How to Approach the Inpatient with Low Platelet Counts

Steven Fein, MD, MPH

What I'm going to tell you

- Hospital-based hematology
- Inpatients with low platelet counts
  - Nonmalignant, not HIT
  - HIT
  - APL leukemia
- What to do about low platelet counts

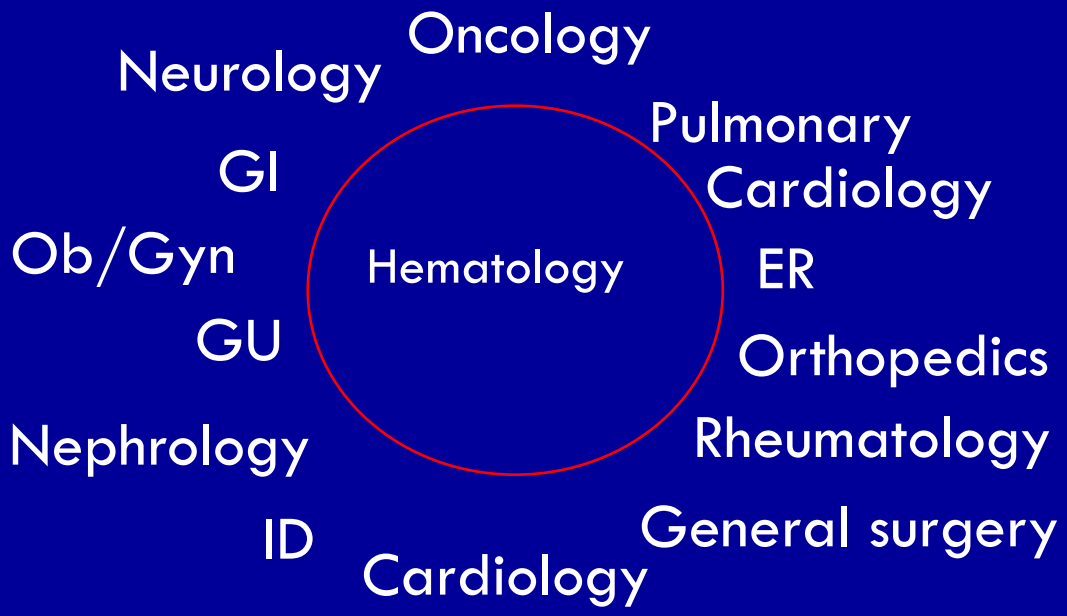
What I'm going to tell you

- Hospital-based hematology
- Inpatients with low platelet counts
  - Nonmalignant, not HIT
  - HIT
  - APL leukemia
- What to do about low platelet counts

Hematology

- Clotting
  - DVT/PE/stroke, "unusual site" clotting
  - Antiphospholipid syndrome
  - Heparin-induced thrombosis (HIT)
- Bleeding
  - Hemophilia, bleeding tendency, anticoagulants
- Abnormal blood counts
  - Myeloproliferative disorder, ITP, Anemia
- Blood cancers
  - Leukemia, lymphoma, multiple myeloma

Hematology interfaces with all specialties



Why hematology?

- Non-malignant hematology
  - Interesting
  - Variety of disorders, all ages
  - Save lives
  - Cutting edge
- Malignant hematology
  - Cure some people with cancer
- Related to the other people doing it

Why do heme and onc go together?

- Historically hematology was focused on bleeding disorders and transfusions
- Blood cancers were the first to be treated successfully
- Oncology was born out of hematology
- Hematology was reinvented with new treatments including immunotherapy, anticoagulants and IV iron infusion

Hospital-based hematology

- Hematology is a fundamental inpatient hospital specialty
- Many patients present with blood conditions
- Many life-threatening conditions require hematology experts
  - Severe bleeding with coagulopathy
    - inherited or acquired hemophilia
    - intracranial hemorrhage
    - pregnancy/postpartum bleeding
  - DVT/PE, HIT, stroke, "unusual site" clotting
  - Low platelet counts, ITP, APL leukemia
  - High blood counts, stroke related to MPD
  - TTP, HUS, HLH, rare hematology conditions

What I'm going to tell you

- Hospital-based hematology
- Inpatients with low platelet counts
  - Nonmalignant, not HIT
  - HIT
  - APL leukemia
- What to do about low platelet counts

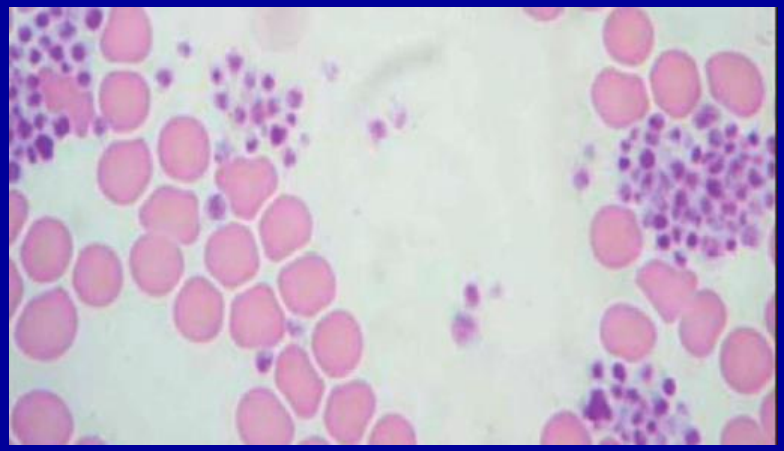
What does low plt count mean?

- Platelet count is a *snapshot* in a complex physiologic process of making and using plts
- Plt count=

  production – (destruction or consumption)
- Usual platelet lifespan 3-5 days

- *Low platelet count not necessarily a bleeding tendency because "healthy" platelets being made*
- *At some low level spontaneous bleeding risk occurs, but it is much lower than you may think*

Platelet clumping



Antibodies bind plts in EDTA
No clinical significance, but
Can affect decisions about
treatment/interventions

Can have low plt with clumps
but uncommon
Citrate count not worth it
"Low count confirmed" means
no clumping seen by lab tech

REVIEW ARTICLE

CRITICAL CARE MEDICINE

Bleeding and Coagulopathies in Critical Care

- Sepsis (especially consider)
  - Human immunodeficiency virus (HIV) infection
  - Disseminated intravascular coagulation
- Major blood loss and hemodilution
- Mechanical fragmentation
  - Post-cardiopulmonary bypass
  - Intraaortic balloon pump
  - Renal dialysis
  - Extracorporeal membrane oxygenation

- Immune-mediated disorder
  - Immune thrombocytopenic purpura
  - Antiphospholipid syndrome
  - Post-transfusion purpura
- Microangiopathic hemolytic anemia
  - Disseminated intravascular coagulation
  - Thrombotic thrombocytopenic purpura
  - Hemolytic–uremic syndrome
- Hypersplenism
- Other disorder
  - Myelodysplastic syndrome
  - Cancer
  - Hereditary thrombocytopenia

Hematologist's perspective on low plts

- Low platelet count is a clue for other diagnoses

- It it's chronic, then assume ITP or hypersplenism
- If it's subacute, then r/o heme malignancy & APL
- If it's acute then r/o HIT, or assume meds/infection

Low platelet count case

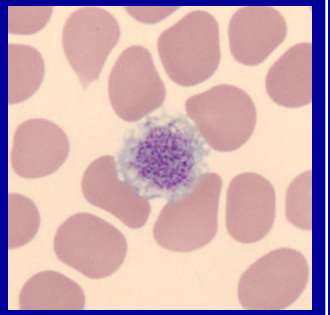
86yo woman
HCV antibody pos
Chronic low plt

02/06/2017 00:00 - 23:59 EST	12/31/2016 00:00 - 23:59 EST	12/30/2016 00:00 - 23:59 EST	12/29/2016 00:00 - 23:59 EST	12/28/2016 00:00 - 23:59 EST	12/27/2016 00:00 - 23:59 EST	1
14.5	14.5		14.9		16.0 (H)	
43.3	42.9		45.3 (H)		48.7 (H)	
5.29	6.36		6.48		7.28	
16 * (!)	55 (L)		40 (L)		47 (L)	

IMPRESSION:
1. Liver showing mild coarsening of the echotexture and some surface irregularity consistent with hepatic cirrhosis. No focal masses are seen.
2. Small right pleural effusion.

IMPRESSION:
Heterogeneous activity within the liver consistent with a cirrhotic liver seen on previous imaging. There is splenomegaly with mild diffuse increased uptake consistent with colloid shift suggesting portal hypertension.

What causes low platelet counts?

Large platelets High MPV 	**ACUTE/SUBACUTE** *Acute* ITP "consumption" Thrombosis Bleeding/hematoma DIC, HIT Hemodilution/IVF Heme malignancy/APL	**CHRONIC** *Chronic* ITP Hypersplenism
Small platelets	**BM suppression** Infection Medications Chemotherapy	**BM dysfunction** Aplastic anemia MDS/heme malignancy AIDS

When to suspect chronic ITP

- Usually patients not ill, not bleeding
- *Incidental* finding on CBC- only low plt count
- Rule out MDS/AA
- Hypersplenism is the same guess as ITP
- Platelets usually large (high MPV)
- ITP patients usually do not bleed unless plts<20, but cirrhosis pts have bleeding

What to do about chronic low plts

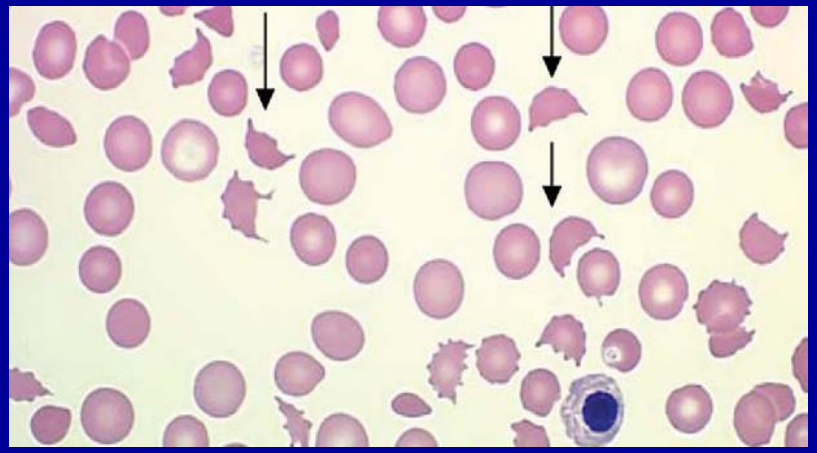
- ITP or hypersplenism (usually platelet count>30)
  - Decide whether bleeding or procedure planned
  - Consider IVIG for planned procedures
  - Transfusions for visible bleeding or procedure
  - Determine safety/appropriateness of anticoagulants
- Bone marrow dysfunction-chronic (MDS/AA)
  - Determine heme malignancy diagnosis and interventions
  - Transfusions for plt<10 or visible bleeding or procedures

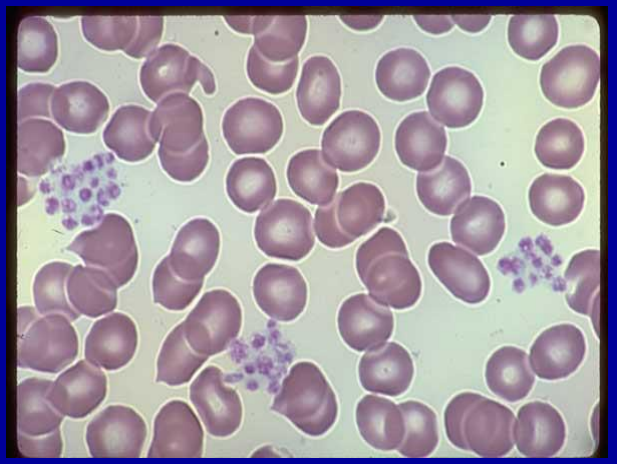
Diagnosing acute ITP exacerbation

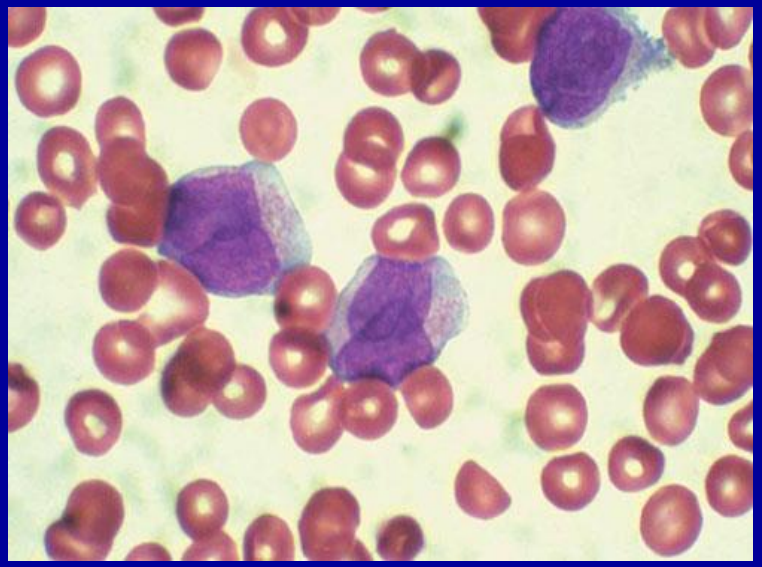
- NOT incidental→usually bruised/bleeding
- Low platelets with normal HCT and WBC

