CCM Specialty Board Tutorial

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Case 1

Case 1

- F/30
- Good past health
- Gum bleeding
- CBC: Hb 12.1 MCV 95.0 platelet 35 WBC 9.3 Promyelocyte 4.1 blast 2.3
- PT 20s INR 1.8 aPTT 48s

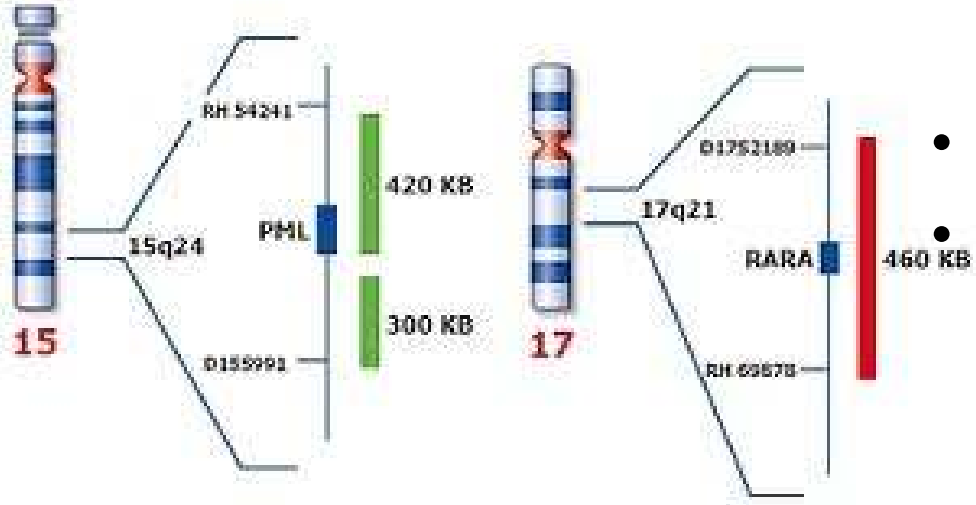
- P/E: Generalised bruises
- No hepatosplenomegaly

Case 1

- Diagnosis: APL/AML-M3
- Started on all-trans retinioic acid 45mg/m2 BD for 3 days
- Plan for daunorubicin today
- high fever (40C), desaturation: SaO2 92% on 8L O2
- Blood test: Hb 11.7 platelet 19 WBC 44.9 Neutrophil 39 blast 0.1

- What is your approach and management?

Acute promyelocytic leukaemia (APL)

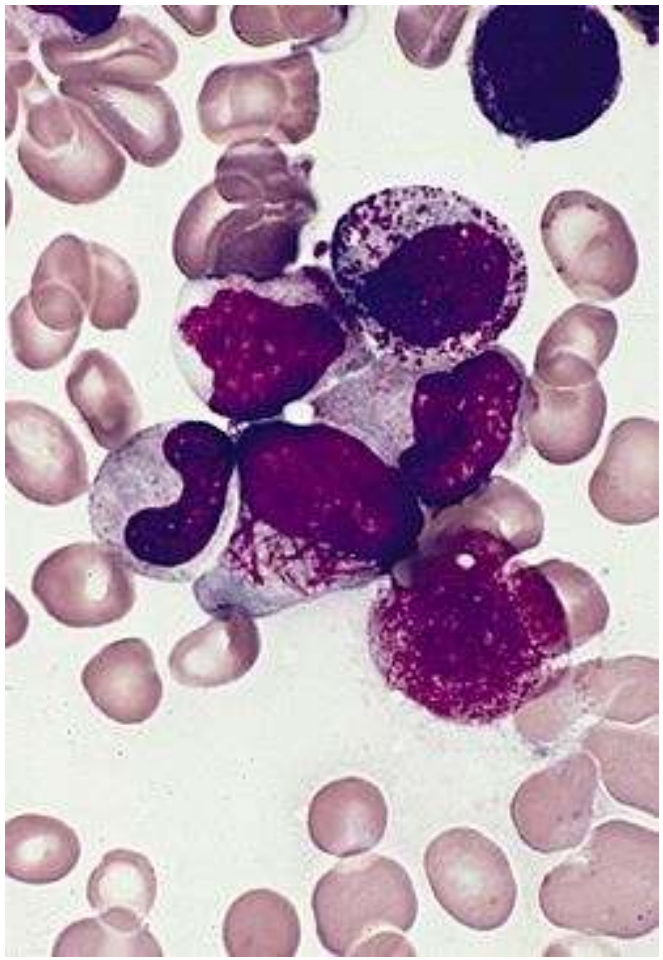


- t(15;17)
- PML (promyelocyte) and RARA (retinoic acid receptor-alpha) gene fusion

APL

- 10% of all AML
- Young
- Leucopenia
- Life-threatening coagulopathy

Peripheral blood smear



- Promyelocytes
- Kidney shaped nucleus
- Densely packed cytoplasmic granules
- Bundles of Auer rods
- → faggot cells

- Strongly positive for myeloperoxidase (MPO)

APL

- Different therapeutic approach
- Risk of DIC prior to and during initial treatment due to release of thromboplastins from leukaemic cells

Induction

- ATRA (All-trans retinoic acid)
- Differentiating agent
- should be started promptly before cytogenetic and molecular test results are available
- 45 mg/m2 per day in divided doses
- Induces differentiation of abnormal clone by overcoming molecular block resulting from t(15;17) translocation → reduce risk of DIC

Induction

- Daunorubicin 50mg/m2 for 3 days
- If WBC <10: start on day 3
- If WBC >10: start immediately

- >> 90% CR rate

- Correct coagulopathy:
- Keep platelet >50
- Cyroprecipitate to correct hypofibrinogenaemia

Consolidaton

- 2 courses of ‘5+2’ regimen:
- Daunorubicin 50mg/m2 for 2 days
- Cytarabine 100mg/m2 for 5 days

Maintenance

- AAA regimen (2 weeks every 2 months for up to 2 years):
- ATRA 45mg/m2
- As2O3 10mg daily
- Ascorbic acid 1g daily

CNS prophylaxis

- For high risk group:

- 4 weekly doses of IT Methotrexate (12mg) at CR1 or CR2 after induction
- WBC >15 at any time point in their clinical course

Minimal residual disease monitoring

- RT-PCR of peripheral blood for PML-RARA
- If 2 consecutive positive results → BMA
- 3 year EFS and OS >80%

HSCT

- Autologous HSCT (Age <65): molecular remission with consolidation after CR2

- Allogeneic HSCT (Age <60): cannot achieve molecular remission with consolidation after CR2 + suitable donor is available

APL differentiation Syndrome

- Differential Diagnosis:
- fluid overload, Pneumonia, diffuse alveolar haemorrhage

- A complication that follows ATRA therapy:
- Marked neutrophilia
- Fever
- pulmonary infiltrates
- Hypoxia
- Fluid overload

Management of ATRA Syndrome

- Treatment:
- dexamethasone 10mg ivi Q12H
- Stop ATRA

- Prevention:
- Start Daunorubicin if WBC >10 or not later than day 3

Case 2

Case 2

- M/58
- History of HT
- Fever for 1 week, easy bruising
- Confusion for 2 days
- Blood test:
- Hb 8.8 MCV 94.0 platelet 24 WBC 360 blasts 251
- P/E: no hepatosplenomegaly

- What is the your approach?

