Bleeding Disorders 2
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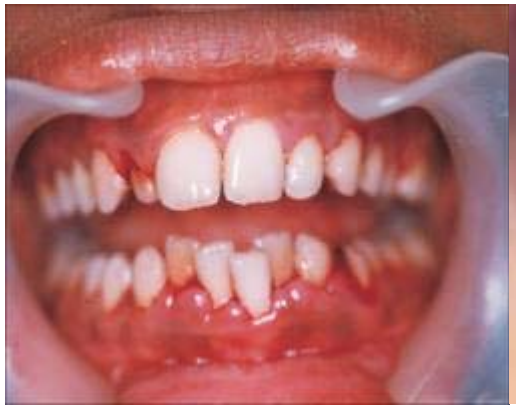
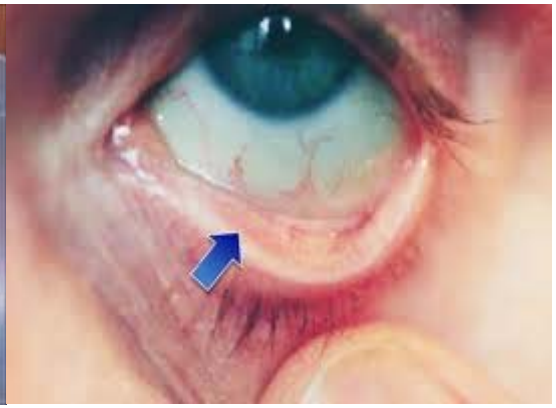
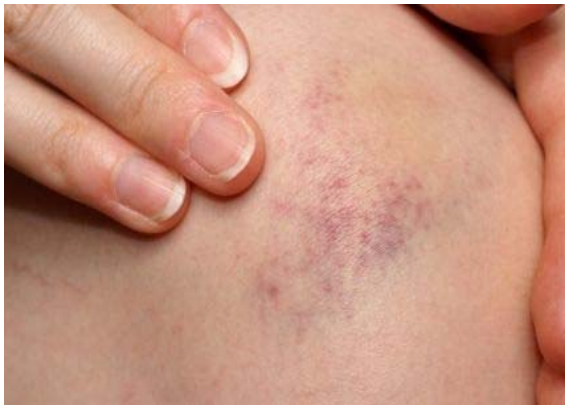
Case 6: GT

18 yr old female was admitted with pallor, abdominal pain and gum bleeding. She has been complaining of mucosal bleeding ever since she remembers. Her periods have always been heavy lasting more than 1 wk. She was admitted before and received bld TX for bleeding. She has summer epistaxis and bad bleeding gums. Her parents are 1st degree relatives. P/E

