Approach to thrombocytopenia and management of ITP

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04-08-2014
Causes of thrombocytopenia

- Thrombocytopenia
  - Pseudo
    - Decreased production
      - Inherited/Acquired
  - True
    - Increased destruction
      - Inherited/Acquired
    - Sequestration
Pseudothrombocytopenia

- 15-20% of all isolated thrombocytopenia.
- Platelet aggregation in the presence of EDTA.
- Detected on Blood smear by manual count.
- Repeat count on fresh citrated sample.
## Decreased production - Inherited

<table>
<thead>
<tr>
<th>Small platelets, MPV &lt;7 fL</th>
<th>Normal platelets, MPV 7-11 fL</th>
<th>Large/giant platelets, MPV &gt;11 fL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wiskott-Aldrich syndrome (X linked)</td>
<td>Familial platelet disorder/acute myeloid leukemia (AD)</td>
<td>May-Hegglin anomaly (AD)</td>
</tr>
<tr>
<td>X-linked thrombocytopenia</td>
<td>Chromosome 10/THC2 (AD)</td>
<td>Fechtner syndrome (AD)</td>
</tr>
<tr>
<td></td>
<td>Congenital amegakaryocytic thrombocytopenia (AR)</td>
<td>Epstein syndrome (AD)</td>
</tr>
<tr>
<td></td>
<td>Thrombocytopenia and absent radii (AR)</td>
<td>Sebastian syndrome (AD)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Mediterranean thrombocytopenia (AD)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Bernard-Soulier syndrome (AR)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Velocardiofacial/DiGeorge syndrome (AD)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>GATA1 mutation (X linked)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Gray platelet syndrome (AD)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Paris-Trousseau thrombocytopenia/Jacobsen syndrome (AD)</td>
</tr>
</tbody>
</table>
Decreased production- acquired

- Drug induced marrow suppression (chemotherapy)
- Radiation therapy
- Infection-Viral (HCV, HIV, CMV), bacterial (sepsis)
- Alcohol
- MDS
- Myelofibrosis
- Infiltration- granuloma, solid tumours
- Aplastic anaemia
- Haematologic malignancy- leukaemia, lymphoma, myeloma
- Nutritional-Vit B$_{12}$ deficiency
Increased destruction-*acquired*

- **Immune-**
  - Immune thrombocytopenic purpura
  - Neonatal alloimmune thrombocytopenia
  - Post transfusion purpura
  - Drugs

- **Nonimmune-**
  - Shortened circulation- DIC, TTP, HIT(immune component)
  - Turbulent blood flow- haemangioma, abnormal cardiac valve, intra aortic balloon pump
Drugs causing thrombocytopenia

- Abciximab
- Acetaminophen
- Carbamezepine
- Chlorpropamide
- Cimetidine
- Danazol
- Diclofenac
- Efalizumab
- Eptifibatide
- Gold
- Valproate

- Hydrochlorothiazide
- Interferon-α
- Methyldopa
- Nalidixic Acid
- Quinidine
- Quinine
- Ranitidine
- Rifampin
- Tirofiban
- Trimethoprim/sulfamethoxazole
- Vancomycin
- Penicillin, cephalosporins

James N. George and Richard H. Aster
Hematology 2009
## Initial evaluation in thrombocytopenia

<table>
<thead>
<tr>
<th>Review bleeding history</th>
<th>Acquired</th>
<th>Congenital</th>
</tr>
</thead>
<tbody>
<tr>
<td>Onset-epistaxis, gum bleed, purpura, menorrhagia</td>
<td>Recent</td>
<td>Lifelong</td>
</tr>
<tr>
<td>Medications</td>
<td>Changes</td>
<td>No</td>
</tr>
<tr>
<td>Bleed after trauma</td>
<td>Usually No in ITP</td>
<td>Yes</td>
</tr>
<tr>
<td>Family history</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Normal previous platelet count</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Response to treatment (steroid, IVIg, anti D)</td>
<td>Yes in ITP</td>
<td>No</td>
</tr>
<tr>
<td>Response to platelet transfusion</td>
<td>Poor increment in ITP</td>
<td>Good increment</td>
</tr>
</tbody>
</table>
Laboratory evaluation

• Complete blood count- MPV, other cytopenia.
• Peripheral blood smear- platelet number, morphology, clumps, white cell or red cell changes.
• Bone marrow examination.
Approach to thrombocytopenia