Hyperviscosity

- Definition:
- An increase in whole blood viscosity as a result of an increase in either red cells, white cells, or plasma components, usually Ig
- eg. PRV, Acute leukaemia, monoclonal Ig (Waldernstrom's Macroglobulinaemia, Multiple Myeloma)

- *Symptomatic if viscosity up to 4-6 Ostwald units (normal: 1.5-1.8 Ostwald units)*

Hyperleucocytosis

- WBC >100
- Can be asymptomatic or symptomatic (leucostasis) due to tissue hypoperfusion

- Pathophysiology:
- 1. accumulation of large number of WBC in microcirculation → impediment of blood flow
- 2. production of various cytokines by large population of metabolically active, rapidly dividing WBC

Symptoms of Hyperleucocytosis

- 1. CNS: neurological deficits, confusion, decrease in conscious level, visual loss…
- 2. Pulmonary: cough, desaturation, chest pain
- 3. Tumour lysis syndrome

Leucostasis

- More likely in leukaemia which are:
- 1. rapidly dividing
- 2. large in size
- 3. less deformable

- In descending order of likelihood:
- AML
- ALL
- CML
- CLL

Management

- 1. Chemotherapy (ASAP)
- The most effective means of reduction of WBC
- Response usually within 24 hours

- 2. Leucopheresis
- Theoretical advantage of removal of WBC and avoidance of tumour lysis syndrome, but limited data in reducing early mortality and OS
- Limitations: logistic arrangements, vascular access in patient with coagulopathy, aggravation of thrombocytopenia, delay chemotherapy

Management

- Intravenous hydration
- Avoidance of unnecessary blood transfusion (until leucocytosis improves)
- Platelet transfusion (platelet >20): bleeding commonly complicates leucostasis because of capillary fragility and plugging of leucocytes in microcirculation
- Allopurinol

Component	Specific Gravity
Plasma	1.025-1.029
Platelet	1.040
Lymphocytes	1.050-1.061
Monocytes	1.065-1.070
Granulocyte	1.087-1.092
RBC	1.093-1.096

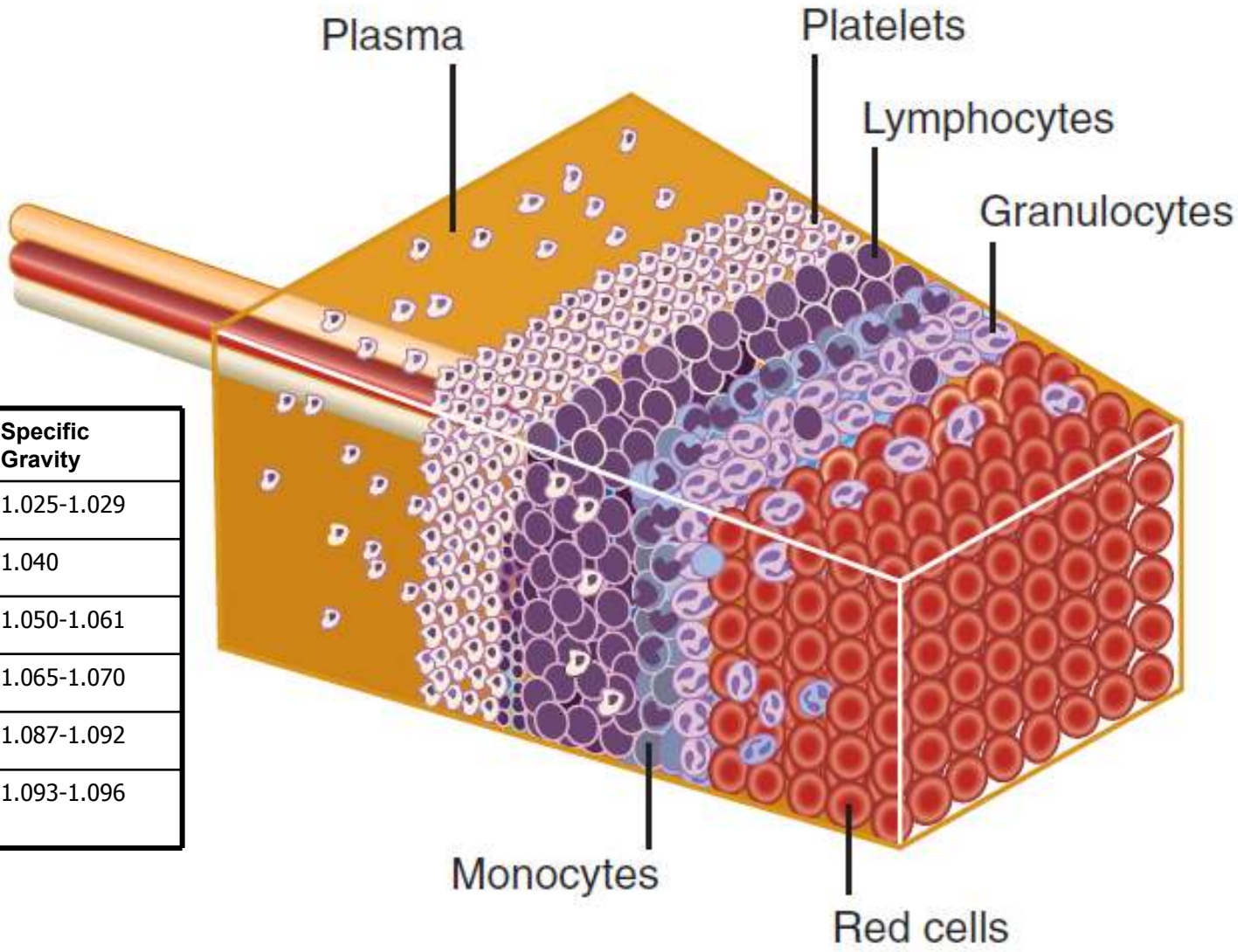


Figure 37-1 Separation of blood components within a centrifugal separation chamber. Blood components placed in a centrifuge are separated based on their density. The densest elements (red blood cells) are farthest from the axis of rotation, and the least dense element (plasma) is closest. *(Image courtesy of Sergio Torloni, MD, Director of Transfusion Medicine, Mayo Clinic, Scottsdale, Ariz.)*

Blood volume

- Need to limit the amount of blood within instrument and tubing (extracorporeal circuit) to avoid hypotension and complications

- Extracorporeal blood <15% of total blood volume

- Male: BV = (0.3669 x H) + (0.03719 x W) + 0.641
- Female: BV = (0.3561 x H) + (0.03308 x W) + 0.1833
- *BV: blood volume (litre)*
- *H: Height (metres)*
- *W: Weight (Kg)*

Cytapheresis

- To deplete or collect a component of the buffy coat

- Therapeutic cytapheresis - to deplete an overabundant/abnormal cellular component

Indications of Leukocytapheresis

- 1. decrease the WBC to relieve symptoms
- 2. prevent tumour lysis syndrome
- 3. pregnant women to prolong pregnancy until the baby can be delivered and mother started on chemotherapy

- *Adjunct therapy, not primary treatment modality*
- *Only temporary effect, chemotherapy should be started ASAP*

Leukocytapheresis

- Total volume processed is usually 8-10L or 2 blood volumes
- → reduction in WBC of around 50%

ASFA 2010	category	recommendation
Symptomatic hyperleukocytosis	1	Grade 1B
Asymptomatic hyperleukocytosis	III	Grade 2C

Case 3

Case 3

- F/28
- 4 days postpartum
- Developed fever and transient confusion
- Hb 8.7 MCV 99 platelet 8 WBC 4.5
- Cr 230 LDH 1650
- Normal LFT
- Normal Blood pressure

Thrombotic Thrombocytopenic Purpura

- First described by Moschcowitz in 1924:
  - A 16 year old girl died

- Pathology:
  - thrombi in arterioles/ capillary in many organs
  - kidneys, brain

