Drug-induced thrombocytopenia in critically ill patients

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Thrombocytopenia occurs in 15% to 58% of intensive care unit patients. The incidence varies based upon patient population, timing and frequency of platelet monitoring, and definition of thrombocytopenia. Up to 25% of acutely ill patients develop drug-induced thrombocytopenia. When drug-induced thrombocytopenia is suspected, nondrug related causes must be evaluated and excluded. Establishing the diagnosis of drug-induced thrombocytopenia is challenging, as hundreds of medications have been implicated. Medications commonly associated with drug-induced thrombocytopenia include glycoprotein IIb/IIIa inhibitors, cinchona alkaloids, antibiotics, anticonvulsants, and heparin. Once the diagnosis is suspected, clinicians should identify the start date of medications to assess the timeline of development. The likelihood of each medication causing thrombocytopenia must be evaluated. The risk vs. benefit of discontinuing the suspected medication and availability of alternative medications must be assessed. The role of corticosteroids, immune globulin, and plasmapheresis is uncertain. Once the offending agent has been discontinued, the overall prognosis is excellent. In the case of suspected or confirmed heparin-induced thrombocytopenia, an alternative anticoagulant should be initiated. Drug-induced thrombocytopenia should be documented in the medical record and reported according to institutional and national standards. This review focuses on immune-mediated drug-induced thrombocytopenia from medications commonly utilized in the critically ill patient. (Crit Care Med 2010; 38[Suppl.]:S145–S154)

KEY WORDS: drug-induced thrombocytopenia; thrombocytopenia; critically ill; intensive care unit; critical care

Thrombocytopenia (TCY) occurs in 15% to 58% of intensive care unit (ICU) patients (1). The incidence varies based on the patient population, the timing and frequency of measurement, and the definition of TCY. TCY either occurring on ICU admission or developing during ICU stay has been independently associated with poor outcomes, including an increased length of stay, bleeding, and risk of death. Bleeding complications from TCY are similar regardless of the cause and include bruising, epistaxis, ecchymoses, petechiae, mucosal bleeding, bleeding from catheter sites, as well as life-threatening gastrointestinal and intracranial bleeding (1–3). Major bleeding occurs in 9% of patients with drug-induced thrombocytopenia (DIT), whereas minor bleeding occurs in 28% (4). The severity of bleeding is inversely proportional to the platelet count. Spontaneous bleeding is a concern when the platelet count is $<50 \times 10^9$/L. In addition to the quantitative TCY, qualitative defects in platelet function can also contribute to bleeding. TCY occurring in the ICU is frequently multifactorial, creating challenges in assessment of the cause (1–3).

DIT was initially described >140 yrs ago with quinine (5). The incidence of DIT is not well defined because reporting is voluntary and reports are not critically evaluated (6). Other challenges in identifying DIT include the multiple potential causes of TCY, lack of a standard definition of DIT, lack of or timing of platelet count monitoring to recognize DIT, and inappropriate over- and undersuspicion of DIT in clinical practice. Despite these limitations, an estimated 10 million persons per year are suspected of having DIT (5). Up to 25% of acutely ill patients have DIT. DIT commonly presents with moderate to severe TCY, with platelet counts of $<50 \times 10^9$/L, with nadirs sometimes $<20 \times 10^9$/L (7, 8). The mechanism of DIT is decreased platelet production from bone marrow suppression, increased platelet destruction, or platelet sequestration (7). DIT can develop from either nonimmune or immune causes. Nonimmune-mediated DIT is the result of bone marrow suppression from agents including antineoplastics, antivirals, ethanol, thiazide diuretics, and tolbutamide, and it develops slowly over a period of several weeks. In contrast, the median time from drug initiation to the development of TCY in immune-mediated DIT is 14 days, with a range of <1 day to 3 yrs (4, 7). In patients with previous exposure, TCY can occur within 1 to 3 days (7, 8).

Six different mechanisms of immune-mediated DIT have been described and are outlined in Table 1 (5, 7). Although rare, penicillin is known to cause TCY through a hapten-dependent mechanism. Penicillin binds covalently to the platelet membrane and elicits an immune response. Quinine and quinidine are known to cause TCY through an "innocent bystander" or drug-dependent antibody mechanism. Here, the antibody binds to the drug, which is noncovalently bound to platelet membrane glycoprotein (GP). The mechanism for antibody development in this type of immune-mediated DIT is not well understood. Tirofiban and eptifibatide bind to the GPIIb/IIIa receptor and induce a conformational change. This change exposes ligand-induced binding sites, which are recognized by naturally occurring antibodies. Abciximab, a mouse human monoclonal antibody,

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Table 1. Mechanisms of immune-mediated drug-induced thrombocytopenia