- No culprit drug causing BM suppression
- Vancomycin causes ITP (not BM suppression)
- **Minimal response to platelet transfusion**

These are not ITP

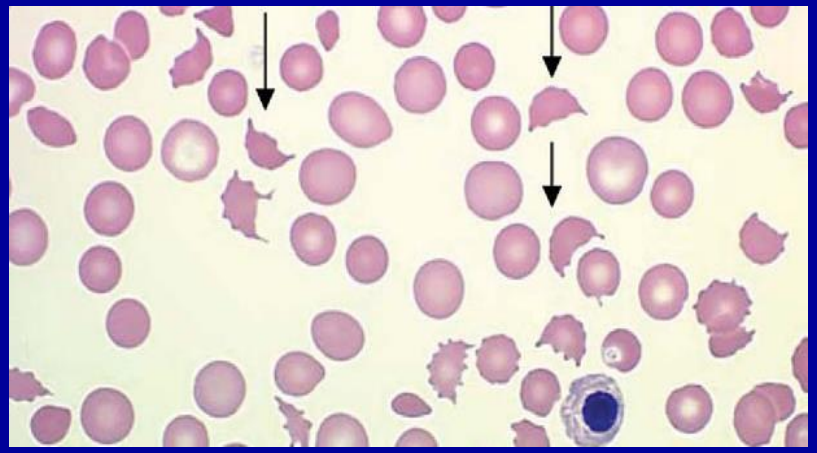




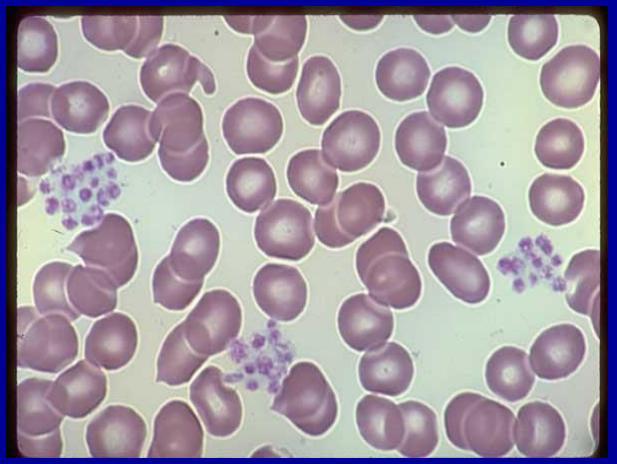


These are not ITP

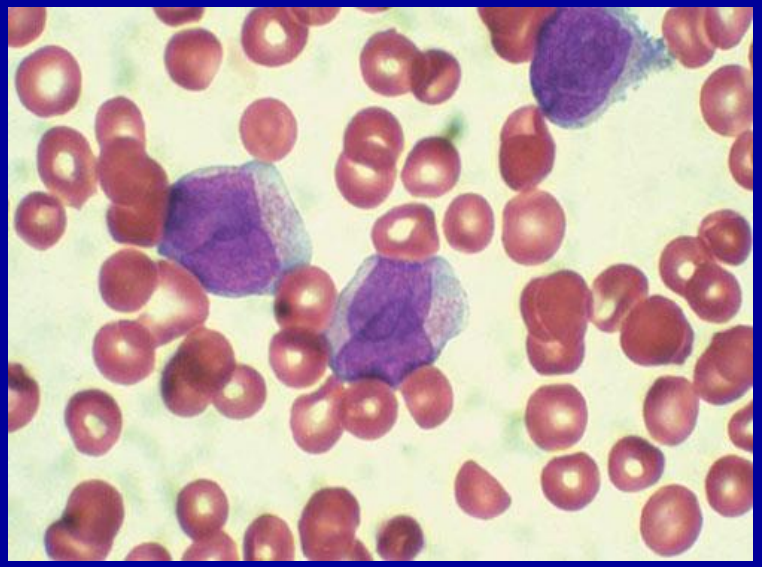
Microangiopathic hemolytic anemia



Platelet clumping

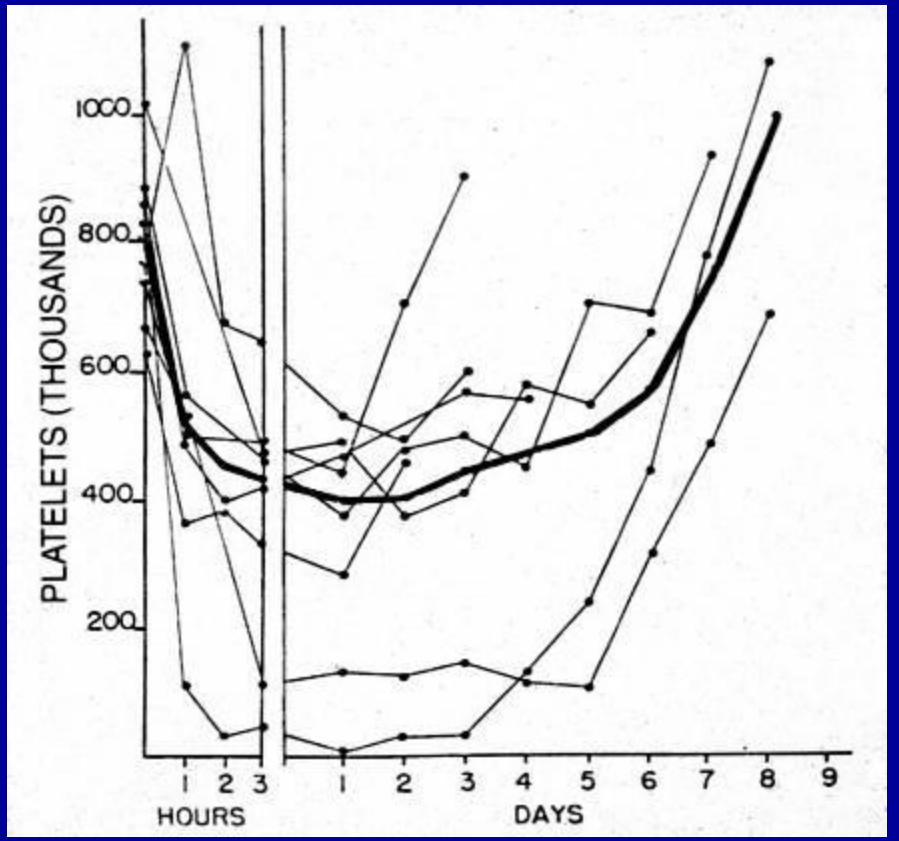


APL leukemia



Classic ITP experiment by William Harrington

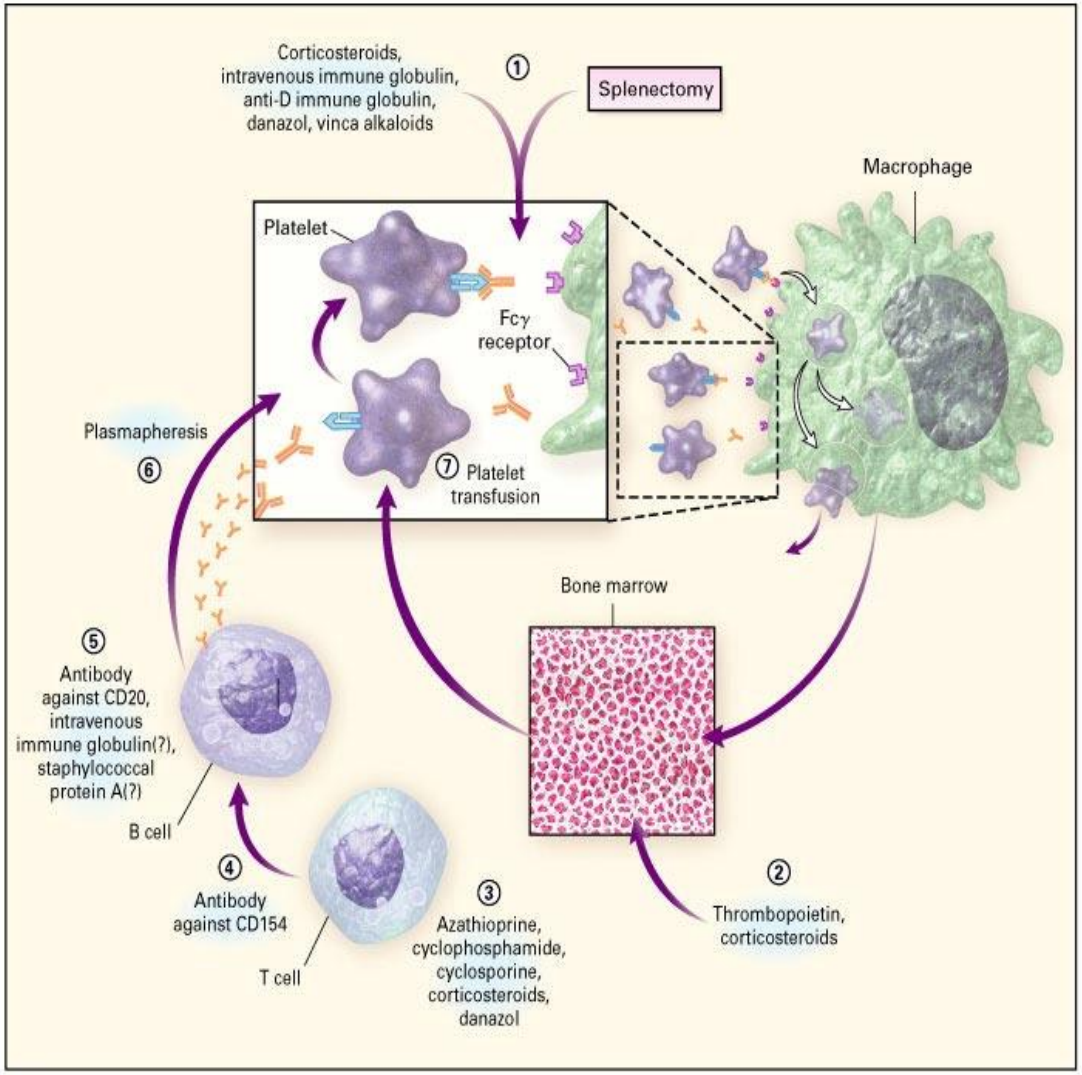
- Blood from patients with chronic ITP injected into himself and 9 other subjects with normal platelet counts
- Thrombocytopenia immediately observed in 8 subjects
- An antiplatelet "factor" in the globulin fraction of plasma, not the albumin fraction, was responsible



Harrington et al. *J Lab Clin Med*. 1951;38:1-10.

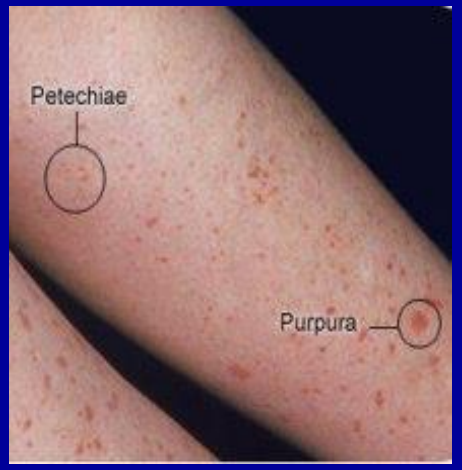
How ITP treatments work

ITP treatments
- steroids
- IVIG
- Rituximab
- Eltrombopag
- Avatrombopag
- Romiplostim
- Fostamatinib



Who to hospitalize for acute ITP

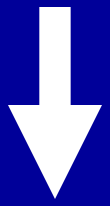
- Very low platelet count (<20,000/µL)
- Mucocutaneous bleeding (mouth, nose)
- Significant patient comorbidity or age>70
- Outpatient management not possible



Management of acute ITP

Steroid pulse

Consider IVIg



Rituximab and/or

Romiplostim/Eltrombopag

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Vancomycin-Induced Immune Thrombocytopenia

Annette Von Drygalski, M.D., Brian R. Curtis, M.S., Daniel W. Bougie, Ph.D., Janice G. McFarland, M.D., Scott Ahl, B.S, Indra Limbu, M.D., Kelty R. Baker, M.D., and Richard H. Aster, M.D.

