

# How to approach haemolysis: Haemolytic anaemia for the general physician

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## ABSTRACT

Haemolytic anaemia can seem like a complicated topic. The constellation of reticulocytosis, increased lactate dehydrogenase levels, increased unconjugated bilirubin levels and decreased haptoglobin levels should prompt general physicians to consider haemolysis as a differential diagnosis. When further approaching haemolytic anaemia, subdividing patients into those who are 'direct antiglobulin test (DAT) positive' (immune) or 'DAT negative' (non-immune) is a simple and clinically relevant way to start to formulate a cause for the haemolytic anaemia. Immune causes of haemolytic anaemia include autoimmune haemolytic anaemia, drugs and delayed haemolytic transfusion reactions. Non-immune causes include the haemoglobinopathies (such as sickle cell disease) and microangiopathic haemolytic anaemias (such as disseminated intravascular coagulation). Early supportive care in haemolytic anaemia is important and may involve blood transfusions as well as interventions to slow the rate of haemolysis, such as steroids in autoimmune haemolytic anaemia. Complications of haemolysis include pigment gallstones, high-output cardiac failure and thromboembolism. Haemolytic anaemia should be referred to the haematologist for further investigation, however, the recognition and early management by the general physician is imperative in improving the patient's outcome.

## Introduction

Haemolytic anaemia is a process that occurs due to the premature destruction of red blood cells. It can either be down to antibodies targeted against red cell antigens or occur from the non-immune breakdown of red cell membranes. If the antibodies are made by the host, the disorder is referred to as autoimmune haemolytic anaemia (AIHA). The incidence of AIHA is around 1/100,000 people per year.<sup>1</sup> It can be considered as secondary (due to an underlying cause) or primary (occurring as its own phenomenon).<sup>2</sup> In haemolytic anaemia, red blood cells are either destroyed in the circulation or within the spleen. This has led to the terminology of

'intravascular' and 'extravascular' haemolysis, respectively. Although in many cases of haemolytic anaemia, there is an overlap between the two.

## Clinical presentation

Patients with haemolytic anaemia can range in presentation from a chronic state of anaemia (such as in patients with sickle cell disease) to those presenting with the profound symptoms of acute anaemia. Patients may present with tiredness, shortness of breath and dizziness. It is also important to ask patients about their transfusion history, jaundice, dark urine, whether any of their symptoms are exacerbated by the cold and whether any new medications have been started recently. If haemolytic anaemia is suspected, patients should have a full multi-system

## Key points

In haemolytic anaemia, red blood cells are either destroyed in the circulation (intravascular) or within the spleen (extravascular).

Subdividing patients into those who are 'direct antiglobulin test (DAT) positive' (immune) or 'DAT negative' (non-immune) is a simple and clinically relevant way to understand haemolytic anaemias.

The constellation of reticulocytosis, increased lactate dehydrogenase levels, increased unconjugated bilirubin levels and decreased haptoglobin levels confirms haemolysis.

Early supportive care in haemolytic anaemias is important and may involve red cell transfusions and folate replacement.

Complications of haemolysis include pigment gallstones, high-output cardiac failure and thromboembolism.

**KEYWORDS:** haemolysis, anaemia, direct antiglobulin test, autoimmune haemolytic anaemia

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examination, paying particular attention to the presence of any lymphadenopathy or splenomegaly.

## Classification

There are a number of different ways to subclassify haemolytic anaemia based on the aetiology, pathophysiology or the results of the direct antiglobulin test (DAT). Subdividing patients into those who are 'DAT positive' or 'DAT negative' is a simple way to remember, helping to differentiate the immune causes from the non-immune causes.

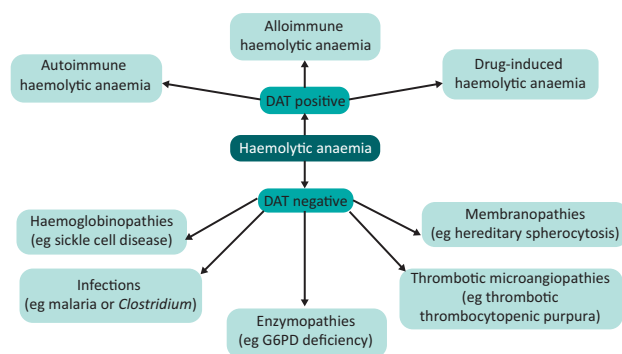
The DAT aims to identify red cells coated with antibodies or complement and should be performed in all patients presenting with a new suspected haemolytic anaemia. The principle of the DAT is using anti-human antibodies to detect immunoglobulins or complement bound *in vivo* to red cell membranes, which leads to agglutination and a positive result.<sup>3</sup> Subsequently, DAT positive haemolytic anaemia implies an immune component, which could be due to an AIHA, drug-dependent antibodies or an alloimmune haemolytic anaemia in the context of a transfusion reaction. In this setting, antibodies can be immunoglobulin (Ig) G, IgM or the immune process can instead be due to complement (C3). There can also be a mixture of both.

