immune system and decreases DHTR/HH by reducing the production of alloantibodies and by preventing the antibody mediated red blood cell destruction. Eculizumab is a drug that reduces the activation of complement which is a key mechanism involved in the immune response causing red blood cell destruction. The drugs are thought to have benefit over current treatment (IVIG, steroids) in the following scenarios:

A) Prevention of DHTR/HH:

Rituximab for the prevention of DHTR/HH in patients requiring elective blood transfusion in a patient who has:

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

B) Management of DHTR/HH

Eculizumab as 2nd line treatment of DHTR/HH in patients with a diagnosis of DHTR/HH and evidence of rapid haemolysis

  AND
- Symptomatic anaemia OR Compromise of another organ system (e.g. respiratory failure, renal failure, neurological symptoms)
  AND
- initial treatment with IVIG and steroids has not slowed the rate of haemolysis.

Rituximab as 3rd line treatment in patients

- in the acute situation when all the criteria for giving eculizumab have been met and eculizumab has been given
  AND
- there is a need for ongoing blood transfusion therapy.

- The aim of this review of people with a haemoglobinopathy is to examine the safety and clinical and cost effectiveness of the use of rituximab to prevent DHTR/HH in those requiring elective blood transfusion, and also the use of eculizumab with or without rituximab to treat patients with DHTR/HH.

- The review will also examine whether, from the evidence identified, there are SCD or thalassaemia patients (i.e. those with multiple alloantibodies) who would benefit more than others from the use of preventative rituximab and therapeutic eculizumab or rituximab than the wider cohort of haemoglobinopathy patients.

## 2 Summary of included studies

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 and Pirenne *et al* 2018 and Uhlmann *et al* 2014) and three case-series studies. (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 outcomes of the review in to prevention of DHTR/HH using rituximab was not definitive. 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. 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

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 suggest a mixed response as, although all patients survived, four of the eight patients experienced a haemolytic reaction although it is possible the treatment reduced the severity of three mild DHTR/HH reactions seen but this was not explicit within the relevant paper by Noizat-Pirenne *et al* 2015. One patient out of five reported in the Noizat-Pirenne *et al* 2015 publication suffered mild vaso-occlusive complications- 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 relevant to this review formed new alloantibodies post procedure at least 3 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 experienced a DHTR/HH reaction more than 28 days after their initial transfusion, so the evidence presented is indirect. This patient survived, detail around the relationship between hyperhaemolysis and drug administration was unclear, and the patient went on to receive final treatment with 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 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 section of this review on rituximab treatment, was treated with rituximab as a second line treatment and eculizumab as a third line treatment. (Chonat *et al* 2018) The patient experienced pain, altered mental status, and development of new diffuse 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. (ibid.)

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 alone. All five patients treated with rituximab at any point of 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 with a combination of therapies reduced the impact of DHTR/HH reactions although this was not explicit in the included 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 new diffuse pulmonary oedema , eculizumab was initiated as a third line treatment approximately two days after initiation of rituximab after which the patient's clinical condition improved. (Chonat *et al* 2018) A patient experiencing congestive heart failure was treated with rituximab and the patient's heart failure continued to worsen and was eventually treated with IVIG and no further rituximab. This patient was not treated with eculizumab at any point during their episode of DHTR. (Uhlmann *et al* 2014) One patient experienced a severe reaction to rituximab and further complications resulting in a splenectomy. (Hannema *et al* 2010) Information 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 and it should be noted this was a criterion for the agreed PICO. (Boonyasampant *et al*. 2015, Chonat *et al* 2018, Hannema *et al* 2010, Pirenne *et al* 2018 and Uhlmann *et al* 2014).

The results highlight the need for additional research studies in this area. 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.

In people with a haemoglobinopathy and DHTR/HH, only one publication detailed a 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) This patient was not treated with eculizumab during their episode of care so the evidence is also indirect. No evidence of safety of eculizumab as a treatment was identified.

From the evidence selected, 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.

## 3 Methodology

- The methodology to undertake this review is specified by NHS England in their 'Guidance on conducting evidence reviews for Specialised Commissioning Products' (2016).
- A description of the relevant Population, Intervention, Comparison and Outcomes (PICO) to be included in this review was prepared by NHS England's Policy Working Group for the topic (see section 9 for PICO).

- The PICO was used by Public Health England's Knowledge & Library Services to search for relevant publications in the following sources: Medline, Embase and Cochrane Library (see section 10 for search strategy).
- The search dates for publications were between 1st January 2006 and 1st January 2019
- The titles and abstracts of the results from the literature searches were assessed using the criteria from the PICO. Full text versions of publications which appeared potentially useful were obtained and reviewed to determine whether they were appropriate for inclusion. Publications which matched the PICO were selected for inclusion in this review.
- Evidence from all publications included was extracted and recorded in evidence summary tables, critically appraised and their quality assessed using the National Service Framework for Long Term Conditions (NSF-LTC) evidence assessment framework.

## 4 Results

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 and Pirenne *et al* 2018 and Uhlmann *et al* 2014) and three case-series studies. (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.

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. 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. A summary of the included studies is shown in Table 1 (Please see evidence summary tables in Section 7 for full details).

**Table 1- Summary of included studies**

| **Prevention of DHTR/HH using rituximab** | | | |
|---|---|---|---|
| **Study** | **Population** | **Intervention and comparison** | **Primary Outcome** |
| Cattoni *et al* 2013 (Case study) | 15-year-old with SCD | 375mg/m² rituximab four days before eritroexchange and 6 days post-surgery<br>No control | Survival and prevention of DHTR reaction |
| Noizat-Pirenne *et al* 2007 | 33-year-old with SCD | 1000mg of rituximab 3 days before hip replacement and 1000mg 7 days after procedure<br>No control | Survival and prevention of DHTR reaction |
| Noizat-Pirenne *et al* 2015 | 5 individuals with SCD:<br>33 years of age<br>53 years of age<br>25 years of age<br>22 years of age<br>27 years of age | 375mg/m² rituximab one month and 15 days prior to surgery<br>1000mg of rituximab one month and 15 days prior to surgery<br>1000mg rituximab one month prior to surgery<br>1000mg rituximab 10 days prior to surgery<br>1000mg rituximab 2 days prior to surgery | Survival and prevention of DHTR reaction |

| | | | |
|---|---|---|---|
| | | No controls | |
| Pirenne *et al* 2018 | 35-year-old with SCD | 1000mg of Rituximab one month and 15 days prior to cardiac surgery<br>No control | Survival and prevention of DHTR reaction |
| **Treatment of DHTR/HH with eculizumab** | | | |
| **Study** | **Population** | **Intervention and comparison** | **Primary Outcome** |
| Vagace *et al*. 2016 | 41-year-old with thalassemia | No information presented on dosage of eculizumab given<br>No control | Survival and stabilisation of haemoglobin/cessation of haemolysis |
| **Treatment of DHTR/HH with rituximab** | | | |
| **Study** | **Population** | **Intervention and comparison** | **Primary Outcome** |
| Boonyasampant *et al.* (2015) | 35-year-old with SCD | 375 mg/m², was given weekly for<br>4 weeks starting on Treatment Day 3<br>No control | Survival and stabilisation of haemoglobin/cessation of haemolysis |
| Chonat *et al* (2018) | 13-year-old with SCD | 4 doses of rituximab started on day 13 post reaction - no detail on dosage provided in publication<br>No control | Survival and stabilisation of haemoglobin/cessation of haemolysis |
| Hannema *et al* (2010) | 1.5-year-old with thalassemia | 375 mg/m² once weekly following 5th blood transfusion of patient- stopped due to allergic reaction<br>No control | Survival and stabilisation of haemoglobin/cessation of haemolysis |
| Pirenne *et al* (2018) | 26-year-old with SCD | 375 mg/m² weekly for 4 weeks) following Bone Marrow Transplant<br>No control | Survival and stabilisation of haemoglobin/cessation of haemolysis |
| Uhlmann *et al* (2014) | 21-year-old with SCD | Rituximab 375 mg/m² on day 6 and day 9 post DHTR episode presentation<br>No control | Survival and stabilisation of haemoglobin/cessation of haemolysis |

## Prevention of DHTR/HH using rituximab

Four publications were included in this section of the evidence review (Cattoni *et al* 2013, Noizat-Pirenne *et al* 2007, Noizat-Pirenne *et al* 2015 and Pirenne *et al* 2018). The publications by Cattoni *et al* 2013, Noizat-Pirenne *et al* 2007 were case reports and the publications by Noizat-Pirenne *et al* 2015 and Pirenne *et al* 2018 were case series.

***In people with a haemoglobinopathy and require elective blood transfusion, what is the clinical effectiveness of rituximab compared to IVIG and steroids or to rituximab and IVIG and steroids to prevent DHTR/HH?***

Based on the inclusion criteria none of the patients fully met the patient description defined in the PICO therefore the evidence presented is indirect. All patients identified received cross matched blood prior to an elective procedure. There was no information on if patients had previously experienced DHTR/HH despite pre-transfusion treatment with IVIG and steroids in the publications by Cattoni *et al* 2013, Noizat-Pirenne *et al* 2015 and Pirenne *et al* 2018. In the Noizat-Pirenne *et al* 2007 publication, the authors reported a prior DHTR/HH reaction following an elective hip surgery which was successfully treated with transfusion of cross-matched blood and steroids alone. All patients had prior experience of DHTR/HH and thus can be considered alloimmunised.

