



TABLE OF CONTENTS

Introduction

Diagnostic Challenge

Assessment and Treatment

Conclusion

References

Drug-Induced Thrombocytopenia: New Options and Treatment Strategies

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Patricia A. Ford, MD

Introduction

More than 140 years have passed since W. H. Vipan first described the clinical manifestations of drug-induced thrombocytopenia (DIT).¹ In that landmark article, published in *The Lancet*, Vipan noted the onset of purpura in patients treated with quinine for malaria. In the years that have followed, hundreds of new drugs have entered the marketplace, and many have been implicated in DIT.² It is perhaps not surprising that the occurrence of DIT is becoming an increasingly common phenomenon. Quite simply, more drugs equal more potential offenders, and this in turn gives rise to increased complexity of diagnosis and treatment.^{2,3}

Our understanding of the pathogenesis of DIT is still evolving. At least 6 different mechanisms have been proposed by which drug-induced antibodies can promote platelet destruction (see [Table 1](#)).⁴ While identification of the offending agent or agents is possible in many cases, the testing required is technically demanding, time-consuming, and not widely available.⁴ Therefore, clinicians must often make the initial decision on whether to discontinue an implicated medication in a patient suspected of having DIT based on clinical manifestations, just as Vipan did more than a century ago.^{1,2,4} A high index of suspicion and a careful history of drug exposure in any patient who presents with acute, often severe thrombocytopenia remain the most important elements of effective assessment and management.⁴

Table 1. Mechanisms of drug-induced immune thrombocytopenia and commonly implicated medications

Mechanism	Designation	Examples
Drug (hapten) links covalently to membrane protein and induces a drug-specific immune response	Hapten-dependent antibody	Penicillin, piperacillin? Cephalosporin antibiotics?
Drug induces antibody that binds to membrane protein only in the presence of soluble drug	Drug-dependent antibody	Quinine, many antibiotics, nonsteroidal anti-inflammatory drugs, anticonvulsants
Drug (ligand) reacts with membrane GPIIb–IIIa and induces a conformational change recognized by naturally occurring antibody?	Fiban-induced thrombocytopenia	Eptifibatide, tirofiban
Naturally occurring or induced antibody is specific for the murine component of abciximab, a chimeric Fab fragment specific for GPIIa	Drug-specific antibody	Abciximab
Drug induces antibody that reacts with platelets in the absence of drug	Autoantibody induction	Gold salts, L-dopa, procainamide
Drug binds to platelet factor 4 to produce a complex for which antibody is specific. The resulting immune complex activates platelets via Fc receptors	Immune complex	Heparin

GP, glycoprotein. Adapted from Aster.⁴

The clinical presentation of DIT ranges from mild to life-threatening bleeding.⁴ Exposure to the offending agent normally occurs 1 week before thrombocytopenia becomes clinically evident, although this can vary depending on the offending agent.⁴ Petechiae, bruising, and epistaxis are common early clinical manifestations.² The majority of patients with DIT experience moderate to severe thrombocytopenia, defined as platelet counts <50,000/ μL , with most of these reaching nadir levels <20,000 μL .² However, platelet counts can be profoundly reduced in some cases, and an acute drop to a level that places patients at risk for spontaneous hemorrhage can quickly occur.² In all cases, DIT should be viewed as a serious condition requiring prompt attention.²

Diagnostic Challenge

As noted, a wide range of medications have been implicated in the onset of DIT (Table 2).⁵ Moreover, patients may be exposed to multiple implicated medications, particularly critically ill patients in whom thrombocytopenia often occurs, creating a diagnostic challenge for the clinician.³

Table 2. Drugs commonly implicated as triggers of drug-induced thrombocytopenia

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

Adapted from Aster.⁵

Both immune and nonimmune processes have been linked to the development of DIT (Table 3).^{2,3} In cases involving immune-mediated DIT, it is imperative that the offending agent be identified and discontinued as quickly as possible, preferably immediately whenever feasible.²

Table 3. Immune and nonimmune mechanisms of platelet destruction in various disorders

