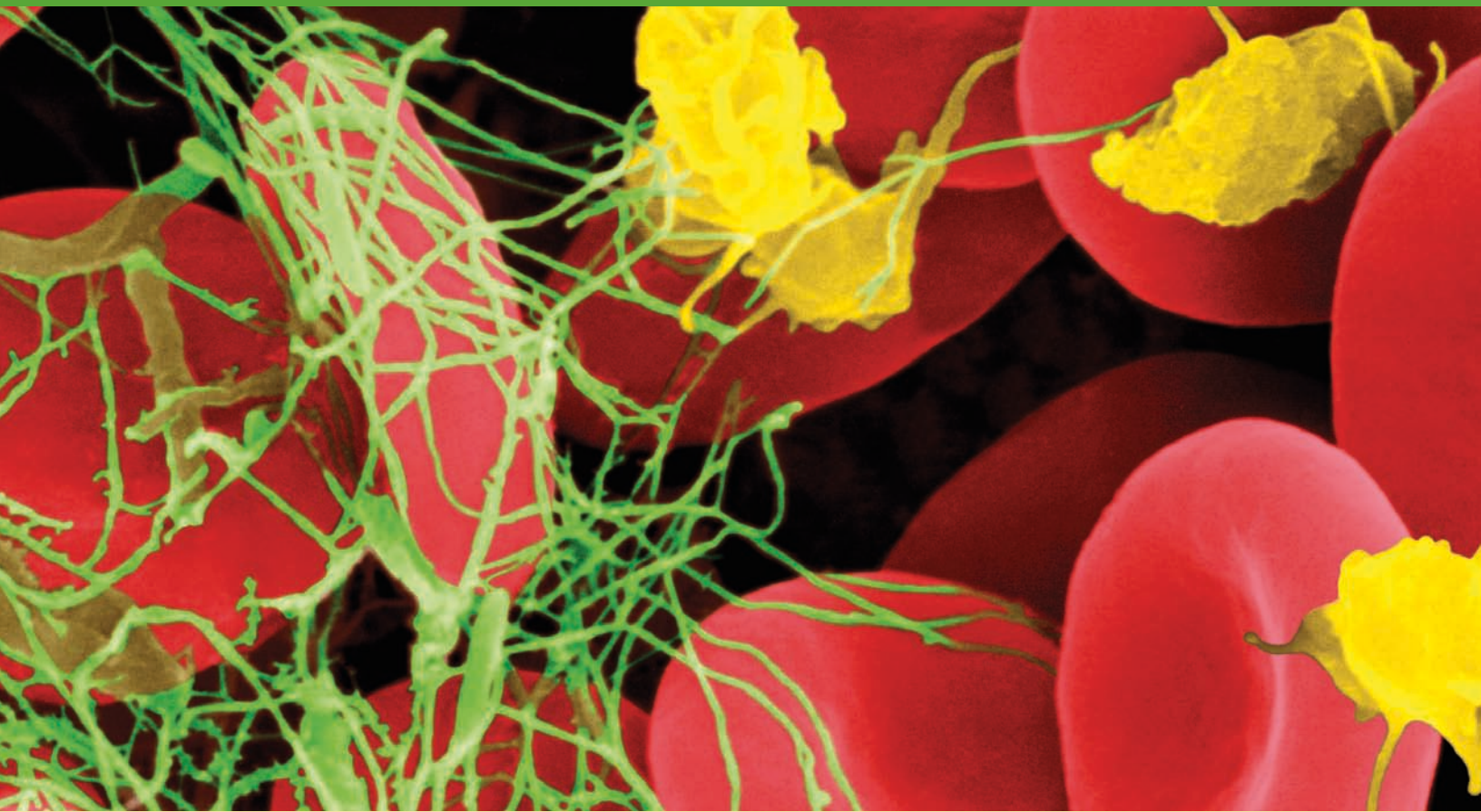


EVOLVING STRATEGIES FOR
**Chronic Idiopathic
Thrombocytopenic
Purpura**

in the Veterans Health Administration System



SPONSORED BY THE
Annenberg Center for Health Sciences at Eisenhower

THIS ACTIVITY IS SUPPORTED BY AN EDUCATIONAL GRANT FROM
GlaxoSmithKline

A maximum of 1 contact hour may be earned
for successful completion of this activity.



INTENDED AUDIENCE

This activity was developed for physicians and other health care providers within the Veterans Healthcare System who have an interest in the diagnosis and management of patients with chronic ITP.

INTRODUCTION

Marked by increased platelet destruction and/or inadequate platelet production, chronic idiopathic thrombocytopenic purpura (ITP) afflicts anywhere from 60,000 to 100,000 people in the United States. Experts estimate that the incidence of chronic ITP seen in the population treated within the Veterans Health Administration (VA) equals or surpasses that of the public at large – and is expected to increase as more women serve in the military and qualify for health benefits. With the preponderance of platelet problems inherent in ITP, patients can suffer from small vessel bleeds, causing bruises, nosebleeds, bleeding from the gums during dental work, other bleeds that may be hard to stop – and even rare, fatal gastrointestinal or intracerebral bleeds. The primary therapeutic goal is to raise platelet counts to high enough levels to prevent bleeding using the least toxic therapy, and guidelines recommend oral glucocorticoids as initial treatment. What's more, there are a number of emerging treatments for refractory ITP including rituximab, TPO receptor agonists, and inhibitors of syk kinase.

