Non-immune acquired haemolytic anaemias

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Causes of Non-immune acquired haemolytic anaemias.

Cause	Mechanisms	Examples
Infections	Intracellular organisms	*Falciparum* malaria Babesiosis *Bartonella*
	Endotoxin-induced DIC	Meningococcal sepsis Pneumococcal sepsis Gram-negative sepsis
	Haemophagocytic syndromes	Atypical mycobacterial infections HIV Viruses
	Enzyme toxins	*Clostridium perfringens* Snake, spider bites
Chemical and physical agents	Oxidative damage	Drugs Industrial/domestic substances
	Heat	Burns
	Osmotic lysis (fresh water), dehydration of red cells (salt water)	Drowning
	Enzyme inhibition	Lead poisoning Copper (Wilson's disease)
Fragmentation (mechanical)	Lysis on prosthetic surfaces	Cardiac haemolysis Perivalvular leak
	Vasculitis, endothelial cell swelling, fibrin shear	Microangiopathic haemolytic anaemia March haemoglobinuria
Acquired membrane disorders	Lipid or cholesterol changes Somatic mutation	Liver disease Paroxysmal nocturnal haemoglobinuria (PNH)

DIC, disseminated intravascular coagulation.

Infections

Infections can cause haemolysis in a variety of ways:

-They may precipitate an acute haemolytic crisis in G6PD deficiency

-cause microangiopathic haemolytic anaemia (e.g. with meningococcal or pneumococcal septicaemia).

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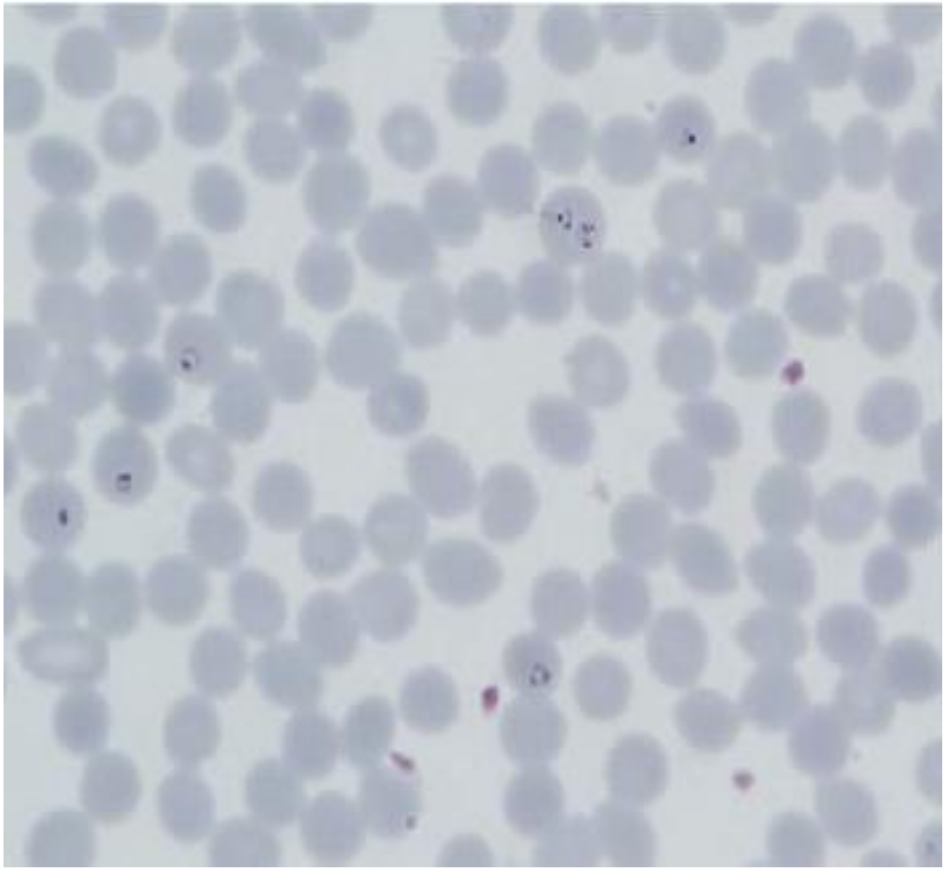
- Malaria causes haemolysis by extravascular destruction of parasitized red cells as well as by direct intravascular lysis. *Blackwater* fever is an acute *intravascular* haemolysis accompanied by acute renal failure caused by *Falciparum* malaria

Falciparum malaria infection



-***Clostridium perfringens*** **septicaemia can cause intravascular haemolysis with marked microspherocytosis**

- *In haemophagocytic syndrome* **destruction of red cells and their precursors in the marrow, spleen or liver and is associated with amarked rise in LDH.**

Chemical and physical agents

-Certain drugs (e.g. dapsone and sulfasalazine) in high doses cause oxidative intravascular haemolysis with Heinz body formation in normal subjects.

