Drug-induced haemolytic anaemia

Haemolysis may be induced by external agents, including drugs, food and environmental chemical agents. In susceptible individuals, haemolysis can be a life-threatening adverse drug reaction. Haemolysis induced by drugs may be immune-mediated or by oxidative haemolysis. Drug-induced immune haemolysis is an idiosyncratic reaction, while oxidative haemolysis is usually associated with G6PD deficiency and follows exposure to identified oxidative stressors.

This review will consider a brief overview of haemolytic anaemia. The pathophysiology, clinical presentation and management of drug-induced immune haemolytic anaemia and oxidative haemolysis will be discussed separately.

Overview of haemolytic anaemia

A normal red blood cell has a lifespan of 120 days. Haemolysis occurs when this lifespan is significantly shortened. In compensated haemolysis (which is asymptomatic) red cell mass is maintained at normal values by increased erythropoiesis. Haemolytic anaemia occurs when the pace of red blood cell production does not match red cell destruction, either because red cell survival is extremely short or because the bone marrow is unable to compensate (e.g. due to folate or iron deficiency).

The site of red blood cell destruction may be intravascular or extravascular (primarily the spleen). Intravascular haemolysis is the destruction of red cells in the circulation with release of cell contents into the plasma. Complement fixation and activation on the red cell surface typically results in intravascular haemolysis. Extravascular haemolysis is the removal and destruction of erythrocytes by the reticuloendothelial system, primarily the spleen. As circulating blood is continuously filtered through the splenic sinusoids, the normal 8 micron red blood cell can deform itself and pass through the 3 micron openings of the splenic cord. A red blood cell (RBC) with membrane abnormality (e.g. hereditary spherocytosis or RBC coated with antibodies) is not able to transverse the sinusoidal network and is then phagocytosed and destroyed by macrophages.

Haemolytic anaemia may be hereditary or acquired. Causes of hereditary haemolysis include membranopathies (e.g. hereditary spherocytosis, hereditary elliptocytosis), enzymopathies (e.g. G6PD deficiency, pyruvate kinase deficiency) and haemoglobinopathies (e.g. thalassaemia, sickle cell disease). Acquired haemolytic anaemia may be immune mediated, either idiopathic, or associated with malignancy, autoimmune disorders, drugs, infections and transfusions. It can also result from mechanical disruption of RBC, resulting in microangiopathic haemolytic anaemia, which is associated with disseminated intravascular coagulation, prosthetic valves and malignant hypertension.

Clinical features common to all types of haemolysis include pallor, fluctuating jaundice and mild splenomegaly. The aim is to confirm haemolysis, find and treat the underlying cause. Table I lists the laboratory findings that help to establish the diagnosis.

Table I. Laboratory findings

Suggest haemolysis
- Full blood count: reticulocytosis with or without low Hb; mild macrocytosis
- Blood smear: polychromasia and basophilic stippling
- Liver function test: increased unconjugated bilirubin and LDH or AST

To confirm haemolysis
- Decreased haptoglobin

Features suggestive of intravascular haemolysis
- *Haemoglobinaemia*
- Haemoglobinuria
- Haemosiderinuria

Hb = haemoglobin; LDH = lactate dehydrogenase; AST = aspartate aminotransferase

Drug-induced immune haemolytic anaemia (DIIHA)

These are IgG- and IgM-mediated disorders that produce positive direct antiglobulin (Coombs') tests that are clinically and serologically indistinct from autoimmune haemolytic anaemia. Drug-induced immune haemolysis may occur by one of three mechanisms. Firstly, the drug (e.g. penicillin) bound to the RBC membrane acts as a hapten stimulating IgG antibody production. Secondly, the drug (e.g. quinine) induces IgM antibody production. The drug antibody immune complex thus formed binds to the RBC membrane and initiates complement activation, resulting in intravascular haemolysis, which is often severe. Thirdly, the drug (e.g. methyldopa) induces the formation of autoimmune anti-erythrocyte IgG antibodies. Haemolysis in this setting is typically mild. Table II lists the examples of drugs reported to cause immune-mediated haemolysis and their clinical and laboratory features.

Discontinuation of the offending drug usually results in prompt resolution of the haemolysis. Corticosteroids have a limited role and have been used in severe cases.

Drug-induced oxidative (non-immune) haemolytic anaemia

The normal RBC undergoes auto-oxidation of haemoglobin to methaemoglobin at a slow rate. The formation and reduction of methaemoglobin is about 1% of total haemoglobin. Some drugs may oxidise haemoglobin to methaemoglobin directly. Drug-induced oxidant damage to red cells presents in a variety of disorders of which methaemoglobinaemia and/or intravascular haemolysis are the main components. This can occur in red cells with impaired oxidant defence or red cells with normal reducing capacity.

Oxidative haemolysis in RBCs with defective metabolism

This is most often associated with G6PD deficiency. G6PD deficiency is the commonest RBC enzymopathy, affecting over 400 million people globally. West Africa, the Mediterranean, the Middle East and South East Asia have the highest prevalence. In southern Africa it has a prevalence of 3.0 - 6.9%. The inheritance is X-linked, affecting males and homozygous females. Heterozygous females are carriers for the gene and have normal G6PD levels.

G6PD deficiency increases the vulnerability of the erythrocytes to oxidative stress. G6PD catalyses nicotinamide adenine dinucleotide phosphate (NADP) to its reduced form NADPH. NADPH protects erythrocytes from oxidative stress. The decreased enzyme activity results in low NADPH and haemolysis occurs following oxidative stressors.

