Hyperhaemolysis

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OFFICIAL

Hyperhaemolysis is an uncommon but potentially fatal severe haemolytic transfusion reaction characterised by a drop in haemoglobin to below the pretransfusion levels (or Hb drop >25% from pretransfusion level) due to haemolysis of both **donor and recipient** red cells. It has been a rare report to STIR but Serious Hazards of Transfusion UK recorded 14 reported cases in their 2024 annual report.

Unlike traditional haemolytic reactions, hyperhaemolysis is often associated with a reticulocytopenia (absolute or reticulocyte count below pre-transfusion baseline).

It is typically but not exclusively seen in sickle cell disease (SCD). There is usually a significant decrease in HbA percentage in patients with SCD or beta thalassaemia major.

It may be triggered by a new red cell alloantibody, but frequently no new red cell antibody is identified. Similarly, the DAT (Direct Antiglobulin Test) may be positive or negative. It may reoccur in the same patient on subsequent transfusion.

Hyperhaemolysis can be classified as acute, within seven days, or delayed, more than seven days post transfusion. This differs from the timeframe used to classify traditional acute vs delayed haemolytic transfusion reactions (within 24 hours or later than 24 hours, respectively).

Differentiating Haemolytic Reactions

	Acute Haemolytic Reactions (AHTR)	Delayed Haemolytic Reactions (DHTR)	Hyperhaemolysis syndrome
Mechanism	Immune mediated - ABO/RhD mismatch - Red cell alloantibodies - O donors with high anti-A/B titres (rare) Non-Immune mediated - physical or chemical destruction	Secondary immune response (anamnestic) to a red cell antibody that was undetected prior to transfusion.	Poorly understood Involves destruction of transfused as well as recipient autologous RBCs Proposed Mechanisms - Complement hyperactivation - Macrophage activation - Oxidative stress
Incidence	ABO-incompatibility 1:40,000 transfusions	1:2500	Extremely rare
Onset	Within 24hrs	24hrs to 28 days	Acute – within 7 days Delayed – longer than 7 days
Clinical Features	Acutely unwell, fever, pain, jaundice, haemoglobinuria	Similar to AHTR but usually less severe, general malaise	Very unwell, pain, fever, haemoglobinuria, shortness of breath, chest pain, jaundice

Culprit Red Cell Alloantibody	Commonly present and detectable pre-transfusion	Likely present pre-transfusion but below level of detection	A new red cell alloantibody is detected in less than half of cases
Positive DAT	Yes	Yes	Acute: DAT usually negative Delayed: DAT often positive
Reticulocytes	High	High	Lower than pre-transfusion

Risk factors associated with Hyperhaemolysis syndrome

Patients at greatest risk
• Haemoglobinopathies e.g. Sickle Cell Disease, Thalassaemia
• Prior history of alloantibodies
• Systemic inflammation at time of transfusion e.g. inter-current infection or pain crisis

Management

The following information is **not a guideline** but provides information on the currently available treatment options for these patients. As this is a rare condition, management should include early referral to a Haematologist for expert opinion.

Treatment of hyperhaemolysis syndrome & prevention of further haemolysis
• Management should be undertaken under the supervision of a Haematologist • ***NB: There are no randomised trials comparing outcomes from various treatment approaches***
• Immunosuppressive therapy, consider o Corticosteroids in conjunction with Intravenous immunoglobulin (Criteria for Clinical Use of Immunoglobulin in Australia) o Other immunosuppressive treatments such as Monoclonal antibodies should be determined with advice from a Haematologist
• Supportive care may include o General: Hydration, Oxygenation, Analgesia o Supporting Erythropoiesis: Erythropoietin, Folate, Vitamin B12, IV iron as needed
• Further Red Cell Transfusions o Should be avoided, if possible, as may exacerbate haemolysis o However, should not be withheld if anaemia is life-threatening o If required, aim to provide extended phenotype-matched blood (ABO, Rh, K, Jk, Fy, Ss) o And when antibodies are present: target antigen negative blood o Monitor very closely for haemolysis in these patients
• **See references for guidelines and further information**

There is yet a lot we do not know about the pathophysiology and optimal treatment of hyperhaemolysis syndrome. Therefore, it is **critical** that all suspected cases of hyperhaemolysis be reported to STIR so that we may share our experiences and improve our collective understanding.

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