

Thrombocytopenia in Hospitalized Patients

Medical Grand Rounds

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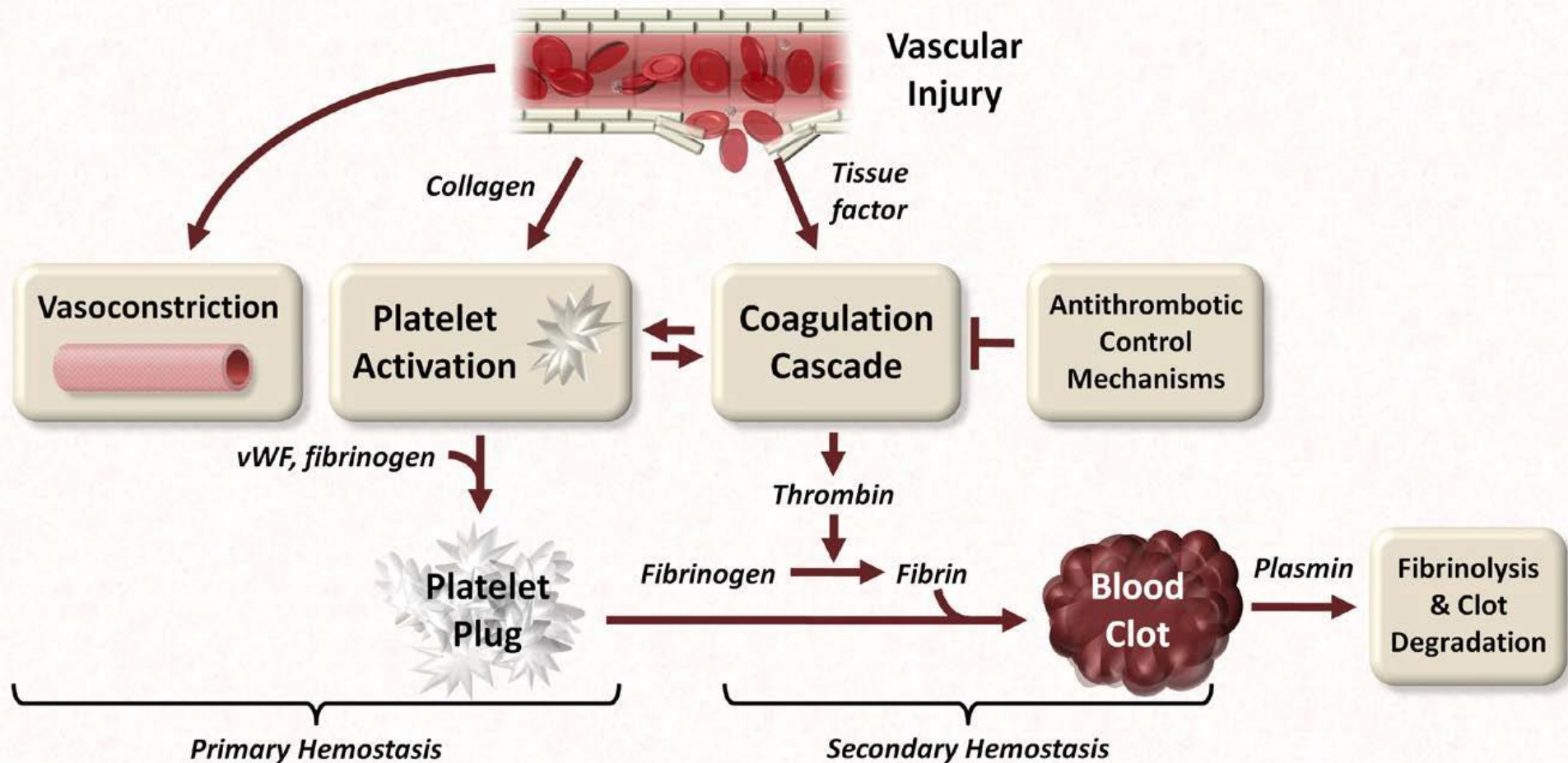
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- A) Relationship with companies who manufacture products used in the treatment of the subjects under discussion : No
- B) Discussion of unlabeled uses: No
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Learning Objectives

- Recognize common causes of thrombocytopenia especially in hospitalized patients
- Recognize dangerous causes of thrombocytopenia
- Be familiar with the management of common causes of thrombocytopenia

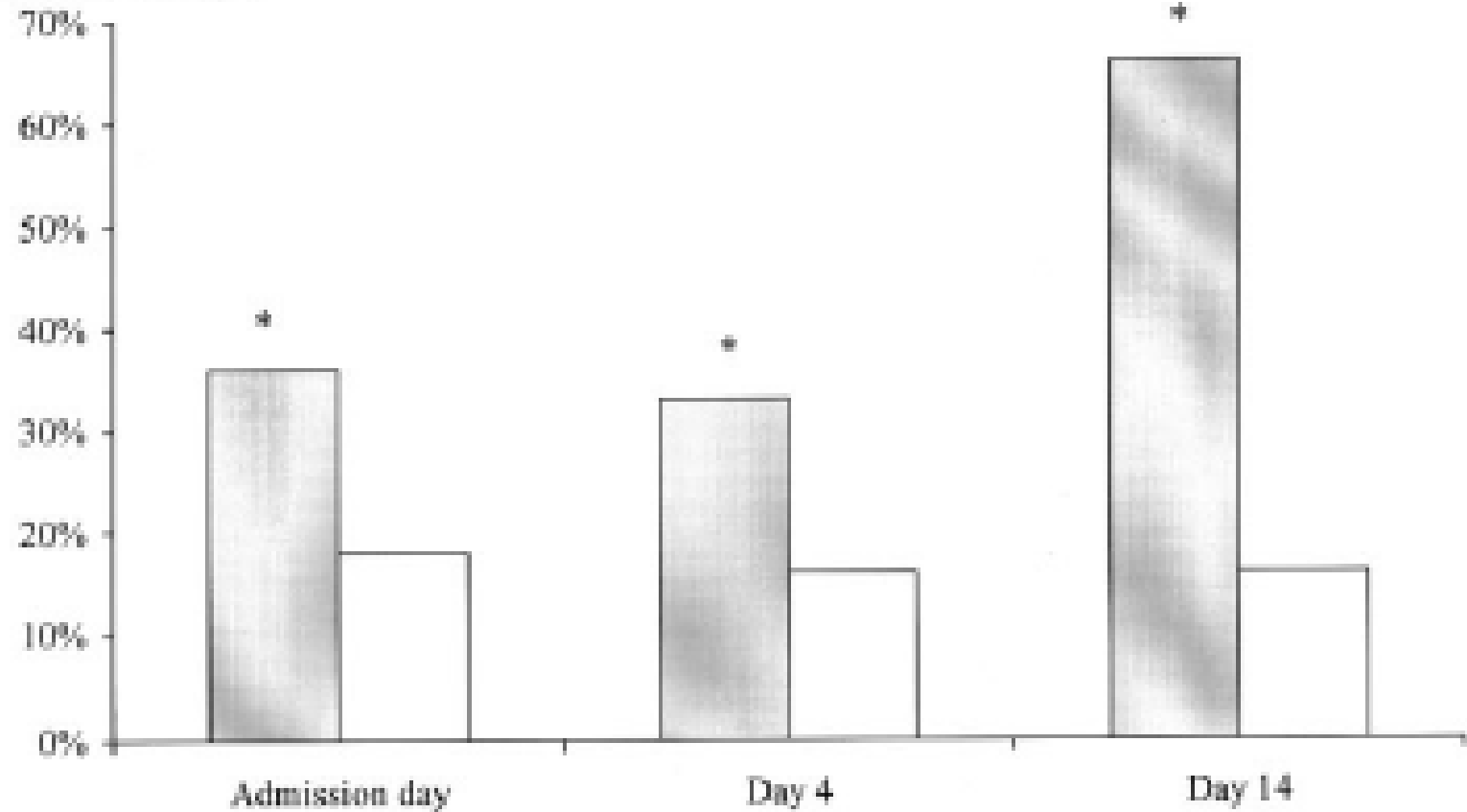
Major Components of Hemostasis



Thrombocytopenia

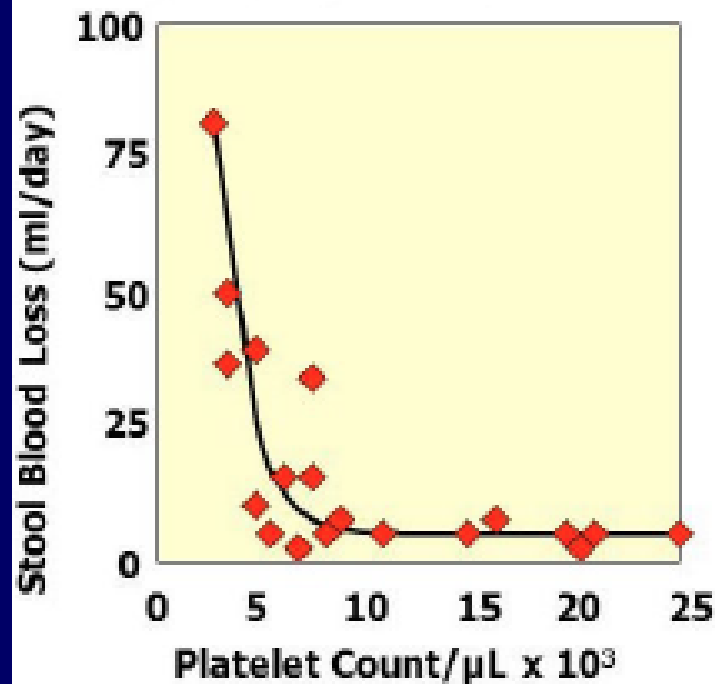
- Platelets have key role in primary hemostasis.
- “Normal”: Approximately 140K-450K/mcL
- “Normal”: 90K to 300K/mcL in people of Mediterranean descent.
- Platelet counts at 20K-50K are associated with mucocutaneous bleeding and less than **10K** is associated with spontaneous intracerebral hemorrhage.
- 1/3 of all Hematology consults in the hospital are for thrombocytopenia.
- 5 to 10% of all hospital patients are thrombocytopenic and in the ICU the number increases to 35%.

