What works in ITP – Voodoo to what’s NEW!

Anne G. Harvey, DNP, CPNP – Pediatric Hematology Nurse Practitioner
Intermountain Healthcare APP Director, Pediatric Oncology, Hematology and Bone Marrow Transplant

Disclosures

• No relevant financial disclosures.

Learning Outcomes

• The learner will be able to describe and classify thrombocytopenia in pediatric patients.

• The learner will be able to describe first and second-line therapies available to treat immune thrombocytopenia in pediatric patients.

• The learner will review American Society of Hematology (ASH) 2019 Clinical Practice Guidelines for Immune Thrombocytopenia in pediatric patients.
What is Immune Thrombocytopenia (ITP)?

- Autoimmune disorder characterized by isolated low platelet counts due to increased destruction and insufficient production.
- Varied disease severity
- Children and adolescents present more suddenly and with more severely low platelet counts than adults.
- Incidence 2-5 per 100,000
- 1-year remission rates:
  - 74% for children <3 year
  - 67% in children 1-6 years of age
  - 62% in children/adolescents 10-20 years of age

Diagnosis of ITP

- Diagnosis of exclusion for ~80% of diagnosed patients.
- Diagnose with history, physical exam, CBC, smear
- Bone marrow biopsy is NOT recommended.
- Antiplatelet antibodies, antiphospholipid antibodies, antinuclear antibodies, TPO levels, or platelet function testing in NOT recommended.
- No changes to diagnosing ITP in the 2019 ASH guidelines.
- If fever, bone pain, family history, risk of infection (HIV, Hep C), lymphadenopathy or other changes in CBC or cell morphology consider differential beyond ITP.

Complications of ITP

- Easy bruising
- Petechiae
- Mucosal bleeding
- Gastrointestinal and/or genitourinary bleeding
- Menorrhagia
- Intracranial hemorrhage.
History of ASH Clinical Practice Guidelines

• ASH Guideline Publications - 1996, 2011 and now 2019
• Paucity of evidence, clinical trials, comparative studies.
• Strong recommendations – most individuals would want and should receive the intervention.
• Conditional recommendations – majority of individuals would want the intervention but shared decision making may be preferred.
• Guidelines recognize the risks of ITP with associated bleeding risk balanced against the risks/benefits of therapies.

Management of Children With Newly Diagnosed ITP

Inpatient vs. Outpatient

• If platelet count <20 x 10⁹/L with mild to no bleeding treatment should remain outpatient.

• Mild bleeding is considered skin manifestations only (bruising, petechiae).

• World Health Organization bleeding score
Recommendations for Newly Diagnosed ITP With Mild to no Bleeding

- Observation rather than corticosteroids (conditional recommendation).
- Observation rather than intravenous immunoglobulin (IVIG) (strong recommendation).
- Observation rather than anti-D immunoglobulin (strong recommendation).

Management of newly diagnosed children with ITP with non-life threatening mucosal bleeding and/or diminished QOL

- Treat with Prednisone 2-4 mg/kg/day (max 120 mg/day) for 5-7 days.
- Considerations:
  - No evidence of benefit for corticosteroid therapy > 7 days.
  - High quality evidence for adverse effects for corticosteroid therapy > 7 days.
    - Hypertension
    - Hypoglycemia
    - Sleep and mood disturbances
    - Gastrointestinal irritation / ulcer

Prednisone rather than Dexamethasone

Conditional recommendation

- Prednisone (2-4 mg/kg/day; max 120 mg daily, for 5-7 days).
- Dexamethasone (0.6 mg/kg/day; max 40 mg/kg/day, for 4 days)

- Considerations:
  - Stability of platelet count is better with prednisone than dexamethasone
  - Side effect profile of prednisone is better than dexamethasone
Management of newly diagnosed children with ITP with non-life threatening mucosal bleeding and/or diminished QOL

- Corticosteroids over IVIG (conditional recommendation)
- Corticosteroids over anti-D immunoglobulin (conditional recommendation)
- Either anti-D immunoglobulin OR IVIG (conditional recommendation)

Considerations:
- Cost of IVIG vs. Anti-D is near equivalent
- Trivial benefit of IVIG over Anti-D
- Risk of intravascular hemolysis with anti-D

Intravenous Immunoglobulin G (IVIG)

- Derived from pooled plasma human donors
- Saturates Fc receptors on phagocytic cells to prevent uptake and destruction of autoantibody-coated platelets.
- 1 mg/kg IVIG X1
- Platelets increase within 24-48 hours for 85% of patients

Considerations:
- Transient response
- Side effects – headache, nausea/vomiting
- Rarely – thrombotic events, renal impairment

Anti-D immunoglobulin

- Prepared from plasma of immunized Rh-negative human donors.
- Can be used as alternative to IVIG for patient with Rh+ blood.
- Acts against D-antigen to block macrophage system and neutralizes binding autoantibodies to platelets.
- IV 50-75 mg/kg

Considerations:
- Transient response
- Side effects – headache, nausea/vomiting, fever
- Rarely – fatal intravascular hemolysis.
Case study #1 – diagnosed with ITP

7-year-old with 2-week history of easy bruising and petechiae.

