



**NATIONAL AND KAPODISTRIAN UNIVERSITY OF ATHENS
MEDICAL SCHOOL**

Disorders of Haemostasis and Platelets

Focus on diagnosis and management

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Internal Medicine – 5th year



Learning objectives

- ☐ Take a bleeding history and tell a platelet-type from a coagulation-type bleed
- ☐ Interpret a prolonged PT or aPTT, and use a mixing study
- ☐ Diagnose and manage haemophilia A and B; recognise acquired haemophilia
- ☐ Work up thrombocytopenia and recognise thrombotic microangiopathy as an emergency
- ☐ Separate TTP, aHUS, DIC and HIT — and start the right treatment before the confirmatory test
- ☐ Diagnose ITP by exclusion and decide who needs treatment



Πρωτογενής vs δευτερογενής αιμόσταση

	Primary haemostasis	Secondary haemostasis
Components	platelets, von Willebrand factor, vessel wall	coagulation factors, fibrin
Bleeding	mucocutaneous: petechiae, epistaxis, menorrhagia	deep: haemarthrosis, muscle haematoma
Timing	immediate, after injury	delayed — hours after injury or surgery
First tests	platelet count, blood film, VWF studies	PT, aPTT, fibrinogen
Examples	ITP, drugs, von Willebrand disease	haemophilia, liver disease, vitamin K deficiency, DIC



The bleeding history is the most sensitive test

- ☐ Ask about the phenotype, not just the fact of bleeding
 - epistaxis needing packing, menorrhagia with iron deficiency, bleeding after dental extraction or tonsillectomy, post-partum haemorrhage
- ☐ Lifelong and familial → inherited · new in an adult → acquired
 - drugs, liver disease, DIC, acquired inhibitor, amyloidosis
- ☐ Family history; X-linked pattern suggests haemophilia
- ☐ Drug chart: antiplatelets, anticoagulants, NSAIDs, SSRIs, herbal supplements
- ☐ Use a structured score (ISTH-BAT) — it detects mild von Willebrand disease, used to screen for a bleeding disorder