Mortality rate (%)



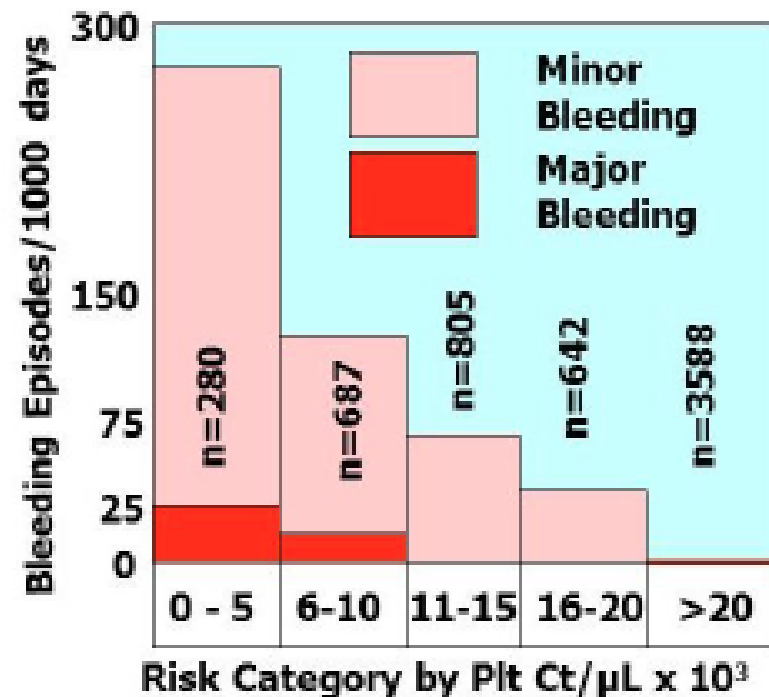
Stool blood loss in 28 aplastic, thrombocytopenic patients

Ann. Review of Med, Vol. 31, 1980



Bleeding risk vs. plt ct

The Lancet, Vol. 338, 1991



Sites of Bleeding

- Skin and mucous membranes: petechiae, ecchymoses, hemorrhagic vesicles, gingival bleeding, and epistaxis
- Menorrhagia
- Gastrointestinal bleeding
- Intracranial bleeding
- Bleeding in joints and soft tissues are manifestations of coagulation factor deficiencies and inhibitors



Thrombocytopenia: Significance depends on its *cause*

E.g.: post cardiac surgery patient:
platelets 60k

- If HIT
 - High risk of arterial and venous thrombosis
 - Treat with a non-heparin anticoagulant
- If sepsis
 - High risk of mortality (organ failure)
- If hemodilution
 - Why was I asked to consult?

Classification

- Pseudothrombocytopenia
- Hemodilution
- Consumption
- Destruction
- Sequestration
- Decreased Production

Basic approach

History

- Is the patient bleeding
- Do the sites of bleeding suggest a platelet defect
- Duration (acute vs. chronic)
- Medications, alcohol/drugs, recent transfusion
- Symptoms of secondary illness (neoplasm, infection, or autoimmune disease)
- Family history of thrombocytopenia or bleeding problems
- Heparin exposure
- Risk factors for HIV infection or history of liver disease

Exam

- scleral icterus, mucosal petechiae, purpura, splenomegaly, bleeding from IV catheter sites, etc.

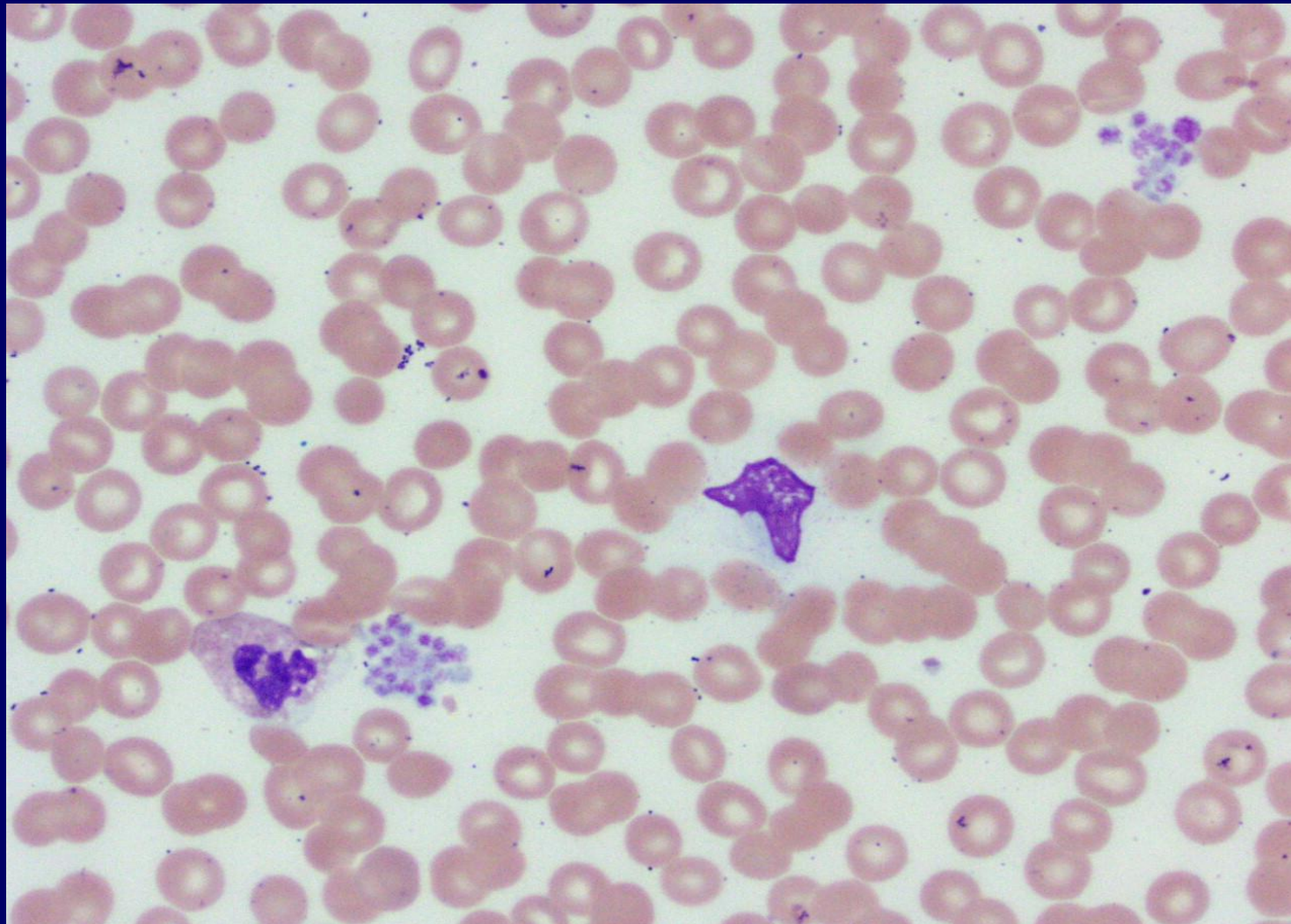
Peripheral blood smear

- Clumping, satellitism, macroplatelets, schistocytes, nucleated RBCs, hypo- and hypersegmented neutrophils, tear drop cells, etc.

A 67-year-old man with acute coronary syndrome received emergency percutaneous coronary intervention with implantation of several stents, one of them in the left main coronary artery, followed by therapeutic dose anticoagulation with unfractionated heparin plus platelet inhibition with aspirin, clopidogrel, and eptifibatide (all in standard doses). Six hours postintervention, the platelet count had dropped from 270K (preprocedure) to 6K (in EDTA-anticoagulated blood as well as in citrated blood), and the patient was admitted to the ICU due to the anticipated risk of major bleeding, although he did not show overt bleeding symptoms.

- Should all antiplatelet drugs, including eptifibatide be stopped?
- Should we transfuse platelets?
- Should we stop heparin?
- Should we give an anti-fibrinolytic (e.g. aminocaproic acid or tranexamic acid)?