Mechanism	Description	Clinical Consequence	Special Laboratory Testing[a]	Prototype Drugs
Hapten-dependent	Drug (hapten) binds covalently to platelet membrane glycoprotein producing a neoepitope recognized by antibody	Hemorrhage	Drug-dependent platelet antibody assay	Penicillin, cephalosporins
Drug-glycoprotein complex (quinine-type)	Drug interacts noncovalently with platelet membrane glycoprotein; antibody bonds	Hemorrhage	Drug-dependent platelet antibody assay	Quinine, quinidine, nonsteroidal anti-inflammatory drugs, sulfonamides
Ligand-induced binding site (fiban-type)	Drug binds to platelet GPIIb/IIIa complex inducing conformational change elsewhere and formation of a neoepitope recognized by antibody	Hemorrhage	Drug-dependent platelet antibody assay	Eptifibatide, tirofiban, lotrafiban
Drug-specific antibody	Drug consists of chimeric Fab fragments against GPIIIa with a murine component that is recognized by antibody	Hemorrhage	Drug-dependent platelet antibody assay	Abciximab
Autoantibody	Drug induces an autoantibody that reacts with a platelet surface glycoprotein in the absence of the drug	Hemorrhage	Anti-platelet antibody assay (nonspecific)	Gold salts, procainamide
Immune complex	Drug reacts with platelet factor 4 to produce an antigenic complex against which antibodies react; resultingimmune complexes bind to platelet Fc receptors resulting in platelet activation	Thrombosis	Heparin-platelet factor 4 antibody assay	Unfractionated heparin, low- molecular-weight heparins

[a]See text for details regarding testing modalities.

Table 2. Nondrug causes of thrombocytopenia

Alcoholism
Anemia
Antiphospholipid syndrome
Blood transfusions/massive transfusion
Burns
Cardiopulmonary bypass
Disseminated intravascular coagulation
Extracorporeal membrane oxygenation
Hemolytic uremic syndrome/uremia
Human immunodeficiency virus
Hyperthyroidism
Hypothermia
Idiopathic thrombocytopenic purpura
Intra-aortic balloon pump
Liver disease/hypersplenism
Myelodysplastic or metastatic disease
Nutritional deficiencies
Paroxysmal nocturnal hemoglobinuria
Pregnancy
Primary hematologic disorder
Pseudothrombocytopenia
Renal replacement therapy
Sepsis/infection
Systemic lupus erythematosus
Thrombotic thrombocytopenic purpura
Vasculitis

Collated from references 2, 7, 9, and 10.

which contains Fab fragments specific for platelet GPIIIa, causes a drug-specific antibody formation. Antibodies react with the murine containing components of the chimeric molecule and result in platelet destruction. Gold salts and procainamide are capable of inducing platelet-specific autoantibodies that result in a clinical presentation similar to that of spontaneous autoimmune TCY. On occasion, antibodies can persist, resulting in prolonged TCY. Immune complex is the last mechanism of immune-mediated DIT. Heparin and low-molecular-weight heparin can bind to platelet factor 4 (PF4), producing an antigenic complex. Some patients form immunoglobin (Ig) G antibodies that bind to this complex and the Fc receptor on platelets. This binding results in platelet activation and destruction.

Establishing the diagnosis of DIT is challenging because hundreds of medications have been implicated (7). When DIT is suspected, nondrug related causes must be evaluated and excluded, including pseudothrombocytopenia, an *in vitro* clumping of platelets without clinical significance (2, 7, 9, 10) (Table 2). Once DIT is suspected, clinicians should identify the start date of medications to establish a clear understanding of the timeline of development. The likelihood of each medication causing TCY must be evaluated utilizing available literature. For noncytotoxic agents, George et al (4) developed a systematic approach for evaluating the causal nature of published cases of DIT. Results of this analysis are updated regularly and posted online at http://www.ouhsc.edu/platelets. Currently, the drug classes most often implicated in causing DIT include the GPIIb/IIIa inhibitors, cinchona alkaloids (quinidine and quinine), antibiotics, including sulfamethoxazole, and vancomycin, anticonvulsants, and sedatives (5). Other medications frequently suspected of causing DIT include heparin-related compounds, antineoplastic agents, ethanol, gold salts, antidiabetic agents, antiretrovirals, histamine 2 receptor antagonists (H2RAs), penicillin, and rifampin (3, 7, 9).

DIT is often suspected in clinical practice. Unfortunately, data evaluating medications causing DIT are often limited to retrospective or observational data. This review focuses on immune-mediated DIT caused by medications commonly used in the critically ill patient.

Heparin

Heparin is the medication most commonly associated with DIT (8). A nonimmune-mediated and an immune-mediated form of TCY occur from heparin. Nonimmune-mediated TCY occurs in 10% to 20% of patients receiving unfractionated heparin 1 to 4 days after initiation. Platelets typically do not decrease to $<100 \times 10^9$/L. Nonimmune-mediated TCY is not associated with hemorrhagic or thrombotic consequences, and heparin

can often be continued (11). Immune-mediated heparin-induced thrombocytopenia (HIT) occurs in approximately 1% of patients receiving unfractionated heparin, in 0.1% to 0.5% of patients receiving low-molecular-weight heparin, and can occur from exposure to heparin flushes and heparin-coated catheters. HIT increases the risk of venous and arterial thrombosis. An estimated 30% to 80% of patients have thrombotic sequelae. The reported incidence of venous thrombosis is four times more common than arterial thrombosis (11, 12). HIT is typically suspected when a patient has >50% decrease in platelet count between days 5 and 14 of therapy that is not otherwise explained. Three different onset time patterns of HIT have been reported. The majority of HIT cases develop approximately 4 to 10 days after exposure to the heparin-related product. Approximately 25% of patients have rapid-onset HIT as a result of recent heparin exposure. Delayed-onset HIT can occur days after heparin has been discontinued. The median platelet count in HIT is approximately 60×10^9/L (12, 13). HIT should also be suspected when patients have unexplained new thrombosis or thrombotic extension (a more likely presentation of HIT than TCY for ICU patients), skin lesions at the heparin injection sites, or anaphylactic symptoms after an intravenous bolus of heparin. Occlusion of the renal replacement filter may also be a sign of HIT. A bedside scoring system called the "four Ts" score is available to assess the clinical probability of immune-mediated HIT. The degree and timing of thrombocytopenia, presence of thrombosis, and other causes of TCY are assessed. Scores range from 0 to 8, with scores ≤3 having a high negative predictive value for HIT. This scoring system has not been validated in an ICU population (14).