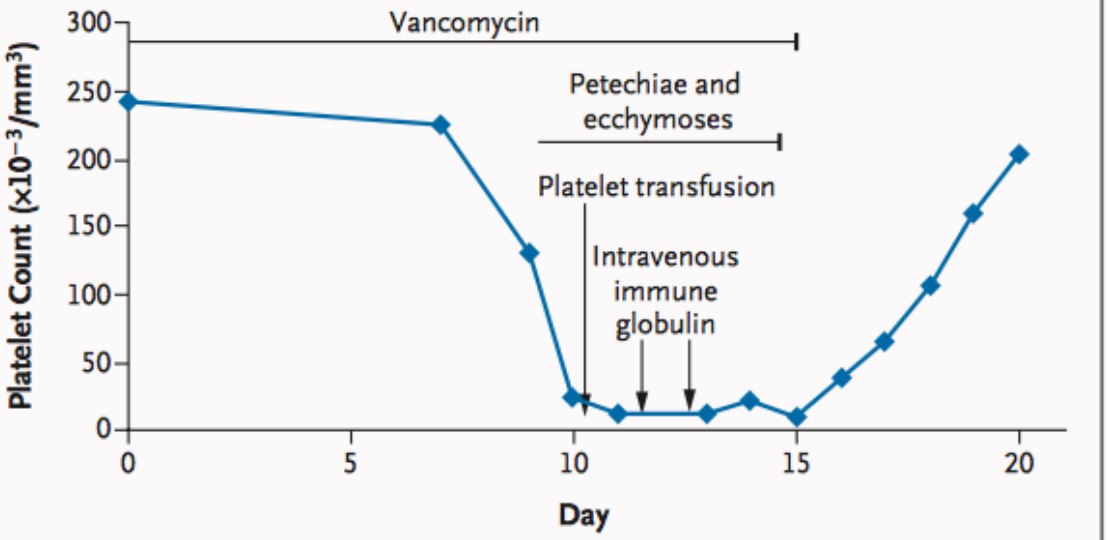


Figure 1. Clinical Course of a Patient with Vancomycin-Induced Thrombocy-

Drug-induced low platelets

Table 1. Drugs Commonly Implicated as Triggers of Drug-Induced Thrombocytopenia.*

Drug Category	Drugs Implicated in Five or More Reports
Heparins	Unfractionated heparin, low-molecular-weight hepa
Cinchona alkaloids	Quinine, quinidine
Platelet inhibitors	Abciximab, eptifibatide, tirofiban
Antirheumatic agents	Gold salts
Antimicrobial agents	Linezolid, rifampin, sulfonamides, vancomycin
Sedatives and anticonvulsant agents	Carbamazepine, phenytoin, valproic acid
Histamine-receptor antagonists	Cimetidine
Analgesic agents	Acetaminophen, diclofenac, naproxen
Diuretic agents	Chlorothiazide
Chemotherapeutic and immunosuppressant agents	Fludarabine, oxaliplatin

Low platelets during pregnancy

- Immune thrombocytopenia purpura (ITP)
  - New diagnosis or exacerbation of underlying ITP
  - Autoimmune, counts low (e.g. 20k)
- *Gestational* thrombocytopenia (ITP variant)
  - "dilution" and autoimmune, 7% of all pregnancies
- Preeclampsia and HELLP Syndrome
- Thrombotic thrombocytopenia purpura (TTP)

ITP during pregnancy

- May be exacerbation of “underlying” non-preg ITP
- May persist after pregnancy
- Peripartum bleeding is uncommon
- Usually treatments more toxic than condition
- Count too low for spinal anesthesia (need plt>80)
- Count too low for *safe* parturition (need plt>50)
- Neonatal thrombocytopenia

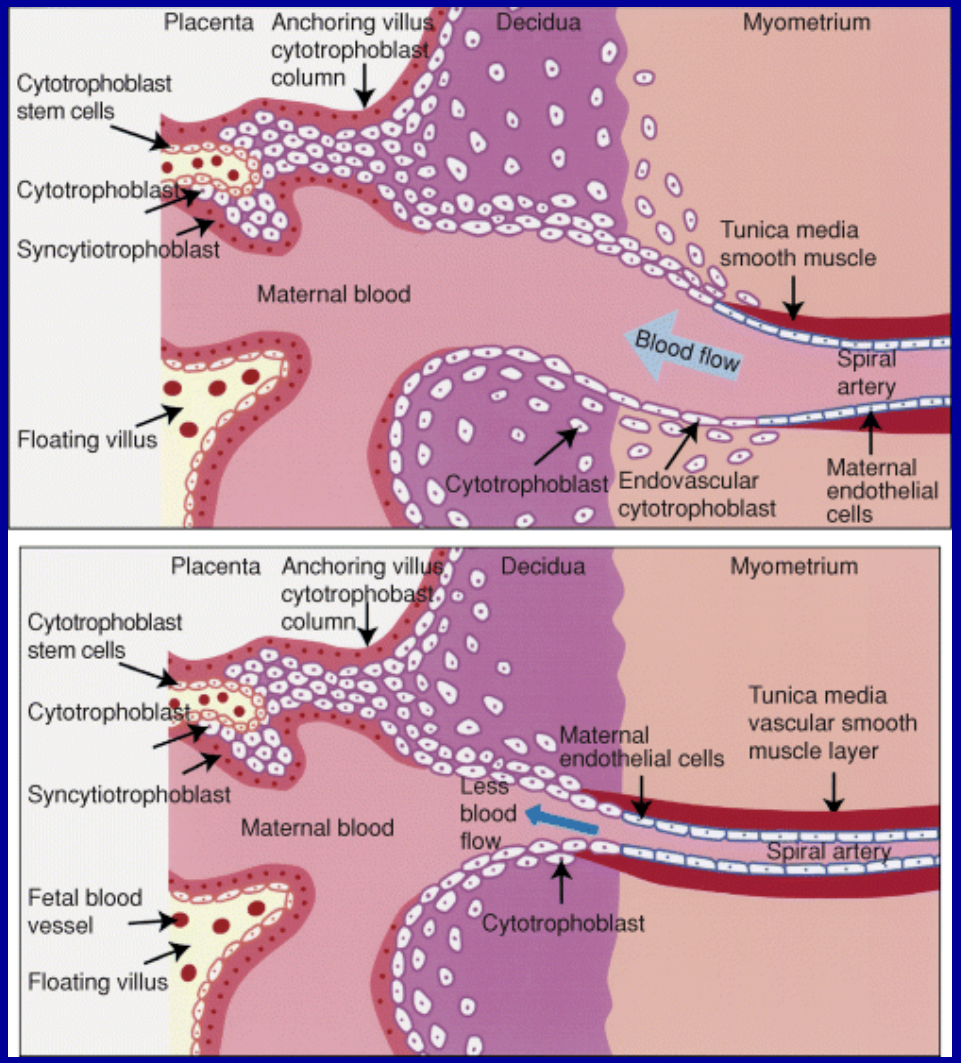
ITP during pregnancy

- Try to minimize steroids-prefer IVIG
- Don't treat numbers until ready for procedures
- May need weekly IVIG for parturition
- C-section not required, but Ob may recommend it
- Epidural needs plt>80
- 5% of babies will have plt<20→they may need IVIG
- Mother needs hematology f/u

Preeclampsia

- Common (6%) and unpredictable
  - Age<20 or age>30
  - Obesity
  - HTN before pregnancy
  - Diabetes a risk factor
- BP>140/90 and proteinuria (>0.3 g/day)
- Platelets low sometimes, but not usually
- Treatment is delivery, Mg to prevent seizure

Pathophysiology of Preeclampsia



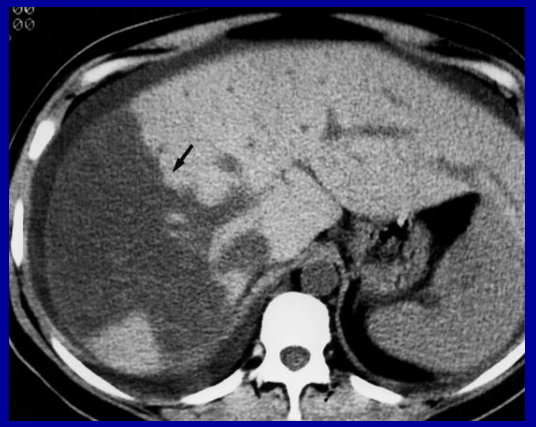
HELLP syndrome

- Same pathophysiology as Preeclampsia
  - 10% or preeclampsia patients

  Hemolysis

  Elevated Liver enzymes

  Low Platelets



- Nausea, abdominal pain, risk for eclampsia
- Treatment is delivery, Mg to prevent seizure

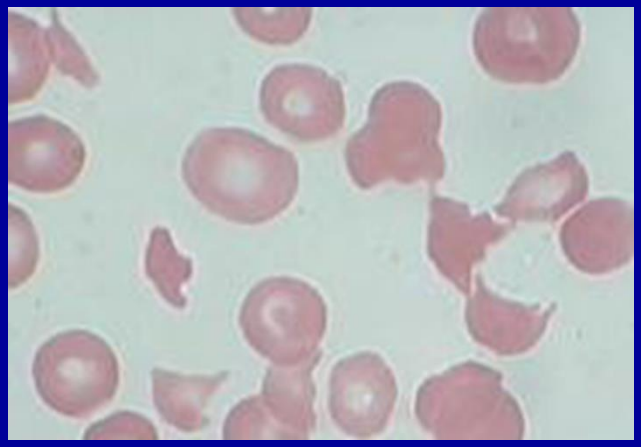
Preeclampsia and HELLP

- Probably thrombotic disorders
- Hepatic infarct → hematoma
- Can lead to DIC, including low fibrinogen
- Consider steroid pulse
- Platelet transfusion if platelet<20

- Risk of recurrence in future pregnancies

Thrombotic Thrombocytopenic Purpura TTP

- Low platelets and clotting/microthrombosis
- Usually young women (autoimmune)
- Occasionally associated with pregnancy
- *Microangiopathic hemolytic anemia*
- Need at least two of pentad:
  - Anemia, thrombocytopenia
  - Fever, Acute renal failure
  - Neurologic signs or symptoms

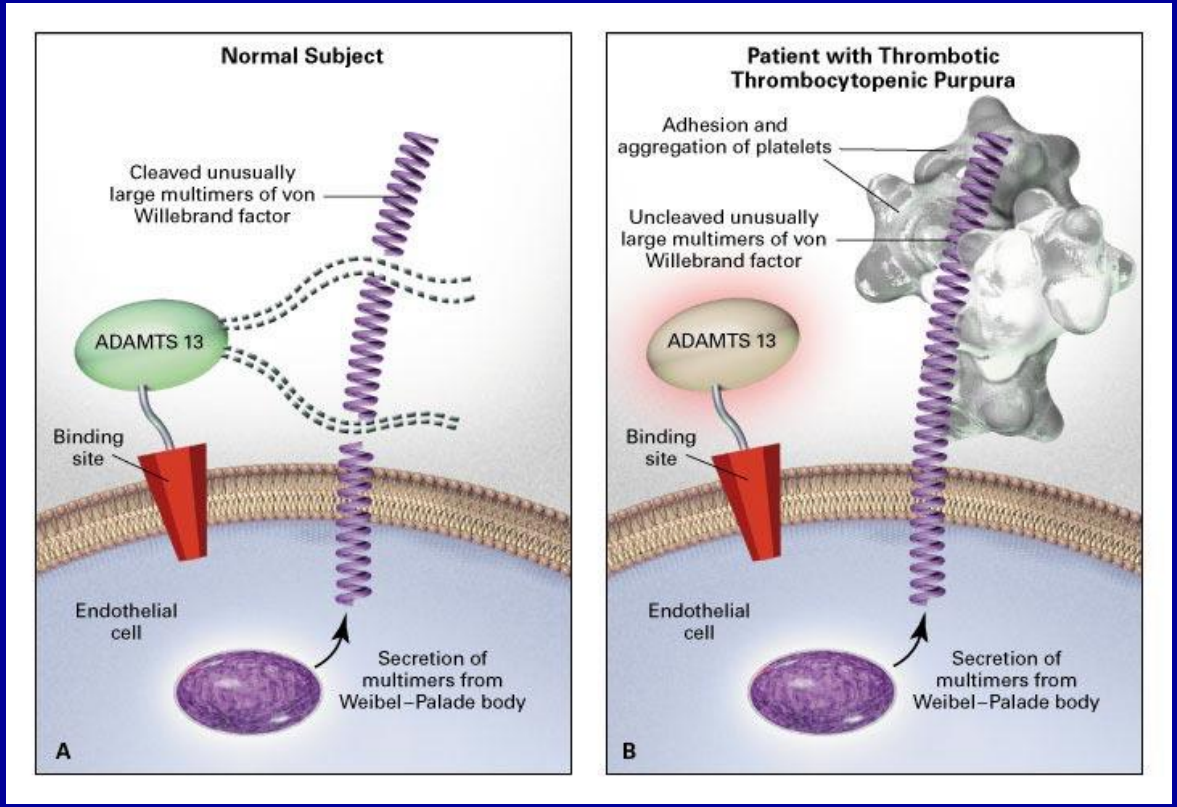


Pathophysiology of TTP

The New England Journal of Medicine

ANTIBODIES TO VON WILLEBRAND FACTOR–CLEAVING PROTEASE IN ACUTE THROMBOTIC THROMBOCYTOPENIC PURPURA

HAN-MOU TSAI, M.D., AND ERIC CHUN-YET LIAN, M.D.