-In Wilson's disease an acute haemolytic anaemia can occur as a result of high levels of copper in the blood.

-Chemical poisoning (e.g. with lead, chlorate or arsine) can cause severe haemolysis.

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-Severe burns damage red cells causing acanthocytosis or spherocytosis.

-Normal red cells when heated *in vitro* to 46 °C for 1 hour show no changes , however they show temperature- and duration dependent changes above 47–50 °C.

Fragmentation haemolysis: mechanical haemolytic anaemias

These arise through physical damage to red cells either on abnormal surfaces (e.g. artificial heart valves or arterial grafts), arteriovenous malformations or as a microangiopathic haemolytic anaemia.

Red cell fragmentation syndromes

-**Cardiac haemolysis:** -**Prosthetic heart valves**
-Patches, grafts
-Perivalvular leaks

-Arteriovenous malformations

-**Microangiopathic:** **- TTP-HUS**
-Disseminated intravascularcoagulation
-Malignant disease
-Vasculitis (e.g. polyarteritis nodosa)
-Malignant hypertension
-Pre-eclampsia/HELLP
-Renal vascular disorders/HELLP syndrom
-Ciclosporin-
-Homograft rejection

Haemolysis associated with cardiac surgery

Cardiac haemolytic anaemia was a term coined to describe haemolysis following cardiac surgery that involved the insertion of prosthetic valves, patches or grafts.

Mechanical trauma to red blood cells is the primary cause of haemolysis in this setting and is mainly due to increased turbulent flow resulting in excessive shearing forces on the surface of the red cells.

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-Secondary physiologic mechanisms include pressure fluctuations, intrinsic abnormalities of the red cell membrane (largely due to fragile, iron poor red cells in iron-deficient patients), interactionwith foreign surfaces and unfavourable flow characteristics of valves

Arteriovenous malformation

Fragmentation of red cells may be seen in Kasabach–Merritt syndrome, in which platelets are trapped in the vascular network of giant arteriovenous malformations, sometimes with evidence of a consumption coagulopathy. The bleeding disorder that ensues is of greater significance than haemolysis in these patients.

A similar pattern is seen in malignant haemangioendothelioma.

Microangiopathic haemolytic anaemias (MAHA)

A condition in which intravascular haemolysis with fragmentation of red cells is caused by their destruction in an abnormal microcirculation.

Proof of microangiopathy may be lacking in those not subjected to a post mortem, and MAHA should be considered a clinical syndrome.

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The three main pathological lesions that give rise to MAHA are :

1-deposition of fibrin strands, often associated with DIC

2- platelet adherence and aggregation .

3- vasculitis.

The vessel abnormalities may be generalized or confined to particular sites or organs.

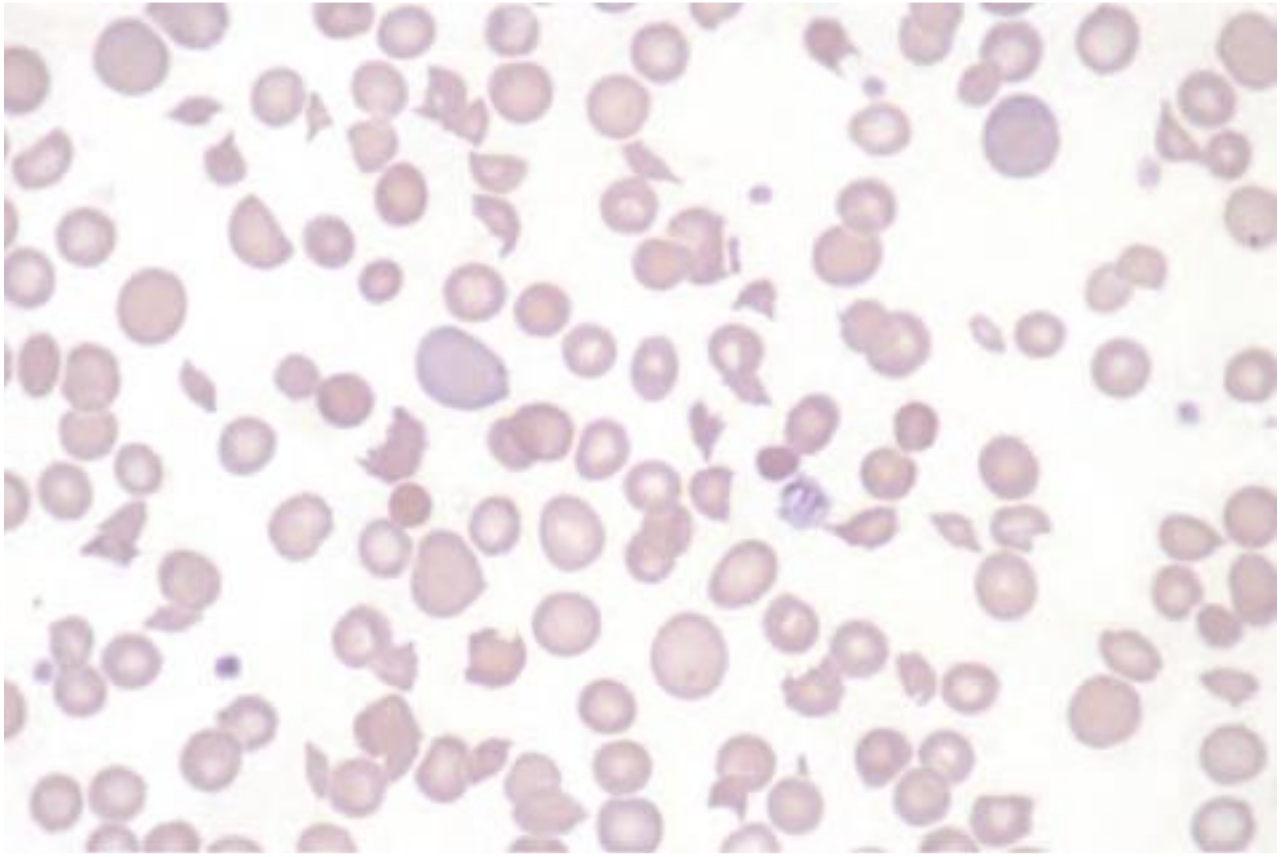
In most cases, haemolysis is of less consequence than the underlying cause of the microangiopathy , but fragmentation of red cells helps to confirm the diagnosis