HIT is the consequence of heparin-dependent platelet-activating IgG antibodies. Heparin binding to PF4 results in a conformational change and induction of IgG antibody production. The heparin/PF4/IgG complex activates platelets through the FcγIIa receptors. PF4 release through platelet activation perpetuates formation of immune complexes and results in further platelet activation. Activated platelets release microparticles, causing thrombin generation and a hypercoagulable state. Monocyte and endothelial activation are also believed to play a role in mediating HIT thrombosis through expression of tissue factor (12, 14).

The diagnosis of immune-mediated HIT requires confirmation of anti-PF4 heparin antibodies through either a functional assay such as the serotonin release assay or a PF4-dependent enzyme immunoassay (EIA). The specificity of the serotonin release assay is greater in detecting HIT antibodies than the EIA. The EIA is very sensitive, and a negative PF4 EIA rules out HIT in 99% of patients (12). The optical density result of the PF4 EIA can be useful. Values higher than one are more likely to indicate the presence of platelet-activating antibodies (3). The major limitation to confidently establishing the diagnosis of HIT in the United States is the lack of routinely available functional assay testing and the poor specificity of PF4 EIAs. The poor specificity of EIA is especially problematic in the cardiovascular surgery population, in which 25% to 50% of patients have heparin antibodies by EIA testing, but platelet activating antibodies are only found in 15% to 20% of patients (8, 15). Rapid immunoassays have been developed; however, their performance in comparison to standard testing has limited their use (12). Results of laboratory testing must be interpreted in conjunction with the clinical presentation.

Risk factors for HIT include the type of heparin product (unfractionated heparin > low-molecular-weight heparin), patient population (surgical > medical), and duration of therapy. In ICU patients, HIT is suspected more often than actually confirmed (3, 14, 16, 17). Verma et al (16) evaluated the frequency of laboratory-confirmed HIT in ICU coronary care unit patients receiving heparin therapy. Using serotonin release assay testing, the incidence of confirmed HIT was 0.39% (16). In a subsequent study, 33 of 261 medical–surgical ICU patients underwent serotonin release assay testing for suspected HIT, and 0% tested positive (3). PF4 EIA testing to confirm suspected HIT in medical–surgical ICU patients resulted in an incidence of HIT of 0.48% and 0.9% (14, 17). Specific ICU populations, which appear to have a higher incidence of HIT, include cardiothoracic surgery patients and those with mechanical circulatory support (i.e., ventricular assist devices) (18–20).

The optimal management strategy for suspected HIT in the ICU depends on the likelihood of the patient actually having HIT. Careful consideration of the probability of HIT is warranted as the potential for overdiagnosis is of concern. Probability categories for HIT in the ICU based on clinical and laboratory data along with recommended management strategies have been recently proposed and are outlined in Table 3 (14). If the diagnosis of HIT is confirmed, then documentation of the syndrome in the medical record is essential. If no thrombosis is evident, then a lower extremity Doppler ultrasound should be performed to detect any developing venous thrombosis. Initiation of direct thrombin inhibitor therapy in the ICU requires careful consideration of agent selection and initial dose. Unfortunately, data from the CATCH registry suggest there is often a delay in initiating direct thrombin inhibitor therapy (21). Clinician experiences with the agent and organ function are important considerations. Lepirudin may be preferred in patients with hepatic impairment with intact renal function. Dosage adjustment is required in patients with renal insufficiency. Argatroban is often the preferred agent in patients with renal impairment. Although bivalirudin is only approved by the Food and Drug Administration for HIT during cardiac interventions, its short half-life and minimal dependence on organ function for elimination are attractive characteristics for use in the critically ill patient. Experience with direct thrombin inhibitor therapy in the ICU setting suggests that lower doses are required to achieve therapeutic anticoagulation compared to a non-ICU setting (14, 20, 22, 23). Heart failure, organ dysfunction, postcardiac surgery status, and anasarca are additional factors suggesting slower elimination rates and lower dose requirements. Initiation of therapy at standard non-ICU doses may increase the risk of bleeding. Therapy should be adjusted to maintain the activated partial thromboplastin time within the therapeutic range. Direct thrombin inhibitor therapy should be continued until adequate platelet recovery. For patients with thrombosis, transition to warfarin will be needed, although this will typically occur after transfer out of the ICU, because warfarin should not be initiated in HIT until substantial platelet recovery occurs. Platelet transfusions should be avoided, because they may potentiate thrombosis (20).