In DAT negative haemolysis, there is no immune component and, instead, red cell membrane destruction can be due to causes such as membrane instability (as seen in haemoglobinopathies), direct destruction of red cell membranes due to toxins (eg *Clostridium perfringens*) and due to microangiopathic haemolytic anaemia (MAHA); such as in haemolytic uraemic syndrome and thrombotic thrombocytopenic purpura; Fig 1).

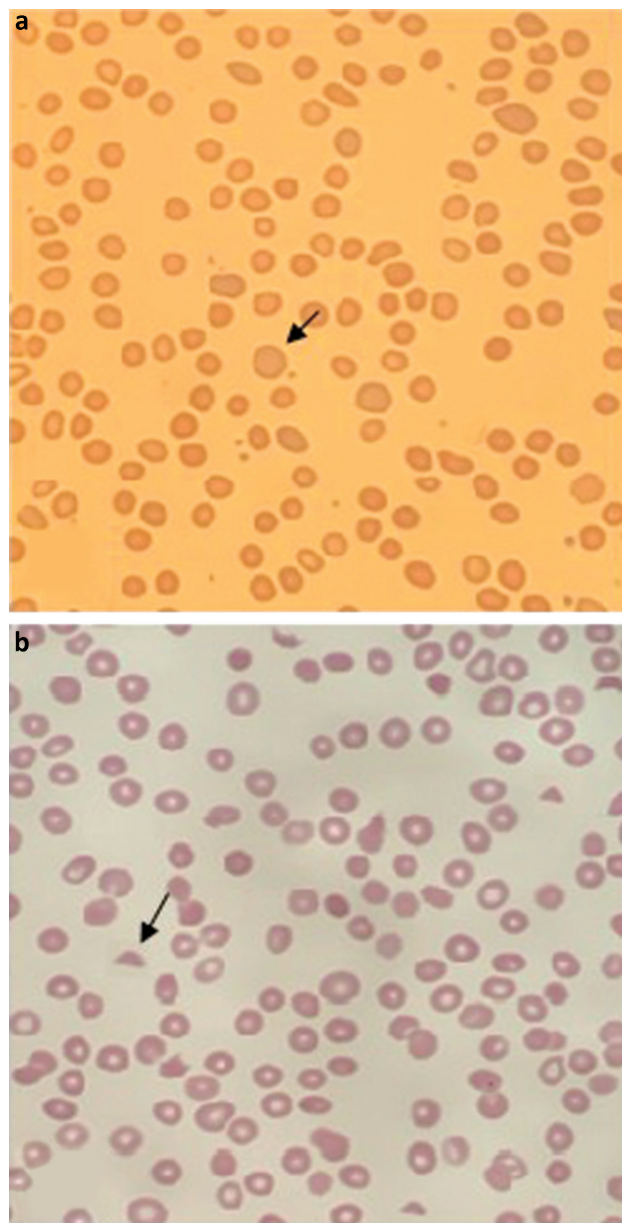
When further classifying AIHA, it can occur on its own (known as primary AIHA) or secondary AIHA driven by an underlying disorder. Alternatively, it can be classified based on whether the red cells fix complement, immunoglobulins or both. Finally, AIHA may also be regarded as 'warm' or 'cold' based on whether the antibody in question binds to red cells optimally at 37°C or at colder temperatures as low as 4°C (as seen in cold agglutinin disease; Fig 2; Table 1).

## Laboratory findings

The initial workup of haemolytic anaemia should include the full blood count, which often shows normocytic or macrocytic



**Fig 1.** Some examples of direct antiglobulin test positive and direct antiglobulin test negative haemolytic anaemia. DAT = direct antiglobulin test; G6PD = glucose-6-phosphate dehydrogenase.



**Fig 2.** a) Polychromasia (arrow) and spherocytes indicating haemolysis. b) Fragments (arrow) and thrombocytopenia suggestive of a microangiopathic haemolytic anaemia.

anaemia. The constellation of reticulocytosis, increased lactate dehydrogenase levels, increased unconjugated bilirubin levels and decreased haptoglobin levels confirms haemolysis. These findings are summarised in Table 2.

The blood film may be useful to identify the cause of haemolysis. Spherocytes are sphere-shaped (rather than biconcave) red blood cells caused by membrane loss and can be found in both inherited cases (such as hereditary spherocytosis) or acquired causes (such as AIHA). Schistocytes are fragmented red blood cells that occur in microangiopathic anaemia, and bite and blister cells are found in oxidative haemolysis such as glucose-6-phosphate dehydrogenase deficiency.

