“Recognizing and Managing Acute Haematological Problems for General Physicians”

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Aim and Methods:

- How to recognize and prioritise the problems
- More general approach
- Mainly clinical (and a bit of academic)
- Not all cases are real cases
- TWO WAY discussion

Case (1):

- 68 year old
- On admissi
  guarding.
- CT abdome
- Blood on ac

Normal Values:

Hb 120 – 165 g/L (female)	PT 11.0 – 13.5 sec	Bili 1-17 umol/L
130 – 175 g/L (male)	APTT 26.0 – 36.5 sec	ALT <50 U/L
MCV 82 – 101 fL	Fibrinogen 1.5 – 3.5	ALP 30 – 130 U/L
WBC 4 – 11 x10^9/L	D-Dimer <500 ng/ml	Na 136 -145 mmol/L
Neu 1.8 – 7.5 x10^9/L	CRP <5mg/L	K 3.5 – 5.0 mmol/L
Lym 1.0 – 4.0 x10^9/L	PCT <0.05 ng/ml	Urea 2.5 – 7.0 mmol/L
Plt 150 – 440 x10^9/L	Alb 35 – 50 g/L	Creat 50 – 117 umol/L

- Auto CP

  Hb 110

  MCV 87

  WBC 16.8

  Neu 12.4

  Plt 468

- Coagulation

  PT 14.5

  APTT 38.5

  Fibrinogen 1.8

  D-Dimer 540

- Biochemistry

  Bili 19

  ALT 54

  Alb 22

  Urea 12.8

  Creat 86

  CRP 256

- Surgical exploration a
- Post surgery -Persiste re-exploration.
- Patient required ITU a
- Blood culture: E.coli -
- Blood (Day 7 post surgery):

Normal Values:

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130 – 175 g/L (male)	APTT 26.0 – 36.5 sec	ALT <50 U/L
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Plt 150 – 440 $x10^9$/L	Alb 35 – 50 g/L	Creat 50 – 117 umol/L

- Auto CP

Hb 97
WBC 3.8
Neu 1.8
Plt 56

- Coagulation

PT 26.4
APTT 48.8
Fibrinogen 0.9
D-Dimer 1200

- Biochemistry

Bili 32
ALT 72
Alb 20
Urea 12.8
Creat 188
CRP 380
PCT 2.2

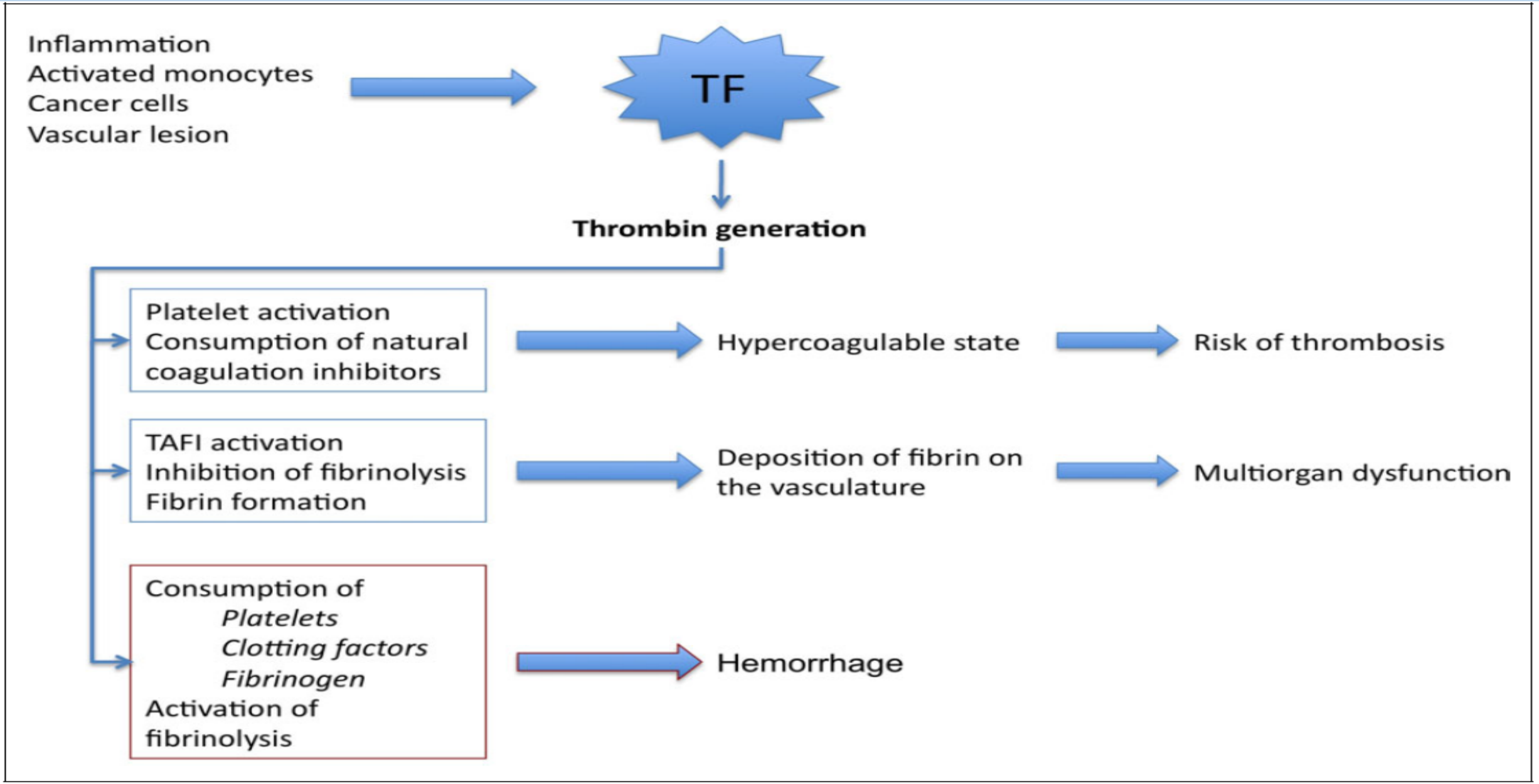
Problems:

- Sepsis
- Multiorgans failure
- Pancytopenia
- DIC

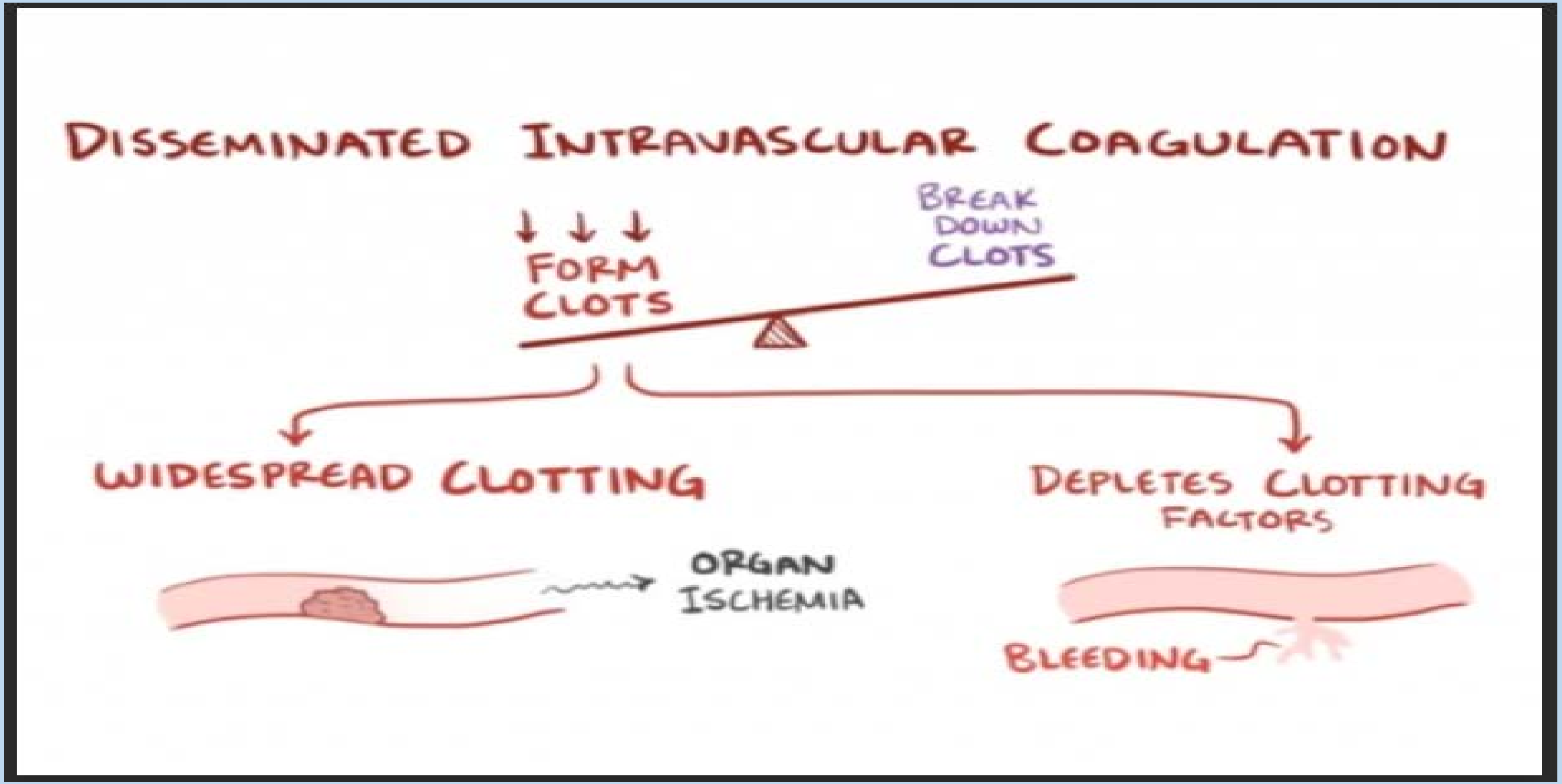
What would you do next (from haematology point of view)?

- Pancytopenia
- DIC

Mechanism of DIC



DIC Equilibirium



ISTH Diagnostic Scoring System for DIC

Table II. ISTH Diagnostic Scoring System for DIC.

Scoring system for overt DIC

Risk assessment: Does the patient have an underlying disorder known to be associated with overt DIC?