In this on-demand webcast, three experts will discuss the epidemiology, differential diagnosis, and disease course of ITP with insights into comorbidities and high-risk groups most often seen in the VA. In addition to reviewing current guideline-based treatment strategies, panelists will provide data from clinical trials about promising new therapies and their mechanisms of action as well as how these new options may fit into patient management. Case studies will provide participants with the opportunity to participate in the educational process, as interactive questions are posed to the audience and the answers are discussed by our panel.

The convenient webcast format of this program provides an opportunity for physicians, nurses, nurse practitioners, pharmacists and other health care professionals involved in the care of patients with ITP to update their knowledge and learn about promising new alternatives to treating ITP based on their individual needs and schedules.

LEARNING OBJECTIVES

Upon completion of this activity, participants should be able to:

- Appropriately and rapidly diagnose ITP in their patients
- Provide treatment utilizing current guidelines and best evidence-based treatment protocols
- Incorporate evolving treatment options into their practice to provide optimal treatment for their patients.

ADDITIONAL PHARMACY LEARNING OBJECTIVES

Upon completion of this activity, participants should be able to:

- Incorporate data on existing and emerging treatment options for ITP to be able to provide optimal consulting input in the VA health system

ADDITIONAL NURSING LEARNING OBJECTIVES

Upon completion of this activity, participants should be able to:

- Utilize an understanding of the disease process and options to better provide optimal care and counseling services to patients with ITP

This activity will address professional practice gaps in knowledge and competence.



ACCREDITATION AND CERTIFICATION

The Annenberg Center for Health Sciences at Eisenhower is accredited by the Accreditation Council for Continuing Medical Education to provide continuing medical education for physicians.

The Annenberg Center designates this educational activity for a maximum of 1 *AMA PRA Category 1 Credit*[™]. Physicians should only claim credit commensurate with the extent of their participation in the activity.

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The following have no significant relationship to disclose.

Carol Marietta, NP

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This activity is supported by an independent educational grant from GlaxoSmithKline.

This activity is an enduring material and consists of a web archive. Successful completion is achieved by reading and viewing the material, reflecting on its implications in your practice, and completing the assessment component.

The estimated time to complete the activity is 1 hour.

This activity was originally released in August 2009 and is eligible for credit through July 31, 2010.

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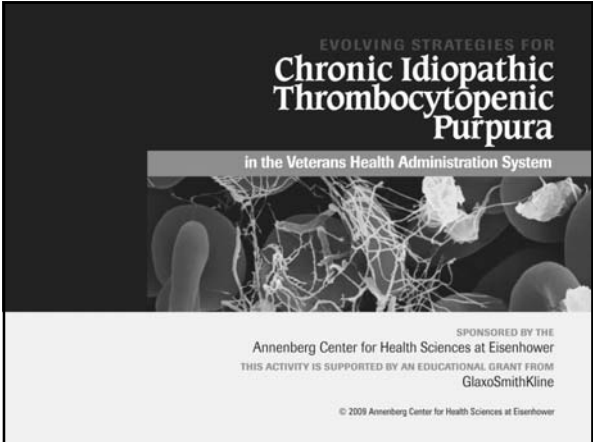
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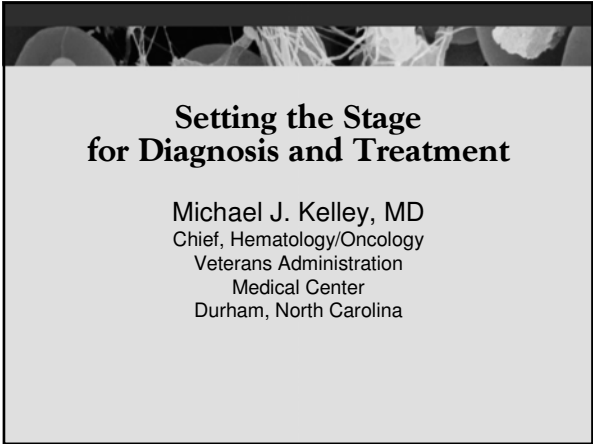
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Evolving Strategies for Chronic Idiopathic Thrombocytopenic Purpura








Evolving Strategies for Chronic Idiopathic Thrombocytopenic Purpura




Key Issues With ITP

- ITP = idiopathic thrombocytopenic purpura, also known as immune thrombocytopenic purpura
- Inconsistent care for patients
- Lack of adherence to guidelines
- Poor collaboration among physicians
- Limited treatment choices
- Higher incidence among VA patients
 - Greater vulnerability and comorbidities
 - Incidence expected to increase as more individuals enter military service, especially women



The Challenge of Diagnosis


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Case: Male With Hematemesis


- 75-year-old male past Hx prostate cancer
- Admitted for hematemesis – found to have a large gastric ulcer penetrated into a duodenal artery
- Went into shock on admittance, resuscitated with 4 units of packed red cells and 4 liters of crystalloid, additional treatment for GI bleed
- CBC (afternoon): Hct 28%, WBC 4,000/mm³, platelet count 60,000/mm³
- CBC (next morning): Hct 26%, WBC 4,800/mm³, platelet count 62,000/mm³
- Vital signs stable

Evolving Strategies for Chronic Idiopathic Thrombocytopenic Purpura



Case: Male With Hematemesis


- Review of medical record reveals previous “stable” CBC
 - Hct 37%
 - WBC 8,100/mm³
 - Platelets 110,000/mm³
- Per medical record, patient irradiated extensively in pelvis about 8 years prior for prostate cancer



Diagnosis?

