

REVIEW ARTICLE

Drug-induced immune thrombocytopenia: pathogenesis, diagnosis, and management

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Summary. Drug-induced immune thrombocytopenia (DITP) can be triggered by a wide range of medications. Although many cases of DITP are mild, some are characterized by life-threatening bleeding symptoms. The pathogenesis of DITP is complex, in that at least six different mechanisms have been proposed by which drug-induced antibodies can promote platelet destruction. It is possible in many cases to identify antibodies that react with platelets in the presence of the sensitizing drug, but the required testing is technically demanding and not widely available. Therefore, a decision on whether to discontinue an implicated medication in a patient suspected of having DITP must be made on clinical grounds. An algorithm is available that can be helpful in assessing the likelihood that a particular drug caused thrombocytopenia, but the most important aspects of patient management are a high index of suspicion and a careful history of drug exposure in an individual who presents with acute, often severe thrombocytopenia of unknown etiology. How drugs induce platelet-reactive antibodies and how, once formed, the antibodies cause platelet destruction following exposure to the drug is poorly understood. Further studies to address these issues and characterize more completely the range of drugs and drug metabolites that can cause DITP are needed.

Introduction

Thrombocytopenia is a recognized side effect of treatment with a wide range of medications. Certain agents, particularly those used for chemotherapy and regulation of immunity, tend to suppress hematopoiesis and produce pancytopenia. A few preferentially inhibit megakaryocytopoiesis to produce isolated thrombocytopenia [1,2]. However, many medications lower platelet levels by accelerating platelet clearance through immune and (less often) non-immune [1,2] mechanisms. In

patients who experience an acute drop in platelet levels, usually within a week or two of starting a new medication, antibody-mediated platelet destruction should be suspected.

Incidence

Epidemiologic studies performed in the US and Europe suggest that about 10 persons per million are affected by drug-induced immune thrombocytopenia (DITP) annually [3], but the incidence could be higher in elderly and hospitalized persons, who are more likely to be exposed to medications. A study performed in the eastern USA estimated that DITP occurred in persons treated with sulfamethoxazole–trimethoprim or quinidine–quinine at rates of 36 and 28 persons per million per week of exposure [4]. As these drugs are among the most common causes of DITP, the incidence of this condition in persons treated with most other medications is undoubtedly lower. Comparable data are not available for drug-induced immune hemolytic anemia. However, samples referred to our center for drug-dependent platelet antibody testing regularly exceed referrals for neutrophil and erythrocyte antibody testing by a ratio of more than 10 : 1, consistent with the likelihood that platelets are targeted by drug-induced antibodies considerably more often than other blood cell types.

Pathogenesis

The etiology of DITP is complex, at least six distinct pathologic mechanisms having been identified (Table 1). Heparin-induced thrombocytopenia (HIT) is technically the most common cause of drug-associated thrombocytopenia, but the drop in platelet levels in patients with HIT is rarely sufficient to provoke bleeding, and thrombosis is the major clinical complication. HIT has a unique pathogenesis, has been extensively reviewed elsewhere [5,6], and will be mentioned only briefly. Excluding heparin-induced thrombocytopenia, ‘quinine-type’ immune thrombocytopenia and thrombocytopenia induced by platelet glycoprotein (GP)IIb–IIIa inhibitors are most likely to be responsible for the drop in platelet count in patients seen clinically.

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

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

GP, glycoprotein.

*Adapted from R. H. Aster [2].

Hapten-induced antibodies

Early immunologic studies suggested that small molecules such as drugs trigger an immune response only when linked covalently to a macromolecule such as a protein, in which form they act as a 'hapten', to induce a humoral immune response. The resulting antibodies recognize the carrier molecule only where the 'hapten' is attached covalently. Accordingly, when drug-induced immune thrombocytopenia was first recognized as a clinical entity, it was suspected that the drug became immunogenic by being linked covalently to a cell membrane protein, thereby becoming capable of inducing a classic 'hapten-dependent' antibody. Upon re-exposure of a sensitized individual to drug, it was presumed that the drug-protein complex was re-formed, providing a target for antibody and enabling it to cause platelet destruction. This mechanism probably accounts for the immune hemolytic anemia formerly seen in a subset of patients treated with massive doses of penicillin [7], a drug that reacts covalently and spontaneously with free amino groups on proteins by virtue of containing a reactive β -lactam structural element. A recent report indicates that the widely used penicillin derivative piperacillin can induce hapten-specific antibodies that are reactive with piperacillin-coated red blood cells, but whether these antibodies actually cause the hemolytic anemia seen in some patients treated with piperacillin is uncertain [8]. A similar process may account for the thrombocytopenia seen rarely in patients treated with penicillin [9], piperacillin [10] and cephalosporin [11,12] antibiotics, but this has not been confirmed experimentally. As will be discussed, the usual *in vitro* behavior of drug-dependent antibodies (DDAbs) found in patients with DITP is distinctly different from that expected of classic 'hapten-specific' antibodies.

