Autoimmune haemolytic anaemia for the non-specialist

Autoimmune haemolytic anaemia is an uncommon disorder, but one that often presents to general medical departments rather than to specialists. Timely diagnosis and appropriate treatment are important to reduce patient morbidity and mortality.

Autoimmune haemolytic anaemias comprise a group of disorders whereby red blood cell survival is shortened by antibodies (Petz and Garratty, 2004). It is relatively rare with an incidence of 1 in 100 000 per year, although it may often go undiagnosed (Lechner and Jager, 2010). Although it is an uncommon disorder, patients with autoimmune haemolytic anaemia often present through general medicine rather than to specialists such as haematologists. Consequently diagnosis and initial management are often undertaken by physicians who need to have a working knowledge of autoimmune haemolytic anaemia. Timely diagnosis and appropriate treatment can reduce the morbidity and mortality associated with this condition.

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Classification

Autoimmune haemolytic anaemia can be divided into warm or cold reactive subtypes, based on the temperature at which the causative antibody displays maximal activity. Autoimmune haemolytic anaemia can be either primary (idiopathic) or secondary to an additional disorder. The classification of autoimmune haemolytic anaemia and the clinical and laboratory features of different types of autoimmune haemolytic anaemia are summarized in *Tables 1* and *2*.

Table 1. Classification of autoimmune haemolytic anaemia

Warm reactive autoimmune haemolytic anaemia	Primary		
	Secondary	Associated with lymphoproliferative disorders, e.g. chronic lymphocytic leukaemia, lymphoma	
		Associated with autoimmune disorders, e.g. systemic lupus erythematosus	
		Associated with non-lymphoid malignancies, e.g. ovarian cancer	
		Associated with chronic inflammatory disorders, e.g. ulcerative colitis	
Cold reactive autoimmune haemolytic anaemia	Cold agglutinin syndrome	Primary	
		Secondary	Post-infection e.g. mycoplasma
			Associated with B cell lymphoproliferative disorder
	Paroxysmal cold haemoglobinuria		
Mixed autoimmune haemolytic anaemia: characterized by the presence of both warm and cold autoantibodies	Primary		
	Secondary	Often associated with connective tissue disorders	

adapted from Bass et al (2014)

Table 2. Characteristics of different types of autoimmune haemolytic anaemia

Characteristics	Warm autoimmune haemolytic anaemia	Cold agglutinin disease	Paroxysmal cold haemoglobinuria	Drug-induced autoimmune haemolytic anaemia
Age	Variable, mean age 50 years	Middle aged, elderly	Usually child	Variable
Clinical manifestations	Variable, usually anaemia, occasionally acute haemolytic syndrome	Moderate chronic haemolytic anaemia, exacerbated by cold	Acute haemolytic anaemia, often with haemoglobinuria. Recent history of viral illness	Variable, most commonly subacute onset, occasionally acute
Immunoglobulin isotype	Immunoglobulin G	Immunoglobulin M	Immunoglobulin G	Immunoglobulin G
Thermal reactivity	37°C	4°C	4°C (biphasic antibody)	4°C
Complement fixation	Variable	Yes	Yes	Variable
Direct antiglobulin test	Immunoglobulin G +/- C3d	C3d, C3	C3d, immunoglobulin G	IgG +/- C3d
Site of red blood cell destruction	Extravascular (spleen)	Extravascular (liver), intravascular	Intravascular	Intra- and extra-vascular
Therapy other than transfusion support	Steroids, splenectomy, rituximab	Avoidance of cold exposure, rituximab	Usually self-limiting	Stop drug
Prognosis	Fair, with significant mortality (11%)	Good, usually chronic, fairly stable anaemia	Excellent after initial stormy course	Excellent

adapted from Petz (2008)

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Clinical presentation

Since autoimmune haemolytic anaemia is the antibody-mediated destruction of red cells (or haemolysis), patients may present with one or a combination of the following:

- Symptoms of anaemia (dyspnoea, fatigue, angina, light-headedness, palpitations, pallor)
- Symptoms of haemolysis (jaundice, dark urine)
- Features of a precipitating disease such as arthritis, hepatosplenomegaly or lymphadenopathy (*Table 1*).

Diagnostic clues

Since anaemia can be a common presentation in hospitals, some diagnostic clues are suggested to entertain the possibility of autoimmune haemolytic anaemia.

Rate of onset of anaemia

Rapid anaemia can only be caused by bleeding or haemolysis. If there is rapid anaemia and no evidence of bleeding, then haemolysis must be considered. A common error is to attribute a marked drop in haemoglobin to bleeding when there is only minimal blood loss (Petz and Garratty, 2004).