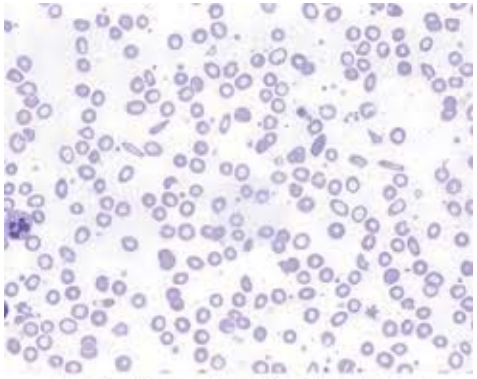


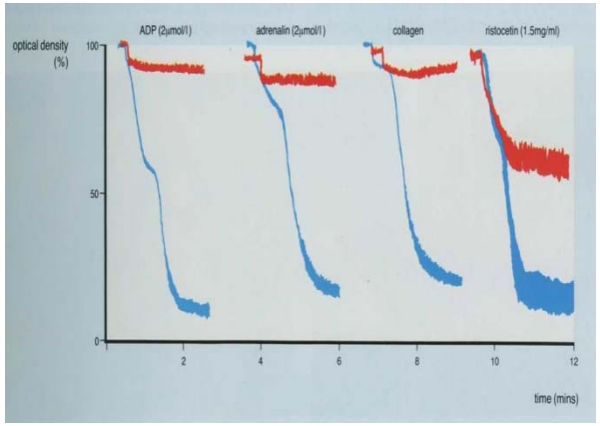


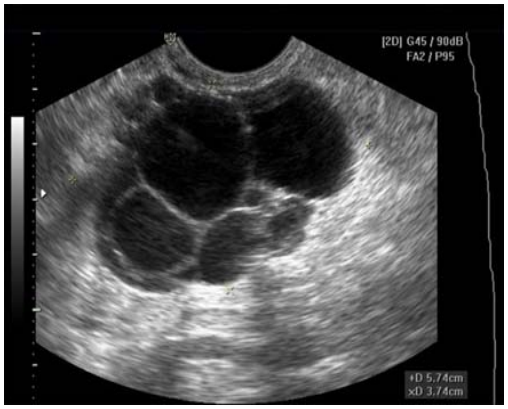


Case 6: investigations & Findings

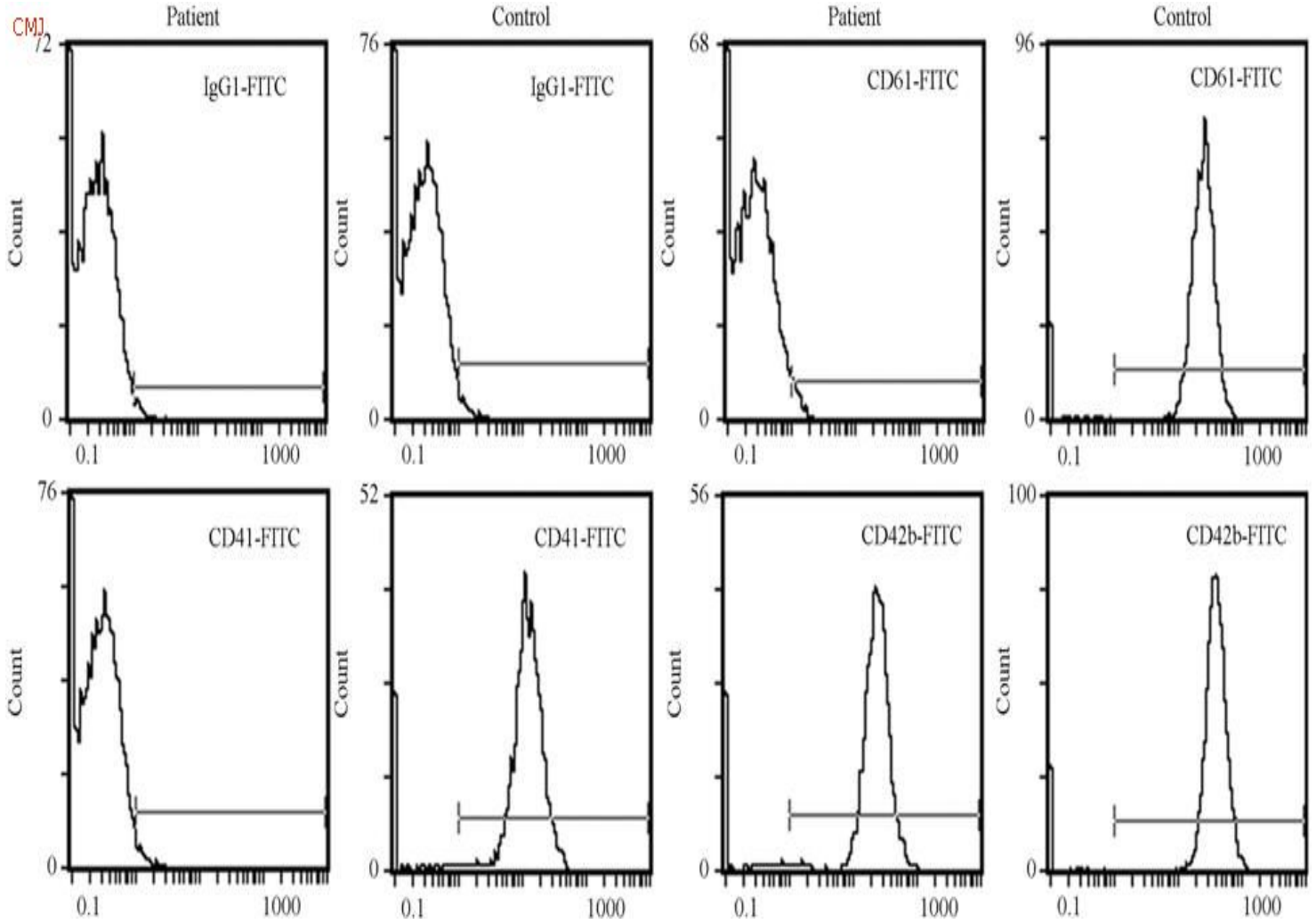
Hb 6, MCV 62, Retcs 0.9% WBC 16k, Plt 240k, PT,PTT, TT: Normal. Bld film shown. BT >15 mnts. VWF 105%. Clot retraction: Absent. Flow shown in a new slide.Diagnosis: Glanzmann Thrombasthenia



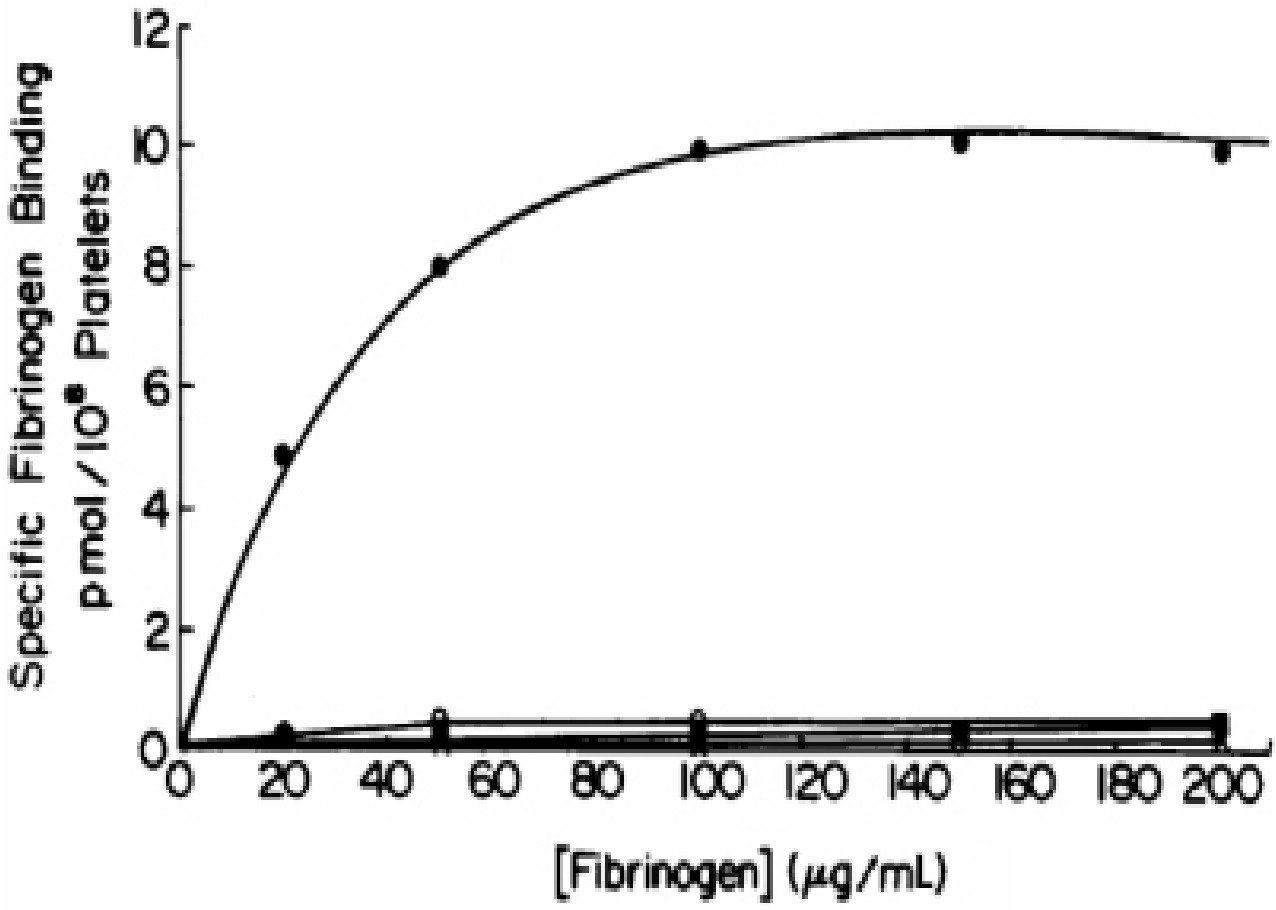




Flowcytometry of platlets with GT



Fibrinogen Binding of Platelet in GT



Case 6: Treatment & Follow- up

1- Bld TX: Packed RBC or washed RBC

2- Local dental measures

3- Iv Tranexemic acid (Cyclokapron) 1g X3 daily 3-4 days

4- Symptomatic for the ovarian cyst

5- If bleeding is not controlled: Plt TX if antibodies are -ve, if antibodies are +ve, use recombinant factor VIIa (Novoseven) 150-200µg/kg iv hr: 0, 3 and 8hrly until bleeding stops.

