Thrombocytopenia

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Thrombocytopenia

Presentation

1. Definition
2. Platelet Physiology, Thromboiesis, & Platelet Function
3. Bleeding Risk
4. Clinical Diagnosis
5. Differential Diagnosis
6. Classification
7. Evaluation : History & Clinical Examination
8. Complementary Examinations
9. ITP
10. Other common etiologies
11. Patient Management
Definition

= platelet count of less than 150,000/µL (150 x 10⁹/L)

→ clinically suspected when there is a history of easy bruising or bleeding in a child

→ incidental finding during routine evaluation
Platelet Physiology

• produced in the bone marrow
• fragmentation of precursor megakaryocytes
• small colorless irregular shaped cell fragment with nonnucleated protoplasm of 2-3 µmeter in diameter
• life span of 5-10 days
• production per day $1\times10^{11}$ with tenfold increase if necessary
• removal by mono-macrophage system
Thrombocytopenia

Platelet production in the bone marrow

Patel et al. J.Clin Invest. 2005
Thrombopoiesis

- thrombopoietin (TPO) primary regulator
- acidic glycoprotein produced in liver, kidney & BM
- TPO acts in conjunction with other cytokines (IL-3, IL-6, TNF-α & IL-11)
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Thrombopoiesis

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Platelet Function

• maintain vascular endothelium integrity

• primary homeostasis: hemorrhage control following small-vessel injury by platelet plug formation

• secondary homeostasis: more extensive injury & injury of larger blood vessels requires platelets but also participation of the coagulation system to provide a firm, stable, fibrin clot.
Platelet Function: doesn’t work alone

- platelet adhesion to damaged blood vessel: requires normal platelet, functional membrane receptor & mediation by von Willebrand factor

- platelet aggregation (plug) depends on enhancement by functional fibrinogen and other mediators
## Thrombocytopenia

### Platelet Count & Bleeding Risk

<table>
<thead>
<tr>
<th>Platelet Count ((\times 10^3/\text{mcL} \ [\times 10^9/\text{L}]))</th>
<th>Signs and Symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;100</td>
<td>None</td>
</tr>
<tr>
<td>50 to 100</td>
<td>Minimal (after major trauma and surgery)</td>
</tr>
<tr>
<td>20 to 50</td>
<td>Mild (cutaneous)</td>
</tr>
<tr>
<td>5 to 20</td>
<td>Moderate (cutaneous and mucosal)</td>
</tr>
<tr>
<td>&lt;5</td>
<td>Severe (mucosal and central nervous system)</td>
</tr>
</tbody>
</table>

*Other variables: function of platelets, anatomic defect, associated coagulopathy*

Buchanan Ped in Review. 2005; 26:401
Thrombocytopenia

Platelet Count & Bleeding Risk

Consolini. Ped in Review. 2011; 32:135
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When history is positive for spontaneous (non-traumatic) bruising or bleeding, either mucosal or cutaneous:

- Petechiae
- Purpura
- Ecchymosis
- Mucosal bleeding: epistaxis, gingival, gastrointestinal, vaginal or abnormal menstruation
- Other signs of bleeding: hematuria, hemoptysis, intracranial
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**CLINICAL DIAGNOSIS**

Petechiae:
- pinhead-sized, red, flat, discrete lesions
- caused by extravasation of red cells from skin capillaries
- do not blanch under pressure
- non-tender, non-palpable
- occurring in crops

Purpura:
- confluent petechiae
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**CLINICAL DIAGNOSIS**

Ecchymoses:
- non-tender bleeding into the skin
- small, multiple and superficial
- variety of colors: red/purple -> extravasated blood; green/yellow/brown -> breakdown of heme
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Differential Diagnosis

• Guided by an understanding of the cause and/or etiology

• Confirmation of diagnosis by laboratory +/- blood smear: platelets < 150,000/µL (150 x 10⁹/L)
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**DIFFERENTIAL DIAGNOSIS**

