Not all thrombocytopenia is ITP…

(… nor is it TTP, HUS, gestational thrombocytopenia, nor HIT)

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Professor of Medicine, Section of Hematology
Yale School of Medicine

Classical approach to thrombocytopenia

↓ Production

- Medications
- Alcohol
- Toxins
- Infections
- Nutritional deficiencies
- Liver disease
- Bone marrow/hematologic disorders
- Inherited thrombocytopenias

↑ Destruction

- Immune thrombocytopenia (ITP)
- Drug-induced ITP
- Thrombotic microangiopathy
- Disseminated intravascular coagulation
- Post-transfusion purpura
- Neonatal alloimmune thrombocytopenia

↑ Sequestration

- Splenomegaly

Case 1: L.S.

L.S. is a 68 year-old woman who is hospitalized for vertigo. She is clinically stable. The hematology service is consulted as her blood counts show isolated thrombocytopenia.

Labs

WBC 11,000/mL (normal 5-11,000)
Hemoglobin 12.5 g/dL (normal 10-13)
Platelets 84,000/mL (normal 150-350,000)
PT 12.0 sec (normal 11-13)
INR 1.0 (normal 0.9-1.1)
PTT 29 sec (normal 23-32)

A repeat platelet count is in the same range as above.

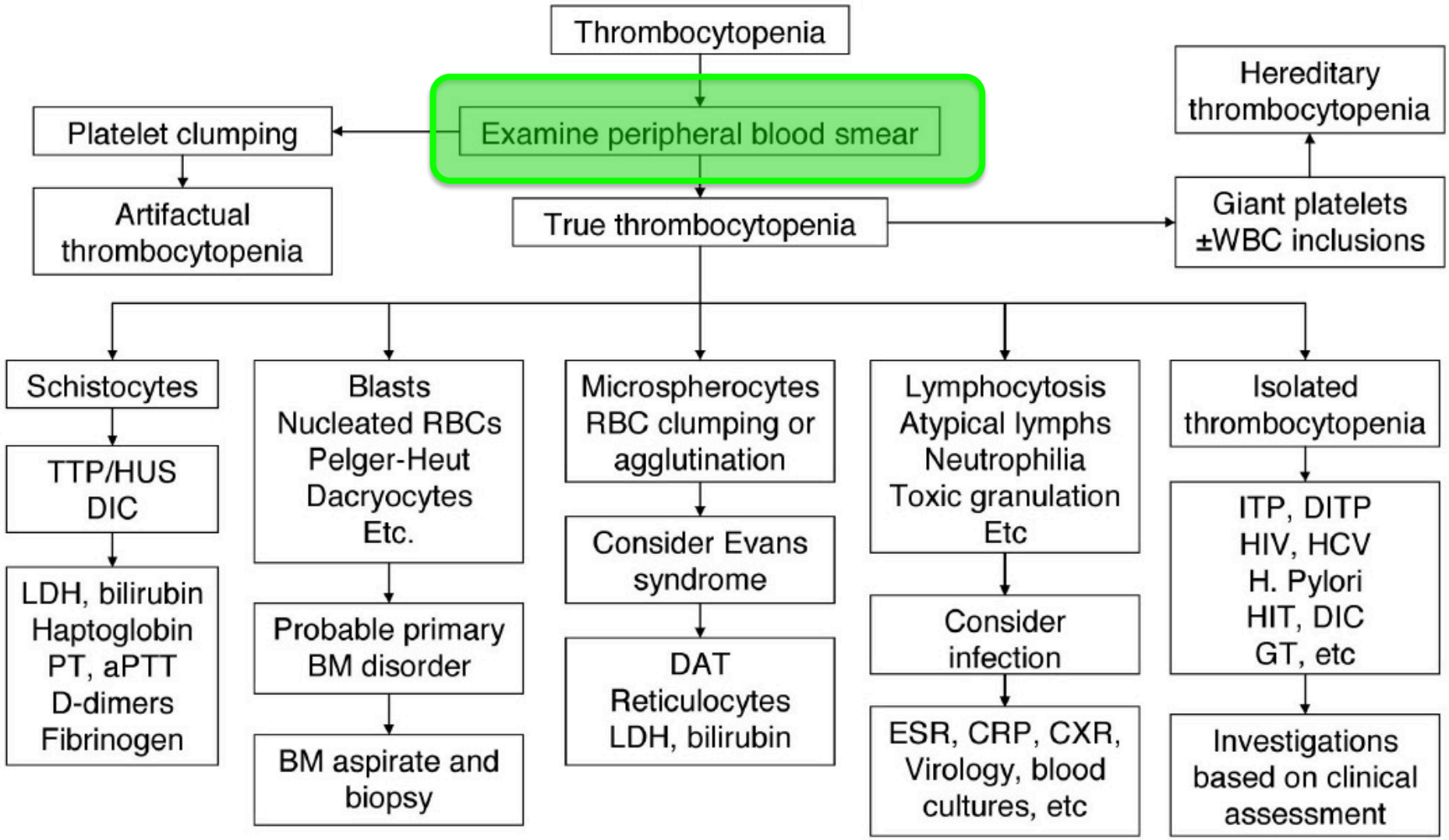
What's the next step in evaluating this patient's thrombocytopenia?

Clinical pearl

The peripheral blood smear is very useful in evaluating thrombocytopenia

- *Assess for pseudothrombocytopenia*
- *Assess for other abnormal cell morphologies*

Smear-based approach to thrombocytopenia



(Stasi R, *Hematology Am Soc Hematol Educ Prog* 2012;2012:191)

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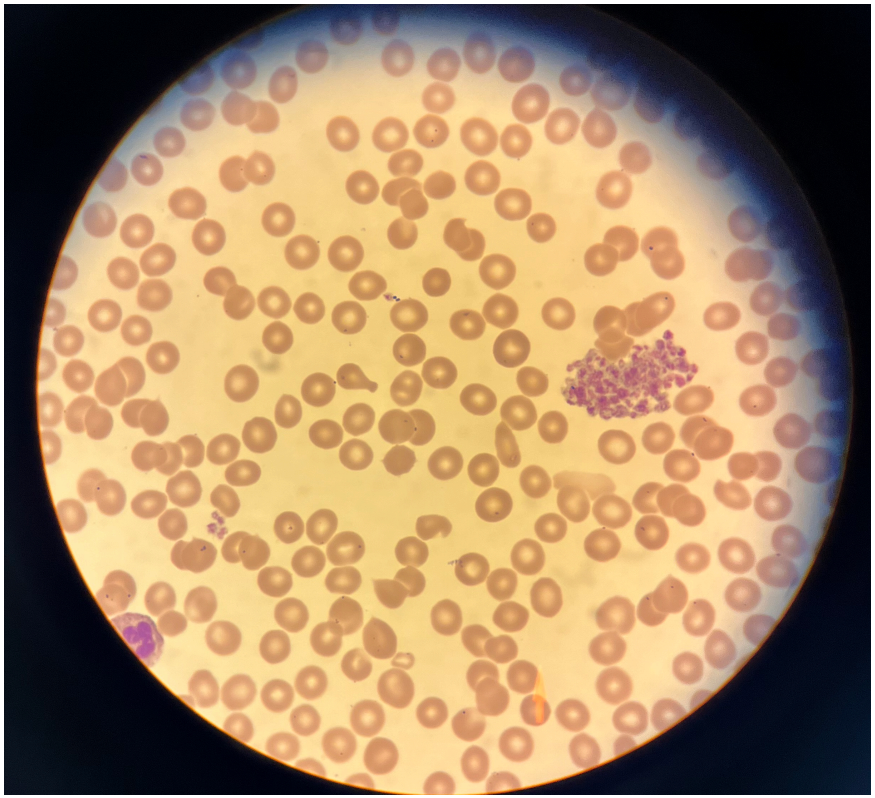
Peripheral blood smear