Platelet Clumping



John Lazarchick, ASH Image Bank 2011; 2011-1038

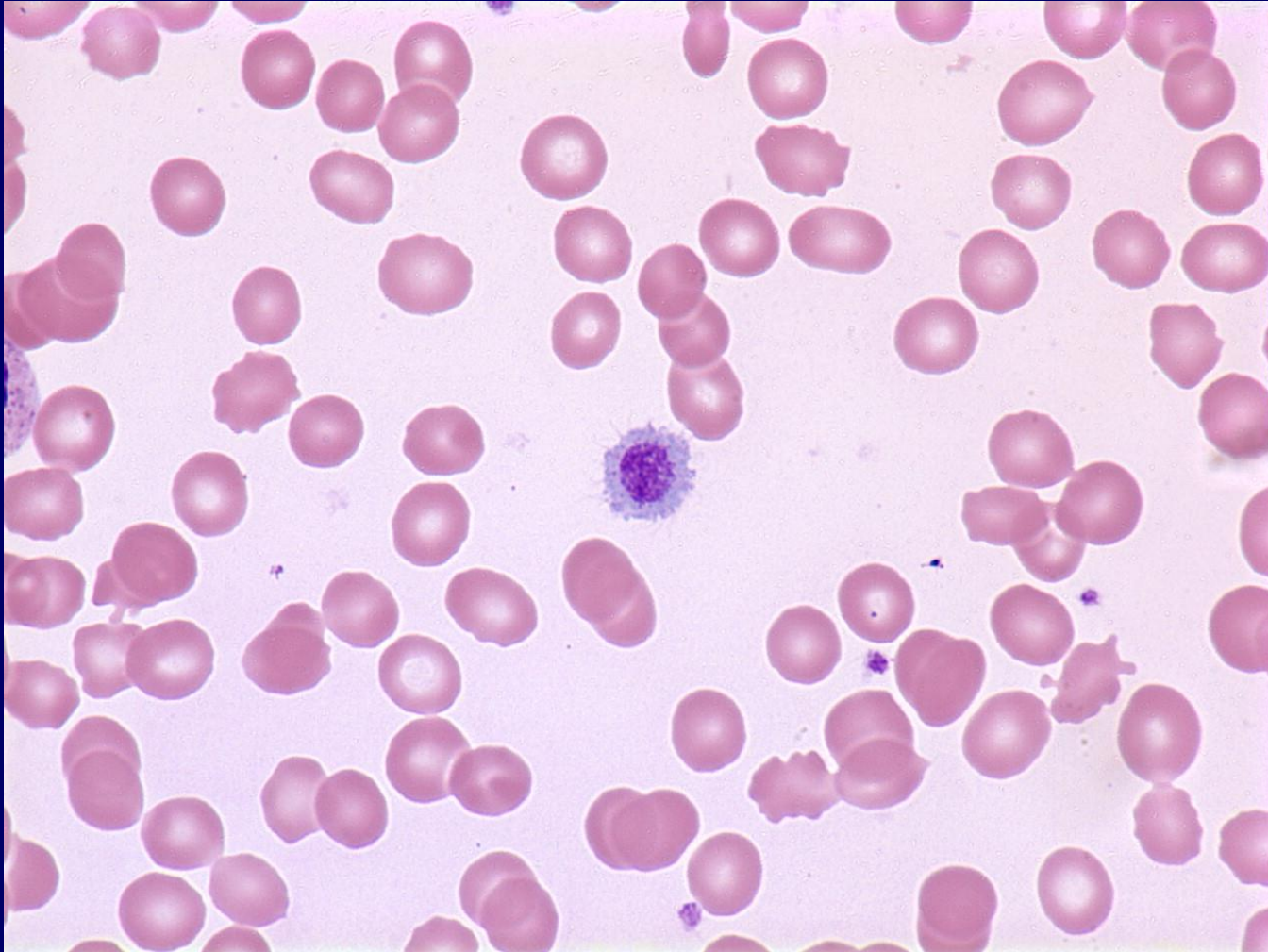
Pseudothrombocytopenia

- Platelet clumping, satellitism, or giant platelets
- Not counted by electronic particle counter
- EDTA-associated (ex vivo phenomenon)
- Count platelets at 100x and multiply by 20 or draw blood in a NaCitrate tube
- Clinically “insignificant”
 - Except when wrong diagnosis of thrombocytopenia leads to inappropriate investigations or therapy

GPIIb/IIIa antagonists

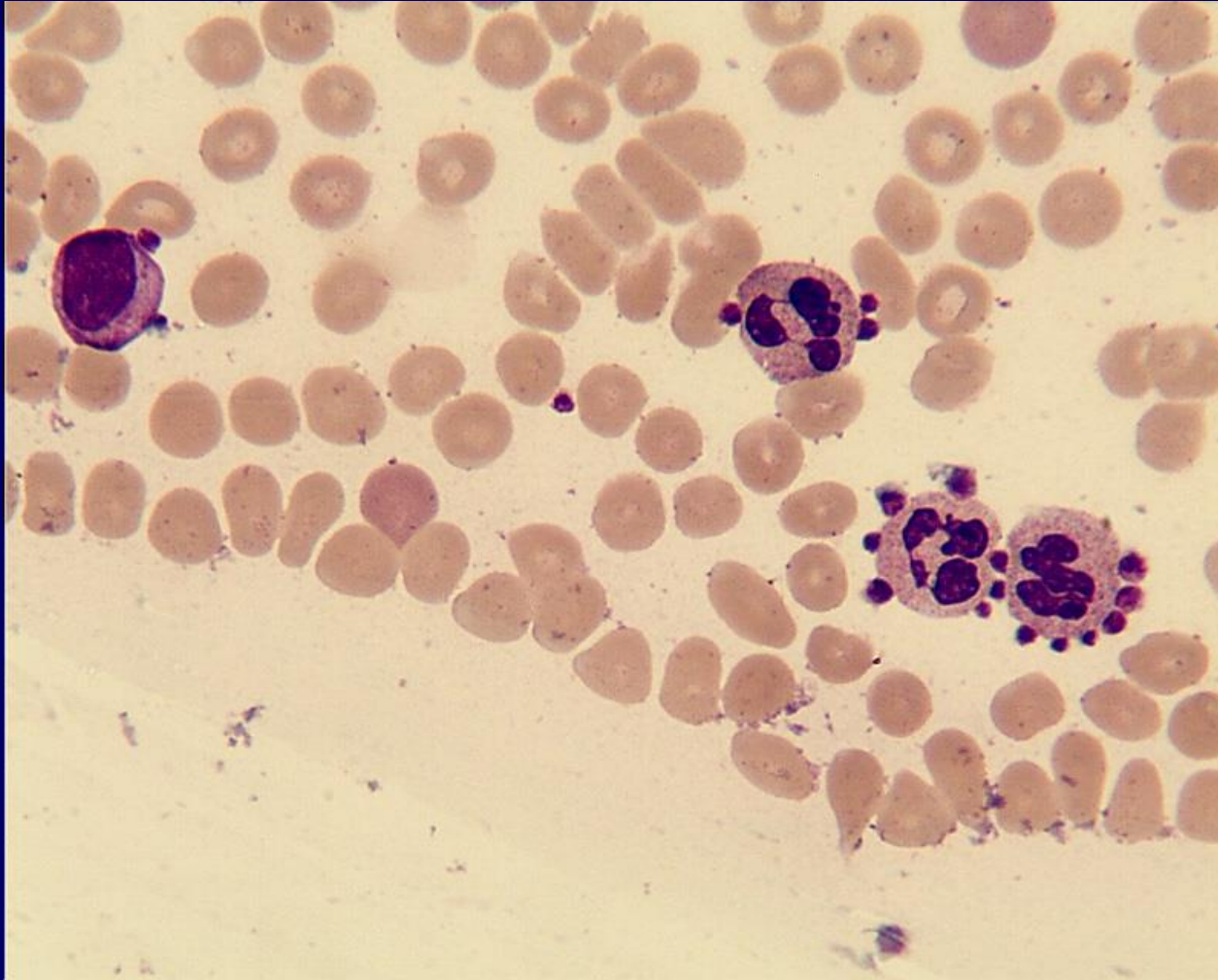
- Real and pseudothrombocytopenia in > 3% of patients
- Must check for pseudothrombocytopenia before stopping antiplatelet therapy or adding prothrombotic treatments 2/2 high risk of in-stent thrombosis
- Abciximab, eptifibatide, and tirofiban

Giant platelet



Peter Maslak, ASH Image Bank 2011; 2011-4198

Pseudothrombocytopenia due to platelet satellitism



Jianfeng Zhu, ASH Image Bank 2014; 2014-18538

An 18-year-old female patient with multiple trauma after a fall from the fourth floor, including subarachnoidal hemorrhage, bilateral hemopneumothorax, and pelvic fracture, was admitted with hemorrhagic shock requiring prehospital resuscitation. Despite severe anemia (hemoglobin, 6.0 g/dL) and coagulopathy (international normalized ratio, 1.3; aPTT, 48 s), the platelet count was normal (299k) at admission. Computed tomography scan revealed retroperitoneal bleeding and ruptured pelvic vessels. Despite transfusion of 2 platelet concentrates as part of the massive transfusion protocol, the platelet count rapidly declined during the first 7 hours after admission to 51k .

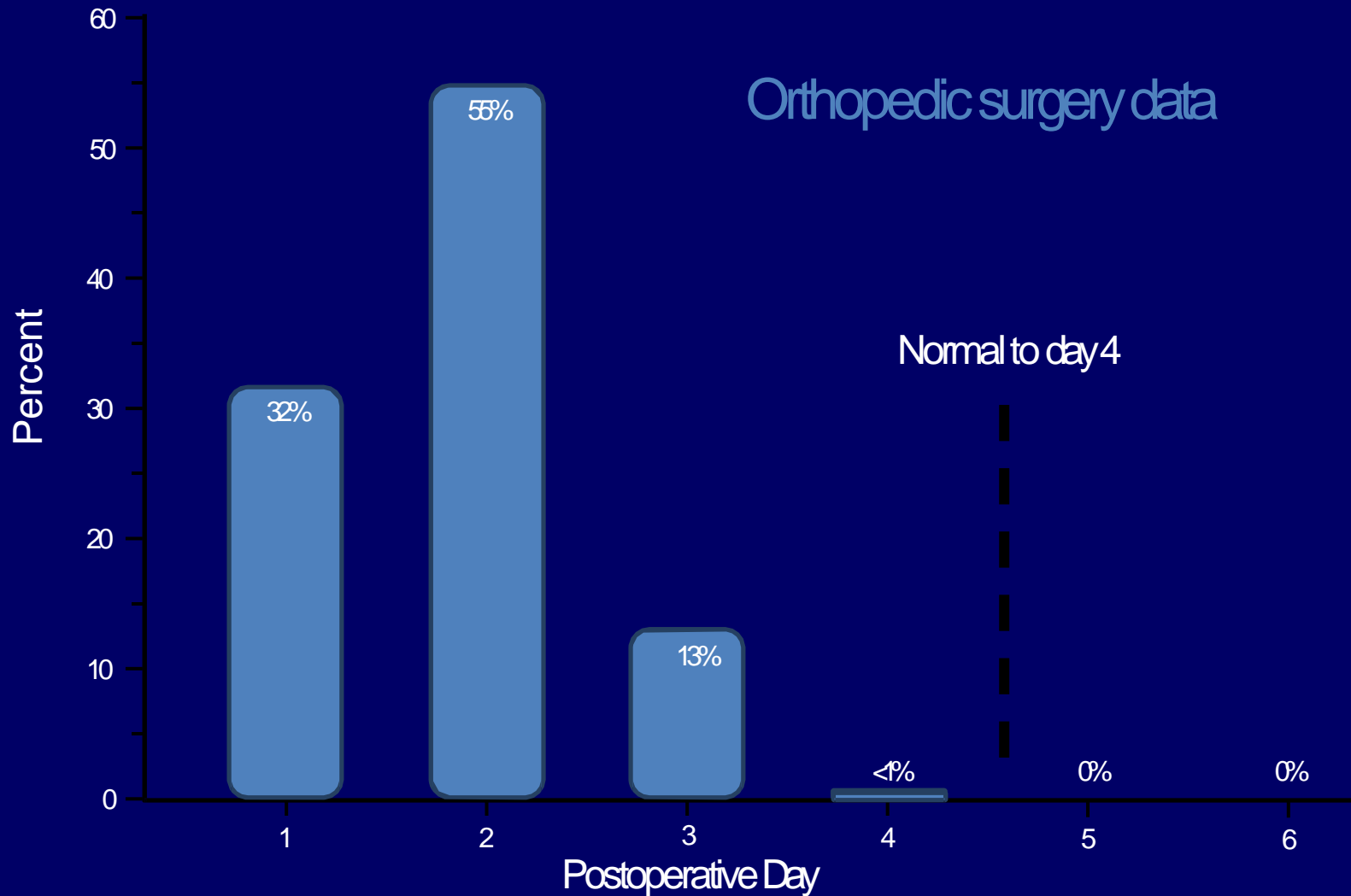
Trauma-induced coagulopathy with hemodilution

- In actively bleeding trauma patients, transfusion of plts alone will usually not stop bleeding.
- Keep plt count >50k in trauma patients and >100k in pts with ongoing massive bleeding and/or TBI.
- Consider anti-fibrinolytic agents such as epsilon aminocaproic acid or tranexamic acid.