Pentad

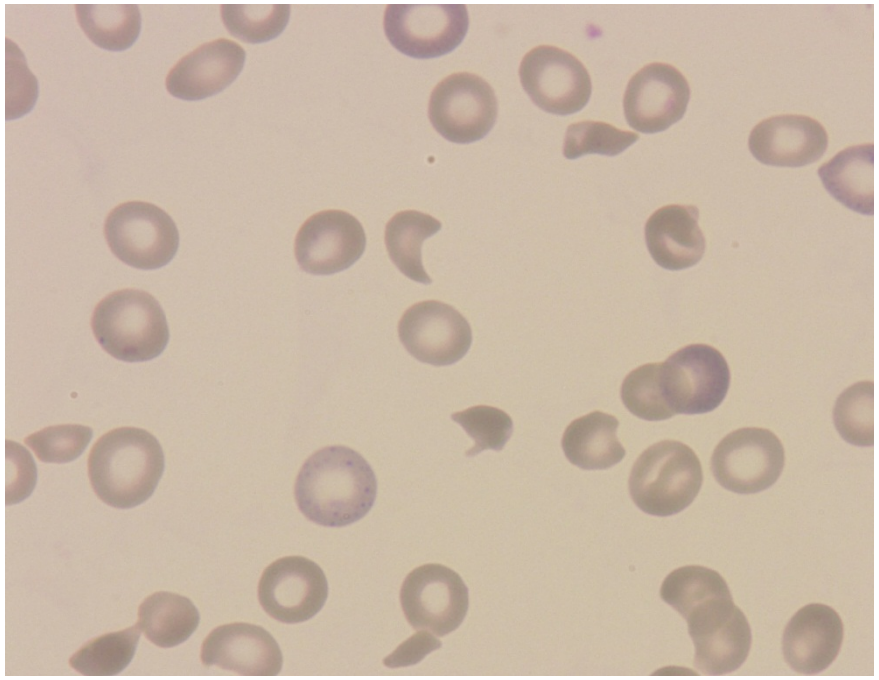
1. Thrombocytopenia:
    - petechiae in lower extremities, Few CNS bleeding

2. Microangiopathic hemolytic anemia (MAHA)
    - PB smear: fragmented RBC (schistocytes/helmet cells)
    - Evidence of intravascular hemolysis: Reticulocytosis, unconjugated hyperbilirubinemia, high LDH, hemoglobinemia, hemoglobinuria, low haptoglobin

3. Renal function abnormalities:
    - Mostly proteinuria, hematuria, Acute renal failure, oliguria

4. Neurological:
    - fluctuating with headache, confusion, coma, and focal deficits in motor, sensory, seizure, visual disturbance

5. Fever



- Schistocytes/helmet cells:
- irregularly shaped, jagged, and have two pointed ends
- No central pallor

Evolution of Diagnostic Criteria

Clinical sign	Percent of patients		
	1925–1964[a]	1964–1980[b]	1982–1989[c]
Thrombocytopenia	96	96	100
Microangiopathic hemolytic anemia	96	98	100
Neurologic symptoms and signs	92	84	63
Renal function abnormalities	88	76	59
Fever	98	59	24

**Classic pentad is seen in only about 40% of patients

Causes of TTP

- Idiopathic
- Secondary
  - Pregnancy/ Postpartum
  - Autoimmune disease
  - Post HSCT/ solid organ transplant
  - Malignancy
  - Infections with bloody diarrhea, ex Shigella, *Salmonella*, *E. coli* O157:H7, HIV
  - Drug toxicity
    - Allergic: quinidine, ticlopidine,,
    - Dose-related toxicity: mytomycin C, cyclosporin A, pentostatin, Gemcitabine

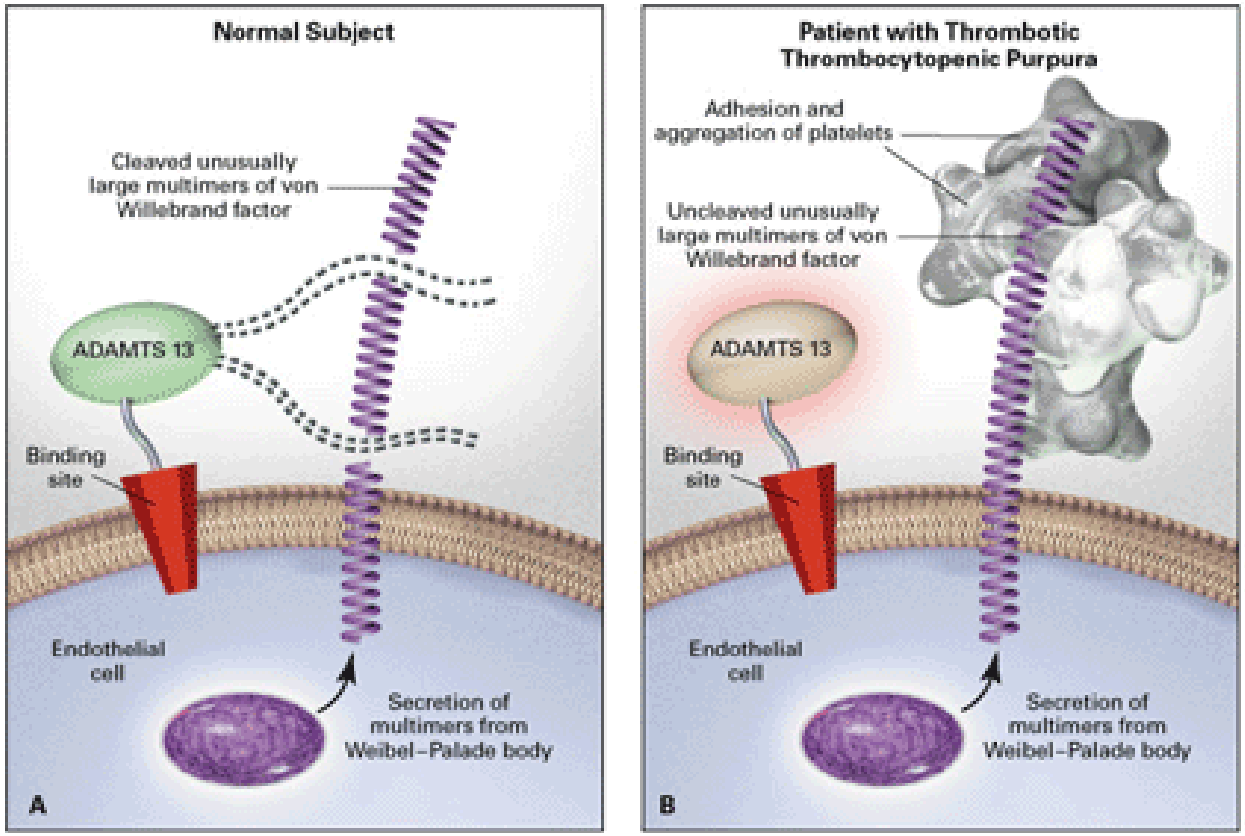
TABLE 2. RELATION BETWEEN DEFECTS IN PLASMA VON WILLEBRAND FACTOR–CLEAVING METALLOPROTEASE, ADAMTS 13, AND THROMBOTIC THROMBOCYTOPENIC PURPURA (TTP).

a disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13

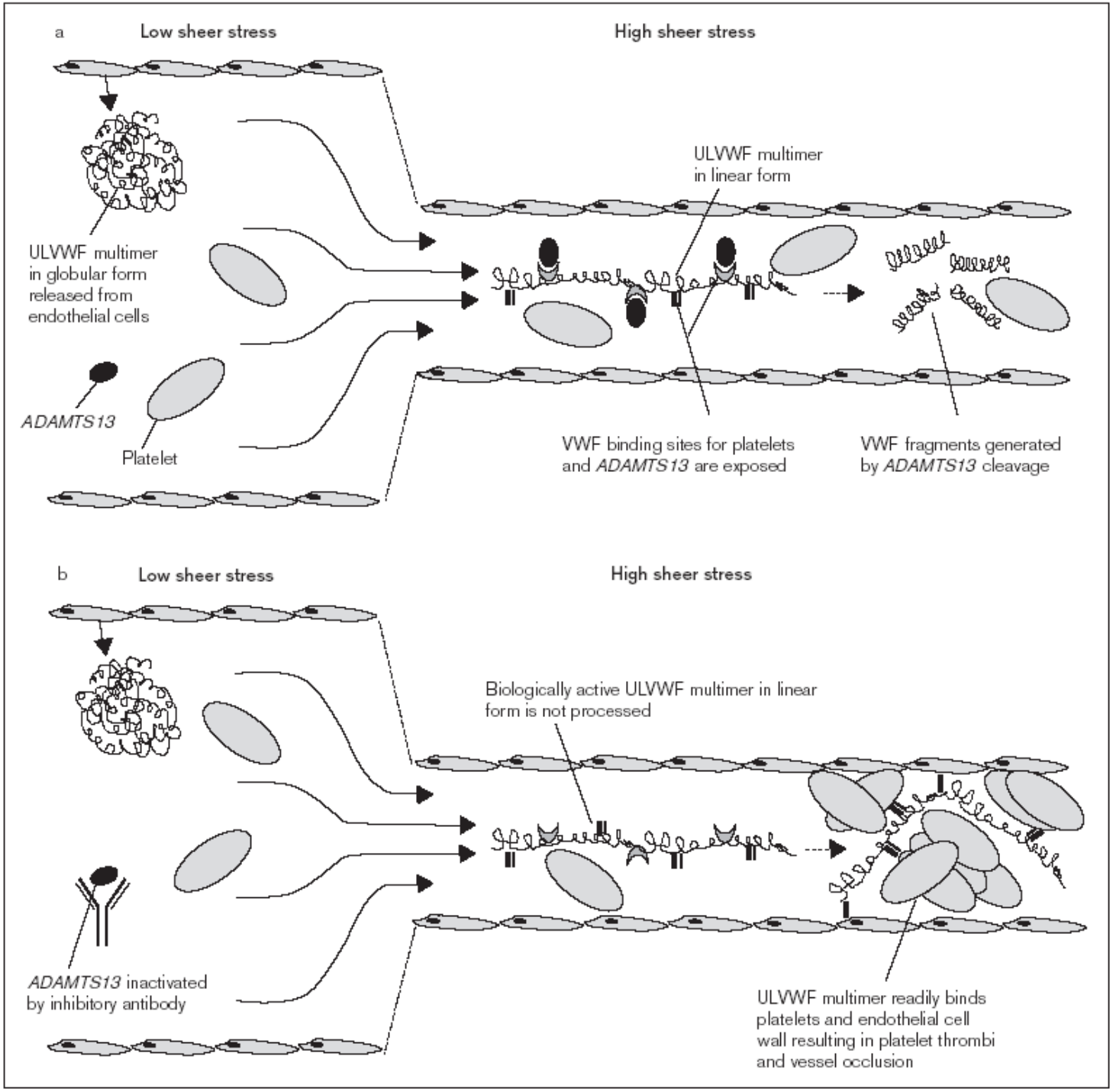
DEFECT	CLINICAL PRESENTATION
ADAMTS 13 plasma activity <5% of normal	
Mutations in the gene for ADAMTS 13	Familial TTP, chronic relapsing TTP
Disease presentation in infancy or childhood	
Disease presentation later in life	
Autoantibodies against ADAMTS 13	Acquired idiopathic TTP
Transient	Single-episode TTP
Recurrent	Recurrent (intermittent) TTP
Ticlopidine-associated*	Ticlopidine-associated TTP
Transient defect in production or survival of ADAMTS 13†	Acquired idiopathic TTP
Normal ADAMTS 13 activity in plasma with defective attachment of ADAMTS 13 to endothelial cells†	Familial and acquired TTP†

*Cases associated with clopidogrel, which is structurally similar to ticlopidine, have been reported.

†This possibility has yet to be proved.



In Panel A, in normal subjects, normal ADAMTS 13 molecules attach to binding sites on endothelial-cell surfaces and cleave unusually large multimers of von Willebrand factor as they are secreted by stimulated endothelial cells. The smaller von Willebrand factor forms that circulate after cleavage do not induce the adhesion and aggregation of platelets during normal blood flow. In Panel B, absent or severely reduced activity of ADAMTS 13 in patients with thrombotic thrombocytopenic purpura prevents timely cleavage of unusually large multimers of von Willebrand factor as they are secreted by endothelial cells. The uncleaved multimers induce the adhesion and aggregation of platelets in flowing blood.


a
Low sheer stress
High sheer stress
ULVWF multimer
in linear form
ULVWF multimer
in globular form
released from
endothelial cells
ADAMTS13
Platelet
VWF binding sites for platelets
and ADAMTS13 are exposed
VWF fragments generated
by ADAMTS13 cleavage
b
Low sheer stress
High sheer stress
Biologically active ULVWF multimer in linear
form is not processed
ADAMTS13 inactivated
by inhibitory antibody
ULVWF multimer readily binds
platelets and endothelial cell
wall resulting in platelet thrombi
and vessel occlusion

Pathophysiology

- Auto-antibody against ADAMTS13
- → severe deficiency of ADAMTS13 activity
- → accumulation of large vWF multimers
- → thrombogenic
- → intravascular platelet aggregation
- → microangiopathic haemolytic anaemia

Management of TTP

Platelet transfusions

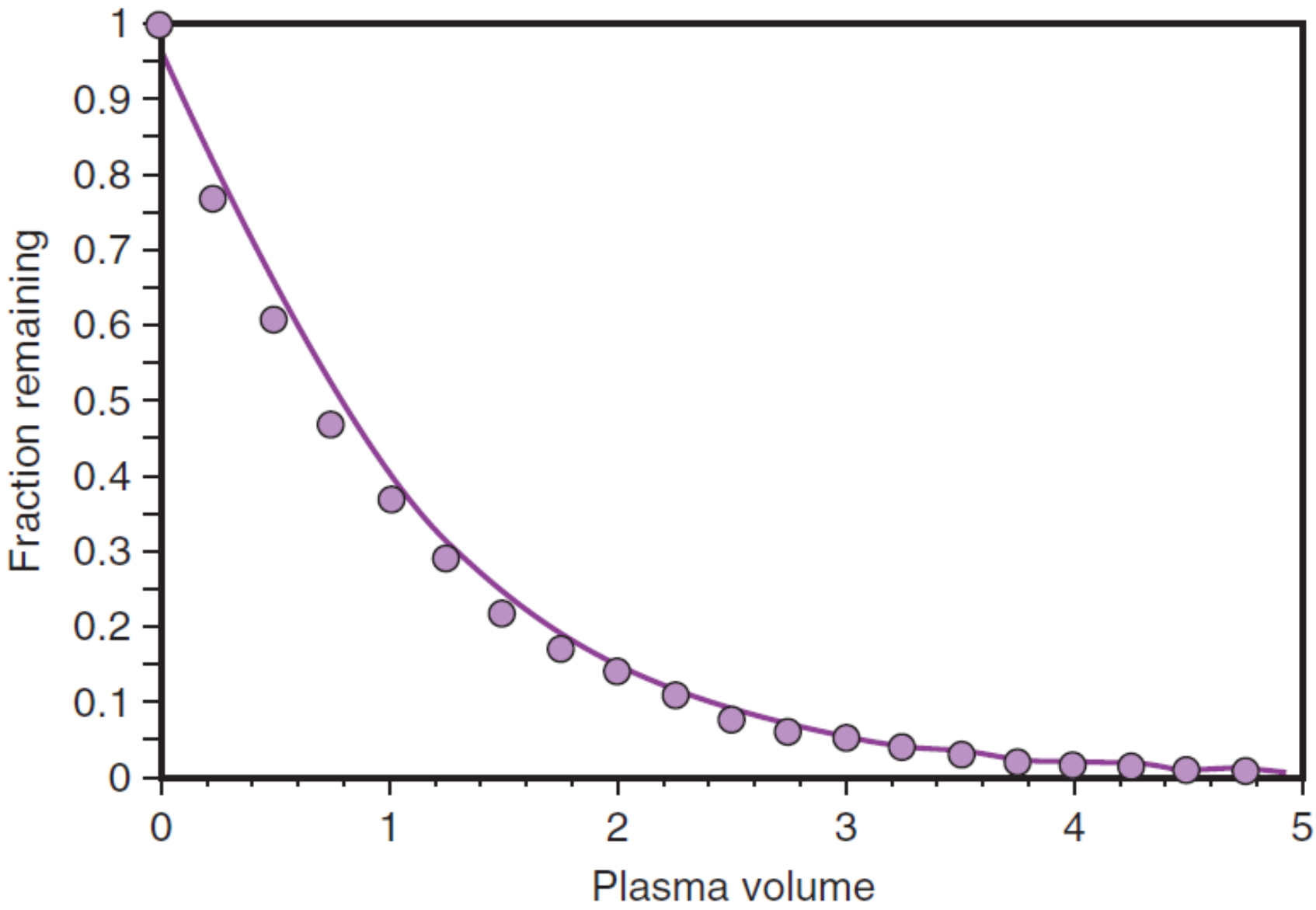
- Contraindicated
- A systemic review of published case reports and case series together with an analysis did not document a risk