In the publication by Noizat-Pirenne *et al* 2015 five out of a possible eight patients were eligible and in the Pirenne *et al* 2018 case series one patient out of a total of three was eligible for

inclusion. One of the patients that was excluded from the Noizat-Pirenne *et al* 2015 publication was due to duplication as the patient was also described in the publication by Pirenne *et al* 2018.

More relevant information on the patient's disease progression and outcomes was available in the Pirenne *et al* 2018 publication therefore the decision was made to not include the information presented in Noizat-Pirenne *et al* 2015.

**Survival**

The eight patients treated with rituximab survived (Cattoni *et al* 2013, Noizat-Pirenne *et al* 2007, Noizat-Pirenne *et al* 2015 and Pirenne *et al* 2018).

**Acute health events- pain, stroke, Acute Chest Syndrome (ACS)**

One patient out of five reported in the Noizat-Pirenne *et al* 2015 publication suffered mild vaso-occlusive complications- haemoglobinuria.

**Acute health events- Acute facility utilisation**

Cattoni *et al* 2013 reported a patient who remained an inpatient following a DHTR/HH reaction and their stay was extended by approximately seven days post reaction. None of the patients reported in Noizat-Pirenne *et al* 2007 and Pirenne *et al* 2018 experienced a DHTR/HH reaction and did not utilise acute facilities beyond their expected elective care stay. Noizat-Pirenne *et al* 2015 reported three episodes of mild DHTR reactions in three patients out the total five patients but there was no information on the impact this had on length of stay in the acute facility following their elective procedures.

**Prevention of new alloantibody formation**

Three included studies indicated that none of the seven patients relevant to this review formed new alloantibodies post procedure at least 3 months following the initial intervention (Noizat-Pirenne *et al* 2007, Noizat-Pirenne *et al* 2015 and Pirenne *et al* 2018). Cattoni *et al* 2013 did not specify if new alloantibodies had been detected. However, a Direct Coombs test was found to be negative at the time the patient was experiencing HH.

**Prevention of further haemolytic transfusion reaction**

Cattoni *et al* 2013 detailed a case where a patient experienced a severe DHTR/HH despite pre-emptive rituximab administration, Noizat-Pirenne *et al* 2015 also reported three cases where a mild DHTR was observed despite pre-operative rituximab administration. Noizat-Pirenne *et al* 2015 also reported two patients who were prevented from further haemolytic transfusion reactions. Noizat-Pirenne *et al* 2007 and Pirenne *et al* 2018 both reported a patient who did not experience further haemolytic transfusion reactions.

**Requirement for further transfusion**

Cattoni *et al* 2013 reported one patient who required a further blood transfusion following a haemolytic transfusion reaction.

***In people with a haemoglobinopathy and require elective blood transfusion, what is the safety of rituximab compared to IVIG and steroids or to rituximab and IVIG and steroids to prevent DHTR/HH?***

No evidence was identified for this question

***In people with a haemoglobinopathy and require elective blood transfusion, what is the cost effectiveness of rituximab compared to IVIG and steroids or to rituximab and IVIG and steroids to prevent DHTR/HH?***

No evidence was identified for this question

***From the evidence selected, are there any subgroups (e.g. people with alloantibodies) that may benefit from rituximab more than the wider population of interest?***

No evidence was identified for this question

## Treatment of DHTR/HH using eculizumab

One publication was included in this section where eculizumab was used as a second line treatment on a patient with β-thalassemia. (Vagace *et al*. 2016) The publication included was a case series study.

Based on the inclusion criteria none of the patients fully met the patient description defined in the PICO therefore the evidence presented is indirect. Only one patient described in the study was treated with eculizumab and this patient did not meet the PICO definition of DHTR/HH as the haemolytic reaction occurred >28 days post transfusion. Initial treatment was with steroids, eritropoyetina and cyclosporine, when eculizumab was initiated the patient was treated with IVIG at the same time. (ibid.)

One publication was found where eculizumab was used with rituximab treatment but there was no indication that there was prior treatment with steroids of IVIG. (Boonyasampant *et al*. 2015) One publication was found where both eculizumab and rituximab were administered to a patient however there was not enough detail to ascertain in what order the drugs were given. (Pirenne *et al* 2018) A further paper was identified where the patient received rituximab as a second line treatment and eculizumab as a third line treatment. (Vlachaki *et al*. 2019) These papers have been included in the next section on treatment with rituximab.

***In people with a haemoglobinopathy and DHTR/HH, what is the clinical effectiveness of eculizumab compared to IVIG and steroids?***

### Survival

The patient identified survived. (Vagace *et al*. 2016)

### Acute health events- pain, stroke, ACS

Treatment with eculizumab and IVIG did not stop the haemolytic reaction and the patient went on to experience splenic sequestration and receive a splenectomy. (ibid.)

### Acute health events- Acute facility utilisation

The patient was admitted to hospital at the beginning of their episode of care. Information was not available on total length of stay or how splenic sequestration affected the length of time admitted (ibid.)

### Prevention of new alloantibody formation

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.)

**Stabilisation of haemoglobin/cessation of haemolysis**

Following splenectomy, the patient's haemoglobin levels stabilised. The publication does not detail the temporal relationship between eculizumab administration and haemoglobin levels. (ibid.)

**Requirement for further transfusion**

The patient received a transfusion prior to their splenectomy operation. (ibid.)

***In people with a haemoglobinopathy and DHTR/HH, what is the safety of eculizumab compared to IVIG and steroids?***

No evidence was identified for this question.

***In people with a haemoglobinopathy and DHTR/HH, what is the cost effectiveness of eculizumab compared to IVIG and steroids?***

No evidence was identified for this question

***From the evidence selected, are there any subgroups (e.g. people with alloantibodies) that may benefit from eculizumab more than the wider population of interest?***

No evidence was identified for this question

## Treatment of DHTR/HH using rituximab

Five publications were included in this section of the evidence review (Boonyasampant *et al*. 2015, Chonat *et al* 2018, Hannema *et al* 2010, Pirenne *et al* 2018 and Uhlmann *et al* 2014).

The publications by Boonyasampant *et al*. 2015, Chonat *et al* 2018, Hannema *et al* 2010 and Uhlmann *et al* 2014 were case reports and the publication by Pirenne *et al* 2018 was a case series. Of the case series included only one patient was deemed suitable for inclusion.

Based on the PICO none of the patients fully met the patient description therefore the evidence presented is indirect. The reasons for not meeting the PICO included: no use of eculizumab in two papers (Hannema *et al* 2010 and Uhlmann *et al* 2014), administration of eculizumab after initiation of rituximab or unclear order of administration (Boonyasampant *et al*. 2015 and Chonat *et al* 2018), no treatment with steroids and IVIG prior to rituximab initiation (Boonyasampant *et al*. 2015, Pirenne *et al* 2018 and Uhlmann *et al* 2014)

Two papers were not included in this section of the evidence review as the patients did not require ongoing blood transfusion therapy which was explicitly listed in the PICO as an indication for treatment with rituximab. (Gardner *et al* 2015 and Vlachaki *et al* 2019).

***For people with a haemoglobinopathy and DHTR/HH in whom eculizumab has not worked and who require ongoing blood transfusion therapy, what is the clinical effectiveness of rituximab compared to IVIg and steroids alone or to eculizumab, IVIG and steroids?***

**Survival**

The five patients included survived. (Boonyasampant *et al*. 2015, Chonat *et al* 2018, Hannema *et al* 2010, Pirenne *et al* 2018 and Uhlmann *et al* 2014)

**Acute health events- pain, stroke, ACS**

Three patients experienced acute health events post rituximab administration. (Chonat *et al* 2018, Hannema *et al* 2010 and Uhlmann *et al* 2014). One 13-year-old patient experienced pain, altered mental status, and development of new diffuse pulmonary oedema, eculizumab was initiated as a third line treatment approximately two days after initiation of rituximab. (Chonat et al 2018) A 1.5-year-old patient was treated with rituximab and then experienced anaphylaxis at which point rituximab was discontinued. The patient went on to have a negative reaction to a bone marrow transplant at which point rituximab was reinitiated alongside increasing their dose of corticosteroids, but treatment was not effective, and the patient was finally treated with splenectomy three months after the bone marrow transplant and seven months later another stem cell boost from their bone marrow donor. This patient was not treated with eculizumab at any point during their episode of DHTR. (Hannema *et al* 2010) A 21-year-old patient experiencing congestive heart failure was treated with rituximab 6 days after admission and the patient's heart failure continued to worsen, by day 13 the patient was critically ill and given further blood transfusions in conjunction with IVIG and no further rituximab. This patient was not treated with eculizumab at any point during their episode of DHTR. (Uhlmann *et al* 2014)

| Paper | Acute Health Event | Eculizumab administration | Steroids and IVIG administration |
|---|---|---|---|
| Chonat *et al* 2018 | Diffuse pulmonary oedema | Post rituximab administration | Initiated at same time as rituximab |
| Hannema *et al* 2010 | Negative reaction to a bone marrow transplant and splenomegaly | Not given | Given as first line treatment |
| Uhlmann *et al* 2014 | Congestive heart failure | Not given | Initiated after rituximab |

