Bleeding Disorders (2) 28.Oct.2015

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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 8 hrly until bleeding stops.
7- Long term contraceptives.
6- Education and counseling.
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
Qualitative platelet defects

**Hereditary defects**

- Defects of platelet **adhesion**
  - Bernard-Soulier disease ("giant platelets syndrome")
  - Von Willebrand's disease

- Defects of platelet **secretion**
  - Storage-pool disease.
  - Gray-platelet disease:

- Defects of platelet **aggregation**
  - Thrombasthenia (Glanzmann's disease)

**Acquired defects:**

- NSAID
  - aspirin (permanently inhibits cyclooxygenase)
  - non-aspirin NSAID (temporarily block cyclo-oxygenase)

- Other antiplatelets
Clinical Manifestations of GT

- Life long mucosal bleeding
- Prolonged bleeding from cuts/wounds
- “Ovarian” bleeding
- “critical” bleeding
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)
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 9–10 days
## Classification of Platelet Disorders

<table>
<thead>
<tr>
<th>Quantitative Disorders</th>
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<tbody>
<tr>
<td>• Abnormal distribution</td>
<td>• Inherited disorders (rare)</td>
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<td>• Dilution effect</td>
<td>• Acquired disorders</td>
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<td></td>
<td>- Cardiopulmonary bypass</td>
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</table>
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
- Trousseau’s syndrome
- 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

- 0: No bleeding
- 1: Minimal, related to trauma
- 2: Spontaneous, self-limited
- 3: Spontaneous, requiring local treatment
- 4: Spontaneous, uncontrolled or poorly controlled

From: Lacey and Penner, Seminars in Thrombosis and Hemostasis (1977)
### WHO Bleeding Grade and Characteristics

<table>
<thead>
<tr>
<th>Grade 1</th>
<th>Grade 2</th>
<th>Grade 3</th>
<th>Grade 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mucocutaneous bleed</td>
<td>Ecchymosis &gt;10cm</td>
<td>Melena*</td>
<td>Grade 4</td>
</tr>
<tr>
<td>Petechiae</td>
<td>Hematoma</td>
<td>Hematemesis*</td>
<td>Debitating</td>
</tr>
<tr>
<td>Ecchymosis &lt;10 cm</td>
<td>Epistaxis</td>
<td>Hemoptysis*</td>
<td>Non-fatal</td>
</tr>
<tr>
<td>Oropharyngeal</td>
<td>Retinal hemorrhage w/o visual</td>
<td>Hematuria*</td>
<td>CNS</td>
</tr>
<tr>
<td>Conjunctival</td>
<td>Packing</td>
<td>Vaginal bleeding*</td>
<td>Any fatal</td>
</tr>
<tr>
<td>Epistaxis</td>
<td></td>
<td>Epistaxis*</td>
<td>bleeding</td>
</tr>
<tr>
<td>No intervention</td>
<td>Retinal hemorrhage w/o visual</td>
<td>Oropharyngeal*</td>
<td></td>
</tr>
<tr>
<td>Vaginal spotting (&lt;2 pads/day)</td>
<td></td>
<td>Musculoskeletal/Soft tissue</td>
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<td></td>
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<td>* With transfusion</td>
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</tbody>
</table>

### Initial Treatment or No treatment of ITP

<table>
<thead>
<tr>
<th>Platelet Count (per µl)</th>
<th>Symptoms</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt; 50,000</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>20-50,000</td>
<td>Not bleeding</td>
<td>None</td>
</tr>
<tr>
<td></td>
<td>Bleeding</td>
<td>Glucocorticoids</td>
</tr>
<tr>
<td></td>
<td></td>
<td>IVIG or Anti-D</td>
</tr>
<tr>
<td>&lt; 20,000</td>
<td>Not bleeding</td>
<td>Glucocorticoids ?</td>
</tr>
<tr>
<td></td>
<td>Bleeding</td>
<td>Glucocorticoids</td>
</tr>
<tr>
<td></td>
<td></td>
<td>IVIG or Anti-D</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Hospitalization</td>
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# Approach to the Treatment of ITP

<table>
<thead>
<tr>
<th></th>
<th>Initial treatment</th>
<th>Curative therapy</th>
<th>Rescue therapy</th>
<th>Chronic therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>IVIG/Anti-D</td>
<td>Glucocorticoids</td>
<td>Glucocorticoids Splenectomy Rituximab</td>
<td>Many agents Thrombopoietin receptor agonists</td>
</tr>
<tr>
<td></td>
<td>Glucocorticoids</td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>

**Rescue therapy**
- High dose glucocorticoids
- IVIG/(Anti-D)

**Chronic therapy**
- Many agents
- Thrombopoietin receptor agonists
## Summary: Thrombopoietin-receptor agonists

<table>
<thead>
<tr>
<th></th>
<th><strong>Romiplostim</strong></th>
<th><strong>Eltrombopag</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Mechanism</strong></td>
<td>TPOR: active site</td>
<td>TPOR: TM domain</td>
</tr>
<tr>
<td><strong>Indications</strong></td>
<td>Chronic ITP</td>
<td>Chronic ITP</td>
</tr>
<tr>
<td><strong>Route</strong></td>
<td>SQ</td>
<td>PO</td>
</tr>
<tr>
<td><strong>Initial dose</strong></td>
<td>1 mcg/kg/wk</td>
<td>50 mg/day</td>
</tr>
<tr>
<td><strong>Overall response</strong></td>
<td>~80%</td>
<td>~80%</td>
</tr>
<tr>
<td><strong>Immunogenicity</strong></td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td><strong>Hepatic toxicity</strong></td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td><strong>Response in splenectomized pts.</strong></td>
<td>Yes</td>
<td>Yes</td>
</tr>
</tbody>
</table>
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
<table>
<thead>
<tr>
<th>Outcome</th>
<th>Incidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>New thrombosis</td>
<td>up to 50%</td>
</tr>
<tr>
<td>Amputation</td>
<td>~10%</td>
</tr>
<tr>
<td></td>
<td>Associated with arterial thrombosis</td>
</tr>
<tr>
<td></td>
<td>Associated with venous limb gangrene</td>
</tr>
<tr>
<td>Death</td>
<td>10-20%</td>
</tr>
</tbody>
</table>

Clinical sequelae of HIT
Heparin-induced Thrombocytopenia (HIT): Clinical Presentation - Temporal aspects

- **Typical-onset HIT** (within 4-14 days)
- **Rapid-onset HIT** (previous heparin exposure)
- **Delayed-onset HIT** (average of 9 days after heparin is stopped)
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, P 122 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.

ADAM-TS 13 severely deficient.
On admission

MRI in TTP: leukoencephalopathy, brain infarcts

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
Thrombotic Thrombocytopenic Purpura: Pentad of findings

- **Clinical findings**
  - Fever
  - Neurologic changes
  - Renal impairment

- **Laboratory findings**
  - Microangiopathic hemolytic anemia (schistocytes) Hgb <10 g/dl and laboratory findings of hemolysis
  - Thrombocytopenia (usually < 20,000/µl)
VWF and Platelet Adhesion

*Blood Flow*

- VWF
- Platelet
- Fibrinogen
- VWF protease (ADAMTS13)

- Adhesion: $\approx 1000 \, \mu m \, s^{-1}$
- Rolling: $\approx 4 \, \mu m \, s^{-1}$
- Activation: $\approx 0 \, \mu m \, s^{-1}$
- Recruitment
- Regulation
VWF Cleaving Protease (ADAMTS13)

A Disintegrin-like And Metalloprotease with Thrombospondin-1 repeats
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