Table II. Mechanisms of drug-induced immune haemolytic anaemia, clinical and laboratory features

Mechanism	Hapten-RBC membrane	Immune complex	Autoantibody
Duration of therapy prior to haemolysis	Days to weeks	Days	Months
Clinical findings	Subacute haemolysis (7-10 days), can be life threatening if drugs continued	Acute onset, can be life threatening with evidence of intravascular haemolysis	Gradual onset of haemolytic anaemia, progressive if therapy continued
Coombs' test	Positive anti-IgG	Positive anti-C3	Positive anti-IgG
Site of haemolysis	Extravascular	Intravascular	Extravascular
Drugs*	Penicillins	Paracetamol	Methyldopa
	Cephalosporins	Chlorpromazine	Diclofenac
		Hydralazine	Ibuprofen
		Hydrochlorothiazide	Mefenamic acid
		Insulin	Interferon alpha
		Isoniazid	L-dopa
		Quinidine	Procainamide
		Quinine	
		Probenecid	
		Rifampicin	
		Sulindac	
		Sulphonamides	
		Streptomycin	
		Tetracycline	

*Disclaimer - the lists provided are examples of commonly used drugs and are not inclusive of all drugs reported to cause haemolytic anaemia.

Table III. Agents* that may cause haemolytic anaemia in G6PD deficiency

- Antimalarials: primaquine, chloroquine, sulfadoxine-pyrimethamine
- Sulphonamides and sulphones: co-trimoxazole, dapsone , salazopyrin
- Other antibacterials: nalidixic acid, nitrofurantoin, chloramphenicol
- Analgesics: aspirin (high doses)
- Miscellaneous: vitamin K analogues, naphthalene (mothballs and henna), probenecid, methylene blue
- Fava beans

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Ingestion of fava beans, drugs, toxins (Table III), and intercurrent illnesses induce oxidative stress. This causes intracellular formation of hydrogen peroxide (H_2O_2) and other oxidising radicals which cause cell lysis.

Clinical presentation depends mainly on the G6PD variant, which may differ in its severity. The Mediterranean variant is the most severe. The main syndromes include acute haemolysis following oxidative stress, neonatal hyperbilirubinaemia and rarely congenital non-spherocytic anaemia. Severe, life-threatening intravascular haemolytic anaemia may occur. Onset is typically within a few days of exposure to the drug or other stressor.

Although G6PD deficiency is not very common in South Africa, clinicians need to have a high index of suspicion in patients who are immigrants from high-prevalence areas. Diagnosis is suggested by family history and haemolysis that follows known oxidative stressors. The diagnosis is confirmed by measuring G6PD levels. Because of the higher enzyme level in young red cells, the enzyme assay may give a false normal level in the phase of acute haemolysis with reticulocytosis. The mainstay of treatment is avoidance of oxidative stressors.

Oxidative haemolysis in RBCs with normal reducing activity

The use of oxidative drugs (e.g. dapsone and salazopyrin – see Table IV) may produce methaemoglobinaemia. Methaemoglobinaemia is characterised by the presence of mild cyanosis, variable haemolysis, and elevated methaemoglobin. Cyanosis is clinically apparent at low concentrations of methaemoglobin. It should be suspected in patients with cyanosis who do not have cardiorespiratory disease. Asymptomatic methaemoglobinaemia is common with prolonged administration of certain drugs (e.g. dapsone). Symptoms develop when 35 - 40% of haemoglobin is in the oxidised form. For severe symptomatic methaemoglobinaemia, methylene blue, an antidote that converts methaemoglobin to haemoglobin is indicated. This is contraindicated in patients with G6PD deficiency, and exchange transfusion should be considered in this setting.

Reporting drug-induced haemolysis

Drug-induced haemolytic anaemia is typically a rare adverse drug reaction which is usually not identified before marketing of new drugs. The identification of offending drugs during post-marketing

Table IV. Methaemoglobin-inducing agents*

- Dapsone
- Salazopyrin
- Nitrites and nitrates
- Topical benzocaine or lignocaine
- Lead poisoning
- Copper in Wilson's disease
- Paraquat ingestion

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surveillance relies on case reports by caregivers and clinical researchers. It is vital to report drug-induced haemolysis when the offending drug is new or not a well-established cause of haemolysis. Adverse drug reactions should be reported to the National Adverse Drug Event Monitoring Centre (NADEMC), tel (021) 447-1618, fax (021) 448-6181.

Recommended reading

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In a nutshell

- Drug-induced haemolytic anaemia is rare, but can be a life-threatening event in susceptible individuals.
- The mechanisms of drug-induced haemolysis are either immune mediated or by oxidative haemolysis (typically in G6PD-deficient individuals or by causing methaemoglobinaemia).
- The mainstay of treatment is discontinuation and avoidance of the offending drugs.

Single Suture

Relief for back pain

People with severe degenerative disc disease may see some relief if a new technique continues to show promise. It appears that disc transplants from dead donors may treat the problem. The usual treatment for degenerative disc disease is painkillers and, as a last resort, spinal fusion, which can lead to decreased mobility and further degeneration of neighbouring discs.

Now, Keith Luk of the University of Hong Kong and Dike Ruan of the Naval General Hospital in Beijing have used donor discs to replace damaged ones in the cervical spine of 1 woman and 4 men. Five years later, symptoms, such as numbness, muscle weakness and a stiff gait, have improved in all patients. And none of the patients had an immune response, even though immunosuppressive drugs were not used.

Luk K, Ruan D. *Lancet* 2007; 369: 993.