- Thrombocytopenia
  - Rule out pseudothrombocytopenia
    - Inherited thromocytopenia
    - Sequestration
      - Look for splenomegaly.
    - Acquired
      - Reduced production.
    - Acquired
      - Increased destruction.
        - Immune or nonimmune
Management of ITP
Management of ITP

• Diagnosis of exclusion.
• History and physical examination.
• Laboratory evaluation including bone marrow examination.
Definitions of ITP

- Primary
- Secondary

- Newly diagnosed ITP: within 3 months from diagnosis.
- Persistent ITP: 3 to 12 months from diagnosis. Includes patients not reaching spontaneous remission or not maintaining complete response off therapy.
- Chronic ITP: lasting for more than 12 months.
- Severe ITP: symptoms at presentation sufficient to mandate treatment, or occurrence of new symptoms requiring additional therapeutic intervention with a different platelet-enhancing agent or an increased dose.

*Standardization of terminology, definitions and outcome criteria in immune thrombocytopenic purpura of adults and children: report from an international working group*  
*Blood. 2009;113:2386-2393*
Refractory ITP

Failure to achieve at least R or loss of R after splenectomy
Need of treatment(s) (including, but not limited to, low dose of corticosteroids) to minimize the risk of clinically significant bleeding.
Need of on-demand or adjunctive therapy alone does not qualify the patient as refractory.
Primary ITP confirmed by excluding other supervened causes of thrombocytopenia

*Standardization of terminology, definitions and outcome criteria in immune thrombocytopenic purpura of adults and children: report from an international working group*

*Blood. 2009;113:2386-2393*
Approaches to the Treatment of ITP

1. Splenectomy

2. Thrombopoietin, thrombopoietic agents, corticosteroids

3. Azathioprine, cyclophosphamide, cyclosporine, corticosteroids, danazol, mycophenolate mofetil

4. Antibody against CD154

5. Antibody against CD20, intravenous immune globulin (Ig)

6. Plasmapheresis

7. Platelet transfusion

Bone marrow

Glycoprotein

Autoantibody

Platelet

Corticosteroids, intravenous immune globulin, Rh0(D) immune globulin, danazol, vinca alkaloids

Macrophage

Michael E. Bromberg

When to treat?
Trigger for treatment

- Platelet count <30,000/cmm
- Platelet count 30-50,000/cmm, symptomatic patient
- No treatment if platelet count >50,000/cmm
## Criteria for assessing response to ITP treatments

<p>| | |</p>
<table>
<thead>
<tr>
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</table>
| **CR** | Platelet count $\geq100 \times 10^9$/L  
Absence of bleeding |
| **R** | Platelet count $\geq30 \times 10^9$/L and at  
least 2-fold increase from the baseline count  
Absence of bleeding |
| **NR** | Platelet count $<30 \times 10^9$/L or less  
than 2-fold increase of baseline count  
Bleeding |
| **Time to response** | Time from starting treatment to time of achievement of CR or R. |

*Platelet counts should be confirmed on at least 2 separate occasions (at least 7 days apart when used to define CR, R or 1 day apart when used to define NR or loss of response.*
## Therapies for the treatment of ITP

<table>
<thead>
<tr>
<th>First line (initial treatment for newly diagnosed ITP)</th>
<th>Anti-D Corticosteroids: dexamethasone, methylprednisolone, prednisolone IVIg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Second line</td>
<td>Azathioprine</td>
</tr>
<tr>
<td></td>
<td>Dapsone</td>
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<tr>
<td></td>
<td>Cyclosporin A</td>
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<tr>
<td></td>
<td>Cyclophosphamide</td>
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<td></td>
<td>Danazol</td>
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<td></td>
<td>Mycophenolate mofetil</td>
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<td></td>
<td>Rituximab</td>
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<tr>
<td></td>
<td>Splenectomy</td>
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<td></td>
<td>TPO receptor agonists</td>
</tr>
<tr>
<td></td>
<td>Vinca alkaloids</td>
</tr>
<tr>
<td>Treatment for patients failing first- and second-line therapies</td>
<td><strong>Category A: Sufficient data</strong></td>
</tr>
<tr>
<td></td>
<td>TPO receptor agonists</td>
</tr>
<tr>
<td></td>
<td><strong>Category B: Minimal data</strong></td>
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<tr>
<td></td>
<td><em>Potential for considerable toxicity</em></td>
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<tr>
<td></td>
<td>Campath-1H</td>
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<td></td>
<td>Combination of first- and second-line therapies</td>
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<tr>
<td></td>
<td>Combination chemotherapy</td>
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<td></td>
<td>HSCT</td>
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</tbody>
</table>
Treatment

