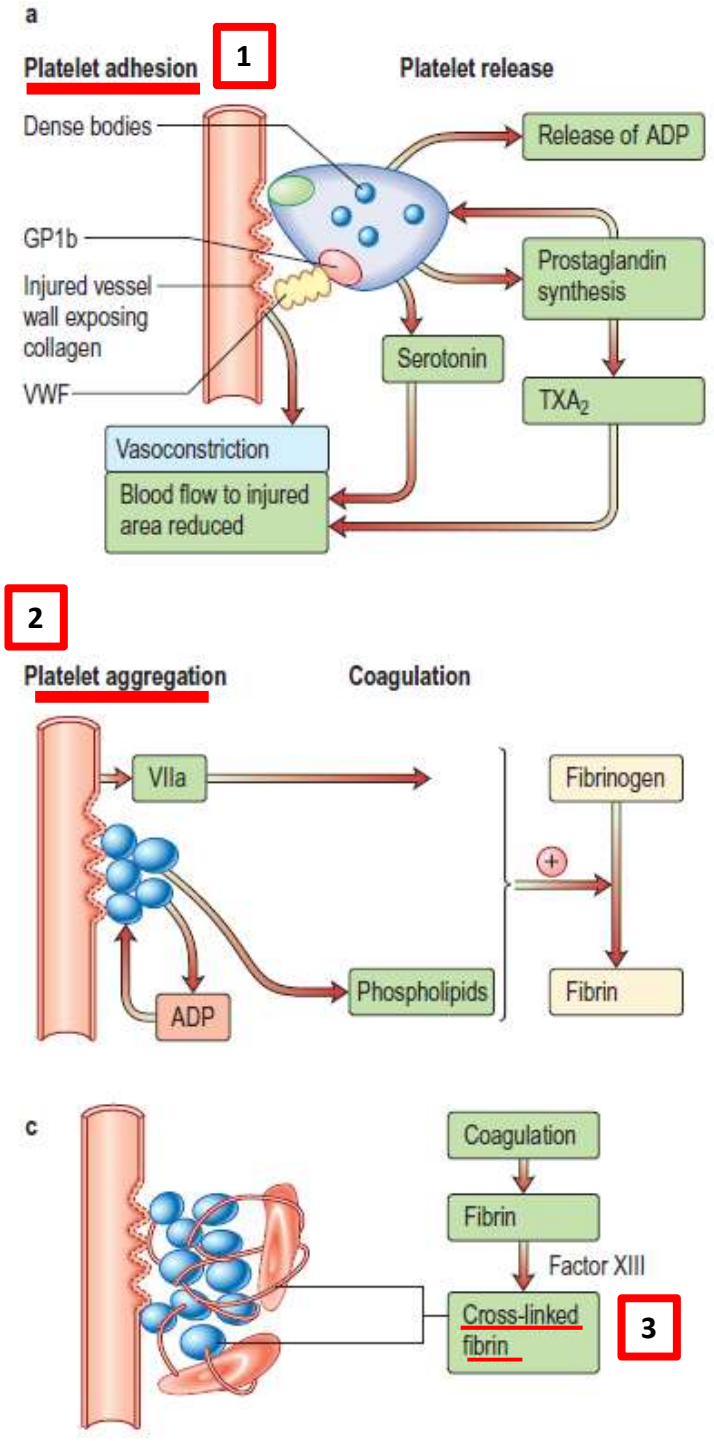
Haemostasis

Haemostasis is a complex process depending on interactions between the vessel wall, platelets, coagulation and fibrinolytic mechanisms.

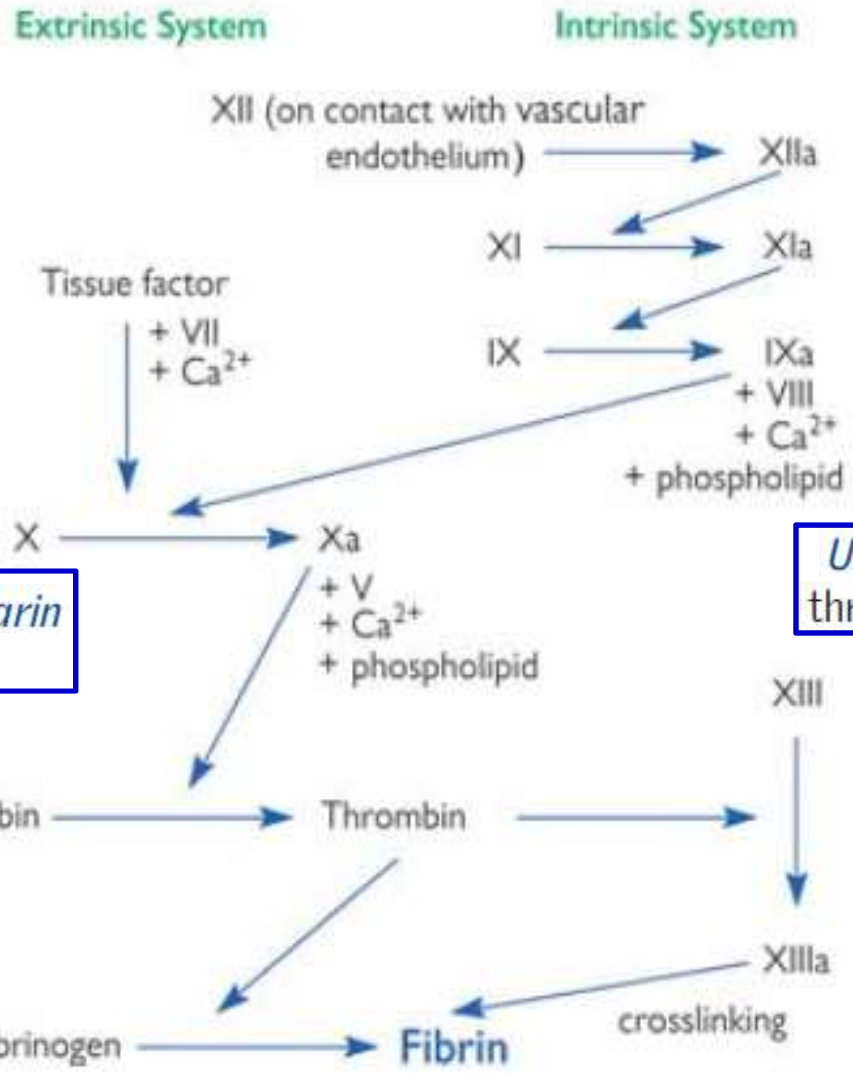
Injury to vessels causes reflex vasoconstriction, while endothelial damage results in loss of antithrombotic properties, activation of platelets and coagulation and inhibition of fibrinolysis

Formation of the haemostatic plug: sequential interactions between the vessel wall, platelets and coagulation factors. (a) Contact of platelets with collagen via the platelet receptor GP1b and factor VWF in plasma activates platelet prostaglandin synthesis which stimulates release of ADP from the dense bodies. Vasoconstriction of the vessel occurs as a reflex and by release of serotonin and thromboxane A_2 (TXA_2) from platelets.
(b) Release of ADP from platelets induces platelet aggregation and formation of the platelet plug. The coagulation pathway is stimulated leading to formation of fibrin.
(c) Fibrin strands are cross-linked by factor XIII and stabilize the haemostatic plug by binding platelets and red cells.



Activated partial thromboplastin time (APTT).
intrinsic system.
factor I, II, V, VIII, IX, X, XI, XII.

Prothrombin time (PT):
extrinsic system.
factors I, II, V, VII, X.



Warfarin
vitamin K
factors
II, VII, IX, and X

Low molecular weight heparin
factor Xa

Unfractionated heparin
thrombin, factor Xa, and IXa.

Fondaparinux
Factor Xa

dabigatran
thrombin

rivaroxaban
apixaban
Factor Xa

Thrombin time

Physiological limitation of coagulation

Without a physiological system to limit blood coagulation dangerous thrombosis could ensue. The natural anticoagulant mechanism regulates and localizes thrombosis to the site of injury.

Antithrombin. Antithrombin (AT), a member of the serine protease inhibitor (serpin) superfamily, is a potent inhibitor of coagulation. It inactivates the serine proteases by forming stable complexes with them, and its action is greatly potentiated by heparin.

Activated protein C. This is generated from its vitamin K-dependent precursor, protein C, by thrombin; thrombin activation of protein C is greatly enhanced when thrombin is bound to thrombomodulin on endothelial cells (Fig. 8.36). Activated protein C inactivates factor V and factor VIII, reducing further thrombin generation.

Protein S. This is a cofactor for protein C, which acts by enhancing binding of activated protein C to the phospholipid surface. It circulates bound to C4b binding protein but some 30–40% remains unbound and active (free protein S).

Other inhibitors. Other natural inhibitors of coagulation include α_2-macroglobulin, α_1-antitrypsin and α_2-antiplasmin.

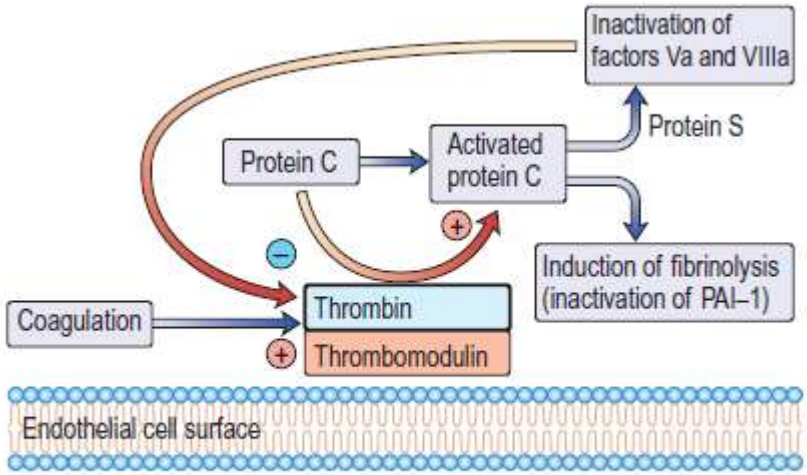


Figure 8.36 Activation of protein C. PAI-1, plasminogen activator inhibitor 1.

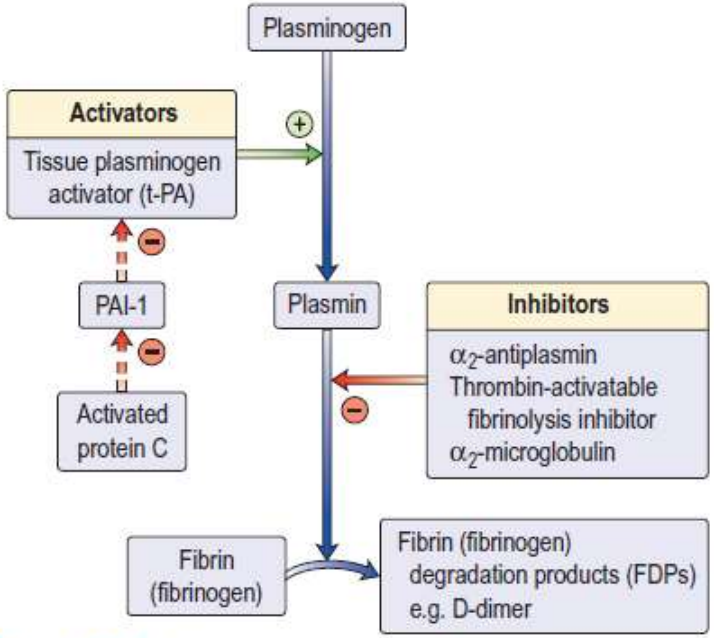
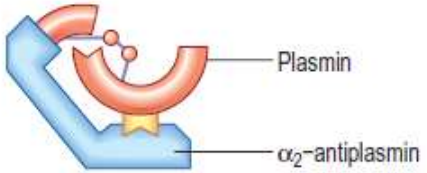
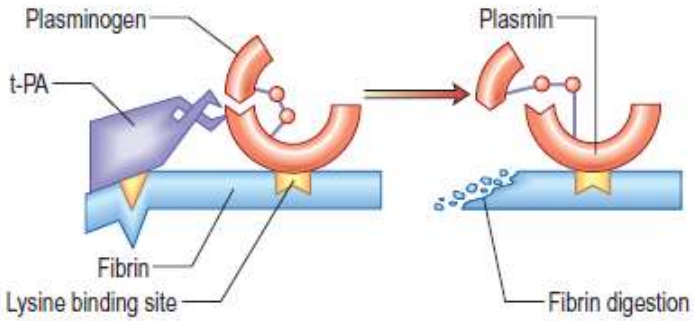


Figure 8.37 Fibrinolytic system. PA-1, plasminogen activator inhibitor-1.

b Plasmin α_2–antiplasmin complex



a Conversion of plasminogen to plasmin



Fibrinolysis

Fibrinolysis is a normal haemostatic response that helps to restore vessel patency after vascular damage. The principal component is the enzyme plasmin, which is generated from its inactive precursor plasminogen (Fig. 8.37). This is achieved principally via tissue plasminogen activator (t-PA) released from endothelial cells. Some plasminogen activation may also be promoted by urokinase, produced in the kidneys. Other plasminogen activators (factor XII and prekallikrein) are of minor physiological importance.

Plasmin is a serine protease, which breaks down fibrinogen and fibrin into fragments X, Y, D and E, collectively known as fibrin (and fibrinogen) degradation products (FDPs). D-dimer is produced when cross-linked fibrin is degraded. Its presence in the plasma indicates that the coagulation mechanism has been activated.

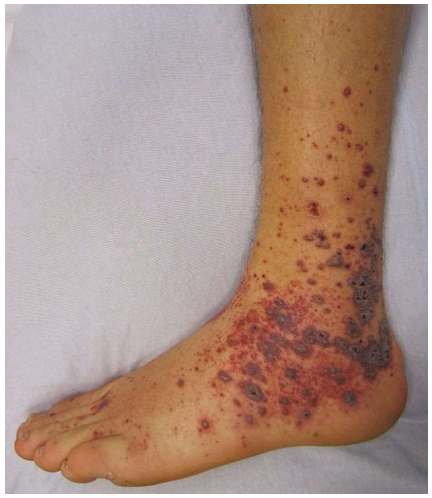
The fibrinolytic system is activated by the presence of fibrin. Plasminogen is specifically adsorbed to fibrin and fibrinogen by lysine-binding sites. However, little plasminogen activation occurs in the absence of polymerized fibrin, as fibrin also has a specific binding site for plasminogen activators, whereas fibrinogen does not (Fig. 8.38).

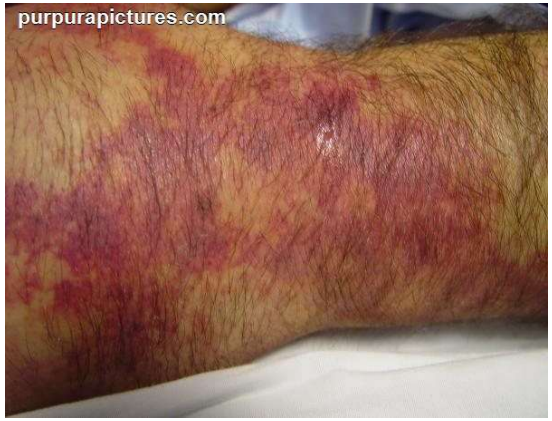
t-PA is inactivated by plasminogen activator inhibitor-1 (PAI-1). Activated protein C inactivates PAI-1 and therefore induces fibrinolysis (Fig. 8.36). Inactivators of plasmin, such as α_2-antiplasmin (Fig. 8.38) and thrombin-activatable fibrinolysis inhibitor (TAFI), also contribute to the regulation of fibrinolysis.

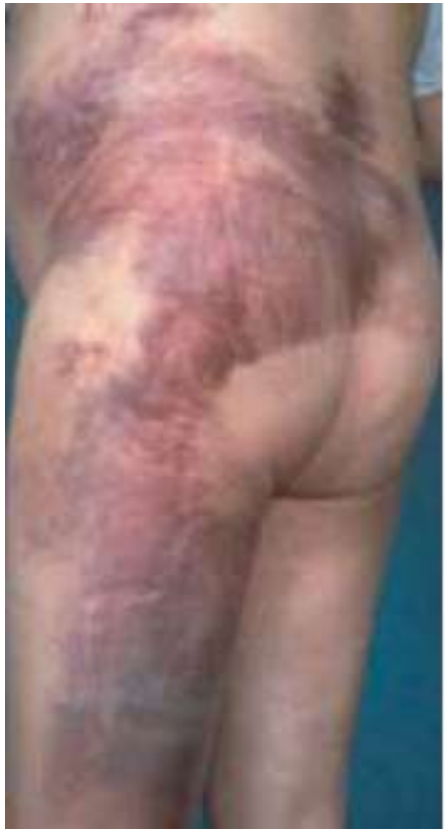
Figure 8.38 Fibrinolysis. (a) The conversion of plasminogen to plasmin by plasminogen activator (t-PA) occurs most efficiently on the surface of fibrin, which has binding sites for both plasminogen and t-PA.
(b) Free plasmin in the blood is rapidly inactivated by α_2-antiplasmin. Plasmin generated on the fibrin surface is partially protected from inactivation. The lysine-binding sites on plasminogen are necessary for the interaction between plasmin(ogen) and fibrin and between plasmin and α_2-antiplasmin.

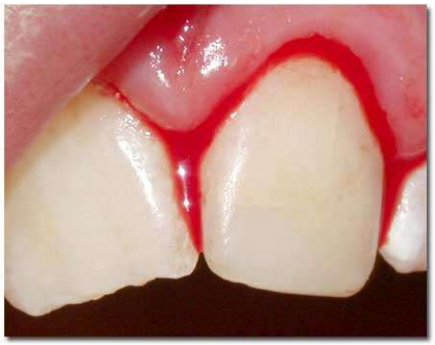
Bleeding disorders

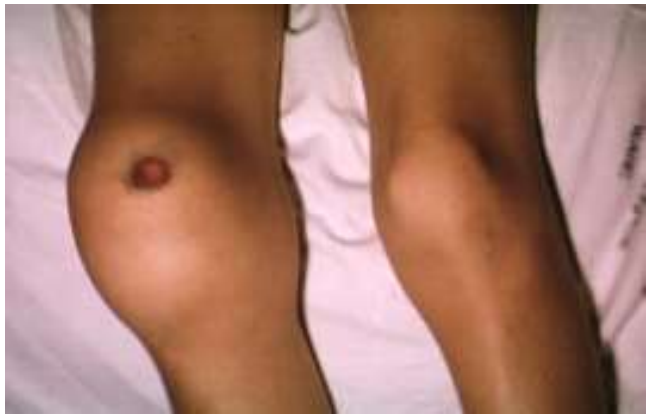
After injury, 3 processes halt bleeding: vasoconstriction, gap-plugging by platelets, and the coagulation cascade (fig 1). Disorders of haemostasis fall into these 3 groups. The pattern of bleeding is important—vascular and platelet disorders lead to prolonged bleeding from cuts, bleeding into the skin (eg easy bruising and purpura), and bleeding from mucous membranes (eg epistaxis, bleeding from gums, menorrhagia). Coagulation disorders cause delayed bleeding into joints and muscle.











