ACQUIRED HAEMOLYTIC ANAEMIA

HAEMOLYSIS OF RED BLOOD CELLS WITHIN THE CIRUCLATION OR IN THE EXTRAVASCULAR SPACES OF THE SPLEEN AND LIVER CAN PRODUCE A SPECTRUM OF DISEASE FORM MILD TO SEVERE HAEMODYNAMIC COMPROMISE

PRESENTING SYMPTOMS AND SIGNS ARE THOSE OF ANAEMIA

RBC DESTRUCTION GENERATES FREE HAEMOGLOBIN THAT IS THEN BROKEN DOWN INTO BILIRUBIN ➔ WHEN THIS EXCEEDS THE LIVER'S CAPACITY TO CONJUGATE IT FOR BILIARY AND FAECAL EXCRETION, JAUNDICE, ABDOMINAL PAIN AND DARKENED URINE MAY DEVELOPMENT

TYPICAL LABORATORY FINDINGS ARE SHOWN BELOW:

Table 232-1 Basic Tests and Findings in the Evaluation of Hemolytic Anemia

Purpose	Test	Finding
Confirm anemia/blood loss	Hemoglobin	Decreased
	Hematocrit	Decreased
Confirm compensatory RBC production	Reticulocyte count	Increased
Confirm hemolysis	Peripheral smear	Schistocytes—intravascular hemolysis, RBCs fragmented by shear mechanism
		Spherocytes—extravascular hemolysis, RBC phagocytosis by macrophages
Confirm hemolysis	Lactate dehydrogenase	Increased, released by RBCs
	Potassium	Increased, released by RBCs
Confirm hemolysis	Haptoglobin	Decreased, indicative of intravascular hemolysis
	Free hemoglobin	Increased, indicative of intravascular hemolysis
	Hemoglobinuria	Present
Confirm hemoglobin breakdown	Total bilirubin	Increased
	Indirect bilirubin	Increased (hepatic conjugation of bilirubin overwhelmed)
	Urinary urobilinogen	Increased

IMMUNE-MEDIATED ACQUIRED HAEMOLYTIC ANAEMIA:

AUTOIMMUNE HAEMOLYTIC ANAEMIA:

- Make antibodies against their own RBCs
- Diagnosis of AIHA requies evidence of an antibody on the patient's RBCs, usually accompanied by an autoantibody in the plasma ➔ DIRECT ANTIGEN (OR DIRECT COOMBS) TEST ➔ combine the patient's anticoagulated, washed RBC with anti-IgG and anti C3d antibodies to detect presence of IgG or complement on the RBC surface

- Differential for positive Coomb's test shown below

Table 232-2 Differential Diagnosis of Positive Direct Antigen (Direct Coombs) Test
Autoimmune hemolytic anemia
Hemolytic transfusion reaction, acute or delayed
Hemolytic disease of newborn
Transplantation
Drug-related hemolytic anemia
IV immunoglobulin therapy
Rh(D) immunoglobulin therapy
Antilymphocyte globulin therapy
Antithymocyte globulin therapy
Sickle cell disease
β-Thalassemia
Renal disease
Multiple myeloma
Hodgkin disease
Systemic lupus erythematosus
Human immunodeficiency virus/acquired immunodeficiency syndrome

- AIHA can take place within the vascular space or extravascualrly within the spleen or liver
    - Many cases initially designed as primary are later found to be associated with lymphoproliferative, autoimmune or infectious diseases
    - Further subclassified as below:

Table 232-3 Categories of Autoimmune Hemolytic Anemia (AIHA)	
Warm antibody AIHA: Autoantibodies adhere most strongly to RBCs at 37°C (98.6°F).	70%–80% of AIHA cases
	50% primary (idiopathic) disease
	50% secondary disease: lymphoproliferative, autoimmune disease, postinfection (transient)
	Usually IgG autoantibody against Rh(D) antigen
	Hemolysis usually extravascular
	Steroid responsive: 70%–80%
Cold-antibody AIHA: Autoantibodies adhere most strongly to RBCs at 0–4°C (32–39.2°F).	**Cold agglutinin disease:** IgM autoantibody against I antigen
	Primary disease: older females
	Secondary disease: lymphoproliferative disorders, post-infection (transient)
	Raynaud phenomenon, livedo reticularis, vascular occlusion
	Attacks precipitated by cold exposure
	Rarely intravascular hemolysis
	Not steroid responsive
	Paroxysmal cold hemoglobinuria: IgG autoantibody against P antigen
	Primary disease: rare, in adults
	Secondary disease: usually in children after upper respiratory infection
	Intravascular hemolysis during cold weather
	Usually not steroid responsive
Mixed type antibody AIHA: Autoantibodies have variable temperature-dependent RBC adherence.	Primary disease: more common in older females
	Secondary disease: lymphoproliferative and autoimmune disorders
	Usually chronic course with severe exacerbations
	Usually steroid responsive

