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

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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 <1 year
  - 67% in children 1-6 years of age
  - 62% in children/adolescents 10-20 years of age

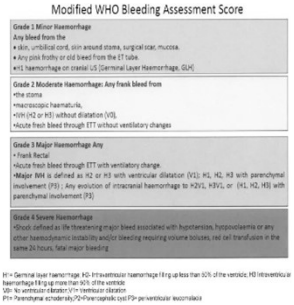
Diagnosis of ITP

- 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.

Modified WHO Bleeding Assessment Score



H1 = Germinal layer haemorrhage; H2= Intraventricular haemorrhage filling up less than 50% of the ventricle; H3 Intraventricular haemorrhage filling up more than 50% of the ventricle
VD= No ventricular dilatation V1= Ventricular dilatation
P1= Parenchymal echodensity;P2=Porencephalic cyst P3= periventricular leucomalacia

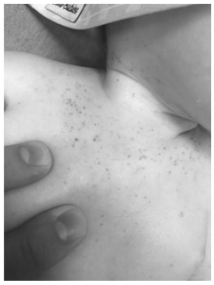
History of ASH Clinical Practice Guidelines

- 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 10^9/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
    - Hyperglycemia
    - 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.

Case study #1 – diagnosed with ITP

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.

Case study #1 – diagnosed with ITP

~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

Case study #1 – diagnosed with ITP

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 x10^9/L

Pt. developed epistaxis that prompted and 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

- Patient stable. No bleeding. Started immunizations.

Management of Children With ITP Unresponsive to First-Line Therapy

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.

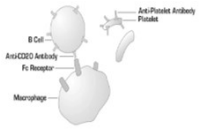
Thrombopoietin Receptor Agonists (TPO-RA)

- Activate TPO receptors on megakaryocytes and induce platelet production via JAK2 & STAT5 kinase pathways.
- Goal to achieve platelet count > 50K.

- 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.

Proposed model by C.M. Bennett and colleagues. Bennett CM, Rogers ZR, Kimmmon DD, et al. Prospective phase 1/2 study of rituximab in childhood and adolescent chronic immune thrombocytopenic purpura. Blood 2006;107:2639-42. Anti-CD20 coating B cells bind to Fc gamma receptors on macrophages. This interaction blocks Fc receptors and retards the ability of macrophages to bind and endocytose immunoglobulin-coating platelets.

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 10^9/L
- Rituximab – weekly X 4 weeks. CBC WNL except platelet count 4 x 10^9/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

Case study #1 – diagnosed with ITP

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

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)

Case study #1 – diagnosed with now CHRONIC ITP

Scheduled for splenectomy

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

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

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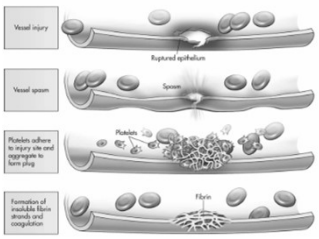
Update on Hemophilia – The A's, the B's and the C's

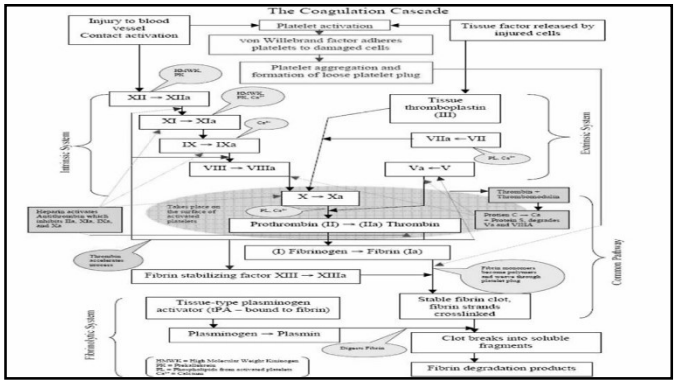
Learning Outcomes

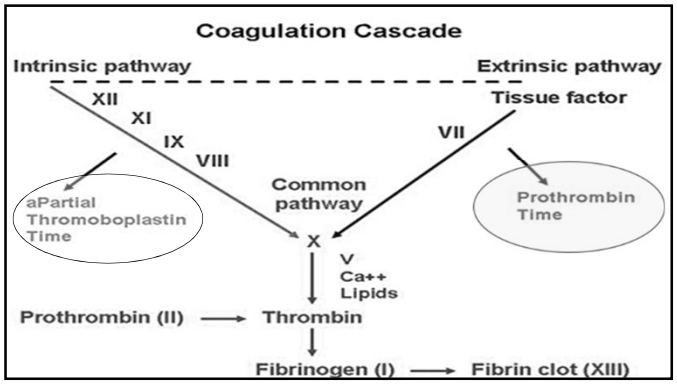
- Learner will define and describe the most common bleeding disorders in pediatric patients.
- Learner will describe factor replacement strategies for bleeding prevention and management in pediatric patients with hemophilia.
- Learner will identify new developments in hemophilia management in pediatric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





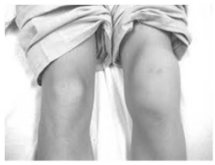


Hemophilia

- 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
- Mucocutaneous bleeding
- Hemarthrosis - HALLMARK



Hemophilia – general management

FACTOR 1st!!

- **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 HL16-19 hours for some FVIII products and longer for FIX products.

Hemophilia A (FVIII)		**Hemophilia B (FIX)**	
Minor = 25 units/kg Major = 50 units/kg		**Minor = 50 units/kg Major = 100 units/kg**	
Advate	Recombinant, SHL	Alprolix	Recombinant, **Fc-fusion**
Afstyla	Recombinant, single-chain with increased binding to VWF to extend HL	Benefix	Recombinant, SHL
Adynovate	Recombinant, **PEGylated**, EHL,	Ixinity	Recombinant, SHL
Alphanate	Human plasma derived, also contains VWF	Rixubis	Recombinant, SHL
Eloctate	Recombinant, **Fc-fusion**	Idelvion	Recombinant, Albumin fusion
Kovaltry	Recombinant, SHL,	Rebinyn	Recombinant, **PEGylated**
Novoeight	Recombinant, SHL. B-domain deleted		
Nuwiq	Recombinant, produced in human cell line, high VWF affinity		
Xyntha	Recombinant, SHL		
Jivi	Recombinant, **PEGylated**, EHL		

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.
  - Tachycardic
  - 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.

Case study #2 —

- Prophylaxis continued with rFVIIIPEGylated product.
- At 15-months of age, unwitnessed fall from bed. Refusing to move left lower extremity.
- 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.

Case study #2 —

The next week he continued to refuse to move or bear weight on his LLE.

- 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.

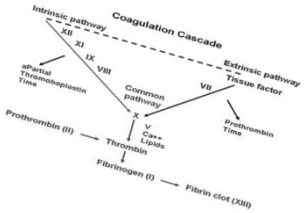
- In clinic, he received a dose of rFVIII PEGylated factor for100% FVIII correction.
- 30 minutes after factor was administered…
  - An activated Partial Thromboplastin Time (PTT) was drawn and found to be >150 seconds.
  - Post-infusion FVIII was <1%!

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 FIX 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

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