Clinical manifestations of bleeding disorders

Bleeding symptoms	Bleeding disorder	
	Platelet defects (qualitative or quantitative)	**Clotting factor deficiencies (eg, factor VIII or factor IX deficiencies)**
Overview of bleeding events	**Mucocutaneous bleeding (oral cavity, nasal, gastrointestinal, and genitourinary sites)**	**Deep tissue bleeding (including joints and muscles)**
Excessive bleeding after minor cuts	Yes	Not usually
Petechiae	Common	Uncommon
Ecchymoses	Generally small and superficial; may be significant, depending upon the defect or degree of thrombocytopenia	May develop large subcutaneous and soft tissue hematomas
Hemarthroses, muscle hematomas	Uncommon	Common in severe deficiency states or in association with injury in those with mild to moderate deficiency states
Bleeding with invasive procedures, including surgery	Often immediate, with degree of bleeding dependent upon the severity of the defect, ranging from none (eg, mild degrees of thrombocytopenia or mild platelet function defect) to mild to severe (eg, Glanzmann thrombasthenia)	May be associated either with procedural bleeding or delayed bleeding, depending upon the type and severity of the defect

Expected results of tests for hemostatic function in representative bleeding disorders

Disorder	Platelet count	PT	aPTT	TT	Fibrinogen
Vasculopathies, connective tissue diseases, or collagen disorders affecting skin	Normal	Normal	Normal	Normal	Normal or increased*
Thrombocytopenia	Low	Normal	Normal	Normal	Normal
Qualitative platelet abnormalities	Normal or low¶	Normal	Normal	Normal	Normal
Hemophilia A (factor VIII deficiency)	Normal	Normal	Long	Normal	Normal
von Willebrand disease	NormalΔ	Normal	Normal or long◇	Normal	Normal
Disseminated intravascular coagulation	Low	Long	Long	Long	Low

Refer to UpToDate topics on the evaluation of unexplained bleeding or bruising for a discussion of these findings and our approach to the evaluation.

PT: prothrombin time; aPTT: activated partial thromboplastin time; TT: thrombin time.

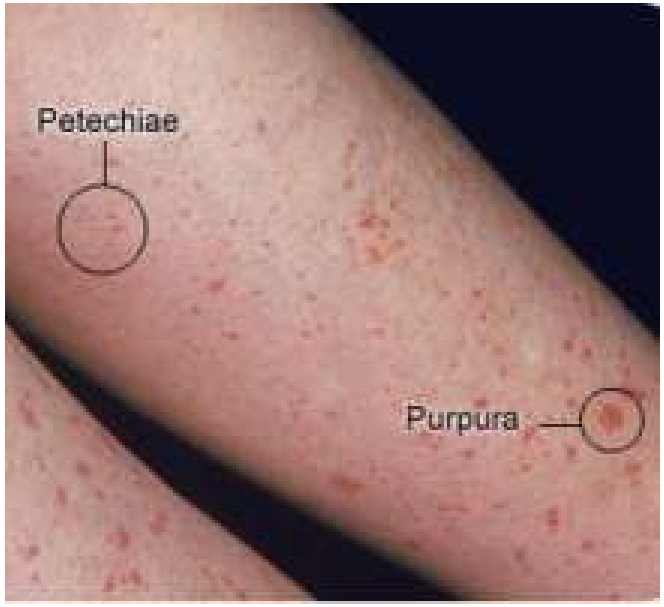
* Fibrinogen may be elevated as an acute phase reactant in disorders of inflammation.

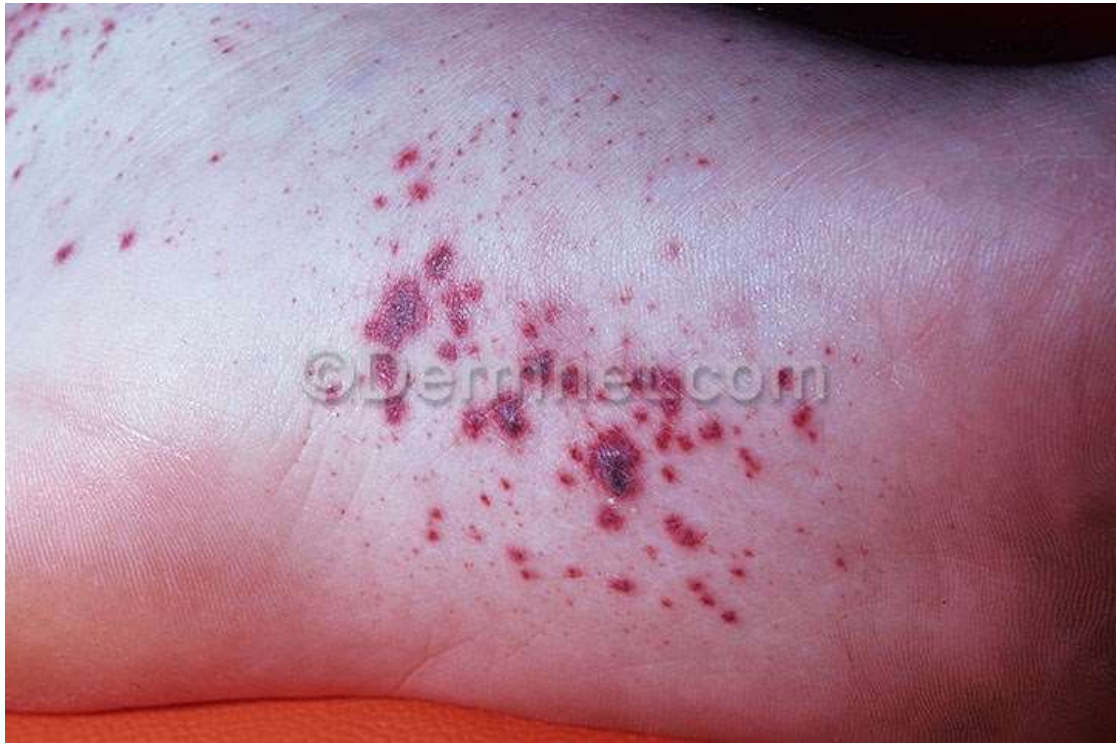
¶ The platelet count in myeloproliferative disorders is usually high (eg, essential thrombocythemia) and platelets may also be qualitatively abnormal, predisposing to hemorrhagic and thrombotic diatheses.

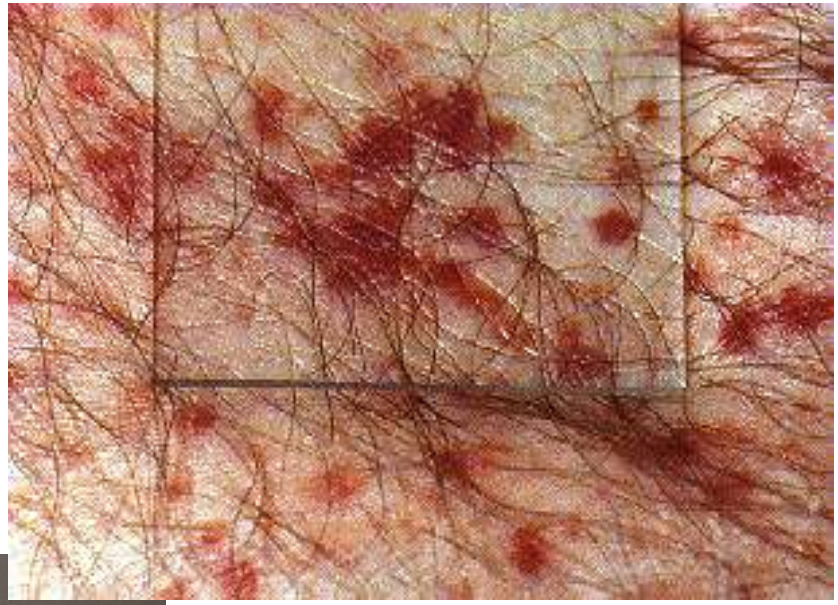
Δ The platelet count may be low in some patients with type 2B von Willebrand disease.

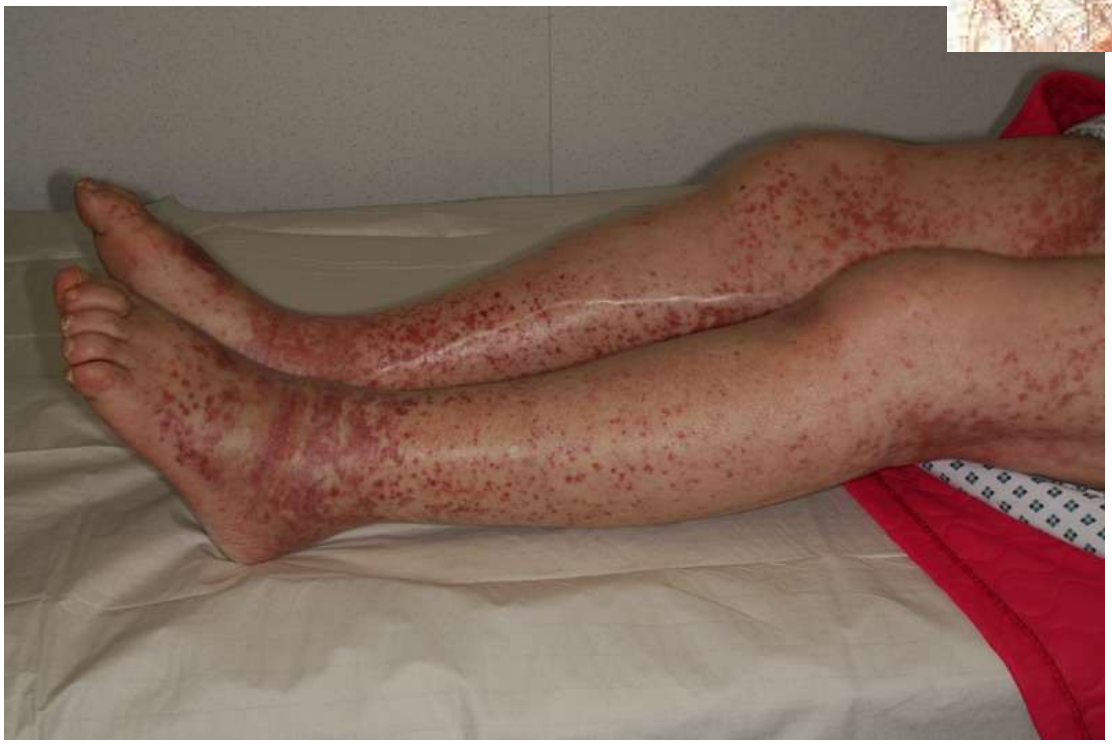
◇ The aPTT may be normal in those with Factor VIII activity >40 percent.

(Table 53-16) *Purpura* are seen when there is an extravasation of red blood cells into the dermis and, as a result, the lesions do not blanch with pressure. This is in contrast to those erythematous or violet-colored lesions that are due to localized vasodilatation—they do blanch with pressure. Purpura (≥3 mm) and petechiae (≤2 mm) are divided into two major groups: palpable and nonpalpable.









Causes of Purpura

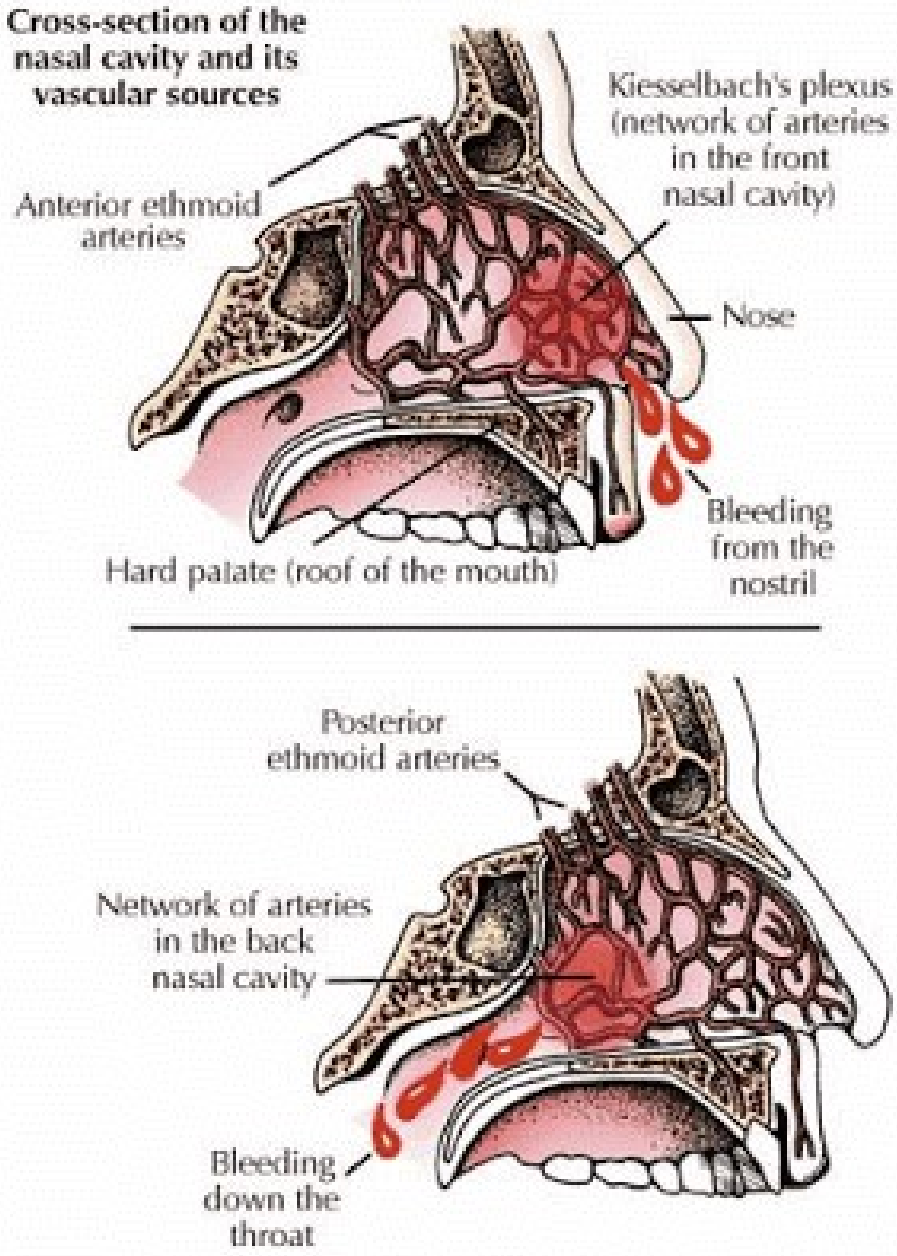
I. Primary cutaneous disorders
- A. Nonpalpable
  1. Trauma
  2. Solar (actinic, senile) purpura
  3. Steroid purpura
  4. Capillaritis
  5. Livedoid vasculopathy in the setting of venous hypertension[a]

II. Systemic diseases
- A. Nonpalpable
  1. Clotting disturbances
     a. Thrombocytopenia (including ITP)
     b. Abnormal platelet function
     c. Clotting factor defects
  2. Vascular fragility
     a. Amyloidosis
     b. Ehlers-Danlos syndrome
     c. Scurvy
  3. Thrombi
     a. Disseminated intravascular coagulation
     b. Monoclonal cryoglobulinemia
     c. Heparin-induced thrombocytopenia and thrombosis
     d. Thrombocytosis
     e. Thrombotic thrombocytopenic purpura
     f. Antiphospholipid antibody syndrome
     g. Warfarin reaction
     h. Homozygous protein C or protein S deficiency
  4. Emboli
     a. Cholesterol
     b. Fat
  5. Possible immune complex
     a. Gardner-Diamond syndrome (autoerythrocyte sensitivity)
     b. Waldenström's hypergammaglobulinemic purpura
- B. Palpable
  1. Vasculitis
     a. Cutaneous small-vessel vasculitis
     b. Polyarteritis nodosa
  2. Septic emboli
     a. Acute meningococcemia
     b. Disseminated gonococcal infection
     c. Rocky Mountain spotted fever
     d. Ecthyma gangrenosum

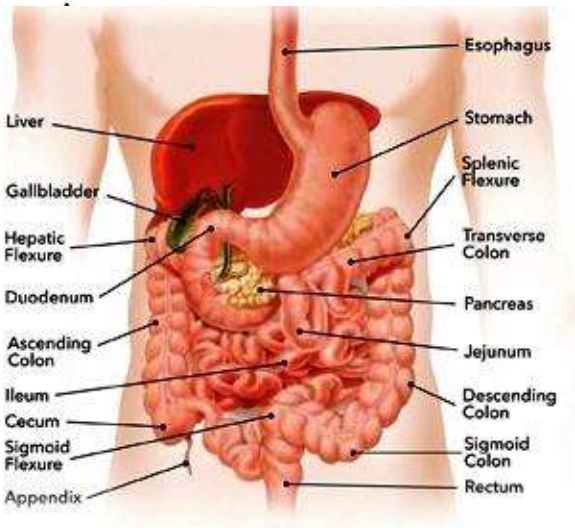
[a]Also associated with underlying disorders that lead to hypercoagulability, e.g. factor V Leiden, protein C dysfunction/deficiency.

[b]Bacterial, fungal, or parasitic.

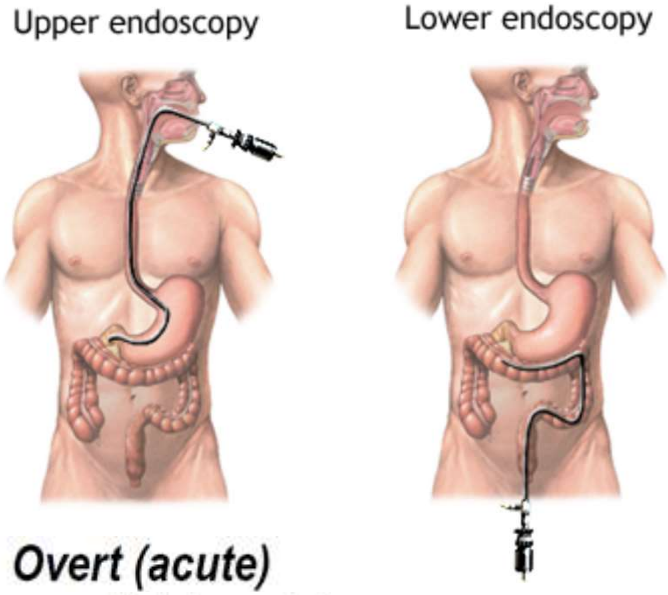
Abbreviation: ITP, idiopathic thrombocytopenic purpura.