'Quinine-type' immune thrombocytopenia

More than a century ago, it was recognized that patients treated with quinine for malaria sometimes experienced acute,

severe bleeding that resolved when quinine was discontinued. It was later found that such patients had virtually no circulating platelets, despite having adequate numbers of megakaryocytes in the bone marrow. Other medications were subsequently shown to be capable of producing a similar clinical picture. In the early 1950s, J. F. Ackroyd and colleagues studied a series of patients who developed severe thrombocytopenia while taking the sedative allylisopropyl-acetylurea (Sedormid). They found that serum from such individuals contained a factor that caused platelet agglutination and lysis in the presence of the drug, and showed that re-exposure to drug after recovery led to a recurrence of thrombocytopenia [13]. In the 1950s, N. R. Shulman and associates showed that the drug-dependent serum factor acting on platelets was an antibody that did not behave as if it were 'hapten-specific', as it reacted with cells only in the presence of soluble drug, its binding was not inhibited by drug at the highest concentrations achievable, and it did not react with cells pretreated with drug and then washed [14,15]. In a series of studies remarkable for their time, Shulman [15] suggested that DDAbs react directly with the sensitizing drug itself to form an 'immune complex', and proposed that this complex reacts with the target cell to cause its destruction as an 'innocent bystander'. In later studies, however, the hypothesized drug-antibody complexes could not be demonstrated experimentally, and it was found that DDAbs react with targets through their Fab domains, not their Fc domains, as would be expected of an immune complex [16,17]. Accordingly, the view became favored that drug reacts non-covalently with target proteins to somehow prime them for recognition by DDAbs [18–20].

Recent studies suggest that DDAbs produced by patients sensitive to quinine and other drugs may be derived from a naturally occurring pool of immunoglobulins that are weakly autoreactive with epitopes on platelet membrane GPs and that drugs capable of causing DITP possess structural elements that improve the fit between these autoantibodies and their targets, raising the association constant for antibody binding to a value

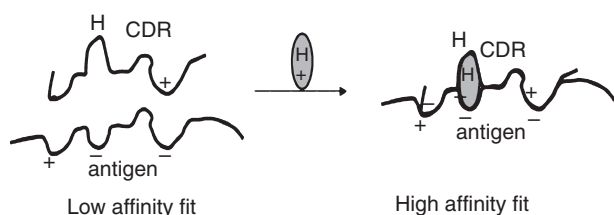


Fig. 1. A model for drug-dependent antibody binding. Left: antibodies capable of causing drug-dependent thrombocytopenia recognize an epitope on a platelet glycoprotein, but the reaction is too weak for significant numbers of antibody molecules to bind in the absence of drug. Right: the sensitizing drug contains structural elements that are complementary to charged (+/−) or hydrophobic domains (H) on the glycoprotein epitope and the complementarity-determining region (CDR) of the antibody and 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. From D. W. Bougie *et al.* (2006) [21] with permission of the publisher.

that allows drug, at pharmacologic concentrations, to promote antibody binding and cause cell destruction [20,21]. This model has not been directly validated, but is consistent with studies showing that quinine is 'trapped' on the platelet surface when antibody binds [22] and with the finding that quinine-dependent, platelet-reactive monoclonal antibodies bind drug at the 1 : 2 ratio expected for a specific antibody–drug interaction [23]. If confirmed by future studies, the model shown in Fig. 1 would reconcile seemingly conflicting hypotheses developed to explain drug-dependent antibody binding, as whether the drug reacts first with antibody or first with the target GP could depend simply on its relative affinity for one or the other of the two macromolecules. An alternative concept proposed to explain drug-dependent antibody binding is that certain drugs induce a structural change in a target GP, leading to the creation of neoepitopes elsewhere in the protein for which the antibodies are specific. This mechanism is unlikely to explain antibody binding induced by drugs such as quinine, which interact only weakly with proteins [14,24] and would not be expected to stabilize an alternative structure. However, it could explain thrombocytopenia in patients treated with platelet inhibitors of the fiban class, which bind tightly to the arginine-glycine-aspartic acid (RGD) recognition site of GPIIb–IIIa and 'activate' the integrin (see below).

