

## REVIEW ARTICLE

## CURRENT CONCEPTS

## Drug-Induced Immune Thrombocytopenia

Richard H. Aster, M.D., and Daniel W. Bougie, Ph.D.

From the Department of Medicine, Medical College of Wisconsin (R.H.A.), and the Blood Research Institute, BloodCenter of Wisconsin (R.H.A., D.W.B.) — both in Milwaukee. Address reprint requests to Dr. Aster at the Blood Research Institute, BloodCenter of Wisconsin, 8727 Watertown Plank Rd., Milwaukee, WI 53226-3548, or at richard.aster@bcw.edu.

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**D**RUG-INDUCED THROMBOCYTOPENIA CAN BE CAUSED BY DOZENS, PERHAPS hundreds, of medications. Because thrombocytopenia can have many other causes, the diagnosis of drug-induced thrombocytopenia can easily be overlooked. On occasion, outpatients with drug-induced thrombocytopenia are treated for autoimmune thrombocytopenia and can have two or three recurrences before the drug causing the disorder is identified.<sup>1</sup> In acutely ill, hospitalized patients, drug-induced thrombocytopenia can be overlooked because thrombocytopenia is attributed to sepsis, the effect of coronary-artery bypass surgery, or some other underlying condition. Although drug-induced thrombocytopenia is uncommon, it can have devastating, even fatal consequences that can usually be prevented simply by discontinuing the causative drug. It is therefore important that clinicians have a general understanding of this condition and the drugs that can cause it.

In this review, we focus on conditions in which exposure to a drug leads to the destruction of circulating platelets, often accompanied by bleeding symptoms. We do not consider thrombocytopenia resulting from dose-dependent hematosuppression, which often occurs after treatment with chemotherapeutic and immunosuppressive agents such as cisplatin and cyclophosphamide.<sup>2</sup> Although heparin-induced thrombocytopenia is the most common drug-related cause of a drop in the platelet count, we do not discuss this condition because of its complexity and because thrombosis, rather than thrombocytopenia, is the major threat to an affected patient. Because heparin is often given together with certain drugs that are likely to cause drug-induced thrombocytopenia (platelet inhibitors and vancomycin), it is important to distinguish between heparin-induced thrombocytopenia and drug-induced thrombocytopenia. Heparin-induced thrombocytopenia was recently reviewed in the *Journal*.<sup>3</sup>

Drug-induced platelet destruction is usually caused by drug-induced antibodies, but this can be difficult to prove. In this review, we include many conditions for which an immune cause has not yet been fully documented. Although platelets are the preferred targets of drug-induced antibodies, drugs can also cause immune hemolytic anemia<sup>4</sup> and neutropenia<sup>5</sup> through similar mechanisms.

## PRESENTATION

Acute thrombocytopenia after exposure to quinine was recognized as a clinical entity about 140 years ago.<sup>6</sup> Subsequently, many other medications were implicated in the development of this condition. Quinine, which is rarely used now as an antimalarial drug but is often prescribed for nocturnal muscle cramps, may still be the most common trigger. People of any age and either sex can be affected.

The course of drug-induced thrombocytopenia in a representative patient is shown in Figure 1. Typically, a patient will have taken the sensitizing drug for about 1 week or intermittently over a longer period before presenting with petechial

hemorrhages and ecchymoses that are indicative of thrombocytopenia. Occasionally, symptoms develop within 1 or 2 days after what is apparently the first exposure to a drug, particularly in patients given platelet inhibitors such as abciximab who may have preexisting, perhaps naturally occurring, antibodies.<sup>7</sup> Systemic symptoms such as lightheadedness, chills, fever, nausea, and vomiting often precede bleeding symptoms. Severely affected patients have florid purpura and bleeding from the nose, gums, and gastrointestinal or urinary tract (“wet purpura”). In such cases, thrombocytopenia is invariably severe (<20,000 platelets per cubic millimeter).