ALLOIMMUNE HAEMOLYTIC ANAEMIA:

- Requires exposure to allogeneic RBC with subsequent alloantibody formation
- A well-known example of this is when the Rh(D)-negative maternal immune system develop IgG alloantibodies on exposure to Rh9D) positive foetal RBC
    - These antibodies can then cross the placenta, leading to foetal RBC destruction in a condition known as HAEMOLYTIC DISEASE OF THE NEWBORN → anaemia can be mild to fatal
    - HYDROPS FOETALIS describes anasarca seen in the severe cases
    - Administration of anti-D IgG with any fetomaternal haemorrhage event and soon after delivery will suppress maternal alloantibodies and prevent haemolytic disease of the newborn
    - Treatment of established disease in the newborn includes intrauterine and intravascular foetal transfusion and may include plasma exchange and IVIG
- Most adults who develop alloimmune haemolytic anaemia HAVE HAD RBC TRANSFUSION IN THE PAST, which sensitises them to allogeneic RBC antigens ➔ subsequent transfusion can result in immediate alloantibody production, hypotension, haemoglobinuria and oliguria

DRUG-INDUCED HAEMOLYTIC ANAEMIA:

- Common drugs that are implicated are listed below:

Table 232-4 Most Often Cited Drugs Inducing Autoantibody Formation
Catechin (antidiarrheal)
Cefotetan (antibiotic)
Ceftriaxone (antibiotic)
Cephalothin (antibiotic)
Diclofenac (NSAID)
Fludarabine (chemotherapeutic agent)
Interferon (chemotherapeutic agent)
Levodopa (antiparkinsonian)
Mefenamic acid (NSAID)
Methyldopa (antihypertensive)
Nomifensine (antidepressant)
Oxaliplatin (chemotherapeutic agent)
Penicillin G (antibiotic)
Phenacetin (NSAID)
Quinidine (antiarrhythmic)
Rifampin (antibiotic)
Tolmetin (NSAID)

- Hence careful review of patient's medications in those with presenting with haemolytic anaemia
- Patients with significant haemolysis and anaemia require hospitalisation and further evaluation
- Steroids can be used in cases of severe-drug-related haemolysis

MICROANGIOPATHIC SYNDROMES:

- The two classic syndromes are THROMBOTIC THROMBOCYTOPAENIC PURPURA and HAEMOLYTIC URAEMIC SYNDROME
    - Both syndromes involve platelet aggregation in the microvascular circulation via mediation of von-Willebrand factors
    - Microangiopathic haemolytic anaemia occurs when RBCs are fragmented during travel through partially occluded arterioles and capillaries
- TTP and HUS have significant overlap
    - TTP is more common in adults, HUS in kids
    - TTP typically produces more prominent neurological effects, with deposition of platelet aggregates in a broader distribution
    - HUS more specifically affects the renal system

THROMBOTIC THROMBOCYTOPAENIC PURPURA:

- CLASSIC PENTAD:
    - CNS dysfunction
    - Renal pathology
    - Fever
    - Microangiopathic haemolytic anaemia
    - Thrombocytopaenia