The great majority of platelet-specific DDABs recognize the GPIIb–IIIa and/or GB1b–IX membrane glycoprotein complexes. Restricted domains of GPIb–IX [25–27] and GPIIIa [28] appear to be favored targets for antibodies induced by the drugs quinine, quinidine, rifampin, and ranitidine. Why platelets are so often targeted by DDABs and how this remarkable class of antibodies is induced upon exposure of some individuals to certain drugs is presently unresolved.

Thrombocytopenia induced by RGD-mimetic platelet inhibitors

RGD-mimetic drugs (fiban) are synthetic agents that bind tightly to the RGD recognition site on GPIIb–IIIa and prevent

the formation of platelet thrombi by blocking the reaction of the activated integrin with fibrinogen and other ligands. Two drugs of this class, tirofiban and eptifibatid, are widely used to reduce complications following percutaneous transluminal coronary angioplasty. In initial trials and in subsequent clinical experience, it was found that between 0.1% and 2% of patients treated with these agents experienced acute, often severe, thrombocytopenia within a few hours of the first exposure to one of these drugs [29,30]. Serologic studies indicate that this complication is caused by antibodies that can be naturally occurring and recognize GPIIb–IIIa in a complex with the particular ligand mimetic that caused thrombocytopenia [29]. It is known that both RGD peptide and peptide-mimetic drugs induce structural changes in GPIIb–IIIa recognized by monoclonal antibodies specific for 'ligand-induced binding sites' on the integrin [31,32]. It has been suggested that antibodies from patients with fiban-induced thrombocytopenia are specific for similar ligand-induced determinants on GPIIb–IIIa, but this has not been formally proved. In general, antibodies from patients with tirofiban-induced thrombocytopenia do not recognize GPIIb–IIIa in a complex with eptifibatid (and vice versa), and neither type of antibody reacts with GPIIb–IIIa associated with RGD peptide [29]. These observations suggest that the ligands may induce slightly different structural changes in the integrin that can be distinguished by the patient antibodies. Why some individuals should have naturally occurring antibodies specific for conformational changes induced in GPIIb–IIIa by RGD-mimetic drugs is an interesting and unresolved question.

Abciximab-induced thrombocytopenia

Abciximab, the first chimeric (mouse–human) monoclonal antibody approved for human use, is a Fab fragment specific for a peptide loop in the βA domain of GPIIIa [33]. Because this epitope is close to the RGD recognition site, abciximab blocks the reaction of fibrinogen with activated GPIIb–IIIa, thereby inhibiting platelet thrombus formation. About 2% of patients given abciximab for the first time [34] and 10–12% given this agent a second time [35] develop acute, often severe thrombocytopenia within a few hours of starting treatment. In such patients, antibodies can usually be detected that react strongly with normal platelets coated with abciximab and appear to be specific for mouse sequences in the drug that confer specificity for GPIIIa [36]. Laboratory identification of such antibodies is complicated by the fact that many normal persons have naturally occurring antibodies, apparently benign, that are specific for the papain cleavage site introduced at the C-terminus of abciximab in the manufacturing process and therefore bind to abciximab-coated platelets. The latter antibodies can be distinguished from pathogenic antibodies specific for mouse sequences by showing that their binding can be inhibited by Fab fragments prepared from normal IgG [36,37]. A subgroup of patients given abciximab maintains normal platelet levels for 6–8 days before experiencing acute thrombocytopenia. Platelet destruction in these individuals is

caused by antibodies produced in response to the initial 1-day infusion of the drug [37]. The newly formed antibodies are able to cause platelet destruction, because platelet-bound abciximab persists in the circulation for up to 2 weeks after treatment [38].

Drug-induced autoantibodies

Clinical and laboratory observations suggest that drugs occasionally trigger the production of platelet-specific autoantibodies, leading to a clinical picture indistinguishable from spontaneous, autoimmune thrombocytopenia (AITP) [39]. A condition similar to AITP occurred in 1–2% of patients treated with gold salts for rheumatoid arthritis [40]. Other medications implicated as possible triggers for AITP include L-dopa, procaine amide, penicillamine, and sulfamethoxazole (Fig. 2) [1,2,39]. How selected medications induce an autoimmune response against platelets is unknown. The suggestion has been made that some drugs perturb the processing of platelet GPs by macrophages, leading to the generation of cryptic peptides not ordinarily seen by the immune system [39], but there is little direct evidence for this. In recent years, various reports have described an AITP-like clinical picture in patients treated for malignant or immune conditions with the chimeric monoclonal antibodies infliximab [anti-tumor necrosis factor- α (TNF- α)], rituximab (anti-CD20), etanercept (anti-TNF- α receptor), and efalizumab (anti-CD11a) [41–44]. Most cases resolved after weeks or months of treatment with corticosteroids. Whether this complication is related to the immunomodulatory effects of these agents is unknown.

