ITP: Where Did My Platelet Go and How Do I Get Them Back?

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Speaker's Disclosure Statement

- I have no industry relationships to disclose
- I will discuss off-label use of medications

Objectives

1. Describe the pathophysiology of immune thrombocytopenia (ITP)
2. Discuss three treatment options for ITP
3. Identify three teaching points for families of a child with ITP

Review of Hemostasis

When the blood vessel endothelium is injured, three events take place simultaneously

- Vasoconstriction (vascular phase)
- Platelet plug formation (primary hemostatic mechanism - platelet phase)
- Fibrin thrombus formation (secondary hemostatic mechanism - plasma phase)

Platelets

- Size: 1-4 µm (younger platelets are larger)
- Number: 150,000-400,000/mm^3
- Distribution
  - ⅓ in spleen
  - ⅔ circulate in bloodstream
- Life span: 7-10 days

Increased Destruction

- Immune
  - Primary ITP
  - Secondary ITP (drug-induced or associated with systemic illness such as SLE or HIV)
- Non-immune
  - Platelet consumption (eg. DIC, HUS)
  - Platelet destruction (eg. drugs, infections, malignant hypertension)

Distribution Disorders

- Hypothermia
- Hypersplenism (eg. portal hypertension; cyanotic congenital heart disease)

Decreased Production

- Hypoplasia or destruction of megakaryocytes (eg. drugs; hematologic disorders, megaloblastic anemias, acquired aplastic disorders, primary chronic ITP)
- Marrow infiltrative process
  - Benign (eg. osteoporosis; storage diseases)
  - Malignant (eg. leukemia, solid tumor metastases)

Immune Thrombocytopenia

- The most frequent cause of symptomatic isolated thrombocytopenia in an otherwise healthy child is immune platelet destruction caused by auto-antibodies (usually IgG) directed against platelet membrane antigens

Autoimmune Disorders

- Autoimmune disorders are caused when the body's immune system, which is meant to defend the body against bacteria, viruses, and any other foreign product, malfunctions and produces antibodies against healthy tissue, cells and organs

Acute Primary ITP

- Anti-platelet antibody in the plasma
- Shortened platelet survival (from days to minutes) in the circulation as well as possible decreased platelet production in marrow
- Thrombocytopenia (platelet count $<100{,}000/mm^3$)

Incidence and Clinical Features

- Incidence: unknown as often transient (1-6 in 100,000 children/year?)
- Age: 50% 1-4 years old, 80% <8 years old
- Sex: male:female ratio higher in children, especially infants
- Predisposing factors
  - 60% have had an infection in prior month
  - MMR-associated ITP 2.6 cases/100,000 doses of vaccine

Bleeding in ITP

- Cutaneous: petechiae, purpura (>80%)
- Mucous membranes: oral/nasal (20%); menstrual, GI or urinary (<3%); incidence of microscopic bleeding unknown
- Serious hemorrhage / transfusion (<3%)
- Intracranial hemorrhage (ICH) is a RARE occurrence (<1%); 90% are supratentorial; 90% had PLT<20K

Laboratory Findings

- Platelet count
  - Always <100,000 /mm^3; Often <20,000/mm^3
  - Mean platelet volume (MPV) increased (= younger, bigger, "juicier" platelets)
- Anemia: in proportion to blood loss
- Blood smear: normal except low platelet count
- Bleeding time: usually abnormal
- PT, APTT, fibrinogen level: usually normal

Bone Marrow Examination

- Marrow findings support the diagnosis of ITP ***only*** when consistent with clinical state and when other causes of secondary thrombocytopenia are excluded
- The main purpose of performing a bone marrow examination is to ***exclude*** other hematologic disorders such as leukemia

Differential Diagnosis

- Infection (screen for HIV, EBV monospot)
- Autoimmune disorders (ANA, complement, anti-ds-DNA, creatinine, UA, Coombs)
- Drug-induced thrombocytopenia
- Malignancy (isolated thrombocytopenia uncommon)
- Bone marrow failure (isolated thrombo-cytopenia uncommon)

Helpful History

- Family history of easy or prolonged bleeding
- Recent live virus vaccine (MMR, Varivax)
- Systemic symptoms (autoimmune disorder)
- Bleeding symptoms (if not proportional to platelet count consider coagulation or platelet disorder)
- Lifestyle - including vigorous and potentially traumatic activities

