Disorders of Hemostasis

Med-1 (MED-411) · Hematology · Lecture 2 of 2

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Case 1

A 19-year-old woman.

- Heavy periods since adolescence
- Easy bruising
- Bled for a long time after her wisdom teeth were removed

Test	Result
Platelets	normal
PT	normal
aPTT	normal

Questions

- Is this a bleeding disorder at all?
- If the screen is normal, which one?
- How do we prove it?

Outline

The route

1. History: take it in full and score it
2. Screen: the tube, the PT, the aPTT
3. Mix: missing factor or inhibitor?
4. Confirm: VWD, platelet function, factor assays

Objectives

- Take and score a bleeding history
- Read every PT and aPTT pattern
- Use a mixing study, read twice
- Diagnose and type VWD
- Recognise platelet function disorders
- Approach acquired bleeding: DIC, liver, vitamin K, anticoagulants

Local bleeding or bleeding disorder?

One site alone (nosebleed, hematuria, hematemesis, hemoptysis): look for a **local lesion**

Investigate with endoscopy or imaging, not a clotting screen

More than one kind of bleeding, or failed challenges: think of a **bleeding disorder**

Spontaneous	After a challenge
Bruising, minor wounds	Tooth extraction
Nosebleeds, mouth and gums	Surgery
Gut, blood in urine	Childbirth
Heavy periods	Circumcision*
Muscle and joint bleeds	At birth, umbilical stump*
Brain	

ISTH-BAT symptom list. *Added from the earlier deck.

Bleeding history

What kind? Skin and mucosa, immediate: plug (platelets, VWF). Joints and muscle, delayed: clot (factors)

Since when? Since childhood: inherited. New in an adult: acquired until proved otherwise

Which challenges? Birth, circumcision, teeth, surgery, childbirth, periods. Passed or failed?

Who else? Family history; consanguinity (Lecture 1)

What else? Antiplatelets, anticoagulants, anti-inflammatories, herbal; kidney, liver, cancer, pregnancy, travel

Tired, feverish and bruising: think of the marrow. Count and film today.

Menstrual history

A 14-year-old girl, tired and pale (case from the earlier deck).

Test	Result	
Hemoglobin	97 g/L (9.7 g/dL)	low
Hematocrit	0.299 L/L	low
MCV	69.7 fL	low
MCH	22.6 pg	low
RDW	18.4 %	high
Platelets	331 ×10⁹/L	normal
White cells	normal	normal

"How are your periods?" "Fine."

Asked for details:

- they last **3 to 4 weeks**
- she changes protection **between every class**

Many girls do not know what a normal period is. Ask for numbers, not adjectives.

Heavy menstrual bleeding

Normal period	Red flags	Causes in a teenager
7 days or fewer	Large clots, gushing	Anovulatory cycles (commonest)
Cycles 21 to 45 days	Soaking through clothes	Bleeding disorders, VWD first
A few hours between changes	Changing at night	Pregnancy, infection, drugs
	Iron deficiency	Fibroids, polyps (rare)

- Riyadh schoolgirls: 16.7% (330 of 1,980) reported heavy periods (Owaidah 2018, self-report)

Heavy since the first period, with other bleeding or a family history: ask the bleeding questions

ISTH bleeding assessment tool

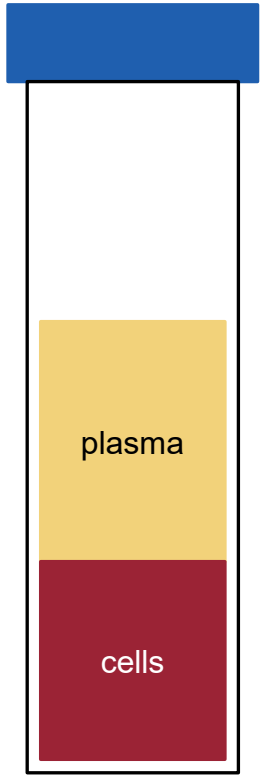
- A structured interview: each bleeding symptom scored by severity, added to one total
- The total is compared with a reference threshold

Pre-test probability	A normal score means
Low: mild bruising, no family history, passed every challenge	A bleeding disorder is unlikely
Intermediate or high: relative with VWD, iron deficiency, failed challenges	Test anyway; the score does not rule out

Case 1: high probability. She needs testing.