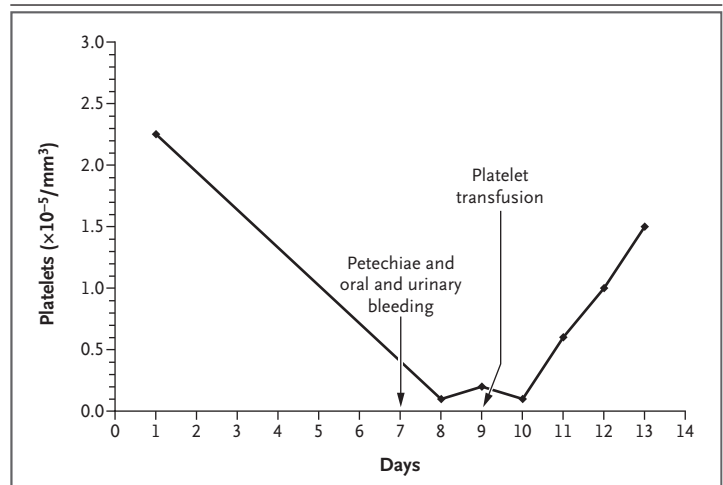
If the causative medication is stopped, symptoms usually resolve within 1 or 2 days, and the platelet count returns to normal in less than a week. For reasons that are poorly understood, patients with drug-induced thrombocytopenia occasionally present with disseminated intravascular coagulation<sup>8</sup> or renal failure and other findings indicative of the hemolytic-uremic syndrome or thrombotic thrombocytopenic purpura.<sup>9</sup>

#### INCIDENCE

The incidence of drug-induced thrombocytopenia is not well defined, in part because reporting is voluntary and is not critically reviewed. On the basis of several epidemiologic studies in the United States and Europe, the estimated minimum incidence is about 10 cases per million population per year but the number could be higher in selected groups, such as hospitalized patients and elderly people.<sup>10</sup> A case-control study of patients in Massachusetts, Rhode Island, and Philadelphia showed that during each week of exposure, trimethoprim-sulfamethoxazole and quinine-quinidine caused thrombocytopenia in 38 and 26 of every 1 million users, respectively.<sup>11</sup> Since these drugs carry relatively high risks of drug-induced thrombocytopenia, the rate at which most drugs cause the condition is probably lower. However, a few drugs (including abciximab and gold salts) cause immune thrombocytopenia in about 1% of patients.

#### CAUSATIVE AGENTS

Many of the drugs shown in multiple studies to be capable of causing drug-induced thrombocytopenia are listed in Table 1, but at least 100 others



**Figure 1. Course of Immune Thrombocytopenia in a Patient Treated with Sulfamethoxazole.**

Trimethoprim-sulfamethoxazole was prescribed for treatment of a urinary tract infection in a 29-year-old woman. On day 7 of treatment, petechiae and ecchymoses, buccal hemorrhage, and gross urinary bleeding developed, and the antibiotic treatment was stopped. Her platelet count was 4000 per cubic millimeter. A platelet transfusion given on day 9 had little effect on the platelet count. Sustained recovery occurred during the next few days. A strong sulfamethoxazole-dependent, platelet-reactive antibody was detected in a blood sample obtained on day 9 and was still present after 3 months and after 5 years. No trimethoprim-dependent antibodies were detected.

have been implicated.<sup>2,12,13</sup> Many of the drugs that are common triggers for this disorder also cause sensitivity reactions involving the skin and other organs.<sup>14</sup>

George and colleagues critically analyzed reports of drug-induced thrombocytopenia published through 2005<sup>13,15</sup> and identified 85 medications for which a cause-and-effect relationship was considered to be “definite” (58 agents) or “probable” (27 agents) on the basis of clinical criteria (Table 2).<sup>13</sup> (A compendium of implicated drugs and case reports updated through August 2004 is available at <http://moon.ouhsc.edu/jgeorge/DITP.html>.) In the analysis by George et al., no weight was given to laboratory demonstration of drug-dependent antibodies. As improved techniques are developed, serologic testing may become increasingly useful for identifying the specific cause of thrombocytopenia in individual cases — albeit after the fact.