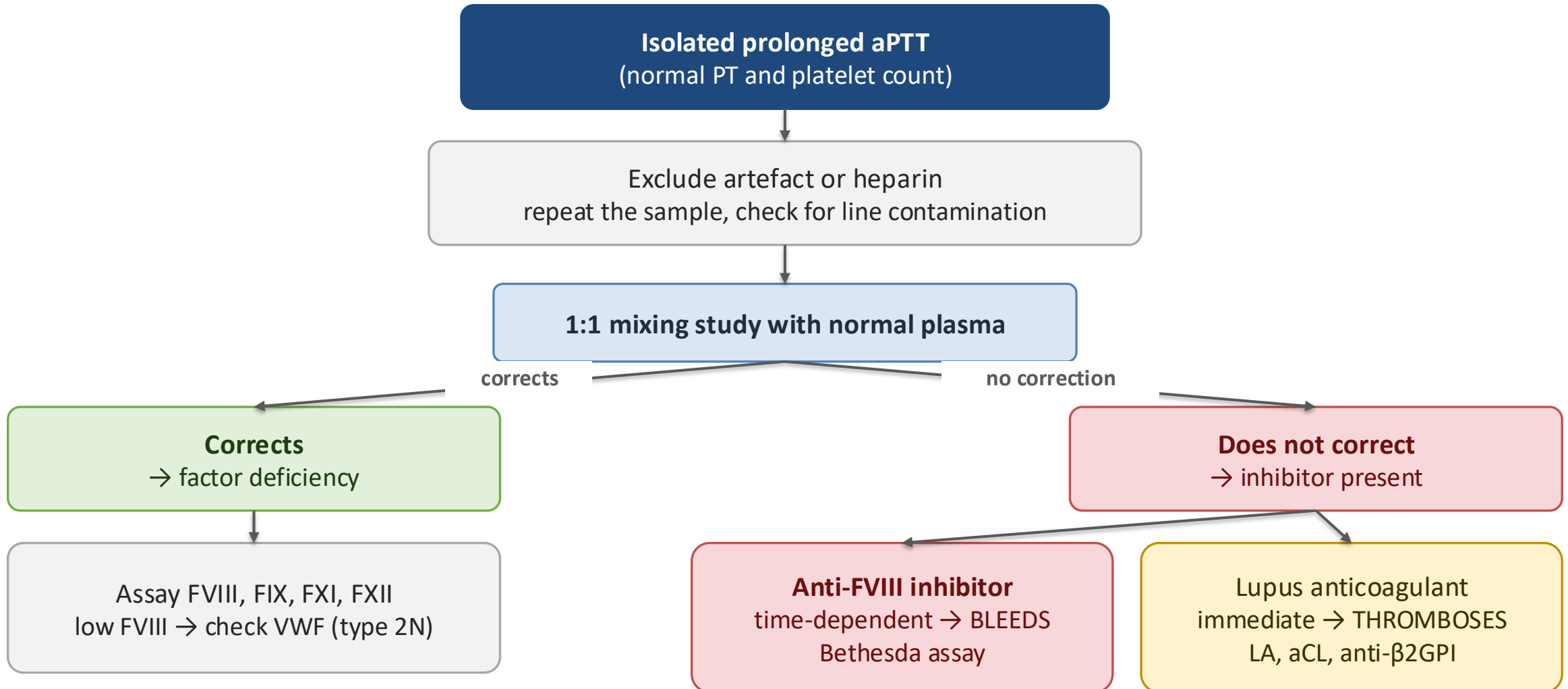
coagulation screen

PT	aPTT	Think of
Normal	Prolonged	FVIII, FIX, FXI, FXII · heparin · lupus anticoagulant · acquired inhibitor
Prolonged	Normal	FVII deficiency · early vitamin K deficiency or warfarin · mild liver disease
Prolonged	Prolonged	common pathway (FII, FV, FX, fibrinogen) · liver disease · DIC · dilution
Normal	Normal	does NOT exclude a bleeding disorder

- First exclude a sampling artefact (underfilled or clotted tube, heparin from a line) and repeat
- ▪ PT that corrects with vitamin K = vitamin K deficiency; one that does not = liver synthetic failure



Isolated prolonged aPTT: the mixing-study algorithm





Bleeding with normal coagulation tests

- ☐ Von Willebrand disease — the commonest inherited bleeding disorder (~1%)
- ☐ Mild factor deficiency — levels of 30–50% are often missed
- ☐ Platelet function defects — Glanzmann, Bernard–Soulier; uraemia, aspirin, MPN
- ☐ Factor XIII deficiency — delayed bleeding, umbilical stump bleeding; needs a specific assay
- ☐ Hyperfibrinolysis (APL, prostate cancer) and vascular causes (HHT, Ehlers–Danlos, amyloidosis, scurvy)
- ☐ DOACs: apixaban may barely change PT/aPTT — request anti-Xa activity

A normal PT and aPTT does not exclude a bleeding disorder — or a therapeutic DOAC level



Haemophilia A and B

	Haemophilia A	Haemophilia B
Deficiency	factor VIII	factor IX
Prevalence	~1 in 5,000 male births	~1 in 30,000 male births
Genetics	X-linked; ~30% no family history	X-linked; up to 50% no family history
Inhibitors	up to ~30% in severe disease	~3–5%

- Severity by factor activity: severe <1 · moderate 1–5 · mild 5–40 IU/dL
- Severe: spontaneous joint and muscle bleeds from infancy · mild: bleeding only after surgery or trauma
- Carrier females can bleed; type 2N VWD mimics haemophilia A (low FVIII, normal F8 gene)



Haemophilia: presentation and diagnosis

- ☐ Haemarthrosis (knee, ankle, elbow), muscle bleeds, delayed post-operative bleeding
 - a warm, swollen, painful joint in a young man is a haemarthrosis until proven otherwise
- ☐ Feared bleeds: intracranial, iliopsoas/retroperitoneal, compartment syndrome, airway
- ☐ Chronic burden: haemophilic arthropathy, deformity, pain
- ☐ Diagnosis: prolonged aPTT, normal PT and platelets → mixing corrects → FVIII or FIX assay
- ☐ Poor response to factor → screen for an inhibitor (Bethesda assay)



Haemophilia: management

- ☐ Acute bleed: raise the factor to a target set by the site
 - joint or superficial muscle bleed 40–60% · CNS, major surgery or life-threatening bleed 80–100%
- ☐ Factor concentrates (standard or extended half-life); DDAVP only in mild haemophilia A
- ☐ Tranexamic acid for mucosal and dental bleeding (not for haematuria)
- ☐ Prophylaxis is standard in severe disease — increasingly non-factor:
 - emicizumab (FIXa–FX bispecific) · anti-TFPI antibodies (concizumab, marstacimab) · fitusiran (antithrombin siRNA)
 - AAV gene therapy for haemophilia B (etranacogene) in selected adults
- ☐ No IM injections, aspirin or NSAIDs; care in a haemophilia centre



Inhibitors and acquired haemophilia A

- ☐ Inhibitor in congenital haemophilia: loss of response to factor (low <5 BU, high ≥ 5 BU)
 - bleed $\rightarrow$ bypassing agent (rFVIIa or aPCC) · long term $\rightarrow$ immune tolerance induction, emicizumab
 - on emicizumab: rFVIIa preferred; avoid aPCC (TMA, thrombosis)
- ☐ Acquired haemophilia A: autoantibody to FVIII in an older patient with no bleeding history
 - ~50% idiopathic; the rest autoimmune disease, cancer, pregnancy, drugs
 - dramatic soft-tissue and muscle bleeding, rarely haemarthrosis
- ☐ Two-arm treatment: stop the bleeding (bypassing agent) + eradicate the antibody (steroids $\pm$ rituximab or cyclophosphamide)

New bruising + isolated long aPTT in an older patient = mixing study before any biopsy or surgery



Case 1 · Heavy periods and iron deficiency at 19

- ☐ Referred by her family doctor with iron-deficiency anaemia: Hb 9.6 g/dL, ferritin 5 µg/L
- ☐ Heavy periods since menarche: flooding, pads changed hourly, 7–8 days
- ☐ Nosebleeds as a child; bled for 2 days after wisdom-tooth extraction
- ☐ Mother: heavy periods, hysterectomy at 38
- ☐ Examination: a few bruises on the shins; no petechiae

Initial tests

Test	Result	Reference
Platelets	248 ×10 ⁹ /L	150–400
PT	12.1 s	11–13.5
aPTT	34 s	27–38
Fibrinogen	3.1 g/L	2–4
ISTH-BAT score	8	≥6 abnormal (women)

Platelets, PT and aPTT are normal. Can we reassure her — and what would you request next?