If yes: proceed

If no: do not use this algorithm

Order global coagulation tests (PT, platelet count, fibrinogen, fibrin related marker)

Score the test results

- Platelet count ($>100 \times 10^9$/l = 0, $<100 \times 10^9$/l = 1, $<50 \times 10^9$/l = 2)
- Elevated fibrin marker (e.g. D-dimer, fibrin degradation products) (no increase = 0, moderate increase = 2, strong increase = 3)
- Prolonged PT (<3 s = 0, >3 but <6 s = 1, >6 s = 2)
- Fibrinogen level (>1 g/l = 0, <1 g/l = 1)

Calculate score:

≥5 compatible with overt DIC: repeat score daily

<5 suggestive for non-overt DIC: repeat next 1–2 d

Management:

- Treat Underlying Cause
- Maintain DIC equilibrium
- Only treat if there is Unbalanced DIC
  - Laboratory
  - Clinical
  - Prophylatic

Case (2):

- 52 year old
  cough, SOB
- Background
- Unwell on a
  84% on roo
- Covid-19 sw
- Blood: Hb 157 PT 19.8 Urea 11.4 CRP 210
  WBC 14.2 APTT 42.8 Creat 110 PCT 0.8
  Neu 8.6 Fibrinogen 2.1 Bili 34
  Lym 1.4 D-Dimer 2600 ALT 67
  Plt 520 Alb 32

Normal Values:

Hb 120 – 165 g/L (female)	PT 11.0 – 13.5 sec	Bili 1-17 umol/L
130 – 175 g/L (male)	APTT 26.0 – 36.5 sec	ALT <50 U/L
MCV 82 – 101 fL	Fibrinogen 1.5 – 3.5	ALP 30 – 130 U/L
WBC 4 – 11 $x10^9$/L	D-Dimer <500 ng/ml	Na 136 -145 mmol/L
Neu 1.8 – 7.5 $x10^9$/L	CRP <5mg/L	K 3.5 – 5.0 mmol/L
Lym 1.0 – 4.0 $x10^9$/L	PCT <0.05 ng/ml	Urea 2.5 – 7.0 mmol/L
Plt 150 – 440 $x10^9$/L	Alb 35 – 50 g/L	Creat 50 – 117 umol/L

Covid-19 Coagulopathy (Immunogenic thrombosis)

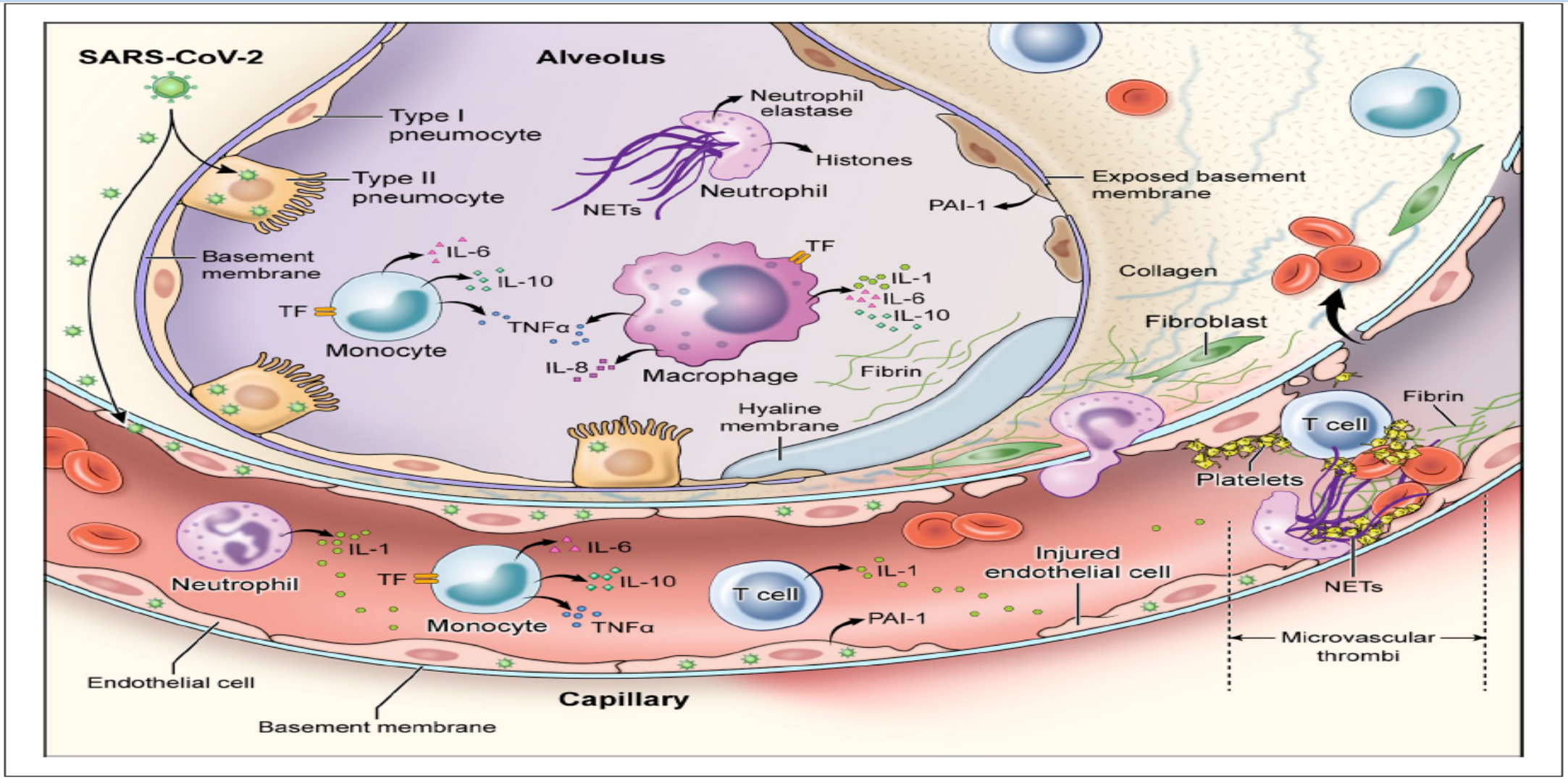
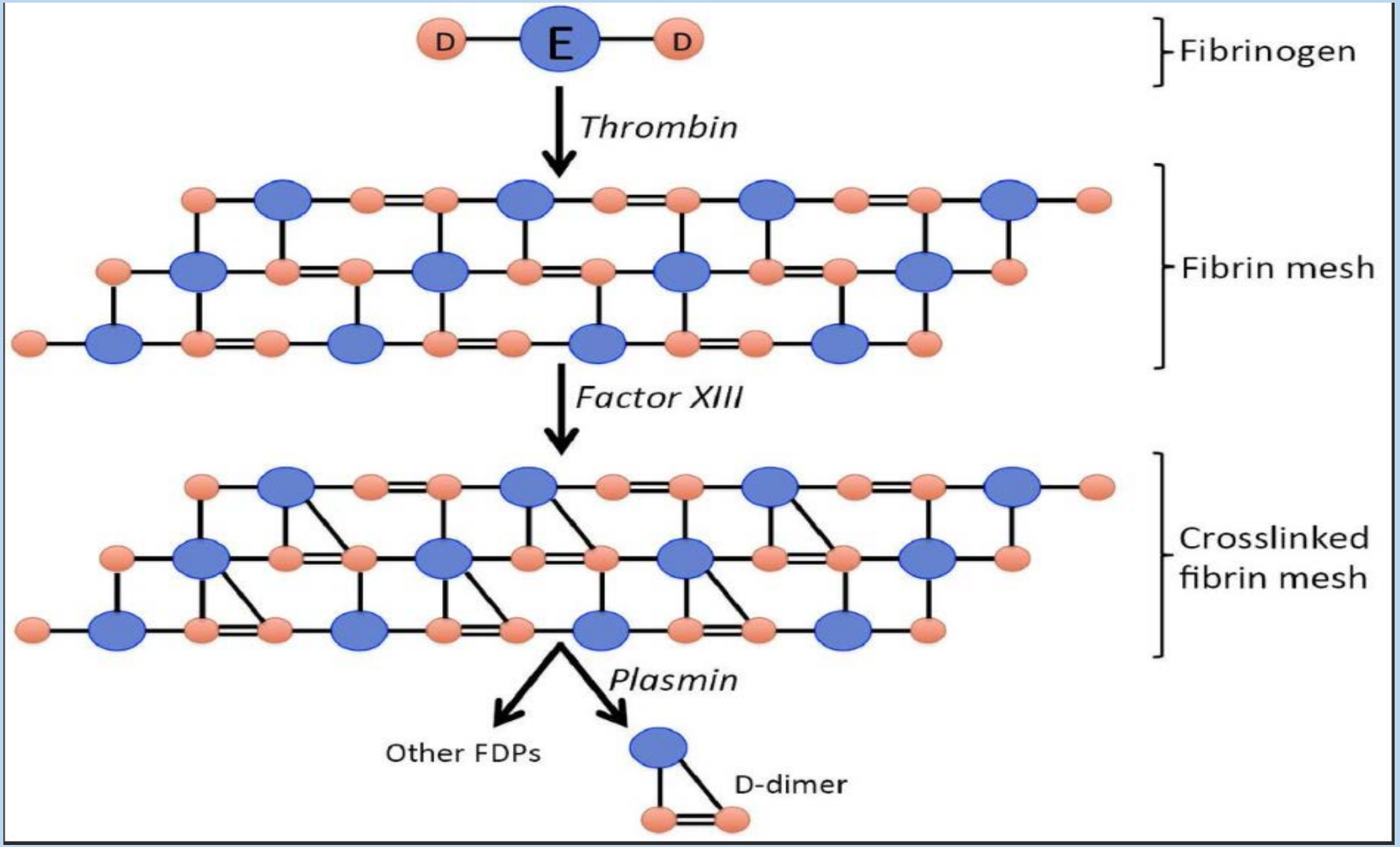


Figure 1. Immune activation and mechanisms of coagulopathy in patients with coronavirus disease 2019 (COVID-19).
Multiple processes may contribute to COVID-19-associated coagulopathy including direct infection of type II pneumocytes and endothelial cells, leading to barrier dysfunction and increased permeability; inflammatory responses characterized by activation of T cells, neutrophils, monocytes, macrophages, and platelets resulting in exuberant inflammatory cytokine release (including IL-1, IL-6, IL-10, TNF-α), monocyte-derived TF and PAI-1 expression; and culminating in the development of microvascular and macrovascular thrombi composed of fibrin, NETs, and platelets.
IL, interleukin; NETs, neutrophil extracellular traps; PAI-1, plasminogen activator inhibitor-1; TF, tissue factor; TNF-α, tumor necrosis factor-alpha.