Steroid

- Suppress autoantibodies inhibiting ADAMTS13 activity
- Potential benefit may be limited to patients with severe ADAMTS13 deficiency
- Patients who are unlikely to have severe ADAMTS13 deficiency eg. severe renal failure/drug associated TTP/E Coli O157:H7 infection are not treated with steroid

Plasma Exchange

- Performing more than one plasma volume exchange increases procedure time, challenges patient tolerance, and increases the cost
- it is considered acceptable to perform 1 to 1.5 plasma volume exchanges per procedure


Fraction remaining
1
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
0
1
2
3
4
5
Plasma volume

1 plasma volume

- Estimated plasma volume (in liters) =
- 0.07 x weight (kg) x (1 - hematocrit)
- 0.07 x 60 x (1- 0.33) = 2.8L

Replacement fluids: Albumin 5%

- hyper-oncotic fluid for most patients and will result in net flow of fluid from extravascular space
- Give for around 60-70% of replacement volume, the rest by NS
- Adv: no viral transmission
- Dis: $, sometimes hypotensive and febrile reactions due to prekallikrein activation

Replacement fluids: FFP

- In TTP
- In repeated PE to prevent dilutional coagulopathy
- Around 60-70% of replaced volume, rest in NS

- Adv: relatively cheap, provides physiologic concentrations of coagulation factors
- Dis: transmission of viral disease, transfusion reactions, ABO-compatible product, an increase risk of citrate reactions (citrate within FFP)

Replacement fluids: Cryosupranatant

- TTP especially with poor response
- Lack fibrinogen and FVIII

Following PE with 5% albumin as replacement fluid

- Decreased levels of fibrinogen, V, VII, VIII, IX, X, vWF
- VIII, IX, vWF: normalised in 4 hours
- V, VII, X: normalised in 24 hours
- Fibrinogen: back to 66% on day 3

- → risk of transient bleeding

Plasma Exchange

- 1. FFP → supply vWF cleaving proteinase
- 2. Remove ULVWF
- 3. Removal of auto-antibodies of ADAMTS13

- Before use of PE: 95% mortality, now down to <10%

Plasma Exchange

- Response is judged by platelet count
- An increase in platelet count is anticipated after day 2 or 3 and often reaches normal within 1 week
- Neurologic recovery may be the first sign of response
- Renal failure is the last to recover

Start treatment if MAHA + thrombocytopenia
Replace with FFP, cryosupernatant

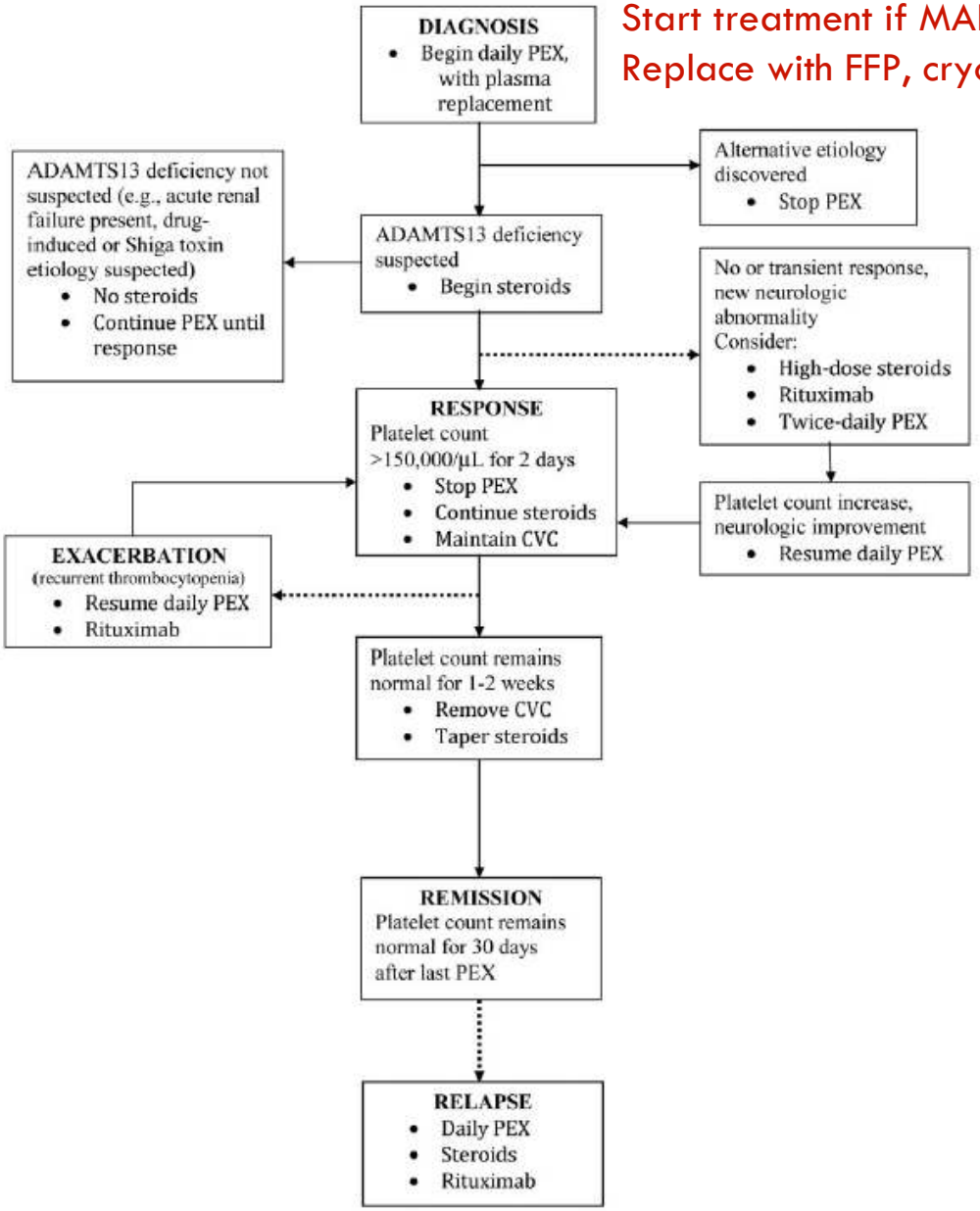


Figure 1. The clinical course of patients with TTP may be complex and cannot be easily represented by a single diagram. Continued search for alternative etiologies for the patient's clinical features is critical, even after beginning plasma exchange. The clinical basis for suspecting severe ADAMTS13 deficiency is described in the text. Exacerbations of TTP, either while continuing daily plasma exchange or after plasma exchange is stopped, and relapses rarely occur in patients without ADAMTS13 deficiency. Although rituximab may be appropriate for 3 different situations illustrated in this algorithm, we have never used more than a single course of rituximab for any patient. Definitions for response, exacerbation, remission, and relapse have been previously described.[17] Broken lines represent complications that occur in a minority of patients. PEX indicates plasma exchange. CVC indicates central venous catheter.