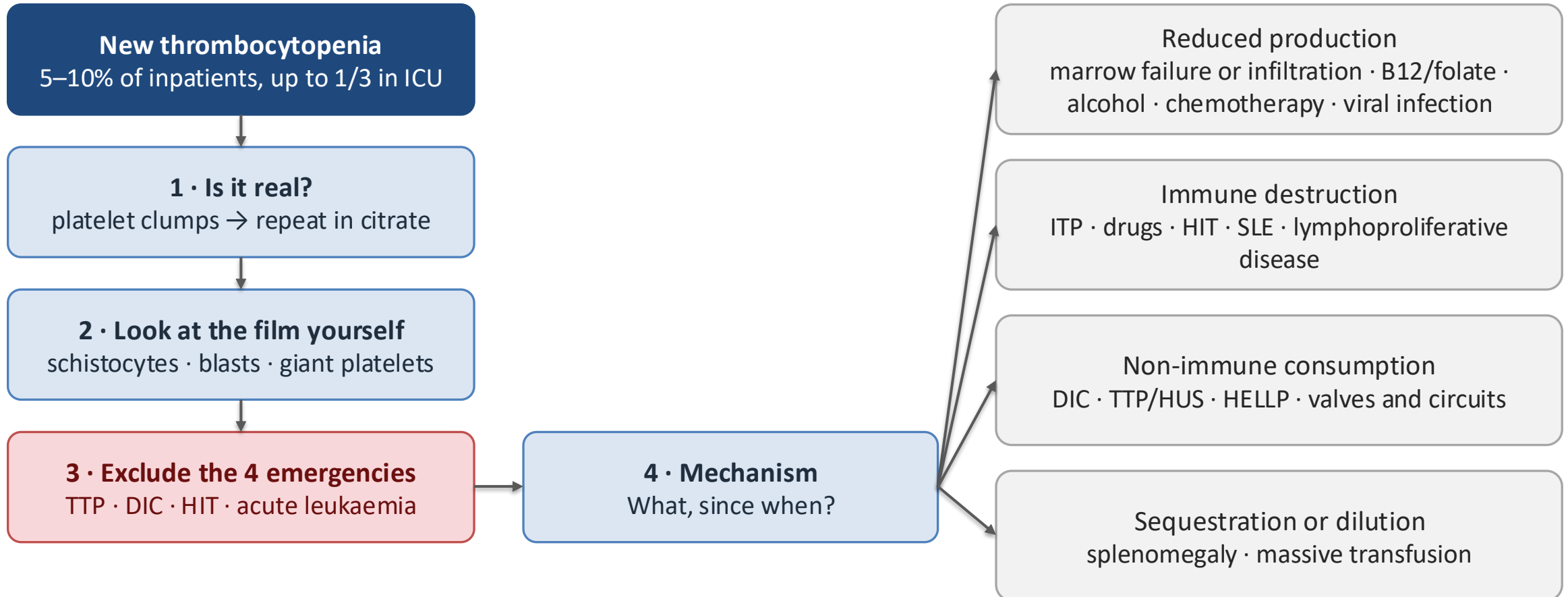


Von Willebrand disease

- ☐ VWF: platelet adhesion, and carrying FVIII · autosomal, both sexes
- ☐ Type 1 (~75%) partial deficiency · type 2 qualitative (2B → low platelets, 2N → mimics haemophilia A) · type 3 virtual absence
- ☐ Tests: VWF antigen, VWF activity, FVIII; multimers in type 2
 - levels rise with stress, pregnancy, oestrogen and inflammation — repeat when well
- ☐ Treatment: tranexamic acid · DDAVP (test response; avoid in 2B) · VWF concentrate for surgery
- ☐ Acquired VWS: aortic stenosis, LVAD, monoclonal gammopathy, ET with platelets $>1000 \times 10^9/L$