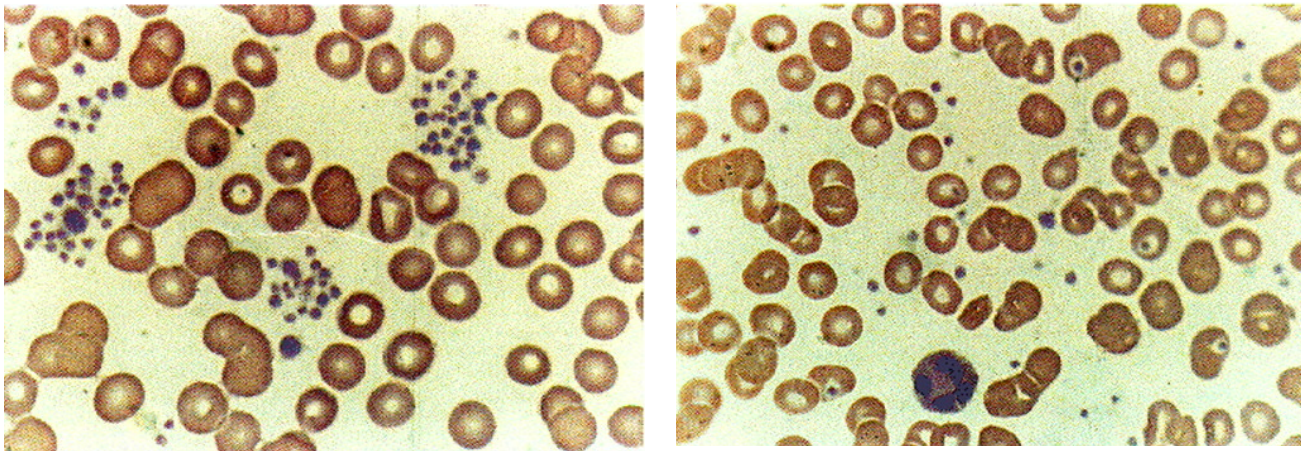
What's the diagnosis?

Pseudothrombocytopenia

- In-vitro phenomenon of no clinical significance
- Occurs in presence of EDTA

  - Mechanism: EDTA alters GPIIb conformation on platelet surface, allowing for binding of anti-GPIIb antibodies, leading to platelet clumping

EDTA



Heparin or citrate

(Shalev O and Lotman A, *N Engl J Med* 1993;329:1467)

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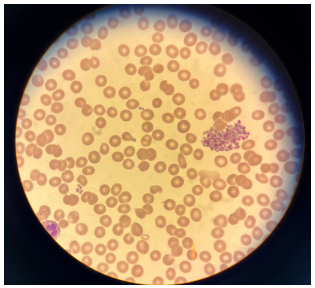


What's the diagnosis?

The patient is diagnosed with pseudothrombocytopenia based on the presence of copious platelet clumping on her blood smear. A repeat platelet count measured in citrate is in the normal range.

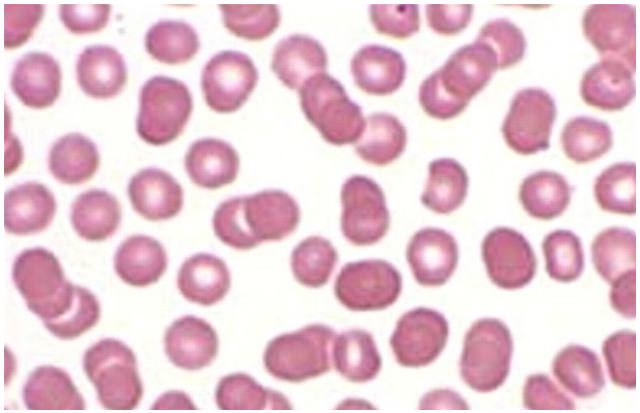
Case 2: E.F.

E.F. is a 73 year-old woman who is hospitalized for pneumonia. She is treated with vancomycin and piperacillin/tazobactam. One week later, she develops copious petechiae on her shins, with blood counts showing new-onset, severe isolated thrombocytopenia.

Labs

WBC	14,500/□L (normal 4-10,000)
Hemoglobin	12 g/dL (normal 12-15)
Platelets	12,000/□L (normal 150-350,000)
PT	13.1 sec (normal 11-15)
INR	1.1 (normal 0.9-1.1)
PTT	28 sec (normal 23-32)

Smear



What's the diagnosis?

Clinical pearl

Severe, rapid-onset thrombocytopenia should raise suspicion for an immunologic cause

In the setting of drugs or medications, consider drug-induced immune thrombocytopenia (DITP)

DITP

- Antibodies against platelets in presence of drug lead to immune-mediated platelet destruction and severe thrombocytopenia

- Multiple drugs have been described in association with DITP

Abciximab (ReoPro™)	Loracarbef	Rifampin
Carbamazepine	Naproxen Glc	Sulfamethoxazole
Ceftazidime	Orbofiban	Sulfisoxazole
Ceftizoxime	Phenytoin	Suramin
Ceftriaxone	Propoxyphene	Tirofiban (Aggrastat™)
Eptifibatide (Integrelin™)	Quinidine	Trimethoprim
Fentanyl	Quinine	Vancomycin
Ibuprofen	Ranitidine	Xemilofiban

- Drug-dependent platelet antibodies to any drug may be checked at

versiti™

Platelet and Neutrophil Immunology Laboratory

(Reese JA et al, *Blood* 2010;116;2237)

Mechanisms of DITP

Hapten-dependent antibody	Hapten links covalently to platelet membrane protein → drug-specific immune response *Penicillin, cephalosporins*
Quinine	Preexisting autoantibody in presence of drug binds to platelet GPIIb/IIIa or GPIb/IX/V *Quinine, sulfa drugs, vancomycin, NSAIDs*
GPIIb/IIIa inhibitor	Drug binds GPIIb/IIIa → conformational change recognized by antibody *Eptifibatide, tirofiban* Drug is a murine monoclonal antibody that induces anti-murine antibody production → antiplatelet antibody *Abciximab*
ITP	Drug-induced autoantibody against platelet antigen *Gold salts, procainamide*
Immune complex	Drug-induced immune complex deposits onto platelets *Heparin (i.e., heparin-induced thrombocytopenia)*

(Aster RH and Bougie DW, *N Engl J Med* 2007;357;580)

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	Quinine, sulfa drugs, vancomycin, NSAIDs
Severe thrombocytopenia, occurring several days after drug exposure	
GPIIb/IIIa inhibitor	Drug binds GPIIb/IIIa ⇒ conformational change recognized by antibody
	Eptifibatide, tirofiban
	Drug is a murine monoclonal antibody that induces anti-murine antibody production ⇒ antiplatelet antibody
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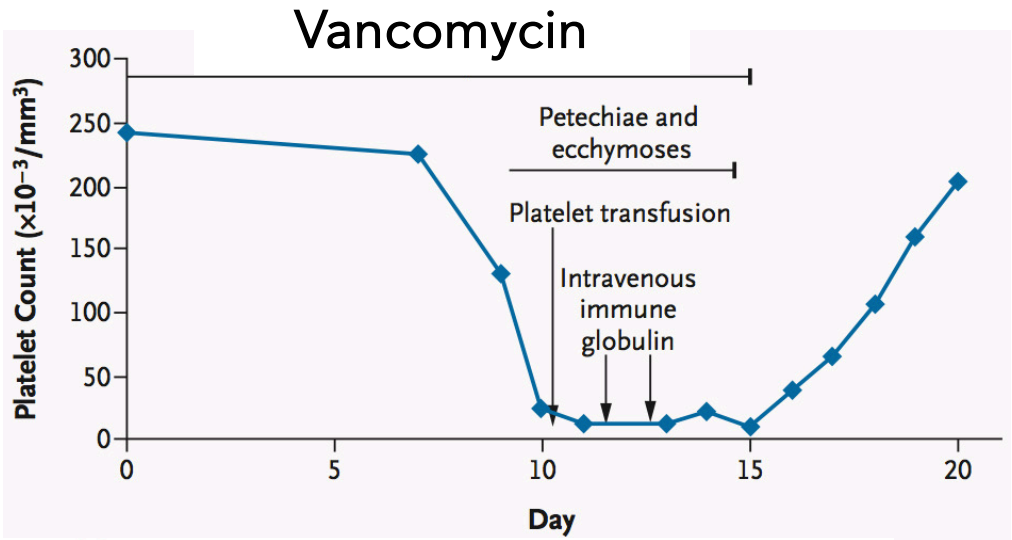
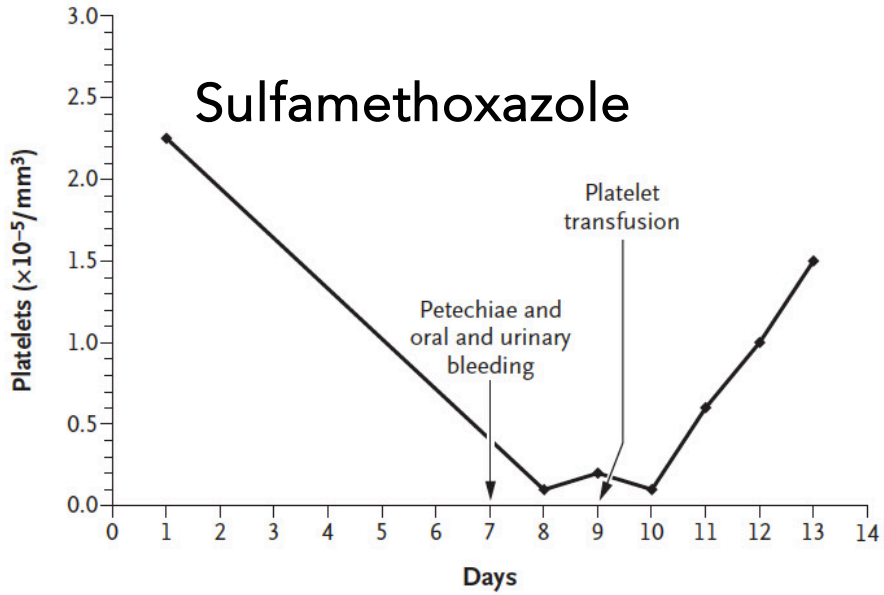
Quinine model of DITP