TTP diagnosis and treatment

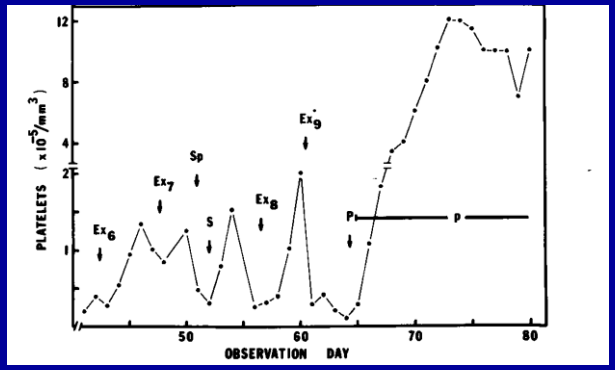
- 1925 Moschcowitz: 16yo girl with stroke and MI

TREATMENT OF THROMBOTIC THROMBOCYTOPENIC PURPURA WITH PLASMA

JOHN J. BYRNES, M.D., AND MOHAN KHURANA, M.D.

THE NEW ENGLAND JOURNAL OF MEDICINE

Dec. 22, 1977

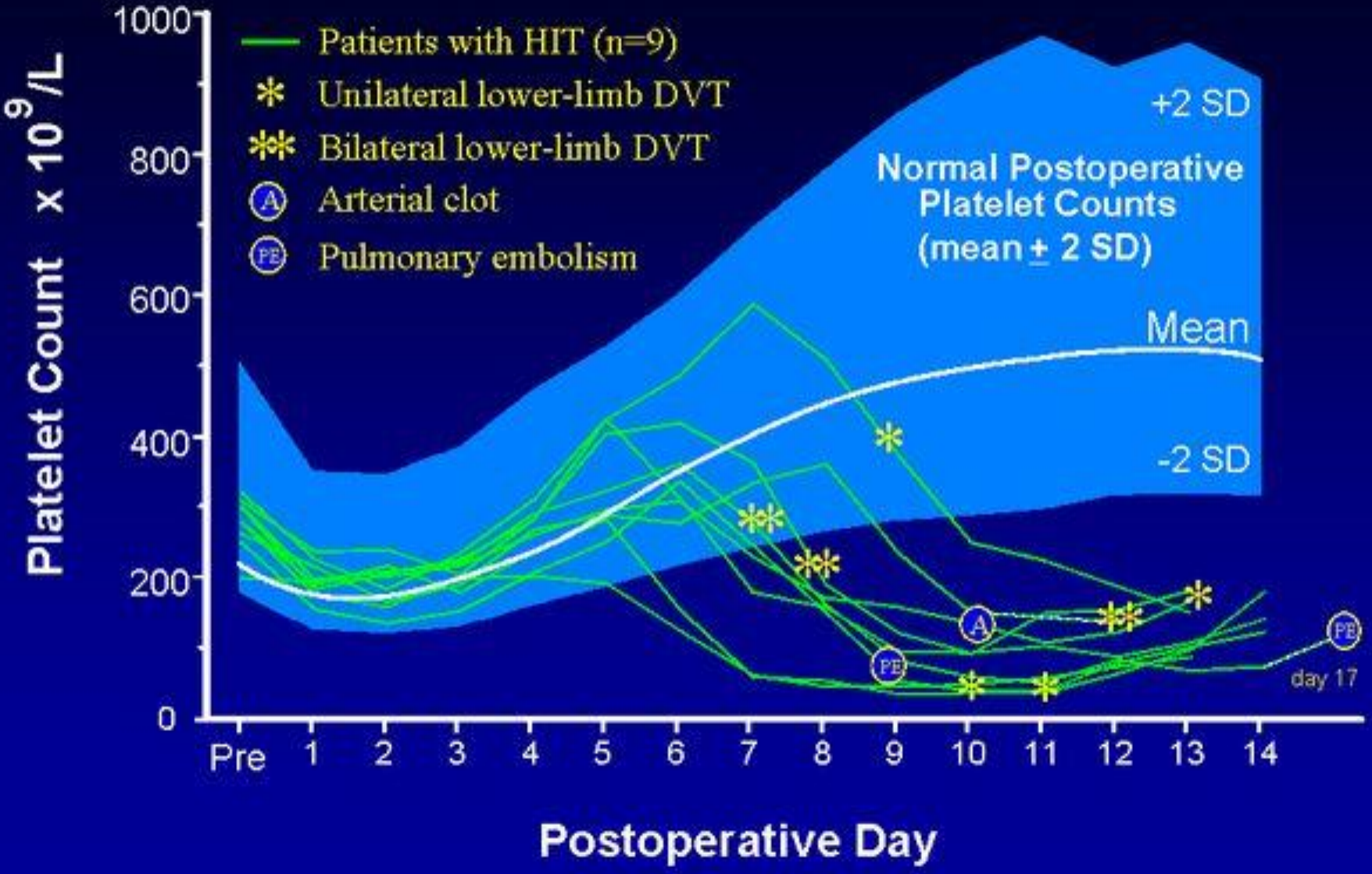


- 1980's Plasma exchange (plasmapheresis)
- 1990's Rituximab and chemotherapy
- 2020's Anti-VWF Antibody

What I'm going to tell you

- Hospital-based hematology
- Inpatients with low platelet counts
  - Nonmalignant, not HIT
  - HIT
  - APL leukemia
- What to do about low platelet counts

HIT Complicating Orthopedic Surgery



Warkentin et al. *N Engl J Med* 1995;332:1330-5

Frequency of HIT (Platelet Fall >50%)

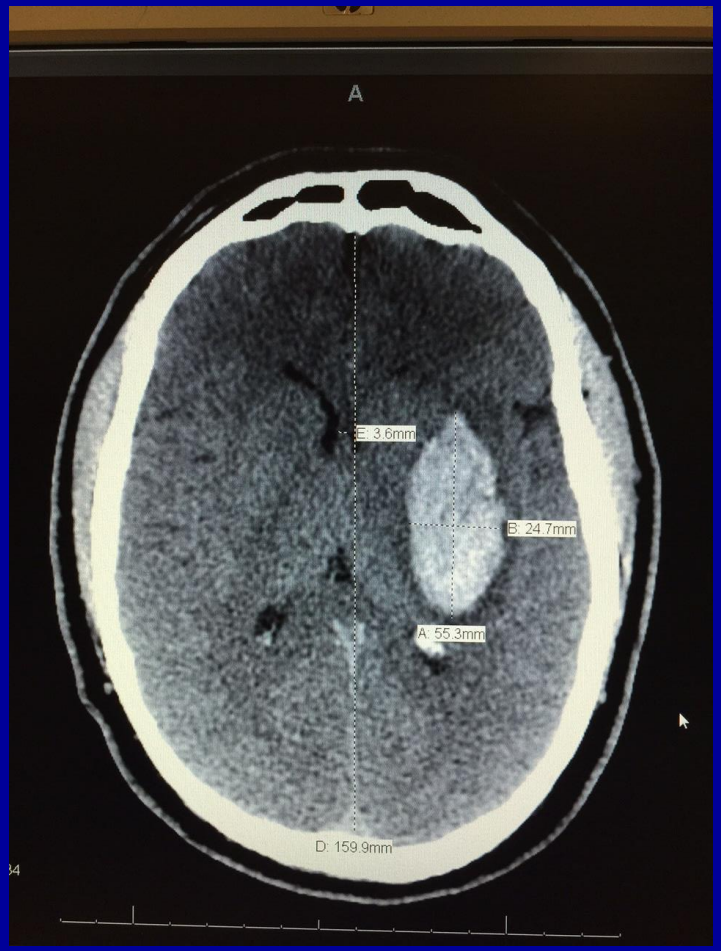
	UFH	LMWH*	
HIT	16/332 (4.8%)	2/333 (0.6%)	$P<0.01$
HIT-IgG**	29/205 (14.1%)	11/182 (6.0%)	$P=0.01$

* enoxaparin

** PF4/heparin-ELISA

Warkentin et al. *Arch Intern Med* 2003; 163: 2518-24.

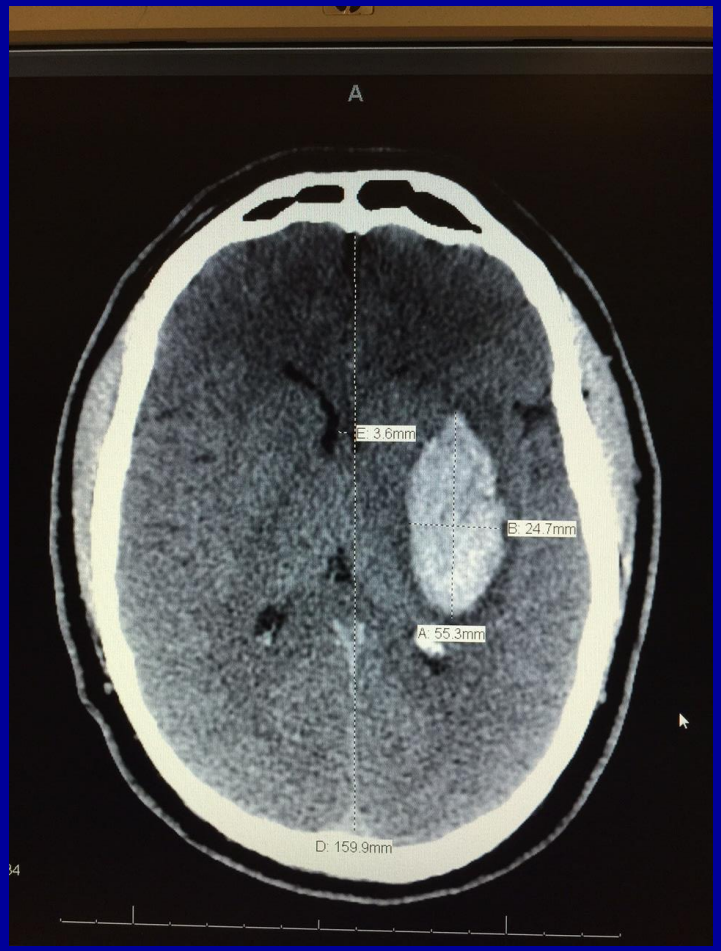
HIT case



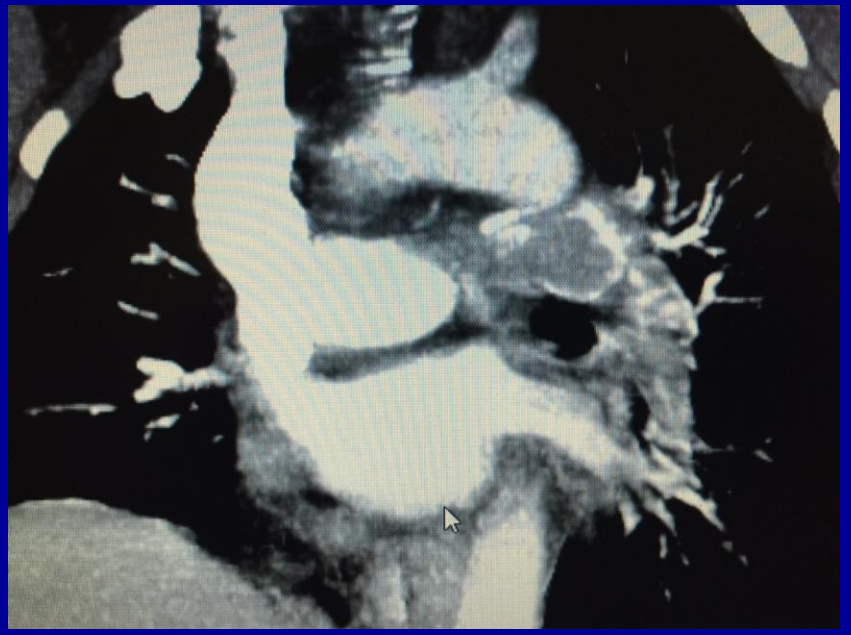
50yo man
Right side weakness
Large bleeding stroke