- Exclusion of:
  - normal active children: bruising typically over pretibial surfaces
  - large soft-tissue hematomas, joint & muscle hemorrhage: hemophilia and other coagulation disorders
  - child abuse: location of bruising may be generalized
  - various forms of vasculitis: large bruises with normal or increased platelet count
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Categorize the different etiologies

• According to age: neonatal

• According to platelet size: congenital/genetic

• Mode of acquisition: acquired versus congenital

• According to etiology: immune (ITP = Immune Thrombocytopenia Purpura) versus non-immune

• According to underlying pathological mechanism
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Classification according to age: neonatal

“Sick” neonate: most common
- infection, asphyxia, respiratory disease or Necrotizing Enterocolitis

“Well” neonate:
- Intra-uterine growth delay
- Mother pre-eclampsia
- congenital amegacaryocytosis
- Transplacental passage of antiplatelet antibody (auto- or allo-)
# Thrombocytopenia

## Classification according to age: neonatal

### Table of Immune Thrombocytopenia in the Neonate

<table>
<thead>
<tr>
<th>Maternal Idiopathic Thrombocytopenic Purpura</th>
<th>Neonatal Alloimmune Thrombocytopenia</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Approximate frequency</strong></td>
<td>1 in 50,000</td>
</tr>
<tr>
<td><strong>Type of antibody</strong></td>
<td>Maternal autoantibody</td>
</tr>
<tr>
<td><strong>Target antigens</strong></td>
<td>Common to all platelets</td>
</tr>
<tr>
<td><strong>Intrauterine hemorrhage</strong></td>
<td>None</td>
</tr>
<tr>
<td><strong>Treatment of fetus</strong></td>
<td>Unnecessary</td>
</tr>
<tr>
<td><strong>Postnatal hemorrhage</strong></td>
<td>Uncommon</td>
</tr>
<tr>
<td><strong>Postnatal treatment</strong></td>
<td>Usually unnecessary; IVIG if platelet count $&lt; 10$ to $20 \times 10^3$/mcL ($&lt; 10$ to $20 \times 10^9$/L)</td>
</tr>
<tr>
<td><strong>Resolution of neonatal thrombocytopenia</strong></td>
<td>Within 2 to 3 months</td>
</tr>
<tr>
<td><strong>Recurrence rate in subsequent pregnancies</strong></td>
<td>High</td>
</tr>
</tbody>
</table>

HPA = human platelet antigen, IVIG = intravenous immune globulin.
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Classification according to acquisition mode

Congenital/Inherited: genetic mutations affecting the platelets, TPO, or/and TPO receptor (cMpl)

- Bernard Soulier Syndrome
- MYH9-related disorders p.ex. May Hegglin syndrome
- Gray Platelet Syndrome
- Von Willebrandt Syndrome
# Thrombocytopenia

## Congenital/Inherited classification

<table>
<thead>
<tr>
<th>Disorder</th>
<th>Inheritance</th>
<th>Clinical Features</th>
<th>Laboratory</th>
</tr>
</thead>
</table>
| Thrombocytopenia-absent Radius (TAR) syndrome | Variable Unclear genetic cause                   | Bilateral absent radii Normal thumbs Other skeletal,   | • Severe thrombocytopenia
|                                                |                                                  |   genitourinary, heart anomalies                                  | • Absent or decreased megakaryocytes                                      |
| Amegakaryocytic Thrombocytopenia              | Autosomal recessive : Mutation in TPO-R          | Absence of skeletal anomalies seen in TAR              | • Severe thrombocytopenia
|                                                |                                                  |                                                  | • Absent or decreased megakaryocytes                                      |
| Wiskott- Aldrich syndrome                     | X-linked recessive : Abnormal gene encodes for   | Atopic dermatitis Thrombocytopenic purpura Increased  | • Small defective platelets
|                                                | platelet function                                | infections due to immunodeficiency                      | • Normal megakaryocytes                                                   |
| Bernard-Soulier syndrome                      | Autosomal recessive : Dysfunction/absence platelet receptor for von Willebrand factor | Easy bruising Gingival & GI bleeding Severe hemorrhage with trauma/surgery | • Macrothrombocytopenia                                                  |
| MYH9-related disease p.ex. May-Hegglin anomaly| Autosomal dominant : Mutation myosin (non-muscle) heavy chain | Bleeding, nephritis, hearing loss, cataracts          | • Macrothrombocytopenia
|                                                |                                                  |                                                  | • leukocyte inclusions                                                    |
| Gray platelet syndrome                        | Autosomal dominant                               | Bleeding, usually mild                                 | • Macrothrombocytopenia
|                                                |                                                  |                                                  | • reduction in granule with pale platelets                                |
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Classification according to the Mechanism