**Acute health events- Acute facility utilisation**

The patients were admitted to hospital at the beginning of their episode of care. Information 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)

**Prevention of new alloantibody formation**

Two patients were reported as not having evidence of further alloantibody formation. (Chonat *et al* 2018 and Hannema *et al* 2010) In the remaining publications results were not reported on if new alloantibodies were formed post treatment. (Boonyasampant *et al*. 2015, Pirenne *et al* 2018 and Uhlmann *et al* 2014)

**Stabilisation of haemoglobin/cessation of haemolysis**

In one patient Hb stabilised at 5.4g/dL by day seven after the initial DHTR reaction, five days after initiation of eculizumab and six days post initiation of rituximab treatment. The publication did not

provide Hb measurements for the time in between the administration of the two drugs so attributing impact for rituximab or eculizumab alone is not possible from the information presented. (Boonyasampant *et al*. 2015)

In one patient Hb stabilised at above 5g/dL by day twenty after the initial DHTR reaction. They treated with steroids as first line treatment from day one of presentation, IVIG and rituximab from day twelve and eculizumab was initiated on day fourteen alongside a blood transfusion at which point the patient's Hb levels began to stabilise. Attributing impact for rituximab or eculizumab alone is not possible from the information presented. (Chonat *et al* 2018)

In one patient rituximab given in conjunction with a blood transfusion caused an anaphylactic reaction at which point it was discontinued. This patient went on to receive a bone marrow transplant and rituximab was re-initiated and tolerated but the patient went on to experience splenomegaly and further anaemia. Full detail on Hb levels post initial anaphylactic reaction to rituximab were not reported. (Hannema *et al* 2010)

In one patient Hb stabilised at 3g/dL by day fifteen after the initial DHTR reaction, nine days post eculizumab initiation. The rituximab administration date is not clear from the information presented so attributing impact for rituximab or eculizumab alone is not possible from the information presented. (Pirenne *et al* 2018)

In one patient Hb stabilised at around 6g/dL fifteen days after the initial DHTR reaction, nine days after rituximab initiation and two days post IVIG initiation. The patient was not treated with eculizumab at any point during the episode. (Uhlmann *et al* 2014)

**Requirement for further transfusion**

All patients described required further blood transfusion and it should be noted this was a criteria for the agreed PICO. (Boonyasampant *et al*. 2015, Chonat *et al* 2018, Hannema *et al* 2010, Pirenne *et al* 2018 and Uhlmann *et al* 2014).

***For people with a haemoglobinopathy and DHTR/HH in whom eculizumab has not worked and who require ongoing blood transfusion therapy, what is the safety of rituximab compared to IVIg and steroids alone or to eculizumab, IVIG and steroids?***

A 1.5-year-old patient was treated with rituximab and then experienced anaphylaxis at which point rituximab was discontinued. Rituximab was later reinitiated alongside increasing their dose of corticosteroids and was tolerated. (Hannema *et al* 2010)

***For people with a haemoglobinopathy and DHTR/HH in whom eculizumab has not worked and who require ongoing blood transfusion therapy, what is the cost effectiveness of rituximab compared to IVIg and steroids alone or to eculizumab, IVIG and steroids?***

No evidence was identified for this question

***From the evidence selected, are there any subgroups (e.g. people with alloantibodies) that may benefit from rituximab more than the wider population of interest?***

No evidence was identified for this question

## 5 Discussion

There is very limited evidence of the impact of rituximab and eculizumab in the prevention and treatment of DHTR/HH from the literature found in this review. The included publications were limited to case reports and case series with small numbers of patients. The study designs did not include comparative analysis and thus limited conclusions can be drawn regarding efficacy in comparison to no treatment.

**Prevention- rituximab**

There is limited evidence to suggest a potential benefit of rituximab administration prior to elective procedures to prevent DHTR/HH reactions. The four included publications lack information on previous treatment failure with IVIG and steroids for a prior DHTR/HH reaction and this limits their suitability according to the pre-defined PICO in section 9.

Of the eight patients detailed by the included publications, one patient experienced a severe reaction despite rituximab administration (Cattoni *et al* 2013) and three experienced mild DHTR reactions (Noizat-Pirenne *et al* 2015). The other four patients did not experience a subsequent DHTR/HH reaction (Noizat-Pirenne *et al* 2007, Noizat-Pirenne *et al* 2015, Pirenne *et al* 2018). All patients survived and there was no evidence of new alloantibody formation following treatment with rituximab.

**Treatment- eculizumab**

There was only one publication eligible for inclusion on the use of eculizumab as a second line treatment and this patient did not meet the PICO as their DHTR reaction occurred more than 28 days after receiving a blood transfusion. Rituximab was given as a second line treatment in some other identified publications which were also excluded from this section but were included in the following section on rituximab treatment.

There was no evidence on whether eculizumab is an effective second line treatment in SCD patients experiencing DHTR/HH.

**Treatment- rituximab**

None of the patients included from the studies fully met the PICO definition. Of those patients treated with eculizumab it is not possible to separate the impact from that of rituximab as administration was very close to rituximab administration or it was not possible to discern order of administration. All the included patients survived and arguably benefited from the use of corticosteroids, IVIG, eculizumab and rituximab to slow the impact of DHTR reactions however due to the very small number of patients, the variety of ages and variation in treatment course it is not possible to draw definitive conclusions about the efficacy of rituximab as a treatment in relation to the other medications provided. Three patients were treated with a combination of steroids, IVIG, rituximab and eculizumab at different points in their disease progression. Two did not receive eculizumab during their treatment course and survived although one suffered severe complications and required a splenectomy

The included publications were all individual patient reports, and this means there is very limited evidence on whether rituximab was an effective third line treatment in SCD or thalassemia patients experiencing DHTR.

## 6 Conclusion

The outcomes of two case studies and two case series with a total of eight patients suggest a mixed response to the use of rituximab administration to prevent DHTR/HH as four of the eight patients experienced a haemolytic reaction although it is possible the treatment reduced the severity of the DHTR/HH reactions seen. The study methodology, including their small size, relatively short follow-up and lack of relevant comparators means that it is not possible to quantify the effect of rituximab in this group of patients, to make recommendations about use of rituximab to prevent DHTR/HH or to draw conclusions about the benefits and risks of rituximab treatment compared with no rituximab treatment. There is no evidence on the cost-effectiveness of rituximab treatment in a prevention context.

There is very limited evidence available on the clinical effectiveness of eculizumab as a second line treatment for patients experiencing DHTR/HH as only one study was identified in the evidence review. The results do not add to our knowledge or understanding of the problem except to highlight the need for additional research studies in this area. There is no evidence on the cost-effectiveness of eculizumab treatment in this context.

There is 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 is not possible to draw definitive conclusions about the efficacy of rituximab as a treatment alone. Of the three patients treated with corticosteroids, IVIG, eculizumab and rituximab there is a possibility that treatment reduced the impact of DHTR/HH reactions. One additional patient treated with corticosteroids, IVIG and rituximab may have experienced a benefit from treatment. One other patient experienced a severe reaction to rituximab and further complications. The results highlight the need for additional research studies in this area. There is no evidence on the cost-effectiveness of rituximab treatment in this context.

## 7 Evidence Summary Table

| Use of rituximab for the prevention of DHTR/HH in patients requiring elective interventions | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| **Study reference** | **Study Design** | **Population characteristics** | **Intervention** | **Outcome measure type** | **Outcome measures** | **Results** | **Quality of Evidence Score** | **Applicability** | **Critical Appraisal Summary** |
| Cattoni *et al* (2013) | Case report | 15 year old with SCD | 375mg/m² rituximab four days before eritroexchange and 6 days post-surgery | Primary | Survival | Patient survived | 1/10 | Indirect- Patient did not fully meet PICO as they received cross matched blood and there was no information on previous DHTR/HH treated unsuccessfully with IVIG and steroids | The publication is a case report of a 15 year old with SCD which limits its relevance to other age groups<br><br>The outcomes are detailed clearly but there is no control group. The publication contains a good amount of detail regarding clinical features of case. |
| | | | | | Acute health events- pain, stroke, ACS | None reported | | | |
| | | | | | Acute health events- Acute facility utilisation | Elective procedure where haemolytic reaction 7 days after elective procedure while still an inpatient. Discharged after four weeks. | | | |
| | | | | | Prevention of further haemolytic transfusion reaction | Despite rituximab administration prior to procedure HH did occur. Administered again 6 days post-surgery and HB continued to fall for 3 more days. | | | |
| | | | | | Requirement for further transfusion | Was given a further transfusion | | | |
| Noizat-Pirenne *et al* (2007) | Case report | 33 year old with SCD | 1000mg of rituximab 3 days before hip replacement and 1000mg 7 days after procedure | Primary | Survival | Patient survived | 1/10 | Indirect- Patient did not fully meet PICO as they received cross matched blood and included information detailed previous DHTR/HH treated successfully with steroids | The publication is a case report of an adult patient.<br><br>The outcomes are detailed clearly but there is no control group. The publication contains a good amount of detail regarding clinical features of case. |
| | | | | | Acute health events- pain, stroke, ACS | None reported | | | |
| | | | | | Acute health events- Acute facility utilisation | None reported | | | |
| | | | | | Prevention of new alloantibody formation | No new alloantibodies formed post procedure | | | |
| | | | | | Prevention of further haemolytic transfusion reaction | Yes- no reaction | | | |