Based on history, exam, and treatment upon admission, the patient likely has

- A. Agammaglobulinemia
- B. Dilutional thrombocytopenia
- C. Familial macrothrombocytopenia
- D. Idiopathic thrombocytopenic purpura
- E. Myelodysplasia




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Evolving Strategies for Chronic Idiopathic Thrombocytopenic Purpura




Case: Male With Hematemesis

- Classic case of dilutional thrombocytopenia
 - Patient had borderline low platelet count before his GI bleed
 - Prior radiation limits ability to rebound and readily reconstitute platelet count
- In the ensuing months, platelet count drifted back to previous level $\sim 100,000/\text{mm}^3$



Case: Female With Low Platelet Count


- 37-year-old woman lifelong history of “low platelet count”
- Has undergone multiple treatments to “increase platelet count”
 - Oral prednisone
 - IV IG
 - Rituximab
 - Splenectomy
- At all times, Hct and WBC normal, platelet count unchanged



Case: Female With Low Platelet Count

- In taking history, find she has never really bled
- Identical twin has “blood just like mine”
- Peripheral blood smear
 - Platelet count consistent with report
 - Platelets very large
 - MPV is elevated to $\sim 16\text{fL}$ (normal: 8-11fL)
- Twin’s CBC same as for your patient


Evolving Strategies for Chronic Idiopathic Thrombocytopenic Purpura



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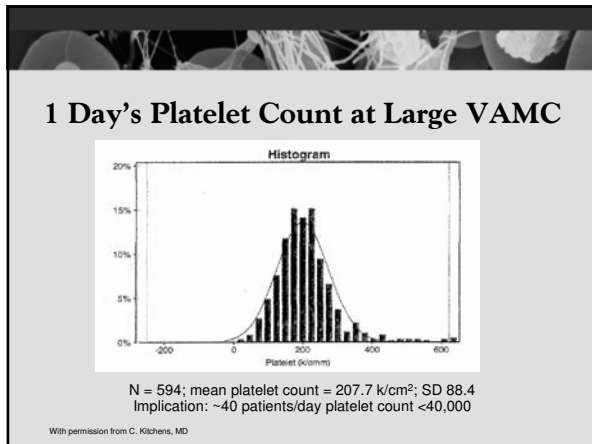
- A. Agammaglobulinemia
- B. Dilutional thrombocytopenia
- C. Familial macrothrombocytopenia
- D. Idiopathic thrombocytopenic purpura
- E. Myelodysplasia



Case: Female With Low Platelet Count

- Classic case of familial macrothrombocytopenia
- No therapy required
- Estimate of platelet “bulk” probably normal, fits her history of normal hemostasis

Evolving Strategies for Chronic Idiopathic Thrombocytopenic Purpura



Case: Male Facing Pacemaker Surgery

70-year-old man about to undergo permanent pacemaker insertion has a preoperative platelet count of 60,000/mm³. Cardiologist asks that you "fix this" so the procedure can take place. Which of the following activities is NOT an appropriate action that can be accomplished expeditiously?


- A. Hematologically directed history and physical examination
- B. Review of any available prior CBCs
- C. Review of the peripheral blood smear
- D. Antiplatelet antibody test
- E. Review of current medications
- F. Reassurance to the cardiologist that hemostasis will be adequate for the planned procedure based on evaluation

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Antiplatelet Antibody Test


- Antiplatelet antibody tests little more sensitivity and specificity than flipping a coin
- Phase I assays lacked sensitivity and specificity
- Phase II assays demonstrated sensitivity but little specificity
- Phase III assays demonstrated specificity but less sensitivity than Phase II assays

Davoren A et al. Am J Hematol. 2005;78:193-97.



History and Physical Exam


- Questions for patient
 - Prior or familial thrombocytopenia?
 - How fared with prior surgeries or injuries?
 - Consider self to be a “bleeder”?
- Does patient currently have
 - Petechiae, purpura, splenomegaly
 - Evidence of chronic liver disease
 - Anything affecting the platelet count
 - Possible systemic cause of thrombocytopenia or of thrombotic thrombocytopenic purpura (TTP)



Review

- Prior CBCs
 - Can determine normal range for platelet count
 - Infer less benign causes if WBC and hematocrit also ↓ with platelet count
- Peripheral blood smear
 - True thrombocytopenia vs pseudothrombocytopenia
 - Causes of low platelet counts
- Current medications
 - Determine if immunosuppression, medications causing thrombocytopenia, patient exposed to heparin or LMWH


Evolving Strategies for Chronic Idiopathic Thrombocytopenic Purpura



Case – Causes of Thrombocytopenia

Potential causes of this degree of thrombocytopenia include all EXCEPT


- A. Mild, chronic idiopathic immune thrombocytopenic purpura (ITP)
- B. Hypersplenism from portal hypertension
- C. Acute drug-induced immune thrombocytopenia
- D. Hereditary macrothrombocytopenia
- E. Pseudothrombocytopenia
- F. Myelodysplasia



Case – Causes of Thrombocytopenia

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Acute Drug-Induced Immune Thrombocytopenia


- Platelet count of $<10,000/\text{mm}^3$
- Recently started on new medicine
- Almost always has petechiae, purpura, epistaxis, and gum bleeding
- Nearly any drug can cause
 - Antibiotics
 - NSAIDs
 - Anti-epilepsy medications