- Previously healthy. No medications.
- No known family history of platelet disorders, bleeding.

**Physical Exam:**
- Scattered bruises and petechiae.
- No organomegaly.
- No lymphadenopathy.

**Labs:** CBC WNL except platelet count 15 x 10^9/L
- Peripheral smear with several large, well granulated platelets. Decreased number, agreed with automated count. No other morphological abnormalities.

Given mild bleeding (skin manifestations only) and good follow up with family, we elected for observation.

- Checking CBC every 2-4 weeks for the next 8-10 weeks.
- CBC WNL except platelet count 4-12 x 10^9/L

Week 10 – continued mild bleeding but also developed epistaxis.

- CBC WNL except platelet count 5 x 10^9/L
- Opted to treat with prednisone 2 mg/kg/day + GI prophylaxis.
- After almost 2 weeks, no change in platelet count. Prednisone tapered off.

~3 months after diagnosis child had continued mild bleeding (bruising/petechiae) and developed epistaxis again.

- CBC WNL except platelet count 6 x 10^9/L
- Opted to treat with IVIG.

Developed aseptic meningitis the following day (severe headache, vomiting) and returned to clinic.

- Treated with NS Bolus, Tylenol, Benadryl and Zofran.
- CBC WNL except platelet count 40 x 10^9/L

The next week - CBC WNL except platelet count 4 x 10^9/L
The next month the child had several dental extractions and oozing for >24 hours.
- CBC WNL except platelet count 9 x 10^9/L and hemoglobin slightly low at 10.9 g/dL.
- Vomiting swallowed blood.
- Opted to treat with Dexamethasone and oral antifibrinolytic.
- Oozing stopped.

The next week - CBC WNL except platelet count 6 x 10^9/L.

Case study #1 – diagnosed with Persistent ITP

Child continued with mild bleeding (skin manifestations only) for 6-8 weeks, but given the lack of significant response to prednisone, IVIG and dexamethasone we elected for observation again.
- Platelet count continued to be <10 x 10^9/L.

Pt. developed epistaxis that prompted ER visit. CBC WNL except platelet count 5 x 10^9/L.
- Opted to try oral Thrombopoietin Receptor Agonist (TPO-RA).
- Epistaxis resolved.
- Dose maxed, still no change in platelet count.
- Stopped oral TPO-RA

Case study #1 – diagnosed with ITP

- Conversation with family
- TPO-RA options
- Vincristine
- Rituximab
- Splenectomy

### Management of Children With ITP Unresponsive to First-Line Therapy

- **Thrombopoietin receptor agonist (TPO-RA)** rather than Rituximab (conditional recommendation)
- **TPO-RA** rather than splenectomy (conditional recommendation)
- **Rituximab** rather than splenectomy (conditional recommendation)

**Considerations:**
- Slightly less bleeding events with TPO-RA over Rituximab (3% vs. 6%)
- 1-month response 57% with TPO-RA, 64.8% with Rituximab
- 6-month durable response with TPO-RA and Rituximab was nearly equivalent.
- Risk of development of hypogammaglobulinemia and risk of infection with Rituximab.

### Thrombopoietin Receptor Agonists (TPO-RA)

- **Eltrombopag (Promacta)**
  - 25-75 mg PO daily
  - 80% response in 7-28 days
  - Risk of hepatotoxicity and thrombotic events
  - Monitoring with monthly LFT's, CBC once stable
- **Romiplostim (Nplate)**
  - 1 mcg/kg SQ weekly – adjust weekly based on counts to max 10 mcg/kg
  - 80% response in 14-21 days
  - Risk of arthralgia, thrombotic events, headache, epistaxis, fatigue
  - In kids, the reconstitution can be complicated.
Rituximab

- Anti-CD20 cytolytic monoclonal Ab inhibits B-cells from producing autoantibodies as well as reverting T-cell abnormalities.
- 375 mg/m² IV over 4 hours. Weekly for 4 weeks.
- 60% response in 7-50 days.
- Risk of reaction (pre-med ALL patients), neutropenia, fevers, infections – effects may last 12 months.

Good practice statement for children and adults when considering splenectomy

- Ensure patient is fully immunized including pneumococcal, meningococcal and haemophilus influenza type B to protect against encapsulated bacterial pathogens.
- Provide counseling regarding antibiotic prophylaxis after splenectomy.
- Provide education regarding recognition and management of fever after splenectomy.
- Delay splenectomy as long as possible.

