Acute Immune Thrombocytopenic Purpura (ITP) in Childhood

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Key Points

ITP is a disorder of decreased platelet survival caused by antibody-mediated platelet destruction.

- Patients with ITP present with manifestations of thrombocytopenia, i.e., petechiae, purpura, and bleeding, but should have an otherwise normal physical examination.
- The only test required to diagnose ITP is a complete blood count and review of the peripheral smear.
- Most children with ITP have only petechiae and purpura and do not require treatment, regardless of their platelet count.
- Children who have active bleeding, who require surgery, who have co-morbid conditions that increase their risk of bleeding, and in whom follow-up is uncertain should be considered for
- treatment.

Preface

These guidelines are intended to help the primary care physician evaluate and manage children with acute immune thrombocytopenic purpura (ITP). Childhood ITP is one of the most common hematologic disorders in childhood with an estimated incidence of 2 to 5 cases per 100,000 children per year, so most primary care physicians will see children with this disorder.1 Most of these children can be managed by their primary care physician without specific treatment but these guidelines will provide assistance in deciding which children with ITP will benefit from referral to a pediatric hematologist for further evaluation and possible treatment.2,3

Definition, Pathophysiology, Assessment, and Diagnosis

Definition

- Acute ITP is a disorder of increased platelet destruction caused by the accelerated clearance of antibody-coated platelets from the circulation.
- The peak age for childhood ITP is from 2 to 5 years.
- A viral infection or immunization often precedes the diagnosis.
- Over 80% of children will have a brief period of thrombocytopenia that resolves spontaneously within 12 months.
- Acute ITP is separated into primary and secondary forms.
    - Primary ITP has no identifiable etiology and is the most common type in children.
    - Secondary ITP has an identifiable etiology. The most commonly identifiable are
        - Autoimmune diseases
        - Viral infections (HCV, HIV)
        - Drugs
        - Vaccines (particularly MMR)[1-3]

Pathophysiology

- The primary mechanism is the binding of anti-platelet auto-antibodies to platelet cell surface glycoproteins.
- The antibody coated platelets bind to Fc receptors on splenic and hepatic macrophages and are removed from the circulation.
- In some cases, the antibodies can also directly damage the platelet progenitor cells (megakaryocytes), resulting in decreased production of platelets.[1-3]

Assessment

- Acute ITP is a disease that affects only the platelets.
    - The production and survival of white blood cells and red blood cells is normal.
    - Evans syndrome is the association of ITP with autoimmune hemolytic anemia.
- Most patients present with manifestations of the thrombocytopenia.
    - Petechiae and excessive bruising
    - Epistaxis
    - Oral bleeding
    - Menorrhagia
    - Hematuria[1-3]

Differential diagnosis

A number of disorders may masquerade as ITP, which is a diagnosis of exclusion; these disorders must be ruled out or be considered very unlikely before a diagnosis of acute ITP is made.

- Bone marrow suppression from viral infections or drugs in which patients usually have anemia and/or abnormalities in white blood cell numbers or differential in addition to the thrombocytopenia
- Bone marrow infiltration from acute leukemia or metastatic solid tumors in which patients typically present with associated anemia and/or abnormalities in white blood cell numbers or differential, fever, bone or joint pain, or lymphadenopathy
- Intravascular platelet destruction
    - Consumptive coagulopathy (DIC)

- Thrombotic thrombocytopenic purpura (TTP)
- Inherited Disorders
  - Giant platelet syndromes, such as Bernard-Soulier and May-Hegglin
  - Type II-B von Willebrand disease
  - Thrombocytopenia-absent radius (TAR) syndrome
  - Wiskott-Aldrich syndrome (WAS)/X-linked thrombocytopenia (XLT)[1-3]

Diagnosis

Physical Examination

- Absence of congenital anomalies
- Evidence of bleeding, such as petechiae or increased bruising, is common.
- Absence of significant lymphadenopathy or hepatosplenomegaly[1-3]