Evolving Strategies for Chronic Idiopathic Thrombocytopenic Purpura




Mild Chronic ITP

- Mild chronic ITP = diagnosis of exclusion and inference
 - Likelihood of chronic ITP as true diagnosis supported by prolonged degree of known thrombocytopenia with otherwise normal CBC
 - Additional autoimmune disease (eg, SLE, hyperthyroidism) enhances diagnosis



Hypersplenism From Portal Hypertension

- Common cause of thrombocytopenia
 - Especially in 50,000-100,000/mm³ range
- Spleen should be palpable
- Signs corroborating liver disease
 - History (alcoholism, hepatitis C)
 - Physical examination (palmar erythema, vascular "spiders" on abdominal wall)
 - Laboratory testing (↑ serum bilirubin and/or ↓ serum albumin)
- Non-alcohol-related causes of splenomegaly: sarcoidosis, hemolytic anemias, lymphoproliferative disorders



Hereditary Macrothrombocytopenia

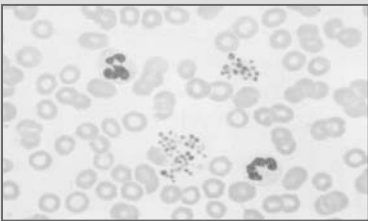
- Platelet bulk normal
- Platelet count may be 60,000/mm³
- Mean platelet volume (MPV) usually >13fL
 - Significantly higher than normal (8-11fL)
- Platelet counts problematic – many machines do not register platelets as large as 13fL
 - Counted as red cells

Evolving Strategies for Chronic Idiopathic Thrombocytopenic Purpura

Myelodysplasia

- Common cause of thrombocytopenia
 - Especially in older patients
- Indications over years
 - Falling hematocrit and/or white count and/or platelet count
 - MCV and RDW increase over time
- Blood smear may show dysplastic forms

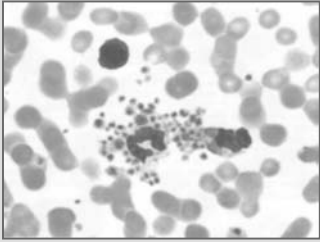
Platelet Clumping



Note that several platelets clump to one another on the peripheral blood smear. This clumping is independent of the nearby neutrophils.

With permission from C. Kitchens, MD

Platelet Satellitism

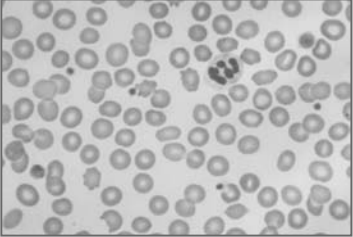


Platelets adhere in a necklace-like pattern around two neutrophils yet do not clump together.

With permission from C. Kitchens, MD

Evolving Strategies for Chronic Idiopathic Thrombocytopenic Purpura

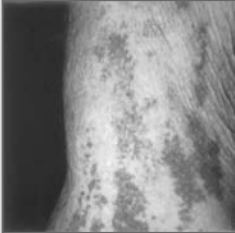
Bernard-Soulier Syndrome



There are six platelets on this blood smear. Notice that two platelets are very large.

With permission from C. Kitchens, MD

Capillary Fragility




This man developed petechiae on his upper arm in the area underneath a blood pressure cuff following determination of his blood pressure. His platelet count was found to be 5,000/L, and he was diagnosed as having ITP.

With permission from C. Kitchens, MD


How many platelets required for adequate hemostasis?

Evolving Strategies for Chronic Idiopathic Thrombocytopenic Purpura




Adequate Hemostasis

- Non-infected, non-febrile patient not undergoing procedure who is not bleeding
 - ~5,000-10,000/mm³ platelets maintain normal endothelial integrity
 - Endothelium morphologically, structurally weakened at lower platelet counts
 - Exhibit petechiae and/or purpura at slightest trauma
 - “Capillary fragility” = significant thrombocytopenia




Transfusion

- If platelet count $\geq 10,000/\text{mm}^3$, no prophylactic transfusion in otherwise stable, non-infected, non-febrile patient
- If platelet count 10,000-50,000/mm³, may infuse platelets prior to surgical or invasive procedure
 - No data showing danger without transfusion
 - No data randomizing patients between those infused with platelets or not
- Platelet transfusions usually not indicated for most minimally invasive routine procedures




Is the cause of the thrombocytopenia concerning or just the degree of the thrombocytopenia?

Evolving Strategies for Chronic Idiopathic Thrombocytopenic Purpura




Cause vs Degree

- Cause of thrombocytopenia = important as degree of thrombocytopenia
 - Patients with pseudothrombocytopenia or macrothrombocytopenia experience normal hemostasis even following trauma or surgery, no transfusion needed
- Hemostasis often excellent in mild chronic ITP
 - Platelets younger, stronger due to high rate of platelet production
 - Chronic ITP patients produce platelets 4-8 X normal rate




Hypersplenism

- Peripheral platelet count often decreased, total body platelet count normal
 - Platelets sequestered passively in enlarged spleen
- If hypersplenism due to portal hypertension that is due to hepatocellular disease, hemostasis may worsen
 - Poor wound healing function of decreased liver function
 - Patients often do not bleed less or experience normal wound healing with transfusions




Disseminated Intravascular Coagulation (DIC)