ASH/ISTH/NHF/WFH 2021 (James et al.)

Sample collection



Blue top: sodium citrate binds calcium

- **Underfilled tube**: too much citrate, times falsely long
- **Hematocrit above 0.55**: less plasma, same citrate, falsely long (altitude)
- **Heparin**: drawn from a line, or wrong order of tubes
- **Clotted or diluted** sample

Unexpected long result in a well patient: repeat on a fresh, full, peripheral sample

PT and aPTT

Prothrombin time (PT)

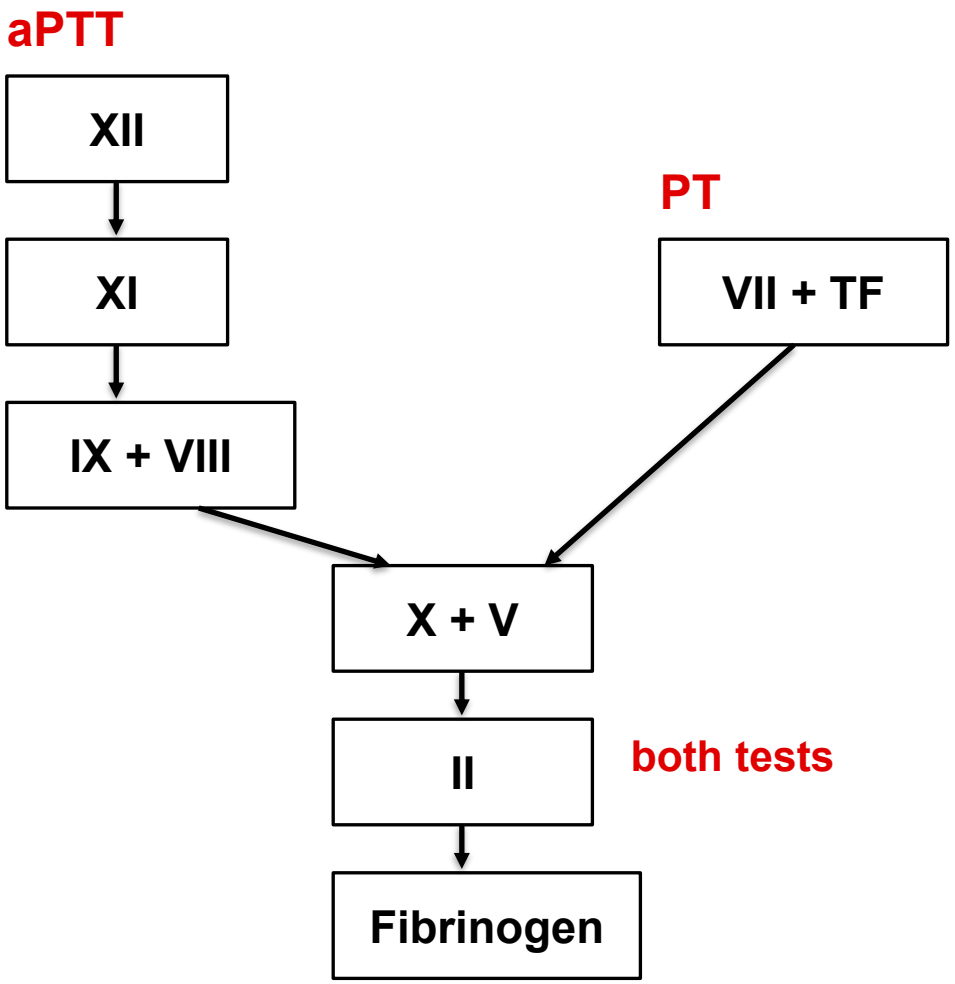
- Tissue factor, phospholipid and calcium together
- Factor VII, then X, V, II, fibrinogen
- About 9 to 15 s
- Reported as INR for warfarin

Activated partial thromboplastin time (aPTT)

- Contact activator (silica, kaolin, ellagic acid) and phospholipid
- Warm to 37 °C, then add calcium
- Factors XII, XI, IX, VIII, then X, V, II, fibrinogen
- About 25 to 35 s

Ranges depend on reagent and analyser; use your laboratory's range.