| Use of rituximab for the prevention of DHTR/HH in patients requiring elective interventions | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| **Study reference** | **Study Design** | **Population characteristics** | **Intervention** | **Outcome measure type** | **Outcome measures** | **Results** | **Quality of Evidence Score** | **Applicability** | **Critical Appraisal Summary** |
| | | | | | Requirement for further transfusion | No further transfusion required | | | |
| Noizat-Pirenne *et al* (2015) | Case series | 5 individuals with SCD:<br><br>33 years of age<br>53 years of age<br>25 years of age<br>22 years of age<br>27 years of age | 375mg/m² rituximab one month and 15 days prior to surgery<br><br>1000mg of rituximab one month and 15 days prior to surgery<br><br>1000mg rituximab one month prior to surgery<br><br>1000mg rituximab 10 days prior to surgery<br><br>1000mg rituximab 2 days prior to surgery | Primary | Survival | All 5 patients survived | 3/10 | Indirect- Patients did not fully meet PICO as they received cross matched blood and there was no information on previous DHTR/HH treated unsuccessfully with IVIG and steroids | This publication is a case series of eight patients. Of these patients one is a duplicate of a patient also described in Pirenne *et al* (2018) and two patients were not relevant to the PICO as rituximab was administered in a context of emergency and not elective care. The duplicated patient was not included as more information was available on clinical outcomes for the individual in the Pirenne *et al* (2018) publication.<br><br>There is no control group. The publication contains a good amount of detail regarding the clinical features of cases but there is limited information on acute facility utilisation or requirement for further transfusion in the patients. |
| | | | | | Acute health events- pain, stroke, ACS | 1 patient with mild vaso-occlusive complications | | | |
| | | | | | Acute health events- Acute facility utilisation | Not reported | | | |
| | | | | | Prevention of new alloantibody formation | No new alloantibodies formed in all 5 patients | | | |
| | | | | | Prevention of further haemolytic transfusion reaction | 2 patients prevented from DHTR/HH, 3 mild DHTR reactions | | | |

| Use of rituximab for the prevention of DHTR/HH in patients requiring elective interventions | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| **Study reference** | **Study Design** | **Population characteristics** | **Intervention** | **Outcome measure type** | **Outcome measures** | **Results** | **Quality of Evidence Score** | **Applicability** | **Critical Appraisal Summary** |
| Pirenne *et al* (2018) | Case series | 35 year old with SCD | 1000mg of Rituximab one month and 15 days prior to cardiac surgery | Primary | Survival | Patient survived | 1/10 | Indirect- Patient did not fully meet PICO as they received cross matched blood and there was no information on previous DHTR/HH treated unsuccessfully with IVIG and steroids | This publication is a case series of three adult patients. Only one received rituximab in a prevention context and the other two patients described were not relevant to the research question. The patient included was also included in the Noizat-Pirenne *et al* (2015) publication and more information on the specifics of the individual was available in this publication than in the previously published information.<br><br>There is no control group. The publication contains sufficient detail on clinical outcomes for the patient. |
| | | | | | Acute health events- pain, stroke, ACS | None | | | |
| | | | | | Acute health events- Acute facility utilisation | None | | | |
| | | | | | Prevention of new alloantibody formation | No new alloantibodies formed at 3 month follow up | | | |
| | | | | | Prevention of further haemolytic transfusion reaction | Yes- No DHTR/HH reaction | | | |

| Use of Eculizumab as 2nd line treatment for the treatment of DHTR/HH | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| **Study reference** | **Study Design** | **Population characteristics** | **Intervention** | **Outcome measure type** | **Outcome measures** | **Results** | **Quality of Evidence Score** | **Applicability** | **Critical Appraisal Summary** |
| Vagace *et al*. 2016 | Case series | 41-year-old with thalassemia | No information presented on | Primary | Survival | Patient survived | 1/10 | Indirect- haemolytic reaction | This publication is a case series of six adult patients. Only one of |

| Use of Eculizumab as 2nd line treatment for the treatment of DHTR/HH | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| **Study reference** | **Study Design** | **Population characteristics** | **Intervention** | **Outcome measure type** | **Outcome measures** | **Results** | **Quality of Evidence Score** | **Applicability** | **Critical Appraisal Summary** |
| | | | dosage of eculizumab given | Primary | Acute health events-pain, stroke, ACS | Treatment with eculizumab and IVIG did not stop the haemolytic reaction and the patient went on to experience splenic sequestration and receive a splenectomy. | | occurred >28 days post transfusion and initial treatment was with steroids, eritropoyetina and cyclosporine, not IVIG and steroids. | the patients described was treated with eculizumab and this patient did not fully meet the PICO definition. The haemolytic reaction occurred >28 days post transfusion and initial treatment was with steroids, erythropoietin and cyclosporine.<br><br>The outcomes are detailed clearly but there is no control group or detail around amount of eculizumab administered. The publication contains a good amount of detail regarding clinical features of the case. |
| | | | | Primary | Acute health events-Acute facility utilisation | The patient was admitted to hospital at the beginning of their episode of care. Information was not available on total length of stay or how splenic sequestration affected the length of time admitted | | | |
| | | | | Primary | Prevention of new alloantibody formation | The patient developed several clinically significant alloantibodies though at what point during their inpatient episode this was identified was not clear. | | | |
| | | | | Primary | Stabilisation of haemoglobin/cessation of haemolysis | Following splenectomy, the patient's haemoglobin levels stabilised. No detail on the temporal relationship between eculizumab administration and haemoglobin levels. | | | |
| | | | | Primary | Requirement for further transfusion | The patient received a transfusion prior to their splenectomy operation. | | | |

| Use of Rituximab for the treatment of DHTR/HH | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| **Study reference** | **Study Design** | **Population characteristics** | **Intervention** | **Outcome measure type** | **Outcome measures** | **Results** | **Quality of Evidence Score** | **Applicability** | **Critical Appraisal Summary** |
| | Case report | | | Primary | Survival | Patient survived | 1/10 | | |

| Use of Rituximab for the treatment of DHTR/HH | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| **Study reference** | **Study Design** | **Population characteristics** | **Intervention** | **Outcome measure type** | **Outcome measures** | **Results** | **Quality of Evidence Score** | **Applicability** | **Critical Appraisal Summary** |
| Boonyasampant *et al.* (2015) | | 35-year-old with SCD | 375 mg/m², was given weekly for 4 weeks starting on Treatment Day 3 | | Stabilisation of haemoglobin/ cessation of haemolysis | Patient Hb stabilised at 5.4g/dL by day seven after the initial DHTR reaction, five days after initiation of eculizumab and six days post initiation of rituximab treatment. | | Indirect- not treated with steroids and IVIG prior to rituximab initiation and eculizumab and rituximab administration happened very close together, so outcomes cannot be separated for the two drugs. | The publication is a case report of an adult patient.<br><br>Publication does not meet PICO fully as patient was not treated with steroids and IVIG prior to rituximab initiation and eculizumab and rituximab administration happened very close together, so outcomes cannot be separated for the two drugs.<br><br>The outcomes are detailed clearly but there is no control group. The publication contains a good amount of detail regarding clinical features of case. |
| | | | | | Requirement for further transfusion | Transfused with four more matched units | | | |
| Chonat *et al* (2018) | Case report | 13-year-old with SCD | 4 doses of rituximab started on day 13 post reaction - no detail on dosage provided in publication | Primary | Survival | Patient survived | 1/10 | Indirect- patient was treated with IVIG at the same time as rituximab and eculizumab administration happened after rituximab initiation. | The publication is a case report of an adult patient.<br><br>Publication does not meet PICO fully as patient was treated with IVIG at the same time as rituximab and eculizumab administration happened after rituximab initiation.<br><br>The outcomes are detailed clearly but |
| | | | | | Acute health events- pain, stroke, ACS | The patient experienced pain altered mental status, and development of new diffuse pulmonary oedema the day after initiation of rituximab treatment | | | |
| | | | | | Prevention of new alloantibody formation | The patient was reported as not having evidence of further alloantibody formation | | | |
| | | | | | Stabilisation of haemoglobin/ cessation of haemolysis | Patient Hb stabilised at above 5g/dL by day twenty after the initial DHTR reaction. They treated with steroids as first line treatment from day one of presentation, IVIG and rituximab from day twelve and eculizumab was initiated on day | | | |

