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Recognition and Management of Immune Thrombocytopenic Purpura and Autoimmune Hemolytic Anemia in the Emergency Department

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Introduction

- Autoimmune cytopenias : ITP & AIHA
- rare in children, but require emergent recognition & treatment.
- should be handled together with an experienced hematologist and often require special attention from the blood bank, so prompt initial management is crucial.

Case 1

Child With Bruising and Petechiae

- previously healthy 6-year-old boy
- He had a cold a few weeks ago, although since that time he has been well with no fevers or other complaints.
- Yesterday: a rash on his legs,
- Today: multiple bruises.
- PE:
  - widespread petechiae & bruising on his trunk & extremities.
  - afebrile & normal vital signs & is otherwise very well appearing.
  - Negatives: no blood blisters ("wet purpura") in his oral cavity, no lymphadenopathy, & no hepatosplenomegaly.

What Blood Work Do You Order?

- complete blood count (CBC) with differential, reticulocyte count & request a peripheral blood smear.
- Results :
  - WBC 8200/mm3, with a normal white count differential,
  - hemoglobin (Hgb) of 12.5 g/dL,
  - hematocrit of 37%,
  - platelet count of 12 000/mm^3.
  - smear : isolated thrombocytopenia with no other hematologic abnormalities.
  - The few platelets she is able to see are large.

Differential Diagnosis of Thrombocytopenia

- the first step : confirm a true low platelet count to exclude pseudothrombocytopenia caused by platelet clumping. -> symptomatic +peripheral smear
- next step: differentiate between a congenital thrombocytopenia syndrome & a recent acquired thrombocytopenia.
- congenital: a known family history of thrombocytopenia, abnormal features on the peripheral smear , or clinical features associated with congenital thrombocytopenia syndromes such as absent radii, mental retardation, hearing loss, or cataract.

Con't-- Acquired thrombocytopenia

- low production vs rapid destruction (either immune mediated or not).

TABLE 1. Causes of thrombocytopenia.

Decreased Platelet Production	Increased Platelet Destruction: Immune Mediated	Increased Platelet Destruction: Nonimmune
Congenital thrombocytopenias	ITP	TTP/HUS
Bone marrow failure Infiltrative bone marrow disease (eg, leukemia)	Drug induced Infection	Heart disease DIC
	Neonatal immune thrombocytopenia	Kasabach-Merritt syndrome Hypersplenism

How Do You Convince the Parents (and Yourself) That the Child Does Not Have Leukemia?

- This presentation is classic for ITP.
- no weight loss, night sweats, or bone pain.
- negative for significant lymphadenopathy or hepatosplenomegaly.
- isolated thrombocytopenia with normal white and red cell morphology on smear and the presence of large platelets.
- If anemia → pt's bleeding history.

TABLE 2. Symptoms of classic ITP vs those of other disorders.

	Classic (Primary) ITP	Concerning Other Disorders or Underlying Disorder
CBC findings	Isolated thrombocytopenia	Decreased WBC, ANC, or Hgb*
Blood smear review	Large platelets Normal-appearing WBCs and erythrocytes	Teardrops or other abnormal red cells Schistocytes
Review of systems	Recent viral illness, but no current systemic symptoms	Ongoing fevers, weight loss, bone pain
Physical examination	Bruises and petechiae	Lymphadenopathy Hepatosplenomegaly

Does the Patient Need a Bone Marrow Examination?

- Current guidelines from the American Society of Hematology state that patients with a "typical" presentation for ITP do not need a bone marrow aspirate to confirm diagnosis.
- Evidence - published case series: no cases of leukemia by bone marrow aspiration in 332 children and adolescents with typical features of ITP and no concerning findings.
- atypical features, such as macrocytic red cells, neutropenia, splenomegaly, or constitutional symptoms, should prompt consideration of a bone marrow evaluation.