7- Long term contraceptives.

6- Education and counseling.

Clinical Manifestations of GT

- Life long mucosal bleeding
- Prolonged bleeding from cuts/wounds
- Purpura, menorrhagia
- Gastritestinal bleeding
- Intracranial haemorrhage (~1%)

GT Laboratory/ Diagnostic tests

- Normal platelet count and morphology
- Prolonged bleeding time
- Absent or impaired clot retraction
- Absent or reduced plt fibrinogen
- No aggregation with physiological aggregating agents
- Absent or reduced GPIIb-IIIa
- Treatment is supportive

Platelet transfusions - complications

- Transfusion reactions
  - Higher incidence than in RBC transfusions
  - Related to length of storage/leukocytes/RBC mismatch
  - Bacterial contamination
- Platelet transfusion refractoriness
  - Alloimmune destruction of platelets (HLA antigens)
  - Non-immune refractoriness
    - Microangiopathic hemolytic anemia
    - Coagulopathy
    - Splenic sequestration
    - Fever and infection
    - Medications (Amphotericin, vancomycin, ATG, Interferons)

Classification of platelet disorders

- Quantitative disorders
  - Abnormal distribution
  - Dilution effect
  - Decreased production
  - Increased destruction
- Qualitative disorders
  - Inherited disorders (rare)
  - Acquired disorders
    - Medications
    - Chronic renal failure
    - Cardiopulmonary bypass

Classification of Platelet Disorders

Quantitative Disorders

- Abnormal distribution
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Qualitative Disorders

- Inherited disorders (rare)
- Acquired disorders
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  - Chronic renal failure
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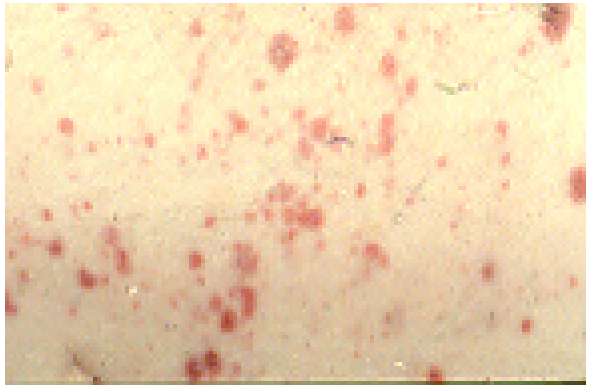
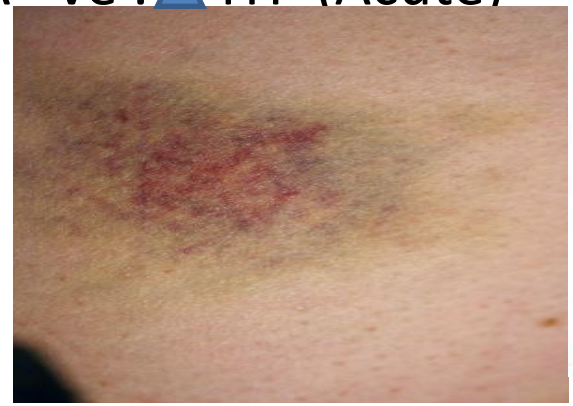
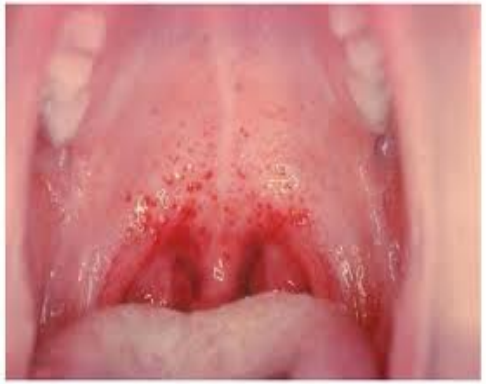
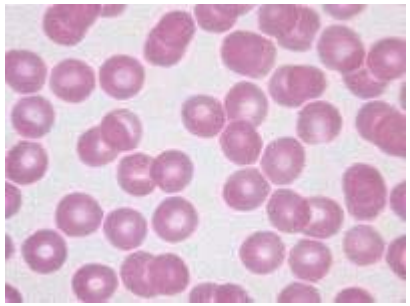
Case 6 B: ITP

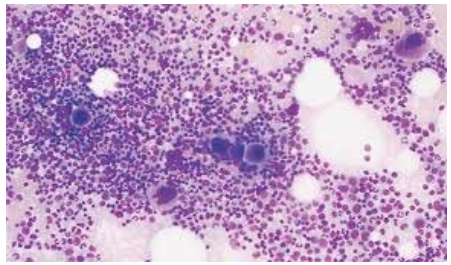
23 yr old female presented with purpuric skin rash, PV bleeding and easy bruising for 5 days. She was previously healthy and she takes no medications.P/E.No LN,no splenomegaly + shown below.Hb 10.5, WBC 10k, plt 10k. Pt, PTT, TT were normal. Bld film.DAT –ve.ANA, >DNA –ve . ITP (Acute)











Case 6 B: Management & Follow-up

1- Start oral Prednisolone 1mg/kg daily.Aim at ± 4 wks, then taper. If no response or relapse: IVG, Other immune suppressors. New TPO agonists, ???splenectomy.

2- Follow up for additional immune disease (SLE, APS) or lympho-proliferative neoplasms.

3- Careful monitoring during pregnancy & delivery (post delivery care of the baby).

Platelets

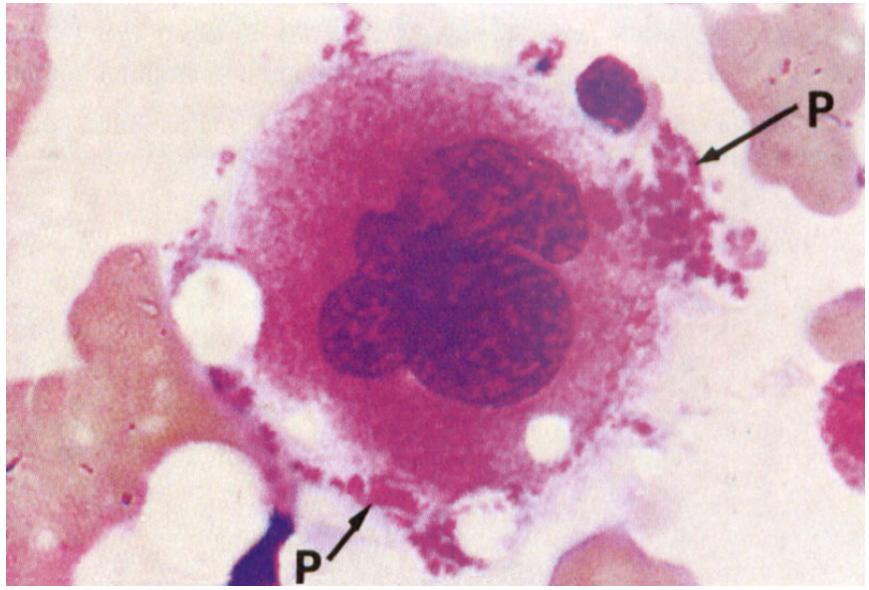
Megakaryocyte – 3000 platelets

Adult must make 10^{11}/day

(100,000,000,000/day)