- Diagnostic criteria have been simplified ➔ all adults with microangiopathic or microvascular haemolysis with thrombocytopaenia with no other explanation → this is to CAPTURE MORE PATIENTS IN FAVOUR OF LIFE-SAVING PLASMA EXCHANGE
- Untreated TTP has a HIGH MORTALITY RATE, while plasma exchange therapy can achieve remission of disease in >80% of patients
    - Exercise caution with this simplified approach, as a number of conditions present with haemolysis and thrombocytopaenia and will not be helped by plasma exchange
        - Malignant HT
        - Sepsis, SLE
        - HELLP syndrome
- **PATHOPHYSIOLOGY:**
    - **Connected to a specific metalloprotease called ADAMTS-13 ➔** also known as vWF-cleaving protease, it functions to cleave vWF that has been unfolded by shear stress within the microvasculature of arterioles
        - Normally, vWF is prevented form forming large multimers by the cleaving action of ADAMTS-13
    - Insufficient ADAMTS-13 activity (whether due to autoantibodies or genetic mutation) leads to accumulation of vWF multimers in the microcirculation with resultant MICROTHROMBUS FORMATION
    - Platelet aggregation in TTP leads to systemic platelet depletion or thrombocytopaenia, shearing of RBCs across the microthrombi ➔ produces MICROANGIOPATHIC HAEMOLYTIC ANAEMIA
    - Microthrombi are concentrated in renal and CNS arterioles, promoting tissue ischaemia and necrosis, with resultant end-organ damage ➔ seizures, stroke, other focal neurological deficits, coma, acute renal injury or acute renal failure
    - Because TTP thrombi do not incorporate fibrin, TTP can be distinguished from DIC by normal coagulation studies
    - Severely deficient ADAMTS-13 activity alone is not sufficient to trigger TTP. Other precipitants include ➔ PREGNANCY, INFECITON, INFLAMMATION, MEDICATIONS
        - Beware, as TTP shares many clinical and laboratory features with PREECLAMPSIA/ECLAMPSIA → symptoms of severe preeclampsia or eclampsia before 24 weeks gestation should raise suspicion for TTP. Derangements of LDH, haematocrit, platelet count tend to be more severe in TTP, whereas LFT anomalies are modest to absent
    - An ADAMTS-13 activity level <5% clearly establishes the presence of TTP when corresponding clinical characteristics exist, although this assay is not routinely available in many hospitals
    - In the setting of HELLP syndrome, high-dose corticosteroids should lead to an improvement of platelet count within 24 hours, if it does not occur, think TTP

        - The maternal mortality rate of TTP has been reduced significantly with the use of plasma exchange, but foetal mortality has remained high due to placental microvascular occlusion, ischaemia and infarction
    - Several drugs are implicated in TTP ➔ ciprofloxacin, levofloxacin, quinine, sirolimus (when given with cyclosporine), risperidone, clopidogrel, lansoprazole, valacyclovir, infliximab, TICLODIPINE (HIGHEST RATES, NOW WITHDRAWN FROM THE MARKET)
- **TREATMENT OF TTP:**
    - Achievement of a normal platelet count is the goal of treatment of TTP plasma exchange therapy
    - Daily plasma exchange which is then weaned in frequency or stopped once normal counts are reached for 2-3 consecutive days
    - Infusion of plasma replaces defective or insurfficient ADAMTS-13 and removal of plasma rids the body of defective ADAMTS-13, autoantibodies and large vWF multimers
    - If plasmapheresis cannot be performed immediately, give FFP
    - Difficult-to-treat TTP may required RBC transfusion, anticonvulsants, antihypertensives and haemodialysis
        - AVOID PLATELET TRANSFUSION, except in life-threatening bleeding situations, as platelets acutely worsen thrombosis, renal failure and potentially lead to death
    - Corticosteroids, rituximab and cyclosporine may play a role in the treatment of autoimmune TTP
    - Patients with ADAMTS-13 activity levels < 10% are particularly at risk for relapse

<u>HAEMOLYTIC-URAEMIC SYNDROME:</u>

- HUS is the most common cause of preventable ARF in childhood and consists of:
    - Microangiopathic haemolytic anaemia
    - Acute nephropathy or renal failure
    - Thrombocytopaenia
- Can be typical or atypical:
    - Typical ➔ occurs inchildren about 1 week into a case of infectious diarrhoea, often bloody and without associated fever ➔ causative agent is SHIGA-TOXIN PRODUCING E. COLI, with serotype O157:H7 predominantly implicated
        - Other less common causes of HUS ➔ Shigella, Campylobacter and Salmonella
    - Atypical → older children and adults and may be difficult to distinguish from TTP
- **PATHOPHYSIOLOGY:**
    - Ingested via contaminated food or water, Shiga-toxin producing E coli O157: H7 possess potent virulence factors that allow invasion of intestinal epithelial cells and subsequent transmural intestinal migration