Laboratory Examination

- CBC with differential and reticulocyte count
  - Isolated thrombocytopenia is typical.
  - Patients with significant bleeding may have mild anemia.
  - Examination of the peripheral smear by a trained observer is mandatory.
    - Decreased platelet numbers without clumps should be seen.
    - Large platelets are typically seen, reflecting rapid platelet production, in a background of decreased numbers of small and normal sized platelets.
    - No blasts, white blood cell inclusions, or immature white cells should be seen.
    - The red cell morphology should be normal and signs of hemolysis (schistocytes, spherocytes) should be absent.
  - Antinuclear antibodies (ANA) and other autoantibody tests. The measurement of ANA or anti-red cell antibodies (direct Coombs) is unnecessary to establish the diagnosis of ITP.[2]
    - The ANA may be indicated in patients who also have history or physical examination features of systemic lupus erythematosus (SLE).
    - The direct Coombs may be indicated in patients with evidence of hemolysis by biochemical or peripheral smear criteria.
  - Anti-platelet antibodies. Anti-platelet antibodies may be elevated in both immune and non-immune thrombocytopenia; therefore, the measurement of anti-platelet antibodies has a low specificity and is not recommended routinely in the evaluation of ITP. [2]
  - Immunoglobulin levels
    - Immunoglobulin levels should be considered in children with a past history suggestive of common variable immunodeficiency (frequent sinopulmonary infections, autoimmune diseases) [2]
    - Most children with common variable immunodeficiency (CVID) and ITP will also have other immune cytopenias (autoimmune hemolytic anemia and/or autoimmune neutropenia)
  - *H. pylori* testing. Eradication of *H. pylori* infection has not been shown to result in the resolution of ITP in children; therefore, testing is not appropriate.[2]
  - Bone marrow aspirate
    - In patients with history, physical examination, CBC, and peripheral smear review features suggestive of acute ITP, examination of the bone marrow is not necessary to establish the diagnosis.[2,4,5]
    - Bone marrow aspiration is not necessary in patients who fail IVIg therapy. [2]
    - The available evidence, from observational studies rather than randomized trials,

suggests that bone marrow aspiration may not be necessary prior to the initiation of corticosteroids or performance of splenectomy provided that both the patient and the peripheral smear have been examined by a hematologist but there is considerable variation in this practice among pediatric hematologists.[1-3]

Referral to Pediatric Hematology

Which patients with ITP should be referred to a pediatric hematologist?

- If more than one blood cell line is low or blasts are present on the peripheral smear
- If the patient has hepatosplenomegaly or significant lymphadenopathy
- If the patient has a positive direct Coombs test
- If the patient fails one or more treatments for ITP

Is Treatment Required?

Treatment Goal

The goal of treatment for ITP is to raise the platelet count to a level sufficient to prevent bleeding, not to raise the platelet count to a "normal" level.[2]

- How common is severe bleeding in acute ITP?
  - Less than 1% of children with ITP and a platelet count <20K will experience severe bleeding.[2]
  - Less than 0.2% of children with acute ITP and a platelet count <20K will experience an intracranial hemorrhage (ICH).[2,6]
- There are no data that demonstrate that the choice of treatment (observation, IVIg, corticosteroids) influences the incidence of severe bleeding or ICH in acute ITP[2]

Treatment Candidates

Which patients with ITP should receive treatment to raise their platelet count?[2]

- Most children with ITP have only petechiae and purpura and do not require therapy regardless of their platelet count.
- Children with active bleeding (e.g. epistaxis, oral bleeding, hematuria) in addition to their skin manifestations should receive treatment.
- Children with ITP who require surgery should receive treatment.
- Children with co-morbid conditions that increase their risk of bleeding should receive treatment.
- Children with ITP in whom follow-up is uncertain should be considered for treatment.
- Children with high activity levels whose thrombocytopenia is causing interference with their usual activities or is causing significant personal or family distress should be considered for treatment.

Available Treatments

Platelet Transfusion

- Transfused platelets are rapidly cleared from the circulation in patients with ITP and are, therefore, not an effective treatment for ITP.