20–30% pooled in spleen

Lifespan 7–10 days



Thrombocytopenia associated with shortened survival (increased destruction)

- Immune mediated thrombocytopenia
  - Drug-induced thrombocytopenia
  - Heparin induced thrombocytopenia
  - **ITP**
  - TTP
- Non-immune destruction
  - DIC
  - Sepsis-associated
- Multifactorial thrombocytopenias
  - Hospital (ICU)-associated thrombocytopenia
  - Cancer associated thrombocytopenia

Acquired thrombocytopenia with shortened platelet survival

Associated with bleeding

- Immune-mediated thrombocytopenia (ITP)
- Most drug-induced thrombocytopenias
- Most others

Associated with thrombosis

- Thrombotic thrombocytopenic purpura
- DIC
- Heparin-associated thrombocytopenia

Pathogenesis of ITP

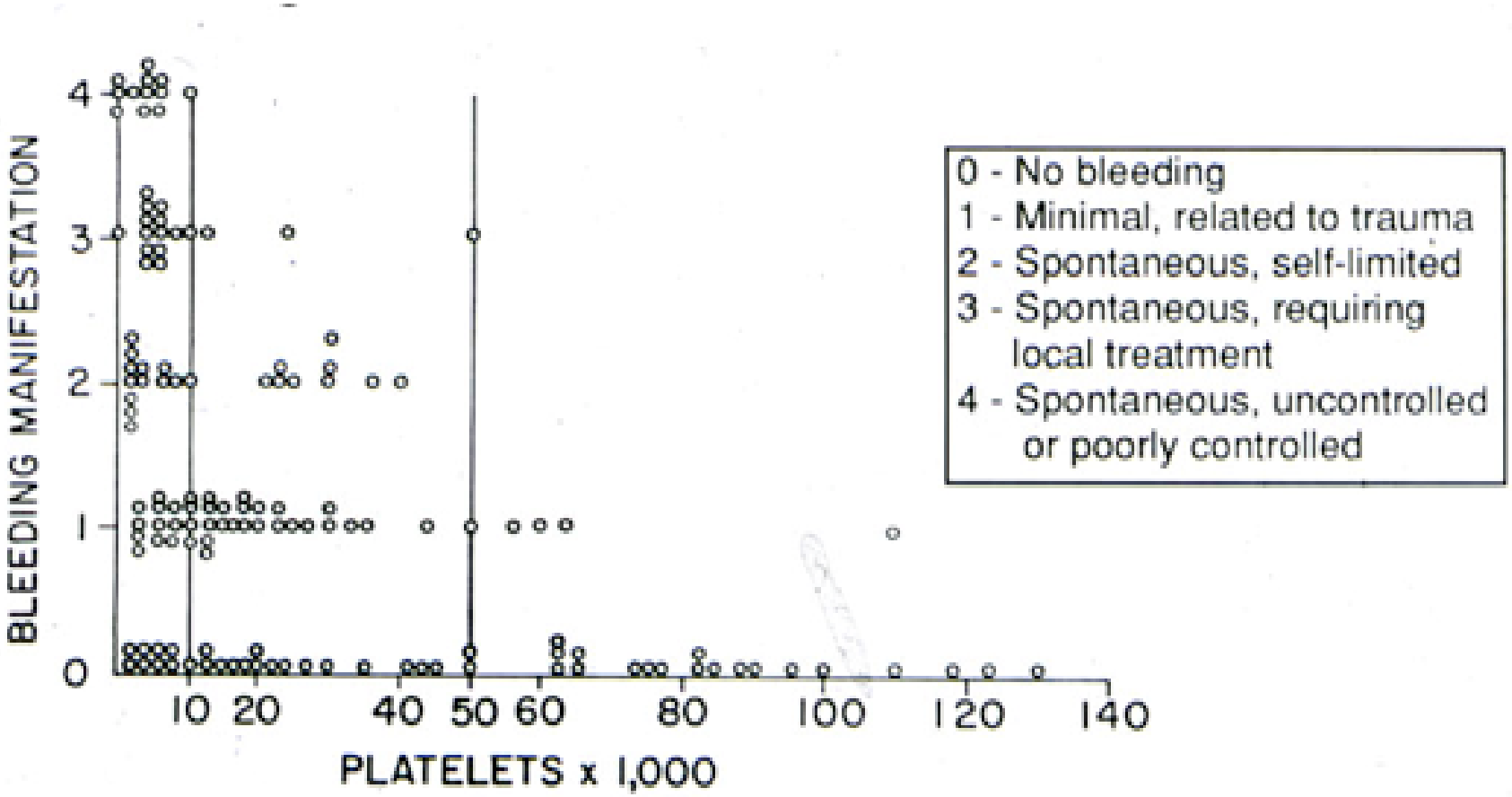
- Increased platelet destruction mediated by autoantibodies
- Auto-antibodies that react with major membrane glycoproteins can be identified in ~80% of patients

- Antibody concentrations diminish with effective treatment and increase with relapse
- Decreased production despite the increase in megakaryocytes in BM

Sites of bleeding in thrombocytopenia

- Skin and mucous membranes
  - Petechiae
  - Ecchymosis
  - Hemorrhagic vesicles
  - Gingival bleeding and epistaxis
- Menorrhagia
- Gastrointestinal bleeding
- Intracranial bleeding

Bleeding Manifestations in Relation to Platelet Count



from: Lacey and Penner, Seminars in Thrombosis and Hemostasis (1977)

WHO Bleeding Grade and Characteristics

Grade 1

Mucocutaneous bleed

Petechiae

Ecchymosis <10 cm

Orophayngeal

Conjunctival

Epistaxis

No intervention

Vaginal spotting (<2 pads/day)

Grade 2

Ecchymosis >10cm

Hematoma

Epistaxis packing

Retinal hemorrhage w/o visual

Bleeding w/o RBC transfusion

Grade 3

Melena*

Hematemesis*

Hemoptysis*

Hematuria*

Vaginal bleeding*

Epistaxis*

Oropharyngeal*

Musculoskeletal/ Soft tissue

* *With transfusion*

- **Grade 4**
- Debilitating
- Non-fatal CNS
- Any fatal bleeding

Miller et al. Cancer 1981; 47:207-214

Initial Treatment or No treatment of ITP

Platelet Count (per µl)	Symptoms	Treatment
> 50,000	None	None
30-50,000	Not bleeding Bleeding	None Glucocorticoids
< 30,000	Not bleeding Bleeding	Glucocorticoids ? Glucocorticoids Hospitalization