Fibrinogen and D-Dimer



- **Interim ISTH guideline**:

  - Prophylatic / Intermediate/treatment dose of LMWH in

    Critically ill Patient

    Significantly raised D-Dimer

    Non-bleeding patient with DIC

    (20% reduction in mortality)

D-Dimer	Weight	LMWH
<1000	<100kg	Enoxaparin 40mg OD
	100-150kg	Enoxaparin 40mg BD
	>150kg	Enoxaparin 60mg BD
1000-3000	<100kg	Enoxaparin 40mg BD
	100-150kg	Enoxaparin 80mg BD
	>150kg	Enoxaparin 120mg BD
>3000	<100kg	Enoxaparin 1.5mg/kg OD

Case (3):

- 62 year old
- Backgrounc
- Medication
- O/E: GCS 9/
- ECG: fast Al
- Blood: Hb 96 PT 25 Urea 12.4 Bili 60 Troponin T 20
  WBC 14.8 APTT 42 Creat 224 ALT 48
  Neu 8.8 Fibrinogen 1.4 K 5.0 ALP 146
  Plt 32 D-Dimer 860 Na 142 Alb 30
- CT Head – No bleeding, probable acute ischemic changes (but not diagnostic)

Normal Values:

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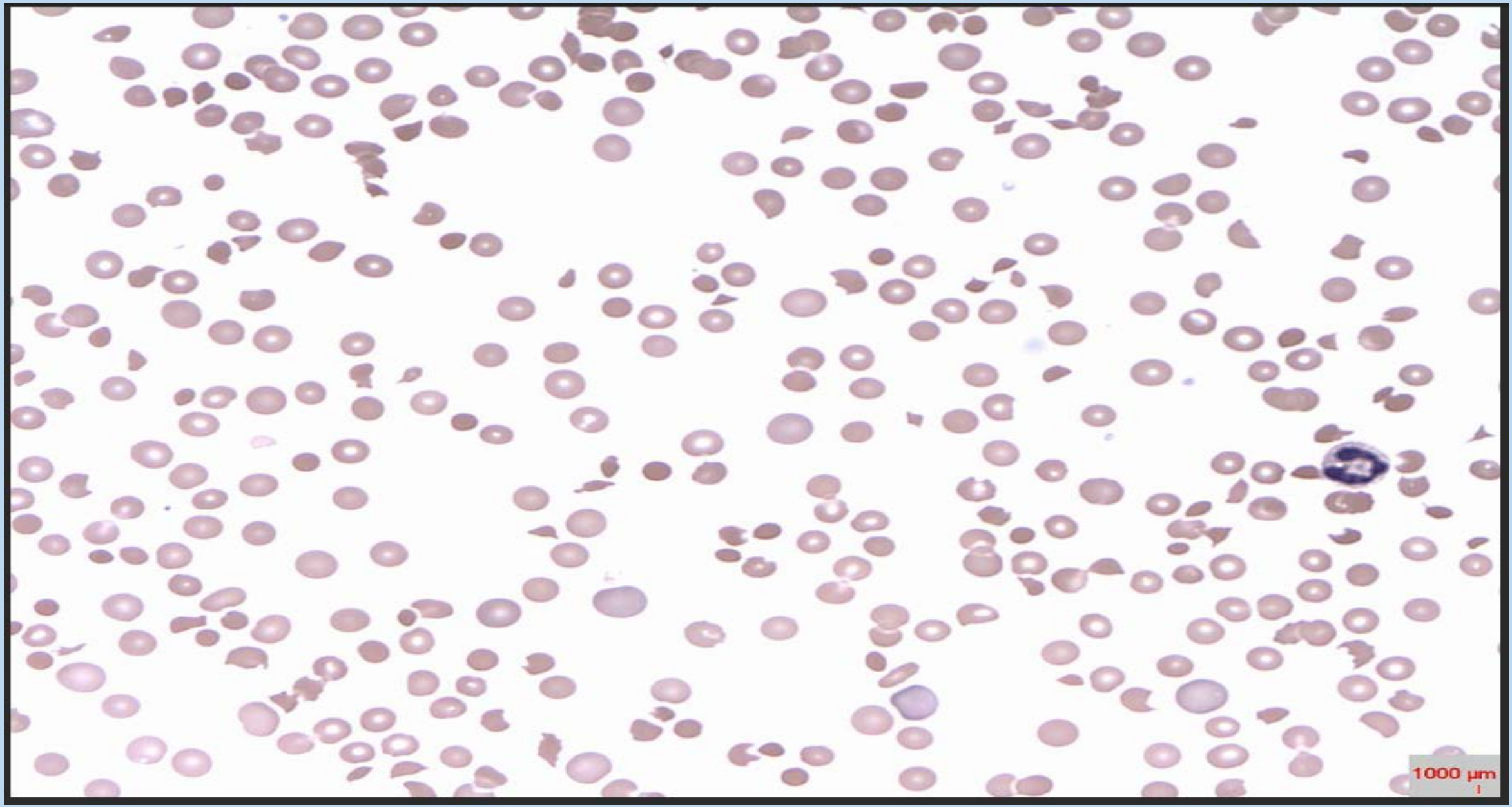
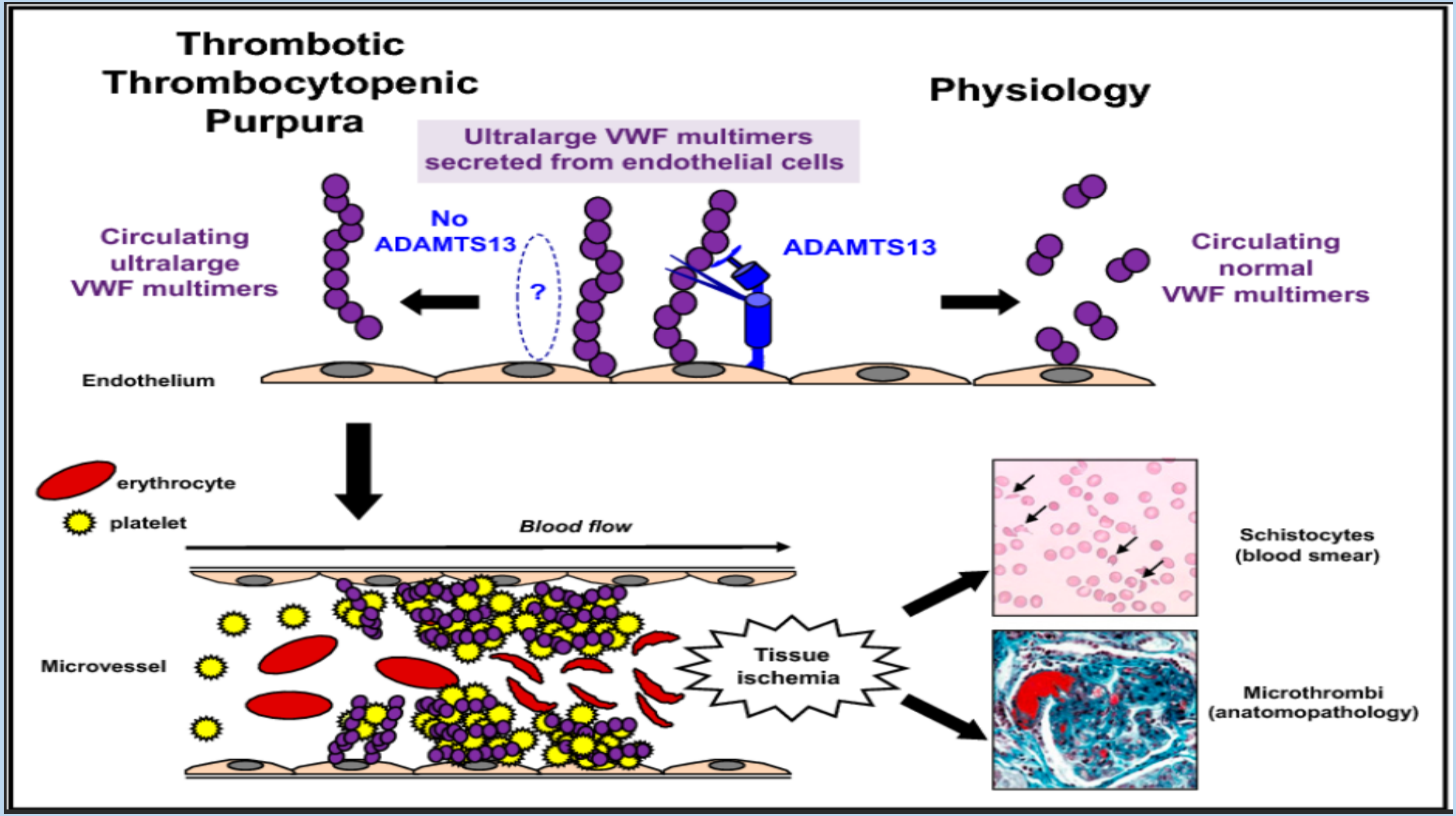
MCV 82 – 101 fL	Fibrinogen 1.5 – 3.5	ALP 30 – 130 U/L
WBC 4 – 11 $x10^9$/L	D-Dimer <500 ng/ml	Na 136 -145 mmol/L
Neu 1.8 – 7.5 $x10^9$/L	CRP <5mg/L	K 3.5 – 5.0 mmol/L
Lym 1.0 – 4.0 $x10^9$/L	PCT <0.05 ng/ml	Urea 2.5 – 7.0 mmol/L
Plt 150 – 440 $x10^9$/L	Alb 35 – 50 g/L	Creat 50 – 117 umol/L

Blood Film



Microangiopathic Haemolytic Anaemia (MAHA)

Pathophysiology of TTP



Investigation:

- ADAMTS13 level
- ADAMTS13 Inhibitor
- Look for causes: - Malignancy
  - Autoimmune

Management:

- Acute Haematological Emergency
- ?Platelet transfusion
- Eradication of ultralarge VWF multimer (or) antibody
  - Plasma Exchange
  - Dilution with FFP
  - Steroid (Methyl Prednisolone)
  - Rituximab (anti-CD20 monoclonal antibody)
  - Caplacizumab (VWF directed antibody fragment)

Case (4):

- 32 year old
  forearms. N
- Previously fi
  history but h
  sometimes e
- O/E: no brui
  no palpable