- DIC causes thrombocytopenia
 - Hemorrhage often worse because of fibrinolysis
- Significant DIC characterized by tissue damage and release of thromboplastic substances
 - Includes various malignancies, obstetrical emergencies, gram-negative or gram-positive sepsis, shock, transfusion reaction, malignant hyperthermia
- In serious DIC, PT, PTT, and thrombin time prolonged, platelet count decreased
 - Treat cause of DIC




Dilutional Thrombocytopenia

- Dilutional thrombocytopenia occurs with massive infusion of platelet-free blood products
- Often occurs in patients
 - Bleeding from a GI lesion
 - With intra-abdominal bleeding from an unligated severed artery
 - Who are hypovolemic
- Debatable whether dilutional thrombocytopenia leads to further bleeding



Epidemiology and Treatment Options


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Professor of Medicine
Harvard Medical School
Chief, Hematology Section
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Case: Male With Bruising


- 68-year-old male admitted with 3-month history of easy bruising
- Reports single episode of epistaxis 4 weeks previously, stopped spontaneously
- Denies prior personal or familial history of bleeding
- No change in medication regimen over past year
- Denies headache, fever, chills, or weight loss

Evolving Strategies for Chronic Idiopathic Thrombocytopenic Purpura




Case: Male With Bruising

- PMH: coronary artery disease → bypass surgery 5 years ago; hyperlipidemia; hypothyroidism; BPH; depression
- Current medications: lisinopril, terazocin, simvastatin, metoprolol tartrate, levothyroxine, aspirin, citalopram
- No smoking or alcohol consumption
- Physical exam: palatal petechiae, multiple ecchymoses, and petechiae on upper and lower extremities



Case: Male With Bruising


- Blood type B positive
- Platelets = 3,000
- Hb/Hct = 12.7/37.1
- RBC indices normocytic/normochromic
- WBC = 8,900 with normal differential
- Peripheral smear – essentially no platelets
- Red and white blood cell morphology normal
- Glucose 97, creatinine 1.0, liver function tests within normal limits



ITP Definition

- Antibody-mediated disease characterized by accelerated platelet destruction
 - Auto-antibodies in ITP also lead to diminished platelet production
- Acute ITP presentation: spontaneous mucocutaneous bleeding with low numbers of circulating platelets (<20,000/ μ l)
- In children, acute ITP frequently occurs post-viral infection
 - Resolves after several weeks with no recurrence
- In adults, acute ITP often becomes chronic
- Women = ~70% of adult ITP patients
- Up to one-half of cases secondary to other causes


Evolving Strategies for Chronic Idiopathic Thrombocytopenic Purpura



What Is Your Next Step?

ITP is diagnosed and aspirin is discontinued. What is your recommendation for initial therapy?


- A. Prednisone 1 mg/kg daily
- B. Dexamethasone 40 mg daily x 4 days
- C. Intravenous high-dose gamma globulin
- D. Intravenous anti-D immune globulin therapy



What Is Your Next Step?

ITP is diagnosed and aspirin is discontinued. What is your recommendation for initial therapy?

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ITP Therapies

- Spontaneous remissions occur in <10% of adults with ITP¹
- Treatment to increase platelet count always initiated in patients with severe thrombocytopenia who are bleeding or at risk for bleeding
- Initial treatment with corticosteroids (usually prednisone)
 - ~10-20% of patients have prolonged response to prednisone
- High-dose pulse dexamethasone in patients with newly diagnosed ITP → platelet count >50,000 in ~85% of patients^{2,3}
 - Advantage: defined duration of dexamethasone treatment vs indeterminate duration of daily oral prednisone treatment⁴


¹Stasi R et al. Am J Med. 1995;98:436-42. ²Cheng Y et al. N Engl J Med. 2003;349:831-6. ³Mazzucconi MG et al. Blood. 2007;109:1401-7. ⁴George JN et al. N Engl J Med. 2003;349:903-5.

Evolving Strategies for Chronic Idiopathic Thrombocytopenic Purpura



Case: Male With Bruising


- Patient weighs 96 kg
- Immediately started on 100 mg of prednisone daily
- Platelet count rises to 37,000 in 3 days; patient discharged
- Platelet count rises to 89,000 8 days following initiation of prednisone, but patient develops steroid-induced diabetes mellitus
- Platelet count remains between 30,000-80,000 as prednisone tapered to 20 mg over 6 weeks
- Patient returns to clinic with new bruises and a platelet count = 4,000



What Is Your Next Step?

Now what is your recommendation for therapy?

- A. Re-institute prednisone 1 mg/kg daily
- B. Dexamethasone 40 mg daily x 4 days
- C. Laparoscopic splenectomy
- D. Intravenous high-dose gamma globulin
- E. Anti-D immune globulin therapy
- F. Danazol 400 mg daily
- G. Rituximab 375 mg/m² weekly x 4 weeks




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Evolving Strategies for Chronic Idiopathic Thrombocytopenic Purpura



Splenectomy


- Splenectomy most effective ITP treatment
 - Complete remissions ~2/3 of patients at 2 years
 - Relapse ~15% over ensuing years¹
- Low hemorrhage-related mortality in patients failing first- or second-line therapy for ITP (~3%)
 - Hemorrhage-related mortality equal to that of splenectomy
 - Has led to use of other treatments prior to splenectomy
 - Attempt to minimize toxicity of chronic corticosteroid therapy

¹Wojcziur K et al. Blood. 2004;104:2623-34.