Case study #1 – diagnosed with ITP

- Started immunizations
- Bone Marrow Biopsy & Aspirate was consistent with ITP: Normocellular marrow (80%) with normal trilineage hematopoiesis and markedly increased number of megakaryocytes, no dysplastic changes and normal cytogenetics.
- Vincristine – maxed, CBC WNL except platelet count 4 x 10⁹/L
- Rituximab – weekly X 4 weeks. CBC WNL except platelet count 4 x 10⁹/L
Case study #1 – diagnosed with ITP

Over the next 4-6 weeks, child continued with mild bleeding (skin manifestations only) and CBC WNL except platelet count 4 x 10^9/L.

- Brother decided to pull out one of the patients loose teeth resulting in an ER visit for mucocutaneous bleeding.
- Hit forehead on sharp edge of a structure resulting in a minor closed head injury with MASSIVE facial bruising, conjunctival hemorrhages. CT scan was negative.

And of course… CBC WNL except platelet count 5 x 10^9/L.

Fully immunized and planning on splenectomy but family continued to be hesitant.

Case study #1 – diagnosed with ITP

Then patient developed epistaxis:

- Injectable TPO-RA – maximum dosing and no change in platelet count. Continued to be <10 x 10^9/L.

Involved genetics:

- Comprehensive Hematology Panel – no mutation that would explain low platelets.
- Complete recovery of lymphocytes (after Rituximab)

Scheduled for splenectomy

- Penicillin VK Prophylaxis
- Continue immunizations and booster recommendations.
- Fever protocol.

Case study #1 – diagnosed with now CHRONIC ITP
Take home points……

• ITP is a seemingly simple problem with great challenges in bleeding and QOL
• Not easy to force into remission for some
• Expensive therapies with complicated side effect profiles
• Involve family dynamic in the decision making.

• Helpful hints…www.hematology.org/ITPguidelines
• ASH Understanding Immune Thrombocytopenia PDF – a simple 1-page guide to ITP
• ASH Clinical Practice Guidelines APP – download in the APP store
• ASH Pocket Guides APP – download in the APP store

References


Update on Hemophilia – The A’s, the B’s and the C’s
Learning Outcomes

• Learner will define and describe the most common bleeding disorders in pediatric patients.
• Learner will describe factor replacement strategies for bleeding prevention and management in pediatric patients with hemophilia.
• Learner will identify new developments in hemophilia management in pediatric patients.

Coagulation

• Primary hemostasis – platelet aggregation to VWF and results in platelet plug formation.

• Secondary hemostasis – mediated by circulating plasma proteins (factors) & results in a hemostatic plug stabilized in a fibrin network.
**Hemophilia**

- Hereditary disorders of decreased coagulation factors (proteins).
- Hemophilia A (FVIII) and Hemophilia B (FIX) are x-linked recessive disorders.
- FVIII deficiency is more common than FIX deficiency.
- 30% of cases are NEW mutations
- Varied severity

**Hemophilia – clinical manifestations**

- Depends on severity:
  - <1% = severe = spontaneous bleeding
  - 1-5% = moderate = significant bleeding after slight trauma or with surgery.
  - 5-25% = mild = may have slight bleeding with trauma, severe bleeding with surgery.
  - >50 = no concerns (usually...)
- Anemia (NOT common)
- Bruising – with indurations
- Soft tissue bleeding
- Gastrointestinal bleeding
- Hemarthrosis - HALLMARK
Hemophilia – general management

- **Heme A (FVIII deficiency)**
  - FVIII 1 unit/kg = 2% increase in circulating factor
  - 50% correction = 25 units/kg, results in low-normal level of circulating factor VIII
  - 100% correction = 50 units/kg, results in normal level of circulating factor VIII

- **Heme B (FIX deficiency)**
  - FIX 1 unit/kg = 1% increase in circulating factor
  - 50% correction = 50 units/kg (or more) results in low-normal level of circulating factor IX
  - 100% correction = 100 units/kg (or more) results in normal level of circulating factor IX

Factor Products

- Global bleeding disorders market is $11.4 billion/year
- There are >8 major U.S. Companies that manufacture factor
- 90% of factor on the market is recombinant
- New biologic drugs cost over $1.5 billion to develop

- **1st generation** - animal / human plasma derived proteins in the culture & final product.
- **2nd generation** – animal / human proteins in culture but not final product.
- **3rd generation** (recombinant - rFVIII) – cultured in various cell lines. No animal / human proteins in the culture or the vial.
- **Full-length molecule**: equivalent to the naturally occurring FVIII or FIX molecule and slightly longer half-life (HL) = 12-16 hours

- **B-domain deleted** rFVIII (BDDrFVIII) - genetically engineered to delete a portion of the molecule. Reduction in glycoprotein size makes manufacturing easier and may allow more thorough vWF binding and may also decrease risk of inhibitor (antibody) formation (HL 12-18 hours).