GPIIb/IIIa receptor inhibitors

TCY is a well-documented side effect of GPIIb/IIIa inhibitors (5, 10, 24). In clinical trials, the incidence of TCY ranged from 0.3% to 5.5%, depending

Table 3. Probability of HIT in the intensive care unit

Probability of HIT	Clinical and Laboratory Findings	Recommended Action
Very unlikely	No TCY or other clinical features Positive PF4 EIA	Maintain heparin Monitor platelet counts Avoid antibody testing with low probability
	TCY and/or new thrombosis Negative PF4 EIA	Check other causes of TCY Ensure adequate anticoagulation Avoid repeat antibody testing unless TCY worsens
HIT is not ruled out	Platelet decrease may be explained by comorbidity Weak positive PF4 EIA (optical density <1.0)	Switch to alternate anticoagulant in prophylactic dose If DTI used start with 25%–50% of expected dose, adjust by aPTT Functional assay result negative or not available Guide treatment by response to alternate anticoagulant Confirm HIT with functional assay
HIT is probable	Unexplained platelet decrease	Stop heparin Initiate therapeutic dose PF4 EIA optical density >1.0, alternate anticoagulation Reduce dose if high bleeding risk Confirm HIT with functional assay
HIT very likely	New thrombosis and TCY with appropriate timing and without other causes Positive PF4 EIA	Stop heparin Initiate therapeutic dose, alternate anticoagulation Reduce dose if high bleeding risk Confirm HIT with functional assay

HIT, heparin-induced thrombocytopenia; TCY, thrombocytopenia; PF4, platelet factor 4; EIA, enzyme immunoassay; DTI, direct thrombin inhibitors; aPTT, activated partial thromboplastin time.
Adapted from Selleng et al (14).

on the agent and definition of TCY (abciximab, 0.4%–5.5%; tirofiban, 0.3%–1.5%; eptifibatide, 1.2%). The increased incidence with abciximab compared to the other agents is thought to be related to the chimeric Fab fragments (24–27). TCY on re-exposure can occur with any GPIIb/IIIa inhibitor, although it is more frequent with abciximab (28–30). In a registry of 1342 patients receiving abciximab, 5% had TCY (platelets $<100 \times 10^9$/L) and 2% had profound TCY (platelets $<20 \times 10^9$/L). Patients with abciximab exposure within the previous 30 days had an increased incidence and severity of TCY (31). The administration of eptifibatide or tirofiban to patients with a history of abciximab-induced TCY does not appear to be associated with an increased risk of TCY (24, 32).

The decrease in platelet count from GPIIb/IIIa inhibitors is usually severe and occurs rapidly, within hours of initial exposure (24, 32, 33). This rapid decrease in platelets is in contrast to most types of DIT (24, 33). Eptifibatide and tirofiban are reversible platelet inhibitors and are rapidly cleared from circulation after discontinuation. In contrast, abciximab is an irreversible platelet inhibitor and can be detected on circulating platelets for up to 2 wks after therapy. Therefore, TCY may occur several days after abciximab administration (6, 24, 32, 33). GPIIb/IIIa inhibitor-induced TCY may be accompanied by other systemic side effects, such as fever, chills, dyspnea, hypotension, and anaphylaxis (24).

Patients using GPIIb/IIIa inhibitor therapy should have their platelet count monitored frequently during therapy. Platelet count monitoring 2, 6, 12, and 24 hrs after initiation should identify most cases of acute TCY (24, 34). Because TCY may occur several days after discontinuation of abciximab, patients should receive discharge counseling on signs and symptoms of bleeding. Outpatient platelet monitoring is not routinely recommended (35). A low platelet count in patients receiving abciximab should be confirmed to rule out pseudothrombocytopenia (23, 24, 31). In clinical trials, pseudothrombocytopenia occurred in approximately 2% of patients. There are no reports of pseudothrombocytopenia related to eptifibatide or tirofiban (35).

Most patients with GPIIb/IIIa inhibitor associated TCY have no severe sequelae. However, TCY in a patient with decreased platelet function can pose the risk of serious bleeding. Bleeding ranges from none to a few petechiae, to oozing from sites of vascular access, to rare life-threatening bleeding such as intracranial hemorrhage (24, 32, 33, 36). Eptifibatide and tirofiban are reversible inhibitors of platelet aggregation and are cleared from the body within hours after discontinuation. Platelet recovery occurs rapidly, which explains the low incidence of clinically significant bleeding (24, 32, 33). Because abciximab is an irreversible inhibitor of platelet aggregation, related TCY may persist for 2 to 5 days after discontinuation (24, 25, 32). If TCY occurs (platelets $<100 \times 10^9$/L), then the GPIIb/IIIa inhibitor should be discontinued, platelets should continue to be monitored, and TCY should be properly managed utilizing platelet transfusions if necessary for significant bleeding (24, 32, 34). In addition to discontinuing the GPIIb/IIIa inhibitor, it may be necessary to discontinue anticoagulants and antiplatelets during the period of TCY to reduce potential bleeding (26, 37). In addition to bleeding complications, tirofiban- and eptifibatide-induced TCY with subsequent thrombosis has been reported (38, 39). Patients with GPIIb/IIIa inhibitor-induced TCY have increased morbidity and mortality compared to patients who do not have TCY (34, 37).