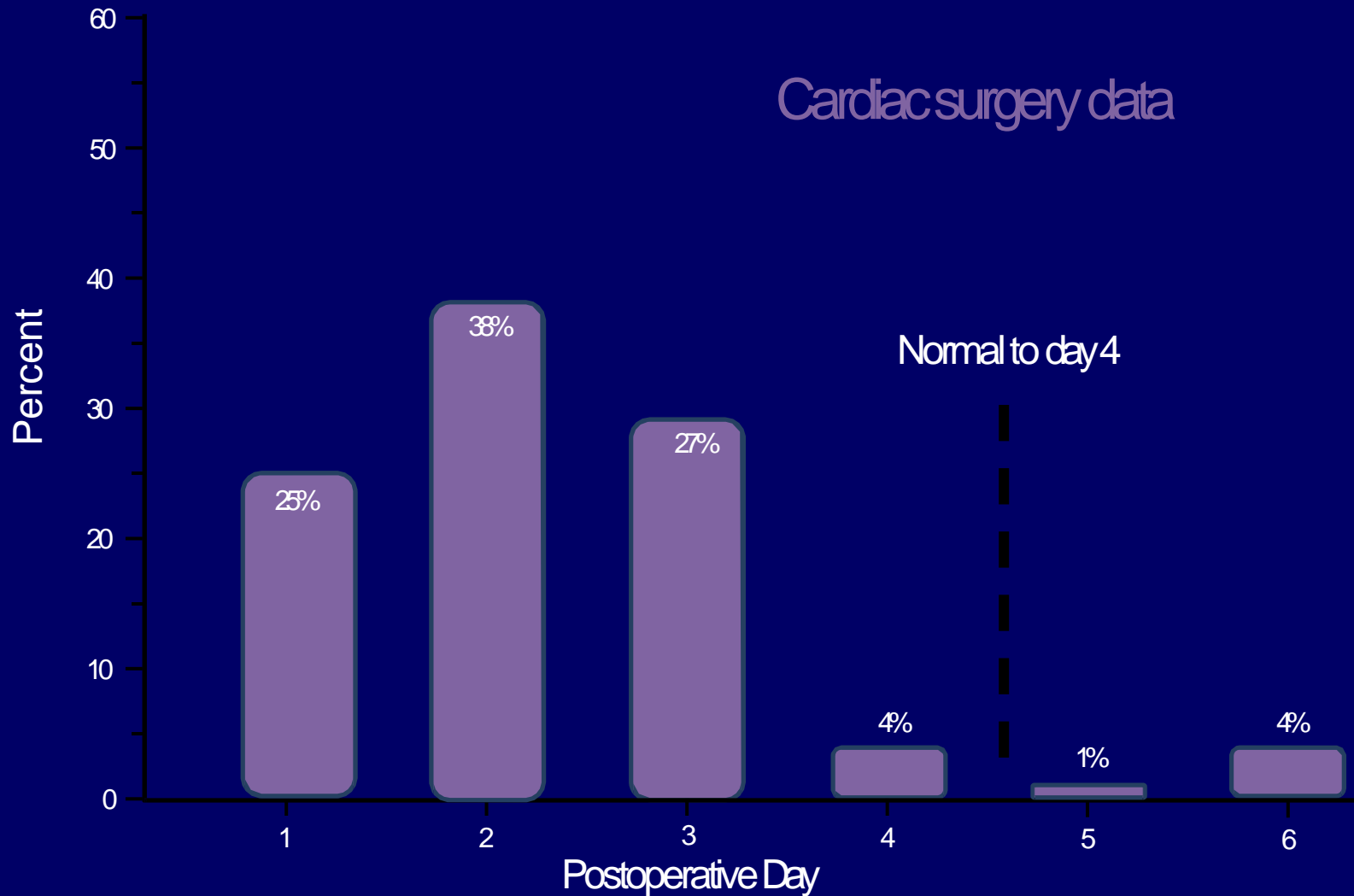
Hemodilution

- Postoperative
- Element of platelet consumption
- What day is the platelet count the lowest after surgery?
- What is the latest day of postoperative platelet count nadir that can still be considered normal?

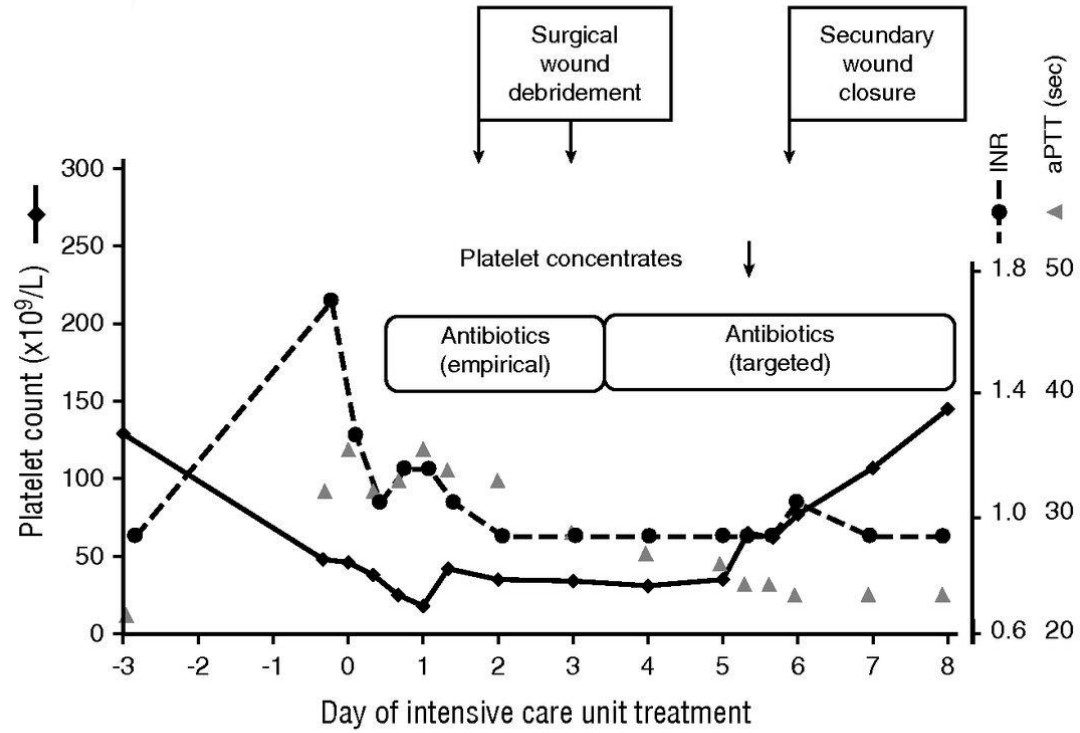
Day of Postop Platelet Count Nadir



Day of Postop Platelet Count Nadir



A 64-year-old man with a history of stage III IgG lambda multiple myeloma status-post one cycle of bortezomib and dexamethasone two days PTA was admitted to the MICU in septic shock. A several-day-old blunt trauma of the right forearm was seen during physical examination. Laboratory studies showed AKI with a creatinine of 3.6 mg/dL, coagulopathy with an INR of 1.7 and a PTT of 35 seconds, and thrombocytopenia with a platelet count of 48K, in addition to evidence of severe inflammation with a procalcitonin level of 223 ng/mL and a CRP level of 242 mg/L.

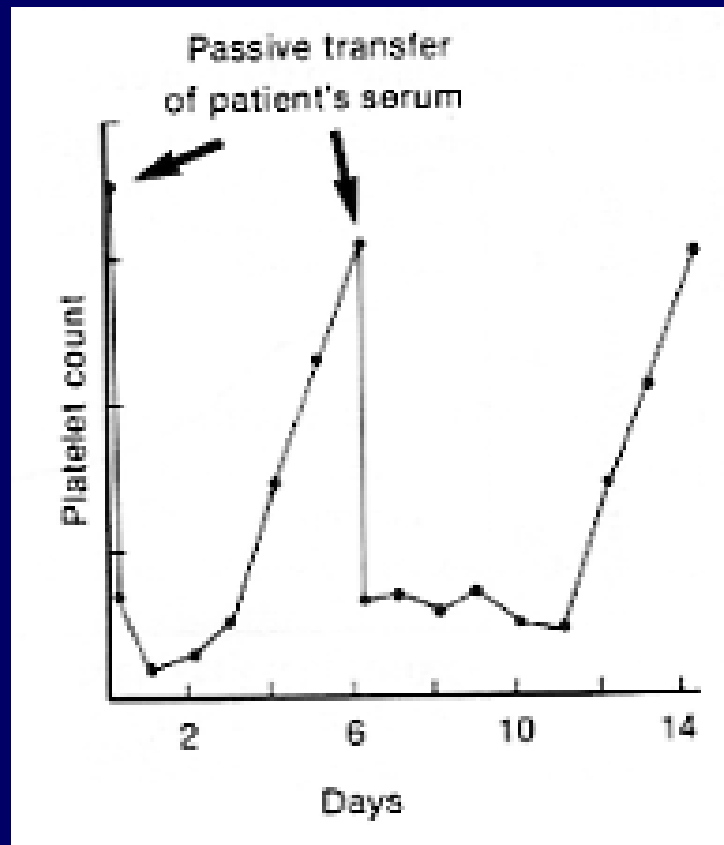
A**B**

Sepsis

- 50% of all thrombocytopenias in severely ill.
- Complex mechanisms
 - Decreased production
 - Increased consumption
 - Sequestration
 - Hemophagocytosis
- Therapy of sepsis
 - Source control
 - Antibiotics
 - Supportive measures
- Platelet transfusion for WHO grade 2 thrombocytopenia or bleeding.