Approach to the Treatment of ITP

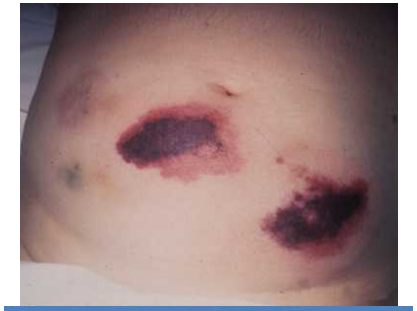
Initial treatment	Glucocorticoids IVIG
Curative therapy	Glucocorticoids Splenectomy Rituximab
Rescue therapy	High dose glucocorticoids IVIG
Chronic therapy	Many agents **Thrombopoietin receptor agonists**

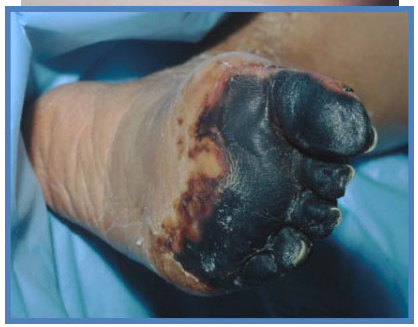
Summary: Thrombopoietin-receptor agonists

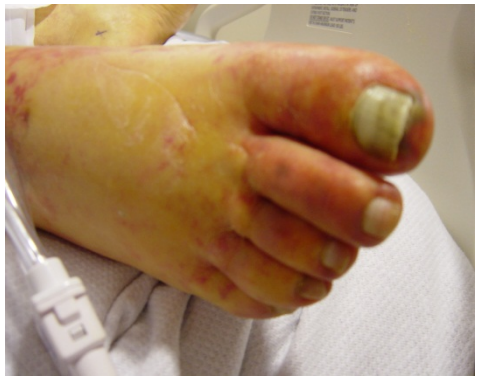
	Romiplostim	**Eltrombopag**
Mechanism	TPOR: active site	TPOR: TM domain
Indications	Chronic ITP	Chronic ITP
Route	SQ	PO
Initial dose	1 mcg/kg/wk	50 mg/day
Overall response	~80%	~80%
Immunogenicity	Yes	No
Hepatic toxicity	No	Yes
Response in splenectomized pts.	Yes	Yes

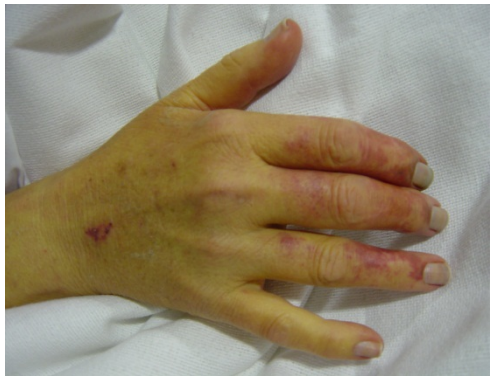
Case 6 C: HIT

56 yr old F underwent open heart surgery 6 days ago. She was given Unfractionated heparin. Her pre-op plt 300K. Patient developed signs of ischemia involving fingers and toes. Plt count 80K, PT 16/12, PTT 65/32. Suspected to have HIT. UFH was stopped and warfarin was given, serious complication happened.