Reading the screen



Prolonged	Factors
PT alone	VII
aPTT alone	VIII, IX, XI, XII
Both	I, II, V, X, or many at once

Prolonged PT, normal aPTT

- Factor VII: the only factor in the PT and not the aPTT
- Shortest half-life of the vitamin K factors (II, VII, IX, X): falls first

Cause	Note
Early warfarin	VII falls before II, IX and X
Vitamin K deficiency	Poor diet, malabsorption, antibiotics
Early liver disease	Less of every factor made
Some DOACs	Can lengthen the PT
Congenital VII deficiency	Rare; 129 on the Saudi registry (WFH 2023)

Prolonged aPTT, normal PT

Bleeds	Does not bleed	Inhibitors
VIII or IX deficiency: hemophilia (Lecture 1)	XII deficiency	Heparin; some DOACs; direct thrombin inhibitors
VWD (low VIII)	Prekallikrein deficiency	Lupus anticoagulant: clots, does not bleed
XI deficiency (variable)	HMW kininogen deficiency	Acquired FVIII antibody: bleeds (Lecture 1)

Prolonged PT and aPTT

Common (acquired)

- DIC
- Severe liver disease
- Vitamin K deficiency, too much warfarin
- Massive transfusion, dilution
- Heparin excess, DOACs, lupus anticoagulant

Rare

- Single deficiency of X, V, II or fibrinogen
- Factor X bound to amyloid

Next

- Fibrinogen, platelets, film, D-dimer

Normal screen, still bleeding

Missed by count, PT and aPTT	Clue
Von Willebrand disease	Commonest inherited; aPTT often normal
Platelet function disorders	Drugs; Glanzmann; Bernard-Soulier
Mild factor deficiencies	Bleeding with surgery
Factor XIII deficiency	Umbilical stump bleeding; brain bleeds
Vascular causes	The vessel wall, not the blood

Case 1: VWF studies next; then platelet function, then factor XIII

Mixing study

- Patient plasma + normal pooled plasma, 1:1
- Repeat the test now, and after 1 to 2 hours at 37 °C

Result	Meaning
Corrects, and stays corrected	Missing factor
Does not correct	Inhibitor: lupus anticoagulant, heparin
Corrects now, prolonged after incubation	Slow inhibitor: antibody against factor VIII

A mix alone cannot prove or exclude acquired hemophilia: measure FVIII and the inhibitor (Tiede 2020)

Case 1: VWF studies

Test	Measures	Result
VWF antigen	How much VWF	Low
VWF activity	How well it binds platelets	Low, in proportion
Factor VIII	The protein VWF carries	Low-normal