Rehabilitation 2 weeks
Subq heparin to prevent DVT/PE

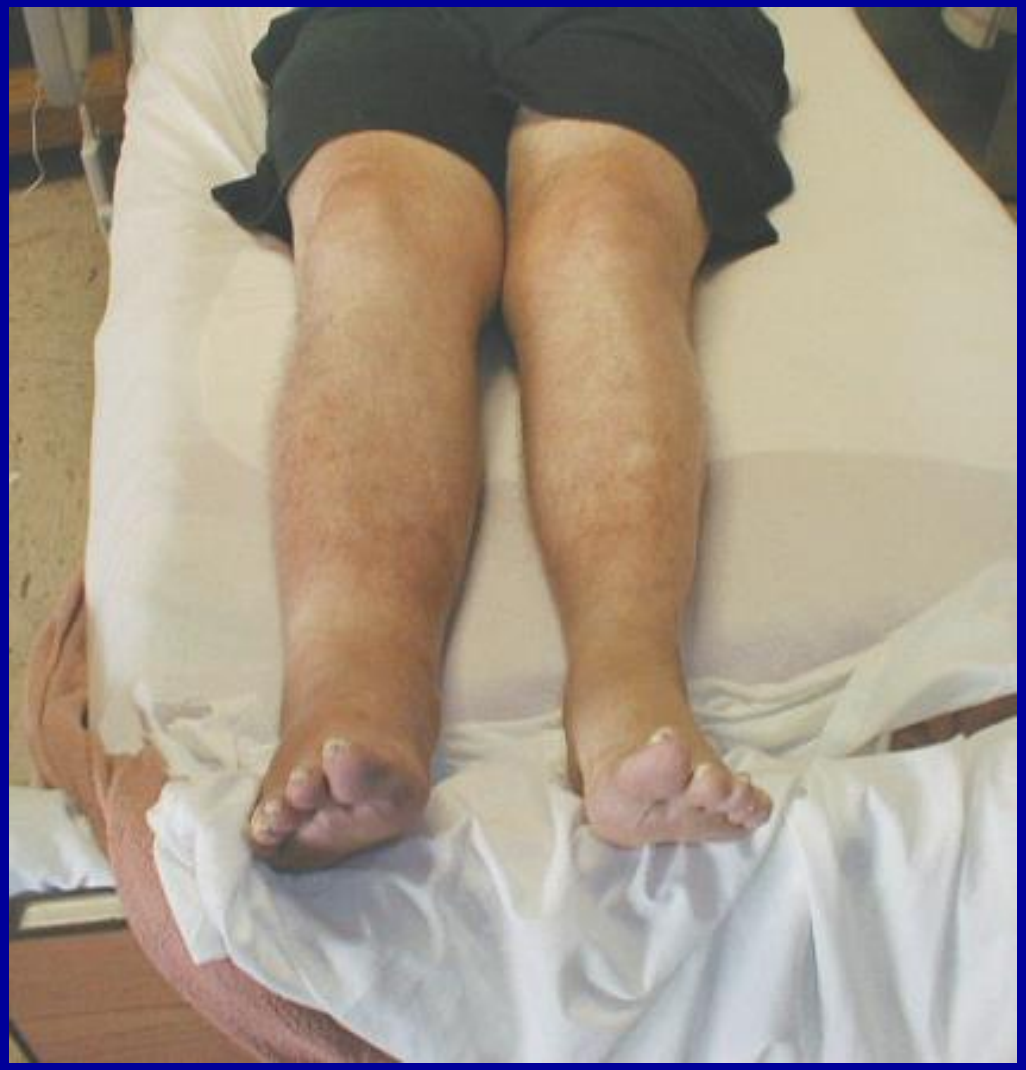
HIT case



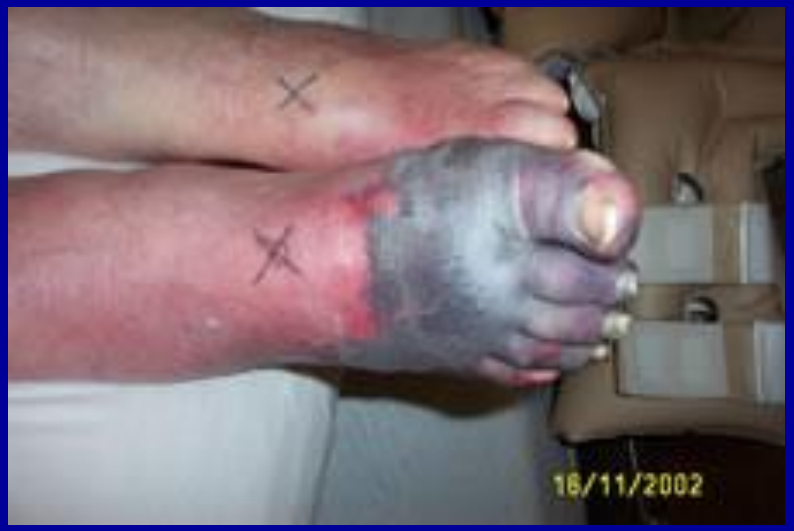
Two weeks later
pulmonary embolus

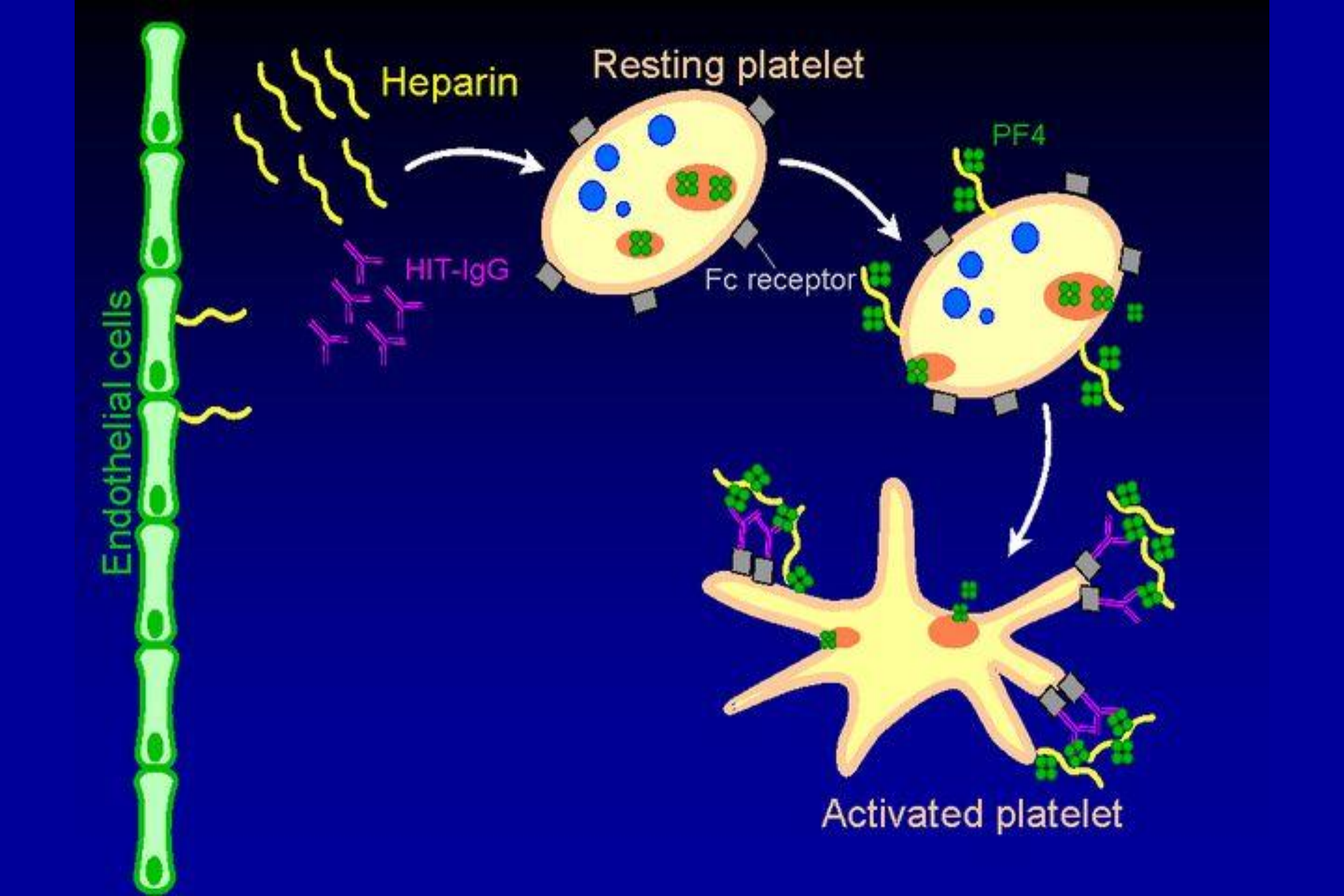


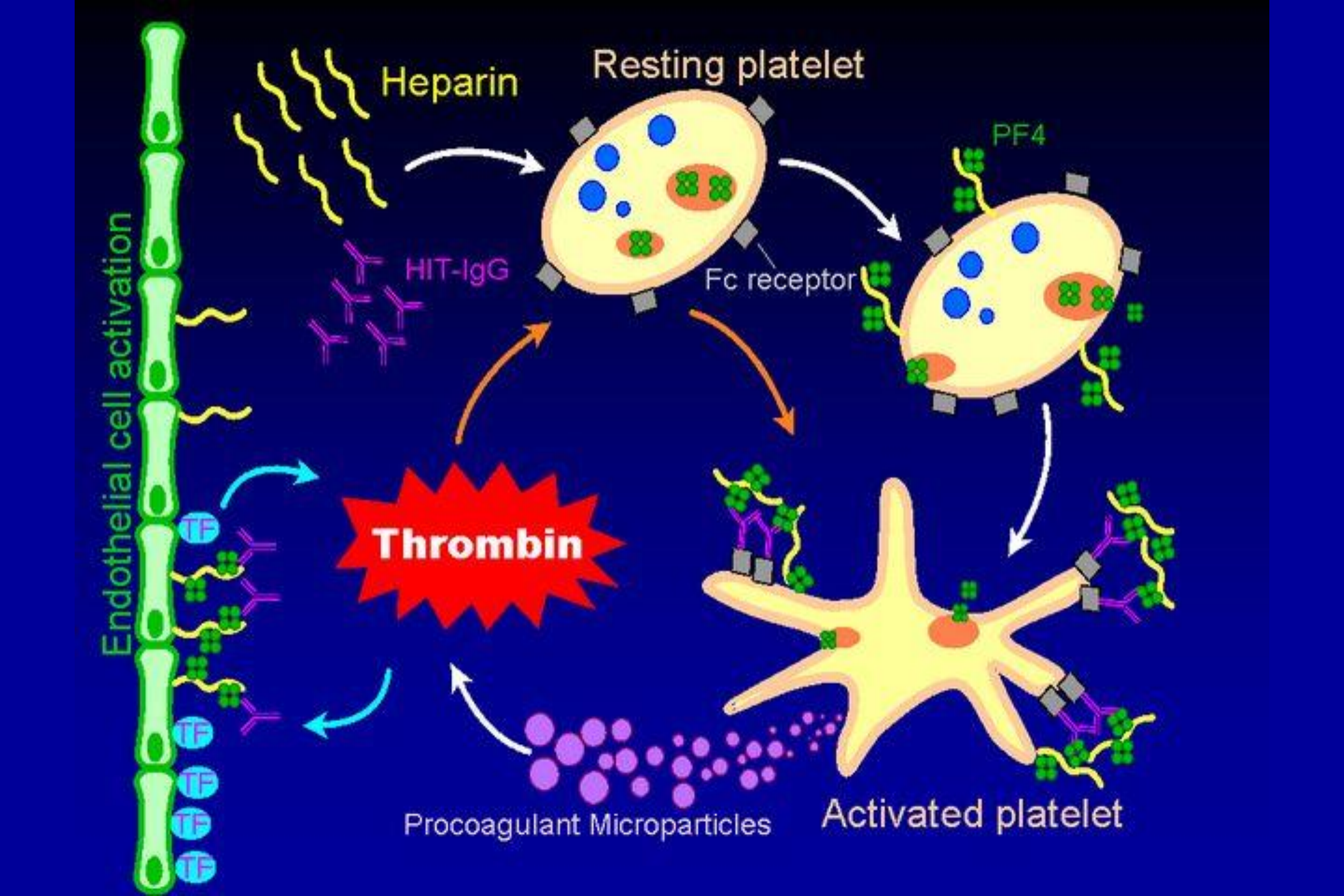
When to suspect HIT

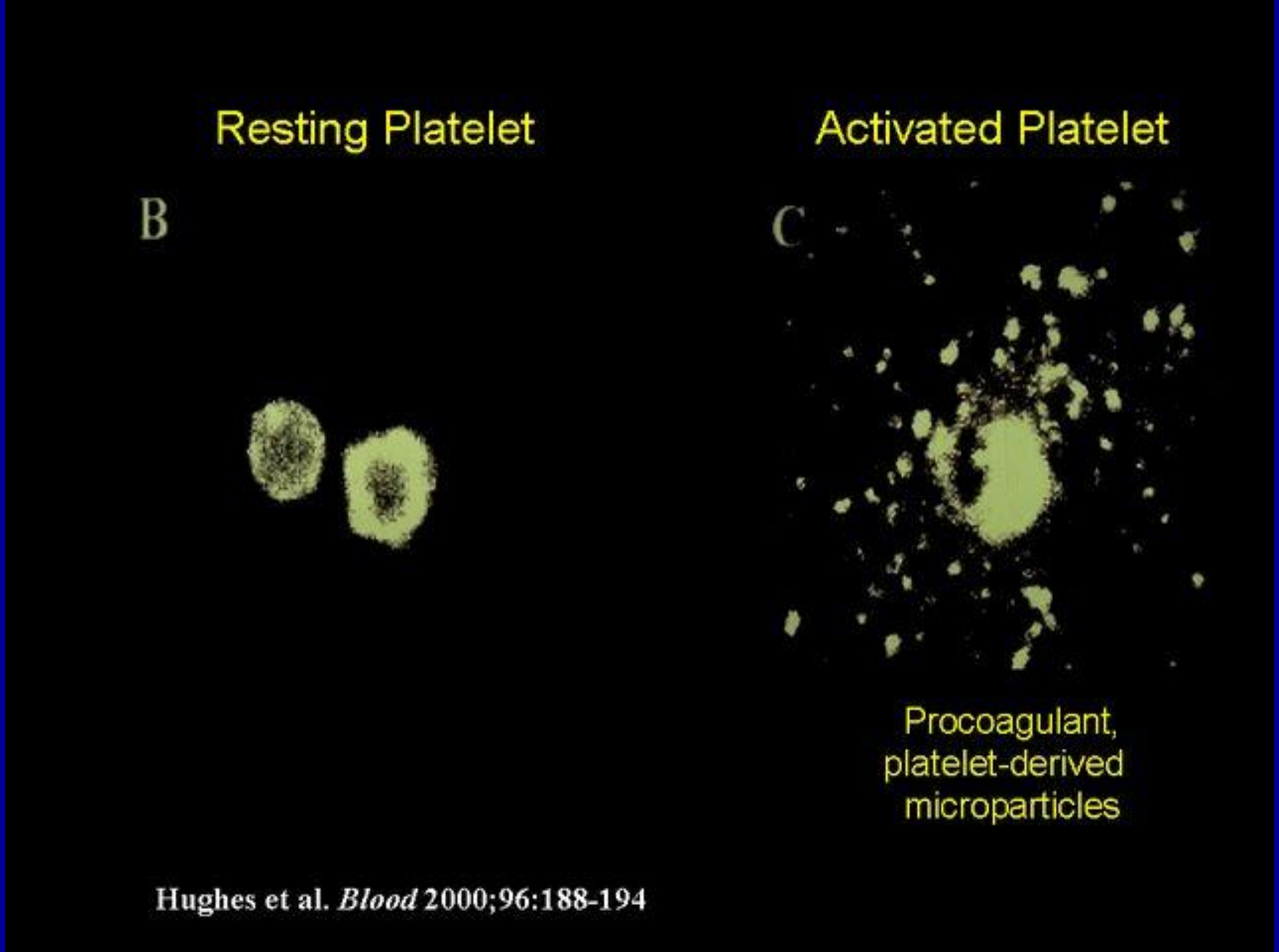


HIT causes clotting



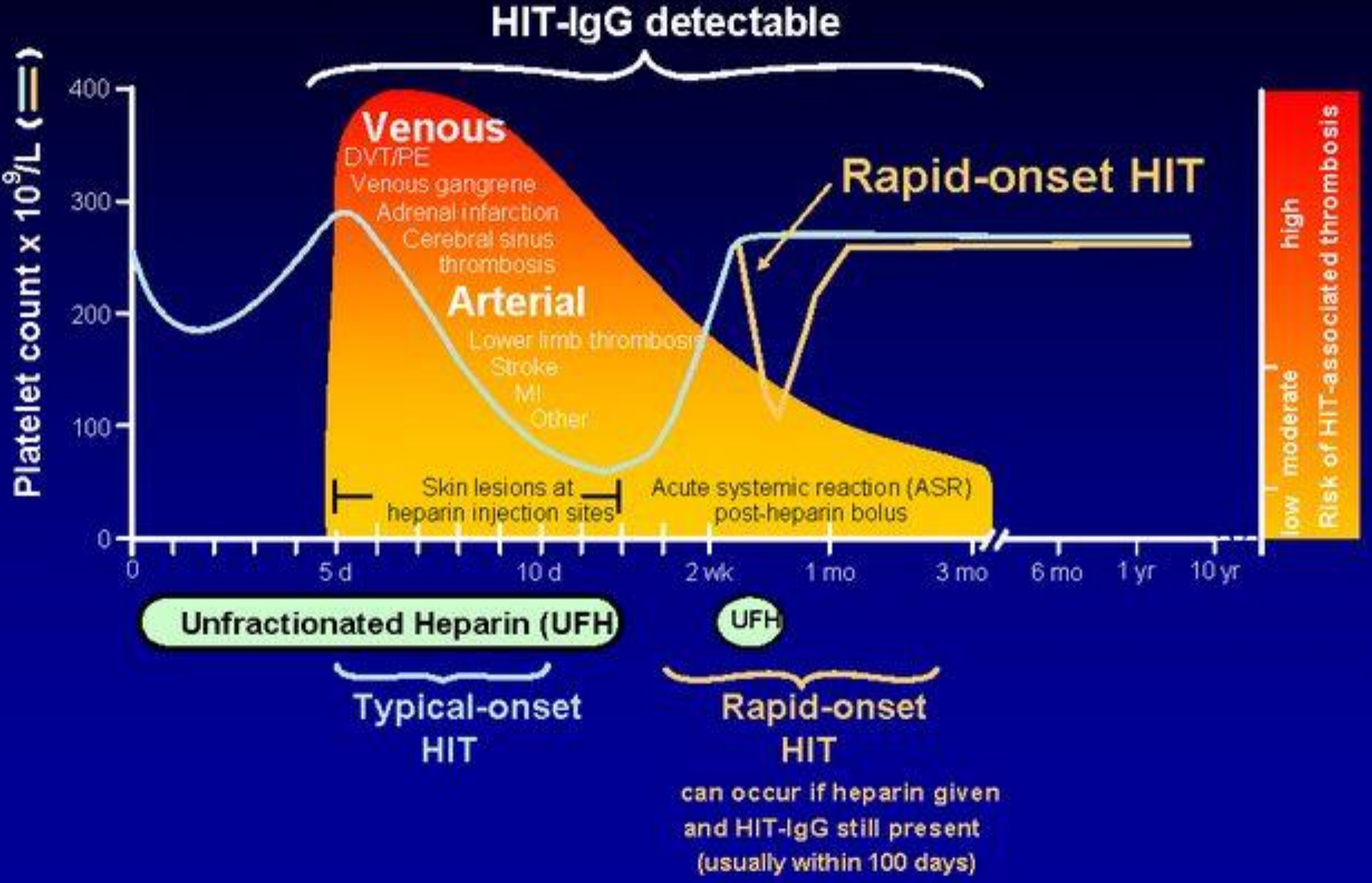

Endothelial cells
Heparin
HIT-IgG
Resting platelet
Fc receptor
PF4