Immune Thrombocytopenic Purpura Basics

- autoantibodies (usually IgG) directed at healthy platelets resulting in clearance of platelets by the spleen.
- Most cases of childhood ITP are "primary" and, although the cause is unknown
- secondary complication of HIV and HCV, which should be tested for in adult patients with newly diagnosed ITP or older pediatric patients with a history of receiving a blood transfusion or who are sexually active.
- drugs (such as sulfonamides)
- after immunization with the measles, mumps, rubella vaccine.

Immune Thrombocytopenic Purpura Basics

- incidence : 3 to 6 cases per 100 000 children per year
- peak incidence is in boys 2 to 5 years old.
- typical presentation: sudden bruising and/or petechiae in a healthy child with a recent viral infection.
- Severe bleeding is rare in ITP, especially with counts above 20 000/mm^3.

Treatment Options in ITP

- Close observation is often the only therapy needed because ITP is a self-limiting condition and serious bleeding is rare, even with very low counts.
- Medical treatment →platelet count of less than 10 × 10^9/L or those with overt mucosal bleeding ; patient participation in high-risk activities, or upcoming invasive procedures; postmenarchal girls.
- first-line therapies: corticosteroids & intravenous immunoglobulin (IVIG).
- Adjuvant therapy : antifibrinolytic agents for mucosal bleeding.

Treatment Options in ITP

- Anti-D immunoglobulin works by causing preferential clearance of antibody-coated erythrocytes instead of platelets, therefore anti-D should be avoided in patients with any signs of hemolysis at baseline. →"black box" warning.
- These therapies (steroids, IVIG, anti-D) may be considered in the ED after consultation with a pediatric hematologist, may not be optimal to administer treatment in the ED.
- second-line agents in severe or chronic cases: mercaptopurine, rituximab or other immunosuppressants, splenectomy, or new oral thrombopoietin-mimetic
  - rarely be indicated in the ED setting, and none are approved by FDA for pediatric ITP.

Anticipatory Guidance for Families

- Most patients can be discharged from the ED with a new diagnosis of ITP provided that adequate follow-up is ensured.
- expected course of the disease & what symptoms require a return to medical care.
- Use of medications with antiplatelet effect should be avoided.
- Specific counseling for girls who are postmenarche.

Emergent Management of Severe Bleeding in ITP

- Rarely, present after trauma with an intracranial hemorrhage or with another source of life-threatening bleeding.
- fastest rate of response: a dose of IVIG (1 g/kg) along with high-dose methylprednisolone (2 mg/kg/dose)
- Platelet transfusions, either as a continuous drip, or at higher than normal doses, along with IVIG or IVIG plus steroids, have been reported to result in rapid increase in platelet count.
- in true emergency situations, emergent splenectomy may need to be considered if medical management fails to raise the platelet count or control the bleeding.

Case 2

Teenager With Syncope and Pallor

- 15-year-old girl ; no significant medical history
- 2 days of fatigue, chills, and pallor.
- She felt short of breath and dizzy and almost fainted at school.
- PE: pale with icteric sclera.
- heart rate 110 beats per minute, with an audible flow murmur.
- The rest of her vital signs are normal.
- no palpable lymphadenopathy or hepatomegaly.
- A CBC shows a normal WBC and platelet count but an Hgb of 5.5 g/dL. reticulocyte count 15%.

Approach to Acute Anemia

- by red cell size (microcytic, normocytic, and macrocytic) or by process (decreased production vs increased destruction or loss).
- elevated reticulocyte count, →a brisk marrow response to increased peripheral destruction, by blood loss or hemolysis
- intrinsic issues with the erythrocyte such as membrane disorders or enzymopathies, or extrinsic issues such as immune-mediated hemolysis or non–immune-mediated hemolysis (ie, mechanical or microangiopathic).
- A review of her medical history should rule out an underlying erythrocyte disorder putting AIHA at the top of the list given her lack of any medical history.

What Blood Work Do You Order? What Do You Expect to Find?