Cross-section of the nasal cavity and its vascular sources
Kiesselbach's plexus (network of arteries in the front nasal cavity)
Anterior ethmoid arteries
Nose
Bleeding from the nostril
Hard palate (roof of the mouth)
Posterior ethmoid arteries
Network of arteries in the back nasal cavity
Bleeding down the throat

Depending on the rate of blood loss, GI bleeding can manifest in several forms and can be classified as overt, occult or obscure. Overt GI bleeding, otherwise known as acute GI bleeding, is visible and can present in the form of hematemesis, "coffee-ground" emesis, melena, or hematochezia. Occult or chronic GI bleeding as a result of microscopic hemorrhage can present as Hemoccult-positive stools with or without iron deficiency anemia[9,10]. The American Gastroenterological Association defines occult GI bleeding as the initial presentation of a positive fecal occult blood test (FOBT) result and/or iron-deficiency anemia when there is no evidence of visible blood loss to the patient or clinician[11]. Obscure GI bleeding refers to recurrent bleeding in which a source is not identified after upper endoscopy and colonoscopy. Obscure bleeding may be either overt or occult[10-12].



gastrointestinal bleeding



Overt (acute)
occult (chronic)
obscure

Upper vs lower

Upper GI bleeding includes hemorrhage originating from the esophagus to the ligament of Treitz, at the duodenojejunal flexure[13]. Lower GI bleeding is defined as bleeding that originates from a site distal to the ligament of Treitz[14]. In recent years upper GI bleeding has been redefined as bleeding above the ampulla of Vater within reach of an upper endoscopy; lower GI bleeding has been further subdivided into mid GI bleeding coming from the small bowel between the ampulla of Vater to the terminal ileum, and lower GI bleeding coming from the colon[11].

Upper gastrointestinal bleeding

Common causes

- Peptic ulcers
- Mallory-Weiss tear
- Oesophageal varices
- Gastritis/gastric erosions
- Drugs (NSAIDs, aspirin, steroids, thrombolytics, anticoagulants)
- Oesophagitis
- Duodenitis
- Malignancy
- No obvious cause

Rare causes

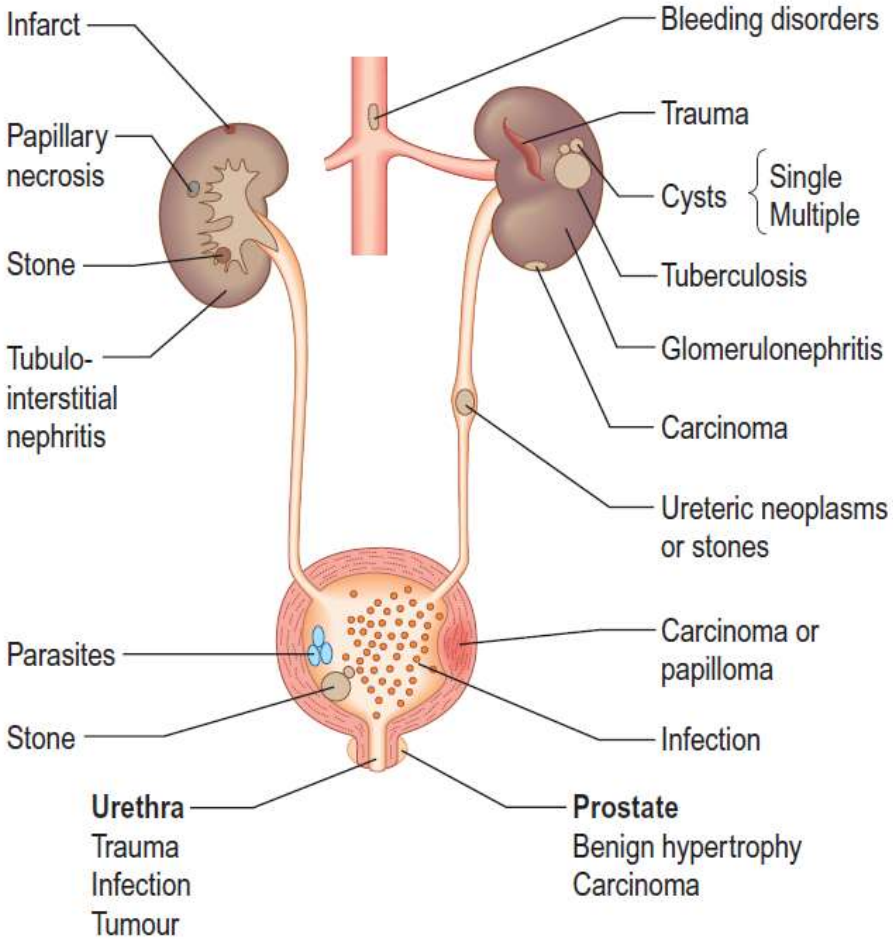
- Bleeding disorders
- Portal hypertensive gastropathy
- Aorto-enteric fistula[2]
- Angiodysplasia
- Haemobilia
- Dieulafoy lesion[3]
- Meckel's diverticulum
- Peutz-Jeghers' syndrome
- Osler-Weber-Rendu synd.

Rectal bleeding

Typical causes

- Diverticulitis, p630
- Colorectal cancer, p618
- Haemorrhoids, p634
- Crohn's, UC, p272-275
- Perianal disease, p632
- Angiodysplasia, p630
- Rarities—trauma, also:
  - ischaemic colitis, p622
  - radiation proctitis
  - aorto-enteric fistula

Sites and causes of bleeding from the urinary tract



Haematuria

- **Visible (macroscopic) VH**
- **Non-visible (microscopy) NVH**
  - **Symptomatic (LUTS—dysuria, hesitancy, urgency) sNVH**
  - **Asymptomatic aNVH**

Intrarenal hematuria

- Kidney trauma
- Renal stones and crystals
- Glomerulonephritis
- Infection (pyelonephritis)
- Neoplasia (renal cell carcinoma)
- Vascular injury (vasculitis, renal thrombosis)

Extrarenal hematuria

- Trauma (eg, Foley placement)
- Infections (urethritis, prostatitis, cystitis)
- Nephrolithiasis (ureteral stones)
- Neoplasia (prostate, bladder)

- Exclude transient causes: (UTI, vigorous exercise, menstruation).
- Check creatinine/eGFR, proteinuria (spot Albumin.Creatinine ratio) and BP.
- Painless VH usually means bladder cancer; refer urgently.
- In aNVH or if systemic symptoms, consider FBC, ESR, CRP, blood film, clotting (do not simply attribute haematuria to anticoagulants/antiplatelet agents).
- Urine MC&S to look for infection, malignant/inflammatory cells, casts, crystals.
- USS and rapid referral to nephrology if rapid decline in GFR or haematuria with proteinuria, casts or dysmorphic cells. Red cell casts ≈ glomerular bleeding.
- Refer to urology: VH, sNVH, persistent aNVH >40yrs

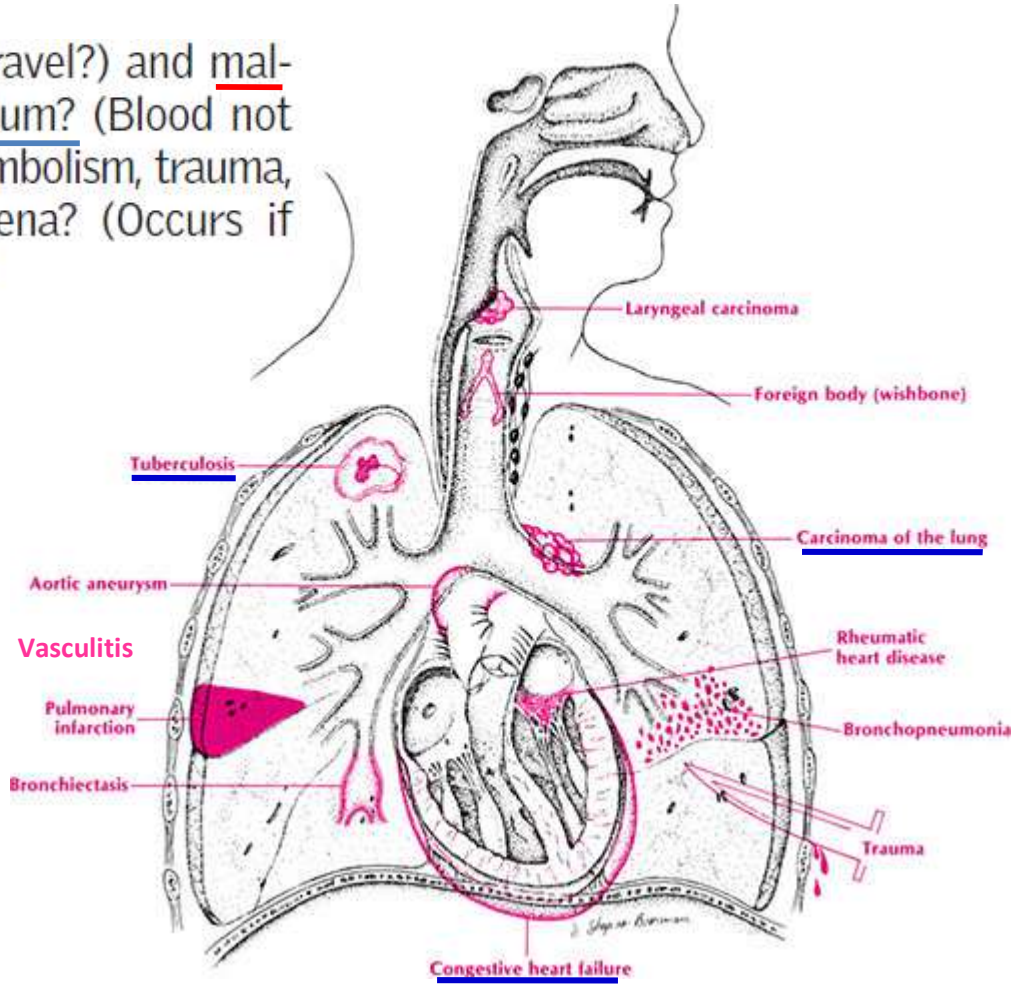
Terms Used to Describe Abnormal Uterine Bleeding

Pattern	Interval	Duration	Amount
Menorrhagia	Regular	Prolonged	Excessive
Metrorrhagia	Irregular	+/- Prolonged	Normal
Menometrorrhagia	Irregular	Prolonged	Excessive
Hypermenorrhea	Regular	Normal	Excessive
Hypomenorrhea	Regular	Normal or less	Less
Oligomenorrhea	Infrequent	Variable	Scanty
Polymenorrhea	Frequent (irregular)	Normal	Normal

Hemoptysis

Blood is *coughed* up, eg frothy, *alkaline*, and bright red, often in a context of known chest disease (*vomited* blood is acidic and dark).

Always think about TB (recent foreign travel?) and malignancy (weight loss?). Mixed with sputum? (Blood not mixed with sputum suggests pulmonary embolism, trauma, or bleeding into a lung cavity.[28]) Melaena? (Occurs if enough coughed-up blood is swallowed.)



MECHANISMS

- **Neoplasms: Invasion of superficial mucosa and erosion of blood vessels; High vascular tumor with fragile walls**
- **Pulmonary venous hypertension: High pressure damage venous walls**
- **Infection: Inflammation and repeated cough disrupts pulmonary vasculature**
- **Vascular damage by vasculitis or pulmunary infarction**

Bleeding disorders

1 Vascular defects *Congenital:* Osler-Weber-Rendu syndrome (p722), connective tissue disease (eg Ehlers-Danlos syndrome, *OHCS* p642, pseudoxanthoma elasticum). *Acquired:* Senile purpura, infection (eg meningococcal, measles, dengue fever), steroids, scurvy (perifollicular haemorrhages), Henoch-Schönlein purpura (p716), painful bruising syndrome—women who develop tingling under the skin followed by bruising over limbs/trunk, resolving without treatment.

2 Platelet disorders *Decreased marrow production:* Aplastic anaemia (p358), megaloblastic anaemia, marrow infiltration (eg leukaemia, myeloma), marrow suppression (cytotoxic drugs, radiotherapy). *Excess destruction: Immune:* Immune thrombocytopenic purpura (ITP, below), other autoimmune causes, eg SLE, CLL, drugs, eg heparin, viruses; *Non-immune:* DIC (p346), thrombotic thrombocytopenic purpura (TTP) or HUS (p308), sequestration (in hypersplenism).

Hemolytic-uremic syndrome (HUS)

Poorly functioning platelets: Seen in myeloproliferative disease, NSAIDs, and ureat.

Glanzmann thrombasthenia

3 Coagulation disorders *Congenital:* Haemophilia, von Willebrand's disease (p726). *Acquired:* Anticoagulants, liver disease, DIC (p346), vitamin K deficiency.

Palpable purpura, abdominal pain and arthritis in a young male with normal thrombocyte count

Kenneth, a **26-year-old male**, presents to the ED with a **one-week history of a rash that has spread from his torso to his upper and lower limbs**. He also complains of **mild but diffuse abdominal pain** and **pain in both knees**. He has been feeling nauseous but has not vomited. Kenneth is otherwise in good health. He reports **a mild respiratory infection that resolved a week ago**.

Kenneth's vitals signs are as follows: Temperature: 36.3°C; Heart rate: 92 beats per minute; Respiratory rate: 12 breaths per minute; Blood pressure: 138/96 mmHg; Oxygen saturation: 98% on room air.

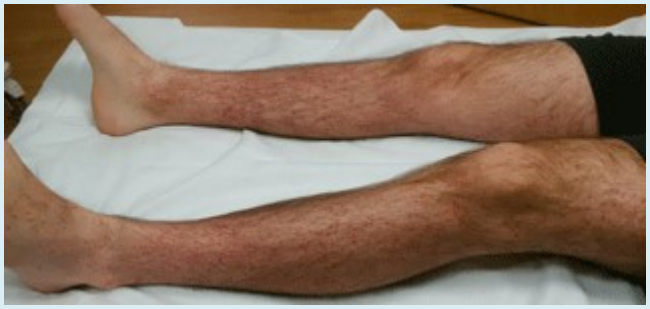
On examination, Kenneth has **red palpable purpura** in crops on his torso and symmetrically distributed on his arms and legs. His **knees and ankles are swollen and warm** to the touch. The rest of his examination is normal. His CBC and renal function tests are all normal; specifically, his **platelets are 340 x 10^9/L**. There is no hematuria.

His urinalysis showed no signs of renal involvement. Kenneth was discharged from the ED and told to treat his joint and abdominal pain with ibuprofen. He was told to follow up with his family doctor in two weeks where monitoring of renal involvement would be continued for six months.

What is the most likely diagnosis? Although there are a number of other diagnoses in the differential (see Table), after consideration of his clinical symptoms Kenneth is most likely suffering from **Henoch-Schönlein purpura (HSP)**, or immunoglobulin A (IgA)–associated vasculitis

Differential Diagnosis for HSP

Differential Diagnosis	Diagnostic Indicator
Idiopathic thrombocytopenic purpura	• CBC would show a low platelet count
Hypersensitivity vasculitis	• Skin biopsy would show no IgA deposition
Systemic lupus erythematosus	• Abnormal results for serum complement or antinuclear and anti-dsDNA antibodies[2]
Rheumatoid arthritis	• Positive rheumatoid factor and/or C-reactive protein[2] • Rash is usually not palpable purpura
Acute abdomen	• Appropriate investigations should be done if a diagnosis of HSP is uncertain

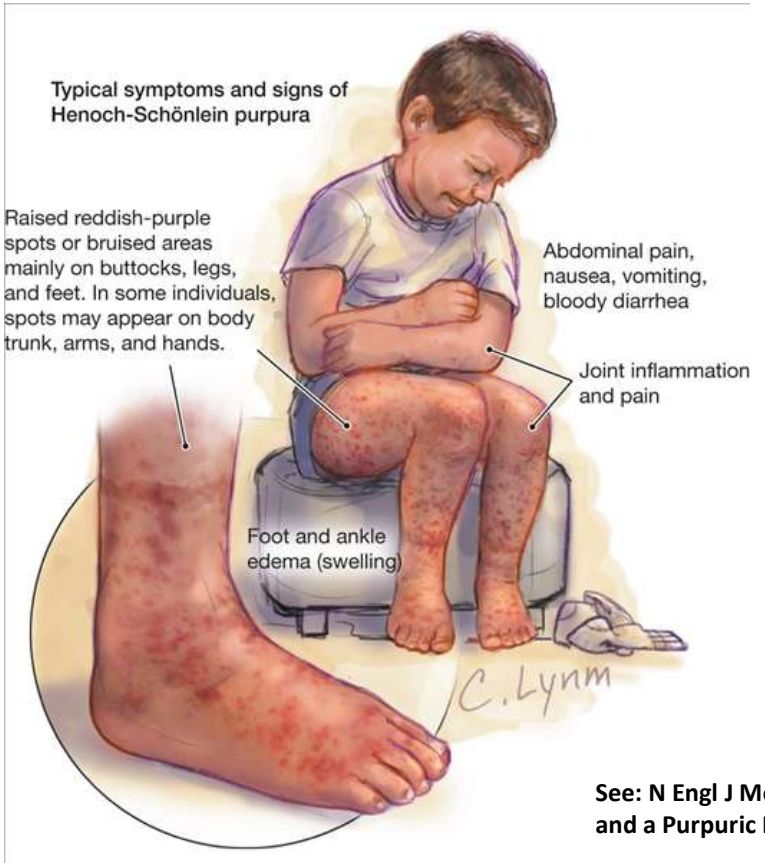


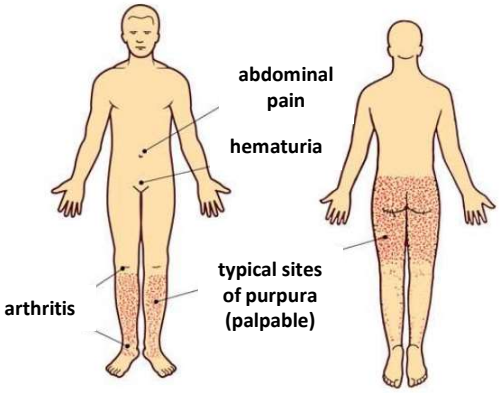
The Canadian J of Diagnosis April 2016

Henoch-Schönlein purpura (HSP) (fig 2) A small vessel vasculitis, presenting with purpura (non-blanching purple papules due to intradermal bleeding), often over buttocks and extensor surfaces, typically affecting young ♂. There may be glomerulonephritis (p300), arthritis, and abdominal pain (±intussusception), which may mimic an 'acute abdomen'. ℞: Mostly supportive.