Activated platelet


Heparin
Resting platelet
PF4
HIT-IgG
Fc receptor
Endothelial cell activation
Thrombin
TF
TF
TF
TF
Procoagulant Microparticles
Activated platelet



Hughes et al. *Blood* 2000;96:188-194

TIMELINE OF HIT

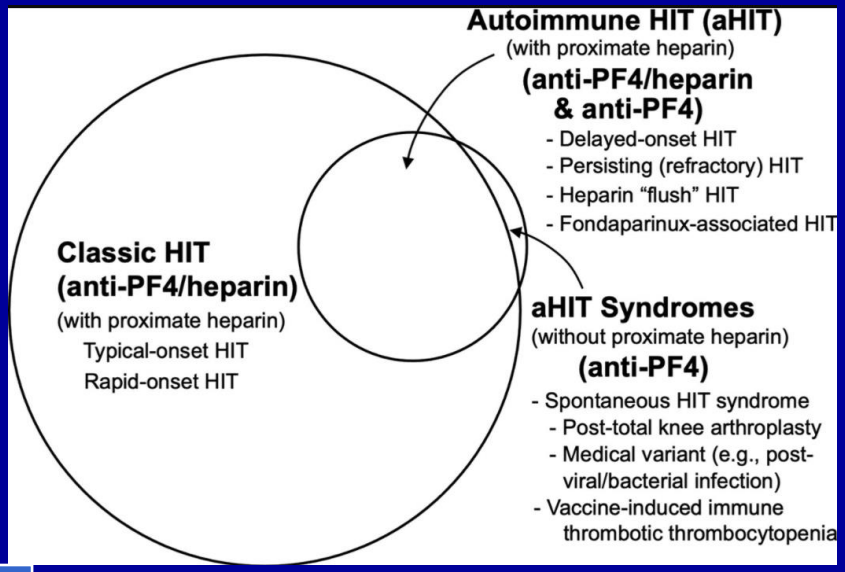


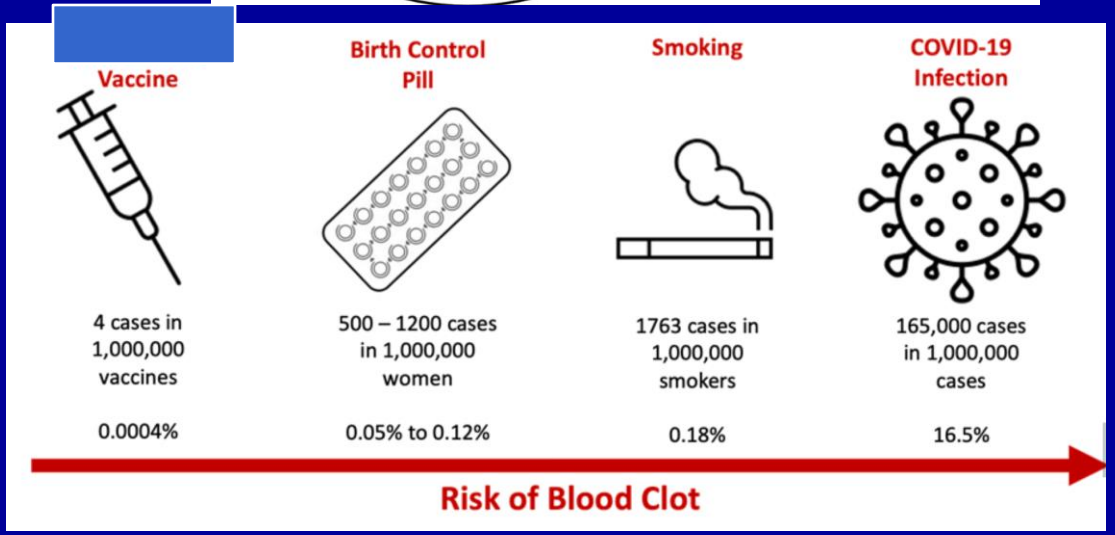
Warkentin & Greinacher. *Heparin-Induced Thrombocytopenia (3rd ed).* New York, Marcel Dekker, 2004

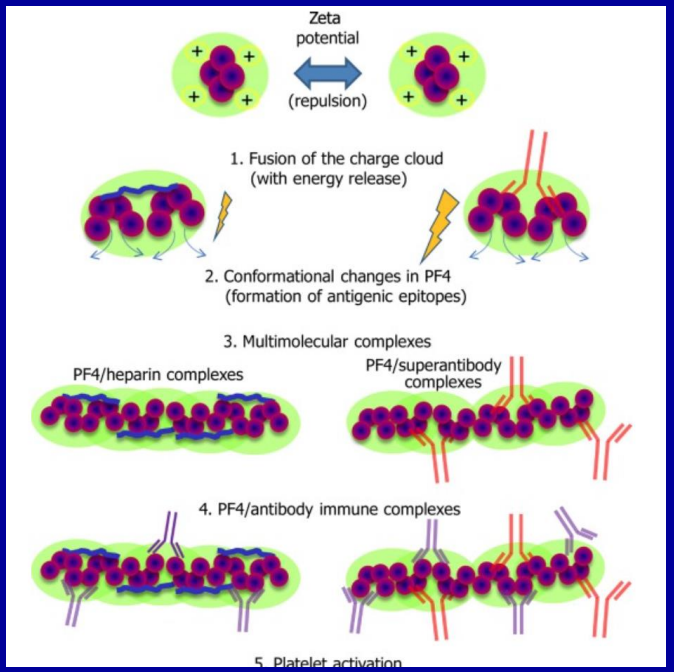
Who gets HIT?