Macrocytosis

Although anaemia with macrocytosis is usually caused by alcohol, medications, or deficiencies of vitamin B_{12} or folate, this tends to develop gradually. More abrupt onset anaemia with macrocytosis suggests haemolysis as the cause. Marked reticulocytosis found in autoimmune haemolytic anaemia is the cause of macrocytosis, since reticulocytes are larger than mature red blood cells.

Features of haemolysis with anaemia

It is unusual for anaemia to be accompanied by jaundice or dark urine in the absence of haemolysis. Haemoglobinuria may often be mistaken as haematuria instigating urology referral or in some cases dismissed purely as concentrated urine in a person with anaemia. The jaundice is characteristically described as lemon-tinged (as a result of the predominance of unconjugated bilirubin).

Unexpected increase in transfusion requirements

Patients undergoing solid organ and bone marrow transplants may develop autoimmune haemolytic anaemia, partly as a result of immune dysregulation. Parameters used to diagnose autoimmune haemolytic anaemia are often abnormal for other reasons, making the diagnosis difficult unless the clinician realizes the significance of increased transfusion requirements (Petz and Garratty, 2004).

Anaemia in a patient with a predisposing condition

Anaemia developing in a patient with an underlying condition known to cause autoimmune haemolytic anaemia (*Table 1*) is a concern. For example, autoimmune haemolytic anaemia is a frequent problem in patients with systemic lupus erythematosus, occurring in up to 10% of patients, but may be easily missed in such patients as chronic anaemia is often a feature of the underlying disease.

Diagnostic tests

The three cardinal features of autoimmune haemolytic anaemia are the anaemia itself, haemolysis and the autoimmune component. As such, relevant diagnostic tests are:

Full blood count

This will confirm macrocytic (and occasionally normocytic) anaemia. In a series of 109 patients, the mean haemoglobin at presentation was 72 g/litre, with approximately one-third of patients having values below this level (Liesveld et al, 1987). The blood film should be examined, checking for polychromasia, spherocytes, red cell fragments, red cell agglutination and other causes of anaemia.

Tests for haemolysis

High unconjugated bilirubin

Breakdown of red blood cells releases haemoglobin into the circulation. The haemoglobin is partly broken down to bilirubin.

Very low or undetectable haptoglobin

Since haemoglobin in the vascular system is harmful, a protective protein called haptoglobin forms a complex with haemoglobin and removes it. This will indirectly result in very low levels of haptoglobin.

Elevated lactate dehydrogenase level

Any tissue breakdown, in this case red blood cells, will cause a very high level of lactate dehydrogenase.

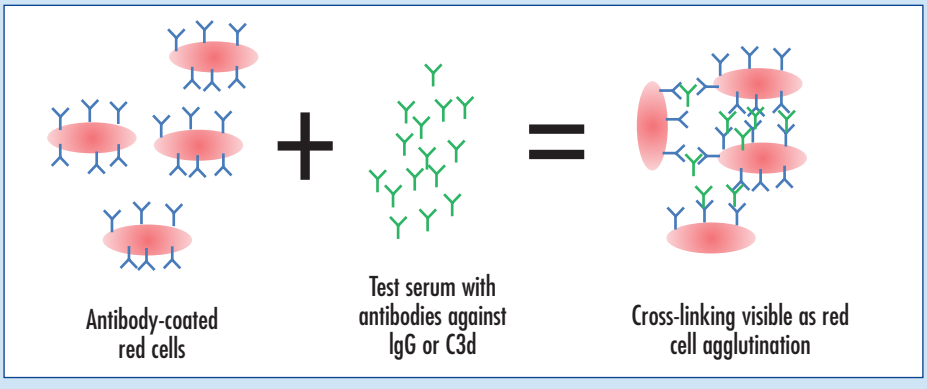
Marked reticulocytosis

The bone marrow compensates for the anaemia by overproducing red cells but allows early egress of immature red cells (reticulocytes).

Antibodies to red blood cells

These are confirmed by direct antiglobulin test or DAT (previously called the direct Coomb's test), usually performed in the blood transfusion laboratory (*Figure 1*). In this test, the patient's red blood cells are washed to remove any adherent proteins. They are then mixed with antibodies prepared against immunoglobulin (IgG) and a part of the complement protein, C3d. Reaction with IgG +/- C3d gives a diagnosis of warm autoimmune haemolytic anaemia; reaction with C3d indicates cold autoimmune haemolytic anaemia (*Figure 2*). The direct antiglobu-

Figure 1. The direct antiglobulin test. Patient with autoimmune haemolytic anaemia has antibodies coated on the red cells. These can be detected using commercial antibodies which are prepared against immunoglobulins or complement fragment C3d. Mixing of the red cells with the commercial serum will cause cross-linking of the red cells which will be visible as red cell agglutination or clumping.



