Haemolytic Transfusion Reactions (HTR) n=49

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Definitions:

Acute haemolytic transfusion reactions (AHTR) are characterised by fever, a fall in haemoglobin (Hb), rise in bilirubin and lactate dehydrogenase (LDH) and a positive direct antiglobulin test (DAT). They generally present within 24 hours of transfusion.

Delayed haemolytic transfusion reactions (DHTR), occur more than 24 hours following a transfusion and are associated with a fall in Hb or failure to increment, rise in bilirubin and LDH and an incompatible crossmatch not detectable pre transfusion.

Hyperhaemolysis is characterised by more severe haemolysis than DHTR, with haemolysis affecting the transfused red cells and the patient's own red cells; there is a decrease in Hb to below pre-transfusion levels, which is often associated with a reticulocytopenia. It may be triggered by a new red cell alloantibody, but frequently no new red cell antibody is identified. Hyperhaemolysis can be divided into acute and delayed hyperhaemolysis.

Key SHOT messages

- Hyperhaemolysis remains a major cause of transfusion-related morbidity, however as the identification and management primarily takes place outside of the transfusion team these cases may not be reported to SHOT
- All clinicians involved in the transfusion process must have an awareness of the signs and symptoms of hyperhaemolysis. Any suspected cases should be followed up, investigated and reported to SHOT to allow better data capture of this reaction type
- When selecting O D-positive red cells for transfusion to O D-negative individuals it is important to check the patient for contraindications in addition to age and childbearing potential e.g. a history of anti-D or if the patient is transfusion dependent
- The serological investigation of a haemolytic transfusion reaction (HTR) should always include a direct antiglobulin test (DAT) and if positive, an eluate should be performed

Abbreviations used in this chapter

AHTR	Acute haemolytic transfusion reactions	IBGRL	International Blood Group Reference Laboratory
DAT	Direct antiglobulin test	IVIg	Intravenous immunoglobulin
DHTR	Delayed haemolytic transfusion reactions	LDH	Lactate dehydrogenase
ED	Emergency department	LISS	Low ionic strength saline
Hb	Haemoglobin	MHRA	Medicines and Healthcare products Regulatory Agency
HTR	Haemolytic transfusion reactions	RCI	Red Cell Immunohaematology
IAT	Indirect antiglobulin test	Sp-ICE	Specialist Services electronic reporting using Sunquest's Integrated Clinical Environment





Recommendation

• Clinical teams involved in the transfusion process should have training in the SHOT reporting system and understand the need to work with the transfusion team to ensure all adverse events related to transfusion are reported

Action: Hospital transfusion teams

Number of cases n=49

Figure 18.1: Key Haemolytic transfusion Types of HTR Overview of HTR clinical findings reactions cases n=49 Typical clinical features reported including fever, Acute HTR n=22 dyspnoea, rigors, tachycardia, reports of pain and haemoglobinuria Total reported in 2019 n=49 No clinical symptoms Deaths n=0 Delayed HTR n=23 of transfusion reaction Major morbidity* **n=11** reported in 12/23 cases Age range: 9 to 91 (median 55) 3/4 cases seen in patients with sickle cell disease, in one of these, patient had DHTR followed by hyperhaemolysis Hyperhaemolysis n=4 One case was in a patient *All reported cases of probable with myelodysplastic hyperhaemolysis where there syndrome and cold is a significant fall in Hb are agglutinin disease considered as major morbidity

The total number of reactions reported is greater than previous years with increases in both the number of acute and delayed reactions. This may indicate an increase in awareness. In contrast to previous years only 1 reaction this year was the result of the emergency transfusion of known antigen-positive blood.

Death n=0

There were no patient deaths reported as a result of the transfusion reaction.

Major morbidity n=11

There were 11 cases reported in which the patient suffered major morbidity.

Hyperhaemolysis n=4

Four cases of hyperhaemolysis syndrome were reported and in contrast to previous years all patients made a full recovery.

Case 18.1: Hyperhaemolysis in a patient with myelodysplastic syndrome and cold agglutinin disease

A haematology patient with a provisional diagnosis of myelodysplastic syndrome was transfused one unit of red cells due to a Hb 64g/L. The patient immediately experienced symptoms of a transfusion reaction including fever, hypotension, nausea and dyspnoea. The transfusion was stopped and the post-transfusion Hb dropped to 54g/L. The patient was transfused another four times over the following 7 days, each time with hydrocortisone cover. However, each transfusion resulted in similar reactions, although the symptoms were less severe. At this point a decision was made to stop transfusion and to treat the patient with intravenous immunoglobulin (IVIg) and erythropoietin. The patient improved and the Hb began to rise over the following 3 weeks with the Hb stabilising at 86g/L 7 weeks after the initial reaction.