Plasma Exchange

- If platelet count not improved after 4-7 days → escalate treatment intensity

- Methylprednisolone 1g daily for 3 days
- Rituximab 375mg/m2 weekly for 4 weeks
- Twice-daily PE
- *CSA, vincristine, cyclophosphamide may be used*
- *splenectomy*

Problems with apheresis

- General: patient's anxiety and discomfort
- Citrate toxicity: parasthesiae, tremors, tetany
- Vascular and cardiac: poor venous access giving poor flow rates
- Metabolic and pharmacological: hypoalbuminaemia, hypoglycaemia, removal of drugs (plasma bound)
- Allergic reactions

Table 7. Long-term outcomes after recovery from TTP

Outcome	Comments
Relapse	In patients with ADAMTS13 deficiency, the risk is estimated to be 41% at 7.5 years; the greatest risk is in the first year after recovery. Patients without ADAMTS13 deficiency rarely relapse.[14]
Pregnancy complications	Women who have had TTP may have a higher risk for pregnancy-related complications. Recurrent TTP is uncommon with a subsequent pregnancy.[58]
Other autoimmune disorders	Patients with acquired (autoimmune) ADAMTS13 deficiency may be at risk for developing other autoimmune disorders.[36]
Minor cognitive abnormalities	Common; manifested by problems with memory, concentration, and fatigue.[62]

Case 4

Case 4

- Good past health
- Presented with weight loss, malaise, abdominal distension
- PE: pallor, cervical lymphadenopathy, hepatosplenomegaly

- Blood test:
- WCC 465 Hb 3.7 plt 97
- Ur 17 Cr 250 K 8.5 PO4 5.16 LDH 4937
- TB 66 ALP 238 ALT 123

Tumor lysis syndrome

- Rapid lysis of tumour cells leads to the release of excessive quantities of cellular contents into the systemic circulation
  - Hyper K, PO4, urate
  - Metabolic acidosis (lactate)
  - Hypo Ca

- ARF (uric acid nephropathy and acute nephrocalcinosis)
- Arrhythmias is fatal

Cairo-Bishop definition

Laboratory TLS	
Urate	ULN or 25% increase from baseline
Potassium	6.0 mmol/l or 25% increase from baseline
Phosphate	1.45 mmol/l or 25% increase from baseline
Albumin corrected Calcium	1.75 mmol/l or 25% decrease from baseline

Laboratory TLS is considered present if 2 of the criterias are fulfilled within 3 days before until 7 days after cytotoxic therapy

Urate criteria not included if rasburicase has been administered within previous 24 hours

Cairo-Bishop definition

Clinical TLS
Laboratory evidence of TLS plus 1 or more of:
Cr > 1.5 x ULN
Cardiac arrhythmia / sudden death
Seizure

High risk disease types

- Burkitt Lymphoma
- Burkitt-type ALL
- Other ALL with WBC >=100
- AML with WBC >= 50

TLS can precede chemotherapy

Preventive strategy

- Vigorous IVF to maintain u/o >100ml/m2/hr
- Diuretics (furosemide, mannitol) may be required
- Rasburicase in high risk cases
- Rasburicase or allopurinal (adjust for renal function) in moderate risk cases

Rasburicase

- A recombinant form of urate oxidase, an enzyme present in most living organisms but not human

- Catalyzes the oxidation of uric acid to **allantoin**, which is at least 5 times more soluble than uric acid and is readily excreted by the kidneys

- Allopurinol blocks the conversion of xanthines to uric acid, so this will reduce the effect of rasburicase. Therefore do **not give allopurinol and rasburicase** together.

Administration

- 0.2mg/kg in 50-100ml NS IV infusion over 30 minutes, once daily for up to 7 days (1 – 3 days is usually adequate)
- No dose adjustment required for renal or hepatic impairment.
- The most common side effect is rash and urticaria.
- Contraindicated in G6PD deficiency.
- Allopurinol may be used if required **only after completing rasburicase** therapy

- Correction of low calcium should be avoided when there is concurrent high phosphate because of the risk of precipitation of insoluble calcium phosphate. **Only symptomatic hypocalcaemia should be corrected**.

- Moderate / asymptomatic hyperphosphataemia may be initially treated by maintaining adequate hydration, use of an oral phosphate binder and dialysis.

- Alkalinisation of urine is not recommended when using rasburicase. Phosphate is more soluble in acid and so there is an increased risk of calcium phosphate precipitation in the kidney if urine is alkalinised.

- Alkalinisation may be considered if rasburicase is not available and the patient is severely acidotic.

Case 5

Case 5

- M/78
- Past health: DM, HT with satisfactory control
- Admitted for slip and fell
- Developed fractured Left Neck of Femur
- Put on Unfractionated Heparin for thromboprophylaxis
- Post op Day 7
- Developed Right Deep Vein Thrombosis
- CBC: Hb 12.7 platelet 56 WBC 4.9
- Indurated erythematous skin lesions over SC injection sites

	Admission	Pre-op	Post-op Day 7
Hb	13.7	13.0	12.7
WBC	5.9	5.3	4.9
Platelet	238	99	56

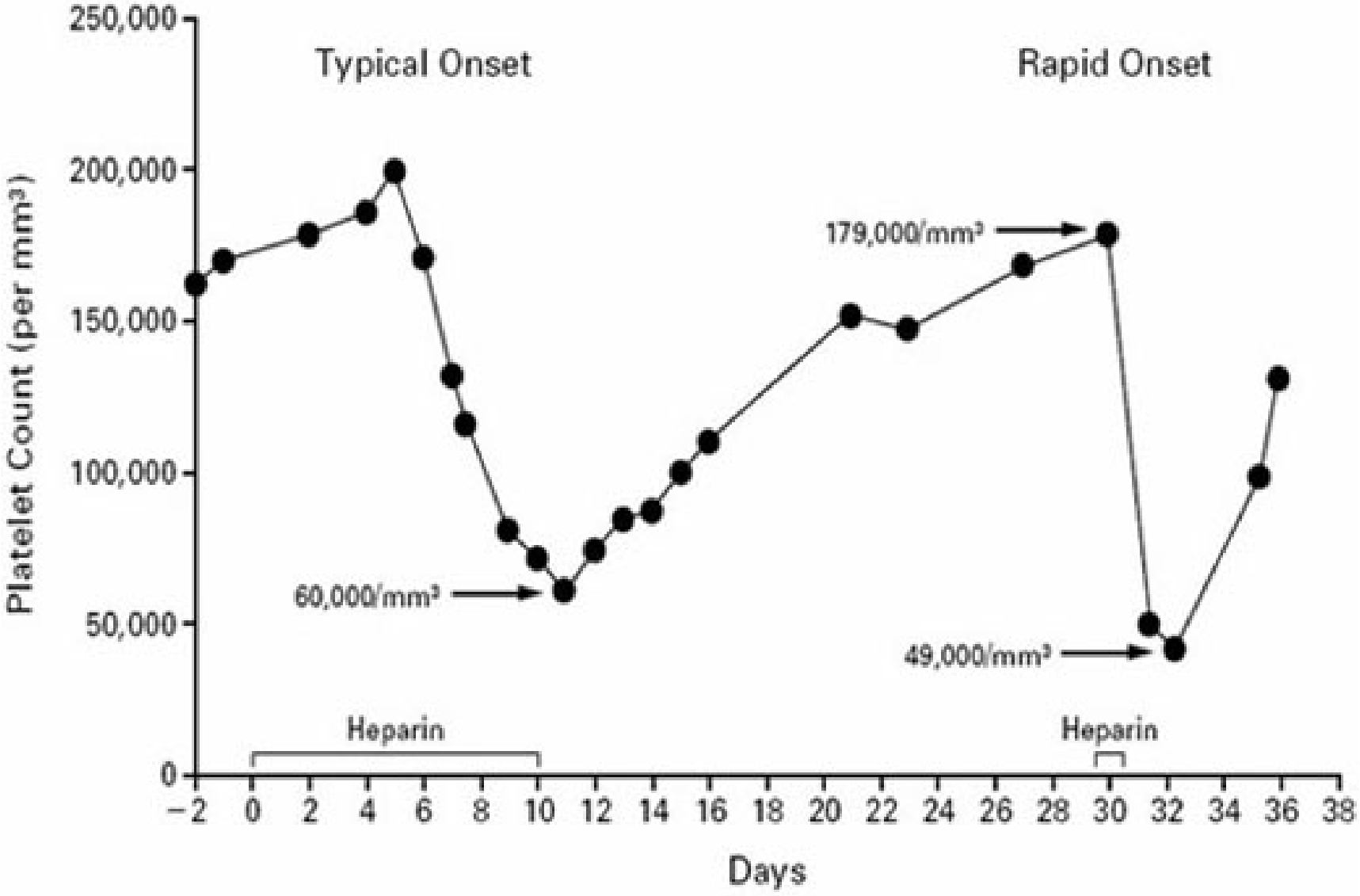
	Admission	Pre-op	Post-op Day 7
Hb	13.7	13.0	12.7
WBC	5.9	5.3	4.9
Platelet	238	99	56
	Heparin Day 0	Heparin Day 6	Heparin Day 13