1. Insufficient production
2. Abnormal distribution
3. Excessive destruction
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Classification according to the Mechanism

1. Insufficient production:
   - Inherited or Genetic
   - Acquired
     - Infection
     - Cyanotic Heart Disease
     - Nutritional Deficiencies
   - Marrow injury or infiltration
     - Acute lymphoblastic leukemia and other malignancies
     - Kasabach-Merritt
     - Acquired aplastic anemia
     - Fanconi pancytopenia
Thrombocytopenia

Classification according to the mechanism

2. Abnormal distribution:
   - Spleen sequestration and trapping
   - Portal hypertension: chronic liver disease
   - Malaria if associated with hypersplenism
   - DIC associated with Sepsis
   - Hemolytic Uremic Syndrome (typical & atypical) and thrombotic thrombocytopenic purpura (TTP): both resulting in microangiopathic hemolytic anemia with platelet consumption and vasculitis
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Classification according to the mechanism

3. Excessive destruction:
   - Microangiopathy
   - Mechanical destruction: ECMO
   - Hereditary platelet abnormalities
   - Immunological TP:
     - Immune (Idiopathic) Thrombocytopenia Purpura
     - Juvenile Arthritis
     - Systemic Lupus
     - Medication or Heparin-use
     - Post-viral infection (CMV, EBV, HIV, Adeno, Parvovirus, …)
     - Post-vaccination (Hib, Hepatitis B, ROR, …)
Most common causes in Infants & Children

- Immune process by antibody production: autoAb p.ex. **Immune (Idiopathic) Thrombocytopenic Purpura**, alloAb, or drug-dependent Ab

- Nonimmune mechanism: bone marrow infiltration (acute leukemia)
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Evaluation: History and Clinical examination

- Past & current bleeding: bruising with & without trauma, nosebleeds, blood in urine or stools, gum bleeding (tooth brushing, dentist), menstrual bleeding?
- Duration & onset of bleeding?
- If abrupt: specific trigger?
- “RED flags” in the history/examination*
# Thrombocytopenia

## Evaluation: History and Clinical Examination

**Red Flags Suggesting a Diagnosis Other Than Immune Thrombocytopenic Purpura**

<table>
<thead>
<tr>
<th>History</th>
<th>Physical Examination</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Fever</td>
<td>• Lymphadenopathy</td>
</tr>
<tr>
<td>• Bone pain</td>
<td>• Splenomegaly</td>
</tr>
<tr>
<td>• Weight loss</td>
<td>• Joint swelling</td>
</tr>
<tr>
<td>• Fatigue</td>
<td>• Short stature</td>
</tr>
<tr>
<td>• Recent history of infections or vaccinations</td>
<td>• Limb defects, including radial agenesis and thumb abnormalities</td>
</tr>
<tr>
<td>• Past medical history of diseases associated with thrombocytopenia</td>
<td>• Cataracts</td>
</tr>
<tr>
<td>(eg, autoimmune disorders, cirrhosis)</td>
<td>• Sensorineural hearing loss</td>
</tr>
<tr>
<td>• Dietary history suggestive of iron, vitamin B12, or folate deficiency</td>
<td>• Oral leukoplakia</td>
</tr>
<tr>
<td>• Exposure to medications known to be associated with thrombocytopenia</td>
<td>• Dystrophic nails</td>
</tr>
<tr>
<td>• Travel history to an endemic area for malaria</td>
<td>• Eczema in male patient</td>
</tr>
<tr>
<td></td>
<td>• Frequent infections</td>
</tr>
<tr>
<td></td>
<td>• Superficial hemangiomas</td>
</tr>
</tbody>
</table>
Thrombocytopenia