Eduard H Henoch, 1820–1910 (German paediatrician); Johann L Schönlein, 1793–1864 (German physician)

HSP, it is generally a benign disease with spontaneous resolution in 94% of children and 89% of adults. Renal involvement and progression to kidney failure is seen more commonly in adults than in children. A renal biopsy would demonstrate membranoproliferative glomerulonephritis similar to IgA nephropathy.





HSP is a vasculitis in which IgA-containing immune complexes are deposited in small blood vessels. It can affect blood vessels in the skin, kidneys, intestines, and joints. Patients generally present with the condition in fall, winter, and spring.

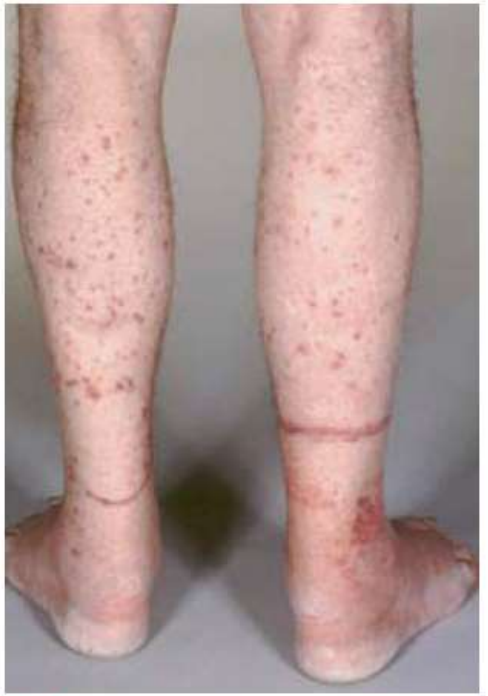
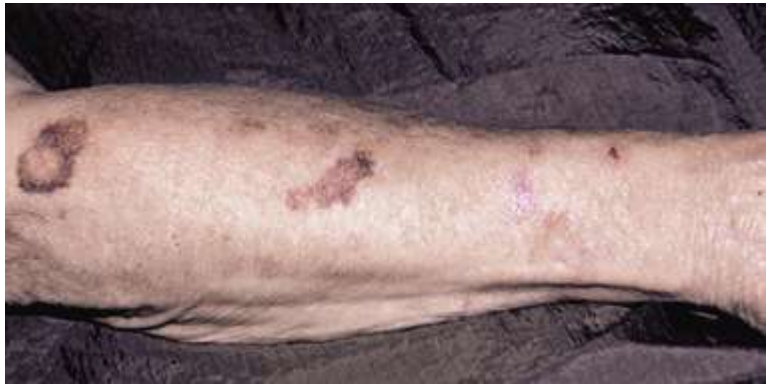


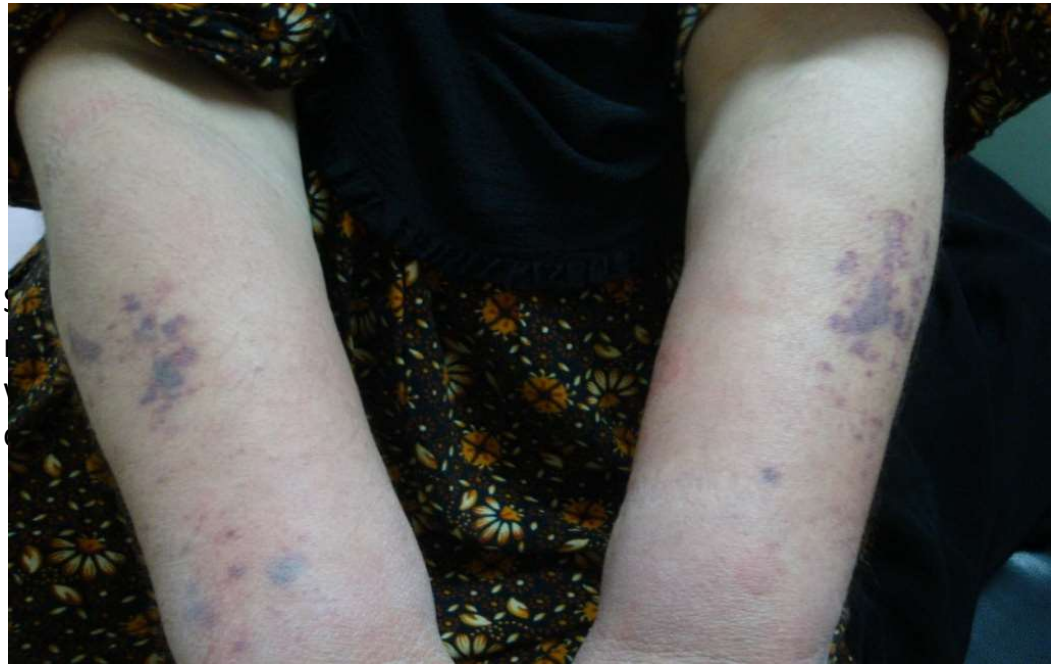
Fig 2. Henoch-Schönlein vasculitis.

The etiology is unknown, but most patients have a recent history of an upper respiratory infection. HSP is especially associated with infections caused by *Streptococcus* species. HSP is the most common systemic vasculitis in children (90% of cases occur in children younger than 10 years), but it affects adults as well.

See: N Engl J Med 2017;376:1868-77. Case 14-2017: A 20-Year-Old Man with Pain and Swelling of the Left Calf and a Purpuric Rash. IgA vasculitis and Crohn's disease with erythema nodosum.

Actinic or senile purpura is a benign clinical entity resulting from sun-induced damage to the connective tissue of the dermis. Actinic purpura is characterized by ecchymoses on the extensor surfaces of the forearms and the dorsa of the hands that usually last 1-3 weeks. See the image below. Bateman first described the condition in 1818 when he noted dark purple blotches and determined that they were due to the extravasation of blood into the dermal tissue. Hence, it is sometimes called Bateman purpura. It is common in elderly individuals and usually occurs after unrecognized minor trauma to the respective areas.

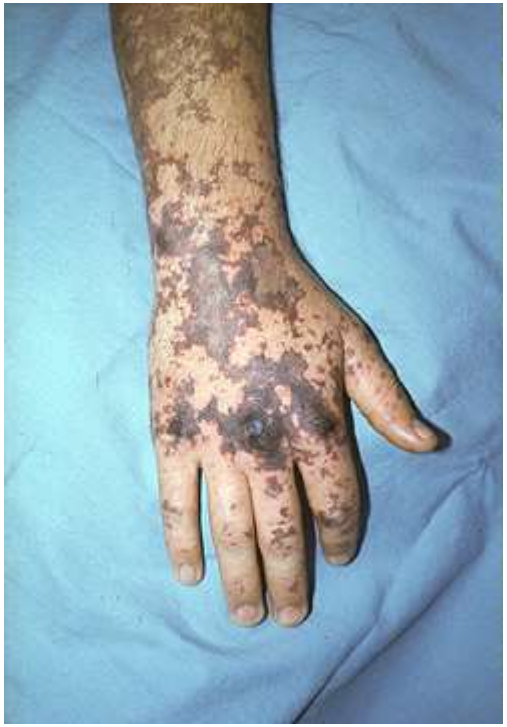




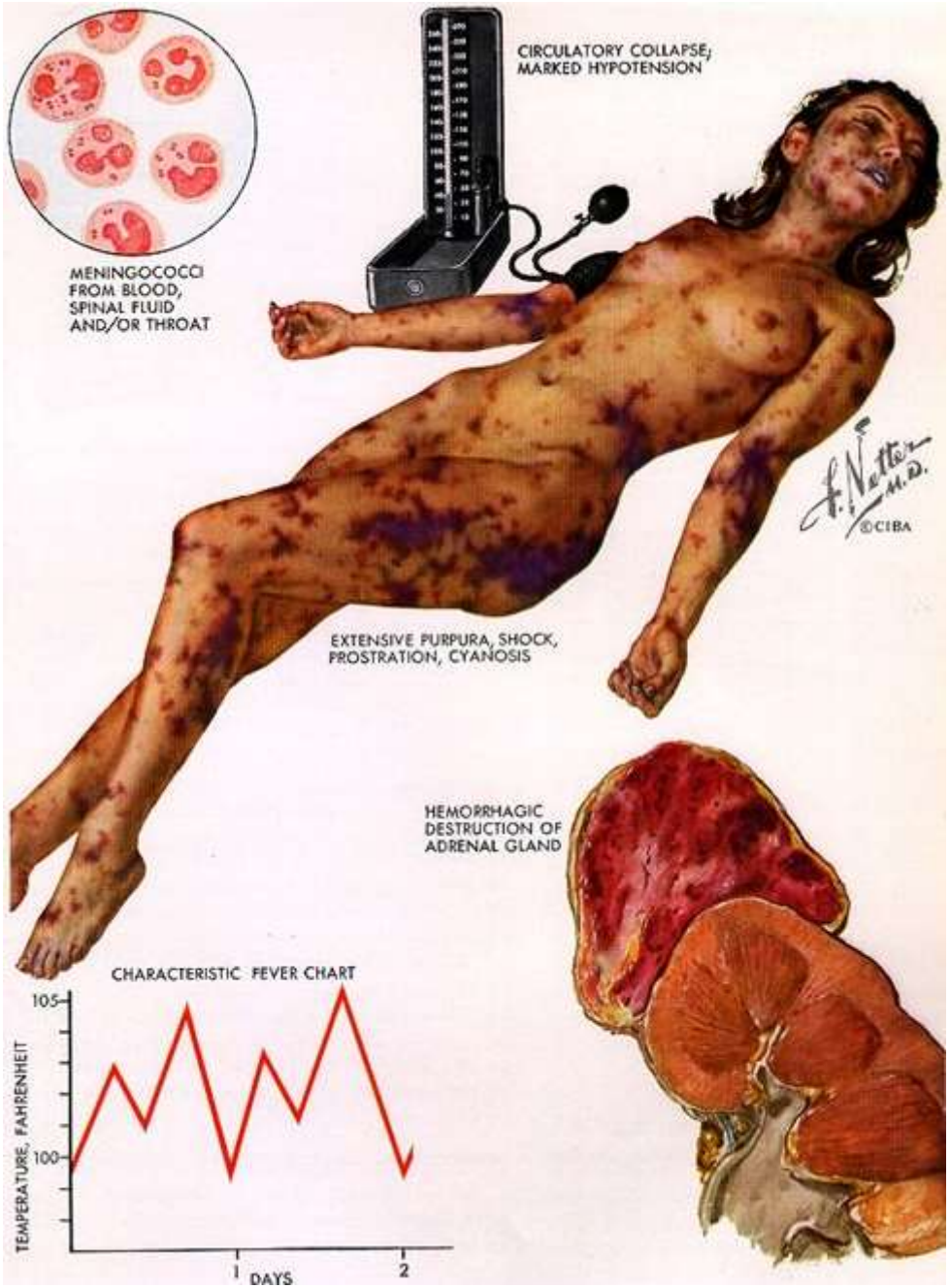
Steroid purpura. A 60-year-old woman suffering a long history of asthma has used to take systemic corticosteroids to control her attacks of shortness of breath. She presented with multiple purpuric lesions with skin atrophy of the dorsal surface of the forearms

Waterhouse-Friderichsen syndrome - Acute adrenal insufficiency may occur as a result of bilateral adrenal infarction caused by hemorrhage or adrenal vein thrombosis associated with meningococcemia. Waterhouse-Friderichsen syndrome has also been reported with sepsis from Pseudomonas aeruginosa and Streptococcus pneumoniae, Neisseria gonorrhoeae, Escherichia coli, Haemophilus influenzae, and Staphylococcus aureus.

Purpura fulminans — Purpura fulminans is a severe complication of meningococcal disease. It is characterized by the acute onset of **cutaneous hemorrhage and necrosis** due to **vascular thrombosis** and **disseminated intravascular coagulopathy**.



Skin lesions in acute meningococcemia can begin as papules but quickly progress to petechiae and purpura. As seen here, the purpuric lesions can coalesce



Airborne (Dengue)

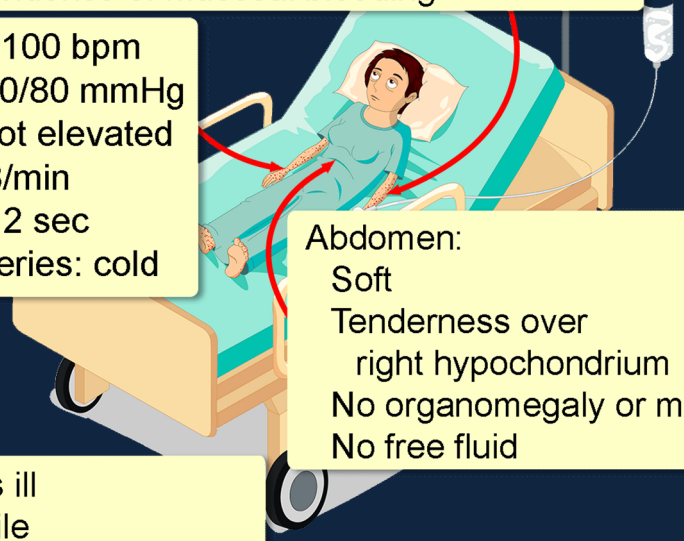
A 49 year old woman developed a **high fever** 5 days ago, in association with a **retro-orbital headache, body aches, anorexia, and intermittent nausea and vomiting**. The fever subsided last night, but the other symptoms still persist. She had returned home just 1 week ago, following a 3 week **trip to Sri Lanka.** Her medical and surgical histories are unremarkable, she does not smoke, and only drinks socially. There is no history of recreational drug abuse or unsafe sex.

Select Relevant Investigations

- **Full Blood Count** WBC: 4,000/mm3 (4,000 - 11,000) Hb: 11 g/dL (11 - 18) Hematocrit: 41% (36.1 - 44.3) **Platelets: 18,000/mm3** (150,000 - 400,000)
- **Dengue IgM ELISA** The report will be available tomorrow.
- **ECG + Portable Echocardiogram** The ECG is significant for a rate of 100 bpm, with a sinus rhythm. No other abnormalities are noted. The echocardiogram shows normal myocardial contractility, and a left ventricular ejection fraction of 68%
- **Liver Function Tests** AST: 82 IU/L (10 - 34) ALT: 70 IU/L (10 - 40) ALP: 72 IU/L (44 - 147) Albumin: 4.0 g/dL (3.4 - 5.4)

Diffuse blanching erythema over all four limbs
No petechiae or ecchymoses
No evidence of mucosal bleeding

Pulse: 100 bpm
BP: 100/80 mmHg
JVP: not elevated
RR: 28/min
CRFT: 2 sec
Peripheries: cold



Abdomen:
Soft
Tenderness over right hypochondrium
No organomegaly or masses
No free fluid

Looks ill
Afebrile
Conscious and alert, but restless
Not pale or icteric

Lungs: Clear
Heart, CNS: No abnormalities

(+) IV Crystalloids

Cardiac Inotropes

Platelet Transfusion

(+) Disease Notification

Diagnosis and reasoning

This middle aged lady has presented in the **early stages of shock**, as manifested by tachycardia, a narrow pulse pressure, prolonged capillary refill time (CRT), and altered mentation (i.e. agitation). Given the history suggestive of recent infection, **distributive shock** is an important possibility; **cardiogenic shock (in the eventuality of myocarditis)** should also be kept in mind. **Hypovolemic shock** is another consideration, considering the presence of vomiting. However, her peripheries are cold, with a prolonged CRT, making distributive shock unlikely; furthermore, her jugular venous pressure (JVP) is not elevated, while there are no clinical findings suggestive of heart failure, ruling out cardiogenic shock. Thus, this appears to be hypovolemic shock; resuscitation with intravenous (IV) crystalloids should commence immediately. In parallel with her acute management, a search for the underlying etiology should be conducted; in this respect, the history of fever soon after foreign travel provides a critical clue. The Centers for Disease Control and Prevention (CDC) Travel Health website provides a listing of the common infectious diseases encountered in each country. A review of the entry on Sri Lanka lists out a wide spectrum of infectious diseases; however, of these, only Dengue is likely to give rise to **diffuse blanching erythema** in conjunction with shock. Note also that **Dengue Shock Syndrome** (DSS) is well known to occur in the critical phase of the disease (i.e. immediately following defervescence); this is secondary to extravasation of fluid into the third space. A full blood count and liver profile are good initial tests; the **marked thrombocytopenia** seen here is supportive of the clinical diagnosis, as is the mild elevation in liver enzymes (as hepatic involvement in dengue is common). A **dengue IgM antibody assay** should also be ordered, although results may take some time to arrive; note that her further management should NOT be postponed pending results. An **ECG and echocardiogram** to assess her cardiac status is also important, as subclinical myocarditis may occur in these patients. While she will most likely continue to require IV fluids for a period of time, fluid resuscitation should proceed cautiously, in accordance with the international guidelines issued by the world health organization (WHO). This is because the fluid extravasated into the third space shifts back into the intravascular compartment during the convalescent phase; in patients who have received indiscriminate fluid supplementation, this shift may give rise to fluid overload with subsequent life threatening pulmonary edema. Note also that **Dengue is a notifiable disease**; the relevant authorities should be informed upon clinical suspicion. Platelet transfusion is not indicated currently, given the absence of bleeding manifestations; cardiac inotropes are not required either, as there is no evidence of cardiac involvement.

Dengue fever (DF) and dengue haemorrhagic fever (DHF)

Incidence: 50–100×10^6/yr (DF); 250,000–500,000/yr get DHF. The global pandemic of this RNA flavivirus relates to poor vector control (eg of Asian tiger *Aedes* mosquitoes), urbanization,[2] poor waste disposal, and migrations bringing new strains (DEN-2) that get more virulent in those who have had mild dengue. Global warming is extending the range of DF (eg to southern USA). English winters are now warm enough to support transmission.[369]

Infants typically have a simple febrile illness with a rash. Older children/adults have flushes (face, neck, chest) ± centrifugal maculopapular rash from day 3, or late confluent petechiae with round pale areas of normal skin ± headache, arthralgia, jaundice, hepatosplenomegaly, anuria. *Haemorrhagic signs:* (Unlikely if AST normal)[370] Petechiae, GI, gum or nose bleeds, haematuria, menorrhagia.