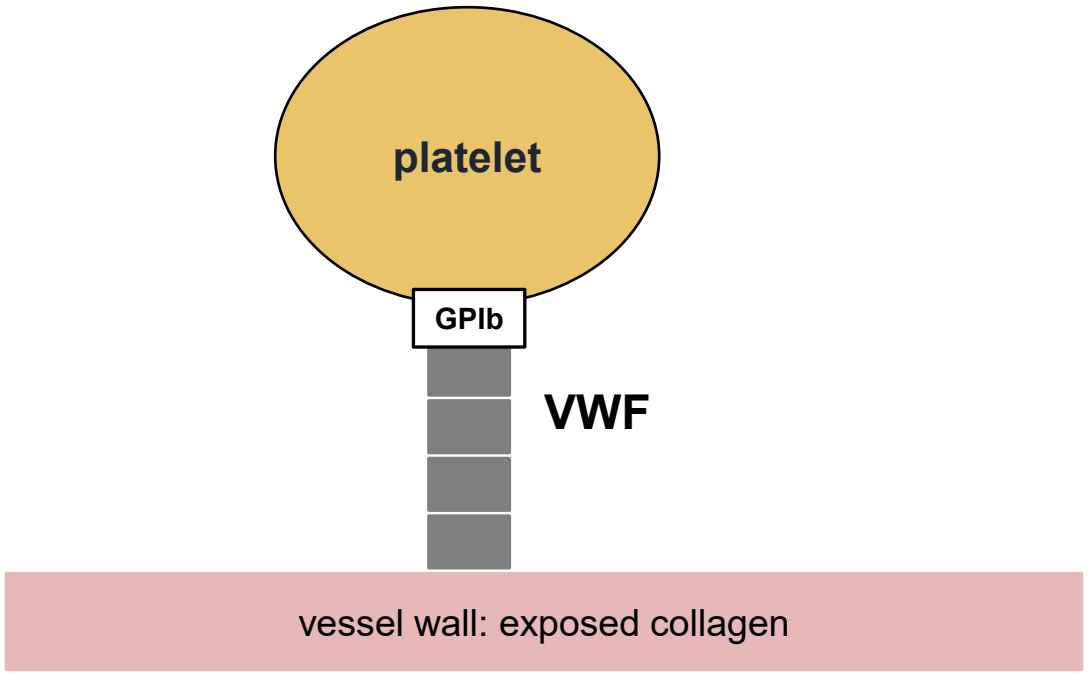
Too little VWF, working normally: **type 1 pattern**

Why is FVIII low? Why is the aPTT normal? Who in the family should be tested?

Managed with hematology: raise VWF or protect the clot

Von Willebrand factor

1. Glues platelets to the wound



2. Carries and protects factor VIII

- Little VWF → FVIII cleared fast → FVIII low → aPTT may be long
- Mild VWD: platelet pattern (nosebleeds, bruising, heavy periods)
- Type 3: FVIII very low; joint bleeds, like hemophilia

VWD: diagnosis

Result	Meaning
VWF < 0.30 IU/mL	VWD, whatever the bleeding history
VWF < 0.50 IU/mL	VWD if bleeding is abnormal
Activity / antigen < 0.7	Type 2 (protein does not work)

- Activity: newer GPIb-binding assays (VWF:GPIbM) preferred to ristocetin cofactor
- Cut-offs agreed by a panel; levels lower in blood group O

ASH/ISTH/NHF/WFH 2021 (James et al.)

VWD: types

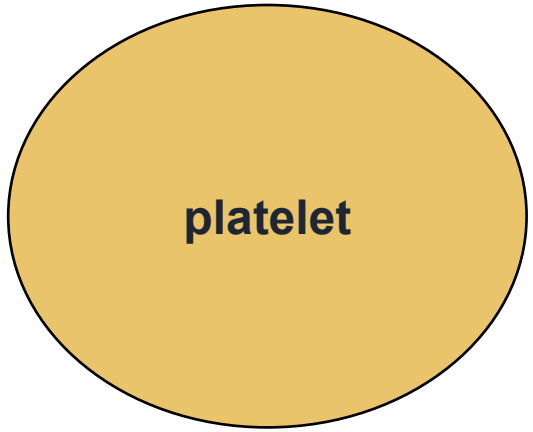
Type	Defect	Notes
1	Too little VWF, works normally	Most patients; usually mild
2A	Large multimers absent	Binds platelets poorly
2B	“Bonus”: binds platelets too well	Low platelet count
2M	“Minus”: binds platelets poorly	Multimers normal
2N	“No” FVIII binding	Low FVIII; mimics hemophilia A
3	Almost no VWF	Severe; FVIII very low

Low VWF on testing about 1 in 100; clinically significant VWD about 1 in 1,000 to 1 in 10,000 (Castaman 2026). Saudi Arabia: 651 registered with VWD (WFH 2023), a registry count.