Rare but convincing examples of drug-induced thrombocytopenia induced by herbal remedies<sup>16,17</sup> and foods<sup>18</sup> have been described, and there are numerous reports of acute, severe thrombocyto-

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

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

\* For a more extensive list, see Aster,<sup>2</sup> Warkentin,<sup>12</sup> and George et al.<sup>13</sup> and the University of Oklahoma Web site (<http://moon.ouhsc.edu/jgeorge/DITP.html>).

**Table 2. Criteria and Level of Evidence for Establishing a Causative Relationship in Drug-Induced Thrombocytopenic Purpura.\***

Criterion and Level of Evidence	Description
Criterion	
1	Therapy with the candidate drug preceded thrombocytopenia, and recovery from thrombocytopenia was complete and sustained after discontinuation of therapy.
2	The candidate drug was the only drug used before the onset of thrombocytopenia, or other drugs were continued or reintroduced after discontinuation of therapy with the candidate drug, with a sustained normal platelet count.
3	Other causes of thrombocytopenia were ruled out.
4	Re-exposure to the candidate drug resulted in recurrent thrombocytopenia.
Level of evidence	
I	Definite — criteria 1, 2, 3, and 4 are met.
II	Probable — criteria 1, 2, and 3 are met.
III	Possible — criterion 1 is met.
IV	Unlikely — criterion 1 is not met.

\* The information is adapted from George et al.<sup>13</sup>

penia after injection of iodinated contrast medium for radiographic studies.<sup>12,13</sup> Whether immune mechanisms are involved is unknown.

Severe thrombocytopenia and other signs and symptoms of thrombotic thrombocytopenic purpura develop in approximately 1 of every 2500 patients treated with the platelet inhibitor ticlopidine and a much smaller fraction of those given the closely related drug clopidogrel, usually after 1 to 2 weeks of treatment.<sup>19</sup> The responsible mechanisms have not yet been defined. Acute,

severe, usually self-limited thrombocytopenia has been described in patients treated with recently developed monoclonal antibodies such as infliximab (anti-tumor necrosis factor- $\alpha$  antibody), efalizumab (anti-CD11a antibody), and rituximab (anti-CD20 antibody).<sup>2</sup> No causative mechanism has yet been identified.

Certain drugs, such as the antiepileptic agent valproate,<sup>20</sup> the cardiac agent amrinone,<sup>21</sup> and the antibiotic linezolid,<sup>22</sup> induce low-grade thrombocytopenia in up to 30% of patients receiving long-

term treatment; the mechanisms of action may be nonimmune but are poorly understood. The decrease in platelets is rarely severe enough to require treatment.

Although chemotherapeutic and immunosuppressive agents typically cause thrombocytopenia by suppressing hematopoiesis, they can also cause immune thrombocytopenia.<sup>23</sup> Drug-induced thrombocytopenia should be suspected, therefore, in patients treated with such drugs if there is an acute drop in the platelet level after exposure. Immune thrombocytopenia caused by vancomycin is probably more common than is generally recognized, and it is easily overlooked in seriously ill patients because the low platelet count can be attributed to other causes.<sup>24</sup> In rare cases, the quinine in tonic water or an aperitif causes immune thrombocytopenia (“cocktail purpura”).<sup>25</sup>

#### PATHOGENESIS

Drug-induced thrombocytopenia, like other idiosyncratic drug-sensitivity reactions, affects only a small fraction of patients taking medications that can trigger the disorder. No predisposing genetic or environmental factors have been identified, and no suitable animal models are available. Mechanisms by which drugs are thought to cause immune thrombocytopenia are summarized in Table 3.

#### THROMBOCYTOPENIA INDUCED BY QUININE AND OTHER DRUGS

The hallmark of thrombocytopenia induced by quinine and many other drugs is a remarkable antibody that binds tightly to normal platelets only in the presence of the sensitizing drug. The epitopes targeted by these antibodies usually reside on glycoprotein IIb/IIIa or Ib/V/IX complexes, the major platelet receptors for fibrinogen and von Willebrand factor, respectively.<sup>26,27</sup>