- Severe thrombocytopenia 5-10 days after drug exposure
- Treatment: stop offending drug

(Von Drygalski A et al , *N Engl J Med* 2007;356;904; Aster RH and Bougie DW, *N Engl J Med* 2007;357;580)

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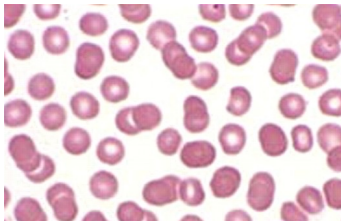


What's the diagnosis?

The patient is suspected of having DITP based on the development of severe isolated thrombocytopenia a week after initiation of antibiotics known to be associated with DITP. Vancomycin and piperacillin/tazobactam are stopped, and she is instead treated with levofloxacin. Four days after changing antibiotics, her platelet count begins to rise. Drug-dependent platelet antibody testing returns a few weeks later showing antibodies against vancomycin.

Case 3: E.S.

E.S. is a 52 year-old man with nonischemic cardiomyopathy due to viral myocarditis. He is admitted for an orthotopic heart transplant. His immune suppression is with tacrolimus, mycophenolate, and prednisone. Over the span of 4 weeks following his cardiac transplant, he suffers from cellulitis, deep venous thrombosis, renal insufficiency, and ARDS requiring intubation. He develops ventilator-associated pneumonia and shock and requires broad-spectrum antibiotics and vasopressor support. In this setting, his blood counts show progressive anemia and thrombocytopenia.

Labs

WBC	15,200/□L (normal 4-10,000)
Hemoglobin	8.5 g/dL (normal 12-15)
Platelets	16,000/□L (normal 150-350,000)
PT	12.7 sec (normal 11-15)
INR	1.1 (normal 0.9-1.1)
PTT	30 sec (normal 23-32)

What's the etiology of his thrombocytopenia?

Clinical pearl

Thrombocytopenia in the setting of critical illness usually reflects "critical illness thrombocytopenia"

Critical illness thrombocytopenia

Increased platelet consumption

Bleeding, sepsis, disseminated intravascular coagulation, surgery, thrombosis, heparin-induced thrombocytopenia, thrombotic microangiopathy, hemophagocytosis, DITP, post-transfusion purpura, extracorporeal membrane oxygenation, cardiac assist device, intraaortic balloon pump

Hemodilution

Decreased platelet production

Medications, toxins,
liver disease,
nutritional deficiencies

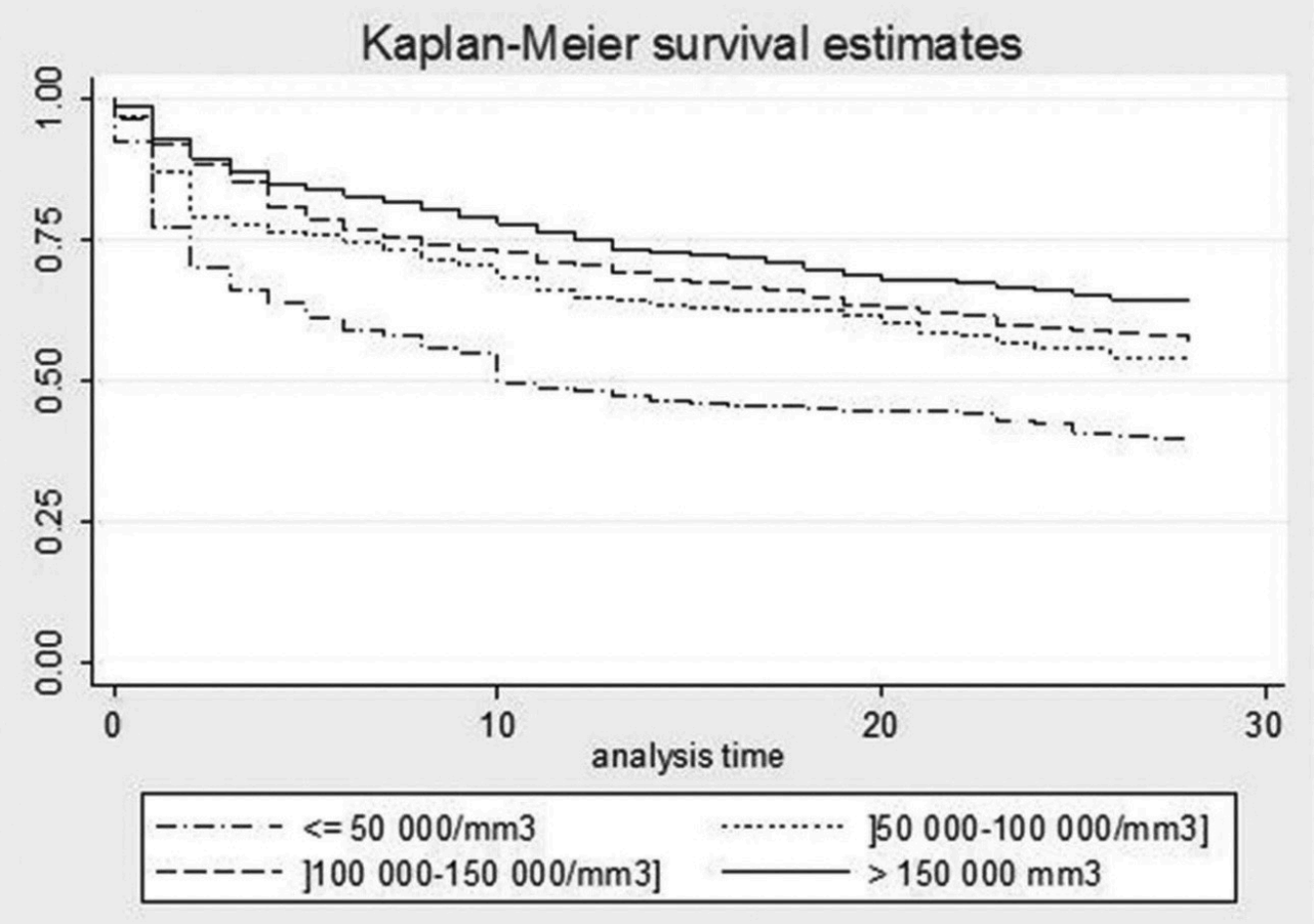
Hypersplenism

Pseudothrombocytopenia

(Greinacher A and Selleng K, *Hematology Am Soc Hematol Educ Prog* 2010;2010:135; Zarychanski R and Houston DS, *Hematology Am Soc Hematol Educ Prog* 2017;2017:660)

Thrombocytopenia is a poor prognostic marker in critically ill patients

Septic Shock Study, 2009-2011



(Thieri-Antier N et al, *Crit Care Med* 2016;44:746)

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PTT	30 sec (normal 23-32)

What's the etiology of his thrombocytopenia?

His thrombocytopenia is attributed to critical illness. Ongoing optimization of medical supportive care is advised.

Case 4: J.D.

J.D. is a 57 year-old woman with cirrhosis due to hepatitis C. In the past, she was treated with sofosbuvir/ledipasvir (Harvoni) and achieved a sustained virologic response. As a result of cirrhosis, she has chronic pancytopenia. She has now been admitted for cough and found on imaging to have a lung mass.