Causes of microangiopathic haemolytic anaemia.

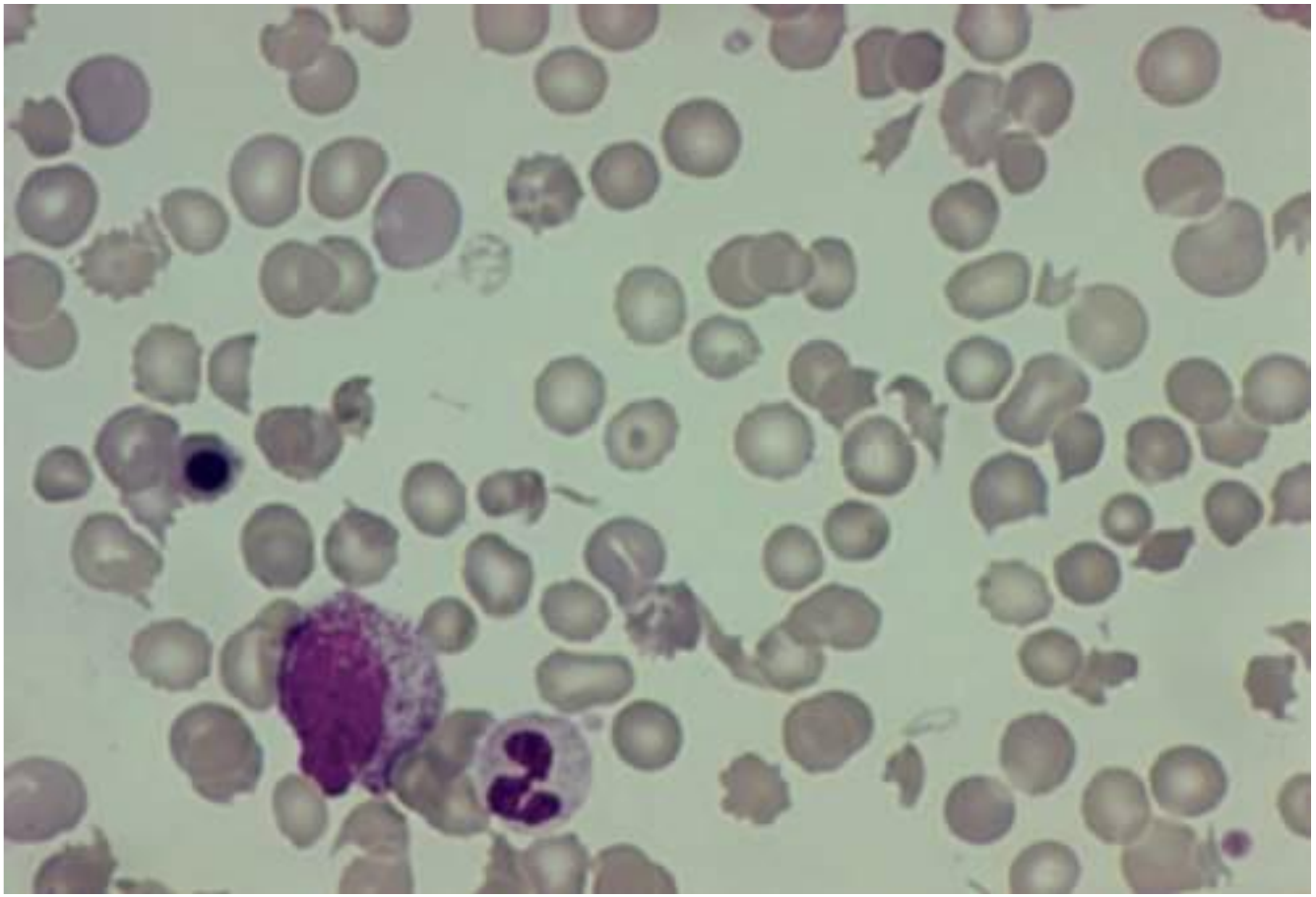
Disease	Microangiopathy
Haemolytic–uraemic syndrome	Endothelial cell swelling, microthrombi in renal vessels
Thrombotic thrombocytopenic purpura	Platelet plugs, microaneurysms, small-vessel thrombi
Renal cortical necrosis	Necrotizing arteritis
Acute glomerular nephritis	
Malignant hypertension	
Pre-eclampsia	Fibrinoid necrosis
HELLP	
Polyarteritis nodosa	Vasculitis
Wegener granulomatosis	
Systemic lupus erythematosus	
Homograft rejection	Microthrombi in transplanted organ
Mitomycin C	Uncertain
Ciclosporin	Renal vessel anomalies
Carcinomatosis	Abnormal tumour vessels, intravascular coagulation (disseminated or localized)
Primary pulmonary hypertension	Abnormal vasculature
Cavernous haemangioma (Kasabach–Merritt)	Local vascular changes, thrombosis