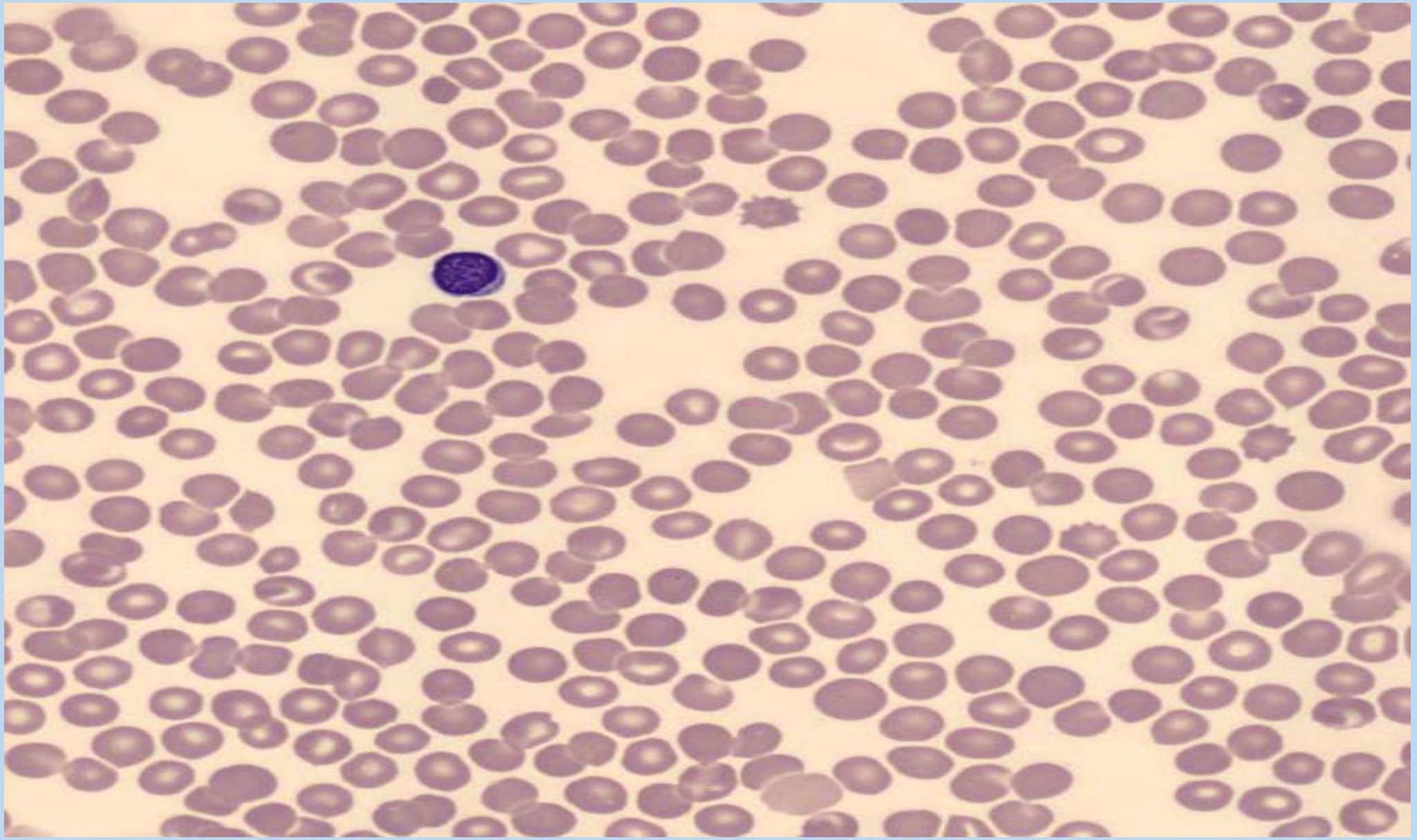
Normal Values:

Hb 120 – 165 g/L (female)	PT 11.0 – 13.5 sec	Bili 1-17 umol/L
130 – 175 g/L (male)	APTT 26.0 – 36.5 sec	ALT <50 U/L
MCV 82 – 101 fL	Fibrinogen 1.5 – 3.5	ALP 30 – 130 U/L
WBC 4 – 11 x10^9/L	D-Dimer <500 ng/ml	Na 136 -145 mmol/L
Neu 1.8 – 7.5 x10^9/L	CRP <5mg/L	K 3.5 – 5.0 mmol/L
Lym 1.0 – 4.0 x10^9/L	PCT <0.05 ng/ml	Urea 2.5 – 7.0 mmol/L
Plt 150 – 440 x10^9/L	Alb 35 – 50 g/L	Creat 50 – 117 umol/L

- Blood:

Hb 135	PT 14.5	Urea 7.8	Bili 56
WBC 11.2	APTT 36.2	Creat 66	ALT 34
Neu 7.2	Fibrinogen 2.4	K 3.8	ALP 145
Lym 3.4	D-Dimer 240	Na 144	Alb 38
Plt 4			

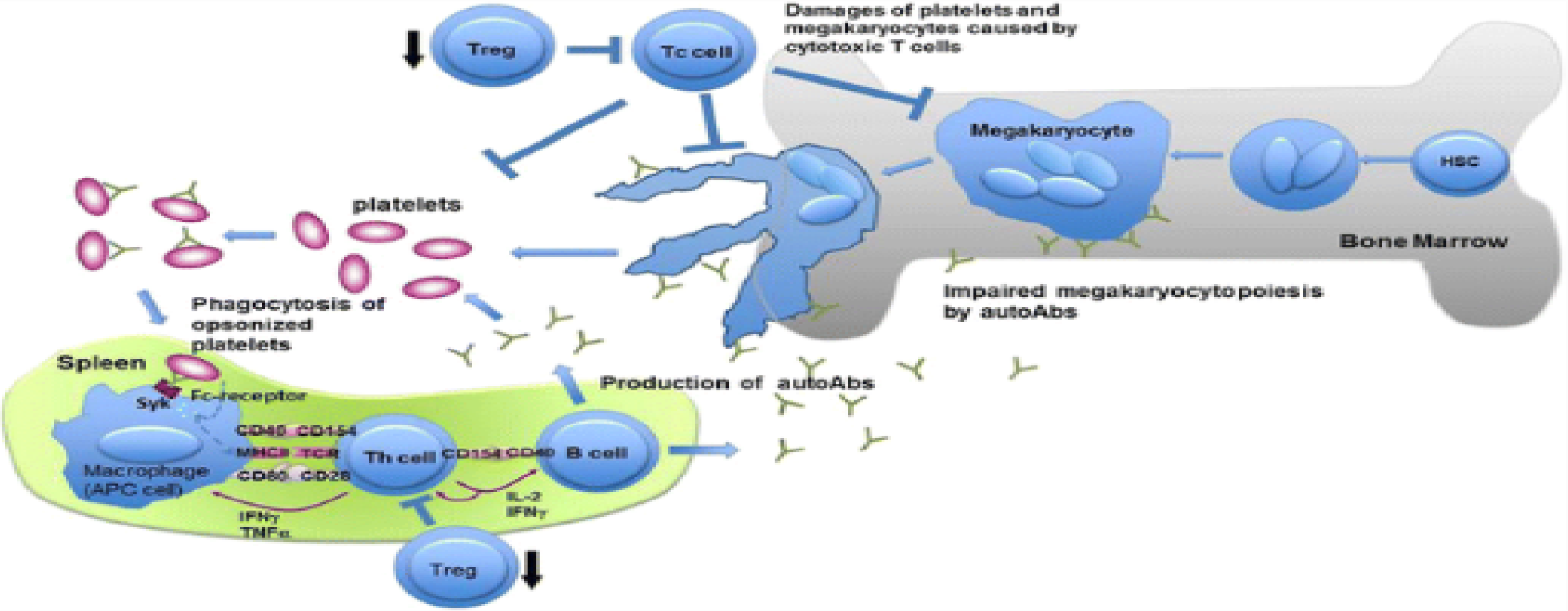
Blood Film



ISTH Recommendation in the diagnosis work up for ITP

Basic evaluation	Tests of potential utility in the management of an ITP patient	Tests of unproven or uncertain benefit
- Patient history	- Glycoprotein-specific antibody	- TPO
- Family history	- Antiphospholipid antibodies (including anticardiolipin and lupus anticoagulant)	- Reticulated platelets
- Physical examination	- Antithyroid antibodies and thyroid function	- PaIgG
- Complete blood count and reticulocyte count	- Pregnancy test in women of childbearing potential	- Platelet survival study
- Peripheral blood film	- Antinuclear antibodies	- Bleeding time
- Quantitative immunoglobulin level measurement*	- Viral PCR for parvovirus and CMV	- Serum complement
- Bone marrow examination (in selected patients; refer to text)		
- Blood group (Rh)		
- Direct antiglobulin test		
- *H pylori*†		
- HIV†		
- HCV†		

Pathophysiology of ITP



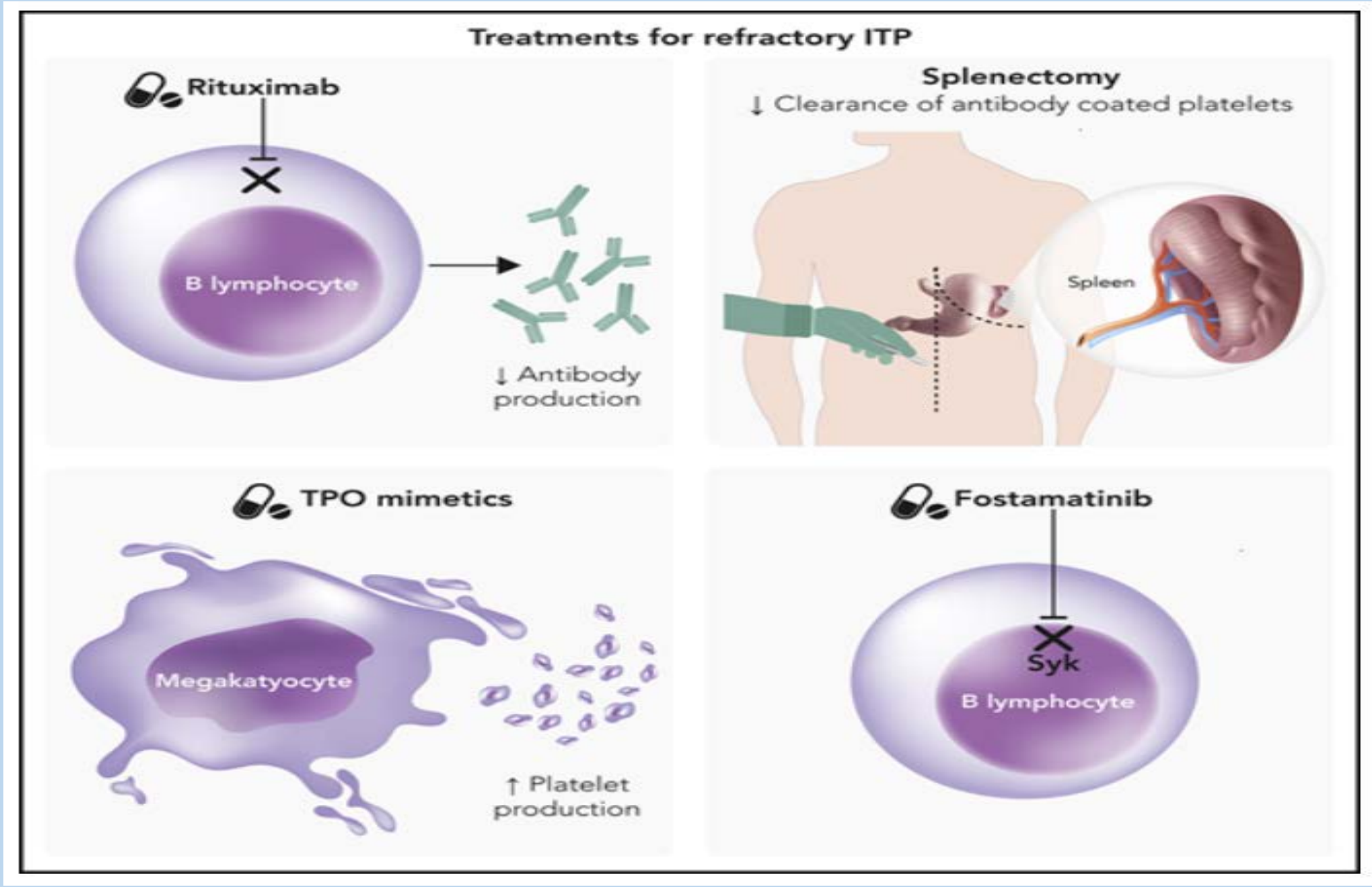
Schematic representation of pathophysiology of cITP. Opsonized platelets by autoantibodies are destroyed by macrophages in spleen and peptide fragments expressed with MHC class II stimulate helper T cells, following activation of autoreactive B cells. Impaired Tregs fail to suppress this vicious cycle. Autoantibodies also suppress megakaryocytopoiesis. Autoreactive cytotoxic T cells may play a role in the destruction of platelets and megakaryocytes. Thrombopoietin receptor (TPO-R) agonists stimulate megakaryocyte proliferation and maturation. Rituximab targets CD20-positive B cells