Case: Male With Bruising


- Therapeutic options discussed; patient reluctant to undergo splenectomy
- Prednisone maintained at 20 mg due to side effects
- Administer infusion of anti-D immune globulin 50 µg/kg
- Platelet count rises to 223,000 1 week later
- Platelet count maintained >90,000 for next month
- Prednisone dose tapered to 10 mg qod



Case: Male With Bruising

- 3 months later, patient returns with petechiae and platelet count = 6,000
- Still taking prednisone 10 mg qod
- Patient receives second course of anti-D immune globulin
 - Good but transient increase in platelet count
 - Bleeding ameliorated
- Platelet count stays at 10,000-20,000 for several weeks
- Patient receives danazol 400 mg daily
- Platelet count improves to 109,000


Evolving Strategies for Chronic Idiopathic Thrombocytopenic Purpura



Globulin Therapies


- Infusions of intravenous immune globulin (IV IG) or anti-D immune globulin (anti-D)
 - Red cells Rh(D) positive, spleen needs to be intact
- No long-term remission, but helps patients with life-threatening bleeding or prior to surgical procedures
- IV IG side effects: headache, nausea, and vomiting
- Both can cause mild alloimmune hemolysis
 - Severe hemolysis possible with anti-D
- Danazol = attenuated androgen
 - Male patients and nonpregnant female patients
 - Responses seen in up to 40% of patients¹

¹Malaise F et al. *Ann J Med*. 2004;116:590-4.



Case: Male With Bruising


- Liver function tests monitored monthly; at 2 months
 - AST = 154 (reference range 10-45)
 - ALT = 360 (reference range 7-52)
 - Normal alkaline phosphatase and total bilirubin
- Elevated liver function tests likely related to danazol
- Medication discontinued; transaminases normalized



Case: Male With Bruising


- Patient continues on prednisone 10 mg daily
- Platelet count = 10,000-20,000
- Continues next 4 months with easy bruising
- Cardiologist seen during follow-up, concerned about patient being off aspirin

Evolving Strategies for Chronic Idiopathic Thrombocytopenic Purpura




Case: Male With Bruising

- Patient finally agrees to splenectomy
 - Performed laparoscopically, no complications
- Post-op platelet count = 150,000, settles ~80,000
- Patient resumes aspirin therapy; platelet count remains >50,000 for next 3 years



Case: Male With Bruising


- Patient presents to ER with lower GI bleed
 - Transfusion 4 units packed RBCs
 - Platelet count ↓ 40,000
 - Aspirin discontinued
- Colonoscopy shows adenocarcinoma of bowel at 30 cm from anal verge
- Resection of tumor in sigmoid colon recommended
- Surgeon requires patient's platelet count = ~75,000 before surgery and ≥ 4 weeks post-op



What Is Your Next Step?

What would be your recommendation for therapy now?


- A. Re-institute high-dose prednisone
- B. Rituximab 375 mg/m² weekly x 4 weeks
- C. Intravenous high-dose gamma globulin
- D. SQ romiplostim weekly
- E. Oral eltrombopag daily



What Is Your Next Step?

What would be your recommendation for therapy now?


- A. Re-institute high-dose prednisone
- B. Rituximab 375 mg/m² weekly x 4 weeks
- C. Intravenous high-dose gamma globulin
- D. SQ romiplostim weekly
- E. Oral eltrombopag daily



Immunosuppressive Therapies

- Success in chronic ITP, usually in patients refractory to splenectomy¹
 - Rituximab
 - Cyclophosphamide
 - Azathioprine
 - Vinca alkaloids
- Retrospective analysis of small non-controlled studies indicated rituximab had overall response rate of ~63% and complete response rate of 43.6%²
 - Rituximab not FDA approved for ITP treatment

¹George JN et al. Blood. 1996;88:3-40. ²Arnold DM et al. Ann Int Med. 2007;146:25-33.



Thrombopoietic Receptor Agonists

- Two approved in 2008 for treatment of patients with chronic ITP with insufficient response to corticosteroids, immunoglobulins, or splenectomy
- Stimulate thrombopoietin (TPO) receptor
- Overcome suboptimal platelet production by bone marrow
- Ameliorate thrombocytopenia while administered
 - May be useful in raising platelet count until longer-term therapy takes effect

Evolving Strategies for Chronic Idiopathic Thrombocytopenic Purpura

Romiplostim

- IgG1 Fc component linked to peptide domain with four binding sites for Mpl, the TPO receptor
- No sequence homology to TPO
- Not likely to → formation of antibodies that react with native endogenous TPO
- Administered as SQ injection weekly
 - Increases platelet counts via dose-dependent rise in platelet count seen as early as day 5

Romiplostim - RCTs

- Parallel placebo-controlled randomized (2:1) trials
- Splenectomized and nonsplenectomized patients with chronic ITP
 - Mean baseline platelet counts $\leq 30,000$
 - Treated with romiplostim or placebo weekly x 24 weeks
- Proportion of patients responding
 - Splenectomized 38% vs placebo 0%; $p = 0.0013$
 - Nonsplenectomized 61% vs placebo 5%; $p < 0.0001$
- 87% romiplostim vs 38% placebo reduced or discontinued concurrent therapy for ITP (eg, glucocorticoids)
- Most adverse events with romiplostim mild or moderate, similar to placebo
 - Serious adverse events include increased bone marrow reticulin
- Thrombotic events occurred with equal frequency in both arms

Kuter DJ et al. Lancet. 2008;371:995-1003.