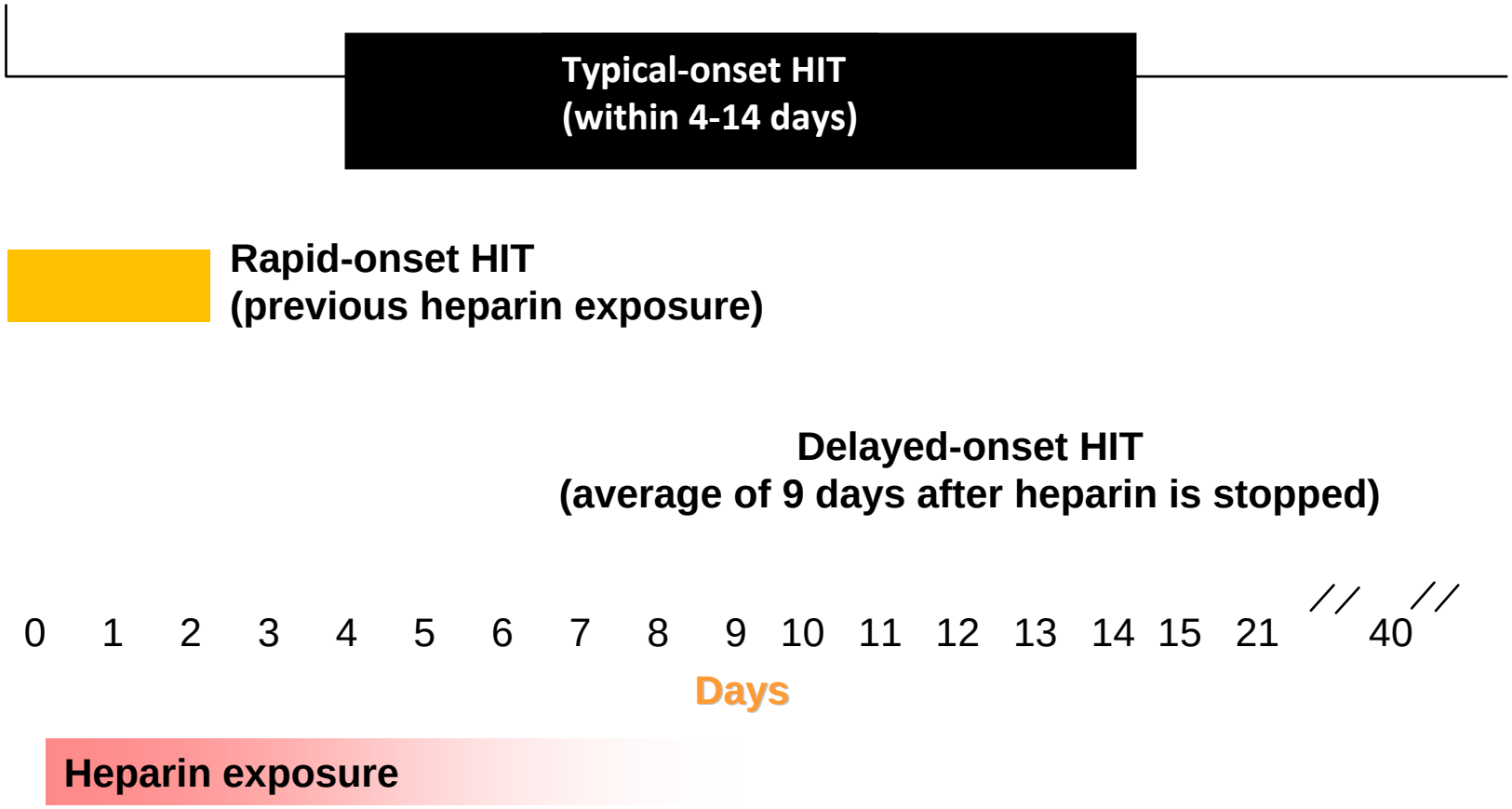
Clinical Suspicion of HIT

- Normal platelet count prior to heparin with a decline to <100,000/µl
  - (or reduction of platelet count by >50%)
- Onset of thrombocytopenia by day 14
- Exclusion of other causes of thrombocytopenia
- Any new thrombotic event while on heparin
- Skin inflammation or necrosis at heparin injection site

Clinical sequelae of HIT

Outcome	Incidence
New thrombosis	up to 50%
Amputation	~10% Associated with arterial thrombosis Associated with venous limb gangrene
Death	10-20%

Heparin-indcued Thrombocytopenia (HIT): Clinical Presentation - Temporal aspects



Six treatment principles of HIT

- **Two Do's**

  *Stop heparin

  *Start alternative A/C
- **Two Don'ts**

  *No warfarin until substantial platelet count recovery

  *No platelet transfusions
- **Two Diagnostics**

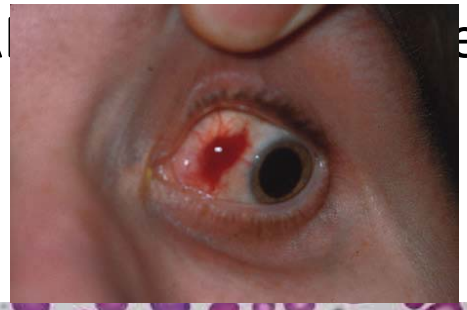
  *Test for HIT

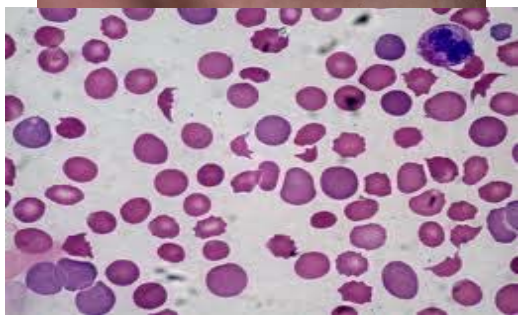
  *Duplex for lower limbs

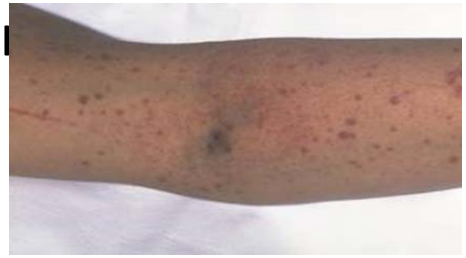
Case 6D: TTP

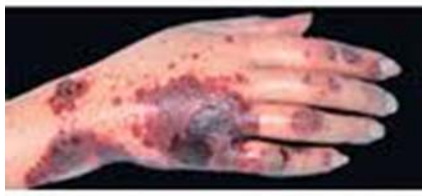
37 yr old lady was admitted with high fever, seizure and confusion for 3 dyas.P/E shown. Temp 40.5,BP 80/50, P122 regular, low volume. Bleeding from needle puncture sites and bruising. Hb 9g/dl, retcs 6%, bilirubin 5 (d1), WBC 19k, Plt 25k, LDH 1400, PT 14/12s, PTT 35/32s, TT 13/11s, Creatinine 2.3. Bld film shown.Fibrinogen. 140mg/dl.