**COMPLIMENTARY EXAMINATIONS**

- Work up according to etiology
- Minimum:
  - complete blood count (CBC) with platelet count & mean platelet volume (MPV)
  - peripheral blood smear (PBS)
- Repeat platelet count (if clinical “nonsense”) to exclude artefact or laboratory error
- Coagulation study: prothrombin time (PT), partial thromboplastin time (PTT), fibrinogen
COMPLEMENTARY EXAMINATIONS

- Complete the work up according to the initial results and suspicion of underlying cause:
  - Platelet function analyzer and platelet aggregation testing
  - Coombs test
  - Presence of schistocytes or spherocytes
  - Bone marrow aspirate: blasts, pancytopenia
  - Viral serology or according to suspicion: HIV, Hepatitis B & C, H. Pylori
  - Screening for inherited disorders, as indicated
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Diagnostic algorithm

Consolini. Ped in Review. 2011; 32:135
ITP = Immune Thrombocytopenic Purpura

- acquired immune-mediated
- Primary: absence of initiating/underlying cause
- Secondary: underlying cause or drug exposure
- incidence of 3 to 8 cases/100,000 children
- presentation between 2 and 10 years (peak 2-5)
- often after a preceding viral illness
- increased risk after MMR immunization: 50% of cases in children < 2 years, transient & rarely severe
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ITP = Immune Thrombocytopenic Purpura

• History :
  ➢ sudden bruising or mucocutaneous bleeding
  ➢ otherwise healthy child
  ➢ NO systemic symptoms (fever, weight loss or bone pain)

• Clinical examination :
  ➢ mucocutaneous bleeding
  ➢ child appears well
  ➢ NO lymphadenopathy or hepatosplenomegaly (or mild due to preceding viral infection)
Thrombocytopenia

ITP = Immune Thrombocytopenic Purpura

Diagnosis of ITP: 2 criteria

1. isolated thrombocytopenia with otherwise normal blood counts & normal coagulation
2. no clinically apparent associated conditions
Thrombocytopenia

ITP = Immune Thrombocytopenic Purpura

Bleeding symptoms

- Serious bleeding is rare: platelet counts < 20 x 10⁹/L
- “wet” purpura: ICH, retinal hemorrhages, mucosal bleeding
- Platelet counts > 30 x 10⁹/L usually asymptomatic & do not seek medical attention
### Thrombocytopenia

**ITP = Immune Thrombocytopenic Purpura**

**Work up**

- CBC, platelet count, blood smear, coagulation testing
- If persistent or chronic: antinuclear Ab, serum immunoglobulins (IgG, A, M), antiphospholipid Ab
- If unexplained etiology & chronic course: consider bone marrow aspirate
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ITP = Immune Thrombocytopenic Purpura

Patient Management

- Platelets < 20 x 10⁹/L & serious bleeding: transfusion for immediate hemostasis (ICH)
- Platelet > 20 x 10⁹/L & asymptomatic:
  1. Restriction of activity
  2. Avoidance of medications with antiplatelet/anticoagulation activity
  3. Treatment indication based on risk of bleeding
  4. Refractory ITP and/or chronic
ITP = Immune Thrombocytopenic Purpura