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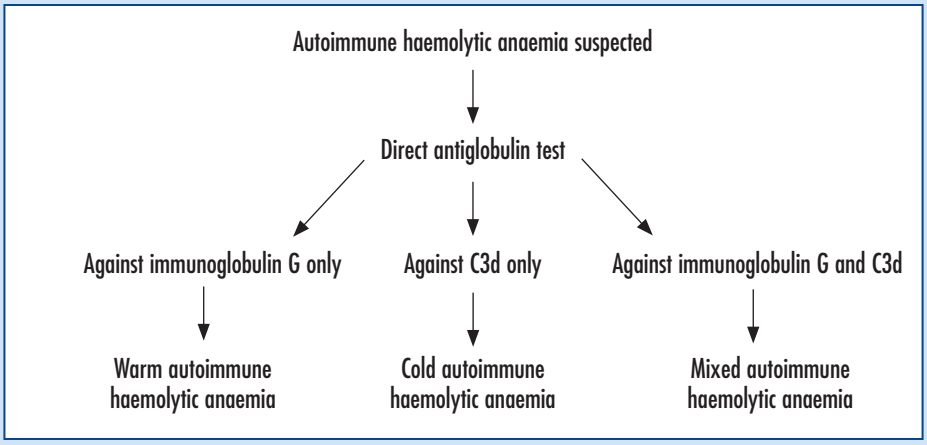

Figure 2. Diagnostic algorithm for types of autoimmune haemolytic anaemia based on the direct antiglobulin test.

lin test can be quantified by noting the degree of agglutination, which is usually reported by the laboratory as 1+, 2+, 3+ and so on.

In addition to the above tests, if a previous underlying condition has not been diagnosed, a search for this may be undertaken (*Table 1*).

Caveats for diagnostic tests

A normal or low reticulocyte count points toward bone marrow underactivity which may, paradoxically, be present in autoimmune haemolytic anaemia, since autoantibodies may be directed against erythroid precursors and red cells. In addition, it can occasionally take a few days for the reticulocyte count to increase in acute onset haemolysis.

Patients with liver disease are likely to have raised bilirubin and lactate dehydrogenase levels, with low haptoglobin levels (Petz and Garratty, 2004). Around 10% of patients with autoimmune haemolytic anaemia have a false-negative direct antiglobulin test. The diagnosis is usually made after exclusion of other causes of haemolysis and on the basis of clinical response to therapy, and is often delayed as a result of diagnostic difficulties. Conversely, a positive direct antiglobulin test may occur in 0.3–8% of hospital patients who do not have clinical evidence of autoimmune haemolytic anaemia (Gehrs and Friedberg, 2002). Causes include haemolytic transfusion reactions, therapies such as intravenous immunoglobulin and antithymocyte globulin, and conditions with elevated serum globulin levels such as renal disease and multiple myeloma.

Drug-induced autoimmune haemolytic anaemia

This type of autoimmune haemolytic anaemia is often overlooked, but around 10% of autoimmune haemolytic anaemia cases can be attributed to drugs. Although uncommon, it is vital to consider the diagnosis as often the only treatment necessary is to stop the offending drug. Around 150 drugs have been considered to be associated with autoimmune haemolytic anaemia. The main culprits are antimicrobials (42%, the majority being cephalosporins), non-steroidal anti-inflammatory drugs (16%), anti-cancer drugs (13%) and antihypertensives or diuretics (6%). A temporal relationship of the autoimmune haemolytic anaemia developing soon after the drug has been started is the diagnostic clue, which can be confirmed on the basis of resolving haemolysis after stopping the suspect drug (Garratty, 2010).

Complications of autoimmune haemolytic anaemia

Thrombosis

Venous thromboembolism is a contributory factor to the deaths of 3–10% of patients with autoimmune haemolytic anaemia. Patients with antiphospholipid antibodies and autoimmune haemolytic anaemia are more at risk, as are those post splenectomy. Although there is insufficient evidence to recommend prophylactic anticoagulation in patients with autoimmune haemolytic anaemia (Petz and Garratty, 2004), it is important to be vigilant for signs and symptoms of thrombosis.

Lymphoma

Patients with lymphoproliferative disorders are at higher risk of developing autoimmune haemolytic anaemia; the converse may also be true. It is postulated that immune dysregulation plays a role in development of both autoimmune haemolytic anaemia and lymphoproliferative disorders (Hoffman, 2009).