- CBC : isolated anemia with a normal or elevated WBC and platelet count.
- reticulocyte count is generally elevated in AIHA
- blood smear is crucial: large population of spherocytes, Clumping of red cells, Nucleated red cells or other red cell precursors
- urinalysis : normal or show high-bilirubin products or hemoglobinuria.
- direct antiglobulin test (DAT, direct Coombs test) is the main diagnostic test for AIHA to identify antibodies on the surface of the erythrocytes.
- usually elevated in AIHA: Indirect bilirubin , LDH, AST

AIHA Basics

- Autoimmune hemolytic anemia occurs less commonly than ITP.

TABLE 3. Classification of primary AIHA.

	Warm Reactive AIHA	Cold Agglutinin Disease	Paroxysmal Cold Hemoglobinuria
Frequency	Most common	Rare in children	Rare in children
Main antibody type	IgG	IgM Binds to I/i antigen	IgG Donath-Landsteiner
DAT	+IgG +/−C3	+C3	+C3 +/−IgG
Binding temperature	37°C	4°C	4°C
Complement binding	+/−	+	+
Location of hemolysis	Extravascular (spleen)	Intravascular or extravascular (liver)	Intravascular
Symptoms	Splenomegaly Jaundice Anemia	Hemoglobinuria Jaundice Anemia	Hemoglobinemia Hemoglobinuria Anemia
Preceding cause	Idiopathic Drugs chemotherapy drugs & antibiotics Autoimmune disease lupus	Mycoplasma infection	Postviral
Treatment	Steroids, IVIG, splenectomy, 6-MP, rituximab	Avoid cold, plasmapheresis for severe cases	Avoid cold, steroids

Ig indicates immunoglobulin; 6-MP, 6-mercaptopurine; DAT, direct antibody test.

AIHA Basics

- Severe AIHA can be life threatening, and transfusion is not a simple solution because the existing antibody will generally coat transfused red cells as well leading to their destruction.
- Although antibodies in AIHA interfere with crossmatching, blood banks can provide *least incompatible blood* in most cases, so involving the blood bank early in the diagnostic process is crucial.

Treatment Options in AIHA

- Vigorous volume replacement with crystalloid should be avoided because this may worsen the patient's anemia
- packed red cells for volume replacement, early communication with the blood bank
- therapy depends on the specific antibody present
- Vital signs & Hgb levels must be monitored frequently because patients can quickly decompensate with ongoing hemolysis during their ED course.
- Corticosteroids are the mainstay of treatment, especially for IgG-mediated warm reactive AIHA. 80% response rate

Treatment Options in AIHA

- Paroxysmal cold hemoglobinuria (a type of AIHA caused by cold-reacting IgG antibodies) in children is generally self-resolving, although a short course of steroids may be helpful.
- Most cases of cold agglutinin AIHA are caused by IgM, which can be removed by plasmapheresis.
- avoid cold exposure; warmed blood.

Emergent Management of Severe Anemia in AIHA

- A decision about transfusion should be based on clinical symptoms (with signs of cardiovascular compromise) and not absolute Hgb.
- Blood counts need to be reevaluated frequently (with a CBC as often every 4-6 hours initially) because Hgb levels can drop quickly in the setting of ongoing hemolysis.
- An important step to facilitate transfusion is to involve hematology & the blood bank for help as soon as the patient is identified.

Tetanus Quick Stick as an applicable and cost-effective test in assessment of immunity status

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Introduction

- Tetanus vaccine and immunoglobulin administration are challenging decisions
- current protocol for immunization against tetanus is based on 2 variables: the vaccination status of the patient & the nature of wound and its exposure.