3. Newly diagnosed ITP with risk of bleeding

- Corticosteroids
  - Oral Prednisone: 2 mg/kg/day over 2-4 week course
  - IV Methylprednisolone: 30 mg/kg/d max 1g over 3 to 7 day course
- Intravenous Immune Globulin (IGIV): 1 g/kg over 1 to 2 day course
- Anti-Rho(D) Immune Globulin: 50-75µg/kg single dose
Thrombocytopenia

ITP = Immune Thrombocytopenic Purpura

4. Refractory ITP with significant bleeding
   - Splenectomy: “curative”
   - Methylprednisolone: 30 mg/kg/d max 1g over 3 day course then 20 mg/kg/d over 4 days
   - Single or combination regimes: cyclosporin A, Azathioprine, Vincristine, Cyclophosphamide, danazol +/- CS, +/- IGIV
   - Rituximab: 375 mg/m2 1x/week for 4 weeks
   - Anti-Rho(D) Immune Globulin: 50-75µg/kg single dose
   - TPO-R agonists: Romiplostim, Eltrombopag
Thrombocytopenia

ITP = Immune Thrombocytopenic Purpura

Patient Management

- Treatment reduces the severity & duration of initial thrombocytopenic episode
- No pharmacological intervention if mild-moderate ITP as bleeding is rare, except
  1. Concomitant or preexisting condition
  2. Undergo procedure with blood loss risk
- No means to predict which child may have “wet” purpura, therefore treatment is often the rule
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ITP = Immune Thrombocytopenic Purpura

Patient Management

- All treatments are temporizing interventions
- Usually given on ambulatory basis if no bleeding risk
- Monitor platelet count 1-2x/week & continue until normal and stable
- Treatment not to be continued until normal platelets counts achieved
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ITP = Immune Thrombocytopenic Purpura

Patient Outcome

- 2/3 recover within 6 months with or without treatment
- 1/3 develop chronic ITP ie. > 12 months
- Chronic ITP more likely in older children (>10 years) and those with bleeding lasting > 14 days
- Chronic ITP does improve over time
- Small % refractory ITP = hemorrhagic symptoms and resistance to corticosteroid and IGIV treatment
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Pathogenesis following viral infections

• Hypothesis:

1. viral destruction of megakaryocytes and platelets
2. immunostimulation causing alterations in cytokines that involved in platelet production
3. Antigene mimicry between virus & platelet antibodies
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Association with Other Cytopenias

- Pancytopenia with systemic symptoms or findings on clinical examination
- URGENT situation!
- Immediate referral to pediatric hematologist
- Safe platelet count will be small part of overall treatment plan!
Management Goal

- guided by understanding of its cause & clinical course
- maintain a “safe platelet count” in order to prevent bleeding: patient/etiology dependent
- correction of the cause not always possible: (congenital) or necessary (asymptomatic and/or mild ITP)
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Management Goal

1. Activity Restrictions to minimize bleeding risk
2. Medication avoidance: antiplatelet or anticoagulant activity p.ex. Aspirin preparations, ibuprofen, other NSAIDs
3. Limit invasive procedures: platelet counts > 50 \times 10^9/L
4. Emergency of Critical Bleeding (ICH): transfusion associated with high dose Methylprednisolone and single dose of IGIV
Thrombocytopenia

**CASE DEFINITION**

- Platelet concentration inferior to $150 \times 10^6$/ml

**Confirmed by blood smear examination**

**Clinical signs of spontaneous bleeding (i.e. non traumatic)**
- Purpura (i.e. petechiae, purpura sensu stricto, ecchymoses)
- Exudative hemorrhage
- Hematomas
- Hematemesis
- Occult bleeding from the rectum
- Epistaxis
- Hemoptyisis
- Hematuria
- Vaginal bleeding outside the menstrual period
- Conjunctival bleeding
- Intracranial bleeding

**THROMBOCYTOPENIA**

- Level I diagnostic certainty

**THROMBOCYTOPENIA**

- Level II diagnostic certainty

**THROMBOCYTOPENIA**

- Level I diagnostic certainty
Thank you for your attention!

Any Questions?
References