Eltrombopag

- Non-peptide TPO mimetic
- 6-week placebo-controlled trial in 118 adults with chronic ITP with platelet counts $< 30,000$

Visit Day	Placebo	Eltrombopag 30 mg	Eltrombopag 50 mg	Eltrombopag 75 mg
8	0	25	45	65
15	0	35	75	85
22	0	25	70	75
29	0	25	70	75
36	0	25	75	75
43	0	25	75	75

Bussei JB et al. N Engl J Med. 2007;357:2237-47. Copyright © 2007 Massachusetts Medical Society. All rights reserved.


Evolving Strategies for Chronic Idiopathic Thrombocytopenic Purpura



RAISE Trial

- Randomized placebo controlled ITP study with eltrombopag (RAISE)
- Phase III randomized, double-blind, placebo-controlled trial in 189 patients with chronic ITP and platelet counts <30,000
- Eltrombopag significantly increased platelet counts (8 x) and decreased bleeding symptoms (65%) → reduction or discontinuation of baseline ITP therapies (p = 0.016) and reduced use of rescue medications (p = 0.001) vs placebo
- Safety data from this and other RCTs indicate eltrombopag toxicities similar to placebo
- LFT monitoring required

Cheng G et al. Blood 2008;112:153. Presented at the 50th Annual Meeting of the American Society of Hematology.



Case: Male With Bruising

- Treatment goal: raising platelet count to safe (~50-100,000) rather than normal level
- No relationship seen between elevated platelet counts and thrombosis in TPO receptor agonist studies
 - Use cautiously in patients with a history of/risk factors for thrombosis
 - Patient undergoing major surgery should receive thromboprophylaxis with UFH, LMWH, or fondaparinux provided platelet count is ≥50,000
- Rituximab could be considered, but significant platelet count elevation lower and less rapid than with TPO mimetic

Rituximab not FDA approved for the management of ITP

EVOLVING STRATEGIES FOR
**Chronic Idiopathic
Thrombocytopenic
Purpura**

in the Veterans Health Administration System



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What is your professional degree?

- MD DO
 RN LPN LVN NP Lic. # _____
 RPh PharmD
 Other _____

What is your specialty?

- Family Practice Critical Care / Intensivist
 Internal Medicine Emergency Med
 Hematology /Oncology
 Other _____

**MUST BE →
COMPLETED**

I hereby certify that I have spent _____ hour(s)
in this educational activity.

Signature _____

Date _____

Post-Test — Based on the material you have read, circle the most correct answer to each question.

- A patient exhibiting acute drug-induced immune thrombocytopenia would likely have a platelet count that at its highest level would be**
 - <10,000 mm³
 - <25,000 mm³
 - <50,000 mm³
 - <75,000 mm³
 - <100,000 mm³
- In hereditary macrothrombocytopenia, lower platelet counts are attributable to**
 - decreased platelet bulk
 - increased platelet bulk
 - increased platelet volume
 - decreased platelet volume
 - familial predisposition to seizures requiring increased use of anti-epilepsy medication
- A non-infected, non-febrile thrombocytopenic patient who is not bleeding nor undergoing a procedure can maintain endothelial integrity with a platelet count as low as 5,000-10,000 mm³.**
 - True
 - False
- For most patients with newly diagnosed chronic ITP, first-line treatment usually consists of**
 - dexamethasone
 - intravenous high-dose gamma globulin
 - intravenous anti-D immune globulin therapy
 - rituximab
 - prednisone
- The most effective therapy for ITP in terms of achieving complete remission is**
 - prednisone
 - dexamethasone
 - eltrombopag
 - splenectomy
 - danazol
- Conditions that must be met to consider the use of intravenous immune globulin or anti-D immune globulin include**
 - platelet count >25,000 mm³
 - mean platelet volume >13fL
 - intact spleen
 - Rh(D)+ red cells
 - "b" and "c"
 - "c" and "d"

7. The thrombopoietin (TPO) receptor agonist romiplostin has no sequence homology to TPO, an advantage over recombinant TPO PEG-conjugated MGFDF because romiplostin

- a. can be administered orally
- b. is unlikely to lead to formation of antibodies that react with native endogenous TPO

- c. increases platelet counts in a dose-dependent fashion with a rise seen as early as day 8
- d. has been shown in randomized clinical trials to perform better in splenectomized, but not non-splenectomized, patients
- e. has not been shown to increase bone marrow reticulin in recipients

Activity Evaluation – Fill in the appropriate circle on each line:

	High		Avg.		Low
How did this compare to other educational events in which you have participated?	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Please evaluate the educational level of this CE activity:	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Please evaluate the educational format for this subject:	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Upon completion of this activity, the degree to which I can better:					
• Appropriately and rapidly diagnose ITP in their patients	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
• Provide treatment utilizing current guidelines and best evidence-based treatment protocols	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
• Incorporate evolving treatment options into their practice to provide optimal treatment for their patients	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
For Pharmacy, the degree to which I can better:					
Incorporate data on existing and emerging treatment options for ITP to be able to provide optimal consulting input in the VA health system	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
For Nursing, the degree to which I can better:					
Utilize an understanding of the disease process and options to better provide optimal care and counseling services to patients with ITP	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Based on content, how effective was the activity in meeting your educational needs, expectations and objectives?	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Evaluate how relevant this information is to your practice:	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
The likelihood you will make even small changes in your practice based on the information presented in this activity is:	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Please rate the degree to which the following enhanced your learning experience:					
• Michael J. Kelly, MD (Chair)	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
• Kenneth A. Bauer, MD	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
• Craig S. Kitchens, MD	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
• Audience polling	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
• Case presentations	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
• Syllabus	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
To what degree do you believe that the subject matter was presented without commercial bias?	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>

If you thought the presentations were commercially biased, please explain: _____

Practical Implications – Please respond to the following statements:

1. What 1 change will you make in your practice based on this activity? _____
 No change, I already follow all guidelines.
2. Based on this activity, how confident are you in your ability to make this change?
 Very confident Somewhat confident Neutral Somewhat unconfident Very unconfident
3. Please list any barriers to overcome before initiating any changes: _____

4. Additional comments: _____

5. What questions remain unanswered for you? _____



Participant Practice Reflection Tool

Please remove from the activity materials and keep as a reference tool.