Monitor: BP; urine flow; WCC↓; platelets↓; PCV; +ve tourniquet test (>20 petechiae/inch^2) + PCV↑ by 20% are telling signs (rapid endothelial plasma leak is the key pathophysiology of DHF). *ΔΔ:* Chikungunya,[3] measles, leptospirosis, typhoid, malaria. *Exclusion:* If symptoms start >2wks after leaving a dengue area, or if fever lasts >2wks, dengue is 'ruled out'. *℞:* Supportive. Prompt IV resuscitation, eg Ringer's lactate. ►►If shocked (mortality 40%) get help; it is traditional to try a bolus of 15mL/kg repeated every ½h until BP rises and urine flows at >30mL/h. Evidence is lacking.[371,372] *Mosquito control:* Problematic![4]

Osler-Weber-Rendu syndrome (hereditary telangiectasia) Autosomal dominant Telangiectasia on the skin and mucous membranes (causing epistaxis and GI bleeds), see fig 1. It is associated with pulmonary, hepatic and cerebral arteriovenous malformations.[100]

William Osler, 1849–1919 (Canadian); Frederick Weber, 1863–1962 (British); Henri Rendu, 1844–1902 (French)—all physicians

Fig 1. Telangiectasia in Osler-Weber-Rendu syndrome.

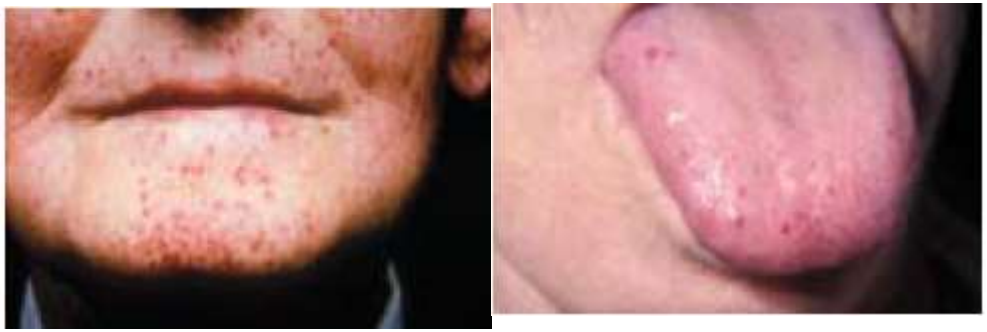
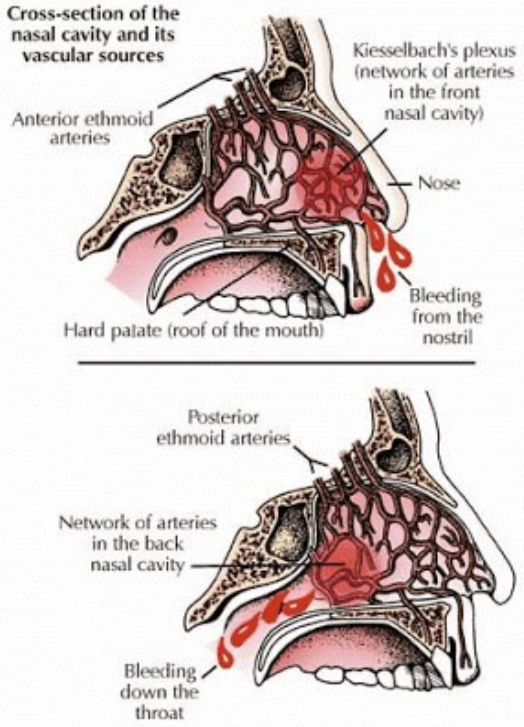


Table 1 The Curacao criteria for the diagnosis of hereditary hemorrhagic telangiectasia

Criteria	Description	Percent manifestation
1 Epistaxis	Spontaneous, recurrent	90
2 Telangiectases	Multiple, at characteristic sites:	80
	Lips	
	Oral cavity	
	Finger tips	
	Nose	
3 Visceral lesions	Gastrointestinal telangiectasia	15-30
	Pulmonary AVMs	50
	Hepatic AVMs	30-70
	Cerebral AVMs	10-20
	Spinal AVMs	< 1
4 Family history	Affected first degree relative	
Diagnosis of HHT:		
Definite: 3-4 criteria	Possible: 2 criteria	Unlikely: 0-1 criterion



Ehlers–Danlos syndrome

Prevalence: 1/10 000

Ehlers–Danlos syndrome (EDS) can be subdivided into at least 10 variants. They are all inherited disorders causing abnormalities in collagen of the skin, joints and blood vessels. Clinically this causes increased elasticity of the skin, hypermobile joints (6–9 on the Beighton scale; see Box 11.19) and fragile blood vessels causing easy bruising or in some cases internal haemorrhage. The skin is hyperextensible but recoils normally after stretching. It is easily injured and heals slowly with scarring like tissue paper. Pseudotumours may occur at the sites of scarring (such as elbows and knees) consisting mainly of fat, but calcification can occur.

Ten different types have been recognized with varying degrees of skin fragility, skin hyperextensibility and joint hypermobility.

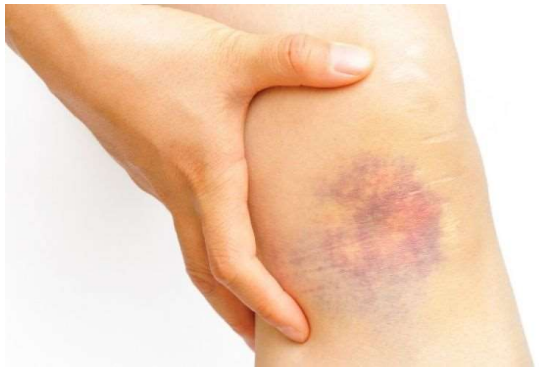
Types I, II and III are inherited in an autosomal dominant fashion; the biochemical basis is unknown. No abnormalities in *COL1A1, COL1A2* and *COL2A1* genes have been found.

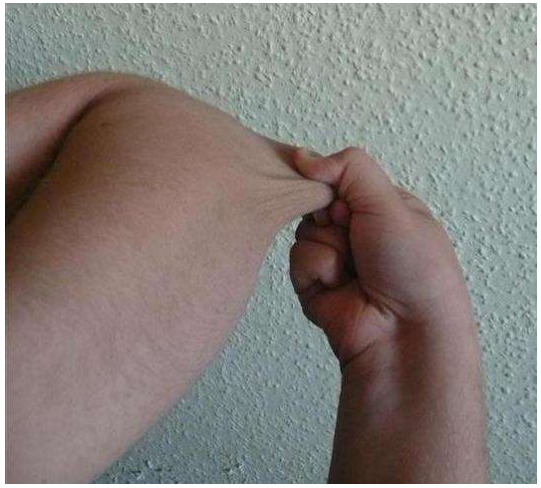
Type IV (vascular type) is also autosomal dominant and involves arteries, the bowel and uterus, as well as the skin. Mutations in *COL3A1* gene produce abnormalities in structure, synthesis or secretion of type III collagen.

Type VI is a recessively inherited disorder and results from a mutation in the gene that encodes lysyl hydroxylase.

Type VII is an autosomal dominant disorder in which there is a defect in the conversion of procollagen to collagen; *COL1A1* and *COL1A2* mutations delete the N-proteinase cleavage sites.

The other forms of Ehlers–Danlos are very rare





Epistaxis and Purpura

A 51 year old man presents with **epistaxis** and **spontaneous bleeding from his mouth** for 2 days, along with passage of **tarry black stools** for a week. There is no history of hemoptysis, hematemesis, hematuria, or recent infection. He denies experiencing joint pain or tenderness. His medical and surgical histories are unremarkable and he is not on any drugs currently. There is no history of transfusion of blood or blood products. Nor is there a family history of bleeding disorders. He does not smoke, and is a life-long teetotaler (astemio). The patient reports he had developed an **upper respiratory infection** 2 weeks prior to the emergency room visit, but the infection has now resolved

Select Relevant Investigations

♦ **FBC and Peripheral Smear**

RBC: 4.45x10^6/mm3 (4.32-5.72x10^6) Hb: 13.9 g/dL (13.5-16.5)
Hct: 42% (41.0-50.0) MCV: 94 f/L (80-100)
MCHC: 33% (31-37) WBC: 6,800/mm3 (5,000-10,500)

Plt: 18,000/mm3 *(150,000-400,000)*

The peripheral smear reveals normocytic normochromic red blood cells with normal white blood cells. There is an inadequate number of platelets. immature forms are present.

♦ **Clotting Profile**

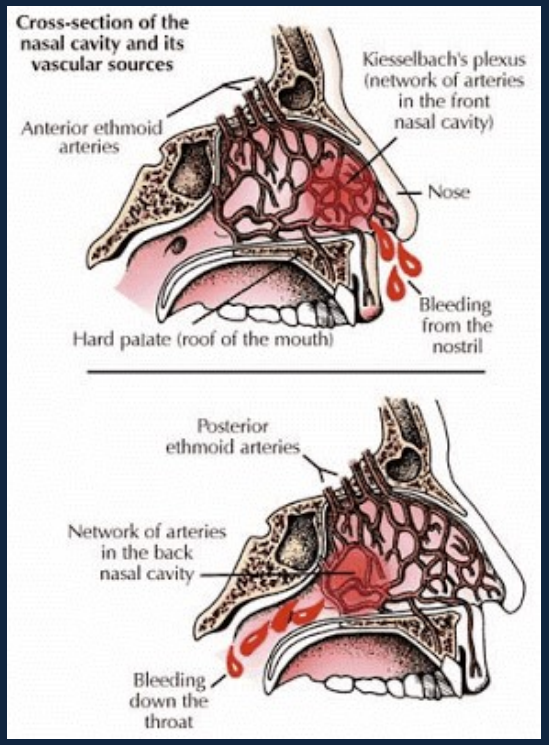
aPTT: 29s (control: 30s) PT: 16s (control: 17s)
Clotting time: 5 min (1-9)

♦ **Bone Marrow Biopsy**

The marrow is normocellular*, with an adequate number of megakaryocytes. There is normal myeloid and erythroid proliferation. No abnormal cells or significant dysplasia are seen. The myeloid:erythroid ratio is 6:1*

♦ **HIV Antibodies**

HIV Antibodies: negative



Average build
Afebrile
Not pale or icteric

Mouth: Erythematous gums
Petechiae and ecchymosis in lower labial mucosa and hard palate
Hematoma in dorsal surface of anterior ⅔ of tongue

Multiple purpuric spots in upper and lower limbs

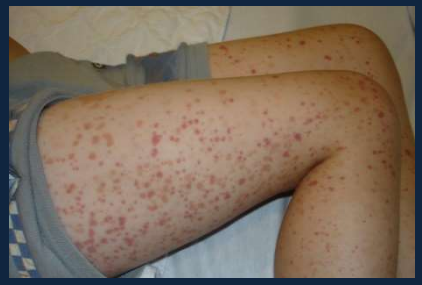
Heart, Lung, CNS: no abnormalities
Abdomen: not distended
No organomegaly
Funduscopy: normal

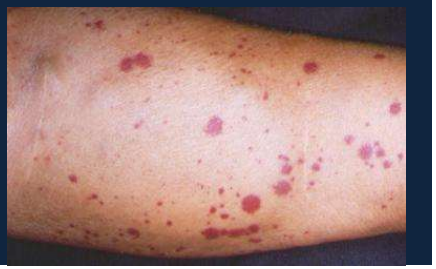
Pulse: 84 bpm, regular
BP: 100/70 mmHg
CRFT: < 2s
RR: 16 cycles per min

Hemodynamic stability

Select Relevant Management

- **Corticosteroids**
- Platelet Transfusion
- IV Immunoglobulin
- Splenectomy





Diagnosis and Reasoning

Bleeding is one of the more common presentations in clinical medicine - and in some ways, one of the most tricky, given the wide spectrum of presentations.

In certain cases, seemingly minor episodes are the first harbinger of severe disease; such patients may potentially progress into fatal bleeding within a matter of minutes to hours.

Consider this middle aged man. He has presented with spontaneous bleeding from his gums, with examination revealing a hematoma in the anterior tongue, and petechiae and ecchymosis in hard palate and lips.

Spontaneous bleeding from the mucosal surfaces of the mouth is in itself an alarming presentation; but note also the presence of multiple purpuric spots in upper and lower limbs; and the presence of malena, suggesting gastrointestinal bleeding.

Thus, this appears to be a coagulopathy; while bleeding from multiple mucosal surfaces is suspicious of a platelet related etiology, this might also be due to a reduction or absence of coagulation factors, or due to use of anticoagulants.

Note also that while on surface, the bleeding appears to be relatively mild, it is essential to assess his vital parameters and determine if he is hemodynamically stable. Fortunately, this seems to be the case.

His drug history is negative for anticoagulants and the absence of a family history argues against an inherited disorder.

Focused investigations should be the next step, starting with a full blood count (FBC), peripheral blood film, and a clotting profile.

The FBC reveals the presence of a marked reduction in platelet counts, with the other cell lines being within normal parameters; the blood film reveals reduced platelets, with no immature forms or giant platelets.

The coagulation profile reveals a normal Partial Thromboplastin Time (PTT) and Prothrombin Time (PT) excluding defects in the intrinsic, extrinsic and common pathways of the clotting cascade.

Thus this appears to be an isolated thrombocytopenia; this could be due to decreased production, increased destruction, medication induced thrombocytopenia, or toxins; note that the latter two are excluded by the history.

The bone marrow biopsy in this patient reveals a cellular marrow with adequate number of megakaryocytes, which excludes decreased platelet production.

While there are many conditions which can give rise to increased destruction of platelets (such as connective tissue diseases, certain viral infections, hypersplenism, etc), his age, gender, and clinical presentation excludes most of these.

The two key conditions which should be considered are HIV induced thrombocytopenia, and Immune Thrombocytopenia (ITP). However, the screening test for HIV is negative, clinching the diagnosis of ITP.

Corticosteroids are the first line management option for ITP. Splenectomy is indicated in patients who remain refractory, or show a poor response to first-line therapies, and is not required right now.

Intravenous (IV) Immunoglobulins are considered an option in patients with severe active bleeding, or who are in need of a rapid platelet rise.

Platelet transfusion is reserved for life-threatening conditions, and is not recommended for mild episodes of bleeding.

Immune thrombocytopenic purpura

ITP is caused by antiplatelet autoantibodies. It is acute (usually in children, 2wks after infection with sudden self-limiting purpura: *OHCS* p197) or chronic (seen mainly in women). Chronic ITP runs a fluctuating course of bleeding, purpura (esp. dependent pressure areas), epistaxis and menorrhagia. There is no splenomegaly. *Tests in ITP:* ↑megakaryocytes in marrow, antiplatelet autoantibodies often present. *Rx:* None if mild. If symptomatic or platelets $<20 \times 10^9$/L, prednisolone 1mg/kg/d, and reduce after remission; aim to keep platelets $>30 \times 10^9$/L—takes a few days to work. If relapse, splenectomy cures ≤80%. If this fails: immunosuppression, eg azathioprine or cyclophosphamide. Platelet transfusions are not used (except during splenectomy or life-threatening haemorrhage) as these are quickly destroyed by the autoantibodies. IV immunoglobulin may temporarily raise the platelet count, eg for surgery, pregnancy. Eltrombopag is a new oral thrombopoietin-receptor agonist that stimulates thrombopoiesis.

THROMBOPOIETIC GROWTH FACTORS

The use of hematopoietic growth factors has markedly changed the practice of medicine. **Erythroid growth factors** (eg, erythropoietin, darbepoetin) and **myeloid growth factors** (eg, granulocyte colony-stimulating factor, granulocyte-macrophage colony-stimulating factor) have allowed the specific stimulation of the production of erythrocytes and neutrophils, respectively. With the discovery of thrombopoietin (TPO) and the development of a variety of peptide and non-peptide TPO receptor agonists, clinically effective **thrombopoietic growth factors** have now entered the clinical armamentarium.

● A number of thrombopoietin (TPO) molecules have been developed; they define a new and growing family of molecules called the thrombopoietin (c-mpl ligand) family, based upon their common **ability to bind and activate the TPO receptor, c-mpl**

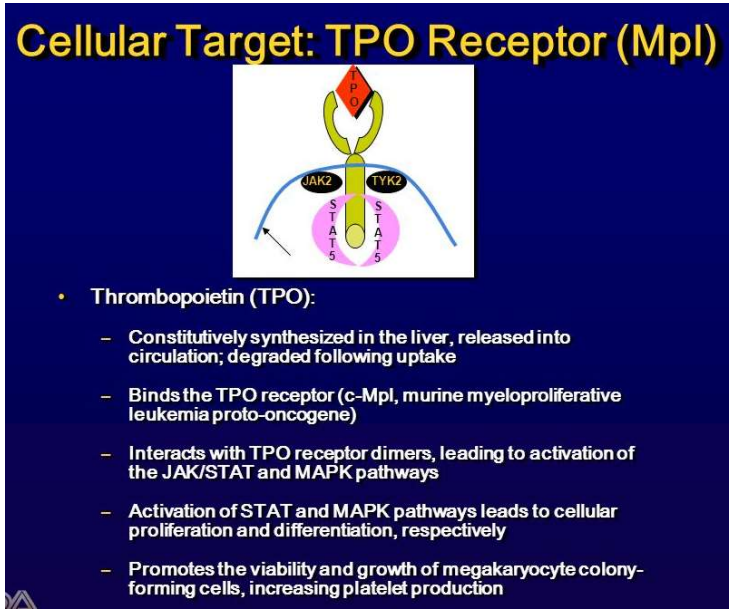
● The two TPO receptor agonists available for use in **immune thrombocytopenia** (ITP) are **romiplostim** (administered as a once-weekly subcutaneous injection) and **eltrombopag** (Revolade cp 25-50 mg, given as a once-daily pill).

● One TPO receptor agonist, eltrombopag, is approved for use in thrombocytopenic patients with **hepatitis C** who are receiving interferon and in patients with **aplastic anemia** for whom immunosuppressive therapy has failed.

● The TPO receptor agonists are currently under evaluation for a wide range of other thrombocytopenic disorders, including those associated with **chemotherapy** and **myelodysplastic syndromes**.

● Side effects of the TPO receptor agonists include **thrombocytosis**, possibly **thrombosis**, bone marrow reticulin fibrosis, and rebound thrombocytopenia. **Hepatotoxicity** has been reported with eltrombopag. Cost may also be an issue in some settings.