| Use of Rituximab for the treatment of DHTR/HH | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| **Study reference** | **Study Design** | **Population characteristics** | **Intervention** | **Outcome measure type** | **Outcome measures** | **Results** | **Quality of Evidence Score** | **Applicability** | **Critical Appraisal Summary** |
| | | | | | | fourteen alongside a blood transfusion at which point the patient's Hb levels began to stabilise. | | | there is no control group. The publication contains a good amount of detail regarding clinical features of case. |
| | | | | | Requirement for further transfusion | Transfused with one more matched unit | | | |
| Hannema *et al* (2010) | Case report | 1.5-year-old with thalassemia | 375 mg/m² once weekly following 5th blood transfusion of patient- stopped due to allergic reaction<br><br>375 mg/m² weekly for 4 weeks) following Bone Marrow Transplant | Primary | Survival | Patient survived | 1/10 | Indirect- patient was not treated with eculizumab during their episode of care | The publication is a case report of a very young patient.<br><br>Publication does not meet PICO fully as patient was not treated with eculizumab during their episode of care<br><br>The outcomes are detailed clearly but there is no control group. The publication contains a good amount of detail regarding clinical features of case. |
| | | | | | Acute health events- pain, stroke, ACS | The patient was treated with rituximab and then experienced anaphylaxis at which point rituximab was discontinued. The patient went on to have a negative reaction to a bone marrow transplant at which point rituximab was reinitiated alongside increasing their dose of corticosteroids, but treatment was not effective, and the patient was finally treated with splenectomy three months after the bone marrow transplant. | | | |
| | | | | | Prevention of new alloantibody formation | The patient was reported as not having evidence of further alloantibody formation | | | |
| | | | | | Stabilisation of haemoglobin/ cessation of haemolysis | In one patient rituximab given in conjunction with a blood transfusion caused an anaphylactic reaction at which point it was discontinued. Full detail on Hb levels post initial anaphylactic reaction to rituximab were not reported. | | | |
| | | | | | Requirement for further transfusion | Transfused with four more matched units | | | |
| | | | | | Treatment complications | The patient was treated with rituximab and then experienced anaphylaxis at which point rituximab was discontinued. Rituximab was later reinitiated alongside increasing their dose of corticosteroids and was tolerated | | | |
| Pirenne *et al* (2018) | Case reports | 26-year-old with SCD | Rituximab administration - no detail on dosage provided in publication | Primary | Survival | Patient survived | 1/10 | Indirect- not initially treated with IVIG and steroids. Order of eculizumab and rituximab | This publication is a case series on three adult patients. Only one patient received eculizumab and rituximab in a |
| | | | | | Stabilisation of haemoglobin/ cessation of haemolysis | Hb stabilised at 3g/dL by day 15 after reaction, 9 days post eculizumab. Rituximab administration date not clear | | | |

| Use of Rituximab for the treatment of DHTR/HH | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| **Study reference** | **Study Design** | **Population characteristics** | **Intervention** | **Outcome measure type** | **Outcome measures** | **Results** | **Quality of Evidence Score** | **Applicability** | **Critical Appraisal Summary** |
| | | | | | Requirement for further transfusion | Transfused with one more matched unit | | initiation is not clear. | treatment context. The included patient did not meet PICO fully as they were not initially treated with IVIG and steroids. In addition, the dates of eculizumab and rituximab initiation are not clear.<br><br>There is no control group. The publication contains sufficient detail on clinical outcomes for the patient but no there is no specific mention of steroid administration, quantity of rituximab administered and the time between eculizumab and rituximab initiation is not clear. |
| Uhlmann *et al* (2014) | Case report | 21-year-old with SCD | Rituximab 375 mg/m² on day 6 and day 9 post DHTR episode presentation | Primary | Survival | Patient survived | 1/10 | Indirect- patient was not treated with eculizumab during their episode of care and the patient was not initially treated with IVIG and steroids. | The publication is a case report of an adult patient.<br><br>Publication does not meet PICO fully as patient was not treated with eculizumab during their episode of care and the patient was not initially treated with IVIG and steroids.<br><br>The outcomes are detailed clearly but there is no control group. The publication |
| | | | | | Acute health events- pain, stroke, ACS | Patient experiencing congestive heart failure was treated with rituximab 6 days after admission and the patient's heart failure continued to worsen, by day 13 the patient was critically ill and given further blood transfusions in conjunction with IVIG and no further rituximab. | | | |
| | | | | | Stabilisation of haemoglobin/ cessation of haemolysis | Patient Hb stabilised at around 6g/dL fifteen days after the initial DHTR reaction, nine days after rituximab initiation and two days post IVIG initiation. | | | |
| | | | | | Requirement for further transfusion | Transfused with one more matched unit | | | |

| Use of Rituximab for the treatment of DHTR/HH | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| **Study reference** | **Study Design** | **Population characteristics** | **Intervention** | **Outcome measure type** | **Outcome measures** | **Results** | **Quality of Evidence Score** | **Applicability** | **Critical Appraisal Summary** |
| | | | | | | | | | contains a good amount of detail regarding clinical features of case. |

| Cost-effectiveness studies | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| **Study reference** | **Study Design** | **Population characteristics** | **Intervention** | **Outcome measure type** | **Outcome measures** | **Results** | **Quality of Evidence Score** | **Applicability** | **Critical Appraisal Summary** |
| None identified | | | | | | | | | |

## 8 Grade of evidence table

| Use of rituximab for the prevention of DHTR/HH in patients requiring elective interventions | | | | | |
|---|---|---|---|---|---|
| **Outcome Measure** | **Reference** | **Quality of Evidence Score** | **Applicability** | **Grade of Evidence** | **Interpretation of Evidence** |
| Survival | Cattoni *et al* (2013) | 1 | Indirect | C | Survival in the context of the publications is the number of patients treated with rituximab that survived elective procedures where there was a risk of DHTR/HH.<br><br>All eight patients described by the four publications reporting this outcome survived. The publication with the strongest evidence was Noizat-Pirenne *et al* (2015) where the five patients described all survived however this evidence was indirect as no information on if patients had experienced prior DHTR/HH despite treatment with steroids or IVIG was available and all patients received matched blood for their elective transfusions.<br><br>A high overall survival rate is important to clinicians, patients and their families. However, this study does not demonstrate that overall survival is improved by the intervention as limited conclusions can be drawn from a small case series. Since the study does not include a comparator, it is not possible to compare the outcomes for these patients with those receiving alternative treatments. The patients were not followed up at specified time intervals following the intervention so long-term survival is not considered. |
| | Noizat-Pirenne *et al* (2007) | 1 | Indirect | | |
| | Noizat-Pirenne *et al* (2015) | 3 | Indirect | | |
| | Pirenne *et al* (2018) | 1 | Indirect | | |
| Acute health events- pain, stroke, ACS | Cattoni *et al* (2013) | 1 | Indirect | C | The publication of the four identified with the strongest evidence was Noizat-Pirenne *et al* (2015) where one of the five patients described experienced an acute health event- haemoglobinuria however this evidence was indirect as no information on if the patient had experienced prior DHTR/HH despite treatment with steroids or IVIG was available and they received matched blood for their elective transfusion.<br><br>Low rates of acute health event reactions are important to clinicians, patients and their families. However, this study does not demonstrate definitively that the risk of acute health events is improved by the intervention as limited conclusions can be drawn from a small case series. Of the five patients described, only one suffered this type of complication which indicates there is very limited evidence that rituximab prevented further acute health events. Since the study does not include a comparator, it is not possible to compare the outcomes for these patients with those receiving alternative treatments. |
| | Noizat-Pirenne *et al* (2007) | 1 | Indirect | | |
| | Noizat-Pirenne *et al* (2015) | 3 | Indirect | | |

| Use of rituximab for the prevention of DHTR/HH in patients requiring elective interventions | | | | | |
|---|---|---|---|---|---|
| **Outcome Measure** | **Reference** | **Quality of Evidence Score** | **Applicability** | **Grade of Evidence** | **Interpretation of Evidence** |
| | Pirenne *et al* (2018) | 1 | Indirect | | |
| Acute health events- Acute facility utilisation | Cattoni *et al* (2013) | 1 | Indirect | C | Acute facility utilisation in the context of the publications is the amount of additional time spent in an acute setting following an elective procedure where patients were treated with rituximab.<br><br>Only one publication presented this information- Cattoni *et al* (2013) where the patient described experienced a DHTR/HH reaction seven days after their elective procedure. The patient was discharged after four weeks however it was not clear what the original intended length of stay was though this provides very limited evidence that acute facility utilisation is still possible despite treatment. The evidence presented was indirect as no information was included on if the individual was treated previously with steroids and IVIG pre-transfusion to no effect<br><br>A reduced rate of acute hospital usage is important to clinicians, patients and their families. However, this study does not demonstrate the intervention prevents acute facility utilisation as there are high levels of uncertainty when drawing wider conclusions from a case study. Since the study does not include a comparator, it is not possible to compare the outcomes for this patient with those receiving alternative treatments. |
| Prevention of further haemolytic transfusion reaction | Cattoni *et al* (2013) | 1 | Indirect | C | Prevention of further haemolytic transfusion reaction in the context of the publications is the number of patients who experienced a DHTR/HH following treatment with rituximab during their post-operative follow up care.<br><br>Four of eight patients experienced a DHTR/HH reaction, the publication with the strongest evidence was Noizat-Pirenne *et al* (2015) where three of the five patients described experienced a mild DHTR reaction. This evidence was indirect as no information was included on if patients had experienced prior DHTR/HH despite treatment with steroids or IVIG was available and all patients received matched blood for their elective transfusions.<br><br>Prevention of further haemolytic transfusion reaction is important to clinicians, patients and their families. However, this study does not demonstrate that prevention of further haemolytic transfusion reaction is improved by the intervention as limited conclusions can be drawn from a small case series. Since the study does not include a comparator, it is not possible to compare the outcomes for these patients with those receiving alternative treatments. |
| | Noizat-Pirenne *et al* (2007) | 1 | Indirect | | |
| | Noizat-Pirenne *et al* (2015) | 3 | Indirect | | |
| | Pirenne *et al* (2018) | 1 | Indirect | | |