Platelet function disorders

GPIb
→ Bernard-Soulier

GPIIb/IIIa
→ Glanzmann



COX
→ aspirin

P2Y12
→ antiplatelet drugs

Inherited (rare)

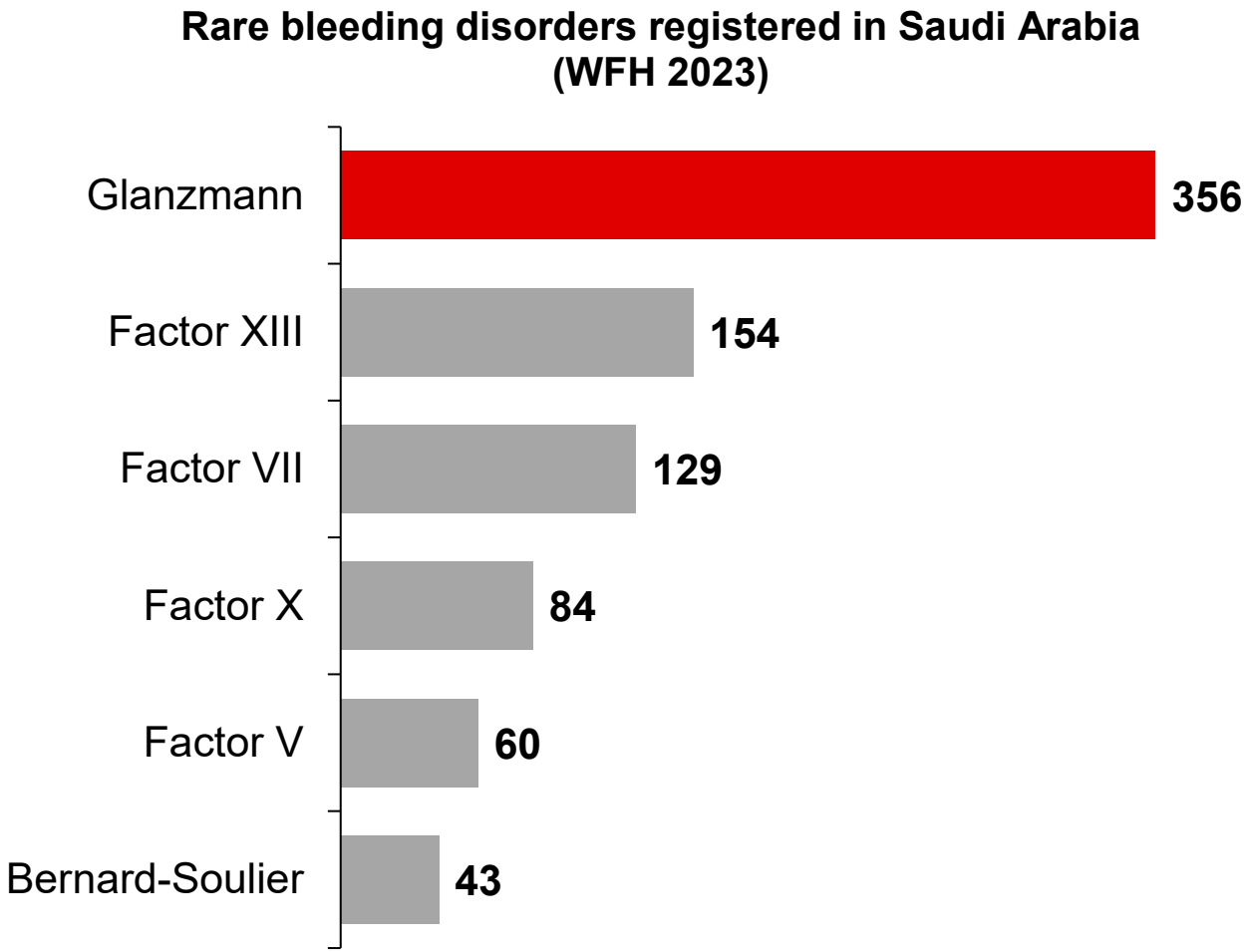
- Glanzmann: GPIIb/IIIa; normal count and size; no aggregation
- Bernard-Soulier: GPIb; large platelets, count a little low
- Storage pool defects