● Two non-peptide TPO receptor agonists (avatrombopag and lusutrombopag) are being developed to treat thrombocytopenia in presurgical patients



Even More Swelling

A 65 year old woman is admitted for **elective replacement of her left knee joint**. Her **preoperative** FBC is as follows: WBC 7,000/mm3, Hb 12 g/dL, **platelets 420,000/mm^3**. An ECG, CXR and fasting plasma glucose are normal. Her medical and surgical histories are unremarkable, and she is not on any drugs. Following an uncomplicated operation, she is started on **DVT prophylaxis with subcutaneous enoxaparin**. On the **5th postoperative day**, she complains of **pain and swelling of her left leg**.

Select Relevant Investigations

♦ **Full Blood Count**

WBC: 8,700/mm3 (4,600-11,000)

Hb: 11.9 g/dl (11.5-18)

Platelets: 152,000/mm^3 *(150,000-450,000)*

♦ **Compression USS L/LL**

There is acute thrombosis of the left popliteal vein, with absence of flow and compressibility.

♦ **D-Dimers**

D-Dimer levels are elevated.

♦ **PF4 antigen assay**

The platelet factor 4 antigen assay is positive.

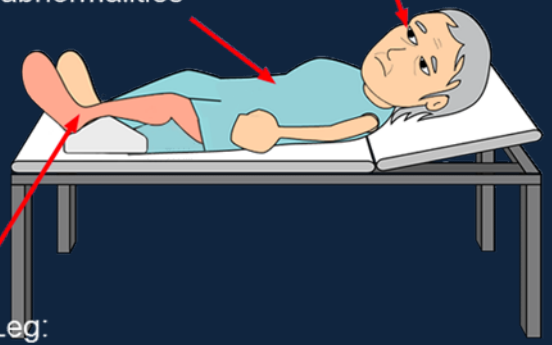
Heparin-induced Thrombocytopenia (HIT)

- Thrombocytopenia within 5–10 days of exposure to heparin.
- Decline in baseline platelet count of 50% or greater.
- Thrombosis occurs in 50% of cases; bleeding is uncommon.

BMI: 20.1
Vital Parameters: stable

Afebrile
Not pale or cyanosed

Heart, Lungs, Abdomen, CNS:
no abnormalities



Left Leg:
Marked erythema and swelling of leg
left calf circumference is 5 cm greater than right calf circumference
Exquisitely tender and warm to touch
Tibialis Posterior and Dorsalis Pedis pulses palpable
No inguinal lymphadenopathy

Select Relevant Management

- Continue Enoxaparin
- **Start Fondaparinux or Argatroban**

(direct thrombin inhibitor)

- Start Warfarin
- Place IVC Filter

Diagnosis and Reasoning

This elderly lady has developed acute lower limb swelling in the immediate postoperative period; examination reveals an erythematous, warm and tender left leg.

This presentation is strongly suspicious of a deep venous thrombosis (DVT); it is important to note that DVT prophylaxis does not necessarily preclude this possibility, as failures occur in up to 10% of such patients.

Cellulitis is the other key differential diagnosis here; however, note that total knee replacement is typically associated with incisional cellulitis (rather than cellulitis of the leg), while there are no further supportive findings such as fever, inguinal lymphadenopathy, a history of diabetes or immune compromise, or a neutrophil leukocytosis in the full blood count (FBC).

Unfortunately, no single clinical finding or complex of findings is diagnostic of DVT; however Well's score is a well validated rule which can be used to estimate the clinical probability.

The Well's score in this patient turns out to be 2 points (due to the presence of the following scoring features: recently bedridden for >3 days [+1 point], and calf swelling >3 cm as compared to asymptomatic leg [+1 point]).

This score falls into the 'intermediate' probability category (i.e. around 17% probability); the 2012 American College of Chest Physicians (ACCP) guidelines on the Diagnosis of DVT recommends that these patients be further evaluated with either a highly-sensitive D-dimer test or ultrasonography, based on the clinical context.

Note that post-surgical patients may have a positive D-dimer result even if DVT is absent; thus ultrasound is preferable here; this reveals the presence of acute thrombosis of the left popliteal vein.

Thus, the swelling is due to a DVT indeed; at this point, it is all too easy to assume that this is a postoperative complication, and immediately commence a DVT management protocol (which typically includes therapy with Warfarin).

However, note one subtle anomaly in the full blood count. This patient's postoperative platelet count was 420,000 mm/3; however, the most recent platelet count is only 152,000/mm3. While the absolute count is still within normal limits, a 63% drop has taken place.

A greater than 50% drop in platelet counts in a patient on therapy with heparin (unfractionated or low-molecular weight) is suspicious of heparin-induced thrombocytopenia (HIT); note also that HIT gives rise to paradoxical venous and arterial thrombosis - thus the presence of a DVT here is further supportive of this.

Unfortunately, no single finding or group of findings is diagnostic of HIT; however, a clinical scoring system has been devised to determine its probability, based on the characteristic features of the disease (these are known as the 4 Ts - Thrombocytopenia, Timing, Thrombosis, no oTher explanations).

This patient's score turns out to be 8 points, indicating a high probability of HIT (with the relevant scoring features being: >50% Platelet fall [+2 points], onset of sequelae of HIT within days 5 to 10 [+2 points]; presence of thrombosis or other sequelae [+2 points]; no other evident cause of platelet fall [+2 points]).

The next step in her evaluation should be diagnostic testing for HIT; a platelet factor 4 (PF4) antigen assay is a good choice in this regard, and turns out to be positive.

Note that a positive PF4 antigen assay alone is not diagnostic for HIT (as the specificity is only 80%); however a positive result combined with a high pretest probability (as in this patient) is considered to be diagnostic of the disease.

Thus, she should be taken off Enoxaparin immediately and started on a direct thrombin inhibitor (such as Fondaparinux or Argatroban).

Note that while PF4 antigen assays only take around 2 hours to perform, they may not be available in some hospitals; in such a scenario, the patient's treatment should not be delayed pending results; a strong clinicopathological suspicion of HIT is sufficient to commence therapy.

Patients with suspected (or diagnosed) HIT should NOT be started on Warfarin; this will reduce levels of the vitamin K-dependent anticoagulant Protein C, and worsen the existing prothrombotic state.

Warfarin therapy should only be commenced once platelet levels stabilize; Argatroban should be continued until the patient's INR reaches the therapeutic range.

The use of Inferior Vena Cava (IVC) filters in patients with HIT is a controversial topic; since this patient is being changed to an alternative anticoagulant, placement of an IVC filter is probably not indicated right now.

However, if she develops further thrombotic events (such as a pulmonary embolism), this decision may need to be reconsidered and expert advice obtained.

Heparin-Induced Thrombocytopenia

N Engl J Med 2015;373:252-61

A 64-year-old woman who is hospitalized with endocarditis and whose condition is clinically stable while she is receiving intravenous antibiotic agents has had a decrease in platelet count from 161,000 per cubic millimeter on day 7 of hospitalization to 60,000 per cubic millimeter on day 9. She has been receiving low-molecular-weight heparin at a dose of 40 mg per day since admission. How should her case be further evaluated and treated?

KEY CLINICAL POINTS

HEPARIN-INDUCED THROMBOCYTOPENIA

- Heparin-induced thrombocytopenia (HIT) is characterized by a decrease in the platelet count of more than 50% from the highest platelet count value after the start of heparin, an onset 5 to 10 days after the start of heparin, hypercoagulability, and the presence of heparin-dependent, platelet-activating IgG antibodies.
- Use of a scoring system that takes into account the timing and magnitude of the platelet count fall, new thrombosis, and the likelihood of other reasons for thrombocytopenia is helpful in assessing the pretest probability of HIT.
- Delayed-onset HIT develops after the cessation of heparin, and spontaneous or autoimmune HIT develops in the absence of heparin exposure.
- Platelet factor 4–heparin antibody tests should be ordered only if clinical features reasonably suggest HIT. These tests have a high negative predictive value but a low positive predictive value.
- Treatment of acute HIT requires the cessation of heparin and the initiation of therapeutic-dose anticoagulation with an alternative agent (argatroban, danaparoid, fondaparinux, or bivalirudin).
- Warfarin should be avoided in patients with acute HIT.

In Her Blood

A 64 year old lady presents 45 minutes after a **generalized tonic-clonic seizure** which lasted for approximately 5 minutes. She recovered consciousness immediately afterwards, but has remained drowsy and confused since then. All of this was witnessed by her daughter. She had complained 'feeling unwell' during the preceding 4 days. Her medical history is only significant for mild hypertension well controlled on Amlodipine alone. A capillary blood glucose and serum electrolytes are within normal parameters, as are serial ECGs, a noncontrast CT of the brain, and a toxicology screen. However, a complete blood count is significant for a **Hb of 8.7 g/dL** (normal:11-18), and **platelet count of 40,000/mm3** (normal: 150,000-400,000). A follow up blood film confirms the presence of anemia and thrombocytopenia, while additionally revealing abundant **reticulocytes** and numerous **schistocytes**.

Select Relevant Investigations

♦ **Renal Functions + Liver Functions**

Blood Urea: 25 mg/dL (0 - 50)
***Serum Creatinine: 1.7 mg/dL** (0.4 - 1.5)*
ALT: 20 IU/L (7-47) AST: 32 IU/L (10-40)
ALP: 94 IU/L (44-147) INR: 1.0 (0.9-1.1)
Total Serum Bilirubin: 1.9 mg/dL (0.2-1.2)
Direct Bilirubin: 0.1 mg/dL (0.1-0.4)

♦ **Coagulation Profile**

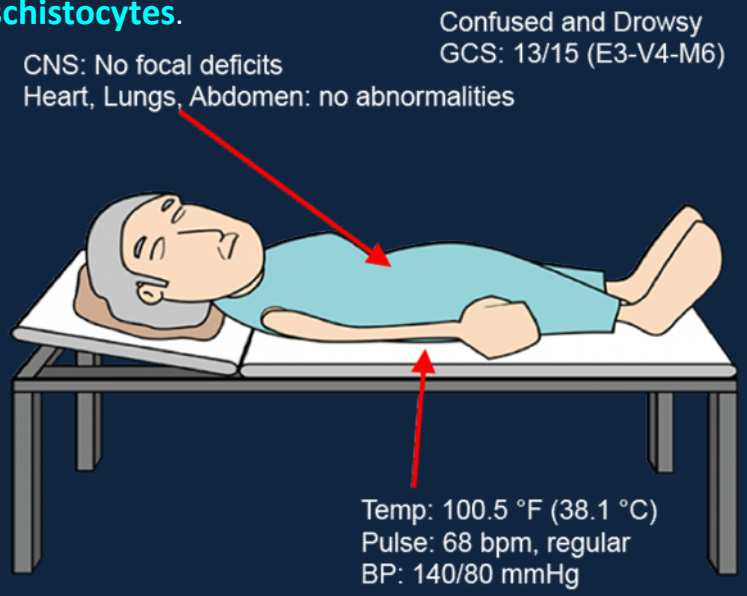
INR: 1.0 (0.9-1.1) PT: 12 sec (11-13.5)
APTT: 35 sec (30-50) TT: 11 sec (10-15)
Fibrinogen: 300 mg/dL (150-400)

♦ **LDH + Haptoglobin**

Lactate Dehydrogenase (LDH): 490 IU/L (105-333)
***Serum Haptoglobin: <10 mg /dL** (45-165)*

♦ **ADAMTS13 Activity Levels**

The results of the ADAMTS13 activity assay will be available in a few hours.



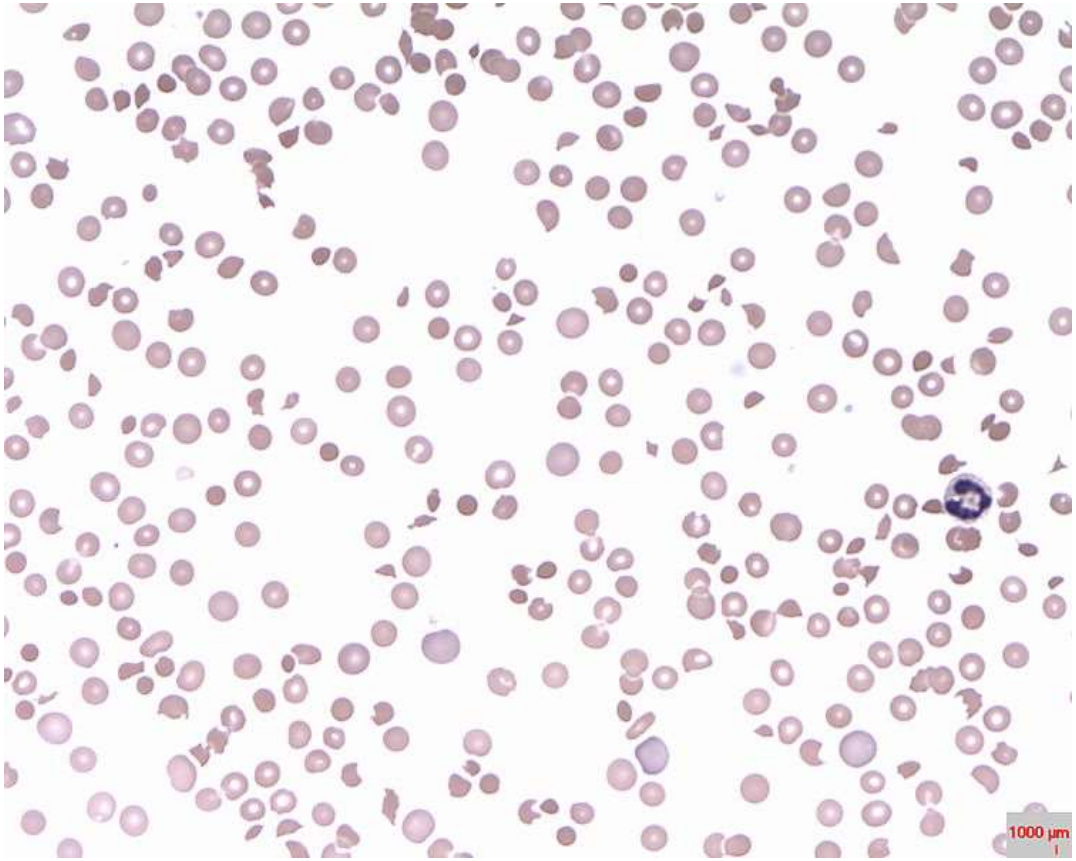
Pale and icteric
Fundi: B/L grade II hypertensive changes
Numerous petechiae present over entire body
No features of meningism

Select Relevant Management

- Aspirin
- **Plasma Exchange**
- **Corticosteroids**
- Sodium Nitroprusside

Thrombotic Microangiopathy

- The thrombotic microangiopathies (TMAs) include thrombotic thrombocytopenic purpura (TTP) and the hemolytic-uremic syndrome (HUS).
- These disorders are characterized by thrombocytopenia, due to the incorporation of platelets into thrombi in the microvasculature, and microangiopathic hemolytic anemia, which results from shearing of erythrocytes in fibrin networks in the microcirculation.
- Microangiopathic hemolytic anemia and thrombocytopenia, in the absence of another plausible explanation, are sufficient for the diagnosis of TMA.
- Fever, neurologic abnormalities, and kidney disease may occur concurrently but are not required for diagnosis.
- Kidney disease occurs in hemolytic-uremic syndrome.
- Relatively few conditions can give rise to MAHA in association with thrombocytopenia; the most prominent of these are Thrombotic Thrombocytopenic Purpura (TTP), Hemolytic Uremic Syndrome (HUS), Disseminated Intravascular Coagulation (DIC), and malignant hypertension.



Peripheral blood smear: patient with thrombotic thrombocytopenic purpura

Reticulocytes

Erythrocytes (mature cells)

A schistocyte is a fragmented part of a red blood cell. Schistocytes are typically irregularly shaped, jagged, and have two pointed ends. A true schistocyte does not have central pallor. Schistocytes are sometimes referred to as "helmet cells". Several microangiopathic diseases, including **disseminated intravascular coagulation** and **thrombotic microangiopathies**, generate fibrin strands that sever red blood cells as they try to move past a thrombus, creating schistocytes. Schistocytes are often seen in patients with hemolytic anemia. They are frequently a consequence of **mechanical artificial heart valves** and hemolytic uremic syndrome, thrombotic thrombocytopenic purpura, among other causes. Excessive schistocytes present in blood can be a sign of microangiopathic hemolytic anemia (MAHA) where the most common cause is **aortic stenosis**.

Diagnosis and Reasoning

The patient who presents following a first seizure is not an uncommon encounter in the emergency department; similar to other emergencies, the initial priority should always be assessment, resuscitation, and stabilization.

In parallel, the most common causes of seizure should be rapidly ruled out; these include electrolyte and metabolic disturbances, central nervous system (CNS) infections, cerebrovascular accidents, and drug overdose/poisoning. Given the history of hypertension, hypertensive encephalopathy (HE) should also be considered.

However, there are no clinical findings which particularly favor the above entities, while the initial battery of tests is also negative.

That said, her examination does reveal several worrisome findings: jaundice, pallor, and widespread petechiae; a follow up complete blood count (CBC) and blood film are mandatory.

The CBC confirms the presence of moderate anemia and severe thrombocytopenia; the blood film is even more alarming, demonstrating the presence of numerous schistocytes.

Note that this suggests at a microangiopathic hemolytic anemia (MAHA); this is further supported by the indirect hyperbilirubinemia, elevated lactate dehydrogenase (LDH) and reduced Haptoglobin levels, and the reticulocytosis seen in the blood smear.

Relatively few conditions can give rise to MAHA in association with thrombocytopenia; the most prominent of these are Thrombotic Thrombocytopenic Purpura (TTP), Hemolytic Uremic Syndrome (HUS), Disseminated Intravascular Coagulation (DIC), and malignant hypertension.

Differentiation between the above conditions requires the judicious use of investigations, including a renal assay and coagulation profile.

TTP immediately presents itself as a likely candidate, given the presence of the classic pentad of MAHA, thrombocytopenia, elevated renal functions, neurologic disturbances, and fever.

While there is a significant overlap in clinical findings between HUS and TTP, patients with the former typically experience far more severe renal impairment, while prominent neurologic manifestations are rare. Furthermore, in HUS, there is often an antecedent history of diarrhea, while the most patients tend to be of a younger age.

DIC is also unlikely given the normal coagulation profile; nor is malignant hypertension probable, given the minimally elevated blood pressure, and absence of other features suggestive of a hypertensive emergency.

It should be appreciated that certain drugs have also been implicated as a cause of MAHA; however, Amlodipine has not been identified as one of these.

Thus, TTP does indeed appear to be the diagnosis; while it is advisable to confirm this via estimation of ADAMTS13 activity levels, it should be noted that results are usually not available acutely.