| Use of rituximab for the prevention of DHTR/HH in patients requiring elective interventions | | | | | |
|---|---|---|---|---|---|
| **Outcome Measure** | **Reference** | **Quality of Evidence Score** | **Applicability** | **Grade of Evidence** | **Interpretation of Evidence** |
| Requirement for further transfusion | Cattoni *et al* (2013) | 1 | Indirect | C | Reducing the requirement for further transfusion in the context of the publications is the number of patients who required additional unplanned blood units following their elective follow up care.<br><br>Two of a total of three patients required further transfusions, the publication with the strongest evidence was Cattoni *et al* (2013) where the patient described required a further transfusion due to a DHTR/HH reaction to prevent severe anaemia. The evidence presented was indirect as no information was included on if the individual was treated previously with steroids and IVIG pre-transfusion to no effect.<br><br>Reducing the requirement for further transfusion is important to clinicians. However, this study does not demonstrate that the intervention reduces the requirement for further transfusion as there are high levels of uncertainty when drawing wider conclusions from a case study. Since the study does not include a comparator, it is not possible to compare the outcomes for this patient with those receiving alternative treatments. |
| | Noizat-Pirenne *et al* (2007) | 1 | Indirect | | |
| Prevention of new alloantibody formation | Noizat-Pirenne *et al* (2007) | 1 | Indirect | C | Prevention of new alloantibody formation in the context of the publications is the number of patients treated with rituximab that had new alloantibodies in their blood at post-operative follow up.<br><br>All seven patients described by the publications survived, the publication with the strongest evidence was Noizat-Pirenne *et al* (2015) where none of the five patients described had formed new alloantibodies between 3 months and 1 year post initial intervention. This evidence was indirect as no information was included on if patients had experienced prior DHTR/HH despite treatment with steroids or IVIG was available and all patients received matched blood for their elective transfusions.<br><br>Prevention of new alloantibody formation is important to clinicians, patients and their families. However, this study does not demonstrate definitively that new alloantibody formation is prevented by the intervention although as no patients developed new antibodies there is limited evidence to suggest this is the case. Limited conclusions can be drawn from a small case series and since the study does not include a comparator, it is not possible to compare the outcomes for these patients with those receiving alternative treatments. |
| | Noizat-Pirenne *et al* (2015) | 3 | Indirect | | |
| | Pirenne *et al* (2018) | 1 | Indirect | | |

| Use of eculizumab as treatment for the treatment of DHTR/HH | | | | | |
|---|---|---|---|---|---|
| **Outcome Measure** | **Reference** | **Quality of Evidence Score** | **Applicability** | **Grade of Evidence** | **Interpretation of Evidence** |
| Survival | Vagace *et al.* 2016 | 1 | Indirect | C | Survival in the context of the publications is the number of patients treated with eculizumab that survived an episode of DHTR/HH.<br>The only patient described by the publication survived. This evidence is indirect as the haemolytic reaction occurred >28 days post transfusion and initial treatment was with steroids, erythropoietin and cyclosporine, not IVIG and steroids.<br>A high overall survival rate is important to clinicians, patients and their families. However, this study does not demonstrate that overall survival is improved by the intervention as limited conclusions can be drawn from a small case study. Since the study does not include a comparator, it is not possible to compare the outcomes for this patient with those receiving alternative treatments. The patient was not followed up at specified time intervals following the intervention so long-term survival is not considered. |

| Use of eculizumab as treatment for the treatment of DHTR/HH | | | | | |
|---|---|---|---|---|---|
| **Outcome Measure** | **Reference** | **Quality of Evidence Score** | **Applicability** | **Grade of Evidence** | **Interpretation of Evidence** |
| Acute health events- pain, stroke, ACS | Vagace *et al.* 2016 | 1 | Indirect | C | The patient described by the publication went on to suffer splenic sequestration. This evidence is indirect as the haemolytic reaction occurred >28 days post transfusion and initial treatment was with steroids, erythropoietin and cyclosporine, not IVIG and steroids.<br>Low rates of acute health event reactions are important to clinicians, patients and their families. However, this study does not demonstrate definitively that the risk of acute health events is improved by the intervention as limited conclusions can be drawn from a small case study. In the patient described, treatment with eculizumab and IVIG did not stop the haemolytic reaction and the patient went on to experience splenic sequestration and receive a splenectomy. Since the study does not include a comparator, it is not possible to compare the outcomes for these patients with those receiving alternative treatments. |
| Prevention of new alloantibody formation | Vagace *et al.* 2016 | 1 | Indirect | C | Prevention of new alloantibody formation in the context of the publications is the number of patients treated with eculizumab that had new alloantibodies in their blood at post-operative follow up.<br>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. This evidence is indirect as the haemolytic reaction occurred >28 days post transfusion and initial treatment was with steroids, erythropoietin and cyclosporine, not IVIG and steroids.<br>Prevention of new alloantibody formation is important to clinicians, patients and their families. However, this study does not demonstrate definitively that new alloantibody formation is prevented by the intervention the included patient was reported to have developed new antibodies. Limited conclusions can be drawn from a small case study and since the study does not include a comparator, it is not possible to compare the outcomes for these patients with those receiving alternative treatments. |
| Stabilisation of haemoglobin/cessation of haemolysis | Vagace *et al.* 2016 | 1 | Indirect | C | Stabilisation of haemoglobin/cessation of haemolysis in the context of the publications is the return of Hb levels to pre-DHTR levels following a DHTR/HH episode.<br><br>Following splenectomy, the patient's haemoglobin levels stabilised. The publication does not detail the temporal relationship between eculizumab administration and haemoglobin levels. This evidence is also indirect as the haemolytic reaction occurred >28 days post transfusion and initial treatment was with steroids, erythropoietin and cyclosporine, not IVIG and steroids.<br><br>Stabilisation of haemoglobin/cessation of haemolysis is important to clinicians, patients and their families. However, this study does not demonstrate that stabilisation of haemoglobin/cessation of haemolysis is reached by the intervention as there are high levels of uncertainty when drawing wider conclusions from a case study. Since the study does not include a comparator, it is not possible to compare the outcomes for these patients with those receiving alternative treatments. |
| Requirement for further transfusion | Vagace *et al.* 2016 | 1 | Indirect | C | Requirement for further transfusion in the context of the publications is the number of patients treated with eculizumab as a 2nd line treatment that required additional units of blood following treatment.<br><br>The patient received another transfusion following eculizumab administration in advance of their splenectomy operation. This evidence is indirect as the haemolytic reaction occurred >28 days post transfusion and initial treatment was with steroids, erythropoietin and cyclosporine, not IVIG and steroids.<br><br>This study does not demonstrate requirement for further transfusion is impacted by the intervention as there are high levels of uncertainty when drawing wider conclusions from a case study. Since the study does not include a comparator, it is not possible to compare the outcomes for these patients with those receiving alternative treatments. |

| Use of rituximab as treatment of DHTR/HH | | | | | |
|---|---|---|---|---|---|
| **Outcome Measure** | **Reference** | **Quality of Evidence Score** | **Applicability** | **Grade of Evidence** | **Interpretation of Evidence** |
| Survival | Boonyasampant *et al.* (2015) | 1 | Indirect | C | Survival in the context of the publications is the number of patients treated with rituximab that survived a DHTR/HH episode.<br><br>None of the patients included fully met the PICO. All the studies dealt with individual patients and did not follow up patients at specified time intervals following the reaction. None of the papers can be described as having stronger evidence than the other included papers as they were all individual case studies.<br><br>A high overall survival rate is important to clinicians, patients and their families. However, none of the studies demonstrate that overall survival is improved by the intervention as there are high levels of uncertainty when drawing wider conclusions from case studies. Since the studies do not include a comparator, it is not possible to compare the outcomes for these patients with those receiving alternative treatments. |
| | Chonat *et al* (2018) | 1 | Indirect | | |
| | Hannema *et al* (2010) | 1 | Indirect | | |
| | Pirenne *et al* (2018) | 1 | Indirect | | |
| | Uhlmann *et al* (2014) | 1 | Indirect | | |
| Acute health events- pain, stroke, ACS | Chonat *et al* (2018) | 1 | Indirect | C | The publication with the strongest evidence was Chonat *et al* (2018) where the patient was treated with both drugs of interest identified in the PICO although order of administration of corticosteroids, IVIG, rituximab and eculizumab was not as specified by the PICO. |