Small molecules, like drugs, are thought to be immunogenic only when linked covalently to a large carrier molecule, usually a protein. Antibodies induced by drug-protein adducts are largely specific for the drug (or the small molecule, called the hapten), although some antibodies recognize the drug and its carrier molecule.<sup>28</sup> Accordingly, early investigators assumed that drug-dependent antibodies found in patients with drug-induced thrombocytopenia were hapten-specific (or drug-specific). This may be true of antibodies that cause hemolytic anemia in patients treated with massive doses of penicillin<sup>29</sup> and perhaps some of those that cause thrombocytopenia in patients given penicillin-like drugs.<sup>30</sup> However, serologic studies in patients with drug-induced thrombocytopenia caused by other drugs failed to support this concept.<sup>31</sup> An alternative hypothesis was that the drug reacts directly with the antibody to produce immune complexes that somehow target

**Table 3. Mechanisms Underlying Drug-Induced Immune Thrombocytopenia.\***

Classification	Mechanism	Incidence	Examples of Drugs
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 antiinflammatory drugs
Fiban-type drug	Drug reacts with glycoprotein IIb/IIIa to induce a conformational change (neoepitope) 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 glycoprotein IIIa	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

\* The information is adapted from Aster.<sup>2</sup>

platelets and cause their destruction.<sup>31</sup> However, these hypothetical drug–antibody complexes were never demonstrated experimentally, and it was later found that drug-dependent antibodies, like other antibodies, react with platelets through their Fab domains rather than through their Fc domains, as would be expected of immune complexes.<sup>32,33</sup> Other possibilities considered were that the drug reacts with the target protein to produce a compound epitope (part drug, part protein) for which the antibody is specific<sup>34,35</sup> and that the drug induces a conformational change in the protein, creating a new target epitope elsewhere in the molecule.<sup>2,36</sup>

A recently proposed model aimed at reconciling several of these hypotheses<sup>37</sup> suggests that drug-dependent antibodies are derived from a pool of naturally occurring antibodies with weak affinity for self antigens,<sup>38</sup> residing in this case on certain platelet membrane glycoproteins. According to this model, the interaction between these low-affinity antibodies and their target antigens is too weak to affect blood cells under normal circumstances. However, certain drugs affect both antibody and antigen in such a way that the strength of the interaction is greatly increased (Fig. 2). When a B cell expressing such an antibody is induced to proliferate and undergo affinity maturation in a patient taking the medication, the resulting antibody can destroy the targeted blood cell if the drug is present.<sup>37</sup> This model suggests that whether the drug binds first to the antibody or to the targeted membrane protein depends simply on its relative affinity for one component or the other.

#### THROMBOCYTOPENIA INDUCED BY PLATELET INHIBITORS

Acute thrombocytopenia, usually mild but occasionally life-threatening, is a common complication of treatment with the platelet inhibitors tirofiban and eptifibatide, which are widely used to prevent restenosis after coronary angioplasty.<sup>7</sup> These ligand-mimetic drugs (“fibans”) inhibit thrombosis by binding to a specific site on the platelet  $\alpha_{IIb}/\beta_3$  integrin (glycoprotein IIb/IIIa) and competitively inhibiting platelet–fibrinogen interaction.<sup>7</sup> Antibodies causing thrombocytopenia in patients given these agents probably recognize structural changes (neoepitopes) induced in the  $\alpha_{IIb}/\beta_3$  integrin when a fiban binds to it, but this theory has not been formally proved. Curiously,

these antibodies can occur naturally, creating the possibility that thrombocytopenia will arise within a few hours after the patient’s first exposure to the drug.<sup>7</sup>