TTP is a hematological emergency which is ideally treated in a specialist center; **plasma exchange** is the mainstay of therapy and should be commenced as early as possible; this should be combined with **corticosteroids**.

As the pathophysiology of TTP is related to platelet aggregation leading to microthrombi, certain guidelines recommend the use of antiplatelet agents (e.g. **Aspirin**); however, they are best commenced during platelet recovery (e.g. when platelet counts are >50,000/mm3).

Note that therapy with **Sodium Nitroprusside** is an option in malignant hypertension; it is potentially deleterious in this anemic patient, as it may lower tissue perfusion.

Thrombotic thrombocytopenic purpura (TTP fig 2) There is an overlap between TTP and HUS, and many physicians consider them a spectrum of disease. All patients have MAHA (severe, often with jaundice) and low platelets. Other features can include AKI, fluctuating CNS signs (eg seizures, hemiparesis, ↓consciousness, ↓vision) and fever. The classic description included the full 'pentad' of features, but with the advent of plasma exchange this is rarely seen. Mortality is higher than childhood HUS and can be >90% if untreated, though reduced to ~20% with plasma exchange. *Pathophysiology:* There is a genetic or acquired deficiency of a protease (ADAMTS13) that normally cleaves multimers of von Willebrand factor (vWF). Large vWF multimers form, causing platelet aggregation and fibrin deposition in small vessels, leading to microthrombi. *Causes:* Idiopathic (40%), autoimmunity (eg SLE), cancer, pregnancy, drug associated (eg quinine), bloody diarrhoea prodrome (as childhood HUS), haematopoietic stem cell transplant. ►*It is a haematological emergency: get expert help.* *Tests:* As HUS. *Rx:* Urgent plasma exchange may be life-saving. Steroids are the mainstay for non-responders, although new therapies such as eculizumab (monoclonal antibody targeting terminal complement pathway C5) have shown promising results in case reports,[45] though seem to be more effective in children than adults.[46] Trials are ongoing. Because thrombotic thrombocytopenic purpura is uncommon, a high index of suspicion is required for rapid diagnosis and prompt initiation of plasma-exchange treatment. ►The unexplained occurrence of thrombocytopaenia and anaemia should prompt immediate consideration of the diagnosis and evaluation of a peripheral blood smear for evidence of microangiopathic haemolytic anaemia.

Microangiopathic haemolytic anaemia (MAHA)

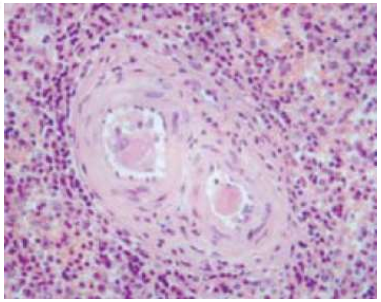
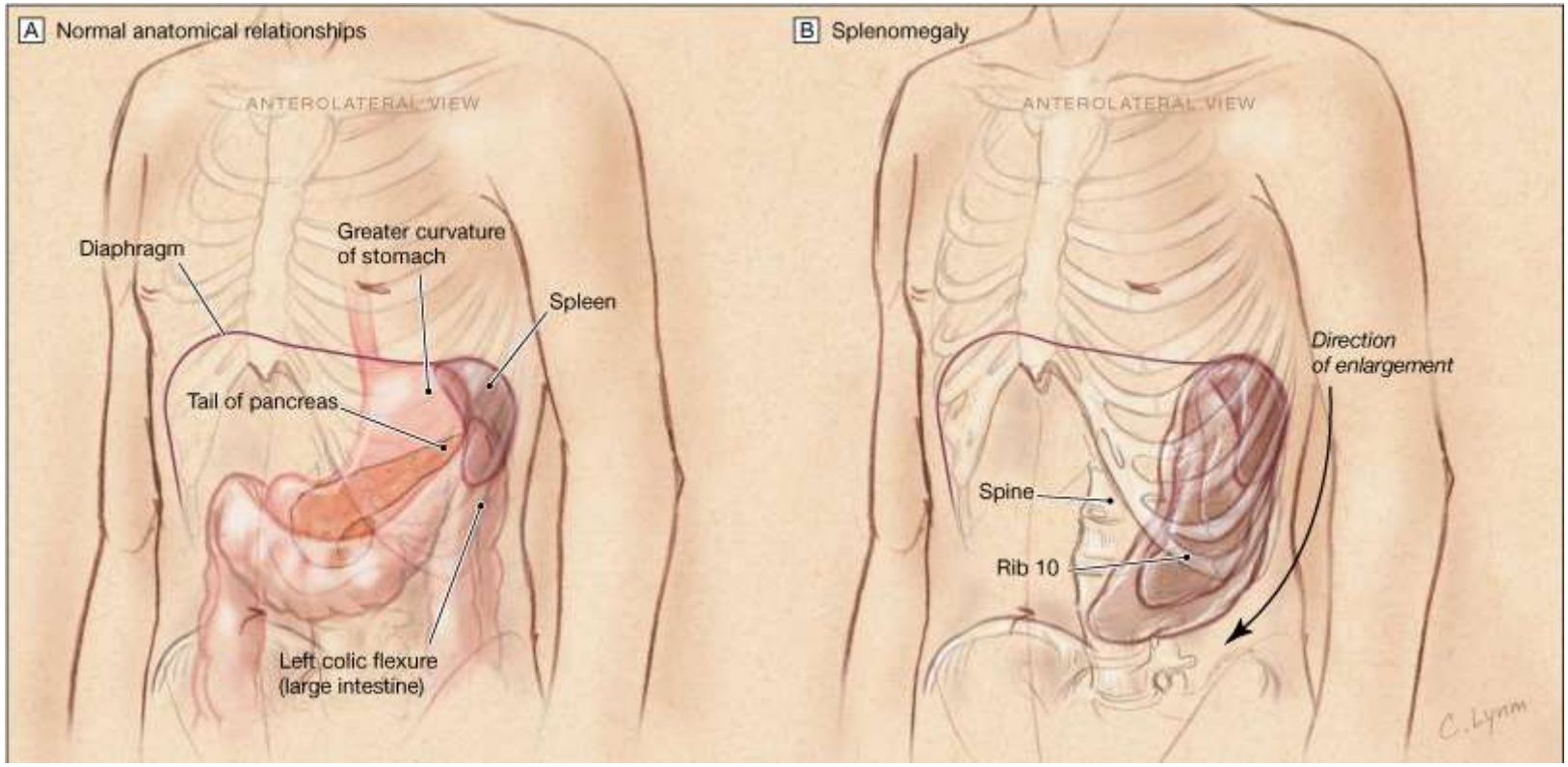
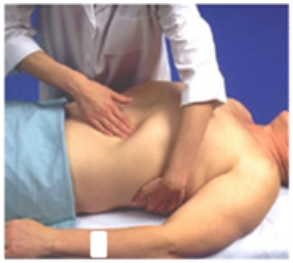


Fig 2. Thrombi in small arterioles due to fibrin and platelet deposition, characteristic of TTP.

Haemolytic uraemic syndrome (HUS) HUS is characterized by *microangiopathic haemolytic anaemia* (MAHA): intravascular haemolysis + red cell fragmentation. Endothelial damage triggers thrombosis, platelet consumption and fibrin strand deposition, mainly in renal microvasculature. The strands cause mechanical destruction of passing RBCs. Thrombocytopenia and AKI result. *Causes:* 90% are from *E. coli* strain O157 ('O' denotes the somatic antigen, as opposed to H, the flagellar antigen). This produces a verotoxin that attacks endothelial cells. This typically affects young children in outbreaks (more common than sporadically) after eating undercooked contaminated meat. *Signs:* Abdominal pain, bloody diarrhoea, and AKI. *Tests:* Haematuria/proteinuria. Blood film: fragmented RBC (schistocytes, p330); ↓platelets, ↓Hb. Clotting tests are normal. *℞:* Seek expert advice. Dialysis for AKI may be needed. Plasma exchange is used in severe persistent disease. *Prognosis:* Worse in non-*E. coli* cases. Mortality 3–5%, good prognosis if caught early.



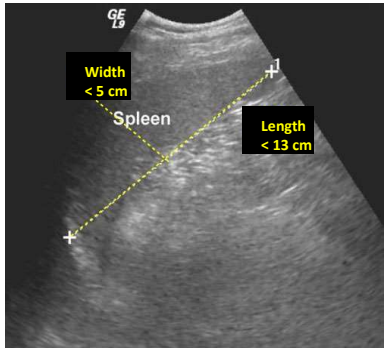
The spleen is located in the left upper quandrant of the abdomen beneath the left hemidiaphragm and lateral to the greater curvature of the stomach.

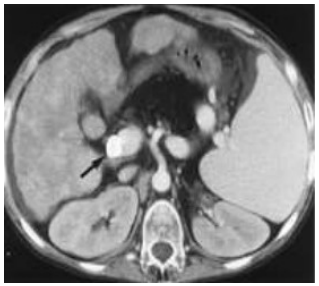


- Pull up with left hand and push in with right hand on inspiration
- Will only be able to feel if 3 times normal size

How do you differentiate the spleen from the kidney on abdominal examination?

- You can't get above the spleen (ribs overly it)
- The spleen moves towards RIF with inspiration, the kidney moves posterior only (if at all)
- The spleen is not ballotable like the kidney





Splenomegaly in a 15-year-old boy with cystic fibrosis, cirrhosis, and portal hypertension. Contrast-enhanced CT scan obtained at the level of the superior mesenteric artery shows a portosystemic shunt (arrow).

Causes of splenomegaly:

- **Congestive**
- **Infective**
- **Inflammatory**
- **Neoplastic,**
- **Infiltrative non-neoplastic**
- **Haematological hypersplenic states**

Congestive
Cirrhosis
Heart failure
Thrombosis of portal, hepatic, or splenic veins
Malignancy
Lymphoma, usually indolent variants
Acute and chronic leukemias
Polycythemia vera
Multiple myeloma and its variants
Essential thrombocythemia
Primary myelofibrosis
Primary splenic tumors
Metastatic solid tumors
Infection
Viral – hepatitis, infectious mononucleosis, cytomegalovirus
Bacterial – salmonella, brucella, tuberculosis
Parasitic – malaria, schistosomiasis, toxoplasmosis, leishmaniasis
Infective endocarditis
Fungal
Inflammation
Sarcoid
Serum sickness
Systemic lupus erythematosus
Rheumatoid arthritis (Felty syndrome)
Infiltrative, nonmalignant
Gaucher's disease
Niemann-Pick disease
Amyloid
Other lysosomal storage diseases (eg, mucopolysaccharidoses)
Langerhans cell histiocytosis
Hemophagocytic lymphohistiocytosis
Rosai-Dorfman disease
Hematologic (hypersplenic) states
Acute and chronic hemolytic anemias, all etiologies
Sickle cell disease (children)
Following use of recombinant human granulocyte colony-stimulating factor

Major causes of splenomegaly

Associations of splenomegaly:

- with fever
- with lymphadenopathy
- with purpura
- with arthritis
- with ascites
- with a murmur
- with anaemia
- with weight loss
- massive splenomegaly

Major causes of splenomegaly

Splenomegaly with fever	With lymphadenopathy	With purpura
• Infection[HS] (malaria, SBE/IE hepatitis,[HS] EBV,[HS] TB, CMV, HIV) • Sarcoid; malignancy[HS]	• Glandular fever[HS] • Leukaemias; lymphoma • Sjögren's syndrome	• Septicaemia; typhus • DIC; amyloid[HS] • Meningococcaemia
With arthritis	**With ascites**	**With a murmur**
• Sjögren's syndrome • Rheumatoid arthritis; SLE • Infection, eg Lyme (p430) • Vasculitis/Behçet's (p558)	• Carcinoma • Portal hypertension[HS]	• SBE/IE • Rheumatic fever • Amyloid[HS] (p364)
With anaemia	**With weight↓**	**Massive splenomegaly**
• Sickle-cell;[HS] thalassaemia[HS] • Leishmaniasis;[HS] leukaemia[HS] • Pernicious anaemia (p328)	• Cancer; lymphoma • TB; • Paraproteinaemia[HS]	• Malaria (hyper-reactivity after chronic exposure) • Myelofibrosis; CML[HS] • Gaucher's syndrome[HS] • Leishmaniasis

HS=causes of hepatosplenomegaly.

Hypersplenism

This can result from splenomegaly due to any cause. It is commonly seen with splenomegaly due to haematological disorders, portal hypertension, rheumatoid arthritis (Felty's syndrome) and lymphoma. Hypersplenism produces:

- pancytopenia
- haemolysis due to sequestration and destruction of red cells in the spleen
- increased plasma volume.

Treatment. This is often dependent on the underlying cause, but splenectomy is sometimes required for severe anaemia or thrombocytopenia.

Hypersplenism — Normally, about one-third of the platelet mass is sequestered in the spleen, where it is in equilibrium with circulating platelets. Splenic sequestration of platelets can be increased to 90 percent in cases of extreme splenomegaly, although total platelet mass and overall platelet survival remain relatively normal.

Splenectomy

Splenectomy is performed mainly for:

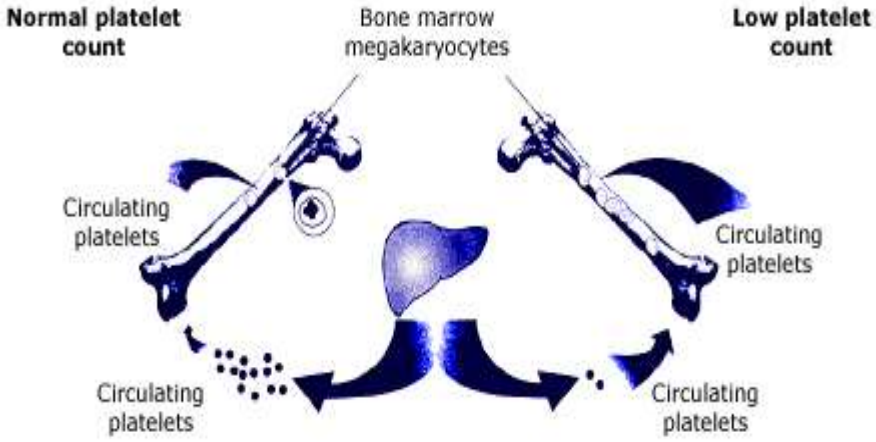
- trauma
- immune thrombocytopenic purpura
- haemolytic anaemias (see p. 386)
- hypersplenism.

Problems after splenectomy

An immediate problem is an increased platelet count (usually 600–1000$\times 10^9$/L) for 2–3 weeks. Thromboembolic phenomena may occur. In the longer term, there is an increased risk of overwhelming infections, particularly pneumococcal infections.

Prophylaxis against infection after splenectomy or splenic dysfunction

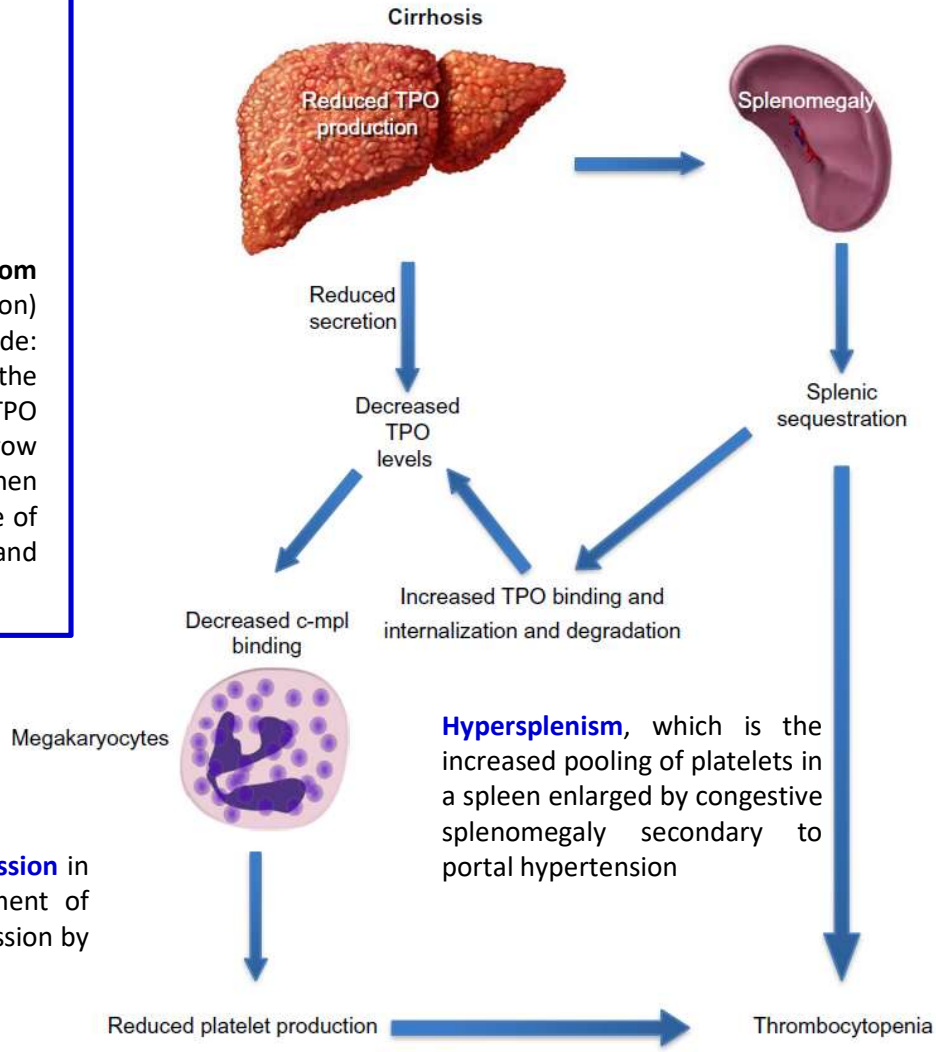
Thrombopoietin physiology



The mechanism by which **TPO regulates platelet production from megakaryocytes. TPO** (size of large arrows indicates relative concentration) is **produced constitutively by the liver** and enters the circulation. Left side: When the **platelet count is normal**, high affinity TPO receptors on the platelets clear most of the TPO and produce a normal plasma TPO concentration, thereby providing basal stimulation of bone marrow megakaryocytes and a normal rate of platelet production. Right side: When **platelet production and the platelet count are low**, the overall clearance of TPO is reduced, subsequently increasing the plasma TPO concentration and megakaryocyte and platelet production.

Thrombocytopenia in liver cirrhosis

In patients with chronic liver disease, **circulating TPO levels are decreased** due to impaired production and secretion and increased internalization and degradation by platelets sequestered in the enlarged spleen. Reduced TPO levels result in decreased megakaryocyte stimulation and platelet production.