Data evaluating the use of corticosteroids or intravenous immunoglobulin (IVIG) for GPIIb/IIIa inhibitor-induced TCY are limited (35, 37). For life-threatening bleeding that has not responded to other interventions, emergent hemodialysis, charcoal hemoperfusion, and plasmapheresis may be considered for eptifibatide and tirofiban. Abciximab binds too tightly to the GPIIb/IIIa receptor and little free drug is present to be removed by these methods (37).

Screening for antibodies may decrease the incidence of TCY, because preexisting and naturally occurring antibodies may increase the risk (24). A positive human anti-chimeric antibody test at baseline in patients re-administered abciximab was associated with a significant increase in the incidence (14% vs. 4%; $p = .002$) and severity of TCY (31). However, laboratory screening for antibodies is not routinely available. Screening is unlikely to be cost-effective secondary to the low incidence of TCY, limited alternatives to

GPIIb/IIIa inhibitor therapy, short duration of TCY, and low risk of clinically significant bleeding (25). Prudent platelet count monitoring, early recognition of TCY, evaluation of other causes of TCY, timely discontinuation of GPIIb/IIIa inhibitor, and proper documentation of GPIIb/IIIa inhibitor-induced TCY on the medical record are essential to early recognition, management, and potential avoidance of TCY.

Heparin and GPIIb/IIIa inhibitors are the cornerstone of therapy in managing acute coronary syndrome. The Global Registry of Acute Coronary Events was utilized to identify the rates of recognition of TCY in patients with acute coronary syndrome and the associated outcomes in a real-world setting (40). This retrospective, observational evaluation was based on data from 52,647 patients, managed at 115 hospitals, with acute coronary syndrome between 2000 and 2007. One hundred fifty-two (0.3%) patients had HIT, 324 (0.6%) had GPIIb/IIIa inhibitor-associated TCY, and 368 (0.7%) had TCY not associated with either heparin or GPIIb/IIIa inhibitors.

For patients receiving both heparin and GPIIb/IIIa inhibitor, the timing and severity of TCY helps distinguish the causative agent. An abrupt decrease in platelet count to $\leq 10 \times 10^9$/L is likely secondary to GPIIb/IIIa inhibitor and not HIT (41). Proper identification of the cause of TCY is imperative because the management of HIT and GPIIb/IIIa inhibitor-induced TCY differ.

Antibiotic-induced TCY

Use of antibiotic agents is common in the ICU, with up to 70% of patients receiving them (42). The incidence of antibiotic-induced TCY in the ICU population is unknown because the majority of data are observational or retrospective. Antibiotic-induced TCY is a complication that is frequently unrecognized in the ICU because of numerous concurrent disease states, including infection and other medications known to cause TCY. Sepsis is the leading cause of TCY in critically ill patients (11). The timing of TCY may help differentiate the etiology. Typically, 5 to 7 days are needed to develop sensitization to an antibiotic after first exposure, whereas disseminated intravascular coagulopathy from sepsis usually occurs within the initial few days (6, 43). In one prospective, observational study of 262 patients with severe sepsis or septic shock, six patients (2.3%) had antibiotic-related TCY, defined as a platelet count $<100 \times 10^9$/L. Five patients received β-lactam antibiotics and one received vancomycin. TCY developed a median of 6 days after antibiotic initiation. Despite recognition of TCY, antibiotic therapy was deemed effective and was continued for a minimum course of 7 days. After discontinuation of antibiotics, platelet counts gradually increased. All patients survived with complete platelet count recovery. One patient experienced trivial bleeding. If TCY occurs during the treatment of severe sepsis or septic shock, then the authors (43) suggest continuing effective antibiotics to complete a 7- to 10-day treatment course while closely monitoring platelet count. This recommendation takes into consideration data demonstrating a delay in effective antibiotics in septic shock is associated with a measurable increase in mortality (44). When evaluating potential antibiotic-associated TCY, the risk of discontinuing the antibiotic and the availability and effectiveness of alternative antibiotic options must be carefully assessed. Antibiotics commonly prescribed to ICU patients and reported as causing TCY are further discussed.

Linezolid

Linezolid is the antimicrobial most likely to cause TCY (42, 45). The mechanism of TCY is not fully understood, although potential mechanisms include direct myelosuppression and immune-mediated platelet destruction (46). During clinical trials, TCY (<75% of the lower limit of normal and/or baseline platelet count) was observed in 2% of patients and appeared to be duration- and dose-dependent (45, 47). The incidence of TCY in postmarketing surveillance is much higher. In a compassionate-use program evaluation, the incidence of TCY was 2% in patients receiving ≤14 days of therapy, 5% in patients receiving 15 to 28 days of therapy, and 7% in patients receiving >28 days of therapy (48). A retrospective evaluation of 19 patients identified TCY (platelet count $< 100 \times 10^9$/L) in 32% in patients who received linezolid >10 days (median duration, 19 days). The average decrease in platelet count was 65%. Gastrointestinal bleeding was observed in one patient, and four patients required platelet transfusions. Platelet counts continued to decrease in all cases after linezolid was discontinued but eventually recovered 4 to 13 days after discontinuation (49). In a subsequent prospective, observational study of 20 patients receiving linezolid, TCY (platelet count $<150 \times 10^9$/L) occurred in 35% (n = 7). The mean decrease in platelet count was 38% after an average duration of 40 days (range, 15–83 days). TCY resolved 7 to 10 days after linezolid was discontinued, with no related adverse clinical effects reported (50).