46-year-old male patient with a 10-year history of ITP suffered traumatic brain contusion from a bicycle accident. At ICU admission, the platelet count was 11k, and the neurosurgeons required 50k platelets in order to control bleeding. The outpatient file of this patient documented previous good platelet count responses to corticosteroids and IVIG.

Immune Thrombocytopenic Purpura



Harrington et al. 1951

ITP: Still Diagnosis of Exclusion

- Thrombocytopenia in the absence of other blood cell abnormalities (normal RBC & WBC, normal peripheral smear)
- No clinically apparent conditions or medications that can account for thrombocytopenia.
- Bone marrow biopsy To look for other causes.
- Does not “Make diagnosis”
- Anti-Platelet Antibody Testing Poor positive/negative predictive values, poor sensitivity with all current testing methods!
- Not recommended

To Obtain a Bone Marrow Biopsy or Not?

- For consideration of “Other” causes of thrombocytopenia.
- Patient 60 yrs. or older.
- Poor response to “conventional” treatment.
- Unclear clinical picture.
- Overall: no consensus

ASH 2011 Recommendations: Diagnostic Approach

- “Insufficient evidence to recommend or suggest the routine use of antiplatelet, antiphospholipid, and antinuclear antibodies, thrombopoietin levels, or platelet parameters obtained on automated analyzers in the evaluation of children or adolescents with suspected ITP.”
- “A bone marrow examination is not necessary irrespective of age in patients presenting with typical ITP.”

Neunert et al. 2011

ITP: Three Clinical Patterns

- Acute ITP: Often Post-infection (viral or bacterial)
- Most common pattern in children.
- Usually self-limited
- Does not usually require treatment in children
- Theory, antibody cross-reactivity?
- Chronic ITP: Most common pattern in adults
- Relapsing ITP: Second most common pattern in adults.

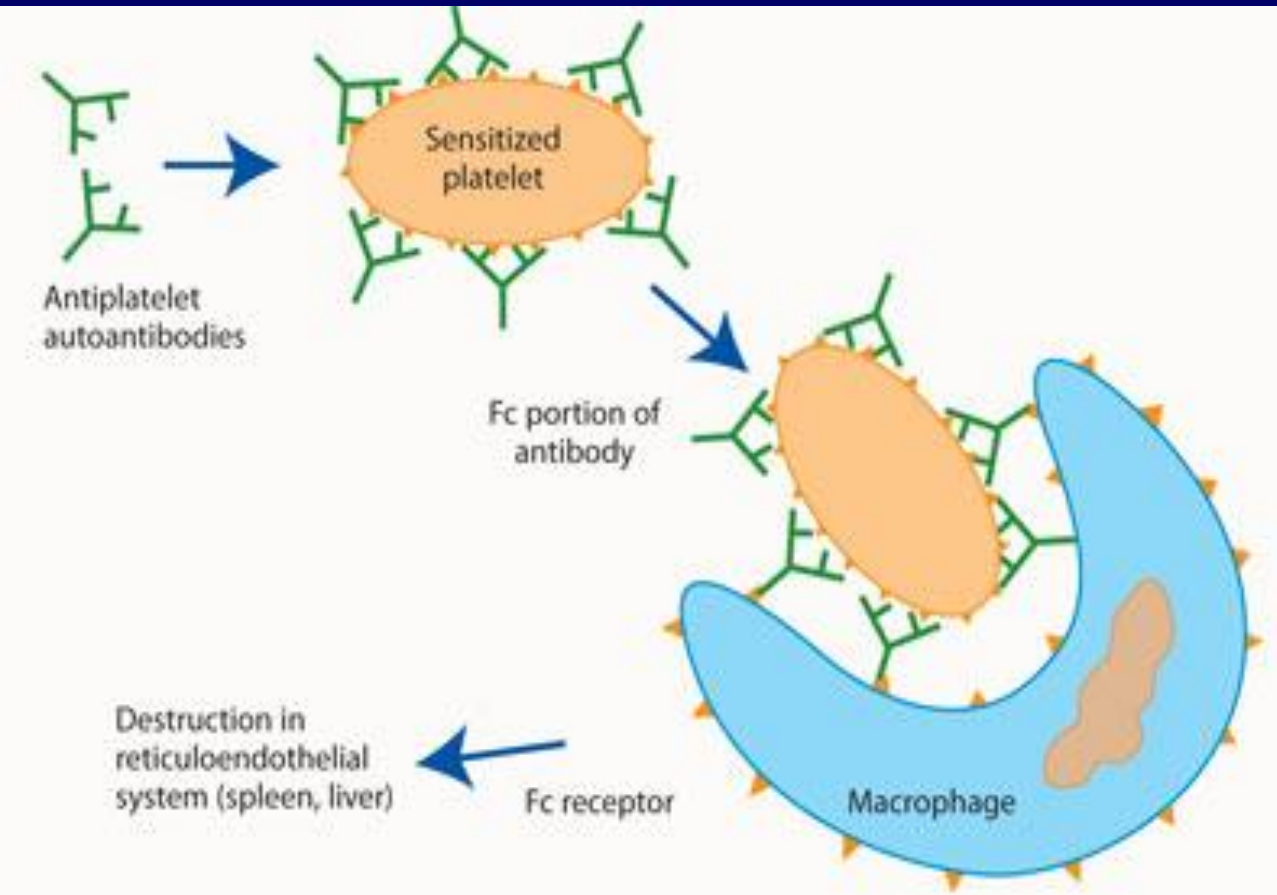
Treatment of ITP: Is treatment worse than the disease?

- “Children with no bleeding or mild bleeding (defined as skin manifestations only, such as bruising and petechiae) can be managed with observation alone regardless of platelet count.” For symptomatic children, typically IVIG first line.
- For adults: “Treatment be administered for newly diagnosed patients with a platelet count $< 30 \times 10^9/L$ ”

Frontline Therapy

| Treatment type | Initial Response, days | Peak response, days |
|----------------|------------------------|---------------------|
| IVIG | 1-3 | 2-7 |
| Anti-D | 1-3 | 3-7 |
| Dexamethasone | 2-14 | 4-28 |
| Prednisone | 4-14 | 7-28 |

IV immunoglobulin



- **IVIG may block Fc receptors on macrophages, sparing platelet opsonization.**
- **Elevated IgG levels may reduce production of antibodies.**
- **Dose: 2 gm/kg total: 1 gm/kg daily x 2**
- **0.4 gm/kg daily x 5**

Chronic ITP Management

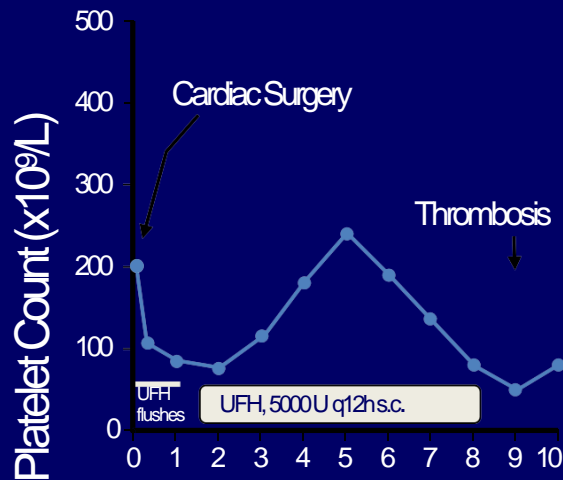
| Treatment type | Initial Response, days | Peak response, days |
|--------------------------------|-------------------------------|----------------------------|
| Splenectomy | 1-56 | 7-56 |
| Rituximab | 7-56 | 14-180 |
| Eltrombopag | 7-28 | 14-90 |
| Romiplostim | 7-14 | 14-60 |
| Danazol | 14-90 | 28-180 |
| Vincristine/Vinblastine | 4-14 | 7-42 |
| Azathioprine | 30-90 | 30-180 |

A 79-year-old female patient on aspirin and clopidogrel after percutaneous coronary intervention status-post stent deployments several weeks earlier developed in-stent thrombosis with myocardial infarction and cardiac arrest. After successful cardiopulmonary resuscitation and coronary angioplasty, the patient was admitted to the ICU. Aspirin and clopidogrel were continued, and therapeutic UFH was started. The patient was in cardiogenic shock with multiple organ failure, and the platelet count dropped from 326k to 28k by day 5 of ICU treatment.

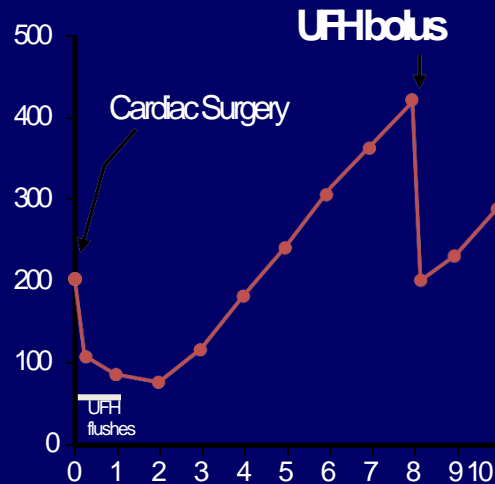
- Typically, ICU patients present with a biphasic platelet count course.
- After an initial decrease to a platelet count nadir 2 to 4 days after ICU admission, platelets recover to higher-than-baseline values (reactive thrombocytosis).
- **Persistent or progressive** thrombocytopenia therefore suggests ongoing consumption, bleeding, or severe organ damage.
- **A slow decrease** in platelet counts over several days is rather typical for infection, septicemia, or bone marrow toxicity.
- Immune-mediated causes, such as HIT or DITP, should be considered when the **platelet count falls rapidly** within 1 or 2 days during the second week of treatment after an initial recovery.