Acute treatment:

Predniso(lo)ne at 1 mg/kg (max dose 80 mg) for 2 weeks, to a **maximum of 3 weeks** Or **Dexamethasone** 40 mg/day for 4 days, repeated up to three times
If response seen, e.g. platelets >50 × 10^9/L, the predniso(lo)ne should be tapered, **aim to stop predniso(lo)ne by 6 weeks (maximum 8 weeks),** even if the platelet count drops during the taper **If there is no response to the initial dose within 2 weeks**, the predniso(lo)ne should be tapered rapidly over 1 week and stopped
Use of IVIg (1 g/kg on one or two consecutive days or 0.4 g/kg/day for 5 days), or IV anti-D (50–75 µg/kg) where available
TPO-RAs and rituximab are not considered initial therapies

- Mucosal bleeding - ivIg
- Platelet transfusion in life threatening bleeding

Treatment for Refractory ITP



Revised Consensus vs ASH guidelines

International Consensus Report	ASH guidelines
Diagnosis: little change	Diagnosis: little change
TPO-RA preferred subsequent treatment but consider rituximab and fostamatinib	TPO-RA second line
Consider Splenectomy only after failure of medical therapies	Splenectomy: patient preference
Earlier use TPO-RA	Earlier use TPO-RA
Limit corticosteroid exposure	Dexamethasone or prednisone Limit corticosteroid exposure
More aggressive treatment in paediatrics	
QoL plays role in decision-making	
Provan D, *et al. Blood Advances* **3**, 3780-3817 (2019)	Neunert C et al. *Blood Advances* **3**, 3829-3866 (2019)

Case (5)

- 71 year ol
- History of
- O/E: Thin
  bruises ov
- X-rays: No
- Blood: Hb 100 PT 13.3 Urea 10.2 Bili 22
  WBC 8.2 APTT 68 Creat 108 ALT 50
  Neu 5.2 Fibrinogen 1.9 K 4.4 ALP 186
  Plt 210 D-Dimer 800 Na 128 Alb 18

Normal Values:

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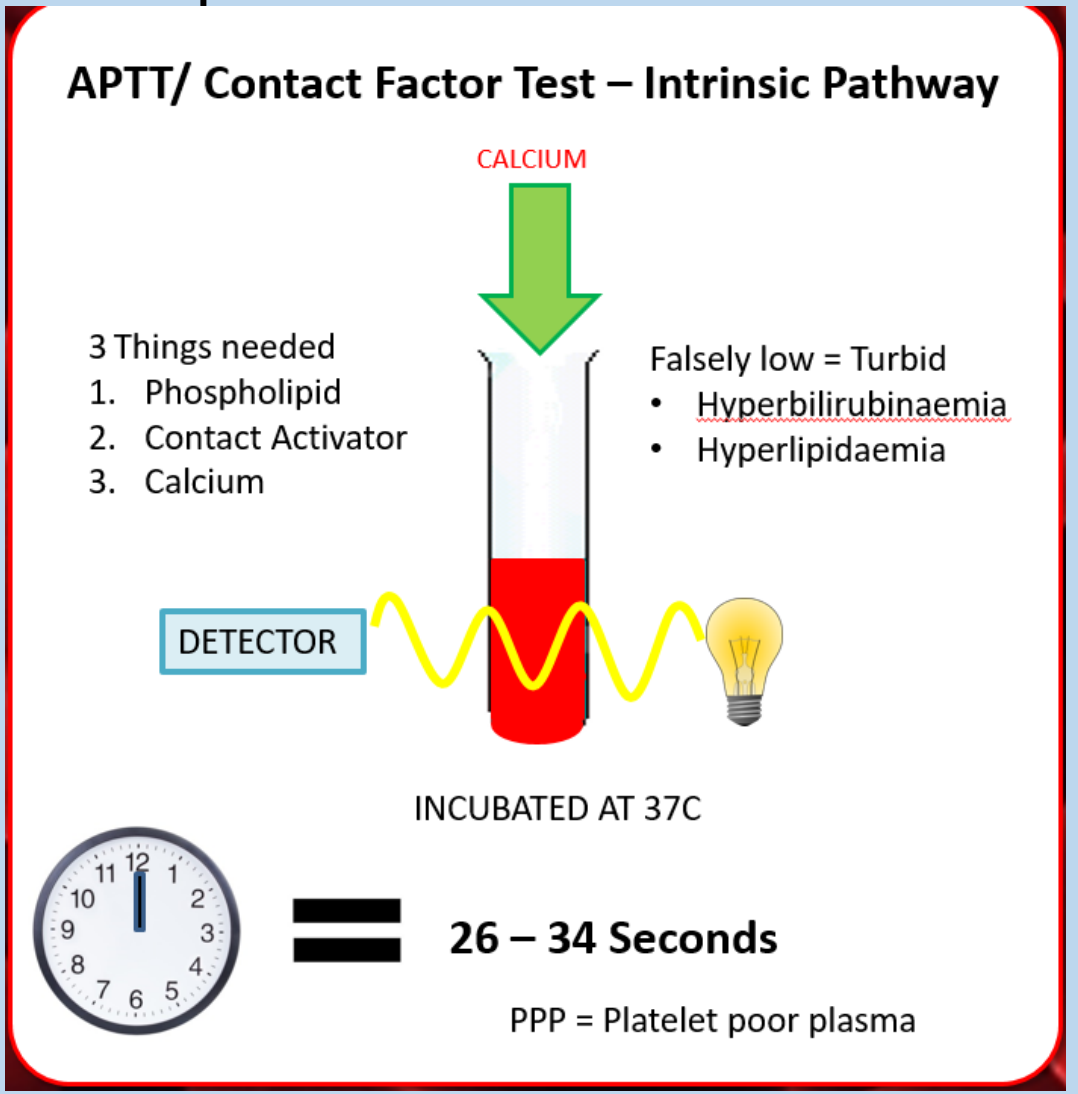
130 – 175 g/L (male)	APTT 26.0 – 36.5 sec	ALT <50 U/L
MCV 82 – 101 fL	Fibrinogen 1.5 – 3.5	ALP 30 – 130 U/L
WBC 4 – 11 $x10^9$/L	D-Dimer <500 ng/ml	Na 136 -145 mmol/L
Neu 1.8 – 7.5 $x10^9$/L	CRP <5mg/L	K 3.5 – 5.0 mmol/L
Lym 1.0 – 4.0 $x10^9$/L	PCT <0.05 ng/ml	Urea 2.5 – 7.0 mmol/L
Plt 150 – 440 $x10^9$/L	Alb 35 – 50 g/L	Creat 50 – 117 umol/L

APTT Measurement:

- Analyser

- Principle



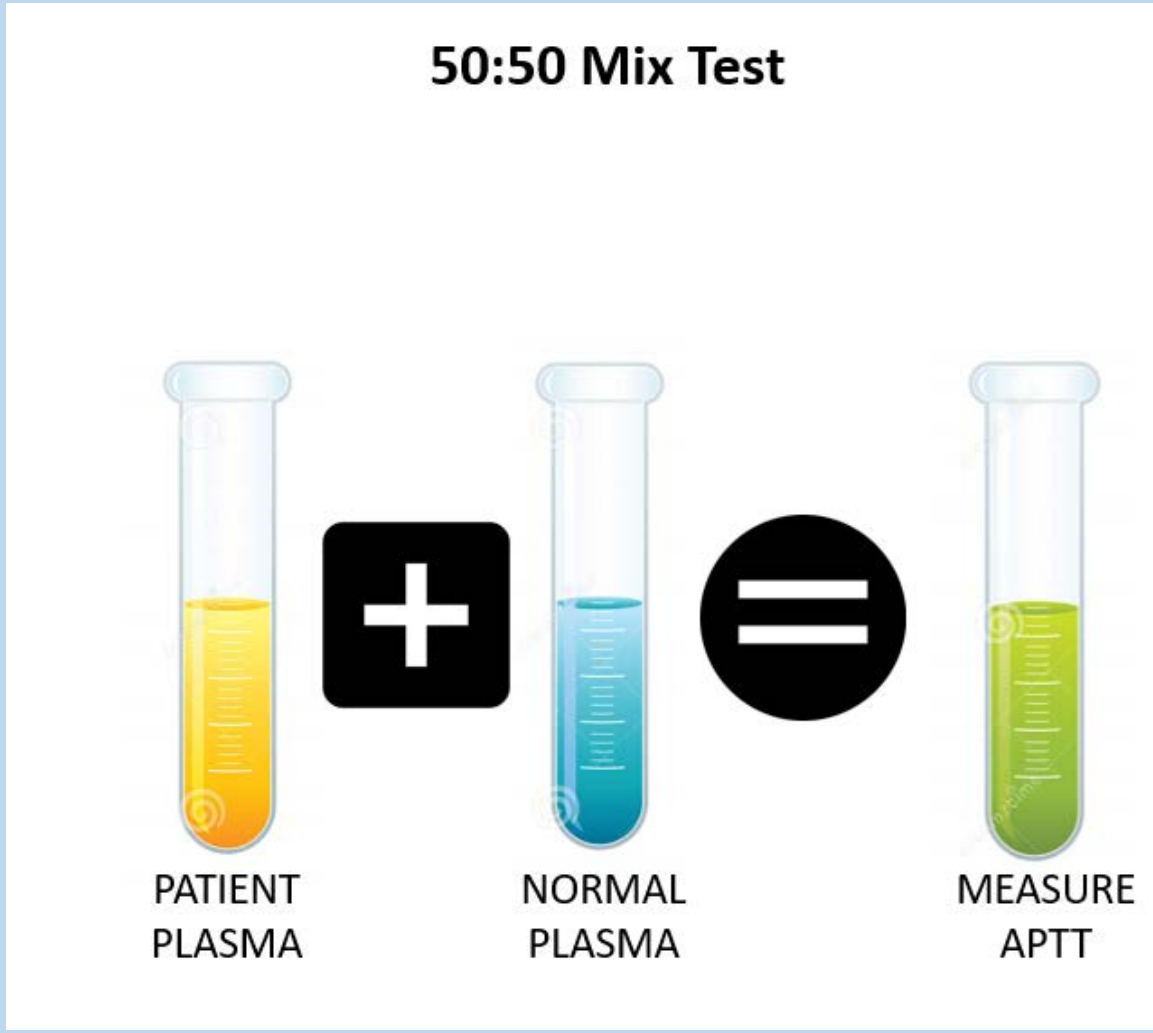
Prolonged APTT

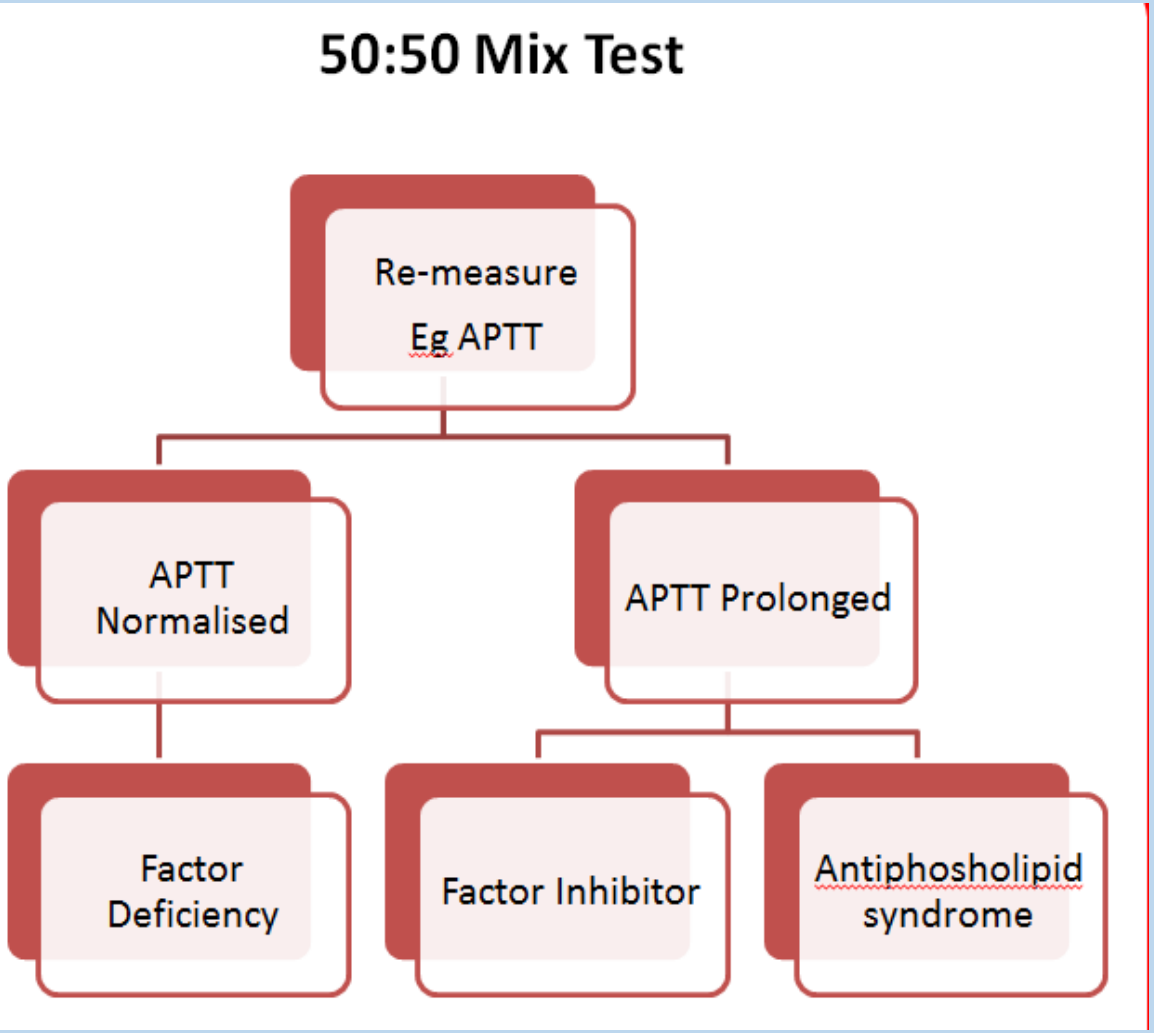
- Clotting Factors deficiency → bleeding (except Factor XII)
- Contact factors deficiency → no bleeding
- Inhibitors
  - Inhibitors to clotting factors → Bleeding
  - Inhibitor to phospholipid → No bleeding

Lupus Anticoagulant

Test – Addition of high concentration of phospholipid
OR
Use Lupus Insensitive Reagent (eg, Actin FS)

How would you Investigate?





- Factor VIII inhibitor – Time dependent
- Factor IX inhibitor – Time independent

- Back to the case:
  - 50:50 mix → APTT 28.7 sec (immediate mix at 37°C)
    → APTT 72 sec (2 hour post 50:50 mix incubated at 37°C)

- Diagnosis?

Acquired Haemophilia

- Investigation:
  - Factor VIII level, VWF level, Inhibitor Assay
  - Look for associated causes (Malignancy, Autoimmune, Rheumatoid Arthritis)

- Management:
  - Steroid (Methyl Prednisolone, Prednisolone)
  - Rituximab

Case (6):

- 52 year old female presentir
  exercise tolerance. No weigh
- O/E: conjuntivae- pale , tinge
  hepatospnenomegaly.
- Blood: Hb 56 PT 11.4 Urea 5.4 Bili 70
  WBC 8.4 APTT 32.1 Creat 40 ALT 35
  Neu 5.6 Fibrinogen 1.8 Na 138 ALP 186
  Plt 286 D-Dimer 1200 K 4.9 Alb 34

- What is the diagnosis?

  or

  What would you like to do?

Normal Values:

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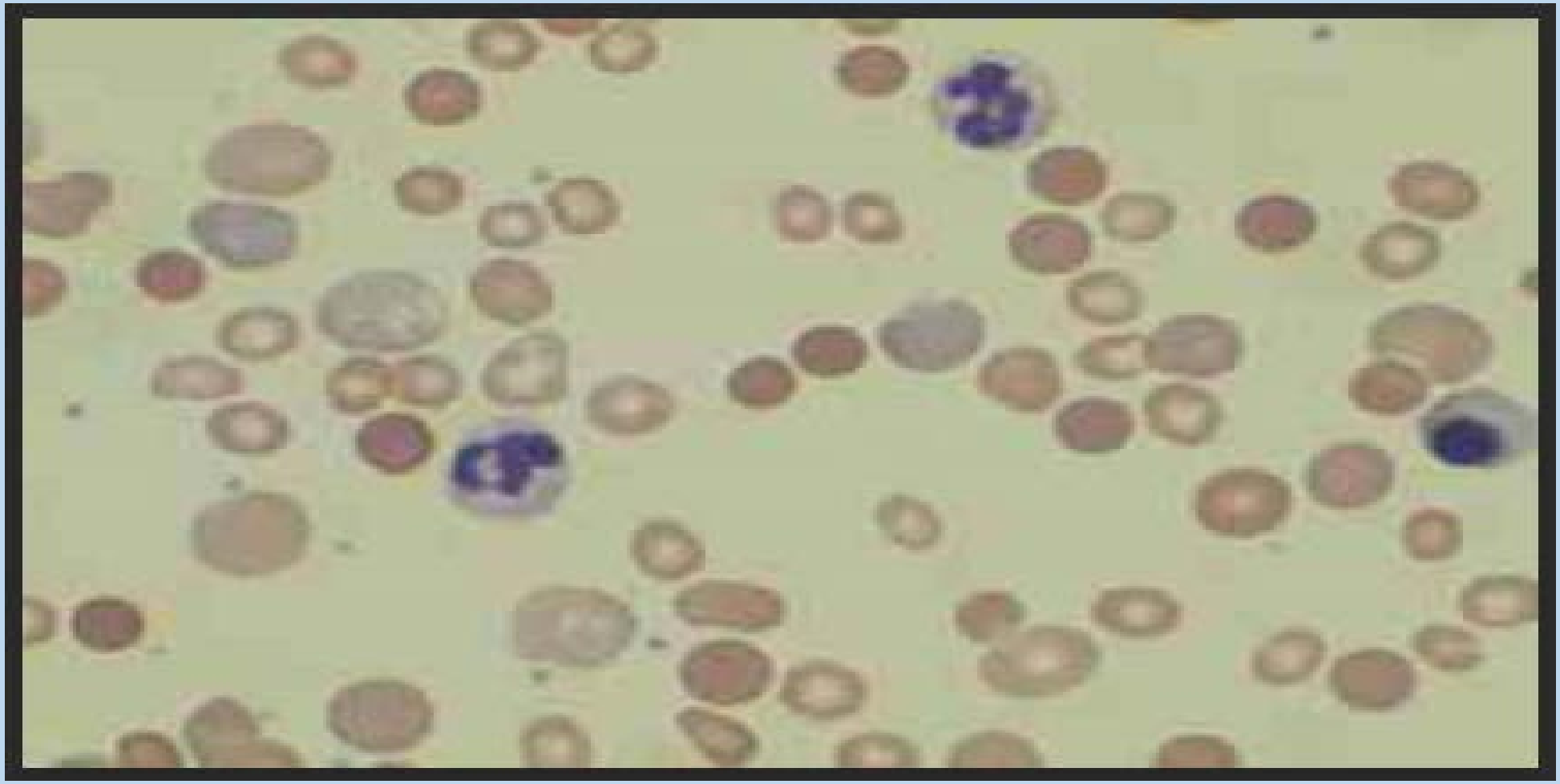
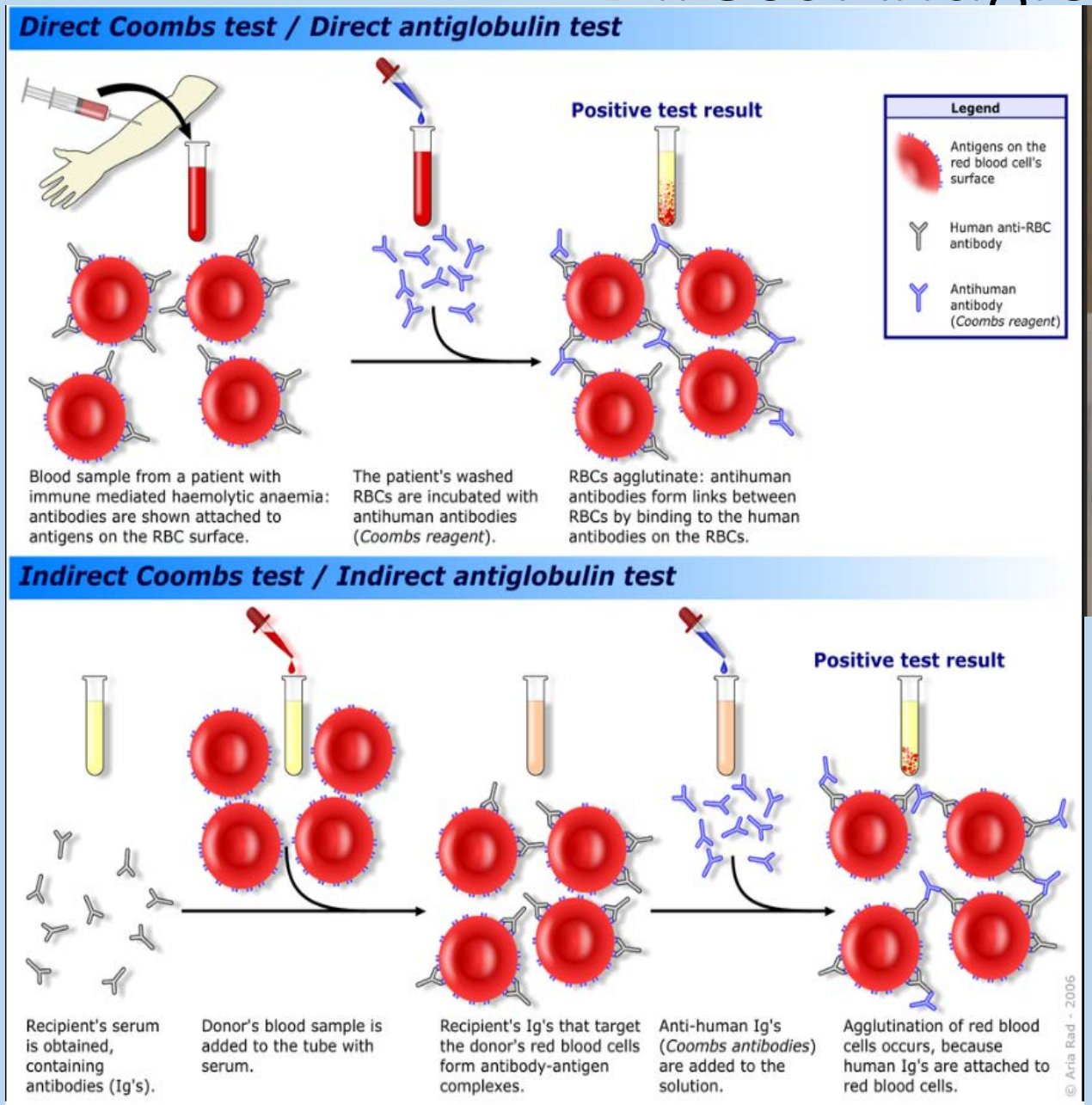
130 – 175 g/L (male)	APTT 26.0 – 36.5 sec	ALT <50 U/L
MCV 82 – 101 fL	Fibrinogen 1.5 – 3.5	ALP 30 – 130 U/L
WBC 4 – 11 $x10^9$/L	D-Dimer <500 ng/ml	Na 136 -145 mmol/L
Neu 1.8 – 7.5 $x10^9$/L	CRP <5mg/L	K 3.5 – 5.0 mmol/L
Lym 1.0 – 4.0 $x10^9$/L	PCT <0.05 ng/ml	Urea 2.5 – 7.0 mmol/L
Plt 150 – 440 $x10^9$/L	Alb 35 – 50 g/L	Creat 50 – 117 umol/L

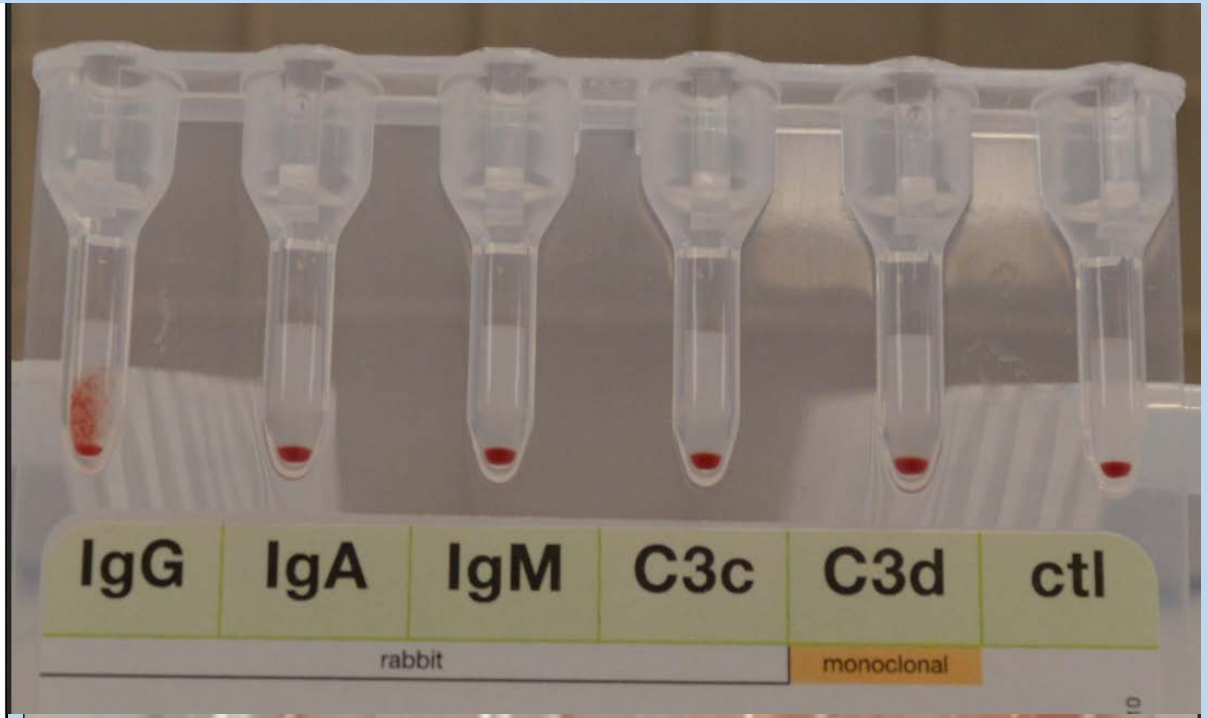
- Blood Film

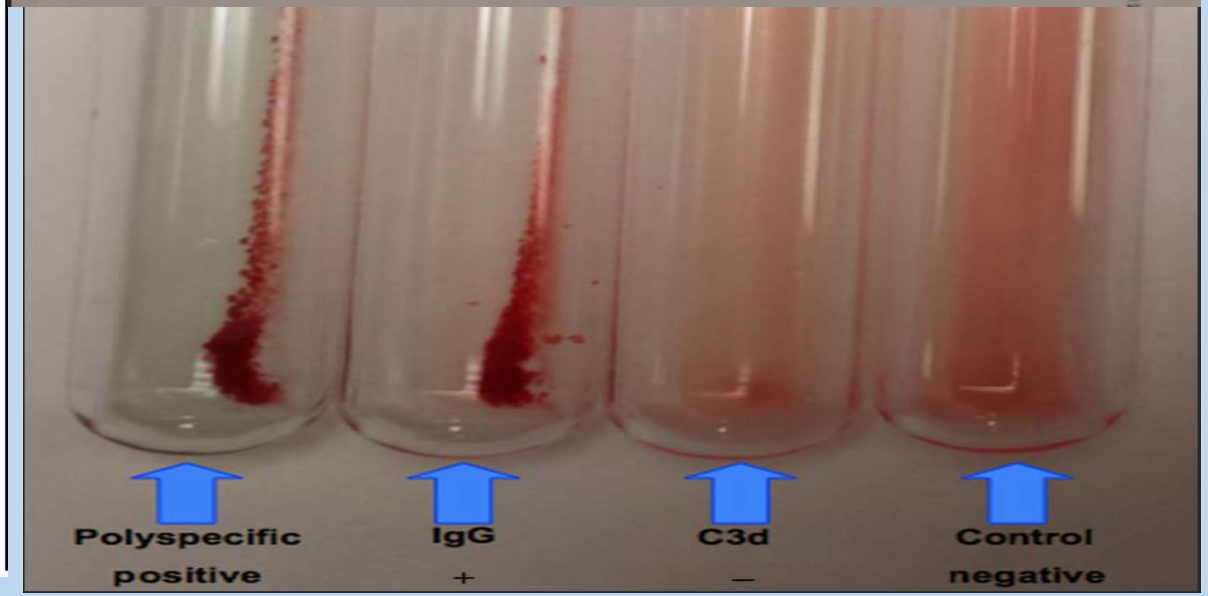


- Retic count – 380
- LDH – 655
- DAT (Direct Antiglobulin Test) in otherwards Direct Coomb’s test
- Heptoglobulin, Urinary haemosiderin