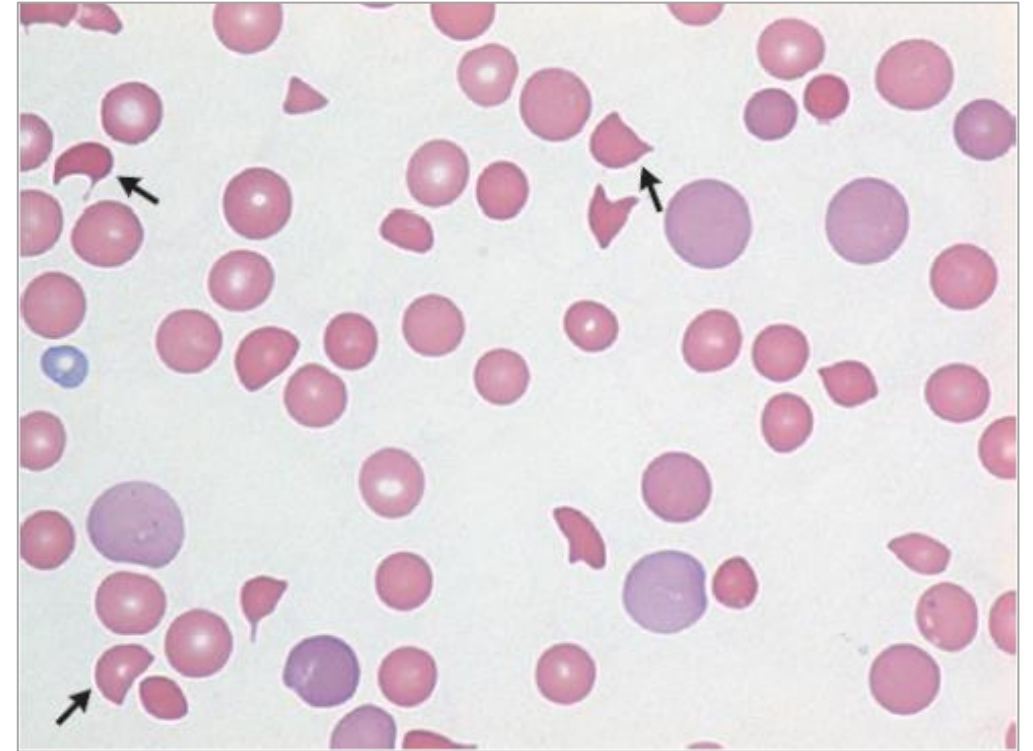
Approach to thrombocytopenia





Case 2 · Confusion, petechiae and anaemia

- ☐ 38-year-old woman; 3 days of headache and fatigue
- ☐ Today: word-finding difficulty and right-hand weakness, resolved within an hour
- ☐ Petechiae on the legs; temperature 37.8 °C
- ☐ **Hb** 7.9 g/dL · **platelets** $14 \times 10^9/\text{L}$ · **WBC** normal · **MCV** 88 fL
- ☐ **LDH** 1,450 U/L · indirect bilirubin $\uparrow$ · haptoglobin undetectable · reticulocytes 6%
- ☐ **DAT** negative · **INR** 1.1 · aPTT and fibrinogen normal
- ☐ **Creatinine** 1.2 mg/dL · troponin mildly raised

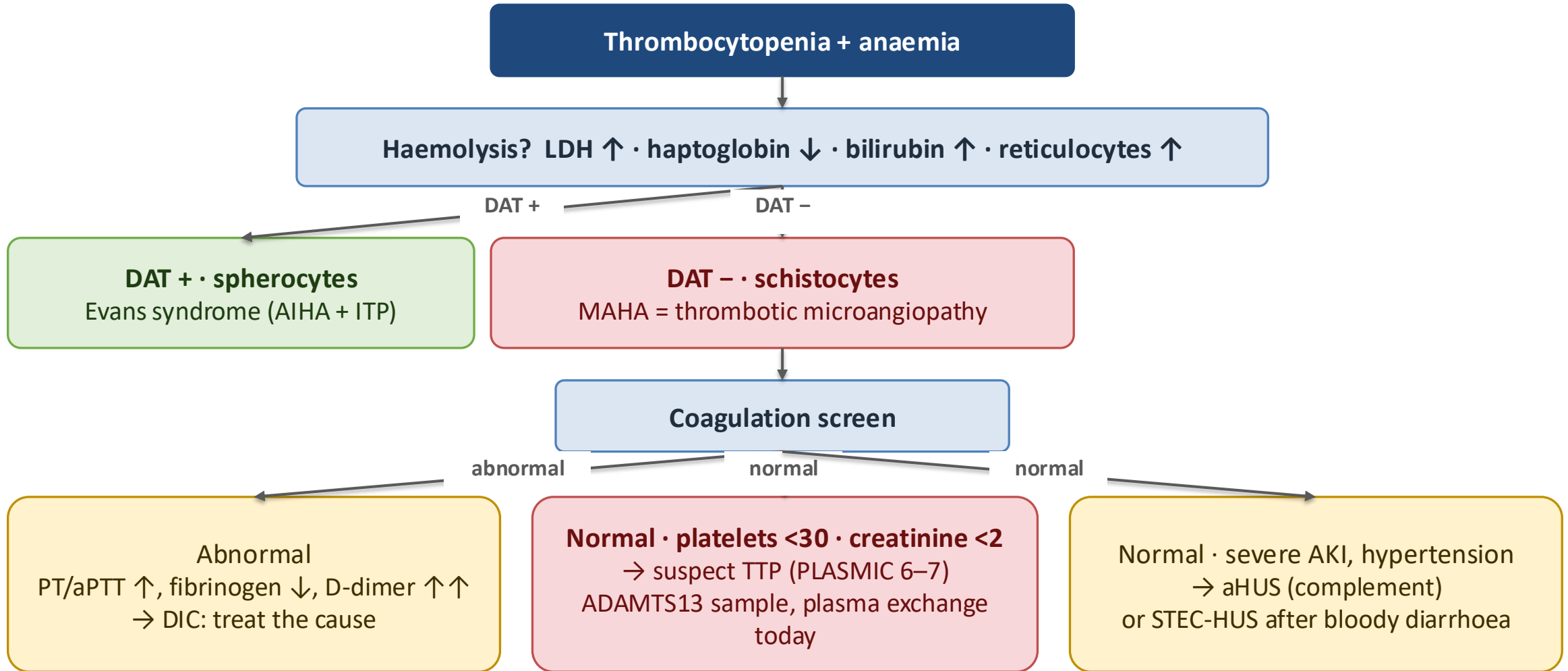


Peripheral blood film. Schistocytes (arrows), polychromasia, very few platelets

What does the film show? Work out the PLASMIC score — and what do you do today?