Acquired (common)

- Aspirin (7 to 10 days), P2Y12 blockers, NSAIDs
- Kidney failure, liver disease, bypass, MPN

Test: light transmission aggregometry

Glanzmann thrombasthenia



- Recessive: clusters where relatives marry (Lecture 1)
- Think of it: heavy periods from menarche, normal count, screen and VWF
- Refer for aggregometry

Case 2

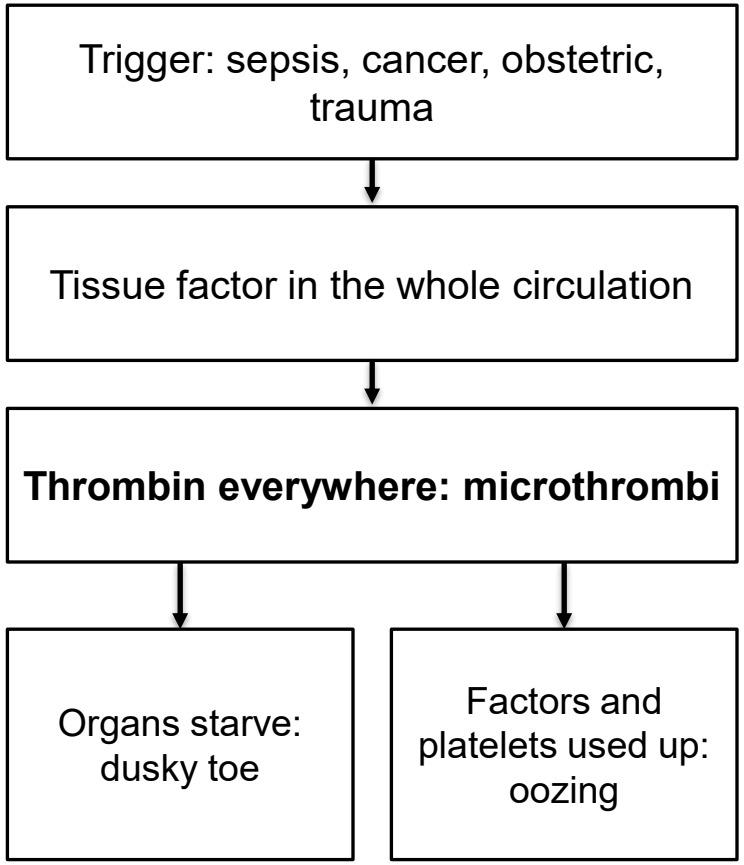
A patient in intensive care with sepsis.

- Oozing from the cannula sites
- One toe has turned dusky

Test	Result
Platelets	40 ×10⁹/L
INR	1.6
Fibrinogen	1.8 g/L
Fibrinogen, 2 days ago	4.2 g/L

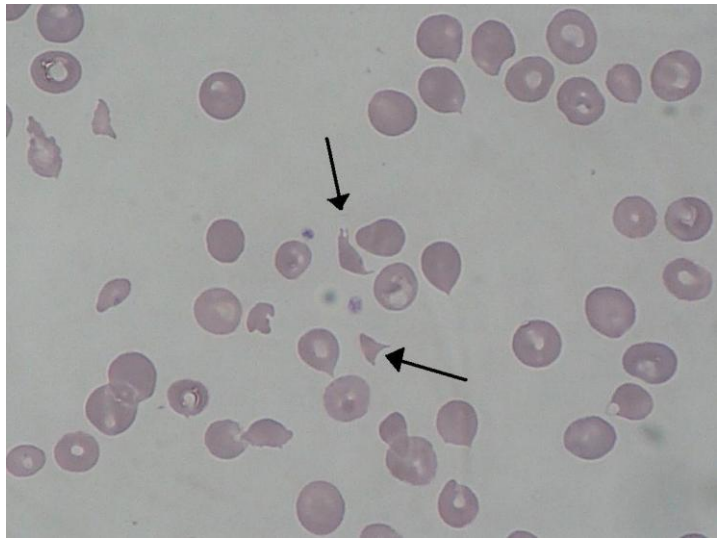
- Why does the same patient bleed and clot at once?
- Why is a fibrinogen of 1.8 worrying?