Table 1 Guide to tetanus prophylaxis in routine wound management 破傷風類毒素 0.5mL肌肉注射

Vaccination history	Clean minor wounds		All other wounds [a]	
<7 y/o	Tdap or Td [b]	TIG [c]	Tdap or Td [b]	TIG [c]
<3 or unknown	Yes	No	Yes	Yes
≥3 doses	No [d] 10	No	No [e] 5	No

Introduction

- waste of resources; booster vaccines have adverse effects
- WHO: tetanus antibody > 0.1 IU/mL →protective
- ELISA: time consuming, expensive, and technician and instrument dependent
- Tetanus Quick Stick (TQS; Nephrotek Laboratory, Rungis, France), an immunochromatographic dipstick test, was developed to determine the tetanus immunity of the patients.
- to investigate the sensitivity, specificity, and the positive and negative predictive values and cost-effectiveness of TQS in the emergency department (ED) setting.

Material and methods

- Blood samples were collected from 200 patients, between January 2009 and April 2009.
- presented to the ED of the Imam Hussein Teaching Hospital (Tehran, Iran) with any kind of wounds or injuries.
- Information including demographic information, tetanus immunization status, wound description, and the preventive measures.

Material and methods

- Tetanus Quick Stick test & ELISA were performed as the standard diagnostic test by an emergency physician and a laboratory technician,
- Subjects' TIG levels of at least 0.1 IU/mL were considered protective
- results of the 2 techniques were compared.

Results

- mean age : 33.2 years (SD = 15.9, 18~ 87), 85% were male.
- DT vaccine was administered to 141 (70.5%) patients & TIG to 105 (52.5%).

Table 2 History of previous tetanus vaccination

Vaccination history	% (n)	Detail
Believe to be vaccinated	42.5% (85)	≤5 y ago (66.5%) 5-10 y ago (17.5%) >10 y ago (16.0 %)
Without previous vaccination	8% (16)	–
No clear history of vaccination	49.5% (99)	–

Table 3 Results of TQS test 137(68.5%)

Type of wounds	Vaccination history	TQS results
Dirty	Unclear	30/60 (50%) positive
Clean and minor	Unclear	25/39 (64%) positive
Any type	incomplete	10/16 (62%) positive
Any type	Complete	72/85 (84%) positive

Results

- Serum TIG levels, assessed by ELISA, indicated that 79% of patients had levels deemed to be protective; this value corresponded to 68.5% for the patients that tested positive using the TQS test.
- Statistical analysis revealed 86.1% sensitivity & 97.6% specificity for the TQS test. The positive & negative predictive values of TQS test were 99.3% and 65.1%, respectively.

Results

- Cost-benefit analysis revealed that application of TQS in patients with tetanus-prone wounds and no clear history of vaccination could have reduced the mean cost per patient from €12.1 per patient to €9.48 per patient, which is a 21.66% reduction).
- Although TQS test in patients with clean minor wounds & no vaccination history could help avoid redundant vaccination, overall, this outcome was not cost-effective (€4 per patient with TQS vs €0.1 per patient without TQS)

Table 4 Cost analysis of the TQS

Determination of antitetanus immunity		Proportion of patients eligible for treatment	Proportion of saved treatments, % (95% CI)		Mean cost/patient	
Patients with tetanus-prone wounds	Vaccination history	100%	–	-21.66%<	12.1	DT+TIG
	TQS	46%	54% (43.5-65.4)		9.48	
Patients without tetanus-prone wounds *	Vaccination history	100%	–		0.1	DT
	TQS	35.4%	64.6% (49.4 -77.8)		4	

* Incomplete vaccination program or last booster 10 years ago. The prices are in euro, taxes included.

Discussion

- consistent with previous studies demonstrating the validity of TQS assessments of immunity against tetanus.
- Although TQS is reliable, its routine use in ERs and other clinical settings is contingent upon economic feasibility.
- Our analysis showed a significant decrease in cost when TQS was applied for patients with dirty, tetanus-prone wounds or injuries and unknown or incomplete vaccination history (€9.48 vs €12.1).

Conclusion

- This study revealed TQS test to be appropriate and cost-effective for ED use especially in evaluating patients who do not remember or cannot give their tetanus immunization history.

Thank you~