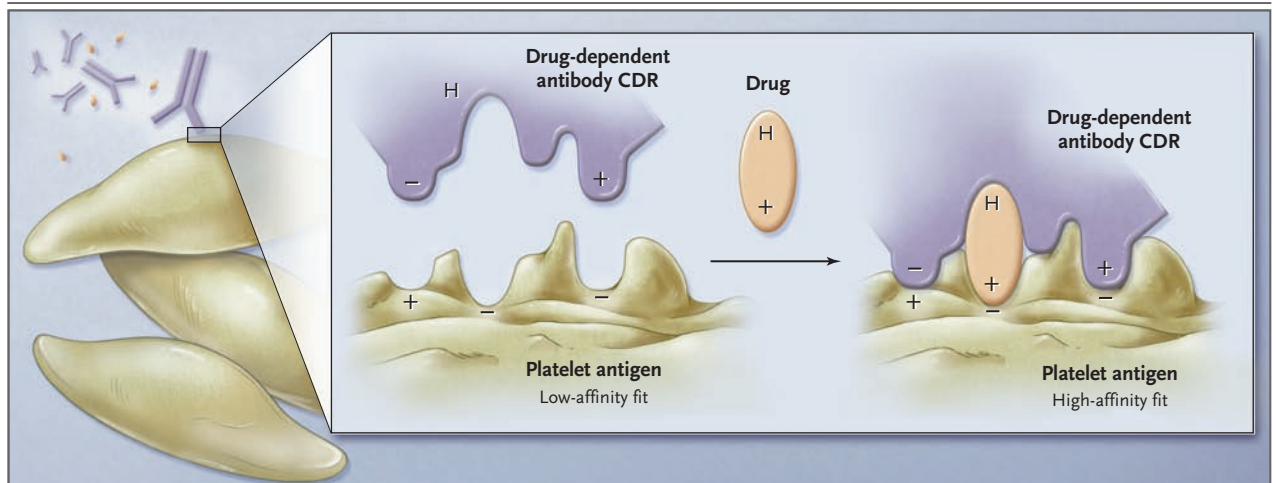
#### THROMBOCYTOPENIA INDUCED BY ABCIXIMAB

Abciximab is a widely used chimeric (human–mouse) Fab fragment that is specific for  $\beta_3$  integrin (glycoprotein IIIa). Like the fibans, it blocks platelet–fibrinogen interaction. Abciximab itself does not cause thrombocytopenia because it lacks the Fc domain required for recognition of antibody-coated platelets by phagocytes. However, in about 1% of patients given abciximab for the first time, and in more than 10% of those treated a second time, acute thrombocytopenia develops within a few hours of starting an infusion.<sup>39</sup> In some patients the onset of thrombocytopenia is delayed until 5 to 8 days after the initial 24- to 48-hour period of exposure to the drug.<sup>40</sup> Abciximab-induced thrombocytopenia is often mild, but fatalities have been recorded.<sup>41,42</sup>

Acute thrombocytopenia after first exposure to abciximab appears to be caused by preexisting antibodies specific for murine structural elements in the abciximab molecule.<sup>40,42</sup> Antibodies that cause delayed thrombocytopenia are newly induced but recognize the same target; they cause thrombocytopenia because abciximab-coated platelets are still present in the circulation 10 to 14 days after treatment.<sup>40</sup>

#### THROMBOCYTOPENIA DUE TO DRUG-INDUCED AUTOANTIBODIES

In rare cases, drugs induce true autoantibodies that are capable of destroying platelets in the absence of the sensitizing agent.<sup>43</sup> About 1% of patients treated with gold salts for rheumatoid arthritis have this complication.<sup>44</sup> Autoantibodies induced by gold may be unique in having specificity for platelet membrane glycoprotein V.<sup>45</sup> Other drugs that are probably capable of inducing autoimmune thrombocytopenia include procainamide, sulfonamide antibiotics, and interferons alfa and beta.<sup>2,12,13,43</sup> Acute, sometimes severe, but usually transient thrombocytopenia can occur several weeks after the vaccination of children or adults for various infectious diseases, but it is rare.<sup>46,47</sup> This condition resembles acute idiopathic thrombocytopenia, which sometimes develops in children after a viral infection, but its cause has not been established.