Hyperhaemolysis can be divided into acute and delayed hyperhaemolysis. Acute hyperhaemolysis usually occurs within 7 days of transfusion and the DAT is usually negative. Delayed hyperhaemolysis usually occurs more than 7 days post transfusion and the DAT is often positive. In contrast to a classical delayed haemolytic transfusion reaction, in delayed hyperhaemolysis both patient and transfused red cells are haemolysed (Danaee et al. 2015). Two of the hyperhaemolysis cases reported to SHOT occurred within 7 days of the transfusion episode and are therefore characterised as acute (1 occurred 5 days post transfusion and 1 at the time of transfusion). Another case occurred 8 days post transfusion, and the fourth case was originally reported as a DHTR but the patient subsequently went on to develop hyperhaemolysis.

The true number of cases of hyperhaemolysis occurring in sickle cell patients is believed to be much higher than that reported to SHOT. The diagnosis of hyperhaemolysis remains a challenge. As there are often no changes in the serological profile in these cases, the transfusion practitioner and transfusion laboratory may not be made aware of the reaction and the case managed entirely by the clinical team. Clinical staff may therefore need educating in the importance of reporting such cases to SHOT and the Medicines and Healthcare products Regulatory Agency (MHRA) to allow the development of a better understanding of the syndrome.

Robust data collection will also help medical professionals to assess the usefulness of new and emerging treatments for hyperhaemolysis, such as the anti-interleukin 6 receptor (IL6R) humanised monoclonal antibody tocilizumab (Watanabe et al. 2016).

Learning point

• It is important that all clinicians involved in the transfusion process have an awareness of the signs and symptoms of hyperhaemolysis and that any suspected cases are followed up, investigated and reported to SHOT to allow better data capture of this reaction type



Clinical and laboratory signs and symptoms

Acute haemolytic transfusion reactions n=22

The clinical symptoms most often reported in acute transfusion reactions include haemoglobinuria, fever, dyspnoea, rigors, tachycardia and reports of pain. These match the major symptoms described in textbooks.

Delayed haemolytic transfusion reactions n=23 (excluding potential cases of hyperhaemolysis)

No clinical symptoms of a transfusion reaction were reported in 12/23 delayed haemolytic transfusion reaction cases submitted to SHOT. This is comparable to other years. Where clinical symptoms were reported the most common symptom was that the patient reported feeling unwell post transfusion. This suggests that hospitals have responded to the recommendation made in the 2015 Annual SHOT

Report that patients are informed of the possible symptoms of a HTR and that patients are responding to this and following up any concerns with their healthcare professionals (Bolton-Maggs et al. 2016).

As in previous years, delayed haemolytic transfusion reactions were more frequently diagnosed based on the laboratory indications, most commonly by the development of a positive DAT. The laboratory diagnosis is usually made as a result of a decreased Hb and increased bilirubin result in combination with a positive DAT. In a majority of cases the LDH, blood film, and ferritin levels are not reported therefore the values given may not be representative of the true picture.

Figure 18.2: Laboratory investigation of haemolytic transfusion reactions

χ Key findings from laboratory investigations reported in HTR

- DAT post transfusion was not available in 4 cases
- In 25 cases the DAT was not repeated on the pre-transfusion sample.
 16/25 of these cases were due to the sample being no longer available in DHTR however in 6 cases of AHTR no pre-transfusion DAT was tested



 In 8/49 haemolytic reactions reported no eluate had been tested despite the patient developing a positive DAT post transfusion, and in 5 of these cases the patient also had a new antibody detectable in the post-transfusion sample

In transfusion reactions, red cell antibodies may be identified in the eluate which are not detectable in the plasma. This is due to the free antibody binding to the corresponding antigen on the transfused cells. Elution tests to identify these antibodies can help confirm the specificity of the individual antibodies implicated in the reaction.

Case 18.2: Anti-Jk^b detected in eluate post transfusion

The patient reported feeling unwell 30 minutes into the transfusion of the second unit. The transfusion was stopped, and a transfusion reaction investigation performed. Both pre- and post-transfusion samples demonstrated a non-specific pan reactive antibody detectable in Biovue[®] and low ionic strength saline (LISS) tube indirect antiglobulin test (IAT). No underlying antibodies were detected in either sample however an eluate on the post-transfusion sample demonstrated the presence of anti-Jk^b.



Learning points

- A direct antiglobulin test (DAT) is a vital component of a transfusion reaction investigation and local policies should be written to include this requirement
- In cases where the post-transfusion DAT becomes positive an eluate can be a useful tool both to confirm the specificity of an implicated antibody and detect antibodies which are not detectable in the plasma

Antibodies implicated in haemolytic transfusion reactions

AHTR due to preformed antibodies

In 4/22 acute transfusion reactions an antibody was detected in the pre-transfusion sample following investigation, despite the initial antibody screen being negative. In 3 of these cases anti-Wr^a was identified and in the 4th a weak anti-E. In a further 2 cases an antibody was identified in a sample previously reported as a non-specific alloantibody.