Baseline platelet count may be a predictor of TCY in patients receiving linezolid. The incidence of worsening TCY in patients with baseline TCY (median baseline platelet count, 30×10^9/L) was 78% in one study with a median reduction in platelet count of 43% (51). In a subsequent prospective study, multivariate analysis revealed pretreatment platelet count as the only independent predictor of TCY (52). End-stage renal disease may also increase the risk of linezolid-induced TCY (53). A retrospective analysis of the relationship between renal function and linezolid-induced TCY was evaluated in 20 patients. Creatinine clearance was a significant predictor of TCY, with the accumulation of a metabolite suspected (54). A retrospective, case-controlled study evaluated the incidence of TCY in 17 patients with renal insufficiency receiving linezolid. TCY (platelet count $<100 \times 10^9$/L) occurred significantly more frequently in patients with renal insufficiency (65% vs. 36%; $p = .039$) (55). In a retrospective case-controlled study of 28 patients with end-stage renal disease on hemodialysis receiving an average 16 days of linezolid, 40% of patients had therapy discontinued prematurely secondary to TCY. The end-stage renal disease group had a higher incidence of severe TCY, defined as a platelet count $<100 \times 10^9$/L (79% vs. 43%; $p = .003$) and a significantly lower platelet count (62×10^9/L vs. 149×10^9/L; $p < .001$). End-stage renal disease was determined to be an independent risk factor for TCY (odds ratio, 6.14; 95% confidence interval, 1.63–23.26; $p = .007$) (56).

The manufacturer of linezolid recommends that complete blood counts be monitored weekly, particularly in those with duration of therapy >2 wks, preexisting myelosuppression, concomitant drugs that produce bone marrow suppression, or chronic infection who have received previous or concomitant antibiotic therapy. The manufacturer also recommends considering discontinuing linezolid in patients who have myelosup-

pression or have worsening myelosuppression (47). Pyridoxine has been used successfully to treat two cases of linezolid-induced anemia and TCY; however, further investigations failed to depict a benefit (57–59).

Vancomycin

Vancomycin may be an under-recognized cause of TCY. Case reports support an immune-mediated mechanism and suggest that there may be an anamnestic response after previous exposure (60, 61). Both hapten-dependent and innocent bystander mechanisms have been postulated (62, 63). Von Drygalski et al (62) described 29 patients with a clinical suspicion and laboratory confirmation of vancomycin-induced TCY over a 5-yr period. Vancomycin-dependent, platelet-reactive antibodies were present in all patients. Sixteen patients had only IgG antibodies, three had only IgM antibodies, and 10 had both IgG and IgM antibodies. Platelet counts decreased a mean of 93% during vancomycin therapy. The mean platelet count nadir of 13×10^9/L was reached an average of 8 days after therapy initiation. Platelet counts returned to 150×10^9/L an average of 8 days after vancomycin discontinuation. Severe TCY persisted the longest in patients with impaired renal function, possibly as a result of reduced clearance. Two patients inadvertently re-exposed to vancomycin had an immediate and severe decrease in platelet count. Ten patients experienced severe bleeding, including florid petechial hemorrhages, ecchymoses, oozing from buccal mucosa, gross hematuria, lower gastrointestinal hemorrhages, intrapulmonary hemorrhages, and excessive bleeding from venipuncture sites (62). In a subsequent prospective observational study of 52 patients receiving vancomycin, TCY (platelet count $<150 \times 10^9$/L) occurred in 11 patients (21%). One patient had previous exposure to vancomycin within the previous month. The mean decrease in platelet count was 39% after an average duration of 30 days of vancomycin therapy. The projected rate of TCY was 5.1 cases per 1000 days of therapy. No adverse clinical effect was attributable to TCY (50).

β-Lactams

In vitro and *in vivo* studies have demonstrated that β-lactams inhibit platelet aggregation and prolong bleeding times to varying degrees (64, 65). *In vitro* data suggest that this inhibition is dose-dependent and reversible (64). β-Lactams have also been reported to cause TCY (42, 65). The mechanism causing TCY is unique to the β-lactam, in which the hapten binds covalently to the membrane glycoprotein to induce a drug-specific immune response (6, 9). A retrospective, case-controlled study of patients hospitalized for TCY between 1990 and 2002, using the PHARMO Record Linkage System (a database that includes one million residents in the Netherlands and enables follow-up of prescription medication use, both inpatient and outpatient, and hospitalizations), revealed that the current use of β-lactam antibiotics was associated with an increased risk of TCY (odds ratio, 7.4; 95% confidence interval, 1.8 –29.6) (66). TCY has been associated with piperacillin more frequently than other penicillins (67). Piperacillin-related TCY is described by a reported case of a 69-yr-old woman who had a petechial rash after 11 days of piperacillin/tazobactam therapy and a decrease in platelet count from 353×10^9/L to 15×10^9/L. Piperacillin/tazobactam was discontinued and platelet count increased to 208×10^9/L 3 days after discontinuation. Antibodies to platelets were detected but only in the presence of piperacillin. Three months after discontinuation, the platelet count remained normal and the platelet antibodies were no longer detected (68).