| Use of rituximab as treatment of DHTR/HH | | | | | |
|---|---|---|---|---|---|
| **Outcome Measure** | **Reference** | **Quality of Evidence Score** | **Applicability** | **Grade of Evidence** | **Interpretation of Evidence** |
| | Hannema *et al* (2010) | 1 | Indirect | | The patient experienced pain altered mental status, and development of new diffuse pulmonary oedema the day after initiation of rituximab treatment and then went on to be given eculizumab after which the patient improved.<br><br>Low rates of acute health event reactions are important to clinicians, patients and their families. However, this study does not demonstrate definitively that the risk of acute health events is improved by the intervention as limited conclusions can be drawn from a small case study. There is very limited evidence that rituximab prevented further acute health events although the evidence may suggest it ameliorated adverse health effects in conjunction with eculizumab. Since the study does not include a comparator, it is not possible to compare the outcomes for these patients with those receiving alternative treatments. |
| | Uhlmann *et al* (2014) | 1 | Indirect | | |
| Acute health events- Acute facility utilisation | Boonyasampant *et al.* (2015) | 1 | Indirect | C | None of the patients included fully met the PICO. None of the papers can be described as having stronger evidence than the other included papers as they were all individual case studies.<br><br>The patients were admitted to hospital at the beginning of their episode of care. Information was not available on total length of stay or how complications experienced affected the length of time admitted.<br><br>A reduced rate of acute hospital usage is important to clinicians, patients and their families. However, these studies do not demonstrate the intervention prevents acute facility utilisation as there are high levels of uncertainty when drawing wider conclusions from case studies. Since the studies do not include a comparator, it is not possible to compare the outcomes for this patient with those receiving alternative treatments. |
| | Chonat *et al* (2018) | 1 | Indirect | | |
| | Hannema *et al* (2010) | 1 | Indirect | | |
| | Pirenne *et al* (2018) | 1 | Indirect | | |
| | Uhlmann *et al* (2014) | 1 | Indirect | | |
| Prevention of new alloantibody formation | Chonat *et al* (2018) | 1 | Indirect | C | Prevention of new alloantibody formation in the context of the publications is the number of patients treated with rituximab that had new alloantibodies in their blood during their episode of care. |

| Use of rituximab as treatment of DHTR/HH | | | | | |
|---|---|---|---|---|---|
| **Outcome Measure** | **Reference** | **Quality of Evidence Score** | **Applicability** | **Grade of Evidence** | **Interpretation of Evidence** |
| | Hannema *et al* (2010) | 1 | Indirect | | The publication with the strongest evidence was Chonat *et al* (2018) where the patient was treated with both drugs of interest identified in the PICO although order of administration of corticosteroids, IVIG, rituximab and eculizumab was not as specified by the PICO.<br><br>The publication reported that the patient did not develop new alloantibodies during their inpatient episode.<br><br>Prevention of new alloantibody formation is important to clinicians, patients and their families. However, this study does not demonstrate definitively that new alloantibody formation is prevented by the intervention. Limited conclusions can be drawn from a small case study and since the study does not include a comparator, it is not possible to compare the outcomes for these patients with those receiving alternative treatments. |
| Stabilisation of haemoglobin/cessation of haemolysis | Boonyasampant *et al.* (2015) | 1 | Indirect | C | Stabilisation of haemoglobin/cessation of haemolysis in the context of the publications is the return of Hb levels to pre-DHTR levels following a DHTR/HH episode.<br><br>The publication with the strongest evidence was Chonat *et al* (2018) where the patient was treated with both drugs of interest identified in the PICO although order of administration of corticosteroids, IVIG, rituximab and eculizumab was not as specified by the PICO.<br><br>The patient Hb stabilised at above 5g/dL by day twenty after the initial DHTR reaction. They treated with steroids as first line treatment from day one of presentation, IVIG and rituximab from day twelve and eculizumab was initiated on day fourteen alongside a blood transfusion at which point the patient's Hb levels began to stabilise. Attributing impact for rituximab or eculizumab alone is not possible from the information presented.<br><br>Stabilisation of haemoglobin/cessation of haemolysis is important to clinicians, patients and their families. However, this study does not demonstrate that stabilisation of haemoglobin/cessation of haemolysis is reached by the intervention as there are high levels of uncertainty when drawing wider conclusions from a case study. Since the study does not include a comparator it is not possible to compare the outcomes for these patients with those receiving alternative treatments. |
| | Chonat *et al* (2018) | 1 | Indirect | C | |
| | Hannema *et al* (2010) | 1 | Indirect | C | |
| | Pirenne *et al* (2018) | 1 | Indirect | C | |
| | Uhlmann *et al* (2014) | 1 | Indirect | C | |
| Treatment complications | Hannema *et al* (2010) | 1 | Indirect | C | The only publication that described a treatment complication was Hannema *et al* (2010).<br><br>A 1.5-year-old patient was treated with rituximab and then experienced anaphylaxis at which point rituximab was discontinued. Rituximab was later reinitiated alongside increasing their dose of corticosteroids and was tolerated indicating the allergic reaction was not permanent. |

| Use of rituximab as treatment of DHTR/HH | | | | | |
|---|---|---|---|---|---|
| **Outcome Measure** | **Reference** | **Quality of Evidence Score** | **Applicability** | **Grade of Evidence** | **Interpretation of Evidence** |
| | | | | | However, this study does not demonstrate that treatment complications are likely as there are high levels of uncertainty when drawing wider conclusions from a case study and the included patient did not have persistent reactions to rituximab. Since the study does not include a comparator, it is not possible to compare the outcomes for these patients with those receiving alternative treatments. |

## 9 Literature Search Terms

<table>
<tr><th colspan="2">PICO table- Prevention</th></tr>
<tr><td>P – Patients / Population<br>Which patients or populations of patients are we interested in? How can they be best described? Are there subgroup<br>s that need to be considered?</td><td>All patients with SCD (all genotypes) or thalassemia (all genotypes) where blood transfusion is required electively in a patient:<br>a) who had DHTR/HH previously despite pre-transfusion treatment with IVIGs and steroids.<br>b) with multiple red cell alloantibodies where compatible blood is not available</td></tr>
<tr><td>I – Intervention<br>Which intervention, treatment or approach should be used?</td><td>For population a)<br>Rituximab<br><br>For population b)<br>Rituximab + Steroid therapy + IVIG</td></tr>
<tr><td>C – Comparison<br>What is/are the main alternative/s to compare with the intervention being considered?</td><td>For both populations a) and b)<br>Steroid therapy and IVIG</td></tr>
<tr><td>O – Outcomes<br>What is really important for the patient? Which outcomes should be considered? Examples include intermediate or short-term outcomes; mortality; morbidity and quality of life; treatment complications; adverse effects; rates of relapse; late morbidity and re-admission; return to work, physical and social functioning, resource use.</td><td><u>Critical to decision-making:</u><br><br>1. Survival<br>2. Acute Health events<br>• Number of acute sickle cell disease complications (e.g. pain, stroke, acute chest syndrome)<br>• Acute Hospital utilisation (days in hospital, days on intensive care unit)<br>3. Prevention of new alloantibody formation<br>4. Prevention of further haemolytic transfusion reactions<br>5. Requirement for further transfusion<br><br><u>Important to decision-making:</u><br><br>1. Treatment complications<br>2. Activities of daily living<br>3. Cost-effectiveness<br>4. Length of ITU/Hospital stay</td></tr>
<tr><td colspan="2">Assumptions / limits applied to search<br><br>Inclusion:<br>English language<br>Studies published from 2006 onwards<br>Case reports, case series, cohort studies, case control studies, RCTs, systematic reviews<br><br>Exclusion:<br>Studies which are not able to be identified and retrieved via one of the following search engines: MEDLINE, Embase, Cochrane.<br>Grey literature including conference publications, abstracts, posters, letters, internet publications, manufacturer documents</td></tr>
</table>