Thrombocytopenia with anaemia: is it a TMA?





Telling the thrombotic microangiopathies apart

	TTP	aHUS	STEC-HUS	DIC
Mechanism	ADAMTS13 <10% (antibody in 95%)	complement dysregulation	Shiga toxin (E. coli O157:H7)	systemic coagulation activation
Platelets	often <30×10 ⁹ /L	usually >30	low	low
Kidney	mild	severe AKI	severe, after diarrhoea	variable
Clues	neurology, troponin rise	severe hypertension	bloody diarrhoea, children	sepsis, trauma, obstetric
PT / aPTT	normal	normal	normal	prolonged
First line	PEX + steroids + caplacizumab + rituximab	eculizumab or ravulizumab	supportive, dialysis	treat the cause

The coagulation screen is the discriminator: normal in TTP and HUS, abnormal in DIC



TTP: mechanism and clinical picture

- ADAMTS13 normally cleaves ultra-large VWF multimers on the endothelium
- Severe deficiency (<10%) → platelet microthrombi → consumption, schistocytes, organ ischaemia
 - 95% acquired (anti-ADAMTS13 IgG) · 5% congenital (Upshaw–Schulman)
- Classic pentad in <10% — do not wait for it
- Neurological signs fluctuate; troponin rise predicts death; severe AKI points to aHUS
- Platelets $10\text{--}30 \times 10^9/\text{L}$, schistocytes, LDH very high, DAT negative, PT/aPTT normal
- Untreated mortality >90%; with modern treatment <10–20%



Predicting TTP before ADAMTS13 returns: PLASMIC score

Component	1 point if
Platelets	$<30 \times 10^9/L$
Haemolysis	reticulocytes $>2.5\%$, haptoglobin undetectable, or bilirubin >2 mg/dL
Active cancer	absent
Transplant	no solid-organ or stem cell transplant
MCV	<90 fL
INR	<1.5
Creatinine	<2.0 mg/dL

- 0–4 low · 5 intermediate · 6–7 high (most have ADAMTS13 $<10\%$)
- A triage tool for starting plasma exchange today — never a reason to withhold it



TTP: management on four axes

1. Replace ADAMTS13 and remove the antibody — plasma exchange the day of suspicion
 - if exchange is not available, give plasma while arranging transfer
2. Suppress the antibody — corticosteroids + rituximab (relapse ~50% → ~10%)
3. Block platelet–VWF binding — caplacizumab
 - faster platelet recovery, fewer exacerbations and exchanges
4. Supportive care — folate, LMWH prophylaxis once platelets $>50 \times 10^9/L$

Congenital TTP: recombinant ADAMTS13 replacement

No platelet transfusion in TTP unless bleeding is life-threatening



aHUS and STEC-HUS

- ☐ STEC-HUS: children after bloody diarrhoea (E. coli O157:H7)
 - supportive care and dialysis; avoid antimotility agents
- ☐ aHUS: uncontrolled alternative complement pathway
 - complement gene variants or anti-factor H antibodies in 40–60%; triggered by infection, pregnancy, surgery
- ☐ Recognise it by what TTP is not: severe AKI, hypertension, platelets >30 , ADAMTS13 $>10\%$
- ☐ Treat: eculizumab or ravulizumab — do not wait for genetics; meningococcal vaccination $\pm$ antibiotic cover
- ☐ Secondary TMA: calcineurin inhibitors, gemcitabine, VEGF inhibitors, transplant, HELLP



Case 3 · Oozing from line sites in septic shock

- ☐ 67-year-old man, day 2 in ICU with E. coli urosepsis, on noradrenaline
- ☐ New oozing from central and arterial line sites; blood-stained urine in the catheter
- ☐ Cool, mottled fingertips
- ☐ On prophylactic LMWH
- ☐ Film: occasional schistocytes, no blasts

Laboratory trend

	Admission	Day 2
Platelets ($\times 10^9/L$)	210	48
PT (s; normal 11–13)	13.2	19.5
aPTT (s)	33	52
Fibrinogen (g/L)	4.2	0.9
D-dimer ($\mu g/mL$ FEU)	1.1	>20

Calculate the ISTH DIC score. Which blood products would you give — and what happens to the LMWH?