Three Presentations of HIT

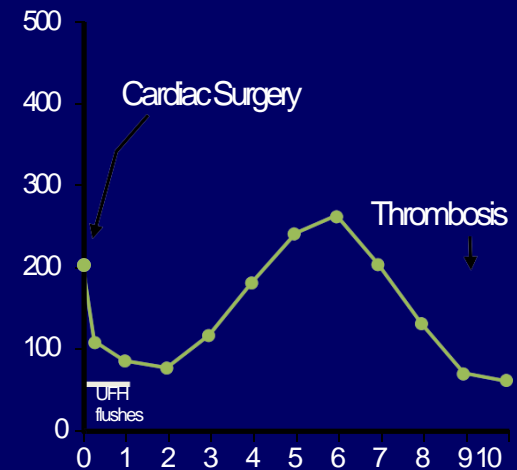
Typical-Onset



Rapid-Onset



Delayed-Onset

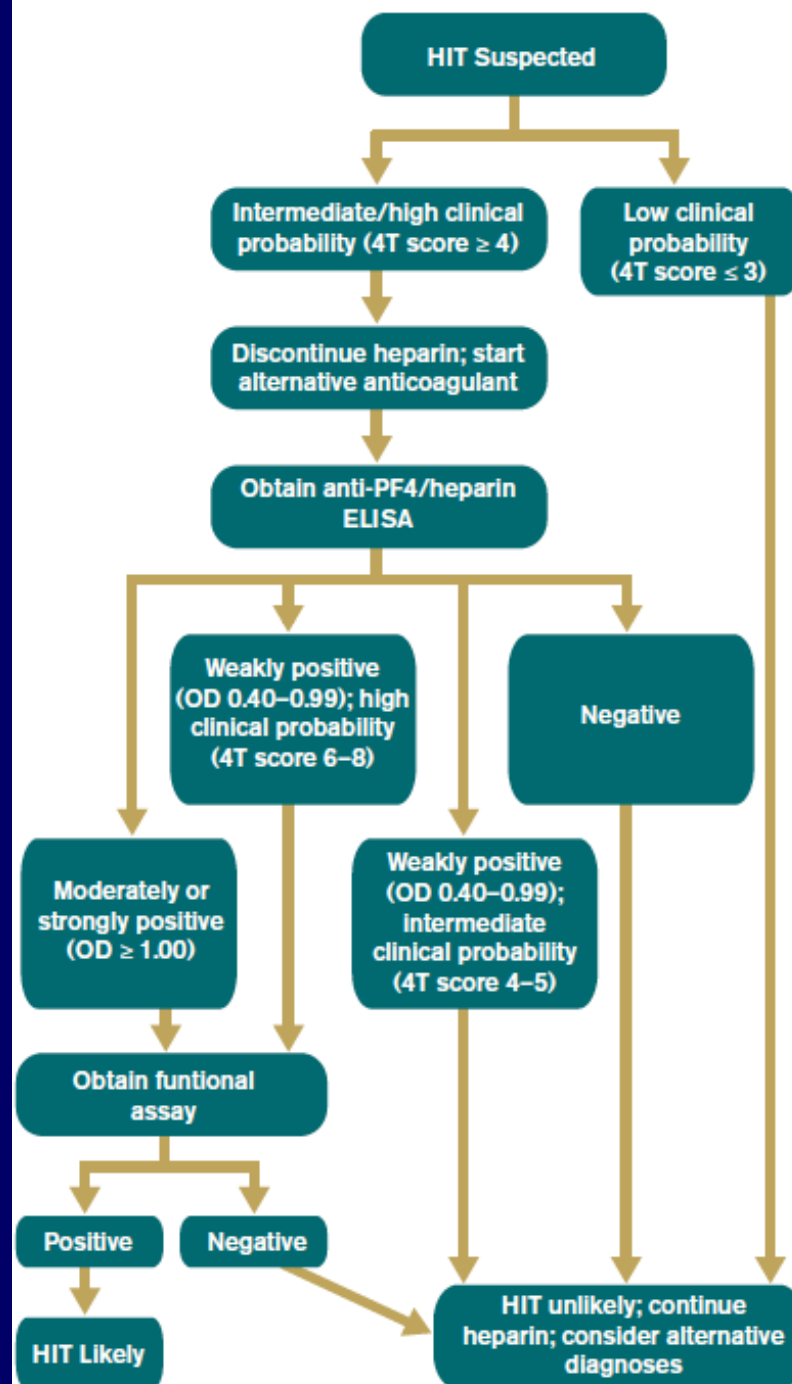


Days after Cardiac Surgery

B. The 4Ts: A clinical probability scoring system

| 4Ts | 2 Points | 1 Point | 0 Points |
|--|---|--|--|
| T hrombocytopenia | Platelet count fall > 50% and platelet nadir $\geq 20 \times 10^9/L$ | Platelet count fall 30–50% or platelet nadir $10\text{--}19 \times 10^9/L$ | Platelet count fall < 30% or platelet nadir < $10 \times 10^9/L$ |
| T iming of platelet count fall | Clear onset between days 5–14 or platelet fall ≤ 1 day (prior heparin exposure within 30 days) | Consistent with days 5–14 fall, but not clear (e.g. missing platelet counts) or onset after day 14 or fall ≤ 1 day (prior heparin exposure 30–100 days ago) | Platelet count fall ≤ 4 days without recent exposure |
| T hrombosis or other sequelae | New thrombosis (confirmed); skin necrosis at heparin injection sites; anaphylactoid reaction after IV heparin bolus | Progressive or recurrent thrombosis; Non-necrotizing (erythematous) skin lesions; Suspected thrombosis (not confirmed) | None |
| o ther causes of thrombocytopenia | None apparent | Possible | Definite |

High probability (6–8 points), intermediate probability (4–5 points), low probability (≤ 3 points).



II. Laboratory Diagnosis

| Assay category | Mechanism | Examples | Sensitivity | Specificity | Comments |
|----------------|--|--|-------------|-------------|--|
| Immunologic | Detects antibodies against PF4/heparin, regardless of their capacity to activate platelets | 1. Polyspecific ELISA 2. IgG-specific ELISA 3. PaGIA | >95% | 50–89% | OD of ELISA result correlates with clinical probability of HIT and odds of a positive functional assay |
| Functional | Detects antibodies that induce heparin-dependent platelet activation | 1. SRA 2. HIPA | 90–98% | 90–95% | Not widely available; requires referral to a reference laboratory |

PF4, platelet factor 4; PaGIA, particle gel immunoassay; OD, optical density; SRA, serotonin release assay; HIPA, heparin-induced platelet activation assay.

| | | |
|---------------------------|---|---|
| Argatroban | Bolus: None Continuous infusion: Normal organ function→2 mcg/kg/min ¹ Liver dysfunction (total serum bilirubin >1.5 mg/dL), heart failure, post-cardiac surgery, anasarca→0.5–1.2 mcg/kg/min ² | Adjust dose to APTT of 1.5–3.0 times patient baseline. Monitor APTT every 4 hours during dose titration. |
| Fondaparinux ⁵ | <50 kg→5 mg SC daily 50–100 kg→7.5 mg SC daily >100 kg→10 mg SC daily Cl _{Cr} 30–50 ml/min→use caution Cl _{Cr} <30 ml/min→contraindicated | Some experts recommend adjusting dose to a peak anti-Xa activity of 1.5 fondaparinux-specific U/ml. Others do not recommend routine monitoring. |
| NOACs ⁶ | At the time of writing, none of the NOACs (e.g. rivaroxaban, dabigatran, apixaban) had been assessed for treatment of patients with suspected or proven HIT and none had FDA approval for this indication. Until supporting data are available, their use cannot be endorsed. | |

- HIT patients are at risk of venous limb gangrene and skin necrosis during initiation of warfarin.
- Warfarin should not be initiated until platelet count is $\geq 150 \times 10^9/L$ (Grade 1C).
- Initial warfarin dose should be ≤ 5 mg/day. Larger loading doses should be avoided (Grade 1C).
- A parenteral non-heparin anticoagulant should be overlapped with warfarin for ≥ 5 days and until INR has reached intended target (Grade 1C).

C. Duration of anticoagulation

- Bilateral lower extremity compression ultrasonography may be considered in patients with HIT, whether or not there is clinical evidence of lower-limb DVT, because silent DVT is common and its presence may influence the recommended duration of anticoagulation.
- For patients with HIT-associated thrombosis (i.e. HITT), anticoagulate for a defined course (typically 3 months) as with other provoked thromboses.
- For patients with HIT without thrombosis (i.e. isolated HIT), the optimal duration of anticoagulation is unknown. Because there is an elevated risk of thrombosis extending 2 to 4 weeks after heparin is stopped, anticoagulation for up to 4 weeks should be considered.
- For all patients, anticoagulation management should be based on an individualized risk/benefit assessment.

D. Platelet transfusion

- Due to theoretical risk that platelet transfusion may precipitate thrombosis in HIT, and because patients with HIT do not have a hemorrhagic diathesis, platelet transfusions should not be given to patients with confirmed or strongly suspected HIT except for bleeding or an invasive procedure with a high risk of bleeding (Grade 2C).
- Platelet transfusion may be appropriate in situations of diagnostic uncertainty.

A 75-year-old female patient with stroke and right-sided hemiplegia, recurrent seizures, dysphagia, and pneumonia required invasive ventilation. She received several drugs, including antibiotics, sedation, aspirin, UFH in prophylactic dose, diuretics, and anticonvulsants. At day 7, valproic acid was added to levetiracetam and lorazepam to control seizures. Ten days later, the platelet count began to fall, reaching values <50k.

DTP and DITP

- In contrast to DTP, DITP typically presents with an abrupt plt count fall evolving within 1 to 2 days, which usually begins 5 to 14 days after starting a new drug, and a nadir below 20k, which is nearly always accompanied by mucocutaneous bleeding.
- In both DTP and DITP, cessation of the drug is most important and usually sufficient. Recovery of the plt count will occur thereafter and is often not very helpful for differentiation between DTP and DITP.
- Plt count recovery usually begins 5 to 7 half-lives after cessation of the drug.
- If a patient with DITP develops major bleeding symptoms, IVIG (1 g/kg body weight on 2 consecutive days) is recommended.
- In case of life-threatening bleeding, transfusion of plts might be considered.
- Laboratory tests for the detection of drug-dependent antiplatelet antibodies are helpful to support the diagnosis DITP. However, these tests are performed only in specialized laboratories and are usually not available to guide acute management.