Case 18.3: Patient visiting from abroad with multiple antibodies

A Ghanaian national visiting the UK was admitted to hospital in sickle crisis. The initial antibody screen was positive, and samples were sent to the Blood Service for investigation. The Red Cell Immunohaematology (RCI) laboratory was unable to identify the antibody and samples were sent to the International Blood Group Reference Laboratory (IBGRL) for further investigation. Two units of crossmatch-compatible blood were issued by the Blood Service and transfused prior to the IBGRL investigation being completed. Following transfusion, the patient required urgent treatment for bleeding in the brain and had evidence of haematuria however this was initially attributed to the sickle crisis. IBGRL subsequently reported anti-D, anti-E and anti-Js^b. The units which had been transfused were negative for the D and E antigens but were both Js^b positive. The patient had stated that she had an antibody, but she did not know which one.

DHTR due to preformed antibodies

In 20/23 DHTR, antibodies were detected in the post-transfusion sample which were not detectable in the pre-transfusion sample. Of the remaining 3 cases, 2 were due to the transfusion of blood which was positive for an antibody which was also detected in the pre-transfusion sample. A further case was reported in which the pre-transfusion antibody screen was negative, however the patient had informed the clinical area of a history of antibodies.

Case 18.4: Patient with anti-E, -C^w, -S, -Jk^a and -k

A patient required urgent transfusion for chronic anaemia after presenting at hospital with Hb 31g/L. The patient had a known history of anti-E, $-C^w$, -S, $-Jk^a$ and -k, however no red cells units of this specification were available at the Blood Service or the frozen blood bank. The anti- Jk^a was not detectable in the sample therefore following discussion between the consultant haematologists at the hospital and Blood Service it was decided to transfuse units which were Jk^a -positive but negative for all detectable red cell antibodies. The patient's Hb initially rose post transfusion however 6 days later the Hb had dropped by 18g/L, the DAT had become positive and anti- Jk^a was detectable in the post-transfusion sample.

Case 18.5: DHTR in an O D-negative female transfused with D-positive blood

A female patient in her 70s presented in the emergency department (ED) with an abdominal aortic aneurysm. The major haemorrhage protocol was activated. The patient's antibody screen was negative, and the patient was transfused with emergency D-positive blood. Six days later the patient experienced symptoms of a transfusion reaction including raised bilirubin, raised LDH, falling Hb, positive DAT and impaired renal function. Anti-D was detected in the post-transfusion sample and was also eluted from the patient's red cells. Following investigation, the patient informed the clinical area that she had developed an antibody in a previous pregnancy.



The antibody specificities implicated in the delayed transfusion reactions reported are shown in Figure 18.3. Anti-Jk^a remains the antibody most frequently implicated in delayed haemolytic transfusion reactions. In common with previous years this is followed by anti-Fy^a and anti-C.





It is important that lifesaving transfusion is not withheld due to a history of alloantibodies. In urgent clinical situations where suitable antigen-negative blood is not available it may be necessary to transfuse blood which is antigen-positive for the patient's confirmed antibody. Where the patient has multiple antibodies clinicians may have to decide which donor red cell antigen to ignore. The data from the SHOT reports on the antibody specificities most commonly indicated in HTR can provide a useful source of information to guide these decisions, with priority given to providing antigen-negative blood to those antibodies more frequently reported. Data from SHOT provides evidence of antibodies frequently involved in transfusion reactions, such as anti-Wr^a which in the last 4 years has been reported in 5 HTR cases. These data may be of use when reviewing and assessing the validity of current donation screening policies, and consideration should be given to extending screening to include antibodies to antigens not routinely tested, when relevant.



Learning points

- When selecting O D-positive red cells for the transfusion to O D-negative individuals it is important to check the patient for contraindications in addition to age and childbearing potential e.g. a history of anti-D or if the patient is transfusion dependent
- Patients should be asked whether they have antibodies as part of the pre-transfusion process and any information obtained relayed to the transfusion laboratory and acted on
- Patient databases such as Specialist Services electronic reporting using Sunquest's Integrated Clinical Environment (Sp-ICE) can provide vital antibody history for antibodies where the level has dropped below the detectable titre. Hospitals should have local polices to decide which patients to check on Sp-ICE

Other unusual cases

Two cases reported involved antibodies not generally considered to be clinically significant, however no alternative cause for the reactions could be identified.

Full details of these 2 cases can be found in the supplementary information on the SHOT website (https://www.shotuk.org/shot-reports/report-summary-and-supplement-2019/).

Conclusion

HTR are recognised as an important cause of transfusion-associated reactions and may be subclinical, mild, or fatal. DHTR and hyperhaemolysis continue to pose diagnostic and therapeutic challenges. HTR are largely preventable and adherence to established protocols for prompt identification and timely management, as well as reporting them, remain the cornerstone of management of HTR.



References

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