Labs

WBC	3,800/□L (normal 4-10,000)
Hemoglobin	10.8 g/dL (normal 12-15)
Platelets	26,000/□L (normal 150-350,000)
PT	11.8 sec (normal 11-15)
INR	1.1 (normal 0.9-1.1)
PTT	30.2 sec (normal 23-32)
Fibrinogen	166 mg/dL (normal 150-400)

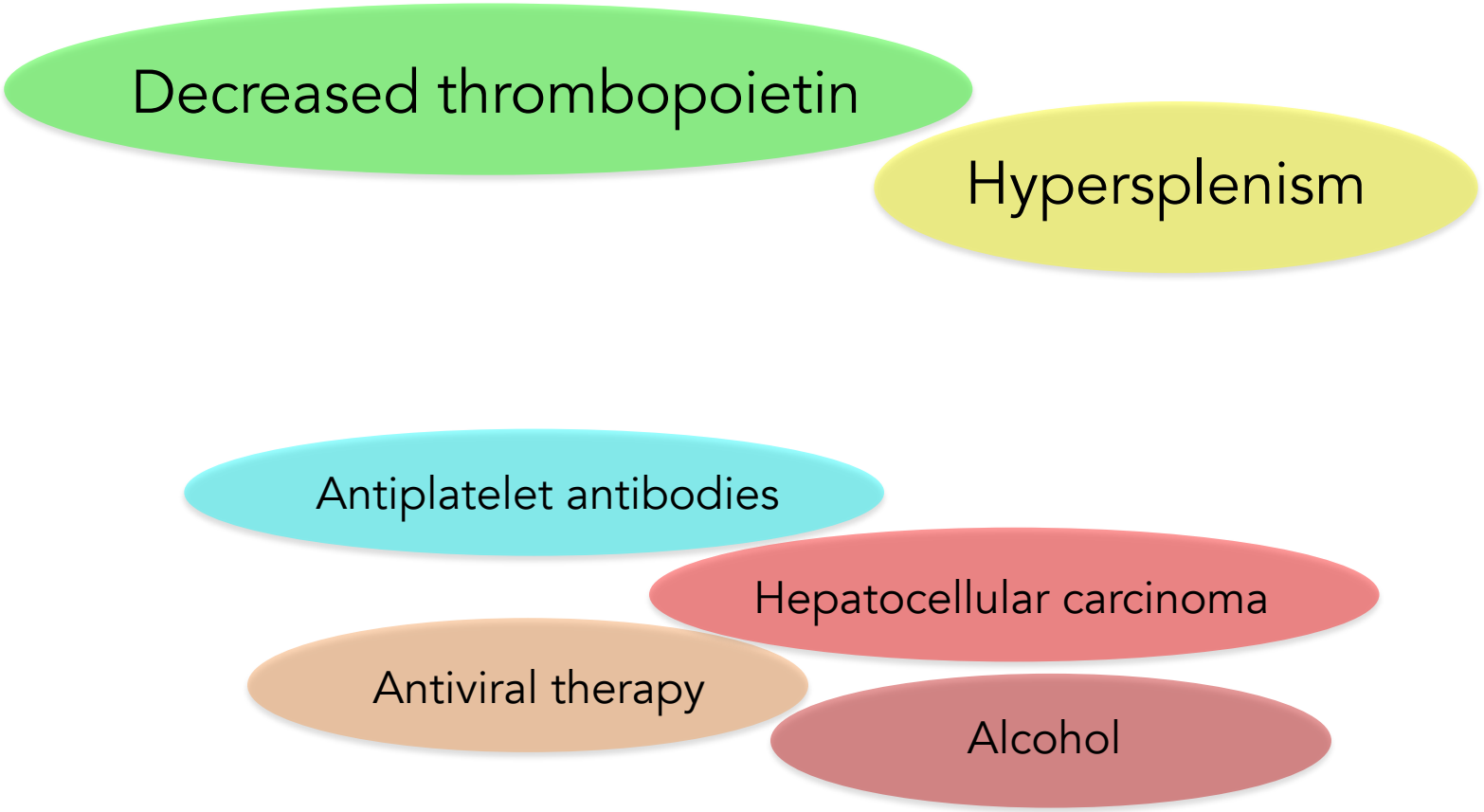
The interventional radiology service would like her platelet count to be at least 50,000/□L before moving forward with a biopsy of the lung mass.

Other than platelet transfusions, how can we increase this patient's platelet count for her procedure?

Clinical pearl

Thrombopoietin receptor agonists (TPORA) are effective and generally safe when used periprocedurally for a limited duration to treat thrombocytopenia due to cirrhosis

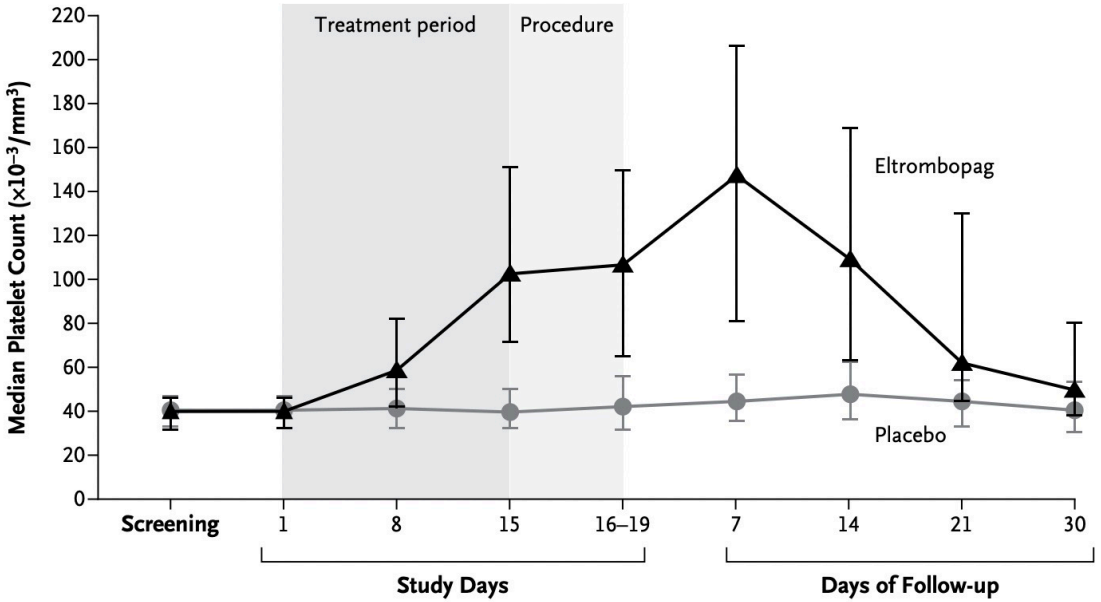
Thrombocytopenia in cirrhosis



(Peck-Radosavljevic M, *Liver Int* 2017;37:778)

TPORA in cirrhosis

Eltrombopag for 14 days was effective but led to splanchnic vein thrombosis in 6 patients



No. with Available Data									
Placebo	147	145	139	132	50	128	116	120	125
Eltrombopag	144	141	134	131	49	125	125	117	127

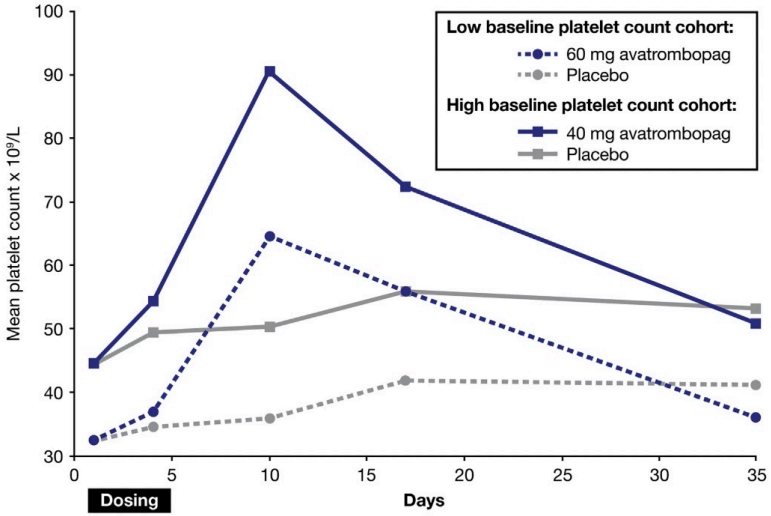
Eltrombopag
Portal-vein and superior-mesenteric-vein thrombosis†
Portal-vein thrombosis
Superior-mesenteric-vein thrombosis
Superior-mesenteric-vein and mesenteric-vein thrombosis
Splenoportal venous thrombosis
Portal-vein thrombosis
Placebo
Acute myocardial infarction
Nonocclusive portal-vein and mesenteric-vein thrombosis