- Platelet transfusions may be a useful adjunct to more definitive therapy in certain situations.
    - Life-threatening bleeding
    - Need for emergency surgery

Corticosteroids

- Mechanism of action
    - Inhibition of synthesis of anti-platelet antibodies
    - Inhibition of phagocytosis of antibody-coated platelets by macrophages
    - Stimulation of platelet production
- Advantages
    - Inexpensive
    - Oral and IV forms are effective.
- Disadvantages
    - Slow response time (4 to 14 days) with peak effect in 7 to 28 days
    - Numerous adverse effects
        - Weight gain
        - Hypertension
        - Hyperglycemia
        - Gastric ulceration
        - Behavioral changes
- Recommended treatment regimen
    - Oral prednisone, 2 mg/kg/day divided BID for 7 days, with or without a gradual taper over the following 21 days, is used by most pediatric hematologists.
    - There are no data that demonstrate that this dosing regimen is superior to any other published dosing regimen.[2]

Intravenous Immunoglobulin (IVIg)

- Mechanism of action. Blockade of Fc receptors on splenic and hepatic macrophages prevents binding and destruction of antibody-coated platelets.
- Advantages. Rapid response time (1 to 3 days) with peak effect from 2 to 7 days.
- Disadvantages
    - Expensive
    - Requires IV access and usually hospital admission
    - Numerous adverse effects
        - Fever
        - Nausea and vomiting
        - Headache
        - Aseptic meningitis
- Recommended treatment regimen is 1 gram/kg IV over 4 to 6 hours

Anti-D (WinRho®)

- Mechanism of action
    - Anti-D binds to the D antigen on the surface of the RBC in Rh+ patients.
    - Anti-D coated RBCs bind to splenic and hepatic macrophages, preventing binding of antiplatelet antibody-coated platelets.
- Advantages: Rapid response (1 to 3 days) with peak effect in 3 to 7 days
- Disadvantages
    - Patient must be Rh+
    - Expensive

- Requires IV access
- Numerous adverse effects
  - Hemolysis
  - Fever
  - Chills
  - Nausea and vomiting
  - Renal failure with severe hemolysis
- Recommended treatment regimen
  - Give 50 mcg/kg (= 250 IU/kg) IV over 3 to 5 minutes.
  - The product causes a Coombs-positive hemolytic anemia.
    - There is an FDA mandated 8 hour observation period with mandatory urine dipstick at baseline and hours 2, 4, and 8 after administration.
    - If the dipstick is positive for blood, begin IV hydration and alkalinization, send a STAT CBC and basic metabolic panel (BMP), and admit the patient and monitor for the development of life-threatening hemolysis and acute renal failure.

Splenectomy

- Mechanism of action. The spleen is the primary site of platelet clearance in most cases of ITP and removal of the spleen results in an improved platelet count in 70%-80% of cases.
- Patients should receive Haemophilus influenzae type B (HIB), Pneumovax (PPV-23) ®, Prevnar®, and Menactra® prior to splenectomy. Refer to the Red Book for up to date recommendations.
- Advantages. Rapid response (1 to 56 days) with peak effect in 7 to 56 days
- Disadvantages
  - Requires general anesthesia and a major surgical procedure
  - Risk of post-splenectomy sepsis that requires long-term penicillin prophylaxis
- When is splenectomy indicated?
  - Children with chronic ITP with significant bleeding who are unresponsive to therapy with IVIg, corticosteroids, WinRho®, and perhaps other medications
  - Children with chronic ITP who have impaired quality of life
  - Due to the high spontaneous remission rate of childhood ITP, splenectomy should be delayed for at least 12 months from the diagnosis of ITP, if possible.

Miscellaneous Treatments

- Most patients with acute ITP who require treatment will respond well to IVIg, corticosteroids, or WinRho® therapy.
- A rare patient with severe bleeding in the setting of acute ITP may require one of the therapies listed here, but they are more commonly used in the setting of chronic ITP.[2]
  - High-dose dexamethasone
  - Danazol
  - Rituxan (anti-CD20 monoclonal antibody)
  - Platelet stimulating agents
    - N-plate® (romiplostim)
    - Promacta® (eltrombopag)
  - Anti-proliferative agents
    - Vincristine or vinblastine
    - Azathioprine or mercaptopurine

This guideline was developed to improve health care access in Arkansas and to aid health care providers in making decisions about appropriate patient care. The needs of the individual patient, resources available, and limitations unique to the institution or type of practice may warrant variations.

References

References

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