FIRST LINE AGENTS
| Treatme
nt strategy | Response rate | Time to initial response | Time to peak response | Duration of sustained response |
<table>
<thead>
<tr>
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</tr>
</thead>
<tbody>
<tr>
<td>Dexamethasone 40 mg daily (0.8 mg/kg) for 4 d every 2-4 wk for 1-4 cycles</td>
<td>Up to 90% of patients respond Initially</td>
<td>2-14 d</td>
<td>4-28 d</td>
<td>50%-80% reported, the latter with 3-6 cycles (during 2-5 y of follow-up)</td>
</tr>
<tr>
<td>Methylprednisolone 30 mg/kg/d for 7 d</td>
<td>As high as 95%</td>
<td>2-14 d</td>
<td>4-28 d</td>
<td>23% of patients have sustained platelet count (&gt; 50 × 10⁹/L) at 39 mo</td>
</tr>
<tr>
<td>Prednisolone 0.5-2 mg/kg/d for 2-4 wk</td>
<td>70%-80% of patients respond Initially</td>
<td>4-14 d</td>
<td>7-28 d</td>
<td>Remains uncertain; estimated 10-y disease free survival 13%-15%</td>
</tr>
</tbody>
</table>
Steroids

**Toxicities** vary with length of administration:

- Mood swings
- Weight gain, anger, anxiety, insomnia, Cushingoid faces
- Dorsal fat, diabetes, fluid retention
- Osteoporosis, skin changes including thinning, alopecia, hypertension, GI distress and ulcers
- Avascular necrosis, immunosuppression, psychosis
- Cataracts, opportunistic infections, adrenal insufficiency
- Hypertension.
- Tolerability decreases with repeated dosing.
- Possibly lower rate of adverse events when used as short-term bolus therapy.
### IVIg

<table>
<thead>
<tr>
<th>Treatment strategy</th>
<th>Response rate</th>
<th>Time to initial response</th>
<th>Time to peak response</th>
<th>Duration of sustained response</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.8-1 g/kg/d for 1d or 0.4 g/kg/d for 5 d</td>
<td>Up to 80% of patients respond initially; half achieve normal platelet counts</td>
<td>1-3 d</td>
<td>2-7 d</td>
<td>Usually transient; platelet counts returning to pretreatment levels 2-4 wk after treatment; persists for months in a few patients</td>
</tr>
</tbody>
</table>
IVIg

Toxicities

• Headaches common: often moderate but sometimes severe
• Transient neutropenia, renal insufficiency, aseptic meningitis, thrombosis, flushing, fever, chills, fatigue, nausea, diarrhea, blood pressure changes and tachycardia
• IVIg preparations may contain small quantities of IgA, which occasionally causes anaphylactoid reactions in patients with IgA deficiency; in these cases use IgA depleted IV Ig
<table>
<thead>
<tr>
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</thead>
<tbody>
<tr>
<td>50-75 μg/kg</td>
<td>Initial response rate similar to IVIg (dose dependent)</td>
<td>1-3 d</td>
<td>3-7 d</td>
<td>Typically last 3-4 wk but may persist for months in some patients</td>
</tr>
</tbody>
</table>

**Toxicities**

Common: hemolytic anemia (dose-limiting toxicity), fever/chills
Rare: intravascular hemolysis, disseminated intravascular coagulation, renal failure, rare death
Treatment

SECOND LINE AGENTS
# Dapsone

<table>
<thead>
<tr>
<th>Treatment strategy</th>
<th>Response rate</th>
<th>Time to initial response</th>
<th>Time to peak response</th>
<th>Duration of sustained response</th>
</tr>
</thead>
<tbody>
<tr>
<td>75-100 mg po daily (1-2 mg/kg)</td>
<td>Response in up to 50% of patients</td>
<td>21-90 d</td>
<td>30-180 d</td>
<td>Sustained response in up to two thirds of responders off therapy</td>
</tr>
</tbody>
</table>