Trimethoprim/sulfamethoxazole

The incidence of trimethoprim/sulfamethoxazole (TMP/SMX)-induced TCY is estimated at one in 25,000 patients (69). The mechanism responsible is not fully established; however, an immune-mediated mechanism is suggested (33, 70). A retrospective analysis of DIT reported to the Danish Committee on Adverse Drug Reactions between 1968 and 1991 revealed 23 reports of TMP/SMX-induced TCY. The average onset of TCY was 9 days, average platelet nadir was 8×10^9/L, and average time to platelet recovery was 7 days (71). There are several case reports of TMP/SMX-induced TCY in the literature. The following cases represent the clinical picture of TMP/SMX-induced TCY. Yamreudeewong et al (72) describe a 54-yr-old woman with severe petechiae and TCY (platelet count 2×10^9/L) after 10 days of TMP/SMX therapy for a sinus infection. Coagulation tests and other blood counts were within normal range. Her platelet count increased to 110×10^9/L 4 days after TMP/SMX was discontinued. The patient received 2 U of platelets and oral prednisone (72). A 58-yr-old man had bruising 8 days after initiation of TMP/SMX for a urinary tract infection. The TMP/SMX was discontinued. He subsequently presented to the hospital with purpuric lesions and rhinorrhagia. Complete blood count, chemistry panel, and coagulation test results were normal, except for a platelet count of $<5 \times 10^9$/L. A bone marrow biopsy revealed increased megakaryocytes. Prednisone 1 mg/kg daily was initiated, and the TCY resolved within 2 wks (70).

Rifampin

Immune-mediated rifampin-induced TCY is a rare complication that has been described in case reports. Pereira et al (73) describe a 28-yr-old man using rifampin for 4 mos to treat pulmonary tuberculosis. He presented with petechiae, ecchymoses, and a platelet count of 7×10^9/L. Rifampin was discontinued, and the patient was treated with platelet transfusions and prednisone. Six days later, the platelet count increased to 317×10^9/L. Using flow cytometry and immunoassays, immune-mediated TCY was confirmed (73). Another case involved a 76-yr-old man receiving rifampin for *Mycobacterium kansasii*. His platelet count decreased from 232×10^9/L to 85×10^9/L over 2 mos, and rifampin was discontinued. Two weeks after discontinuation, the platelet count normalized and the patient was rechallenged. The following day, the platelets decreased and rifampin was discontinued. Two weeks after discontinuation, the patient was discharged with a normal platelet count (74).

Fluoroquinolones

Fluoroquinolones, which are structurally similar to quinine, may be an under-recognized cause of DIT. Most DIT reviews fail to include fluoroquinolones (75). In clinical trials, the incidence of reported TCY was <1% (76–78). A literature review identified 29 probable or definite cases of fluoroquinolone-induced TCY utilizing the criteria developed by George et al (4). The mean platelet nadir of 25×10^9/L occurred after an average of 10 days. Platelets recovered a mean of 8 days after fluoroquinolone discontinua-

tion. Minor bleeding occurred in 10 patients. Three patients were treated with corticosteroids, and two patients received platelet transfusions with intravenous Ig. All patients survived. Cheah et al (75) further described a case in detail. A 76-yr-old man admitted to the ICU with community- acquired pneumonia was treated with ciprofloxacin. Platelets decreased from 171 $\times$ 10^9/L to 120 $\times$ 10^9/L over 4 days. Ciprofloxacin was discontinued and platelets increased to 200 $\times$ 10^9/L. Thirty days later, the patient received one dose of ciprofloxacin, and platelets decreased from 285 $\times$ 10^9/L to 40 $\times$ 10^9/L within 12 hrs. Platelet-reactive antibodies were present. Platelets increased to 172 $\times$ 10^9/L 6 days after ciprofloxacin was discontinued (75).

H2RAs

In ICU patients, H2RAs are frequently the first medication suspected of causing TCY and are routinely substituted with a proton pump inhibitor when platelets decrease. The incidence of H2RA induced TCY is unknown; however, it is potentially overly suspected. The literature evaluating H2RA-induced TCY is limited to case reports and case-controlled studies. In an evaluation of 29 published case reports (69% involving cimetidine), 90% of patients had at least one additional independent risk factor for TCY. The average duration of therapy was 14 days, during which platelets decreased an average of 82% to a mean platelet nadir of 39 $\times$ 10^9/L. The mean time to platelet recovery was 7 days after discontinuation (79). A retrospective review of 50 neurosurgical patients found an increased incidence of TCY in patients who received famotidine (34% vs. 11%; $p = .002$). The mean time to development of TCY (platelet count $<150 \times 10^9$) was 2 days. Platelets recovered without discontinuation of famotidine in 53% of patients. No patients required transfusions, and no clinical sequelae developed (80). The mechanism of H2RA-induced TCY is proposed to be either direct bone marrow suppression or the development of platelet antibodies (79, 81). There are conflicting data regarding the potential for cross-reactivity among H2RAs (82, 83).

Valproic acid

TCY is the most common hematologic abnormality associated with sodium valproate therapy, regardless of the indication (84, 85). Sodium valproate can also impair platelet function and increase bleeding time. The overall incidence of TCY is 5% to 40%, with some reports suggesting a relationship to dose; however, TCY can occur at therapeutic levels. Several mechanisms have been proposed, including peripheral platelet destruction, damage to the platelet membrane, and immune-mediated destruction. TCY typically develops after several months of therapy. Bleeding is uncommon because the level of platelet count decrease usually is not severe. TCY typically resolves within a few days after dose reduction. Drug discontinuation typically is not needed. Platelet count monitoring is recommended on initiation of therapy and at quarterly intervals.