Action 1: Appropriately and rapidly diagnose ITP in your patients

- What am I currently doing? _____
- Changes I need to make to match optimal practice. How can I use what I learned in this activity to get where I need to be? _____

- Barriers to those changes and steps to deal with the barriers. _____

Action 2: Provide treatment utilizing current guidelines and best evidence-based treatment protocols

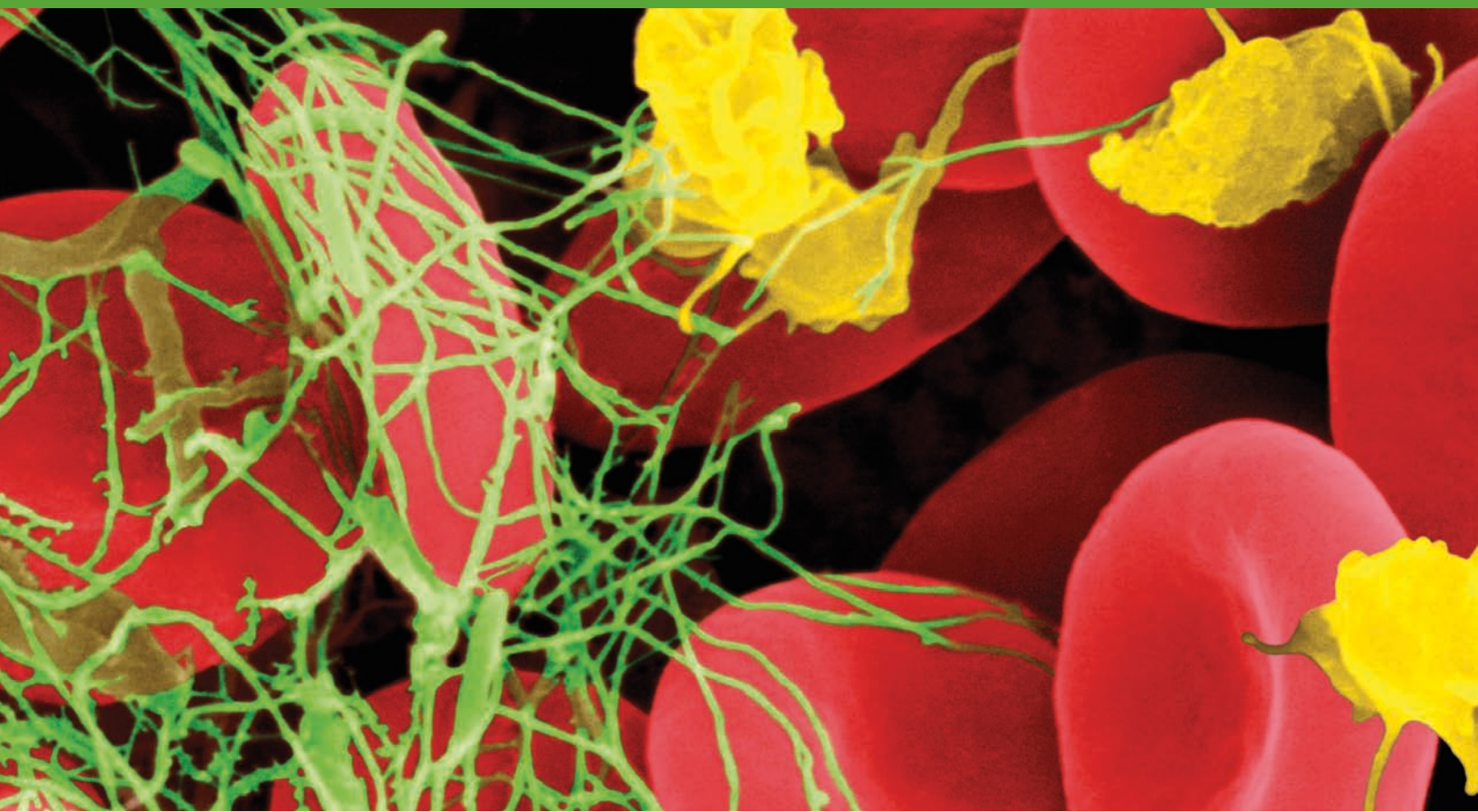
- What am I currently doing? _____
- Changes I need to make to match optimal practice. How can I use what I learned in this activity to get where I need to be? _____

- Barriers to those changes and steps to deal with the barriers. _____

Action 3: Incorporate evolving treatment options into their practice to provide optimal treatment for their patients

- What am I currently doing? _____
- Changes I need to make to match optimal practice. How can I use what I learned in this activity to get where I need to be? _____

- Barriers to those changes and steps to deal with the barriers. _____



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