The peripheral blood contains many deeply staining red cell fragments

Blood film in microangiopathic haemolytic anaemia (in this patient Gram-negative septicaemia). Numerous contracted and deeply staining cells and cell fragments are present



Blood film from a patient with carcinoma and bone marrow metastases.
Note fragmentation of red cells, low platelets and leucoerythroblastic changes (circulating nucleated red cell and metamyelocyte)



Thrombotic thrombocytopenic purpura

-is an acute syndrome characterized by fever, neurological signs, haemolytic

anaemia with fragmented red cells and profound thrombocytopenia.

-There is severe deficiency of von Willebrand factor cleaving protease (VWFCP; also known as ADAMTS13)

The diagnosis is made on the basis of the clinical presentation and evidence for haemolytic anaemia with fragmentedred cells and thrombocytopenia. It can be confirmed with an assay which confirms low ADAMTS13 level.

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-Thrombocytopenia, schistocytes in the blood film and an impressively elevated serum lactate dehydrogenase (LDH) value are sufficient to suggest the diagnosis.

-**Coagulation tests are normal** in contrast to the findings in DIC .

ADAMTS13 is absent or severely reduced in plasma.

The destruction of red cells occurs at the site of intravascular occlusions; at post mortem, platelet and fibrin plugs are found in capillaries .

HUS in children has many common features but organ damage is limited to the kidneys.

There is also usually diarrhoea and epileptic seizures may occur.

Many cases are associated with *Escherichia coli* infection with the verotoxin 0157 strain or with other organisms, especially *Shigella*.

March haemoglobinuria

Haemoglobinuria following running has been documented for about 100 years.

Its origin is mechanical , with destruction of red cells occurring in the feet. It can be cured by wearing soft shoes or running on soft ground.

It is benign except that it may lead to extensive invasive investigations unless recognized.

The blood film does not show any red cell fragmentation or consistent abnormality.

Occasionally, haemoglobinuria after running is accompanied by nausea , abdominal cramps and aching legs, and enthusiastic athletes with this condition may exhibit mild splenomegaly and jaundice.

Acquired disorders of the red cell membrane

The most common acquired disorder is *paroxysmal nocturnal haemoglobinuria (PNH),* caused by somatic mutation of the phosphatidylinositol glycan A (*PIGA*) gene on the X chromosome, which leads to failure to produce the glycosylphosphatidylinositol (GPI) anchor needed to transport and attach many proteins to the red cell membrane..

Intravascular haemolysis occurs through the unchecked action of activated complement .

The lipids of the membrane are in equilibrium with the lipids of the plasma and changes in the ratio of free cholesterol

to phospholipids in plasma may affect red cell shape and, in some instances, lead to haemolysis. This is most commonly seen

in liver disease .