- **Fc-Fusion product** - fused with the Fc fragment of IgG. This inhibits lysosomal degradation of the factor by endothelial cells and extends the half-life of the product for FVIII up to 15-22 hours.

- **Albumin fusion** - fused to albumin molecule to offer extended half-life by avoiding degradation. (HL 15-36 hours for FVIII and <70 hours for FIX)

- **PEGylated** - small PEG molecules coat the factor molecule so that receptors on the liver are unable to bind and phagocytose the product. This offers extension of half life of HL 16-19 hours for some FVIII products and longer for FIX products.

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<tr>
<th>Hemophilia A (FVIII)</th>
<th>Hemophilia B (FIX)</th>
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<tr>
<td><strong>Minors</strong></td>
<td><strong>Majors</strong></td>
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**Case study #2**

- 5-day old male, born at term following uncomplicated pregnancy and delivery.
  - **Healthy at birth.** No medications. Circumcision in PCP’s office.
  - **Oozing from circumcision site for >24 hours, diapers saturated with blood.**
  - **Physical Exam:**
    - No bruising or petechiae.
    - Bleeding at circumcision site.
    - Tachycardia
    - Pale
  - **Labs**: CBC WNL except hemoglobin 8.3 g/dL. PTT prolonged at 105 seconds. PT normal.
  - **FIX normal, FVIII <1%**
### Case study #2

- **Child admitted.**
  - Given 10 mL/kg PRBC’s & 50 units/kg of rFVIII product for 100% FVIII correction.
  - Urology consulted and applied stitch to bleeding site.
  - Bleeding slowed.
  - 24 hours later, given 25 units/kg rFVIII product for 50% FVIII correction.
  - No further bleeding, VSS and discharged to home.
  - At 13-months of age, child had port-a-cath placed and initiated prophylaxis with rFVIIIPEGylated product.

- **Prophylaxis continued with rFVIIIPEGylated product.**
- **At 15-months of age, unwitnessed fall from bed.**
- **Clinic visit with imaging evaluation for possible fracture. Negative.**
- **Physical exam – happy alert child, mild swelling and tenderness of left thigh.**
- **Additional dose of factor 100% FVIII correction and 50% FVIII correction the following day.**

- **The next week he continued to refuse to move or bear weight on his LLI.**
- **Physical exam – happy alert child, mild swelling and tenderness of left thigh.**
- **Additional dose of rFVIII PEGylated factor for 100% FVIII correction and 50% FVIII correction the following day.**

- **Parents reported improvement but at his next clinic visit, despite prophylaxis, he again had pain in his left thigh and scattered bruising.**
- **In clinic, he received a dose of rFVIII PEGylated factor for 100% FVIII correction.**
- **30 minutes after factor was administered...**
  - An activated Partial Thromboplastin Time (PTT) was drawn and found to be >130 seconds.
  - Post-infusion FVIII was <1%!
Case study #2

- 1:1 Mixing studies resulted in a **CORRECTED PTT**
- Plasma sample confirmed the presence of Anti-PEGylation antibodies.
- The patient transitioned to a standard half-life rFVIII product and has done very well.

Inhibitors & latest developments

- Antibodies that neutralize factor.
- Requires the use of a “by-passing agent” like:
  - FEIBA – plasma derived, contains non-activated FII, FIX, and FX and activated FVII, HL 6-12 hours
  - NovoSeven – recombinant FVII, HL 3.5 hours

Novel Substitution Therapies

- Emicizumab (Hemlibra) – recombinant, bispecific antibody that bridges FX and FX achieving hemostasis without FVIII.
  - SQ administration, 30 day HL
  - Acute bleeds still treated with FVIII products
  - Thrombotic microangiopathy events reported with concurrent use of emicizumab and activated prothrombin complex concentrate (FEIBA).
Novel Rebalancing Therapies

- Fitusiran
  - Targets anticoagulation pathway with siRNA (small interfering RNA) that inhibits antithrombin synthesis.
  - Antithrombin is a natural anticoagulant.
  - Targets BOTH Hemophilia A and B with and without inhibitors.
  - Monthly SQ injection

Concizumab
- Monoclonal antibody against Tissue Factor Pathway Inhibitor (TFPI).
- TFPI is a natural anticoagulant.
- Targets BOTH Hemophilia A and B with and without inhibitors.
- Weekly SQ injection

Gene Therapy

- Goal is to transform disease severity and eliminate the need for prophylaxis and most patients have discontinued prophylaxis.
- Several international studies are underway.
- Most studies use an adeno-associated viral vector with a codon-optimized human factor IX gene.
- The therapy is administered as a single dose to adult males with severe Hemophilia B.
- Increase in LFT’s have been seen in few subjects.
- Long term effects still unknown

THE END
References


• FDA package insert for listed drugs