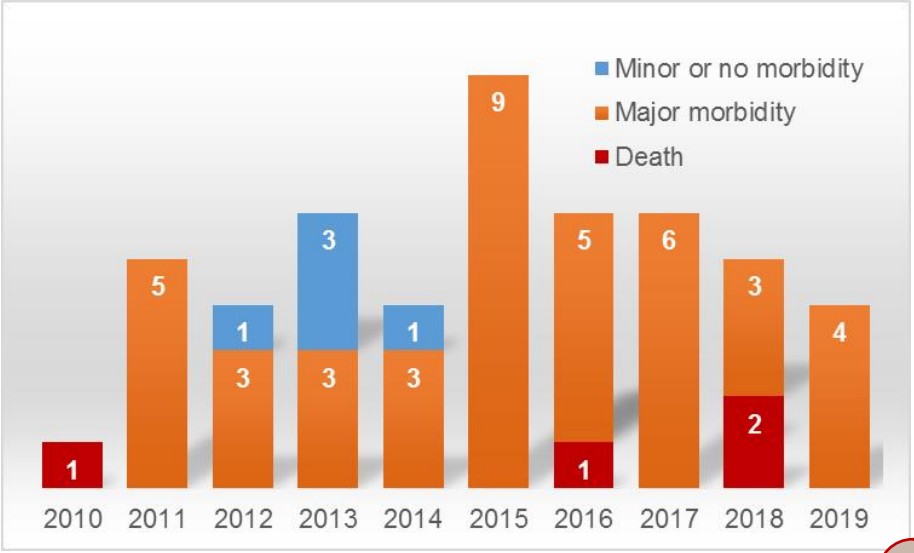
SHOT Bite No. 15:
Hyperhaemolysis

SHOT Serious Hazards of Transfusion

January 2021

Hyperhaemolysis (HH) is a severe and potentially life-threatening complication of transfusions. Whilst it is predominantly seen in patients with sickle cell disease there are several reports of this complication in patients with other haemoglobinopathies as well as patients with a range of other haematological diagnoses who have blood transfusions as part of their management. HH is a complex syndrome characterised by destruction of transfused and autologous red blood cells following transfusion resulting in haemoglobin drop to below pre-transfusion level, reticulocytopenia with significant decrease to below baseline level and absence of new detectable alloantibodies in acute HH in contrast to delayed events. Prompt recognition and appropriate management of all hyperhaemolytic transfusion reactions is vital. Reporting to SHOT helps optimise learning from these events.

Hyperhaemolysis cases reported to SHOT 2010-2019 n=50



92% of HH cases were in sickle cell patients (46/50), with 10% reported in paediatric patients (5/50)

We are aware that hyperhaemolysis is under-reported to SHOT. Improved reporting helps optimise learning from these events.

HH can be seen in non-haemoglobinopathy patients as well so all clinicians handling transfusions need to be aware of this complication.

Patients need to be educated to seek help promptly in cases of delayed events.

Described Clinical and Laboratory Features:

HH can be acute but can easily be differentiated from acute haemolytic transfusion reactions. It can be delayed as well and it may be difficult to differentiate between delayed haemolytic transfusion reactions (DHTR) and delayed hyperhaemolysis

Clinical features of hyperhaemolysis include severe pain, often low-grade fever, jaundice and haemoglobinuria

Key laboratory features include rapid Hb drop to below pre-transfusion level, decline in post transfusion HbA level; reticulocytopenia, raised bilirubin and LDH with or without the presence of a new alloantibody & +/- positive DAT

Close monitoring of patients with serial monitoring of laboratory parameters is needed

Pathophysiology: The causes and mechanisms of HH are not fully known and our understanding is constantly evolving.

Bystander haemolysis: is defined as the haemolysis of RBC negative for the antigen targeted by the antibody. Sickled erythrocytes are more susceptible to complement activation and this has been postulated as an example of the bystander mechanism in the destruction of autologous RBC in delayed antibody-mediated HH, but has never been confirmed

Macrophage activation with direct erythrophagocytosis has been proposed as a mechanism in acute HH. Several concurrent processes have been suggested to be responsible for macrophage activation: triggering of activation pathways, increased RBC expression of adhesion molecules, and inflammatory environment. High ferritin levels seen in these patients reflect this macrophage activation

In sickle patients, **additional causes** such as acute vaso-occlusive events, infections and exposure to certain drugs can cause accelerated haemolysis. Some cases may also reflect occult splenic sequestration or aplastic crisis detected during a period of resolving reticulocytosis

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Treatment Recommendations:

Immunosuppressive therapy

Rationale: These agents can either inhibit erythrophagocytosis, reduce haemolysis by immunomodulation or suppress macrophage activation

1st line: corticosteroids and intravenous immunoglobulins

2nd line: in patients with ongoing brisk haemolysis- Eculizumab

Link to the commissioning policy: https://www.england.nhs.uk/wp-content/uploads/2020/09/1821_Rituximab_Eculizumab_Clinical_Commissioning_Policy.pdf

Supportive therapy

Erythropoietin, Intravenous iron, Folic acid and Vitamin B12 replacement as needed

Transfusions during hyperhaemolysis episode can accelerate haemolysis and transfusion decisions must be made taking into consideration all factors. **In life threatening anaemia, transfusion should not be withheld. These decisions need to be made after discussion with specialists**

Prevention of HH and DHTR in patients requiring elective blood transfusion - IVIg and steroids are 1st line preventative treatment. Rituximab can now be used as 2nd line prevention for adult and post-pubescent patients only

Challenges:

Knowledge

- Although overall there is better understanding of hyperhaemolysis its presentation and treatment, there are still many areas of uncertainty
- There are no randomised controlled trials looking at outcomes of various treatment approaches or duration of treatment
- There is very little knowledge with regards to the long-term consequences of hyperhaemolysis and the incidence of end organ damage

Management

- Further unanswered questions include:
  - What is the incidence of VTE?
  - How are these patients managed in subsequent transfusions and what are their outcomes?
- ***Reporting these cases to SHOT helps expand the knowledge base, ensures shared learning from experiences and may address some of these issues in the future***

Reporting

- The number of reported cases over the last few years has decreased and yet day to day clinical practice shows that more patients with hyperhaemolysis are being managed regularly
- There needs to be better communication and a better way of capturing these patients, reporting them and collecting data
- One approach would be incident reporting these events, so that transfusion practitioners and lab managers can be alerted and report these

References:

Guidelines on red cell transfusion in sickle cell disease Part I principles and laboratory aspects. Bernard A Davies et al British Journal Haematology 2017; **176:** 179-191.

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