Disseminated intravascular coagulation

- ☐ Always secondary: systemic coagulation activation → consumption + fibrinolysis
- ☐ Thrombosis and bleeding at the same time: organ failure from microthrombi + bleeding
- ☐ Triggers: sepsis · trauma, burns · cancer and APL · obstetric (abruption, amniotic fluid embolism, HELLP) · liver failure
- ☐ Investigations: falling platelets, prolonged PT/aPTT, low fibrinogen, very high D-dimer
 - no single diagnostic test — a score, repeated over time
- ☐ Two special forms: chronic DIC in cancer (thrombosis) and APL (hyperfibrinolysis, catastrophic bleeding)



DIC: ISTH score and management

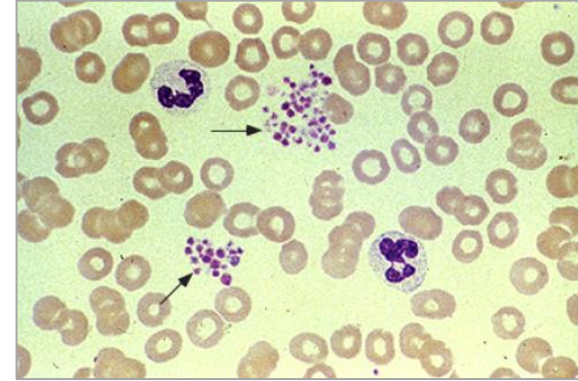
Parameter	0	1	2	3
Platelets ($\times 10^9/L$)	>100	50–100	<50	—
D-dimer / fibrin marker	no rise	—	moderate	strong
PT prolongation	<3 s	3–6 s	>6 s	—
Fibrinogen (g/L)	>1	≤ 1	—	—

- Score ≥ 5 = overt DIC; $< 5 \rightarrow$ repeat daily
- Treat the cause · no bleeding $\rightarrow$ LMWH prophylaxis
- Bleeding or procedure: platelets $> 50 \times 10^9/L$, FFP, fibrinogen > 1.5 g/L
- Tranexamic acid only in hyperfibrinolytic bleeding (trauma); not routine in APL

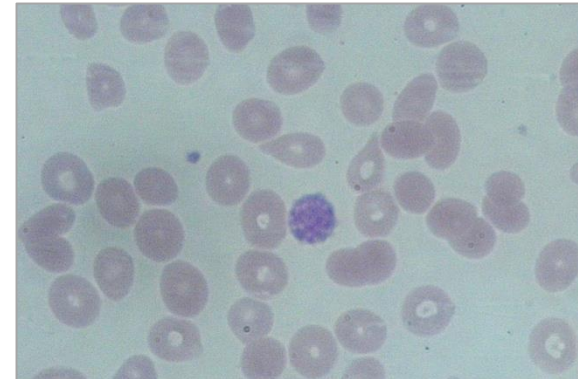


Case 4 · Petechiae after a sore throat

- ☐ 24-year-old man; sore throat 2 weeks ago
- ☐ 3 days of petechiae on the legs and gum bleeding when brushing; one nosebleed
- ☐ Occasional ibuprofen; no other drugs
- ☐ Feels well; no lymphadenopathy or splenomegaly
- ☐ **Platelets** $9 \times 10^9/\text{L}$ · **Hb** 14.8 g/dL · **WBC** $6.9 \times 10^9/\text{L}$, normal differential
- ☐ PT, aPTT and fibrinogen normal



A · Platelet clumps (arrows) in EDTA: pseudothrombocytopenia — repeat in citrate



B · Our patient: an isolated large platelet; red and white cells normal

Is the thrombocytopenia real? What must you exclude before calling it ITP — and does he need treatment?



Immune thrombocytopenia: what it is

- ☐ Isolated platelets $<100 \times 10^9/L$ with no other cause — a diagnosis of exclusion
- ☐ Two mechanisms → two treatment strategies:
 - antibody-mediated destruction (spleen) → steroids, IVIG, rituximab, splenectomy, BTK/SYK inhibition
 - impaired megakaryocyte production → thrombopoietin receptor agonists
- ☐ Secondary ITP: SLE, APS, CLL, CVID, HIV, HCV, H. pylori, drugs
- ☐ Newly diagnosed <3 months · persistent 3–12 · chronic >12 months
- ☐ Anti-platelet antibody tests are not needed for diagnosis