- ACS/cardiac cath patients
- Cardiac surgery second heparin exposure
- Heparin/LMWH used to be used for DVT/Afib
- Heparin/LMWH for DVT prev post-op
- Heparin/LMWH for DVT prev non-surgical
- Autoimmune HIT (no heparin exposure)
- Vaccine-induced thrombosis (VIT)

Vaccine-induced thrombosis



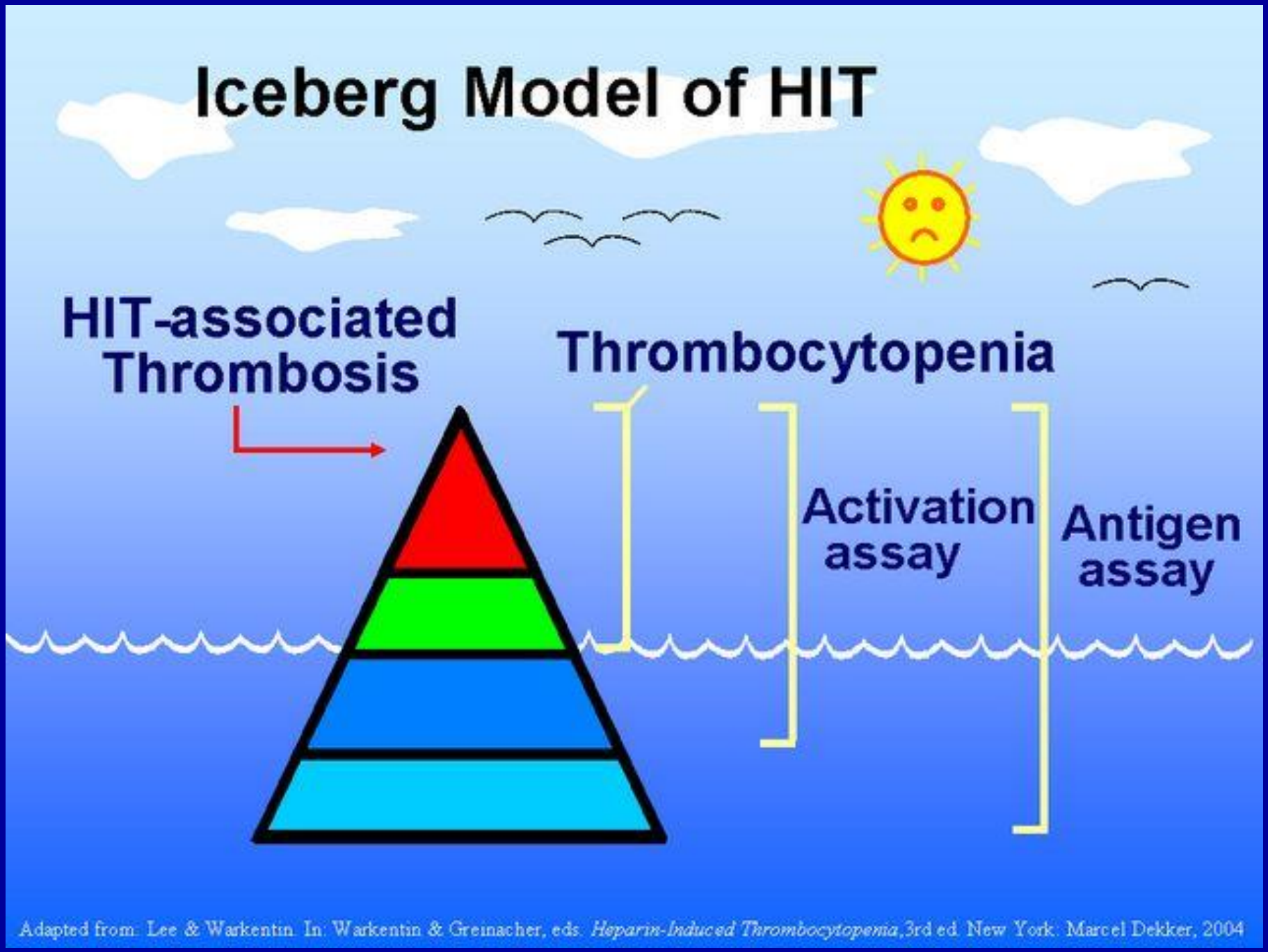




HIT clinical spectrum

- Subclinical
- Low platelets without obvious clot
- Superficial venous thrombosis
- DVT/PE
- Arterial thrombosis and stroke
- Venous limb gangrene and distal infarction
- Adrenal infarction and retroperitoneal hem

Iceberg Model of HIT



Adapted from: Lee & Warkentin. In: Warkentin & Greinacher, eds. *Heparin-Induced Thrombocytopenia*, 3rd ed. New York: Marcel Dekker, 2004

Defining clinical HIT

Old definition:

- Platelets <150
- Platelet decrease 50%
- 5-7 days after 1st heparin/LMWH

4 T criteria for HIT testing:

Thrombocytopenia

Thrombosis

Timing

No oTher cause

New definition:

- Thrombosis or unusual bleeding during/after receiving heparin/LMWH
- Unexplained clinical deterioration/hypotension
- Skin nodules or blisters
- Timing of heparin/LMWH unimportant
- Platelet decrease not necessary

When to suspect HIT

- Clotting after receiving heparin or LMWH
- Unexplained clinical deterioration
  - Hypotension, dyspnea, hypoxia
- Decreasing platelet count
- Re-admitted cardiac or post-op patient
- Recent cardiac catheterization
- "Coumadin failure"
- Dark spots at heparin injection sites

Why HIT is so controversial

- Heparin is a standard, widely accepted medication that is usually beneficial
- HIT presentation is variable
  - Not always a large thrombus or low platelets
  - Probably a spectrum of HIT severity
- Hep/PF4 antibody not always detrimental
  - "False positive" or clinically insignificant HIT

HIT testing 4T criteria

Table 1. 4T Scoring System for Evaluating the Pretest Probability of Heparin-Induced Thrombocytopenia.*

Variable	Score		
	2	1	0
Acute thrombocytopenia	Platelet count decrease of >50% and nadir ≥20,000/mm^3	Platelet count decrease of 30–50% or nadir 10,000–19,000/mm^3	Platelet count decrease of <30% or nadir ≤10,000/mm^3
Timing of onset	Day 5–10, or day 1 if recent heparin exposure	>Day 10 or unclear exposure	≤Day 4 with no recent heparin exposure
Thrombosis	New thrombosis or anaphylactoid reaction after heparin bolus	Progressive or recurrent thrombosis	None
Other cause of thrombocytopenia	None	Possible	Definite
Total score	6–8, indicating high score	4 or 5, indicating intermediate score	0–3, indicating low score

Who should be tested for HIT?

- Recent heparin or LMWH plus
- Two of 4T criteria:
  - Thrombocytopenia
  - Thrombosis
  - Timing appropriate
  - No oTher explanation for low plts
- Thrombosis during or after heparin/LMWH

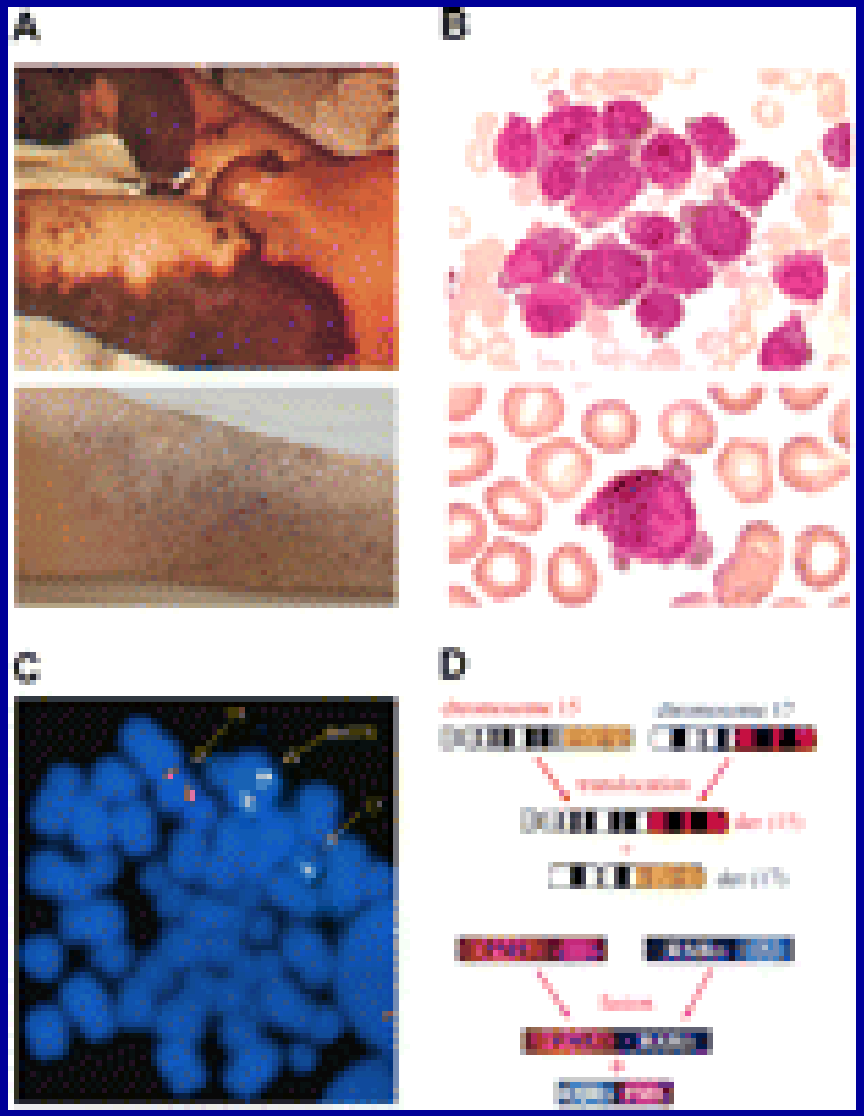
Who should be treated for HIT?

- Clinical/pathologic HIT plus clotting or clinical deterioration: argatroban
- HIT without clotting: consider fondaparinux
- Heparin antibody without clinical HIT: avoid heparin/enoxaparin
- Clinical HIT without PF-4 correlate: consider argatroban and repeat PF-4 Ab

What I'm going to tell you

- Hospital-based hematology
- Inpatients with low platelet counts
  - Nonmalignant, not HIT
  - HIT
  - APL leukemia
- What to do about low platelet counts

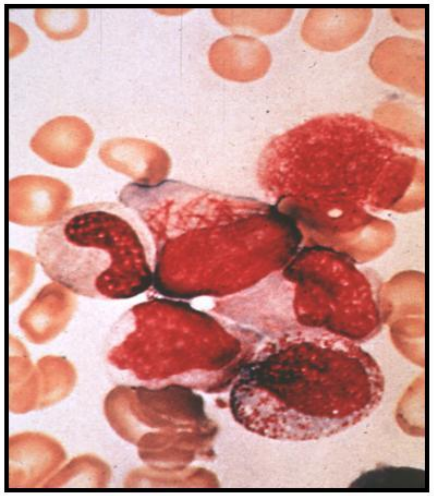
Acute Promyelocytic Leukemia



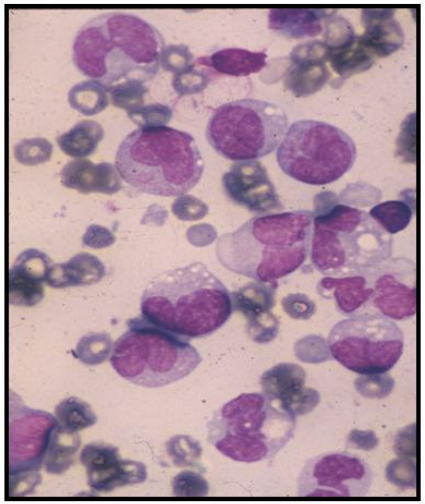
Acute Promyelocytic Leukemia (APL)

APL Cells: Morphology

FAB M3



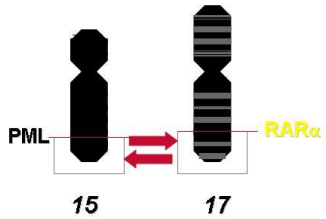
FAB M3 Variant (25%)



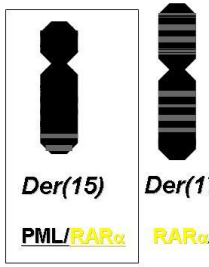
Bennett et al Ann Intern Med 1985; 103:620,
Bennett JM, Catovsky D, Daniel MT, Flandrin G, Galton DA, Gralnick HR, Sultan C. Br. J. Haematol 1980;44:169,

APL Chromosomal Changes

t(15;17)(q22;q11-22)