Immune	Immune and Nonimmune	Nonimmune
<ul style="list-style-type: none"> • Idiopathic ITP • Alloimmune destruction (posttransfusion, neonatal, posttransplantation) 	<ul style="list-style-type: none"> • Drug-induced thrombocytopenia • Infection-associated thrombocytopenia • HELLP syndrome 	<ul style="list-style-type: none"> • Disseminated intravascular coagulation • TTP-HUS • Antiphospholipid antibody syndrome • Physical destruction (cardiopulmonary bypass, giant cavernous hemangiomas)

HELLP, hemolysis with a microangiopathic blood smear, elevated liver enzymes, and low platelets in pregnancy; ITP, immune thrombocytopenic purpura; TTP-HUS, thrombotic thrombocytopenic purpura-hemolytic uremic syndrome. Adapted from Drews.³

Nonimmune DIT

Platelet production is dependent on adequate marrow function, as well as a sufficient megakaryocyte population.² Numerous antineoplastic medications induce marrow suppression, including myeloablative chemotherapeutic compounds, certain antiviral agents, tolbutamide, and thiazide diuretics.² In most cases, a

dose-dependent decrease in platelet count can be observed.²

Myeloablative chemotherapeutic compounds represent the most commonly cited agents responsible for the onset of nonimmune DIT.² Thrombocytopenia is usually an anticipated consequence of therapy with myelosuppressive agents and can be cumulative with subsequent cycles; diagnosis in these cases is therefore typically straightforward, and treatment is usually easily managed with platelet transfusion² and sometimes a dose reduction of chemotherapy. There is normally a slow time course for DIT related to marrow suppression, a reflection of the time required to deplete megakaryocyte production (**Figure 1**).²

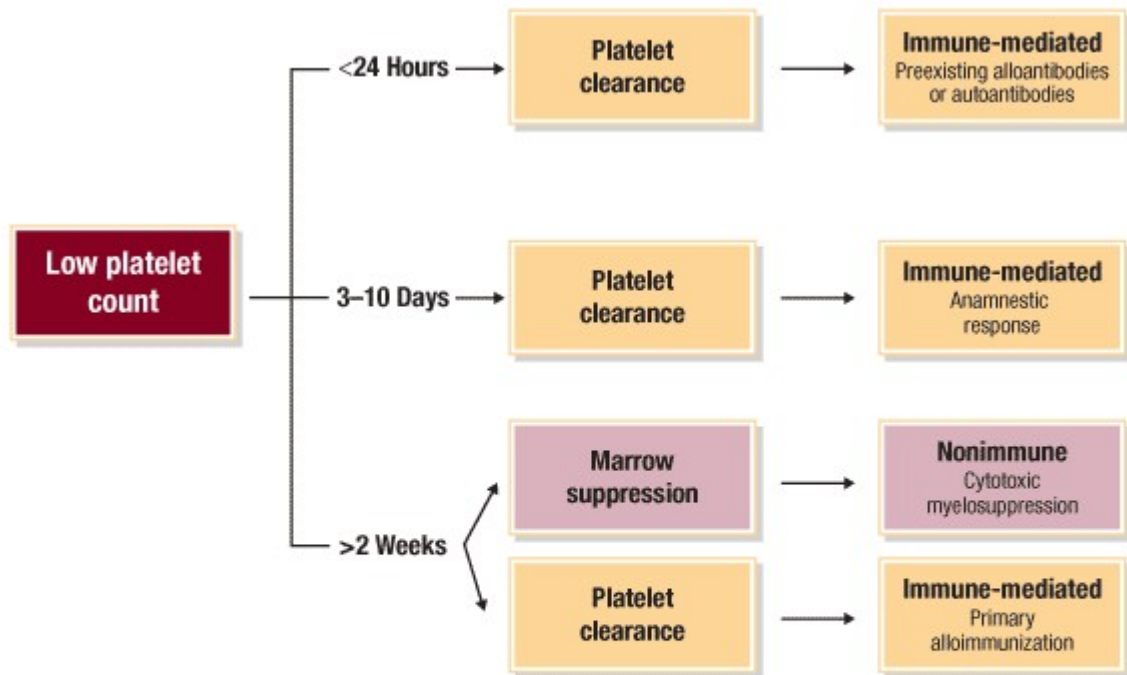


Figure 1

Categorization of drug-induced thrombocytopenia by time of onset of thrombocytopenia.
Adapted from Kenney.² Reprinted with permission from *Archives of Pathology & Laboratory Medicine*. © 2009. College of American Pathologists.