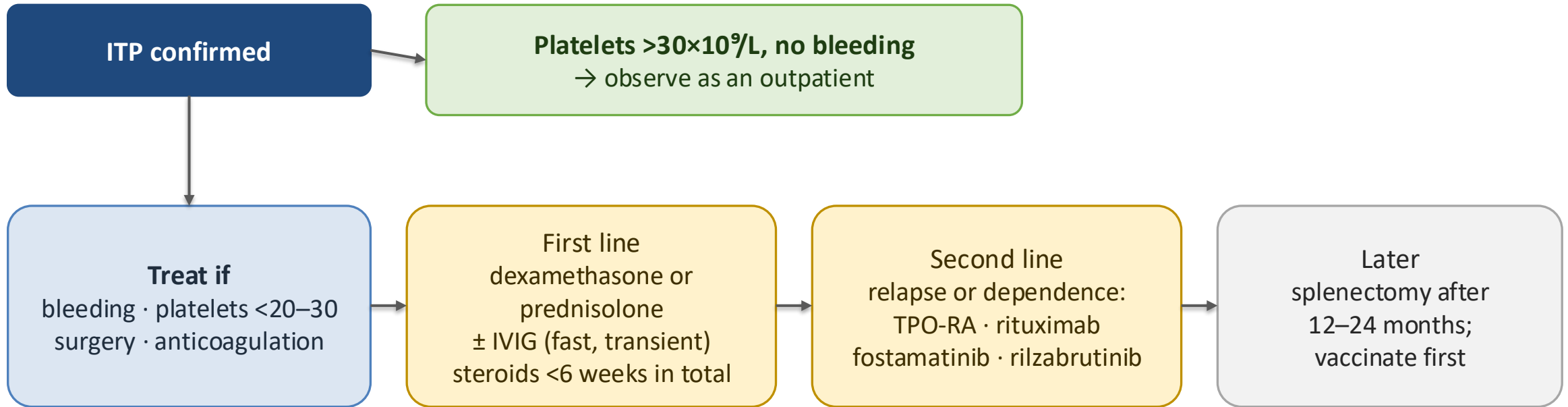
ITP: the diagnostic work-up

- ☐ The diagnosis rests on what is NORMAL: WBC, Hb, film, PT/aPTT
 - film: large platelets only — no clumps, schistocytes, blasts or dysplasia
- ☐ FBC and film, reticulocytes, DAT, immunoglobulins, PT/aPTT/fibrinogen, LFTs, creatinine
- ☐ HIV, HBV, HCV, H. pylori, ANA, antiphospholipid antibodies, TSH, pregnancy test
- ☐ Marrow only if atypical: other cytopenias or abnormal film, no response, relapse, before splenectomy
- ☐ Review the drug chart — stopping the drug is test and treatment

The commonest error: treating 'ITP' without looking at the blood film



ITP: who to treat, and with what





ITP with major bleeding: the emergency bundle

- ☐ Intracranial, GI or other life-threatening bleed, or platelets $<10-20$ with active bleeding
- ☐ Stop antiplatelet and anticoagulant drugs; give everything at once:
 - IV methylprednisolone 1 g/day for 1–3 days
 - IVIG 1 g/kg/day for 1–2 days — the fastest agent
 - platelet transfusion — appropriate here, unlike TTP and HIT
 - tranexamic acid
- ☐ Early TPO-RA if response is poor; surgery or endoscopy proceed in parallel

Platelets: GIVE in ITP bleeding · WITHHOLD in TTP · WITHHOLD in HIT



Heparin-induced thrombocytopenia: the paradox

- ☐ IgG against PF4–heparin activates platelets via FcγRIIa → massive thrombin generation
- ☐ Low platelets, but the patient THROMBOSES
- ☐ Typical onset day 5–10 · within hours if heparin in the last 100 days
- ☐ Relative fall >50%; nadir usually $20\text{--}150 \times 10^9/\text{L}$ — the count may stay 'normal'
- ☐ UFH ~10× LMWH; post-surgical > medical; rare with fondaparinux
- ☐ Thrombosis venous:arterial $\approx 4:1$; ~50% have thrombosis at diagnosis

HIT is not a bleeding disorder — it is a hypercoagulable state with a low platelet count



HIT: the 4Ts score decides what to do next

	2 points	1 point	0 points
Thrombocytopenia	>50% fall, nadir ≥ 20	30–50% fall, or nadir 10–19	<30% fall, or nadir <10
Timing	day 5–10, or ≤ 1 day if heparin in past 30 days	unclear, or after day 10	≤ 4 days, no recent heparin
Thrombosis	new thrombosis, skin necrosis, post-bolus reaction	progressive, recurrent or suspected	none
oTher cause	none apparent	possible	definite

- 0–3 low (HIT excluded) · 4–5 intermediate · 6–8 high
- Score ≥ 4 : stop heparin and start a non-heparin anticoagulant NOW, then test
- Anti-PF4 ELISA: sensitive, not specific · functional assay confirms