Bone marrow depression

- Toxic bone marrow depression
- Chemotherapy, linezolid, nonsteroidal anti-inflammatory drugs, azathioprine, and valproic acid

Classic drug-dependent antibodies

- Drug, platelet glycoproteins, and antibodies form a 3-molecular complex, which results in increased platelet destruction by the reticuloendothelial system; onset typically 7 to 20 d after start of a new drug or immediately in case of re-exposure; platelet nadir <20k
- Quinine, quinidine, antibiotics (TMP/SMX, vancomycin, rifampicin cephalosporins), antiepileptics (valproate, carbamazepine, phenytoin), diuretics (furosemide, thiazides), ranitidine, nonsteroidal anti-inflammatory drugs

Hapten-induced antibodies

- Drug acts as a hapten that binds to large molecules (eg, proteins) on the platelet surface and stimulates antibody production; onset typically 7 to 20 d after start of an antibiotic; platelet nadir variable, often $>20k$
- Penicillin and cephalosporins

Fiban-induced antibodies

- Drug binds to epitopes on GPIIbIIIa on platelets, causing a conformational change that enhances affinity of preexisting antiplatelet antibodies; onset within hours after start of the drug or 7 to 10 d in a subset of patients after start of the drug, even if the drug is no longer present (antibodies cross-react with native GPIIbIIIa; platelet nadir often <20k; exclude pseudothrombocytopenia)
- Tirofiban and eptifibatide

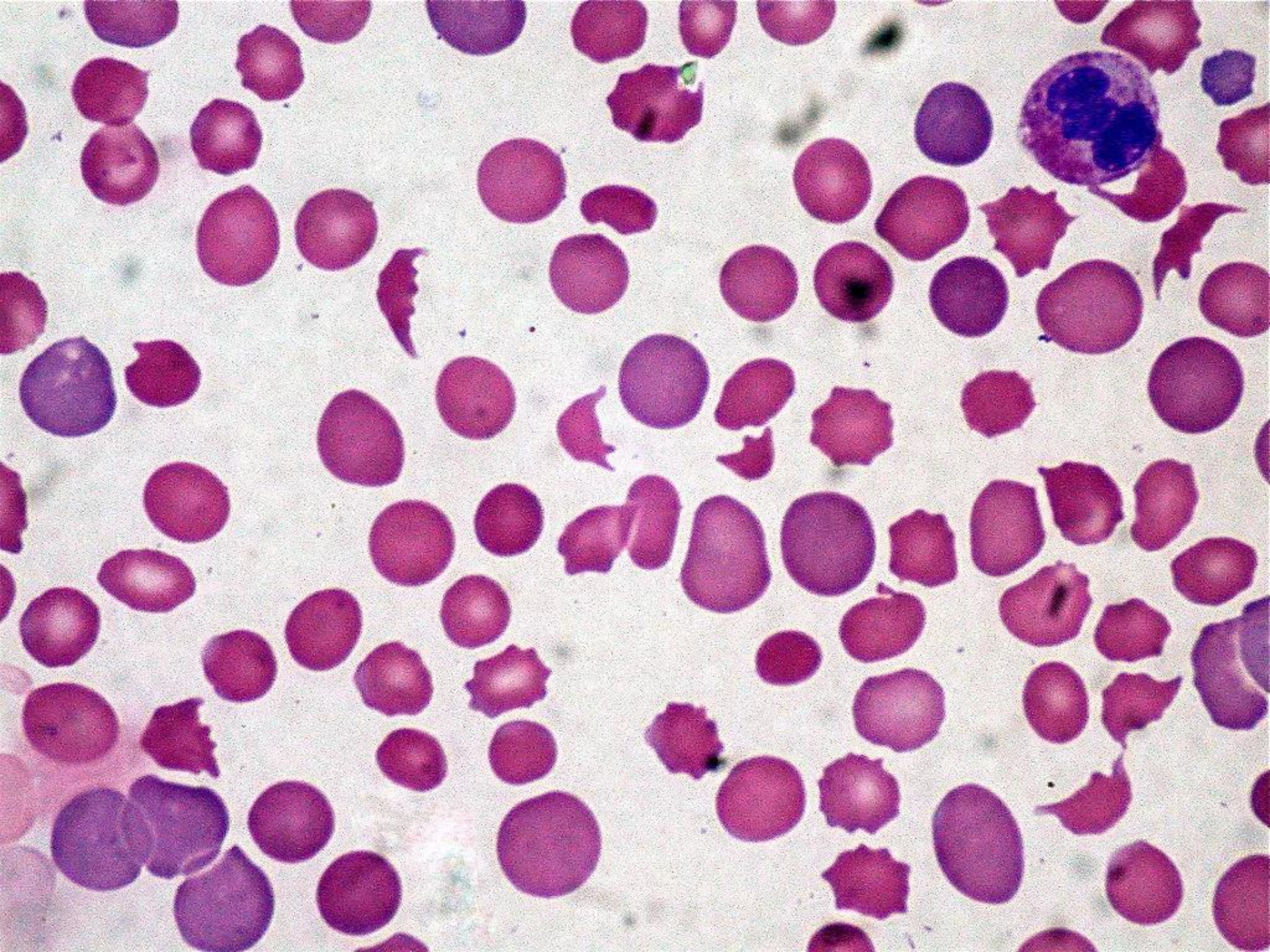
Drug-specific antibodies

- Fab fragments of a monoclonal antibody bind to GPIIb/IIIa on platelets and become targets of naturally occurring antibodies, provoking increased platelet destruction; onset within hours after start of the drug; platelet nadir often $<20k$; exclude pseudothrombocytopenia
- Abciximab

Autoantibodies

- Production of platelet-specific autoantibodies is induced and maintained by a drug (exact mechanism unknown)
- Procainamide, levodopa, and gold

70 year-old man with a history of ischemic cardiomyopathy status-post orthotopic heart transplant five months previously, now has anemia and thrombocytopenia with an onset of 1-2 weeks ago, & getting progressively worse. Hemoglobin 7 g/dL, Platelets 35k. On tacrolimus and mycophenolate mofetil for immunosuppression. Reticulocyte count was 8.5%. The peripheral blood smear showed greater than 5 schistocytes per high power field. LDH is 1500. Haptoglobin is < 7.



MAHA versus TMA

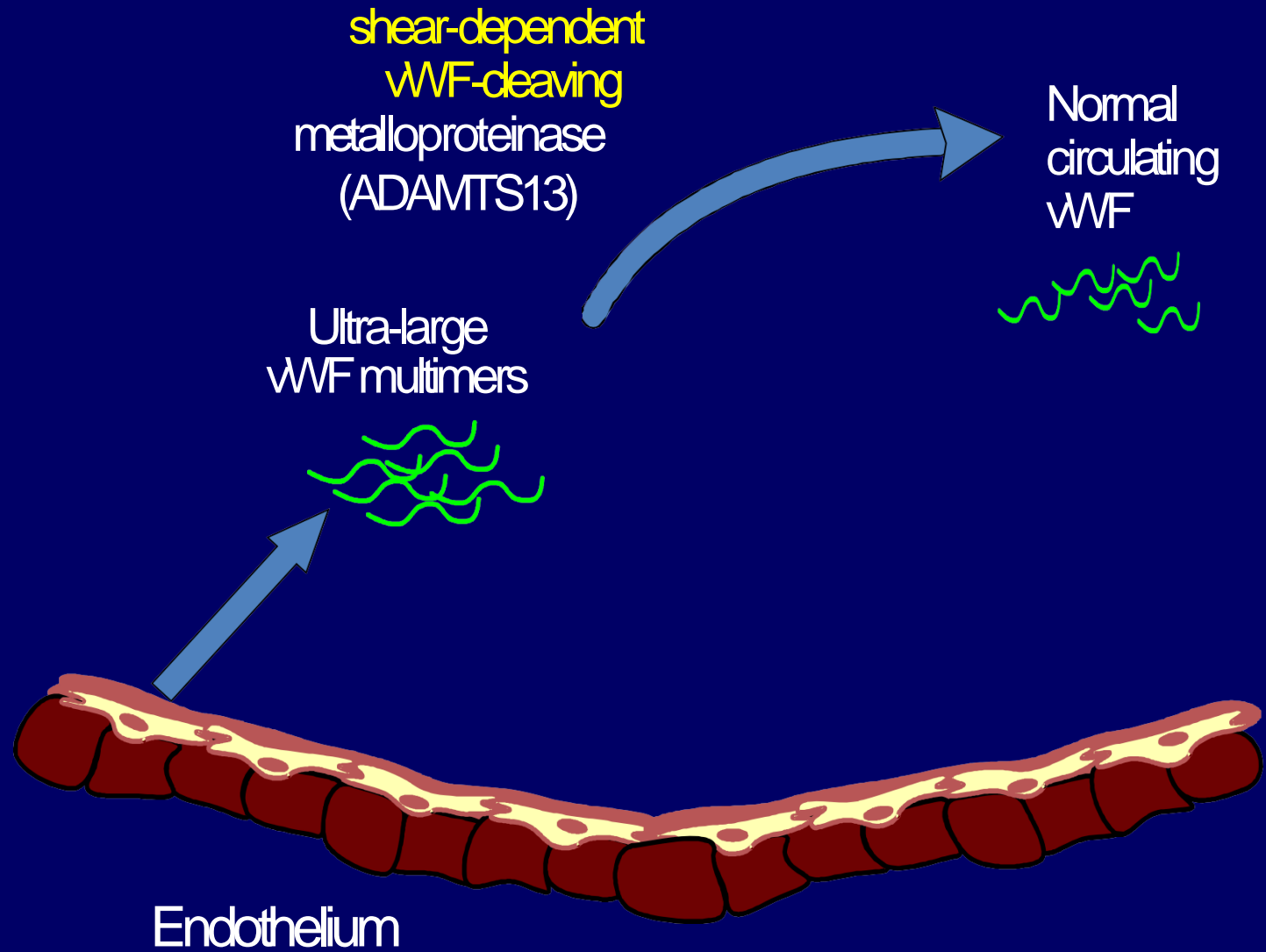
- Microangiopathic hemolytic anemia (MAHA) is a descriptive term for non-immune hemolytic anemia resulting from intravascular red blood cell fragmentation that produces schistocytes on the peripheral blood smear.
- Thrombotic microangiopathy (TMA) describes a specific pathologic lesion of arterioles and capillaries that leads to microvascular thrombosis. Not all MAHA is caused by a TMA, but nearly all TMAs cause MAHA and thrombocytopenia.