Management

Autoimmune haemolytic anaemia is an uncommon, heterogeneous disease; there are unfortunately few prospective clinical trials to guide decision making. Treatment recommendations in autoimmune haemolytic anaemia are therefore usually based on a combination of experience and data from retrospective case studies. Autoimmune haemolytic anaemia often has an acute onset followed by a chronic, insidious disease course. The majority of patients do not achieve long-term remission or cure, so the primary goal of treatment is to keep the patient clinically comfortable and to prevent haemolytic crises (Lechner and Jager, 2010).

When should we transfuse?

The first management decision to make is whether the patient requires transfusion. This is especially so since there may be problems with transfusion as a result of:

- Technical difficulty in obtaining cross-match compatible blood; detailed compatibility test procedures are needed, and often done in specialized reference laboratories (Barros et al, 2010)
- Subsequent delay of 24–48 hours in providing blood
- Significant risk of alloantibody formation, leading to increased haemolysis (Shirey et al, 2002; Zeerleder, 2011).

Owing to these difficulties, a number of authorities recommend limiting transfusion to patients with life-threatening anaemia or with a high risk of cardiac or cerebrovascular events (Gehrs and Friedberg, 2002; Zeerleder, 2011). Although this may be advisable, occasionally this can be dangerous. There are reports of patients with life-threatening anaemia who were not transfused because their physicians were concerned that compatible blood could not be obtained (Petz, 2004). When assessing the need for transfusion, it is critically important to consider the rate of anaemia

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progression, comorbidities and likely timescale for compatible blood to be obtained. Close communication between the clinician and transfusion laboratory is essential (Michel, 2014).

Which treatments are available for autoimmune haemolytic anaemia?

First-line treatment of warm autoimmune haemolytic anaemia is with corticosteroids, which will achieve a response in 80% of patients with 20% attaining a complete, long-lasting remission (Petz and Garratty, 2004; Barros et al, 2010; Lechner and Jager, 2010). Although most patients will respond to initial treatment, most will also require second-line therapy. About 20% will not respond to steroids, 20% will require an unacceptably high long-term dose of steroids (generally >15 mg/day) (Lechner and Jager, 2010) and around 40% will relapse. Length of time to relapse varies from a number of weeks to a number of years (Crowther et al, 2011). Supplementation with folic acid is recommended in all patients with autoimmune haemolytic anaemia to compensate for the excessive red cell turnover.

The two second-line treatments with proven short-term efficacy are splenectomy and rituximab (Lechner and Jager, 2010). Cure rates of up to 20% have been reported with splenectomy. With respect to rituximab, 70–80% of patients respond initially (Birgens et al, 2013; Maung et al, 2013; Bass et al, 2014). Remission rates among responders have been reported as 80% after 2 years and 70% after 3 years (Lechner and Jager, 2010; Birgens et al, 2013). A multicentre retrospective study of rituximab use in relapsed or resistant autoimmune haemolytic anaemia reported a relapse rate of 50% among responders after a median of 16.5 months (Maung et al, 2013). Intravenous immunoglobulin is not recommended for routine use in autoimmune haemolytic anaemia. Danazol has been tried in some patients with good success.

Management of secondary autoimmune haemolytic anaemia involves treatment of the underlying disease, which often includes either steroid as part of a chemotherapy regimen, or immunosuppression for autoimmune disorders (Lechner and Jager, 2010).

Fewer patients with cold autoimmune haemolytic anaemia require treatment, since the anaemia is usually milder and follows a fairly stable course (Petz, 2008). Patients should be advised to avoid the cold, and if transfusion is needed, this must be done through a blood-warmer. Since haemolysis primarily takes place in the liver, splenectomy is ineffective, and response to steroids has only been demonstrated in a small number of patients (Gehrs and Friedberg, 2002). Rituximab is now recommended as first-line treatment for cold agglutinin syndrome, although complete and sustained responses are uncommon (Petz, 2008; Zeerleder, 2011).

Conclusions

Presentation and disease course varies significantly between individuals with autoimmune haemolytic anaemia. Since diagnosis is usually straightforward, it is important to focus on instances where there is diagnostic difficulty, since these are the occasions where considering the diagnosis early may make a real difference to patient outcome. Given the heterogeneity and rarity of the disease, there is a poor evidence base for treatment decisions. However, rituximab has emerged over the last decade as an efficacious second-line agent. There is a need for randomized, controlled, prospective clinical trials to further evaluate the place of rituximab in treatment of autoimmune haemolytic anaemia. BJHM

Conflict of interest: none.

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KEY POINTS

- Autoimmune haemolytic anaemias are a diverse group of disorders with significant associated morbidity and mortality.
- Diagnosis requires evidence of anaemia, haemolysis and an autoimmune component.
- The need for transfusion should be considered early.
- Most patients will require several lines of therapy during a chronic disease course.

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