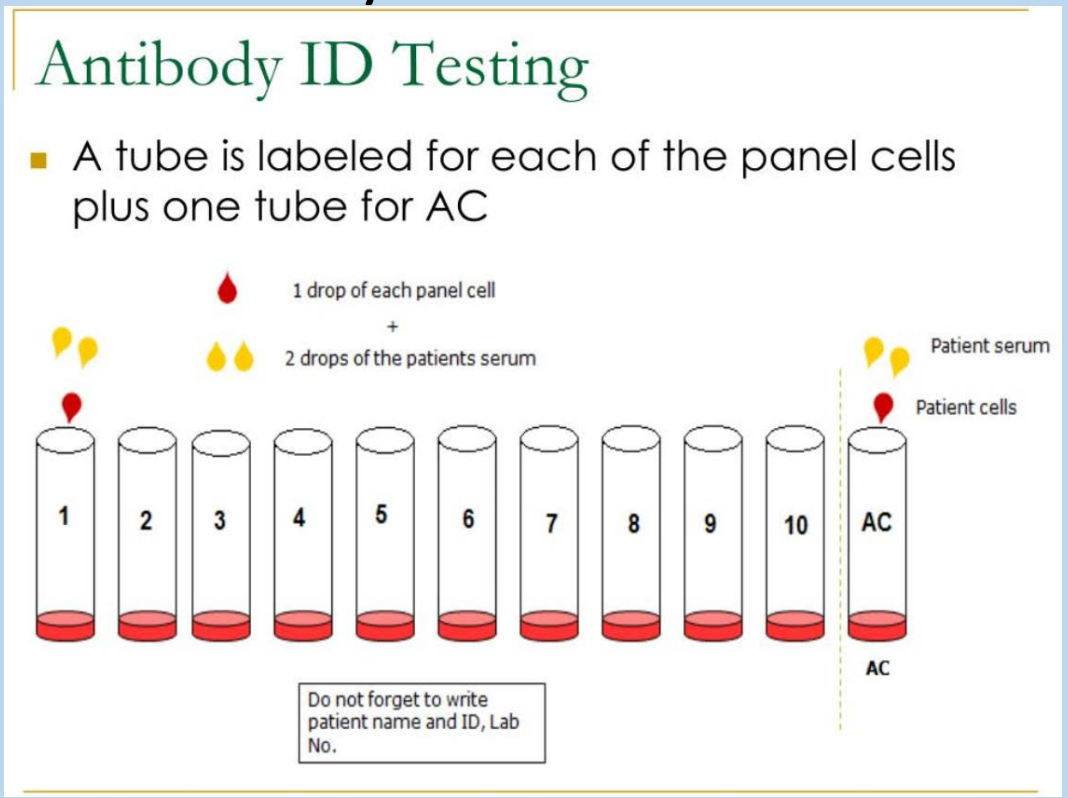
Direct Antiglobulin test

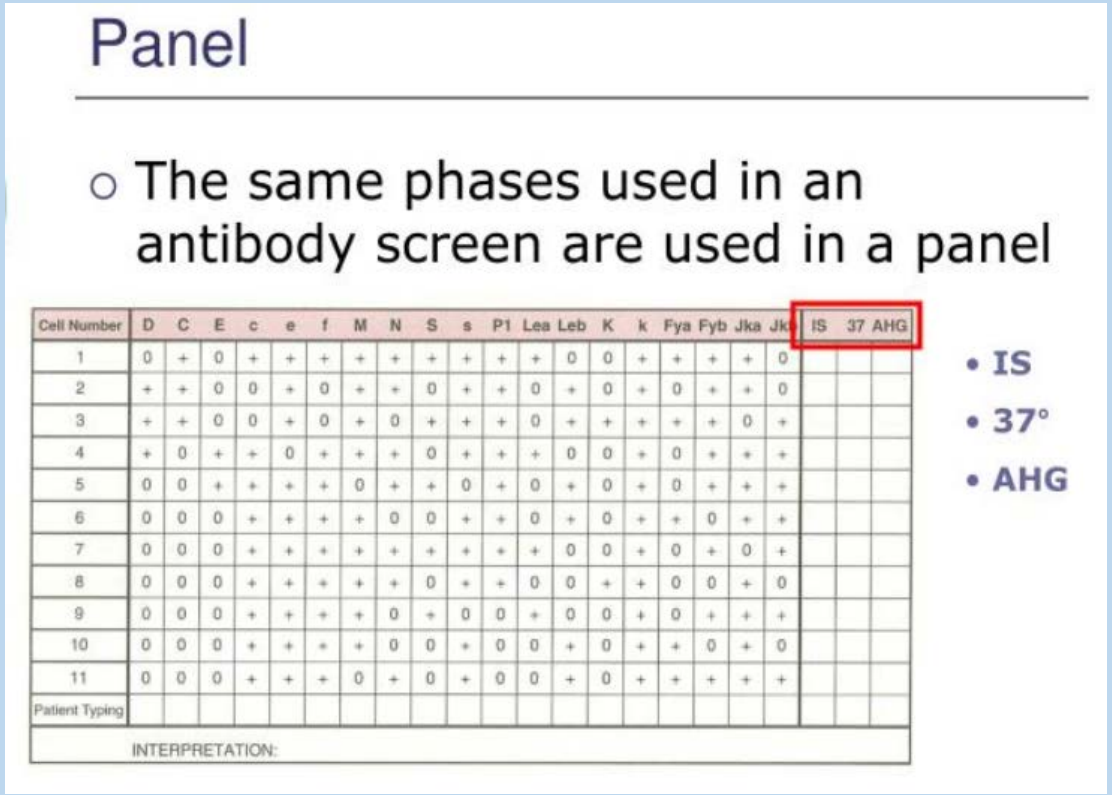






- What does it tell you of Positive DAT test?
  - If no haemolysis – just telling you that antibody attached to RBC
  - If haemolysis – immune mediated
- How would you investigate for Autoimmune Haemolysis?
  - Antibody Panel





Cell Number	D	C	E	c	e	f	M	N	S	s	P1	Lea	Leb	K	k	Fya	Fyb	Jka	Jkb	IS	37	AHG
1	0	+	0	+	+	+	+	+	+	+	+	+	0	0	+	+	+	+	0			
2	+	+	0	0	+	0	+	+	0	+	+	0	+	0	+	0	+	+	0			
3	+	+	0	0	+	0	+	0	+	+	+	0	+	+	+	+	+	0	+			
4	+	0	+	+	0	+	+	+	0	+	+	+	0	0	+	0	+	+	+			
5	0	0	+	+	+	+	0	+	+	0	+	0	+	0	+	0	+	+	+			
6	0	0	0	+	+	+	+	0	0	+	+	0	+	0	+	+	0	+	+			
7	0	0	0	+	+	+	+	+	+	+	+	+	0	0	+	0	+	0	+			
8	0	0	0	+	+	+	+	+	0	+	+	0	0	+	+	0	0	+	0			
9	0	0	0	+	+	+	+	0	+	0	0	+	0	0	+	0	+	+	+			
10	0	0	0	+	+	+	+	0	0	+	0	0	+	0	+	+	0	+	0			
11	0	0	0	+	+	+	0	+	0	+	0	0	+	0	+	+	+	+	+			
Patient Typing																						
INTERPRETATION:																						

- Warm - igG or Cold - C3d

Management of AIHA

- Acute: - Steroid (prednisolone 1mg/kg/day)
  - ivIG (1g/kg/day for 2 days ot 0.4g/kg/day for 5 days)
  - ? Blood transfusion
  - Folic acid
  - VTE ptophylaxis
- Refractory – Rituximab
  - Other immunosuppressant (MMF, Cyclophosphomaide)
  - Splenectomy
  - EPO
- For cold AIHA – look for underlying lymphoproliferative disorder
  - Blood transfusion with blood warmer
  - avoid extreme cold weather

Case (7):

- 45 year old woman w
  admitted following ro
- Patient is on warfarin
- CT scan showed splen
- Require emergency sp
- Blood: Hb 65 INR 4.3
  WBC 16.4 PT 58 sec
  Neu 12.2 APTT 39 sec
  Plt 122 Fibrinogen 1.4

Normal Values:

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Neu 1.8 – 7.5 $x10^9$/L	CRP <5mg/L	K 3.5 – 5.0 mmol/L
Lym 1.0 – 4.0 $x10^9$/L	PCT <0.05 ng/ml	Urea 2.5 – 7.0 mmol/L
Plt 150 – 440 $x10^9$/L	Alb 35 – 50 g/L	Creat 50 – 117 umol/L

How would you manage?

RAPID REVERSAL OF VITAMIN K ANTAGONISTS (e.g, WARFARIN)

James Paget University Hospitals NHS
NHS Foundation Trust

STOP: Vitamin K Antagonist (VKA)

Request: Urgent coagulation screen for INR [Document time of last dose of VKA]
NB: Patients **on warfarin** presenting with a **strong** suspicion of intracerebral bleed should be given Prothrombin Complex Concentrate (Beriplex) before the results of any investigations – however bloods **must** be taken first

→ NOT BLEEDING PATIENT FOR SURGERY
Delay for > 6 hours and omit dose and give vitamin K 5-10 mg IV
If surgery < 6 hours or patient for immediate surgery and INR>2 consider discussion with haematology consultant

Bleeding

INR >2 or INR <2 with continued bleeding or LIMB/EYE/BRAIN bleed

MILD BLEED

- Mechanical compression

MAJOR BLEED

- Control haemorrhage
  - Mechanical compression
  - Surgical/radiological intervention
- Optimise tissue oxygenation
  Maintain BP and Urine Output
- Tranexamic acid (1g IV)
- Blood product replacement therapy as per Major Haemorrhage Protocol

LIFE/LIMB/EYE/BRAIN THREATENING BLEED

Prothrombin Complex Concentrate (Beriplex)
Dose is based on weight and INR
See quick reference chart over page or dose can be calculated as iu/Kg body weight
(weight >100Kg is dosed as for 100Kg)

INR	2.0 – 3.9	4.0 – 6.0	>6.0
Dose	25 iu/Kg	35 iu/Kg	50 iu/Kg

1ml = 25iu when reconstituted as directed

Rate: no more than 8ml/min or 0.12ml/Kg/min if <70Kg
- Repeat INR 30 minutes post PCC
- Repeat dosing **must** be discussed with a Consultant Haematologist

To obtain Prothrombin Complex Concentrate contact Blood Bank x 2443 or via switchboard out of hours
*** Give Vitamin K 5-10mg iv before PCC**

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- Rapid Reversal
  - Mechanical measure
  - Tranexamic acid
  - Vitamin K
  - Prothrombin Complex Concentrate (Beriplex or Octaplex)
  - ? Role of FFP

- DOAC reversal
  - Dabigatran → Idarucizumab (monoclonal antibody that bind dabigatran)
  - Direct Xa Inhibitor (Rivaroxaban, Apixaban, Endoxaban, Betraxaban, Darexaban, Letaxaban, Eribexaban)
    →Andexanet alfa (recombinant activated factor X)
  - role of PCC / FFP ?

Questions Time

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