- The ensuing colonic inflammation produces a HAEMORRHAGIC COLITIS
- Once absorbed into the systemic circulation, Shiga toxin binds with greatest affinity to receptors found on the surfaces of glomerular and renal tubular epithelial cells
  - Toxin-mediated microvascular injury promotes platelet aggregation (thus systemic depletion) and thrombus formation at the injury site
  - Further up-regulation of epithelial and endothelial cell receptors with high affinity for Shiga-toxin creates a vicious cycle of thrombosis and microangiopathic haemolytic anaemia via shearing of RBC over microthrombi contributes to tissue ischaemia and necrosis
- Microthrombi within the β-islets lead to hyperglycaemia
- Onset of HUS is typically 2-14 days after diarrheoa develops → easy to miss. Send for specific stool testing for O157:H7 toxin in case of bloody diarrhoea and send EUC to detect nephropathy

- **TREATMENT:**
  - HUS is treated with SUPPORTIVE CARE
  - Early saline or Hartmann's can stop renal failure developing
  - RBC or platelet transfusion may be required for significant anaemia or thrombocytopaenia
  - Should ARF develop ➔ short burst of haemodialysis may be required
  - Infection with E coli O157:H7 SHOULD NOT BE TREATED WITH ANTIMOTILITY DRUGS BECAUSE THESE AGENTS INCREASES THE RISK OF HUS
  - The use of antibiotics is controversial, because IN VITRO studies have found that antibiotics may increase Shiga toxin expression from the bacteria and case-control studies in humans have found that antibiotic treatment may increase the risk of developing HUS

<u>MACROVASCULAR HAEMOLYSIS:</u>

- The presence of a prosthetic heart valve sets the stage for turbulent blood flow with high shear stress
  - HAEMOLYSIS IS MOST OFTEN ASSOCIATED WITH PARAVALVULAR LEAK → i.e. when infection or calcification promote valve dehiscence
  - Patients may present with mild anaemia, florid CHF or with symptoms of infective endocarditis
- Macrovascular haemolysis can also occur after intracardiac patch repair, aortofemoral bypass, in patients with coarctation of the aorta, severe aortic valve diseaes or LVAD or in those relying on extracorporeal circulation (bypass, plasma exchange or haemodialysis)
- Increased SCHISTOCYTOSIS correlates with more severe haemolysis
- Patients with ongoing mild macrovascular haemolysis should receive iron/folate replacement in addition to β-blockers to decrease RBC shear stress

    - Pentoxifyline, a xanthine derivative that reduces blood viscosity and improves haemolysis with prosthetic valves
- Severe haemolysis needs transfusion

ADDITIONAL CAUSES OF HAEMOLYSIS:

INFECTION:

- Destruction of RBC occurs in the course of many infectious diseases:
    - MALARIA, especially Falciparum, which causes intravascular haemolysis (hence Blackwater fever)
    - CLOSTRIDIUM PERFRINGENS ➔ cause direct lysis of RBC via toxin production
    - LEPTOSPIROSIS ➔ bacterial illness, contracted through ingestion or contact with water/food contaminated by animal urine. Toxin-induced haemolysis. Weil's syndrome is a particularly severe form of leptospirosis characterised by intravascular haemolysis, jaundice, nephropathy and haemorrhage

ENVENOMATION:

- Snakes (especially brown, black and taipan family)
- Can occur with bee, wasp and hornet stikngs → associated with rhabdomyolysis, ATN and ARF

CHEMICAL EXPOSURE:

- Inhalation of arsine gas can cause rapid, massive intravascular haemolysis with subsequent jaundice, haemoglobinuria, potential renal failure and death
    - Treatment is supportive ➔ oxygen and bronchodilators, hydration, urinary alkalinisation, haemodialysis and tranfusion as needed
- NAPHTHALENE ➔ can occur after toxic ingestion of household mothballs → timely activated charcoal and polyethylene glycol whole bowel irrigation prevent absorption and enhance elimination may help. Treatment is otherwise supportive

TRAUMA-INDUCED HAEMOLYSIS:

- Exertional or march haemoglobinuria occurs after significant bodily force is applied against a hard surface such as concrete
- Transient red or dark urine a few hours after exercise
- Occurs in runners, soldiers, karate participants, bare-foot dancers