Acute versus Chronic ITP

- ITP may be acute, chronic or recurrent
- Acute: PLT count returns to normal (>150K) within 12 months; 50% by 1 month, 75% by 6 months
- Chronic: PLT count remains low beyond 12 months; ~20% of children; 50% of chronic ITP in children will still resolve within 5 years of diagnosis
- Children with chronic ITP tend to have insidious onset, be older (>10 years), and have higher platelet counts at initial diagnosis

Acute versus Chronic ITP

Feature	Acute	Chronic
Age	2-5 years	Adult
Sex	~Equal	Female:Male 3:1
Preceding infection	~60-75%	Unusual
Associated autoimmune condition (eg. SLE)	Uncommon	More common
Onset	Acute	Insidious
Platelet count	<20,000/mm^3	40,000-80,000/mm^3
Duration	Often <3 months	Months-years
Prognosis	Spontaneous remission in 80% of cases	Fluctuating chronic course

Recovery Rate By Age

Age	Recovery Rate	Time to Remission (days)
2-12 months	86%	38.7 $\pm$ 40.1
2-8 years	70%	45.1 $\pm$ 40
9-15 years	46%	54.5 $\pm$ 48.3

Imbach (2003): Journal of Pediatric Hematology/Oncology; 25 (Suppl 1); S68-S73.

Treatment

Treatment Options

Acute ITP

- Observation (ie "watchful waiting")
- Intravenous immune globulin (IVIG)
- Intravenous anti-D immune globulin (WinRho)
- Glucocorticoids (prednisone, dexamethasone)

Refractory or chronic ITP

- Rituximab
- Thrombopoietin receptor agonists
- Splenectomy

To Treat or Not to Treat

- Institutions vary in whether or not to treat ITP and the platelet threshold for treatment
- Many institutions will treat for a platelet count <10,000-20,000/mm^3, especially very young/active children or mucosal bleeding at higher platelet count
- Some only treat if significant bleeding is present
- Goals of treatment: raise platelet count above threshold that stops bleeding or eliminates risk of serious bleeding; improve quality of life

Watchful Waiting

- **Observation ≠ "doing nothing"**
- "Primum non nocere" - Hippocrates
- All treatments have potential for toxicity
- Balance risk of bleeding against risk of toxicity
- Families need to understand the rare risk of serious hemorrhage, strategies to decrease risk of bleeding, signs of serious bleeding, and who to call with concerns

Steroids

- Proposed mechanisms of action
  - Inhibit phagocytosis of antibody-coated platelets in the spleen prolonging platelet survival
  - Improve vascular integrity promoting primary hemostasis
  - Inhibit platelet antibody production
- Considerations
  - Less rapid effect than IVIG
  - Inexpensive, oral administration

Steroids

- Dose: High dose over short course decreases side effects and more rapidly increases PLT count
  - Prednisone 1-2 mg/kg/day x7-21 days, taper
  - Prednisone 4 mg/kg/day x7 days, taper
  - Dexamethasone 24 mg/m^2/day x4 days, no taper
- Toxicity
  - Gastritis
  - Weight gain
  - Hypertension
  - Alterations behavior/sleep

Intravenous Immune Globulin (IVIG)

- Proposed mechanism of action
  - Slows phagocytosis and production of anti-platelet antibodies
  - Blocks antibody binding to platelets
  - Prevents uptake of antibody coated platelets
  - Assists in clearance of persistent viral infections
- Response: 80% have increase in PLT count to >20K within 24 hours

IVIG

- Dose: 0.8-1 gm/kg IV
- Toxicity
  - Flu-like symptoms including headache, fever, and nausea/vomiting, consider pre-medication
  - Transient neutropenia
- Considerations
  - IV infusion
  - Expense

Recurrent ITP

- If good response and manageable side effects (use of pre-medications, slower infusion time, changing brand of IVIG if needed), then can repeat prior therapy
- If poor response (platelet count or duration of therapy), then can treat with different therapy or combination of therapies