DIC: mechanism



Test	Finding
PT, aPTT	Long
Fibrinogen	Falling
Platelets	Falling
D-dimer	High
Film	Schistocytes

Repeat the tests: the trend makes the diagnosis



Schistocytes

Paulo Henrique Orlandi Mourão, Wikimedia Commons, CC BY-SA 3.0

DIC: causes

- Sepsis
- Cancer, especially acute promyelocytic leukemia
- Obstetric: abruption, amniotic fluid embolism, severe pre-eclampsia, retained dead fetus
- Major trauma, burns, heatstroke
- Envenomation, including snakebite
- Hemolytic transfusion reaction

Treatment: treat the cause

Schistocytes and low platelets

	TTP	HUS	DIC
Defect	Severe ADAMTS13 deficiency	Shiga toxin, or complement	Clotting switched on by another illness
Patient	Adult, often a young woman	Child after bloody diarrhea	Sepsis, cancer, trauma, obstetric
Organ	Brain and heart	Kidney	Variable: bleeding and clotting
PT, aPTT, fibrinogen	**Normal**	**Normal**	**Long; fibrinogen falling; D-dimer high**
Urgency	Emergency: hematology today	Supportive care	Treat the cause

Case 3

On warfarin, nosebleed

PT long, INR above target; no liver disease

- Warfarin blocks vitamin K: II, VII, IX, X not finished
- Liver healthy: PT corrects with vitamin K
- Deficiency: poor diet, malabsorption, antibiotics

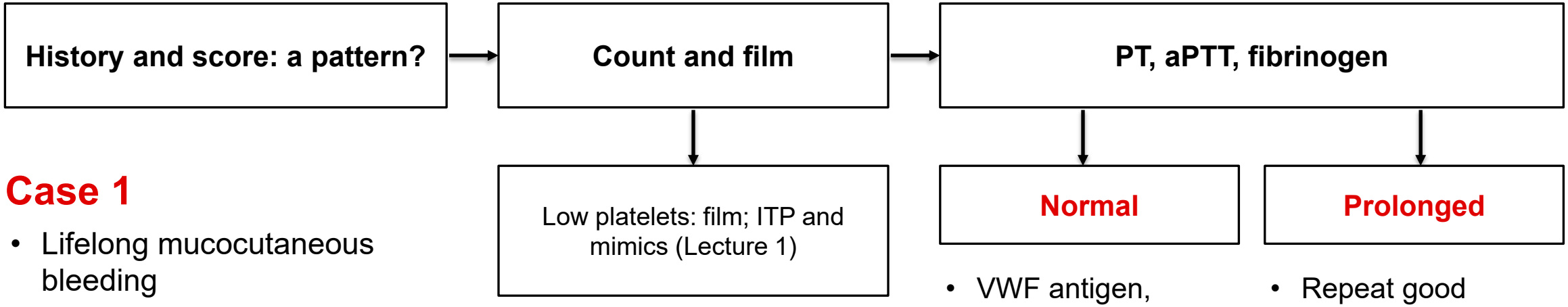
Cirrhosis, before paracentesis

PT long, INR raised; not bleeding

- Vitamin K does not fully correct: synthesis lost
- Fewer brakes made too: balance reset

INR does not measure her bleeding risk

Work-up summary



Case 1

- Lifelong mucocutaneous bleeding
- Normal count, PT, aPTT
- VWF low, activity in proportion

Type 1 VWD

- VWF antigen, activity, FVIII
- Platelet function
- Factor XIII

- Repeat good sample
- Mix: now and incubated
- Factor assay or inhibitor

Read next

Hematology Handbook: ch 21, 23, 24, 25, 29

Casebook: Case 53 (The Bleeding Patient); Case 51, section 6 (DIC)

Free book: Bloody Easy Coagulation Simplified, 2nd edition (Lin, Selby and colleagues)

Thrombosis: handbook ch 26; VTE again in Med-2