Hypersplenism, which is the increased pooling of platelets in a spleen enlarged by congestive splenomegaly secondary to portal hypertension

Inadequate production of platelets due to **bone marrow suppression** in selected cases may also play a crucial role in the development of thrombocytopenia in cirrhosis. Possible etiologies include suppression by viruses, alcohol, iron overload, and medications.

THROMBOPOIETIC GROWTH FACTORS

The use of hematopoietic growth factors has markedly changed the practice of medicine. Erythroid growth factors (eg, erythropoietin, darbepoetin) and myeloid growth factors (eg, granulocyte colony-stimulating factor, granulocyte-macrophage colony-stimulating factor) have allowed the specific stimulation of the production of erythrocytes and neutrophils, respectively. With the discovery of thrombopoietin (TPO) and the development of a variety of peptide and non-peptide TPO receptor agonists, clinically effective thrombopoietic growth factors have now entered the clinical armamentarium.

● A number of thrombopoietin (TPO) molecules have been developed; they define a new and growing family of molecules called the thrombopoietin (c-mpl ligand) family, based upon their common **ability to bind and activate the TPO receptor, c-mpl**

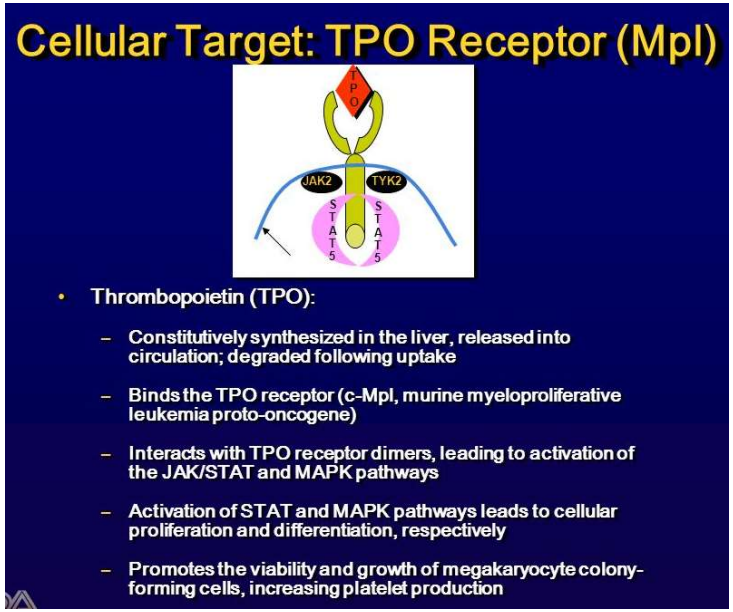
● The two TPO receptor agonists available for use in **immune thrombocytopenia** (ITP) are **romiplostim** (administered as a once-weekly subcutaneous injection) and **eltrombopag** (Revolade cp 25-50 mg, given as a once-daily pill).

● One TPO receptor agonist, eltrombopag, is approved for use in thrombocytopenic patients with **hepatitis C** who are receiving interferon and in patients with **aplastic anemia** for whom immunosuppressive therapy has failed.

● The TPO receptor agonists are currently under evaluation for a wide range of other thrombocytopenic disorders, including those associated with **chemotherapy** and **myelodysplastic syndromes**.

● Side effects of the TPO receptor agonists include **thrombocytosis**, possibly **thrombosis**, bone marrow reticulin fibrosis, and rebound thrombocytopenia. **Hepatotoxicity** has been reported with eltrombopag. Cost may also be an issue in some settings.

● Two non-peptide TPO receptor agonists (avatrombopag and lusutrombopag) are being developed to treat thrombocytopenia in presurgical patients



3 Coagulation disorders

Congenital: Haemophilia, von Willebrand's disease (p726). *Acquired:* Anticoagulants, liver disease, DIC (p346), vitamin K deficiency.

- **Acquired haemophilia** is a bleeding diathesis causing big mucosal bleeds in males and females caused by suddenly appearing autoantibodies that interfere with factor VIII.[51] *Tests:* APPT↑; VIII autoantibody↑; factor VIII activity <50%. *Rx:* Steroids.
- **Liver disease** produces a complicated bleeding disorder with ↓synthesis of clotting factors, ↓absorption of vitamin K, and abnormalities of platelet function.
- **Malabsorption** leads to less uptake of vitamin K (needed for synthesis of factors II, VII, IX, and X). Treatment is IV vitamin K (10mg) or FFP for acute haemorrhage.
- *DIC:* Widespread activation of coagulation, from release of procoagulants into the circulation with consumption of clotting factors and platelets, with ↑risk of bleeding. Fibrin strands fill small vessels, haemolysing passing RBCs, and fibrinolysis is also activated. *Causes:* Malignancy, sepsis, trauma, obstetric events: *OHCS* p88. *Signs:* (fig 1) Bruising, bleeding anywhere (eg venepuncture sites), renal failure. *Tests:* Platelets↓; PT↑; APTT↑; fibrinogen↓ (correlates with severity); fibrin degradation products (D-dimers) ↑↑. Film: broken RBCs (schistocytes). *Rx:* Treat the cause. Replace platelets if $<50\times10^9$/L, cryoprecipitate to replace fibrinogen, FFP to replace coagulation factors. Heparin is controversial. Activated protein C reduces mortality in DIC with severe sepsis or multi-organ failure.[66] The use of all-transretinoic acid (ATRA) has significantly reduced the risk of DIC in acute promyelocytic leukaemia (the commonest leukaemia associated with DIC).

3 Coagulation disorders *Congenital:* Haemophilia, von Willebrand's disease (p726). *Acquired:* Anticoagulants, liver disease, DIC (p346), vitamin K deficiency.

Haemophilia A Factor VIII deficiency; inherited in an X-linked recessive pattern in 1:10,000 male births—usually due to a 'flip tip' inversion in the factor VIII gene in the X chromosome. There is a high rate of new mutations (30% have no family history). *Presentation* depends on severity and is often early in life or after surgery/trauma—with bleeds into joints leading to crippling arthropathy, and into muscles causing haematomas (↑ pressure can lead to nerve palsies and compartment syndrome). *Diagnose* by ↑APTT and ↓factor VIII assay. *Management:* Seek expert advice. Avoid NSAIDs and IM injections (fig 2). *Minor bleeding:* pressure and elevation of the part. Desmopressin (0.3μg/kg/12h IVI over 20min) raises factor VIII levels, and may be sufficient. *Major bleeds* (eg haemarthrosis): ↑factor VIII levels to 50% of normal. *Life-threatening bleeds* (eg obstructing airway) need levels of 100%, eg with recombinant factor VIII. *Genetic counselling:* OHCS p154.

Haemophilia B (Christmas disease) Factor IX deficiency (inherited, X-linked recessive); behaves clinically like haemophilia A.

Von Willebrand's disease (VWD) Von Willebrand's factor (vWF) has 3 roles in clotting: **1** to bring platelets into contact with exposed subendothelium, **2** to make platelets bind to each other, and **3** to bind to factor VIII, protecting it from destruction in the circulation. There are >22 types of vWD; the commonest are:

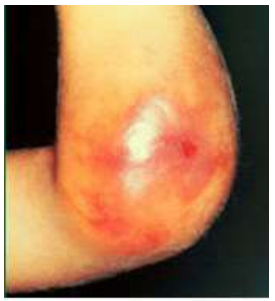
Type I: (60–80%) Autosomal dominant Deficiency (↓levels) of vWF. Symptoms are mild.

Type II: (20–30%) Abnormal vWF, with lack of high molecular weight multimers. Usually autosomal dominant inheritance. Bleeding tendency varies. There are 4 subtypes.

Type III: (1–5%) Undetectable vWF levels (autosomal recessive with gene deletions). vWF antigen is lacking and there is ↓factor VIII. Symptoms can be severe.

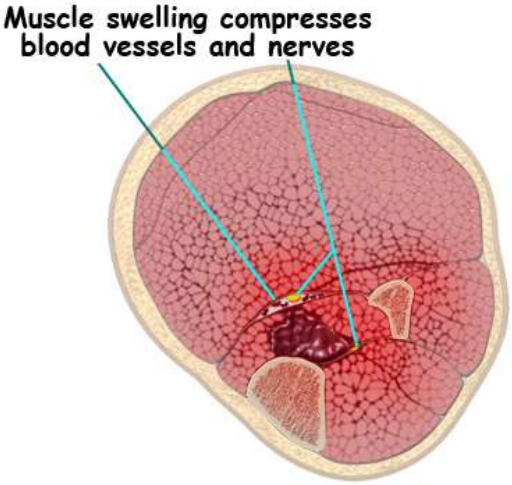
Signs are of a platelet-type disorder (p338): bruising, epistaxis, menorrhagia, ↑bleeding post-tooth extraction. *Tests:* APTT↑, bleeding time↑, factor VIIIC↓ (clotting activity), vWF Ag↓; INR and platelets ↔. *Rx:* Get expert help. Desmopressin is used in mild bleeding, vWF-containing factor VIII concentrate for surgery or major bleeds. Avoid NSAIDs.

Erik Adolf von Willebrand, 1870–1949 (Finnish physician)



HEMARTHROSIS

MUSCLE HEMATOMA
↓
COMPARTMENT SYNDROME



Scattered

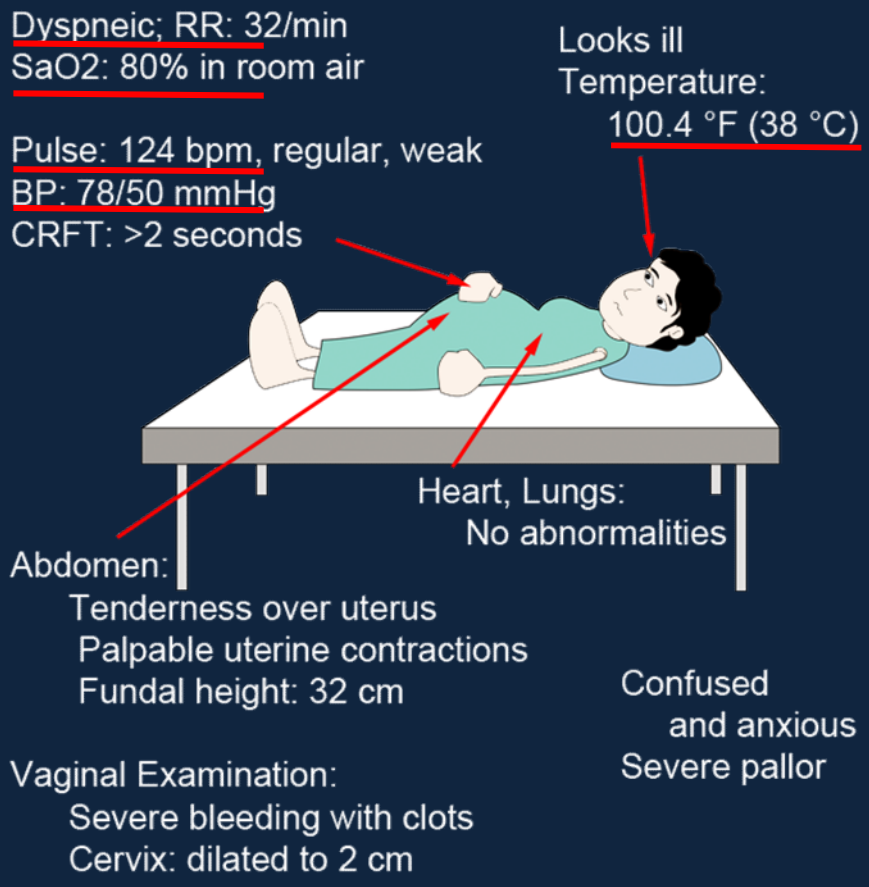
A 37 year old woman at 30 weeks of her first pregnancy presents with severe abdominal pain and profuse vaginal bleeding for 45 minutes. Her pregnancy has progressed normally until now. There is no personal or family history of bleeding tendencies, and her medical history is unremarkable. A cardiotocograph (CTG) shows a baseline heart rate of 170 bpm, and 6 uterine contractions within 10 minutes. No decelerations are seen. An ultrasound scan demonstrates a **partially separated anterior placenta,** with **intra-placental hemorrhage**.

Select Relevant Investigations

♦ **Full Blood Count**
WBC: 11,600/mm3 (4000-11,000) N: 76% (50-70)
L: 21% (20-40) ***Hb: 7.4 g/dL*** *(11.5-17.5)*
Hematocrit: 22.2% (36-44)
Platelets: 42,000/mm3 *(150,000-400,000)*
♦ **Group & Crossmatch Blood**
Group: O positive 4 units of blood crossmatched.
♦ **Coagulation Profile**
aPTT: 93 seconds *(30-40)* ***PT: 40 seconds*** *(10-12)*
Fibrinogen: 146 mg/dL *(373- 619 in 3rd trimester)*
♦ **Quantitative D-Dimer Assay**
D-Dimers: 8805 ng/mL *(≤250)*

Select Relevant Management

- Urgent Delivery
- Blood Transfusion
- Corticosteroids Stat
- Recombinant Protein C stat



Diagnosis and Reasoning

This lady has presented with clinical features of placental abruption; this diagnosis is confirmed by the ultrasound scan.

There is cardiotocographic evidence of fetal distress; but even more importantly, there is obvious maternal distress, with her vital signs indicating the presence of grade III hypovolemic shock.

She needs immediate resuscitation, including administration of high flow oxygen to maintain an oxygen saturation of over 95%, and a blood transfusion. This should be followed by urgent delivery via cesarean section (as the cervix is unfavorable).

A full blood count and coagulation profile should be ordered in parallel, and corticosteroids administered to promote fetal lung maturity (these may confer some benefit, even during such a short time period).

However, the test results reveal a deranged coagulation profile; in the context of an obstetric emergency, this is suggestive of disseminated intravascular coagulation (DIC); this is confirmed by the presence of elevated D-Dimers (which are a form of fibrin degradation products).

The DIC will most likely correct itself spontaneously following delivery; thus, her coagulation abnormalities should be corrected urgently, so that surgery can proceed.

Note that recombinant human activated protein C is not indicated in the management of DIC anymore, as there is very little evidence to indicate benefit, while several studies have showed potential harm.

Disseminated Intravascular Coagulation (DIC)

DIC: Widespread activation of coagulation, from release of procoagulants into the circulation with consumption of clotting factors and platelets, with ↑risk of bleeding. Fibrin strands fill small vessels, haemolysing passing RBCs, and fibrinolysis is also activated. *Causes:* Malignancy, sepsis, trauma, obstetric events: *OHCS* p88. *Signs:* (fig 1) Bruising, bleeding anywhere (eg venepuncture sites), renal failure. *Tests:* Platelets↓; PT↑; APTT↑; fibrinogen↓ (correlates with severity); fibrin degradation products (D-dimers) ↑↑. Film: broken RBCs (schistocytes). *Rx:* Treat the cause. Replace platelets if $<50\times10^9$/L, cryoprecipitate to replace fibrinogen, FFP to replace coagulation factors. Heparin is controversial. Activated protein C reduces mortality in DIC with severe sepsis or multi-organ failure.[66] The use of all-transretinoic acid (ATRA) has significantly reduced the risk of DIC in acute promyelocytic leukaemia (the commonest leukaemia associated with DIC).

Table 58–1 • COMPARISON OF DIC, TTP, AND ITP

	Etiology	Clinical Course	Treatment
Disseminated intravascular coagulopathy (DIC)	Secondary to some other process: sepsis, trauma, metastatic malignancy, obstetric causes.	Can be relatively mild indolent course or severe life-threatening process; ongoing coagulation and fibrinolysis can cause thrombosis or hemorrhage; consumption of coagulation factors is seen as prolonged PT and PTT.	Treatment aimed at underlying cause. No proven specific treatment for the coagulation problem: if bleeding, replace factors and fibrinogen with fresh-frozen plasma (FFP) or cryoprecipitate; if clotting, consider anticoagulate with heparin.
Thrombocytopenic thrombotic purpura (TTP)	Multiple causes, many seemingly trivial: drugs/infection lead to endothelial injury and release of von Willebrand factor (vWF), triggering formation of microvascular thrombi.	May present as septic-appearing patient with fever, altered mental status, thrombocytopenia, microangiopathic hemolytic anemia, and renal failure. Normal PT and PTT. Mortality, mainly due to CNS involvement.	Plasmapheresis (removal of the excess/abnormal vWF), most patients recover. Corticosteroids.
Immune thrombocytopenic purpura (ITP)	Antiplatelet antibody leading to platelet destruction.	Children: following a viral illness with resolution; in adults, a more indolent course with progression and rarely spontaneous resolution. Isolated thrombocytopenia, normal PT, PTT.	Oral corticosteroids; intravenous immunoglobulin (IVIg); splenectomy if refractory.

Products *Whole blood:* (rarely used) Indications: exchange transfusion; grave exsanguination—use crossmatched blood if possible, but if not, use 'universal donor' group O Rh−ve blood, changing to crossmatched blood as soon as possible. ►Blood even <2d old has no effective platelets. *Red cells:* (packed to make haematocrit ~70%) Use to correct anaemia or blood loss. 1u ↑Hb by 10–15g/L. In anaemia, transfuse until Hb ~80g/L. *Platelets:* (p358) Not usually needed if not bleeding or count is >20 × 10^9/L. 1u should ↑platelet count by >20 × 10^9/L. Failure to do so suggests refractoriness—discuss with haematologist. If surgery is planned, get advice if <100 × 10^9/L. *Fresh frozen plasma (FFP):* Use to correct clotting defects: eg DIC (p346); warfarin overdosage where vitamin K would be too slow; liver disease; thrombotic thrombocytopenic purpura (p308). It is expensive and carries all the risks of blood transfusion. Do not use as a simple volume expander. *Human albumin solution* is produced as 4.5% or 20% protein solution and is for use as protein replacement. 20% albumin can be used temporarily in the hypoproteinaemic patient (eg liver disease; nephrosis) who is fluid overloaded, without giving an excessive salt load. Also used as replacement in abdominal paracentesis (p779). *Others* Cryoprecipitate (a source of fibrinogen); coagulation concentrates (self-injected in haemophilia); immunoglobulin (*anti-D*, *OHCS* p9).

Prophylactic platelet transfusion

Therapeutic platelet transfusion

Platelets: (p358) Not usually needed if not bleeding or count is >20 × 10^9/L. 1u should ↑platelet count by >20 × 10^9/L. Failure to do so suggests refractoriness—discuss with haematologist. If surgery is planned, get advice if <100 × 10^9/L.

Cut off increases in conditions of poorly functioning platlets: NSAID, myeloproliferative diseases, increased urea, sepsis, fever.