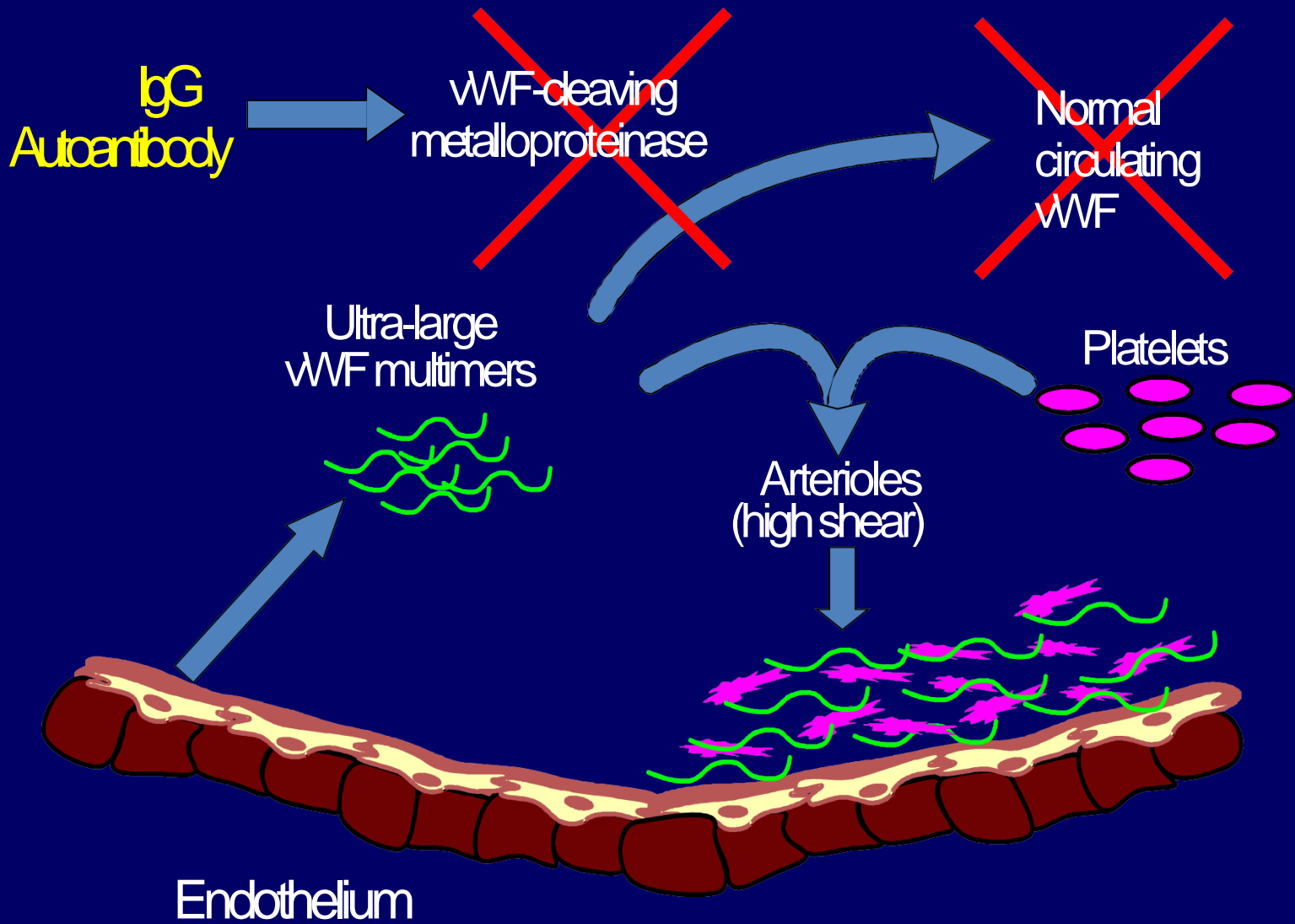
Thrombotic Microangiopathies

- **Thrombotic thrombocytopenic purpura (TTP)**
 - Primary (idiopathic)
 - Autoimmune (e.g., SLE)
 - Inflammatory (pregnancy, post-surgery, pancreatitis)
- **Miscellaneous**
 - Drug (quinine, clopidogrel, cyclosporine, mitomycin, gemcitabine,..)
 - Transplantation-associated
 - Cancer-associated
 - HIV-associated
- **Hemolytic uremic syndrome (HUS)**

Thrombotic Thrombocytopenic Purpura

- Rare but important disease entity
- Sporadic & relapsing form
- Caused by congenital defect of &/or antibody against vWF-cleaving metalloproteinase (ADAMTS13)
- Universally fatal without treatment
- With treatment > 90% survival, usually without sequelae





Thrombotic Thrombocytopenic Purpura

- Microangiopathic hemolytic anemia – Blood smear is critical to assess
- Thrombocytopenia
- Mental status changes
- Fever
- Renal insufficiency
- DO NOT SEE coag abnormalities!

TTP – Differential Diagnosis

- DIC
- HUS
- Lupus vasculitis
- Malignant hypertension
- HEELP syndrome (pregnancy only)
- Transplant rejection

TTP - Treatment

- Corticosteroids
- Plasmapheresis/Plasma Exchange
 - Easier to manage fluids
 - Replaces missing metalloproteinase
 - Removes antibody to metalloproteinase
- Rituximab – Moving towards standard of care
- Vincristine, Splenectomy, Rituximab – For refractory cases
- Aggressive – 1.5-2 plasma volume exchanges daily; sometimes need to continue x weeks
- Survival > 90%; sequelae minimal if begun early

TTP

- Drug-induced
 - Calcineurin inhibitors (tacrolimus, cyclosporine)
 - ADP receptor blockers (ticlopidine, clopidogrel, prasugrel)
 - Multiple chemotherapeutic agents (gemcitabine, mitomycin, platinum compounds, etc)
- Treatment is to stop the drug; class switches possible for 1st two
- Chemo-induced MAHA often untreatable

Hemolytic Uremic Syndrome

HUS appears to be a **distinct syndrome**:

Distinct pathogenesis

no deficiency of vWF-cleaving metalloproteinase

Distinct etiology

prodromal *E. coli* gastroenteritis

?immune

[Greinacher et al. 2011]

HUS and Shiga Toxin

E. coli O157:H7 is an infectious disease caused by transfer of a gene from *Shigella dysenteriae* to a strain of enteropathogenic *E. coli*

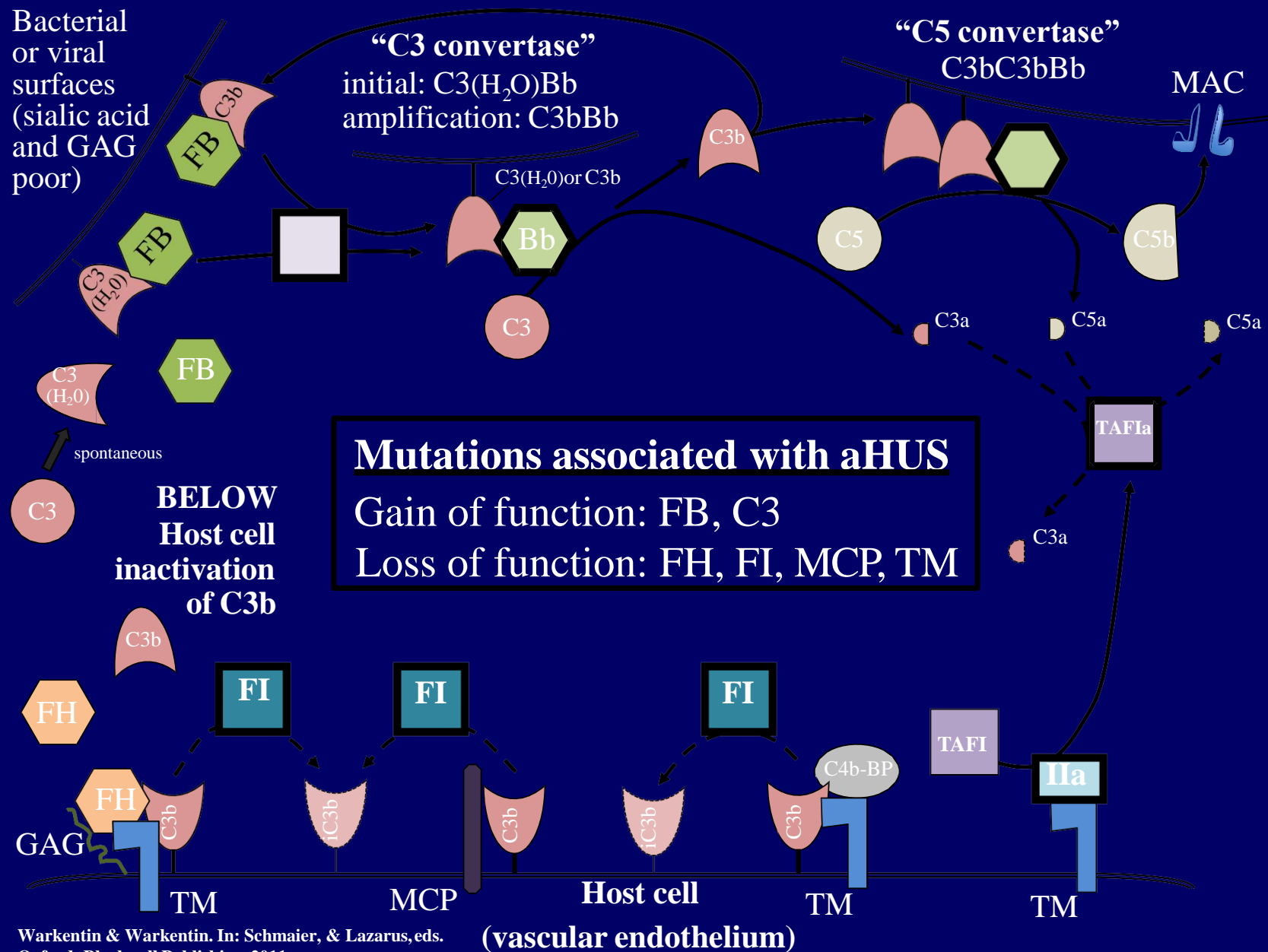
Shiga toxin of *E. coli* (formerly called verotoxin [verocytotoxin])

HUS usually caused by *E. coli* (*Shigella* in third world)

Risk of HUS post-*E. coli* O157:H7 infection: 8-14% risk *increased*
with antibiotics (odds ratio, 14)

~75% of pediatric HUS has prodromal *E. coli* O157:H7 infection

~25% **atypical HUS (aHUS)**



- Thrombocytopenia is common in the hospital and even more common in the ICU.
- It's a sensitive marker for disease severity and mortality.
- Transfusions can be helpful in situations of plt loss or consumption, but they might be hazardous in pt's with increased intravascular plt activation.