**Table 1. A classification system for some examples of autoimmune haemolytic anaemia**

	Warm AIHA	Cold AIHA (cold agglutinins)	Mixed AIHA
<b>Primary</b>	IgG +/- C3 (mostly IgG)	C3/C3d (known as CHAD)	IgG + C3
<b>Secondary</b>	IgG +/- C3 (mostly IgG)	C3/C3d	IgG + C3
Secondary examples	Lymphoproliferative disorders (eg CLL and NHL)	Lymphoproliferative disorders (eg NHL)	Lymphoproliferative disorders (eg NHL)
	Infections (eg CMV)	Infections (eg EBV)	Autoimmune disorders (eg SLE)
	Autoimmune disorders (eg SLE)	Autoimmune disorders (eg SLE)	

AIHA = autoimmune haemolytic anaemia; CHAD = cold haemagglutinin disease; CLL = chronic lymphocytic leukaemia; CMV = cytomegalovirus; EBV = Epstein-Barr virus; NHL = non-Hodgkin lymphoma; SLE = systemic lupus erythematosus.

## Management

Management depends on the cause of the haemolytic anaemia and involves supportive care in the form of transfusions if the patient is symptomatic. Folic acid supplementation is required due to rapidly exhausted folate stores in the setting of amplified red cell production during acute haemolysis.

In the setting of AIHA, treating the underlying condition (such as infection, malignancy or removing causative drugs) is required. Corticosteroids are often used in warm AIHA to stop antibody production. Warm AIHA is more likely to respond to corticosteroids than cold AIHA and remission is often seen after 1 to 3 weeks, then steroids can be reduced with close monitoring of haemolytic markers to avoid a relapse. If steroids fail, rituximab may be used that targets CD20 on B cells and suppresses the autoantibody. Rarely, splenectomy is required to remove the site of red blood cell destruction and antibody production. In patients with cold AIHA, they should avoid exposure to cold weather and keep warm. A more in-depth review of the treatment of secondary AIHA has been summarised.<sup>4</sup>

There are various causes of non-immune haemolytic anaemia and each will be managed with supportive care and according to the cause. Inherited DAT negative haemolytic anaemias consist of membrane disorders (such as hereditary spherocytosis) that require monitoring and management of complications (such as gallstones). Occasionally splenectomy may be required.<sup>5</sup> Examples of red cell enzyme defects include glucose-6-phosphate dehydrogenase deficiency, where it is important to avoid precipitating haemolytic anaemia; for example, avoiding certain drugs and fava beans. Haemoglobinopathies (such as sickle

cell anaemia) involve supportive care, particularly when there is a vaso-occlusive crisis. Treatment typically involves oxygen supplementation, analgesia, hydration and treatment of infection, if present.

There are many causes of non-inherited DAT negative haemolytic anaemias. These include the MAHAs such as thrombotic thrombocytopenic purpura, which is a medical emergency. It should be managed initially with plasma exchange and corticosteroids.<sup>6</sup> Another MAHA is disseminated intravascular coagulation that should be managed by treating the underlying cause and correcting abnormal coagulation indices, if the patient is bleeding.

Other noteworthy DAT negative haemolytic anaemias include 'march haemoglobinuria', which is seen after repetitive impacts on the body, particularly affecting the feet.<sup>7</sup> Prosthetic valve haemolysis is also an important cause of DAT negative haemolysis and, if there is a significant worsening of haemolytic anaemia, it may indicate valve dysfunction and should be discussed with a cardiologist.

## Complications

Haemolysis increases the risk of venous thromboembolism (VTE). The risk is particularly high in the haemoglobinopathies and in disorders such as AIHA.<sup>8</sup> VTE prophylaxis is important in these patients, particularly when they are admitted to hospital. Other complications of haemolytic anaemias include pigment gallstones secondary to chronic haemolysis and high-output cardiac failure, which can occur in severe cases of haemolytic anaemia. ■

**Table 2. Summary of laboratory tests to confirm haemolysis**

Test	Finding in haemolysis	Cause
Reticulocyte count	Raised	Bone marrow response to anaemia can lead to macrocytosis
Lactate dehydrogenase	Raised	Released from the breakdown of red blood cells
Unconjugated bilirubin	Raised	Increased haemoglobin breakdown
Haptoglobin	Decreased	Binds to free haemoglobin
Direct antiglobulin test	Positive in immune cases of haemolytic anaemia	Detects immunoglobulins or complement bound <i>in vivo</i> to red cell membranes
Blood film	May show abnormal red blood cells	Morphology dependent on the cause of haemolysis
Urinalysis for haemoglobinuria	A positive urine dipstick for blood, but microscopy negative of red blood cells	Occurs in severe acute intravascular haemolytic anaemia that exhausts haptoglobin-binding capacity; free haemoglobin is filtered by the glomerulus and haemoglobinuria occurs

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