| PICO table- Treatment | |
|---|---|
| **P – Patients / Population**<br>Which patients or populations of patients are we interested in? How can they be best described? Are there subgroup<br>s that need to be considered? | For eculizumab:<br><br>All patients with SCD (all genotypes) or thalassemia (all genotypes) with a diagnosis of DHTR/HH AND evidence of rapid haemolysis<br>AND<br>Symptomatic anaemia OR Compromise of another organ system (e.g. respiratory failure, renal failure, neurological symptoms)<br>AND<br>Initial treatment with IVIG and steroids has not slowed the rate of haemolysis.<br><br>For rituximab:<br><br>As above AND eculizumab has been given and is not working AND there is a need for ongoing blood transfusion therapy.<br><br>[For information: DHTR case definition: patients with a significant drop in haemoglobin (Hb) in the absence of an alternative cause within 21 days of transfusion associated with one or more of: new red cell alloantibody (or antibodies), haemoglobinuria, an HbA level that decreases more rapidly than expected post transfusion, relative reticulocytopenia or reticulocytosis from baseline and significant rise in lactate dehydrogenase (LDH) from baseline]. |
| **I – Intervention**<br>Which intervention, treatment or approach should be used? | 1 Eculizumab use as 2nd line treatment (following 1st line IVIG and steroids) and supportive care<br><br>2 Rituximab use as 3rd line treatment (following 1st line IVIG and steroids, 2nd line eculizumab) and supportive care<br><br>. |
| **C – Comparison**<br>What is/are the main alternative/s to compare with the intervention being considered? | 1 IVIG and steroids and supportive care<br><br>2 IVIG and steroids, eculizumab and supportive care |
| **O – Outcomes**<br>What is really important for the patient? Which outcomes should be considered? Examples include intermediate or short-term outcomes; mortality; morbidity and quality of life; treatment complications; adverse effects; rates of relapse; late morbidity and re-admission; return to work, physical and social functioning, resource use. | *Critical to decision-making:*<br><br>1. Survival<br>2. Acute Health events<br>• Number of acute sickle cell disease complications (e.g. pain, stroke, acute chest syndrome) or other medical complications (e.g. acute or chronic renal failure)<br>• Acute Hospital utilisation (days in hospital, days on intensive care unit)<br>3. Prevention of new alloantibody formation<br>4. Prevention of further haemolytic transfusion reactions<br>5. Stabilisation of haemoglobin/cessation of haemolysis<br>6. Requirement for further transfusion |

| | |
|---|---|
| | *Important to decision-making:*<br><br>1. Treatment complications<br>2. Activities of daily living<br>3. Cost-effectiveness<br>*4.* Length of ITU/Hospital stay |
| **Assumptions / limits applied to search**<br>Inclusion:<br>English language<br>Studies published from 2006 onwards<br>Case reports, case series, cohort studies, case control studies, RCTs, systematic reviews<br><br>Exclusion:<br>Studies which are not able to be identified and retrieved via one of the following search engines: MEDLINE, Embase, Cochrane.<br>Grey literature including conference publications, abstracts, posters, letters, internet publications, manufacturer documents | |

## 10 Search Strategy

The search was conducted by Public Health England's Knowledge & Library Services. Publications were limited to publications published in English from 1st January 2006 to 12th February 2019 excluding conference abstracts, commentaries, letters, editorials and case reports.

HDAS (MEDLINE, EMBASE): search date 12th of February 2019

1. Haemoglobinopathies OR "Sickle cell disease" OR SCD OR thalassemia OR DHTR or "Delayed Haemolytic Transfusion Reaction*" OR HH OR Hyperhaemolysis AND Rituximab OR Eculizumab (149)
2. Haemoglobinopathy AND Rituximab OR Eculizumab (4)
3. Haemoglobinopathy OR SCD OR sickle cell disease OR Thalassemia AND Rituximab OR Eculizumab (118)
4. "Delayed Haemolytic Transfusion Reaction*" OR DHTR OR HH OR Hyperhaemolysis AND haemoglobinopathies (15)
5. "Delayed Haemolytic Transfusion Reaction*" OR DHTR OR HH OR Hyperhaemolysis AND Rituximab OR Eculizumab (60)
6. Haemoglobinopathies OR "Sickle cell disease" OR SCD OR thalassemia OR DHTR or "Delayed Haemolytic Transfusion Reaction*" OR HH OR Hyperhaemolysis AND Rituximab OR Eculizumab (149)
7. DHTR or "Delayed Haemolytic Transfusion Reaction*" OR HH OR Hyperhaemolysis AND haemoglobinopathie* AND Rituximab OR Eculizumab (2)

Cochrane Library: search date 12th of February 2019

1. DHTR or Delayed Haemolytic Transfusion Reaction* OR HH OR Hyperhaemolysis AND Haemoglobinopathies OR Sickle cell disease OR SCD OR thalassemia AND Rituximab OR Eculizumab (60)

2. DHTR or Delayed Haemolytic Transfusion Reaction* OR HH OR Hyperhaemolysis OR Rituximab OR Eculizumab AND Haemoglobinopathies OR Sickle cell disease OR SCD OR thalassemia (103)

## 11 Evidence Selection

- Total number of publications reviewed: 285
- Total number of publications considered potentially relevant: 43
- Total number of publications selected for in depth comparison to PICO criteria: 13
- Total number of publications selected for inclusion in this briefing: 9

Of the three references submitted with Preliminary Policy Proposal two were not included.

| Clinical Impact | References supplied in the Preliminary Policy Proposal | Inclusion or exclusion notes |
|---|---|---|
| Most clinically impactful publication | Noizat-Pirenne F, Habibi A, Mekontso-Dessap A *et al*. The use of rituximab to prevent severe delayed haemolytic transfusion reaction in immunized patients with sickle cell disease. Vox Sang 2015; 108 (3):262-267 | Included in literature review |
| Second most clinically impactful publication | Dumas G, Habibi A, Onimus T *et al*. Eculizumab salvage therapy for delayed haemolytic transfusion reaction in sickle cell disease patients. Blood 2016; 127: 1062-1064 | Excluded as publication is a letter to the editor and not a published article |
| Third most clinically impactful publication | Boonyasampant M, Weitz IC, Kay B *et al*. Life threatening delayed hyperhaemolytic transfusion reaction in a patient with sickle cell disease: effective treatment with eculizumab followed by rituximab. Transfusion 2015; 55: 2398-2403 | Included in literature review |

## 12 Excluded publications

Several publications were excluded as they did not meet the PICO. Please see below the details of four publications which were not included in this evidence review with the rationale for exclusion.

| Publication reference | Exclusion reason |
|---|---|
| Gardner *et al.* 2015. How we treat delayed haemolytic transfusion reactions in patients with sickle cell disease. British Journal of Haematology 170(6) 745-756. | Patient did not receive ongoing blood transfusion therapy |

| | |
|---|---|
| Habibi *et al*. 2014. 99 episodes of delayed haemolysis post transfusion reaction among adult patients with sickle cell disease; clinical presentation, prognosis, and treatment. Blood. Conference: 56th Annual Meeting of the American Society of Hematology, ASH 124(21). | Not clear which patients had eculizumab and rituximab by outcome |
| Vidler *et al.* 2015. Delayed haemolytic transfusion reaction in adults with sickle cell disease: A 5-year experience. British Journal of Haematology 169(5) 746-753. | No patients given eculizumab and unclear which patients had rituximab by outcome |
| Vlachaki *et al.* 2019. Successful Outcome of Hyperhemolysis in Sickle Cell Disease following Multiple Lines of Treatment: The Role of Complement Inhibition. Hemoglobin 1-3. | Patient did not receive ongoing blood transfusion therapy |

## 13 References


Boonyasampant, 2015. Life-threatening delayed hyperhemolytic transfusion reaction in a patient with sickle cell disease: effective treatment with eculizumab followed by rituximab. Transfusion 55(10) 2398-403.

Cattoni, A., Cazzaniga, G., Perseghin, P., *et al*. 2013. An attempt to induce transient immunosuppression pre-erythrocytapheresis in a girl with sickle cell disease, a history of severe delayed hemolytic transfusion reactions and need for hip prosthesis. Hematology Reports 5(2) 36-38

Chonat, S., Quarmyne, M. O., Bennett, C. M., *et al*. 2018. Contribution of alternative complement pathway to delayed hemolytic transfusion reaction in sickle cell disease. Haematologica 103(10) e483-e485.

Hannema, S. E., Brand, A., van Meurs, A., *et al*. 2010. Delayed hemolytic transfusion reaction with hyperhemolysis after first red blood cell transfusion in child with beta-thalassemia: challenges in treatment. Transfusion 50(2) 429-32.

Noizat-Pirenne, F., Bachir, D., Chadebech, P., *et al*. 2007. Rituximab for prevention of delayed hemolytic transfusion reaction in sickle cell disease. Haematologica 92(12) e132-135

Noizat-Pirenne, F., Habibi, A., Mekontso-Dessap, A., *et al*. 2015. The use of rituximab to prevent severe delayed haemolytic transfusion reaction in immunized patients with sickle cell disease. *Vox Sanguinis* 108(3) 262-267

Pirenne, F. & Yazdanbakhsh, K. 2018. How I safely transfuse patients with sickle-cell disease and manage delayed hemolytic transfusion reactions. Blood 131(25) 2773-2781

Uhlmann, E. J., Shenoy, S. & Goodnough, L. T. 2014. Successful treatment of recurrent hyperhemolysis syndrome with immunosuppression and plasma-to-red blood cell exchange transfusion. Transfusion 54(2) 384-388.

Vagace, J. M., Cardesa, R., Corbacho, A., *et al*. 2016. Etiopathological mechanisms and clinical characteristics of hyperhemolysis syndrome in Spanish patients with thalassemia. Annals of Hematology 95(9) 1419-1427.