(Afdhal NH et al, *N Engl J Med* 2012;367:716)

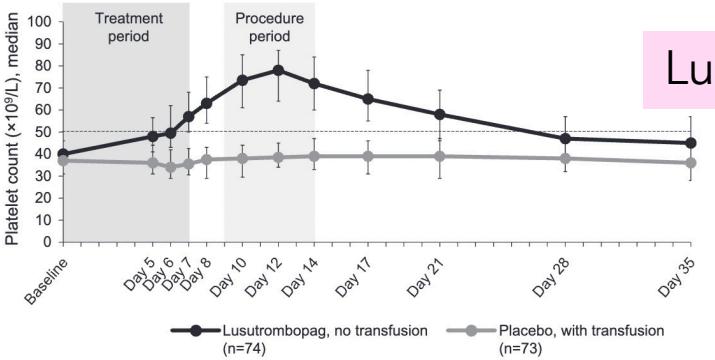
TPORA in cirrhosis

Avatrombopag for 5 days, lusutrombopag for 4-7 days, and romiplostim for ≤ 4 weeks were all effective and showed no increase in thrombosis

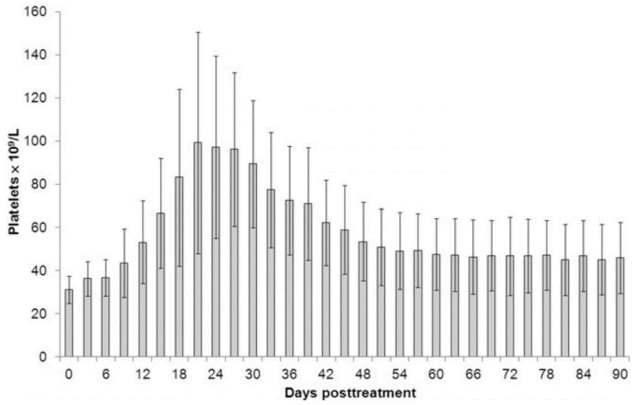
Avatrombopag



Lusutrombopag



Romiplostim



Yale University School of Medicine

(Moussa MM and Mowafy N, *J Gastroenterol Hepatol* 2013;28:335; Terrault N et al, *Gastroenterology* 2018;155:705; Peck-Radosavljevic M et al, *Hepatology* 2019;70:1336)

Yale CANCER CENTER

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INR	1.1 (normal 0.9-1.1)
PTT	30.2 sec (normal 23-32)
Fibrinogen	166 mg/dL (normal 150-400)

The interventional radiology service would like her platelet count to be at least 50,000/□L before moving forward with a biopsy of the lung mass.

Other than platelet transfusions, how can we increase this patient's platelet count for her procedure?

She is treated with avatrombopag for 5 days. Within several days, her platelet count rises above 50,000/□L, and she is able to proceed with biopsy of her lung mass.

Case 5: A.L.

A.L. is a 68 year-old man with mesothelioma who is undergoing treatment with carboplatin and pemetrexed. As a result of his chemotherapy, he has developed pancytopenia. He is now admitted for acute-onset dyspnea and has been diagnosed with bilateral pulmonary emboli involving the segmental vessels of the right and left upper lung lobes.

Labs

WBC	2,400/□L (normal 4-10,000)
Hemoglobin	10.8 g/dL (normal 12-15)
Platelets	32,000/□L (normal 150-350,000)
PT	13.2 sec (normal 11-15)
INR	1.1 (normal 0.9-1.1)
PTT	28.9 sec (normal 23-32)

What's the best anticoagulation strategy for this patient?

Clinical pearl

A dose-adjusted anticoagulation strategy is effective and safe in treating cancer-associated thrombosis (CAT) and thrombocytopenia

Thrombocytopenia in cancer

Antineoplastic therapy

Direct cancer effects
Myelophthisis of bone marrow, splenic infiltration leading to hypersplenism

Thrombotic microangiopathy

Systemic effects
Infection, sepsis, liver disease, thrombosis, critical illness

Immune disorders
ITP, heparin-induced thrombocytopenia

(Lliebman HA, *Thromb Res* 2014;133 Suppl 2:S63)

Two anticoagulation strategies for CAT and thrombocytopenia

With platelet transfusions

Platelet count ≥ 50,000/mcL	Full-dose anticoagulation • LMWH (e.g., enoxaparin 1 mg/kg twice-daily, or 1.5 mg/kg once-daily) • DOAC (e.g., apixaban 5 mg twice-daily; or rivaroxaban 20 mg once-daily)
Platelet count < 50,000/mcL	Full-dose anticoagulation • LMWH • DOAC Transfuse platelets to raise platelet count ≥ 50,000/mcL

No platelet transfusions

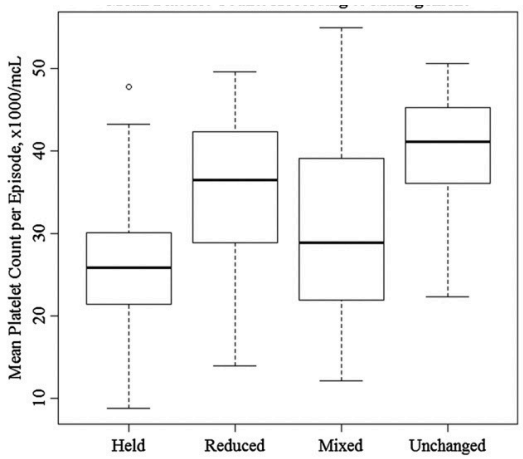
Platelet count ≥ 50,000/mcL	Full-dose anticoagulation • LMWH • DOAC
Platelet count 25,000-50,000/mcL	Half-dose anticoagulation • LMWH (e.g., enoxaparin 0.5 mg/kg twice-daily, or 0.75 mg/kg once-daily) • DOAC (e.g., apixaban 2.5 mg twice-daily; or rivaroxaban 10 mg once-daily)
Platelet count < 25,000/mcL	No anticoagulation

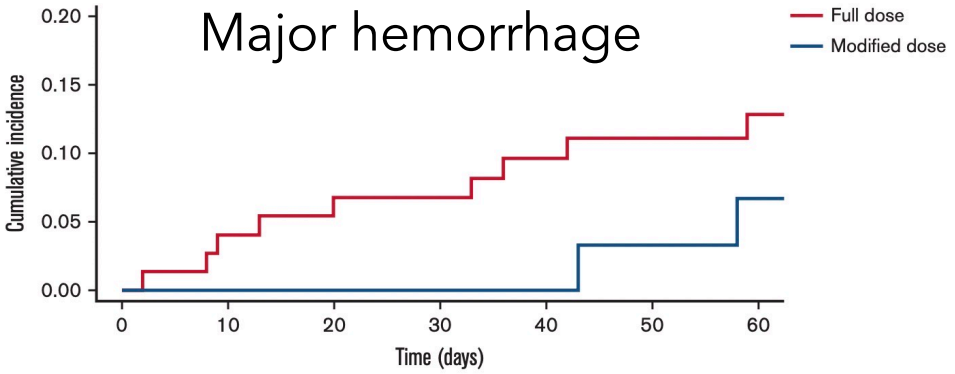
(Goshua G et al, *Hematology Am Soc Hematol Educ Prog* 2022)

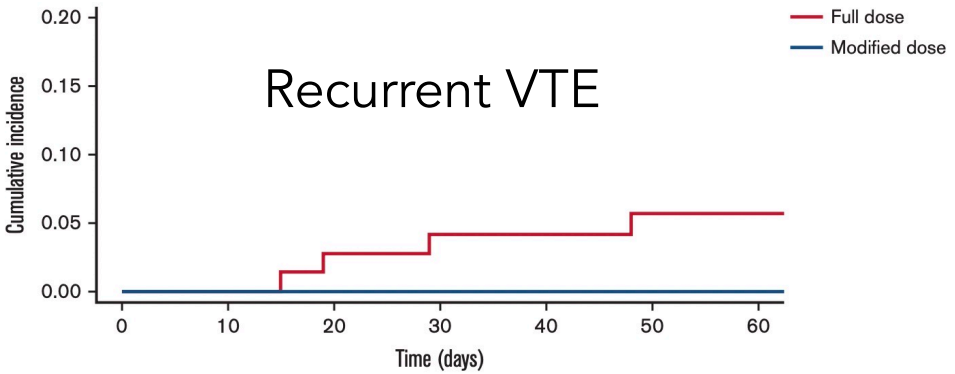
Dose-adjusted anticoagulation in CAT and thrombocytopenia