**Toxicities**
- Infrequent and treatable/reversible: abdominal distension, anorexia, nausea, methemoglobinuria, hemolytic anemia in those with G6PD deficiency
- Rare-motor neuropathy
- Severe: skin rash may require drug to be stopped
## Azathioprine

<table>
<thead>
<tr>
<th>Treatment strategy</th>
<th>Response rate</th>
<th>Time to initial response</th>
<th>Time to peak response</th>
<th>Toxicities</th>
<th>Duration of sustained response</th>
</tr>
</thead>
<tbody>
<tr>
<td>1-2 mg/kg (maximum: 150 mg/d)</td>
<td>Up to two-thirds of patients; 40% in anecdotal reports</td>
<td>30-90 d</td>
<td>30-180 d</td>
<td>Low incidence and generally mild: weakness, sweating, transaminase elevations, severe neutropenia with infection, pancreatitis</td>
<td>Up to a quarter of patients off therapy maintain response</td>
</tr>
</tbody>
</table>
## Splenectomy

<table>
<thead>
<tr>
<th>Treatment strategy</th>
<th>Response rate</th>
<th>Time to initial response</th>
<th>Time to peak response</th>
<th>Toxicities</th>
<th>Duration of sustained response</th>
</tr>
</thead>
<tbody>
<tr>
<td>Splenectomy</td>
<td>80% of patients respond; approximately two-thirds achieve a lasting response</td>
<td>1-56 d</td>
<td>7-56 d</td>
<td>Hemorrhage, peripancreatic hematoma, subphrenic abscess, wound infection, death, pneumococcal infection, fever, overwhelming sepsis syndrome, thrombosis</td>
<td>Response sustained with no additional therapy in approximately two-thirds of patients over 5-10 y</td>
</tr>
</tbody>
</table>
Treatment

FAILURE OF SPLENECTOMY
## TPO receptor agonists

<table>
<thead>
<tr>
<th>Treatment strategy</th>
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<th>Duration of sustained response</th>
</tr>
</thead>
<tbody>
<tr>
<td>romiplostim</td>
<td>Overall platelet response rate: non-splenectomized, 88%; splenectomized, 79%</td>
<td>5-14 d</td>
<td>14-60 d</td>
<td>Up to 4 y with continual administration of the drug</td>
</tr>
<tr>
<td>Doses 1-10 μg/kg subcutaneously weekly</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### Toxicities
Adverse events in at least 20% of patients: headache, fatigue, epistaxis, arthralgia and contusion (similar incidence in placebo groups) Treatment-related serious adverse events: increased bone marrow reticulin, worsening thrombocytopenia upon discontinuation, thrombosis
## TPO receptor agonists

<table>
<thead>
<tr>
<th>Treatment strategy</th>
<th>Response rate</th>
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<th>Time to peak response</th>
<th>Duration of sustained response</th>
</tr>
</thead>
<tbody>
<tr>
<td>eltrombopag 25-75 mg orally daily</td>
<td>Platelet responses (platelet count &gt; 50 × 10⁹/L on d 43 of study): 70% receiving 50-mg dose, 81% receiving 75-mg dose</td>
<td>7-28 d</td>
<td>14-90 d</td>
<td>Up to 3 y with continual administration of the drug</td>
</tr>
</tbody>
</table>

### Toxicities

Adverse events in at least 20% of patients: headache. Treatment-related serious adverse events: increased bone marrow reticulin, worsening thrombocytopenia upon discontinuation, thrombosis, liver function abnormalities in 13%
### Rituximab

<table>
<thead>
<tr>
<th>Treatment strategy</th>
<th>Response rate</th>
<th>Time to initial response</th>
<th>Time to peak response</th>
<th>Duration of sustained response</th>
</tr>
</thead>
<tbody>
<tr>
<td>375 mg/m² weekly ×4 (lower doses may also be effective)</td>
<td>60% of patients; complete response in 40% of patients</td>
<td>7-56 d</td>
<td>14-180 d</td>
<td>Sustained response &gt; 3-5 y in 15%-20% of responders. Responders may require retreatment months to years later</td>
</tr>
</tbody>
</table>