Immune-Mediated DIT

Immune-mediated DIT is by far the more common and more problematic form of DIT to diagnose.² As the literature has noted, platelets appear to be affected by immune-mediated, drug-dependent destruction more than other marrow-derived cell types.^{2,6} The mean delay in the onset of immune-mediated thrombocytopenia is reported to be 1 to 2 weeks following a patient's exposure to the offending drug, but this can range in individual patients, which may further complicate diagnosis.²

The proposed mechanisms of action involved in immune-mediated DIT are varied and just partly understood. Only a small percentage of patients are affected by this disorder, and no predisposing genetic or environmental factors have been identified.⁵ The mechanisms believed to be involved in DIT are summarized

in [Table 4.5](#)

Table 4. Mechanisms underlying drug-induced immune thrombocytopenia			
Classification	Mechanism	Incidence	Examples
Hapten-dependent antibody	Hapten links covalently to membrane protein and induces drug-specific immune response	Very rare	Penicillin, possibly some cephalosporin antibiotics
Quinine-type drug	Drug induces antibody that binds to membrane protein in presence of soluble drug	26 cases per 1 million users of quinine per week; probably fewer cases with other drugs	Quinine, sulfonamide antibiotics, nonsteroidal anti-inflammatory drugs
Fiban-type drug	Drug reacts with GPIIb/IIIa to induce a conformational change (neopeptide) recognized by antibody (not yet confirmed)	0.2%–0.5%	Tirofiban, eptifibatid
Drug-specific antibody	Antibody recognizes murine component of chimeric Fab fragment specific for platelet membrane GPIIIa	0.5%–1.0% after first exposure; 10%–14% after second exposure	Abciximab
Autoantibody	Drug induces antibody that reacts with autologous platelets in absence of drug	1.0% with gold; very rare with procainamide and other drugs	Gold salts, procainamide
Immune complex	Drug binds to platelet factor 4, producing immune complex for which antibody is specific; immune complex activates platelets through Fc receptors	3%–6% among patients treated with unfractionated heparin for 7 days; rare with low-molecular-weight heparin	Heparins

GP, glycoprotein. Adapted from Aster.⁵

Heparin-Induced Thrombocytopenia

Heparin remains the most common offending agent involved in drug-induced, antibody-mediated thrombocytopenia.⁷ Heparin-induced thrombocytopenia (HIT) is a life-threatening disorder that occurs in susceptible individuals following exposure to unfractionated or, less commonly, low-molecular-weight heparin.⁸ The classic presentation of HIT includes platelet count <150,000 per cubic millimeter or a relative decrease in platelet count of $\geq 30\%$ from baseline.⁸⁻¹⁰ As in other cases of DIT, diagnosis can be challenging, particularly in patients with complicated medical conditions and/or in those who have recently undergone cardiac surgery.⁸ [Table 5](#) summarizes the clinical populations at risk for HIT, and provides recommendations for monitoring platelet count.⁸

Table 5. Incidence of heparin-induced thrombocytopenia according to population at risk, and recommendations for monitoring of platelet count

Therapy	Risk	Clinical Population at Risk	Incidence of PF4-Heparin Antibodies*	Incidence of HIT	Platelet-Count Monitoring
			Percentage		
Heparin (new or remote [>100 days] exposure)	High	<ul style="list-style-type: none"> • Patients undergoing orthopedic surgery 	14	3–5	At baseline and at least every other day from days 4 to 14 of heparin therapy or until heparin continued†‡
	Intermediate	<ul style="list-style-type: none"> • Adults undergoing cardiac surgery • Children undergoing cardiac surgery 	25–50	1–2	
	Intermediate	<ul style="list-style-type: none"> • General medical patients • Patients with neurologic conditions • Patients undergoing percutaneous coronary intervention for acute coronary syndrome • Patients undergoing acute hemodialysis 	8–20	0.8–3.0	
Low-molecular-weight heparin (new or remote [>100 days] exposure)	Low to rare	<ul style="list-style-type: none"> • General pediatric patients • Pregnant women • Patients undergoing chronic hemodialysis 	0–2.3	0–0.1	Not essential†
	Intermediate	<ul style="list-style-type: none"> • Medical patients • Patients with neurologic conditions • Patients undergoing surgical or orthopedic procedures 	2–8	0–0.9	At baseline and every 2 to 4 days after days 4 through 14 of low-molecular-weight heparin therapy or until therapy discontinued†‡
	Rare	<ul style="list-style-type: none"> • Pregnant women • General pediatric patients 	Unknown	0–0.1	Routine monitoring not recommended†
Heparin or low-molecular-weight heparin (exposure within 100 days)	Unknown	<ul style="list-style-type: none"> • All clinical populations 	Unknown	Unknown	At baseline, within 24 hr, and every other day from days 4 through 14 until heparin is discontinued†‡