Enoxaparin, apixaban, or rivaroxaban

Enoxaparin

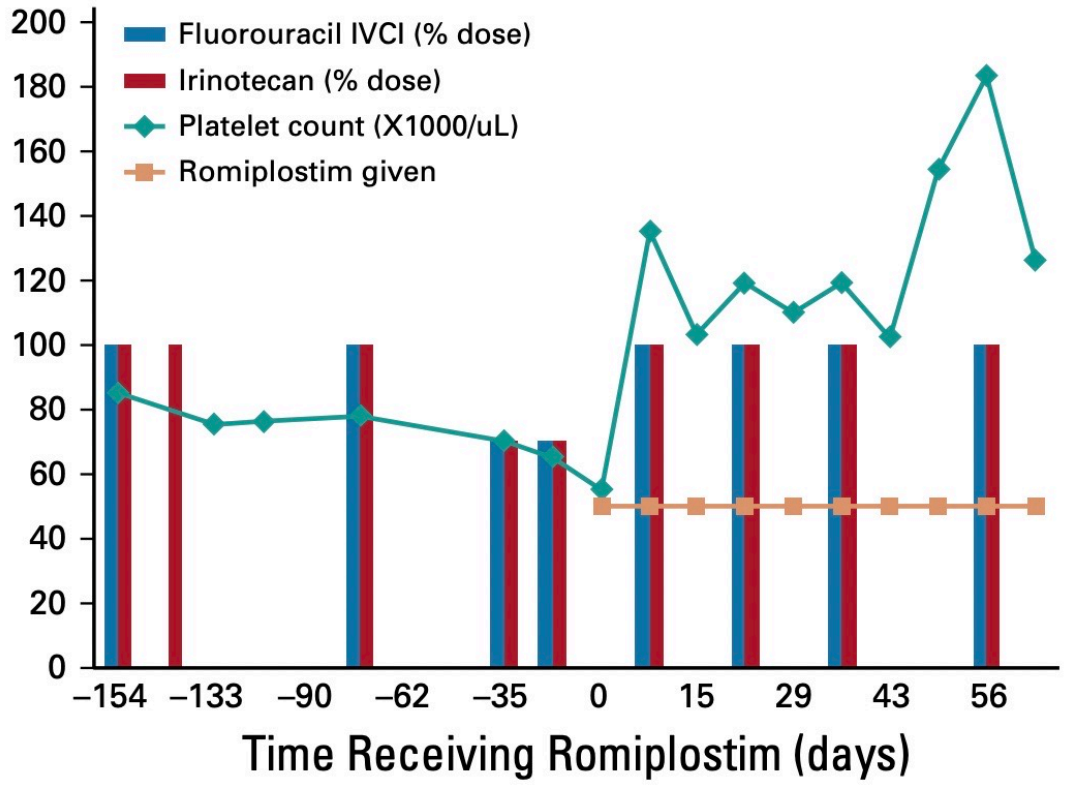






(Mantha S et al, *J Thromb Thrombolysis* 2017;43:514; Carney BJ et al, *Blood Adv* 2021;5:5546)

TPORA in cancer-associated thrombocytopenia



Romiplostim is effective and safe in treating chemotherapy-induced thrombocytopenia

- *Less effective for thrombocytopenia due to myelophthisis*
- *Utility in anticoagulation for CAT with thrombocytopenia is uncertain*

(Soff G et al, *J Clin Oncol* 2019;37:2892)

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PTT	28.9 sec (normal 23-32)

What's the best anticoagulation strategy for this patient?

He is started on anticoagulation with apixaban 2.5 mg twice-daily and tolerates this well without bleeding complications.

Case 6: R.K.

R.K. is a 40 year-old woman with a longstanding history of menorrhagia, who is discovered by her primary care physician to have severe and symptomatic iron deficiency anemia. She is started on oral iron supplementation and transfused 1 unit of packed RBC. One week later, she presents to the emergency department with diffuse petechiae and wet purpura and is found to have new-onset, severe thrombocytopenia.

Labs 1 week ago, prior to RBC transfusion		Labs now	
WBC	5,300/□L (normal 4-10,000)	WBC	4,200/□L (normal 4-10,000)
Hemoglobin	6.0 g/dL (normal 12-15)	Hemoglobin	9.5 g/dL (normal 12-15)
Platelets	420,000/□L (normal 150-350,000)	Platelets	14,000/□L (normal 150-350,000)

What's the diagnosis, and how should she be treated?

Clinical pearl

Severe, rapid-onset thrombocytopenia should raise suspicion for an immunologic cause

In the setting of transfusions, consider post-transfusion purpura (PTP)

PTP

- Most individuals have HPA-1a antigen on platelets
- In HPA-1a$^{(-/-)}$ individuals exposed to HPA-1a, anti-HPA-1a antibodies may develop
  - In such patients who are transfused blood products containing HPA-1a^{+} platelets, severe thrombocytopenia may develop 5-10 days after transfusion
  - Both an alloantibody response against HPA-1a^{+} platelets and an autologous response against native HPA-1a^{-} platelets are observed

(Jawkins J et al, *J Blood Med* 2019;10;405)

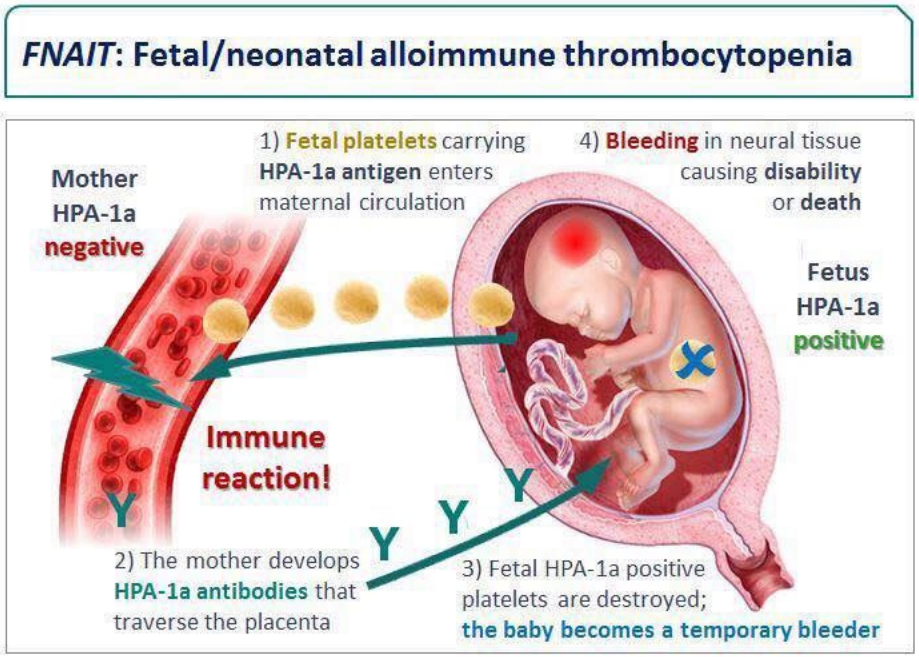
PTP

- Diagnosis: HPA-1a genotyping and antibody testing

- Treatment:
  - IVIg 400-500 mg/kg/d for 1-10 days, or 1-2 g/kg/d for 1-2 days
  - If needed, HPA-1a$^-$ platelets may be transfused

(Jawkins J et al, *J Blood Med* 2019;10;405)

PTP is analogous to fetal/neonatal alloimmune thrombocytopenia (FNAIT)



First-line treatment: weekly IVIg +/- steroids

(https://www.naitbabies.org/; Winkelhorst D et al, *Blood* 2017;129:1538)

R.K. is a 40 year-old woman with a longstanding history of menorrhagia, who is discovered by her primary care physician to have severe and symptomatic iron deficiency anemia. She is started on oral iron supplementation and transfused 1 unit of packed RBC. One week later, she presents to the emergency department with diffuse petechiae and wet purpura and is found to have new-onset, severe thrombocytopenia.