**Toxicities**

Low rate, usually mild-to-moderate first-infusion fever/chills, rash, or scratchiness in throat. More severe reactions include serum sickness and (very rarely) bronchospasm, anaphylaxis, pulmonary embolism, retinal artery thrombosis, infection, and development of fulminant hepatitis via reactivation of hepatitis B. Rare cases of progressive multifocal leukoencephalopathy
### Cyclophosphamide

<table>
<thead>
<tr>
<th>Treatment strategy</th>
<th>Response rate</th>
<th>Time to initial response</th>
<th>Time to peak response</th>
<th>Toxicities</th>
<th>Duration of sustained response</th>
</tr>
</thead>
<tbody>
<tr>
<td>(1-2 mg/kg orally daily for at least 16 wk) or IV (0.3-1 g/m² for 1-3 doses every 2-4 wk)</td>
<td>24%-85% of patients</td>
<td>1-8 week</td>
<td>16 weeks</td>
<td>Most are mild to moderate: neutropenia, acute deep venous thrombosis, nausea, vomiting</td>
<td>Up to 50% show a sustained response</td>
</tr>
</tbody>
</table>
## Vinca alkaloids

<table>
<thead>
<tr>
<th>Treatment strategy</th>
<th>Response rate</th>
<th>Time to initial response</th>
<th>Time to peak response</th>
<th>Toxicities</th>
<th>Duration of sustained response</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vincristine</td>
<td>Highly variable transient response in 10%-75% of patients</td>
<td>7-14 d</td>
<td>7-42 d</td>
<td>Neuropathy (repeated dose, elderly) neutropenia, fever, inflammation/thrombophlebitis at the infusion site</td>
<td>A normal platelet count was observed in 6 of 9 (9/12 had response) patients under long-term 3-36 mo monitoring; average, 10 mo</td>
</tr>
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<td>Vinblastine</td>
<td>Highly variable transient response in 10%-75% of patients</td>
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<td>7-42 d</td>
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</table>
## Mycophenolate mofetil

<table>
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<tr>
<th>Treatment strategy</th>
<th>Response rate</th>
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<th>Time to peak response</th>
<th>Toxicities</th>
<th>Duration of sustained response</th>
</tr>
</thead>
<tbody>
<tr>
<td>1000 mg twice daily for at least 3-4 wk</td>
<td>Up to 75% of patients; complete response in up to 45%</td>
<td>2-4 weeks</td>
<td>4-6 weeks</td>
<td>Mild and infrequent: headache (most common and doselimiting), backache, abdominal distension, anorexia, nausea</td>
<td>Sustained for short time after Treatment discontinuation</td>
</tr>
</tbody>
</table>
## Danazol

<table>
<thead>
<tr>
<th>Treatment strategy</th>
<th>Response rate</th>
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<th>Time to peak response</th>
<th>Toxicities</th>
<th>Duration of sustained response</th>
</tr>
</thead>
<tbody>
<tr>
<td>200 mg 2-4 times daily</td>
<td>67% complete or partial response; 40% in anecdotal reports</td>
<td>14-90 d</td>
<td>28-180 d</td>
<td>Frequent side effects: acne, increased facial hair, increased cholesterol, amenorrhea, transaminitis</td>
<td>46% remained in remission at a median of 119 ± 45 mo and mean duration of danazol therapy was 37 mo</td>
</tr>
</tbody>
</table>
General management

• Tranexamic acid—extremely useful in the control of mucous membrane bleeding.
• Combination OCP—menorrhagia.
• Avoid IM injections.
• Avoid platelet transfusions
Special situations

• Pregnancy
  Steroid, IVIg/Anti D, Azathioprine, Dapsone.

• CNS bleed
  IVIg/Anti D, Dexamethasone, emergency splenectomy
Algorithm for management of ITP in children

1. Diagnosis of ITP

2. Prednisolone 1 mg/kg for 4 weeks
   - Response
   - No response or recurrence after steroid taper.
     - Dapsone 2 mg/kg
       - Response
       - No response. Azathioprine 2 mg/kg
         - Response
         - No response. Splenectomy after age > 11 years
Algorithm for management of ITP in adults

1. Diagnosis of ITP
2. Prednisolone 1 mg/kg for 4 weeks.
   - Response
   - No response or recurrence after steroid taper.
     - No response. Dapsone 2 mg/kg or Azathioprine 2 mg/kg for 3-6 months.
       - Response
       - No response. Splenectomy.
         - Response