History and Physical Examination that suggest Heparin Induced Thrombocytopenia (HIT)

Feature	Comments
Fall in platelet count ≥ 50%	From highest platelet count after heparin exposure; platelet count fall is 30-50% in 10% of cases
Fall in platelet count begins 5-14 days after heparin exposure	
Fall in platelet count begins 48 hours after heparin exposure	In patients with previous heparin exposure within last 100 days
Nadir platelet count ≥ 20 x 10^9/L	May be < 20 x 10^9/L in cases associated with thrombosis and DIC
Venous or arterial thrombosis	Occurring ≥ 5 days after heparin exposure and up to 30 days after heparin cessation
Skin necrosis	At subcutaneous heparin injection sites
Anaphylactoid reaction	Within 30 minutes after intravenous heparin bolus
Absence of alternative causes of thrombocytopenia	Such as infection, other medications known to cause thrombocytopenia, cardiopulmonary bypass within previous 96 hours, etc.
Absence of petechiae and other significant bleeding	

Patient Population	Frequency
Cardiac surgery	
Adults (unfractionated heparin postoperatively)	1.0% to 2.4%
Pediatrics	1.3%
Cardiac transplantation	11%
Orthopedic surgery	
Unfractionated heparin postoperatively	4.8%
LMWH postoperative	0.6%
Medical	
Cardiovascular disease	0.3%
Critical care	0.4%
Those treated with subcutaneous, unfractionated heparin	0.8%
New treated with hemodialysis	3.2%
Obstetrics	Rare
Overall (hospital-wide surveillance studies)	1.0% to 1.2%

Risk Factors	OR
Duration of heparin therapy (> 1 wk vs < 1 d)	Approximately 20–100
Type of heparin (UFG vs LMWH)	Approximately 10–15
Type of patient (surgery vs medical)	Approximately 3–4
Sex (female vs male)	Approximately 1.5–2.0
Type of Heparin:	bovine > porcine


Typical Onset
Rapid Onset
Platelet Count (per mm³)
250,000
200,000
150,000
100,000
50,000
0
179,000/mm³
60,000/mm³
49,000/mm³
Heparin
Heparin
−2 0 2 4 6 8 10 12 14 16 18 20 22 24 26 28 30 32 34 36 38
Days

The 4Ts model

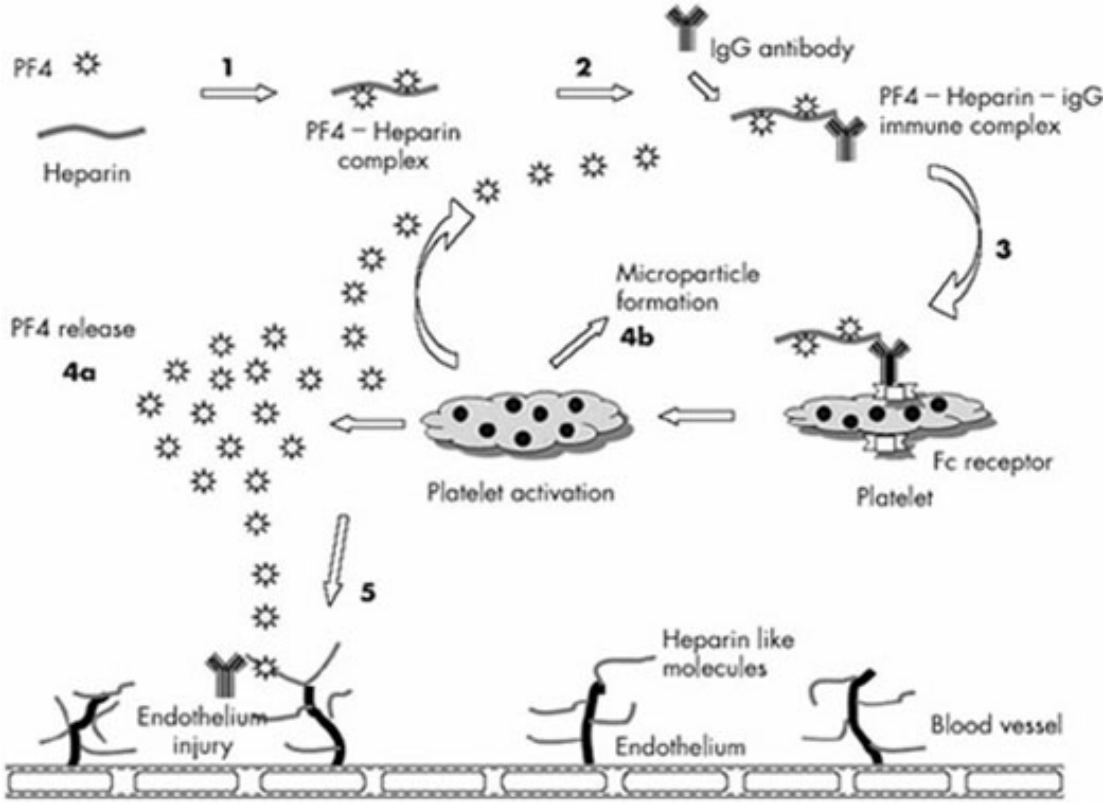
*First day of immunizing heparin exposure considered day 0; the day the platelet count begins to fall is considered the day of onset of thrombocytopenia (it generally takes 1–3 d more until an arbitrary threshold that defines thrombocytopenia is passed).

4T's	2 Points	1 Point	0 Points
Thrombocytopenia	Platelet count fall > 50% and platelet nadir ≥ 20 x 10^9/L	Platelet count fall 30-50% or platelet nadir 10-19 x 10^9/L	Platelet count fall < 30% or platelet nadir < 10 x 10^9/L
Timing of platelet count fall	Clear onset between days 5-14 or platelet fall ≤ 1 day (prior heparin exposure within 30 days)	Consistent with days 5-14 fall, but not clear (e.g. missing platelet counts) or onset after day 14 or fall ≤ 1 day (prior heparin exposure 30-100 days ago)	Platelet count fall ≤ 4 days without recent exposure
Thrombosis or other sequelae	New thrombosis (confirmed); skin necrosis at heparin injection sites; anaphylactoid reaction after IV heparin bolus	Progressive or recurrent thrombosis; Non-necrotizing (erythematous) skin lesions; Suspected thrombosis (not confirmed)	None
oTher causes of thrombocytopenia	None apparent	Possible	Definite

High probability: 6-8 points; intermediate probability: 4-5 points; low probability: ≤3 points.

Adapted from Lo GK et al., J Thromb Haemost 2006. The 4Ts model has not been externally validated. It may be used as a guide for clinicians, but should not substitute for clinical judgment. In clinical studies, the 4Ts model has demonstrated excellent sensitivity (low probability score indicates low probability of HIT), but limited specificity (intermediate or high probability score may or may not indicate the presence of HIT).