Labs 1 week ago, prior to RBC transfusion	
WBC	5,300/□L (normal 4-10,000)
Hemoglobin	6.0 g/dL (normal 12-15)
Platelets	420,000/□L (normal 150-350,000)

Labs now	
WBC	4,200/□L (normal 4-10,000)
Hemoglobin	9.5 g/dL (normal 12-15)
Platelets	14,000/□L (normal 150-350,000)

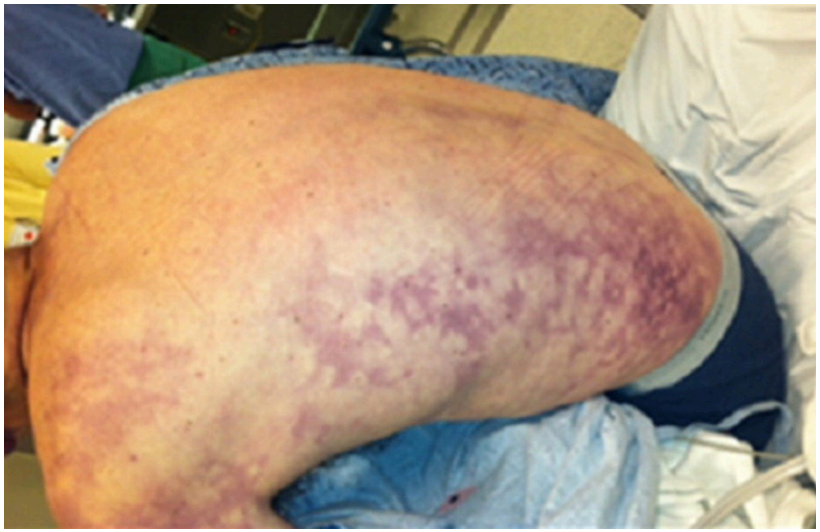
What's the diagnosis, and how should she be treated?

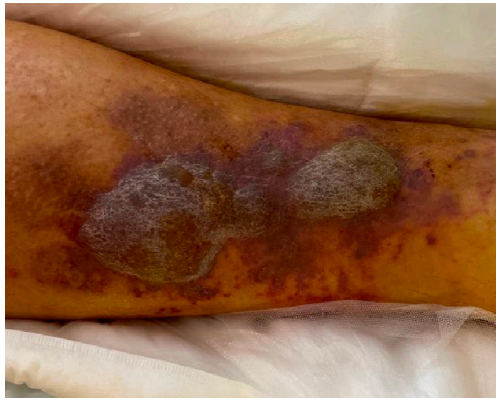
Based on severe thrombocytopenia occurring a week after RBC transfusion, she is suspected of having PTP. She is treated with IVIg. HPA-1a testing later returns showing an HPA-1a$^{(-/-)}$ genotype with anti-HPA-1a antibodies, confirming a diagnosis of PTP.

Case 7: B.H.

B.H. is a 37 year-old man who is admitted to the hospital for fever and fatigue. On initial presentation, he is in shock, requiring fluid resuscitation and vasopressor support. Blood cultures return positive for *Klebsiella pneumoniae*. He is treated with broad-spectrum intravenous antibiotics.

Exam





(Collling ME and Bendapudi PK, *Transfus Med Rev* 2018;32:69-76)

Labs

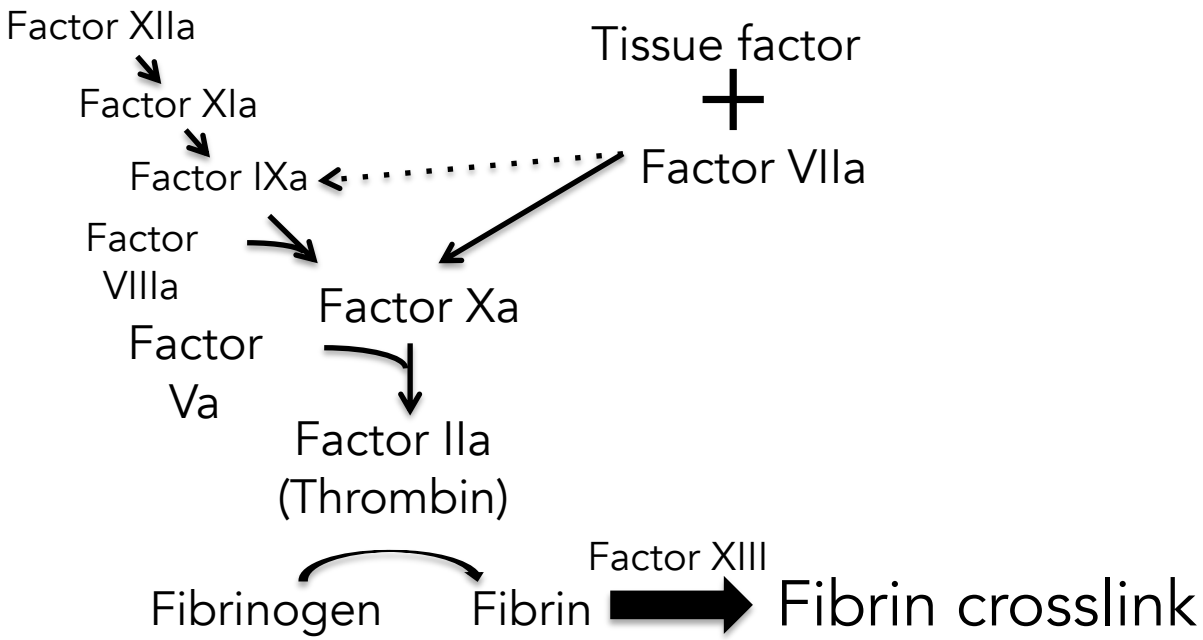
WBC	14,400/□L (normal 4-10,000)
Hemoglobin	11.8 g/dL (normal 12-15)
Platelets	45,000/□L (normal 150-350,000)
PT	27.2 sec (normal 11-15)
INR	2.4 (normal 0.9-1.1)
PTT	49 sec (normal 23-32)
Fibrinogen	65 mg/dL (normal 150-400)

What's the diagnosis, and how should he be treated?

Clinical pearl

Purpura fulminans (PF) is an extreme thrombotic form of disseminated intravascular coagulation (DIC) and should be treated with anticoagulation, plasma transfusions, and protein C and antithrombin replacement