Chronic ITP

- 10-20% of children with ITP
- Platelet count often high enough that not at risk for bleeding, but may impact quality of life (ability to travel, participate in sports) or require acute intervention prior to surgery/procedure
- First line treatments for chronic ITP are the same as newly diagnosed ITP: IVIG, Anti-D immune globulin and steroids given as short pulses; chronic steroid use should be minimized

Thrombopoietin Receptor Agonists

- Chronic ITP both antibody-mediated platelet destruction and decreased platelet production
- Thrombopoiesis stimulating proteins increase platelet production/differentiation
- Considerations
  - Maintenance therapy (do not induce remission)
  - Long term side effects not fully known

Eltrombopag (Promacta)

- Dosing
  - Start at 25 mg/day for patients 1-5 years old and 50 mg/day for patients >6 years old
  - Adjust to maintain PLT>50K; max dose 75 mg/day
  - Dose reductions for patients of East Asian ancestry
  - Take 2 hours before or 4 hours after medications/ products containing polyvalent cations such as antacids, calcium-rich foods, and mineral supplements.
- Complications: URI and nasopharyngitis; elevated LFTs

Romiplostim (Nplate)

- Dosing
  - Start at 1 mcg/kg weekly SQ injections
  - Adjust by 1 mcg/kg increments to maintain PLT>50K; max dose 10 mcg/kg week
  - Do not dose if PLT>400K
  - Discontinue if no response after maximum dose x4 weeks
  - Not FDA approved for <18 years of age
- Complications: arthralgia, dizziness, insomnia, myalgia; thrombosis, marrow fibrosis

Rituximab

- Chimeric murine/human anti-CD20 monoclonal antibody targets antibody-producing lymphocytes
- Dose: 375 mg/m^2 IV weekly x4 weeks
- Response rate: 40-50%; can retreat
- Side effects: Urticarial rash, flu-like symptoms (headache, fever, chills); serum sickness (5-10% children with ITP)
- Considerations: B cell recovery may take 6+ months; follow IgG level / replete with IVIG

Splenectomy

- Spleen is site of synthesis of most anti-platelet antibodies and destruction of most platelets
- ~ 70% of patients will respond to splenectomy; higher efficacy in those who respond to other therapies
- The post-splenectomy platelet count usually rises rapidly and may reach >1 million at 1-2 weeks post-splenectomy before normalizing

Post-Splenectomy Sepsis

- Encapsulated organisms, greatest risk <5 years
- Immunizations prior to splenectomy
  - Pneumoccocal vaccine
  - Meningococcal conjugate vaccine
  - Haemophilus influenzae type b (HIB)
- Recommend medical alert bracelet
- Consider prophylactic antibiotics (penicillin); carry full course of treatment antibiotics

Life Threatening Hemorrhage

- IVIG or WinRho + high dose IV steroids
- Platelet transfusion (2-3x normal dose; consider continuous infusion)
- Surgery consult for emergent splenectomy if unable to control bleeding
- Neurosurgery evaluation if concern for ICH (significant headache, neurologic signs)
  - 25% mortality
  - 33% neurologic sequelae

Family and Patient Education

- Activity restriction: avoid contact or collision sports especially those with high risk for head trauma if PLT count <50K or mucosal bleeding
- Avoid injections; if necessary give SQ
- Avoid medications that decrease platelet number or function (eg. aspirin-containing products, ibuprofen, NSAIDs, anticoagulants)

Patient Education

- Signs of low or dropping platelet count
- How to prevent bleeding/bruising
  - Prevent constipation
  - Prevent damage to skin and mucous membranes
  - Consider regulating menses with OCPs
- Signs of serious bleeding
- What to do in an emergency situation (how to stop bleeding, who to call)

Case Studies

Excellent Resources

APHON ITP family booklet
http://apps.aphon.org/Store/ProductDetails.aspx?productId=313
Children's Hospital of Boston
www.danafarberbostonchildrens.org/conditions/blood-disorders/immune-thrombocytopenic-purpura/itp-kids.aspx
Children's Blood Foundation (CBF)
www.childrenscbf.org

Excellent Resources

Intercontinental Cooperative ITP Study Group (ICIS)
www.itpbasel.ch
ITP Foundation
www.itpfoundation.org
Platelet Disorder Support Association
www.pdsa.org
National Institutes of Health
www.nhlbi.nih.gov/health/health-topics/topics/itp