HIT, heparin-induced thrombocytopenia.

* Rates of seropositivity were determined by antigen or serologic enzyme-linked immunosorbent assays.

† Recommendations for monitoring platelets are those of the American College of Chest Physicians.

‡ Recommendations for monitoring platelets are those of the British Committee for Standards in Haematology.

Adapted from Arepally.⁸

Two types of HIT have been noted in the literature. There is the more common type I form, which occurs in 10% to 20% of patients and is not associated with hemorrhagic or thrombotic sequelae, and the type II form, in which 30% to 80% of patients experience thrombotic sequelae.³ Importantly, the immune mechanism behind HIT initially results in platelet activation *before* platelet consumption.² Early recognition is therefore pivotal for preventing thrombosis, limb loss, and even death.¹¹

For further discussion on the incidence, diagnosis, and treatment of HIT, [CLICK HERE](#).

Assessment and Treatment

Decreasing serum fibrinogen levels and increasing TTs, PTs, aPTTs, and fibrin degradation products demonstrate the presence of a consumptive coagulopathy in the setting of thrombocytopenia (**Table 6**).³ An inverse relationship between bleeding severity and platelet count has been noted, although there have been reports of patients with profound thrombocytopenia who have no bleeding symptoms.⁴ Patients with platelets <10,000 μL often present with extensive purpuric lesions on the skin and mucosal surfaces, hematuria, and gastrointestinal hemorrhage (“wet purpura”).⁴

Table 6. Cause of prolonged prothrombin time or prolonged activated partial thromboplastin time		
Test results	Causes of test result pattern	
	Inherited	Acquired
PT - Prolonged aPTT - Normal	<ul style="list-style-type: none"> Factor VII deficiency 	<ul style="list-style-type: none"> Vitamin K deficiency Liver disease Warfarin administration Inhibitor of factor VII
PT - Normal aPTT - Prolonged	<ul style="list-style-type: none"> Deficiency of vWF or factors VIII, IX, XI, or XII 	<ul style="list-style-type: none"> Heparin administration Inhibitor of vWF or factors VIII, IX, XI, or XII (PT may be slightly prolonged) Antiphospholipid antibody*
PT - Prolonged aPTT - Prolonged	<ul style="list-style-type: none"> Deficiency of prothrombin, fibrinogen, or factor V or X Combined factor deficiencies 	<ul style="list-style-type: none"> Liver disease Disseminated intravascular anticoagulation Supratherapeutic warfarin administration Supratherapeutic heparin administration Combined warfarin and heparin administration Inhibitor of prothrombin, fibrinogen, or factor V or X

aPTT, activated partial thromboplastin time; PT, prothrombin time.

*Associated with thrombosis, rather than bleeding. Adapted from Drews.³

Treatment of DIT and related coagulopathies begins with identification and discontinuation, when feasible, of offending agent(s).^{2,4} Clinicians are advised to consider the distinctive aspects of each patient's clinical presentation, as well as the potential advantages and disadvantages of various treatment approaches, when making treatment decisions for their patients.¹¹

The following treatment options may be considered:

Red Blood Cell Transfusions

Red blood cell (RBC) transfusions may be useful in cases in which hemoglobin is ≤ 7 g/dL in patients older than 65 years and patients with chronic cardiovascular or respiratory disease. Transfusion is also recommended for patients with acute blood loss >1500 mL or $>30\%$ of blood volume.¹² Other indications include patients with preoperative anemia and hemoglobin <9 g/dL with impending major blood loss.¹³