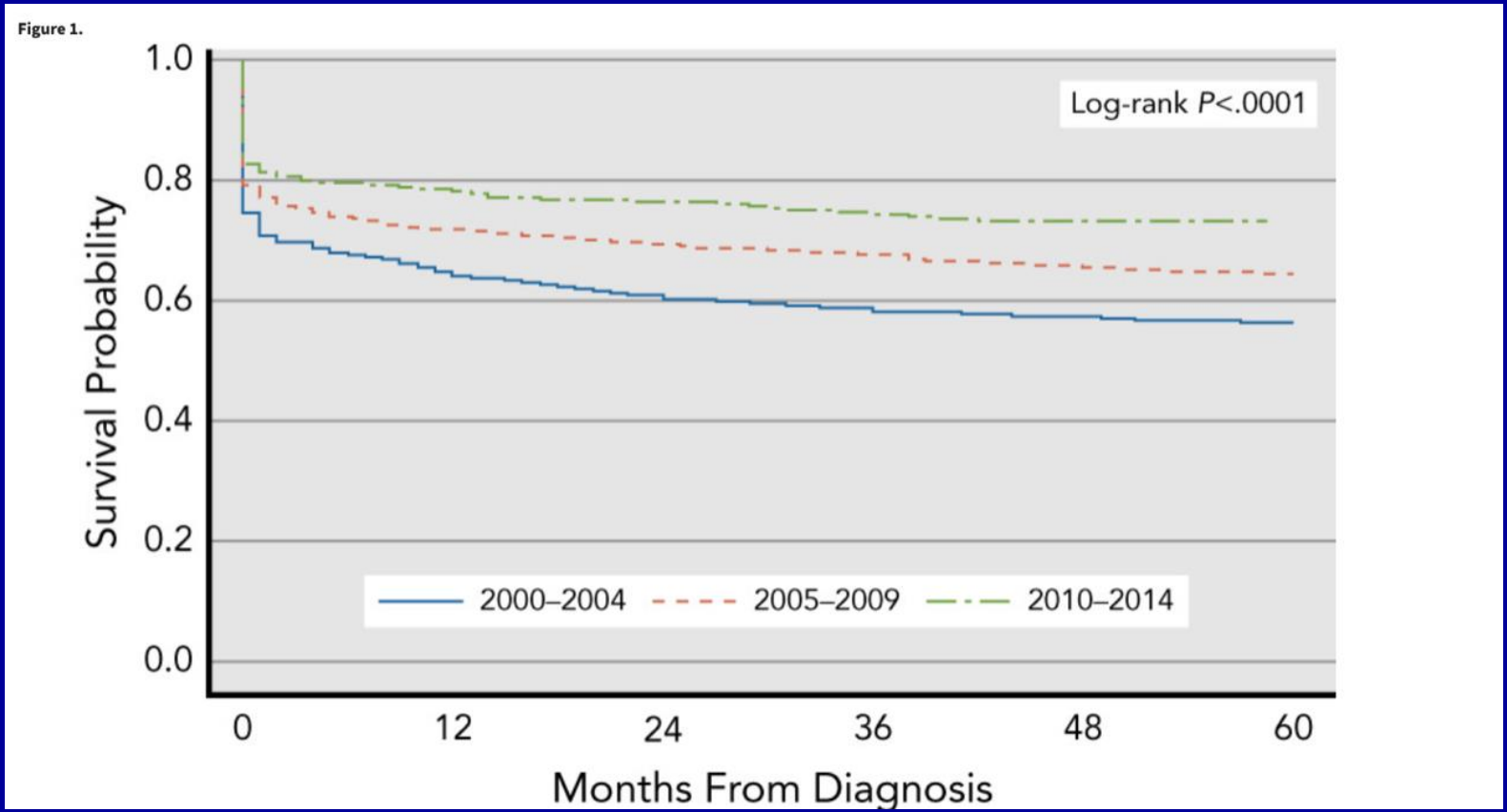


PML = promyelocytic leukemia
RAR = retinoic acid receptor

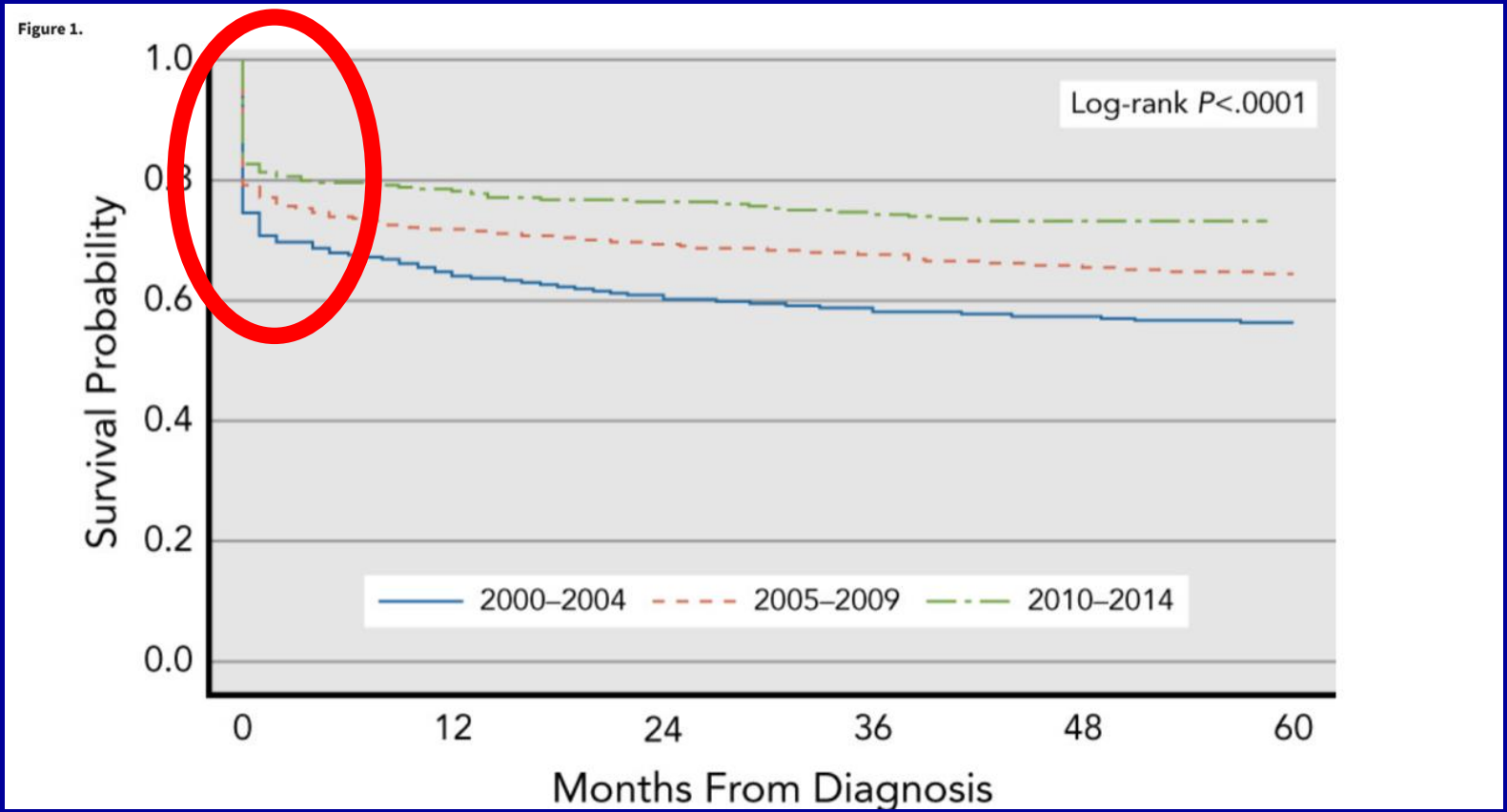


Parmar S, Tallman MS. *Expert Opin Pharmacother.* 2003;4:1379-1392.
Slack JL, Waxman S, Tricot G, Tallman MS, Bloomfield CD. *Oncologist.* 2002;7(suppl 1):1-13.

Acute promyelocytic leukemia (APL)



Acute promyelocytic leukemia (APL)



Don't miss an APL patient

- Deadly if missed
- Most APL patients are young
- Need high suspicion for APL
  - Bleeding out of proportion to low plt count
  - Plt count increases after plt transfusion
  - "spontaneous" intracranial bleeding
  - Abnormal WBC differential
  - Low fibrinogen

What to do for a new APL patient

- Challenging to explain APL to patients and families
  - The patient may die while waiting for treatment to take effect
  - The patient may die despite the best effort to prevent ICH
  - If bleeding is avoided, the disease may be curable (>90%)

- Start cryo and platelet transfusions around the clock (not prn)
- Bone marrow biopsy is not urgent- you can test blood FISH and flow
- Consider tretinoin before diagnosis is confirmed, but cryo more impt
- Transfer to leukemia center

What I'm going to tell you

- Hospital-based hematology
- Inpatients with low platelet counts
  - Nonmalignant, not HIT
  - HIT
  - APL leukemia
- What to do about low platelet counts

What to do about acute low plts

- Determine likelihood of HIT, consider testing
- Determine likelihood of heme malignancy
- Consider stopping linezolid or pip/tazo if possible

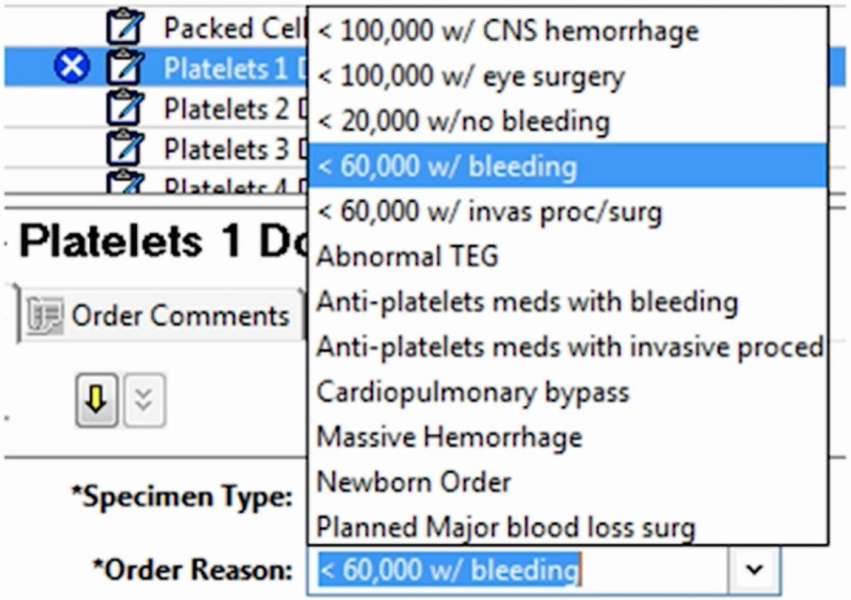
- Focus on whether patient is bleeding or clotting
- Consider safety/appropriateness of anticoag
- Transfusions only for count <10-20 or visible bleeding or invasive procedure planned

When to consider platelet transfusions

- Low plt count <10-15
- Visible bleeding <50

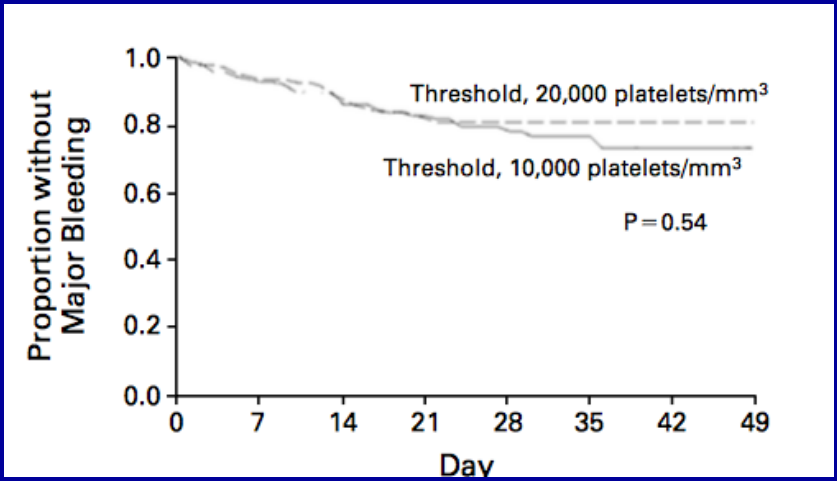
- Invasive procedure <50
- Ob C-section <50

- CNS procedure <80
- Ob spinal <80

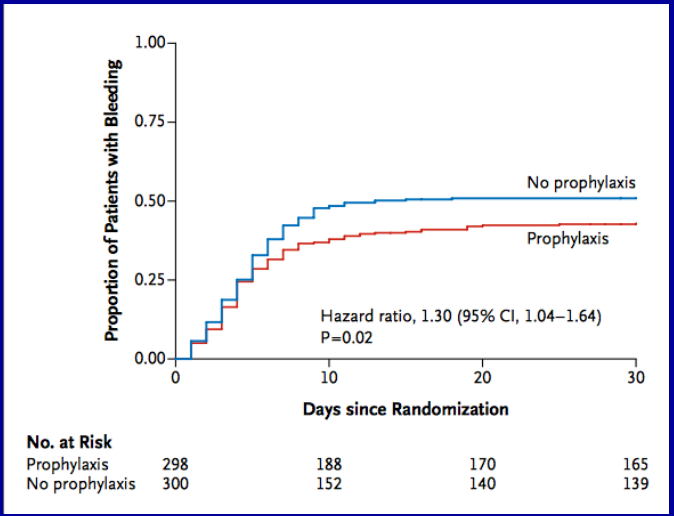


THE THRESHOLD FOR PROPHYLACTIC PLATELET TRANSFUSIONS IN ADULTS WITH ACUTE MYELOID LEUKEMIA

Transfusion at 10k vs. 20k



No transfusion vs. 10k



How to think about LMWH in patients with low plt counts

- The reason to avoid LMWH for plt 30-100 is concern for HIT, not concern for bleeding risk

- If HIT is not suspected, then OK for LMWH

My anticoag recommendations for patients with low plt counts

- Risk/benefit decision based on presumed or established diagnosis (i.e., is it ITP?)

  AND assessment of bleeding tendency
- If plt>30 and no bleeding seen then LMWH OK
- If bleeding seen or presumed, avoid anticoagulants
- If plt<30 then avoid anticoagulants

What we have discussed

- Low plt count diagnosis: acute vs. chronic
- Acute low plt count diagnosis: non-HIT vs. HIT
- Low plt count does not usually pose risk for bleeding tendency until about plt<20
- Low plt count that looks like HIT should prompt testing and possible intervention
- Anticoagulants are OK for patients with low platelets after assessing risk/benefit profile