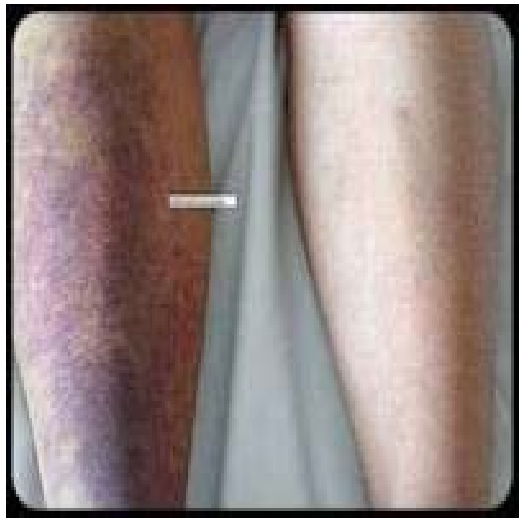
A ely deficie





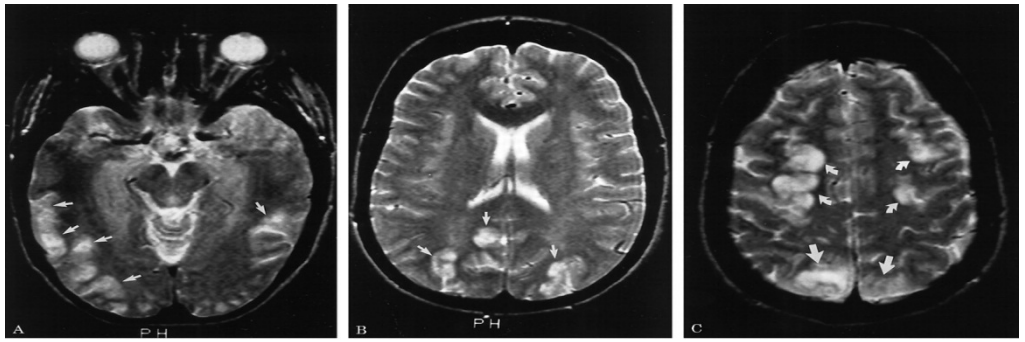




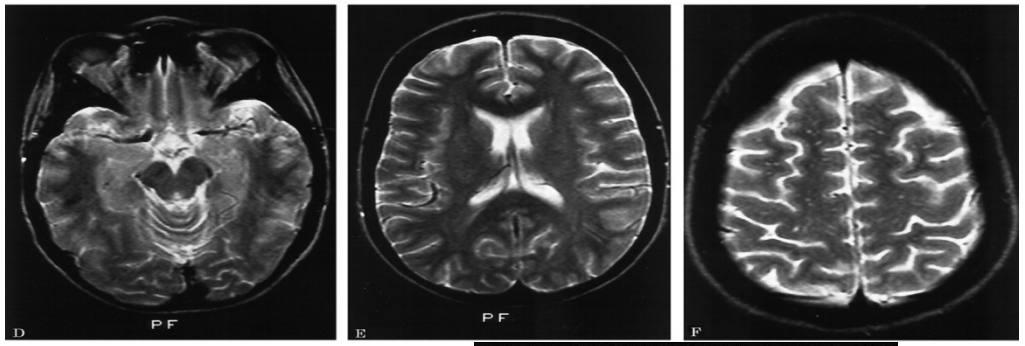


MRI in TTP: leukoencephalopathy, brain infarcts

On admission

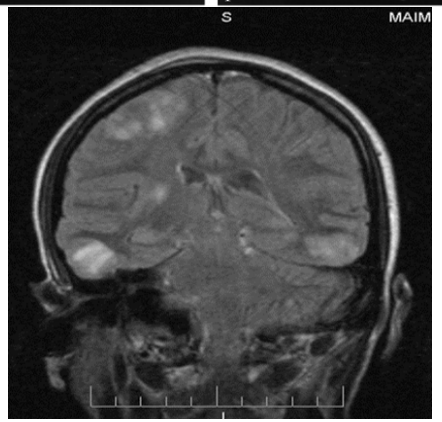


12 wks later



reversible cerebral edema

Brain Infarcts may be seen



Case 6 D: Management & follow-up

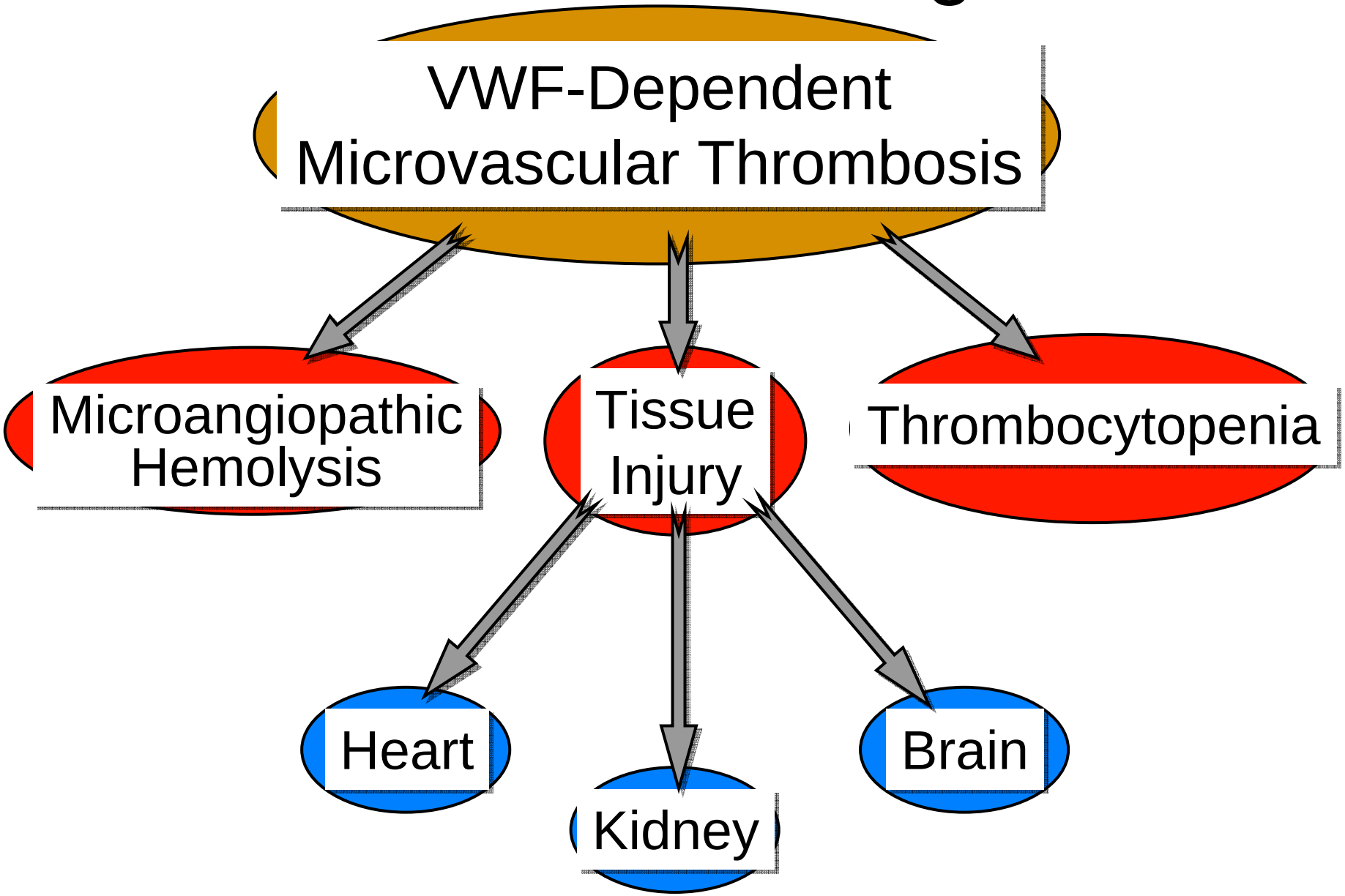
1- Plasma exchange daily until recovery

2- Monitor LDH, Plt count and clinical status

3- Monitor ADAM TS 13

4- Careful follow-up post recovery for ?relapse

Thrombosis Preceding TTP?

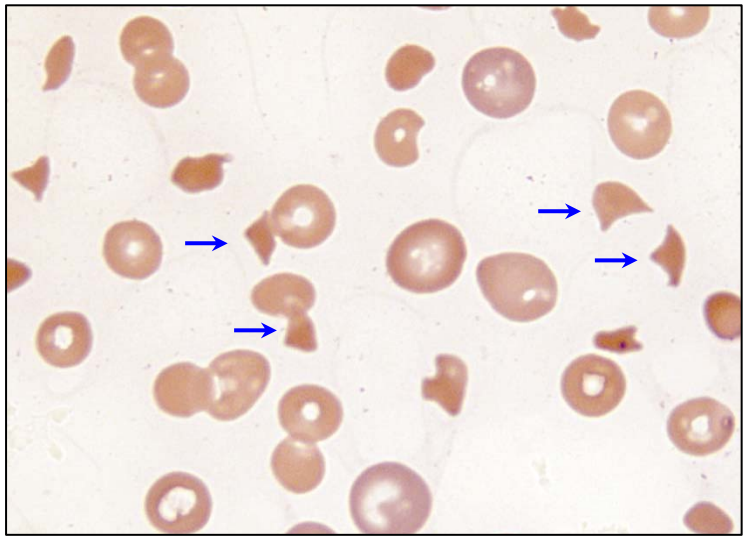


Thrombotic Thrombocytopenic Purpura

A Disorder of VWF Proteolysis

A classic pentad of signs:

- Microangiopathic hemolytic anemia
- Thrombocytopenia
- (Neurologic dysfunction)
- (Renal disease)
- (Fever)



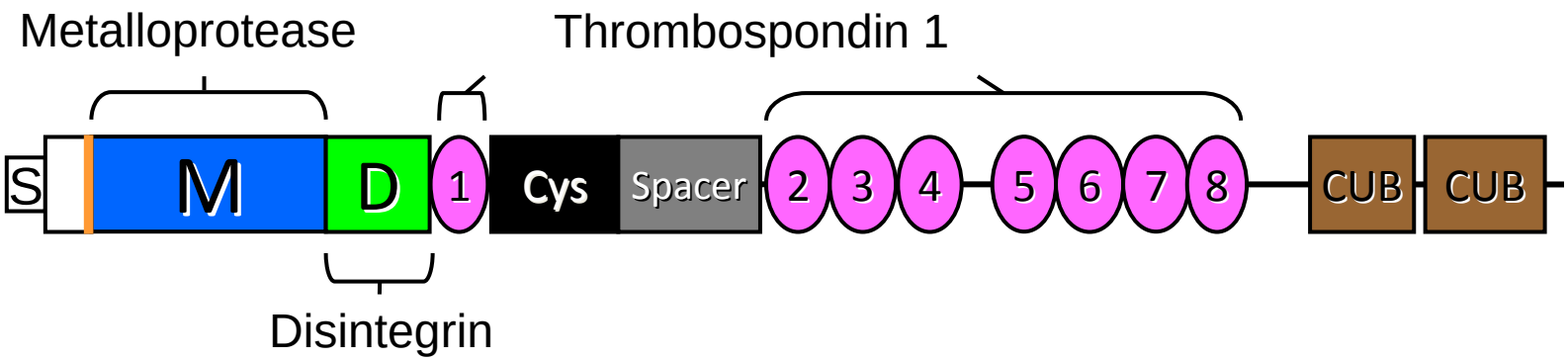
≈ 4 per million incidence

Strikes mainly young adult women

Untreated, mortality >90%

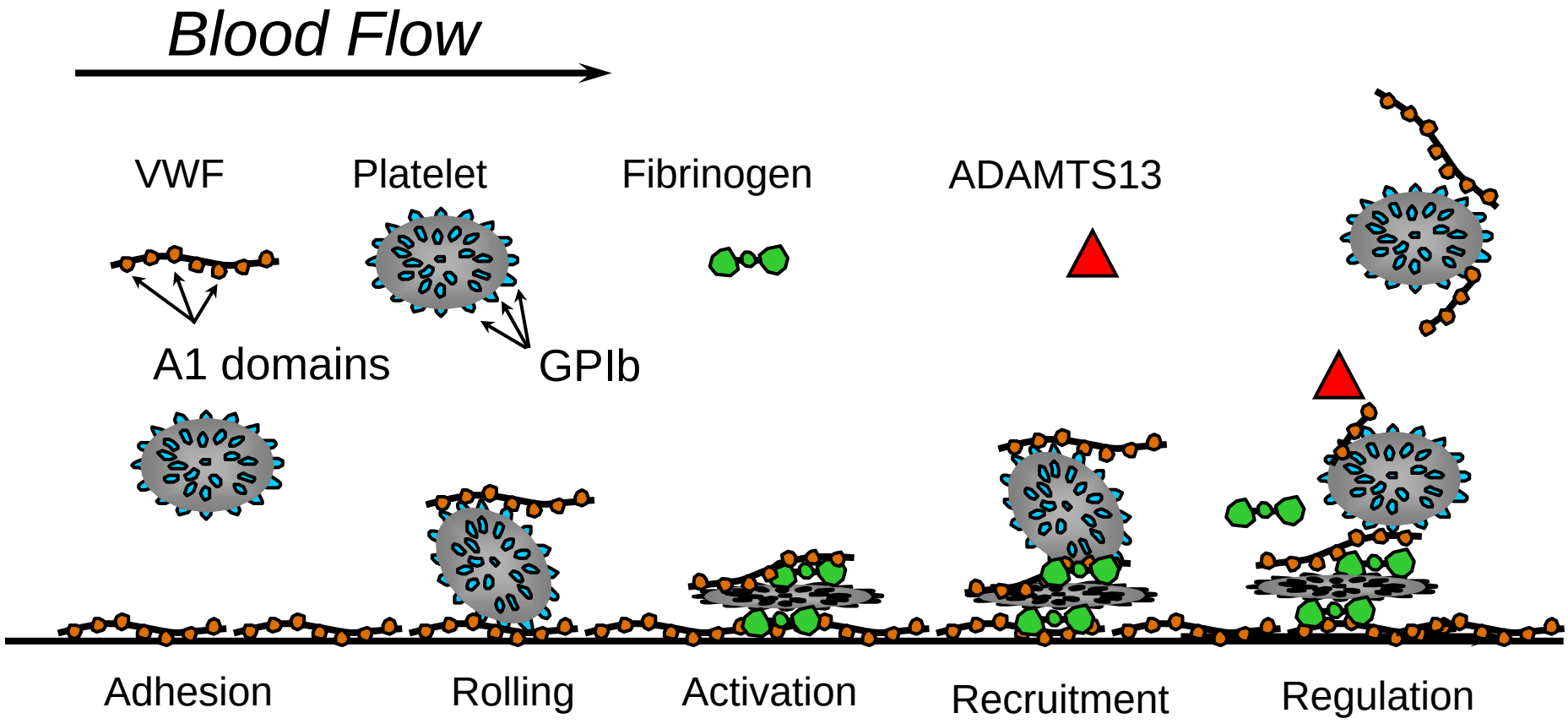
Treated with plasma exchange, mortality <20%

VWF Cleaving Protease (ADAMTS13)



*A D*isintegrin-like *A*nd *M*etalloprotease
with *T*hrombo*S*pondin-1 repeats

VWF and Platelet Adhesion



Thrombotic Thrombocytopenic Purpura: Treatment

- Initial treatment:
  - Plasma exchange (plasmapheresis) daily

- Relapsed or refractory disease:
  - Plasmapheresis ± Rituximab immunosuppressive therapy
  - Other (Vincristine; Splenectomy)
- Adjunctive therapy (unproven role)
  - Glucocorticoids
  - Aspirin