**Figure 2. Model for the Binding of a Drug-Dependent Antibody to an Epitope on a Platelet Glycoprotein.**

Antibodies capable of causing drug-dependent thrombocytopenia react weakly with an epitope on a target glycoprotein. The binding affinity ( $K_A$ ) for this interaction is too low to allow a sufficient number of antibody molecules to bind in the absence of the drug ("low-affinity fit"). The drug contains structural elements that are complementary to a negatively charged site on the glycoprotein and a hydrophobic site (H) on the complementarity-determining region (CDR) of the antibody. The drug interacts with these sites to improve the fit between the two proteins, increasing the  $K_A$  to a value that permits binding to occur at levels of antibody, antigen, and drug achieved in the circulation after ingestion of the drug ("high-affinity fit"). Adapted from Bougie et al.<sup>37</sup>

Platelet-specific autoimmunity induced by drugs is clinically similar to acute idiopathic autoimmune thrombocytopenia.<sup>43</sup> The possibility that drug-induced autoimmune thrombocytopenia is not uncommon remains speculative.

#### DIAGNOSIS

Drug-induced thrombocytopenia should be suspected in any patient who presents with acute thrombocytopenia of unknown cause. In considering this diagnosis, the clinician should keep in mind that 5 to 7 days of exposure is usually needed to produce sensitization in a patient given a drug for the first time. As previously noted, platelet inhibitors are exceptions to this general rule. In adults, the presence of severe thrombocytopenia (<20,000 platelets per cubic millimeter) increases the likelihood that a patient has drug-induced thrombocytopenia, and it should be strongly suspected in any patient with a history of acute, transient thrombocytopenia. Because patients sometimes do not report exposure to drugs later found to be the responsible agents,<sup>1</sup> a detailed, careful history of drug exposure is essential. Patients should be asked specifically about quinine, quinidine, sulfonamides, herbal remedies, folk medicines, common nonprescription drugs

such as acetaminophen, and recent vaccinations. Thrombocytopenia caused by undisclosed drug use has been described.<sup>48</sup>

In patients with sensitivity to quinine, quinidine, sulfonamides, and many other drugs, it is often possible to identify antibodies that react with normal platelets in the presence of the drug but not in its absence.<sup>23,42,49</sup> However, testing is technically demanding and not widely available (except for heparin) and is therefore not useful in the immediate care of a patient. Testing can be helpful in documenting the cause of thrombocytopenia after the fact and, more generally, in determining which drugs can cause drug-induced thrombocytopenia. Unfortunately, in patients with a history that is typical of drug-induced thrombocytopenia, antibody tests may be negative.<sup>2,36</sup> One important reason for this is that a drug metabolite produced in vivo can be the sensitizing agent.<sup>34,50</sup> The range of drug metabolites capable of inducing drug-induced thrombocytopenia is not well defined, but this type of sensitivity may be more common than has been thought.<sup>34,50</sup>

If there is a strong suspicion that thrombocytopenia was drug-induced and documentation of drug sensitivity is critical for diagnosis or management, a diagnostic challenge can be considered. Just 1 or 2 mg of a drug can cause a substan-

tial drop in platelet levels,<sup>51</sup> and a conventional dose can cause severe thrombocytopenia and bleeding.<sup>52</sup> Therefore, it is important to start with a few milligrams of the drug and to monitor platelet counts closely for 24 hours. Antibodies sometimes become undetectable after a few months, in which case the drug may initially have no effect on the platelet count.

#### TREATMENT AND PROGNOSIS

Many patients with drug-induced thrombocytopenia have only petechial hemorrhages and occasional ecchymoses and require no specific treatment other than discontinuation of the sensitizing medication. When there is uncertainty about the causative drug, all medications should be discontinued, and pharmacologic equivalents with different chemical structures substituted as necessary. Patients who have severe thrombocytopenia and “wet purpura” should be aggressively treated with

platelet transfusions because of the risk of fatal intracranial or intrapulmonary hemorrhage.<sup>2,53,54</sup> Corticosteroids are often given, but there is no evidence that they are helpful if the thrombocytopenia is drug-induced. Intravenous immune globulin<sup>55</sup> and plasma exchange<sup>56</sup> have been used in acutely ill patients, but the benefit of these treatments is uncertain.<sup>2</sup>

Once established, drug sensitivity probably persists indefinitely. Therefore, patients should be advised to avoid permanently the medication thought to be the cause of thrombocytopenia. Fortunately, drug-induced antibodies tend to be specific for the sensitizing drug,<sup>57</sup> and patients usually tolerate pharmacologic equivalents, even those with quite similar structures.

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