DIC is due to abnormal activation of the coagulation cascade …



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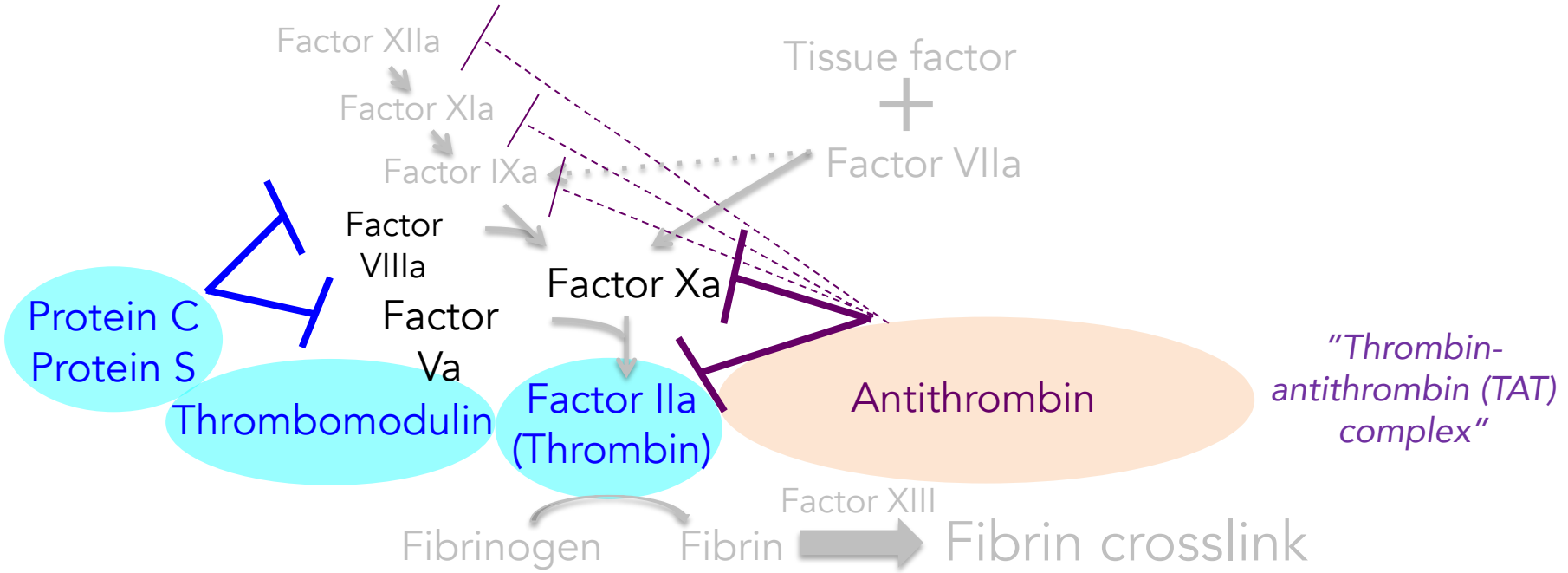
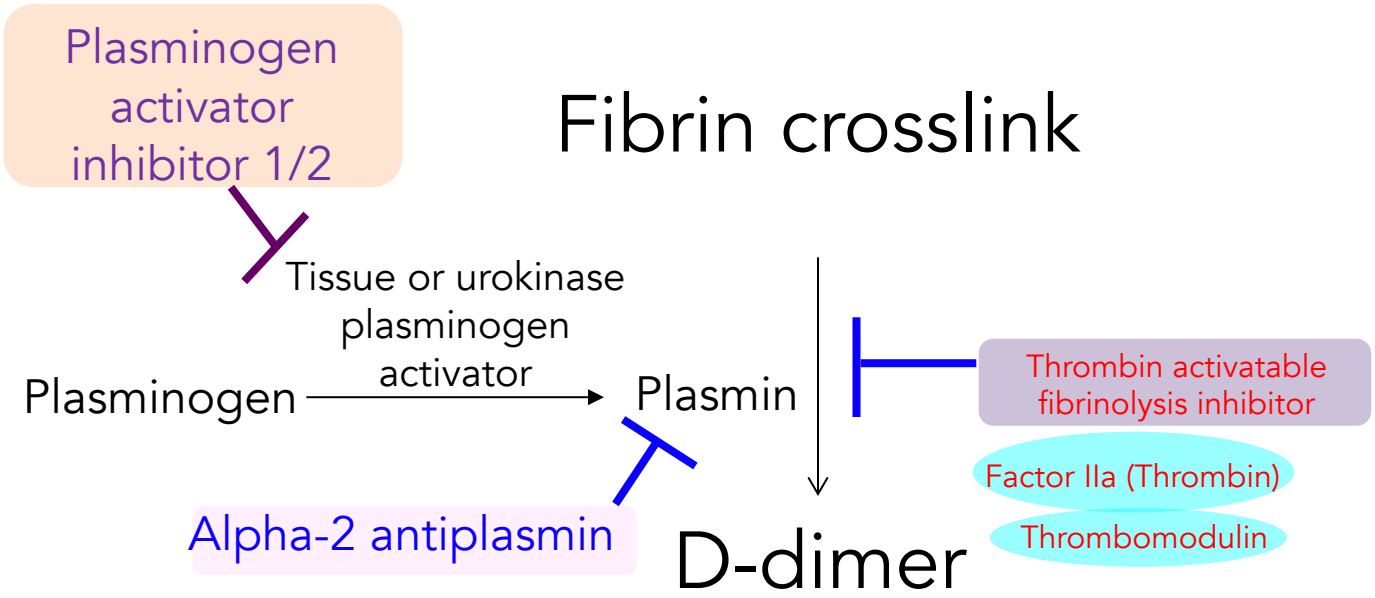


… with consumption of endogenous anticoagulants

DIC is due to abnormal activation of the coagulation cascade …



"Plasmin-alpha-2 antiplasmin (PAP) complex"

… and with abnormalities of fibrinolysis

DIC is due to abnormal activation of the coagulation cascade, with consumption of endogenous anticoagulants and abnormalities of fibrinolysis leading to fibrin-rich thrombi

- ↑ D-dimer
- ↓ Fibrinogen
- ↑ Prothrombin time (PT)
- ↓ Platelet count
- ↑ TAT complexes
- ↓ Antithrombin
- ↓ Protein C (PC)
- ↓ Protein S (PC)
- ↑ PAP complexes

ISTH DIC score

Scoring system for overt DIC

Risk assessment: Does the patient have an underlying disorder known to be associated with overt DIC?

If yes: proceed

If no: do not use this algorithm

Order global coagulation tests (PT, platelet count, fibrinogen, fibrin related marker)

Score the test results

- Platelet count (>100 × 10^9/l = 0, <100 × 10^9/l = 1, <50 × 10^9/l = 2)
- Elevated fibrin marker (e.g. D-dimer, fibrin degradation products) (no increase = 0, moderate increase = 2, strong increase = 3)
- Prolonged PT (<3 s = 0, >3 but <6 s = 1, >6 s = 2)
- Fibrinogen level (>1 g/l = 0, <1 g/l = 1)

Calculate score:

≥5 compatible with overt DIC: repeat score daily

<5 suggestive for non-overt DIC: repeat next 1–2 d

(Levi M et al, *Br J Haematol* 2009;145:24)

Types of PF

	Inherited	Autoimmune or postinfectious ("idiopathic")	Acute infectious
Mechanism	Inherited PC or rarely PS deficiency	Neutralizing antibodies against PS or rarely PC	Aberrant tissue factor expression with concomitant failure of thrombomodulin-PC system
Associations		☐ Varicella zoster virus ☐ Human herpesvirus-6	☐ *Neisseria meningitidis* ☐ *Haemophilus influenza* ☐ *Streptococcus pneumoniae* ☐ Other encapsulated organisms ☐ *Staphylococcus aureus* ☐ *Capnocytophaga canimorsus* ☐ Rickettsial infection ☐ *Plasmodium falciparum*
Clinical setting	Neonatal	≤ 2 weeks after viral infection	Septic shock
Laboratory findings	☐ Thrombocytopenia ☐ Elevated D-dimer or fibrin split products ☐ Hypofibrinogenemia ☐ Prolonged PT and/or aPTT ☐ Low PC, PS, and antithrombin activities		

(Goshua G et al, *Hematology Am Soc Hematol Educ Prog* 2022)

Treatment of PF

Days of presentation	Laboratory monitoring	Treatment				
		Intravenous unfractionated heparin	Fresh frozen plasma	Cryoprecipitate	PC replacement	Antithrombin concentrate
0-3	☐ Complete blood count ☐ D-dimer or fibrin split products ☐ Fibrinogen ☐ PT and PTT ☐ Anti-Xa (while on heparin) ☐ Antithrombin, PC, and PS activities	80 units/kg bolus followed by 18 units/kg/hour, targeting anti-Xa 0.3-0.7 U/mL	2 units followed by 1 unit every 4 hours	10 units, targeting fibrinogen ≥ 100 mg/dL	PC concentrate 100 units/kg or prothrombin complex concentrate 25-50 U/kg, targeting PC activity > 80%	85 units/kg, targeting antithrombin activity > 80%
4-5			1 unit every 6 hours			
6-7			1 unit every 8 hours			

☐ **Consider intravenous vitamin K 5 mg at time of presentation**

☐ **In patients on anticoagulation, platelets may be transfused to maintain platelet count ≥ 30,000/mcL, but platelets should not be transfused in absence of anticoagulation or bleeding**

☐ **For acute infectious purpura fulminans: broad-spectrum antibiotics with coverage against Neisseria meningitidis and other encapsulated organisms as well as methicillin-resistant Staphylococcus aureus until a culprit microorganism is identified**

(Goshua G et al, *Hematology Am Soc Hematol Educ Prog* 2022)

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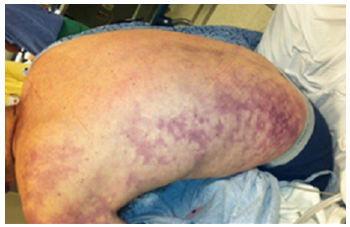

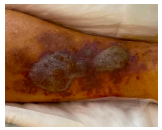

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Fibrinogen	65 mg/dL (normal 150-400)

What's the diagnosis, and how should he be treated?

He is diagnosed with PF. He is transfused fresh frozen plasma and cryoprecipitate, started on anticoagulation with intravenous heparin, and given intravenous vitamin K, prothrombin complex concentrate, and antithrombin concentrate.

Hats off to the best!