Platelet Transfusions

Platelet transfusions are the standard treatment for DIT associated with the use of myelosuppressive agents, but they may also be employed in other cases of DIT.² Because platelets play an instrumental role in managing patients who are bleeding or at risk for bleeding, prophylactic use of platelet transfusions to prevent bleeding in the patient with thrombocytopenia may be considered.³ Other indications for platelet transfusions include the following:

- Platelet count $\leq 10,000$ per microliter blood
- Platelet counts $\leq 50,000$ per microliter blood *and* bleeding due to thrombocytopenia or platelet dysfunction
- Platelet counts $\leq 50,000$ per microliter blood *and* potential for bleeding from an invasive procedure (surgery, placement of subclavian venous access, lumbar spinal puncture, etc)
- Platelet counts $>100,000$ and evidence of bleeding due to platelet dysfunction intractable to DDAVP or cryoprecipitate

Plasma Product Transfusions

Plasma product transfusions are the treatment of choice when bleeding arises due to malfunction, consumption, or underproduction of plasma coagulation proteins.³ As with platelet transfusion, plasma product transfusions may be used prophylactically in the critical care setting to correct coagulopathies prior to invasive or surgical procedures. In cases involving active bleeding, clinicians should administer plasma products until bleeding stops or coagulopathy ceases.³

The choice of plasma product is dependent upon the patient's clinical circumstances. Fresh frozen plasma (FFP) is the most common plasma product used to correct clotting factor deficiencies, including coagulopathies related to DIT.³

Recombinant Factor VIIa

Recombinant factor VIIa (rVIIa) enhances coagulation at the site of injury, apparently by enhancing platelet-surface thrombin generation independently of its usual cofactor, tissue factor.³ It is indicated for the treatment of factor VIII or IX deficiency and inhibitors in patients with hemophilia A and B, but it has been gaining widespread use in off-label applications as well, including the treatment of DIT. Reported off-label applications include the following:

- Trauma
- Hepatic failure
- Postprocedural bleeding (tooth extraction)
- Prior to liver transplantation
- Prior to invasive procedures, such as liver biopsy, GI endoscopy, or ethanol injection
- Reversal of warfarin effect
- Upper GI bleeding
- Platelet dysfunction
- Cardiac surgery
- Intracranial hemorrhage
- rVIIa may be used for rapid reversal of warfarin anticoagulation when vitamin K administration is insufficient¹⁴

New and Upcoming Treatments: Thrombopoietin Agents

Two new thrombopoietin agents are the newest agents for the treatment of thrombocytopenia.

Eltrombopag is the first nonpeptide, thrombopoietin-receptor agonist to be developed as a treatment for thrombocytopenia of various etiologies.¹⁵ It was approved by the FDA in November 2008 for the treatment of thrombocytopenia in patients with chronic immune (idiopathic) thrombocytopenic purpura who are refractory to first-line treatments. Eltrombopag stimulates thrombopoiesis, leading to increased platelet production.^{16,17}

Romiplostim is a thrombopoietin (TPO) peptide mimetic given by subcutaneous injection that activates the TPO receptor by binding to the distal hematopoietic receptor domain just like TPO.¹⁷ It was approved by the FDA in August 2008, also for the treatment of thrombocytopenia in patients with chronic immune (idiopathic) thrombocytopenic purpura who are refractory to alternative treatments.¹⁸

Both eltrombopag and romiplostim increase platelet count in healthy humans as well as in >80% of patients with immune thrombocytopenic purpura (ITP).¹⁷ Although initially restricted to the second-line treatment of ITP, these agents could potentially help treat many thrombocytopenic disorders in the future.¹⁷

Conclusion

DIT is a common, serious condition with increasing prevalence. Clinicians should include DIT consideration as an important component of the differential diagnosis of patients with thrombocytopenia. Once a diagnosis of DIT has been made, the offending agent(s) should be identified and removed, with appropriate treatment initiated.

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Additional contributing author: Kathleen Casey Krafon

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