Pathophysiology



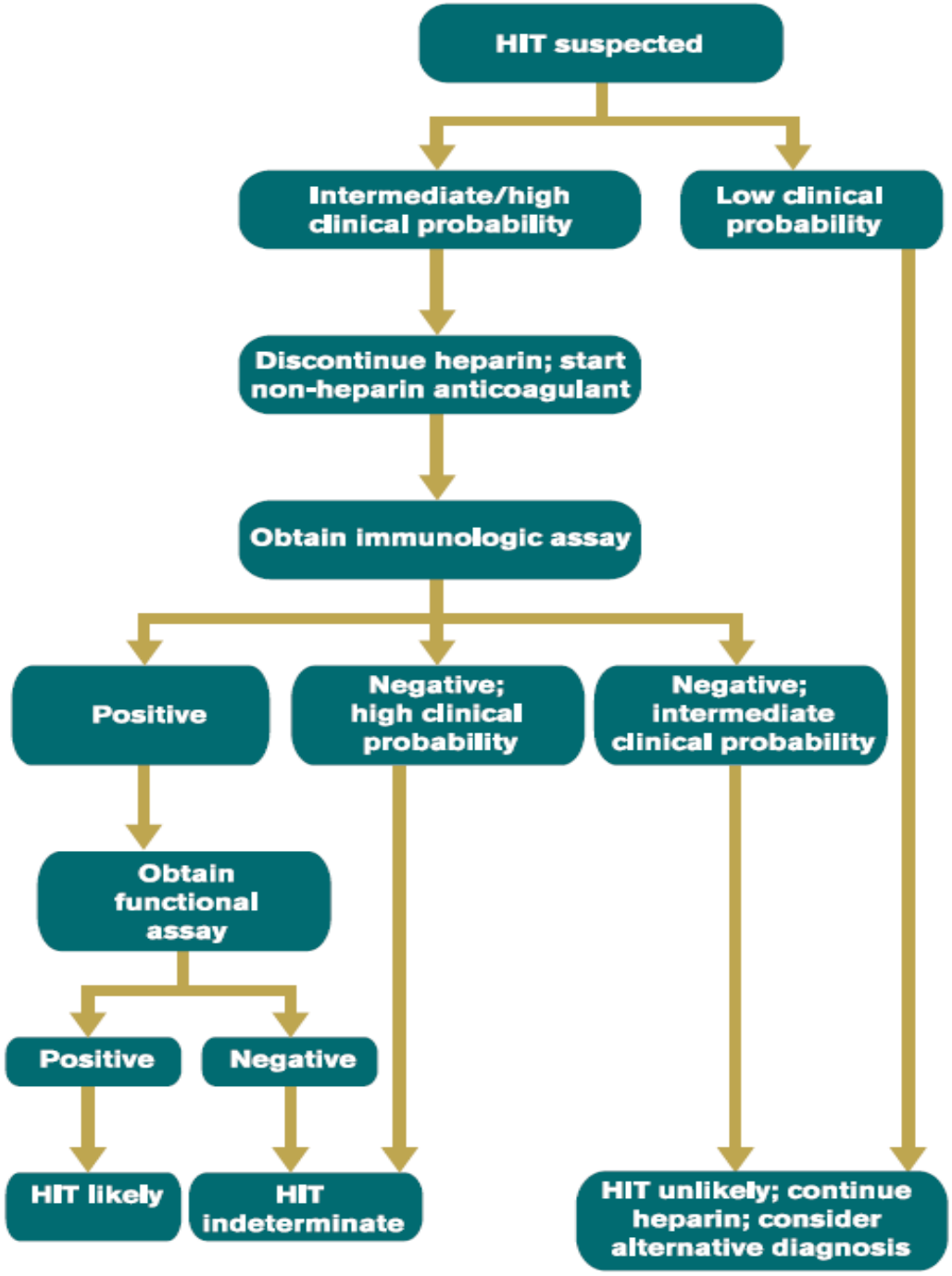
PF4: 70-amino acid protein that self-associates to form tetramers of approximately 30kDa
HIT IgG recognise a heparin-induced conformational change in the PF4 tetramer
Ability to induce the conformational change depends on (1) chain length and (2) degree of sulphation of glycosaminoglycan

Laboratory Diagnosis

Assay category	Mechanism	Examples	Sensitivity	Specificity	Comments
Immunologic	Detects antibodies against PF4/ heparin, regardless of their capacity to activate platelets	1. Polyspecific ELISA 2. IgG-specific ELISA 3. PGIA	>95%	50-89%	OD of ELISA result correlates with clinical probability of HIT
Functional	Detects antibodies that induce heparin-dependent platelet activation	1. SRA 2. HIPA 3. PAT	>90%	>90%	Not available at many centers; may require referral to a reference laboratory

PF4, platelet factor 4; PGIA, particle gel immunoassay; OD, optical density; SRA, serotonin release assay; HIPA, heparin-induced platelet activation assay; PAT, platelet aggregation test.

Treatment Algorithm



Non-heparin anticoagulants: selection/dosing/monitoring

Agent	Graded recommendation[1]	Initial dosing	Monitoring
Danaparoid[2]	1B	**Bolus:** Weight <60 kg ▸ 1500 U Weight 60-75 kg ▸ 2250 U Weight 75-90 kg ▸ 3000 U Weight >90 kg ▸ 3750 U **Accelerated initial infusion:** 400 U/hr x 4 hrs, then 300 U/hr x 4 hrs **Maintenance infusion:** Normal renal function ▸ 200 U/hr Renal insufficiency ▸ 150 U/hr	Adjust dose to anti-Xa level of 0.5-0.8 U/ml (if assay is available).
Lepirudin	1C	**Bolus:**[3] 0.2 mg/kg (only if life- or limb-threatening thrombosis is present) **Continuous infusion:**[3] Cr <1.0 mg/dl ▸ 0.10 mg/kg/hr Cr 1.0-1.6 mg/dl ▸ 0.05 mg/kg/hr Cr 1.6-4.5 mg/dl ▸ 0.01 mg/kg/hr Cr >4.5 mg/dl ▸ 0.005 mg/kg/hr	Adjust dose to APTT of 1.5-2.0 times patient baseline. Monitor APTT every 4 hours during dose titration.

Argatroban	1C	**Bolus:** None **Continuous infusion:** Normal organ function ▸ 2 mcg/kg/min Liver dysfunction (total serum bilirubin >1.5 mg/dl), heart failure, post-cardiac surgery, anasarca ▸ 0.5-1.2 mcg/kg/min	Adjust dose to APTT of 1.5-3.0 times patient baseline. Monitor APTT every 4 hours during dose titration.
Bivalirudin[4]	2C	**Bolus:** None **Continuous infusion:** Normal organ function ▸ 0.15 mg/kg/hr Renal or hepatic insufficiency ▸ dose reduction may be necessary	Adjust dose to APTT of 1.5-2.5 times patient baseline.
Fondaparinux[5]	2C	No specific recommendations given minimal data supporting efficacy and appropriate dosing in HIT	

Adapted from Warkentin TE et al., Chest 2008.

[1]American College of Chest Physicians Grading System: 1=strong recommendation; 2=weak recommendation; A=based on high quality evidence; B=based on moderate quality evidence; C=based on low quality evidence

[2]Not available in U.S.

[3]Lower than FDA-approved dosing.

[4]FDA-approved for patients with HIT only during percutaneous coronary intervention.

[5]Not approved for treatment of HIT.

Transitioning to Warfarin

- HIT patients are at risk of venous limb gangrene during initiation of warfarin.
- Warfarin should not be initiated until platelet count is $\geqslant$ 150 x 10^9/L (Grade 1B).
- • Initial warfarin dose should be $\leqslant$ 5 mg/day. Larger loading doses should be avoided (Grade 1B).
- • A parenteral non-heparin anticoagulant should be overlapped with warfarin for $\geqslant$ 5 days and until INR has reached intended target (Grade 1B).

Duration of anticoagulation

- Bilateral lower extremity compression ultrasonography should be performed in all patients with HIT, whether or not there is clinical evidence of lower-limb DVT (Grade 1C), because the finding of DVT may influence the recommended duration of anticoagulation
- For patients with HIT-associated thrombosis (i.e. HITT) → 3-6 months
- For patients with HIT without thrombosis (i.e. isolated HIT) → unknown
- *anticoagulation for at least one month should be considered*

Platelet transfusion

- Due to theoretical risk that platelet transfusion may precipitate thrombosis in HIT, prophylactic platelet transfusions should not be given to patients with confirmed or strongly suspected HIT (Grade 2C)

- *Platelet transfusion may be appropriate in situations of diagnostic uncertainty, high bleeding risk, or clinically significant bleeding*

Case senarios

- 1. AML M3 with ATRA Syndrome
- 2. AML with hyperviscosity
- 3. TTP
- 4. Tumour lysis Syndrome
- 5. HIT

Thank you