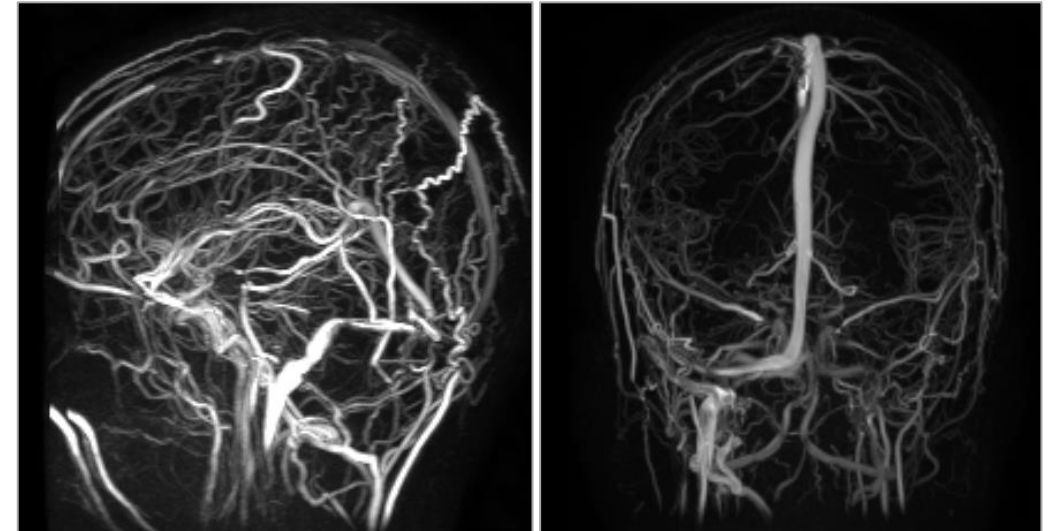
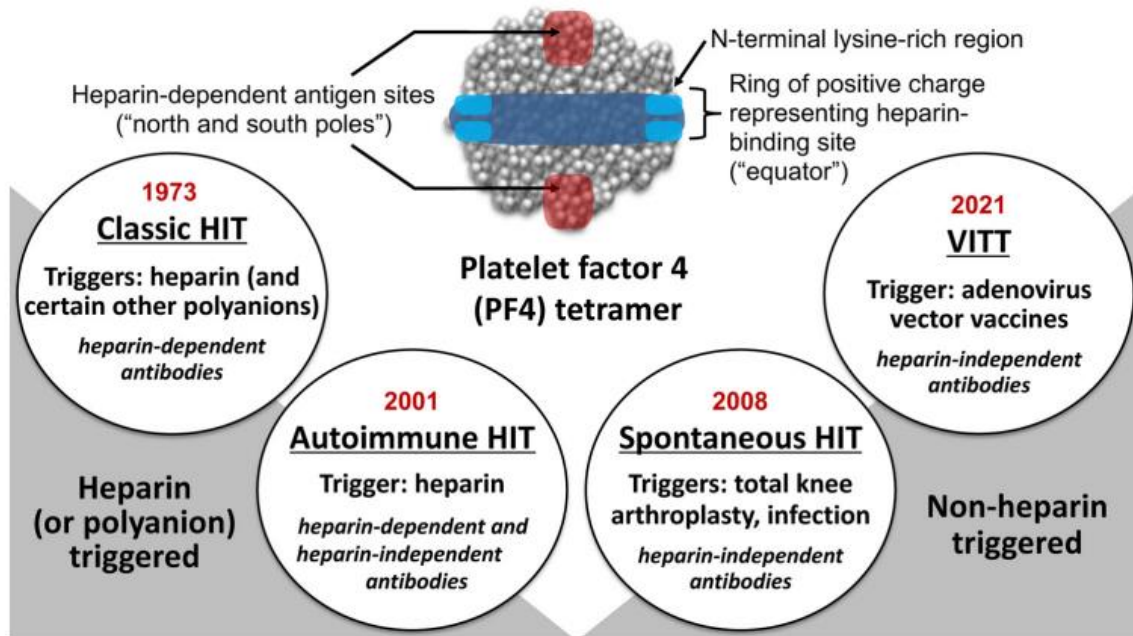
HIT: management — 2 do's, 2 don'ts, 2 checks

- ☐ DO stop ALL heparin, including flushes and line locks
- ☐ DO start a non-heparin anticoagulant at THERAPEUTIC dose
 - argatroban (renal failure) · fondaparinux · bivalirudin · DOAC if stable
- ☐ DON'T give warfarin while platelets are low (venous limb gangrene)
- ☐ DON'T give prophylactic platelets
- ☐ CHECK anti-PF4 antibodies, and leg ultrasound for silent DVT
- ☐ Duration: no clot → until platelet recovery (~4 weeks) · clot → 3–6 months



The wider anti-PF4 family, including VITT

- Same antibody target, different triggers: heparin, spontaneous, vaccine
- VITT: clot 5–30 days after adenoviral vaccine → IVIG + non-heparin anticoagulant



Case: 22-year-old, 12 days after an adenoviral-vector vaccine, with worsening headache, photophobia and vomiting. MR venography: transverse and superior sagittal sinus thrombosis. Platelets $30 \times 10^9/L$, D-dimer 16 mg/L.



Τι δεν πρέπει να μας ξεφύγει

- ☐ MAHA + low platelets + NORMAL coagulation → TTP: ADAMTS13 sample, plasma exchange today
- ☐ Low platelets on heparin + new thrombosis → HIT: stop heparin, therapeutic non-heparin anticoagulant (fondaparinux)
- ☐ New echhymosis + isolated long aPTT in an older patient → acquired haemophilia
- ☐ Haemophilia + head injury or tense joint → factor first, imaging second
- ☐ Platelets <20 with bleeding → ITP : steroids, IVIG, platelets, TXA
- ☐ Low platelets, long PT, low fibrinogen, very high D-dimer → DIC: treat the cause
- ☐ No prophylactic platelets in TTP or HIT · never warfarin in acute HIT

Every new thrombocytopenia: a blood film and a drug chart review before anything else



Take-home messages

- ☐ The bleeding phenotype localises the defect: mucocutaneous → platelets/VWF, deep → a factor
- ☐ A long aPTT may mean bleeding (factor, inhibitor) or thrombosis (lupus anticoagulant) — mixing test
- ☐ MAHA + thrombocytopenia is an emergency: coagulation, creatinine and platelets sort TTP / aHUS / DIC
- ☐ TTP is treated on suspicion — and not with platelets unless bleeding is life-threatening
- ☐ ITP is a diagnosis of exclusion, treated for haemostasis, not a number
- ☐ HIT is prothrombotic: stop heparin, anticoagulate fully, no warfarin, no prophylactic platelets