Phenytoin

Thrombocytopenia from phenytoin is presumed to be immune-mediated. A literature search between 1970 and 1995 revealed <50 case reports of phenytoin-induced TCY (86). Holtzer et al (86) described a 36-yr-old neurosurgical patient whose platelet count decreased from 287 $\times$ 10^9/L to 8 $\times$ 10^9/L 15 days after phenytoin initiation (level 20 mg/L). There were no signs of bleeding. Phenytoin discontinuation and platelet transfusions were unsuccessful, and IVIG was initiated. After two doses, the platelet count increased to 255 $\times$ 10^9/L (86). Another neurosurgical case involved a 66-yr-old woman. The patient had received 5 days of phenytoin prophylaxis when she underwent resection of an intracranial tumor. The preoperative platelet count was 186 $\times$ 10^9/L. Four hours after the operation, the patient was taken back to surgery for an intracranial hemorrhage at the operative site. The platelet count was 2 $\times$ 10^9/L, hemoglobin was 8.9 g/dL, and clotting times were normal. Phenytoin was discontinued and platelets were transfused. On postoperative day 3, platelets increased to 80 $\times$ 10^9/L. The patient died of complications on postoperative day 5 (87). Another case report described an 8-yr-old girl who had fever, rash, thrombocytopenia, and leukopenia 19 days after phenytoin initiation. Her platelet count was 16 $\times$ 10^9/L and phenytoin level was 20.4 mg/L. Phenytoin was discontinued and IVIG was administered. Platelet count increased to 66 $\times$ 10^9/L and 106 $\times$ 10^9/L 24 and 48 hrs after IVIG administration, respectively. After 3 mos, the platelet count remained stable at 182 $\times$ 10^9/L (88).

Antiarrhythmics

Amiodarone and extended-release procainamide have been reported to cause TCY. Weinberger et al (89) reported two cases of amiodarone-induced TCY, which were confirmed by re-challenge and a strongly positive lymphocyte stimulation test. Extended-release procainamide has been reported to cause platelet counts $<15 \times 10^9$/L in several reports (90, 91). The onset to thrombocytopenia development in one case series averaged 40 days (range, 9–71 days), with a mean time to platelet count normalization of 8 $\pm$ 3 days (91). An immune-mediated mechanism has been suggested.

Diazepam

Diazepam is not frequently associated with DIT. Cimo et al described a 45-yr-old woman treated with penicillin, chlorpheniramine, and diazepam. One week later she had petechiae and ecchymosis, with a platelet count of 10 $\times$ 10^9/L. Prednisone was initiated and platelets were increased to 500 $\times$ 10^9/L over 7 days. Prednisone was discontinued and platelets remained normal. Testing revealed the presence of diazepam-dependent platelet antibodies (92).

Management of DIT

On suspicion of DIT, the timing and severity of TCY should be assessed and the available literature should be utilized to determine probability. Other causes of TCY, including pseudothrombocytopenia, should be excluded. In clinical practice, medications may be inappropriately assumed to be the cause of TCY or may be inadvertently not considered. Both extremes occur because TCY is often multifactorial. The literature on DIT is mainly observational and retrospective, with a significant portion being limited to case reports. The risk vs. benefit of discontinuing the suspected medication and the availability of alternatives must be evaluated. If the perceived consequence of TCY is greater than the risk of discontinuing the medication, then the offending medication should be immediately discontinued or substituted with an agent of different chemical structure. Eliminating suspected medications one at a time may provide the most useful infor-

mation if the patient's condition allows (i.e., TCY is not severe) (6, 9). There are tests to detect the presence of various drug-dependent antibodies; however, they are not readily available, delays in results limit the usefulness, and the presence of antibodies does not necessarily predict a reaction. Lack of sensitivity and specificity are also problematic. The current role of testing is limited to the potential prevention of future episodes of DIT (9).

After drug discontinuation, bleeding typically ceases in 1 to 2 days. The median time to platelet count recovery in immune-mediated DIT is 4 to 10 days (4–6). In patients with compromised organ function, the time to recovery may be prolonged. If platelets have not recovered within 2 wks, then the cause may be multifactorial and should be re-evaluated. In some cases, TCY may persist for weeks. Re-challenge for the sole purpose of establishing a diagnosis should be avoided. Platelet transfusions can be administered to symptomatic patients with DIT or in patients at risk for spontaneous intracranial hemorrhage from severe TCY (3, 9). Platelet transfusions should be avoided in patients with HIT and direct thrombin inhibitor therapy should be initiated (19). The overall prognosis, once the offending agent has been discontinued, is excellent (3, 9). The roles of corticosteroids, IVIG, and plasmapheresis in DIT are uncertain, with experience limited to isolated cases or case series. Currently, there is no role for platelet growth factors (5, 9).

Once diagnosed, DIT should be documented in the medical record and reported according to institutional guidelines. The adverse drug reaction should also be reported to the manufacturer and regulatory agencies. Clinicians are encouraged to publish convincing case reports of DIT in order to strengthen the body of literature available.

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