HIT

About 5% of patients given unfractionated heparin and a smaller percentage of those treated with low molecular weight heparin for at least 5–7 days develop low-grade thrombocytopenia, which in itself is rarely symptomatic. A subset of

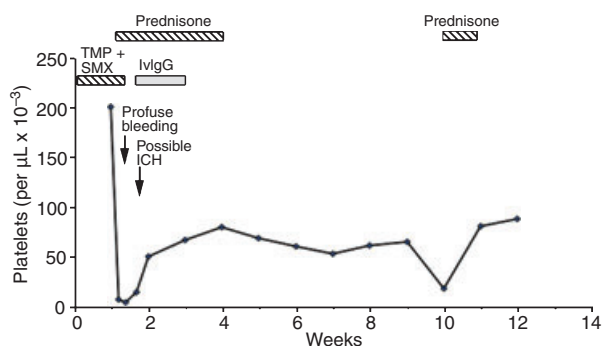


Fig. 2. Development of chronic autoimmune thrombocytopenia in a patient who presented initially with thrombocytopenia caused by sulfamethoxazole (SMX)-dependent, platelet-reactive antibodies. SMX-dependent antibodies were identified in acute-phase serum together with glycoprotein (GP)IIb–IIIa-specific non-drug-dependent autoantibodies. Persistent non-drug-dependent antibodies reactive with autologous platelets were identified during weeks 1, 5, and 9. ICH, intracranial hemorrhage; IvIgG, intravenous γ -globulin; TMP, trimethoprim. From R. H. Aster (2000) [38] with permission of the publisher.

patients, however, experience venous or arterial thrombosis, which can be life-threatening [45]. HIT is caused by antibodies that recognize complexes of heparin and platelet factor 4 (PF4), a 32-kDa CXC chemokine found in platelet α -granules. Recent reports suggest that HIT antibodies can recognize PF4 released from platelets and bound to chondroitin sulfate, the major glycosaminoglycan present on the platelet surface [46]. The thrombotic tendency associated with HIT may be the result of procoagulant microparticles released from platelets upon activation of Fc receptors [47]. Other mechanisms may also be operative [48]. Further discussion of HIT is beyond the scope of this review. For detailed information, readers are referred to recent publications [5,6].

Implicated drugs

Selected drugs implicated as causes of immune thrombocytopenia by the several mechanisms described above are listed in Table 1. In some conditions, only a few agents, for example fibrinolytic drugs, abciximab, and heparin and heparin derivatives, are known to be responsible. However, at least 100 different medications have been implicated as possible causes of drug-dependent, 'quinine-type' immune thrombocytopenia [1,2]. Many of the cases have been described only as anecdotal case reports, from which it is hard to judge whether drug sensitivity was involved, but some drugs have been implicated sufficiently often to make a cause-and-effect relationship almost certain. George and co-workers analyzed cases of drug-induced thrombocytopenia reported through 2008, and assembled a database listing implicated drugs that is periodically updated and can be accessed online at <http://www.ouhsc.edu/platelets>. They also devised a set of four clinical criteria to assess the likelihood that individual drugs are capable of causing DITP (Table 2). About 51 drugs were considered to be 'definite' (Level 1) and 17 others 'probable' (Level 2) causes of DITP on the basis of having met four or three of these criteria,

Table 2 Criteria used to evaluate causative relationships in drug-induced thrombocytopenic purpura*

| Criterion | Description |
|-------------------|--|
| 1 | Therapy with the candidate drug preceded thrombocytopenia |
| 2 | Recovery from thrombocytopenia was complete and sustained after therapy with the drug was discontinued |
| 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 for thrombocytopenia were excluded |
| 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 met |
| IV | Unlikely: Criterion 1 not met |

*Adapted from J. N. George *et al.* [49].

respectively [49–52]. Classes of drugs implicated include the cinchona alkaloids quinine and quinidine, non-steroidal anti-inflammatory agents, various antibiotics, especially sulfamethoxazole and vancomycin, anticonvulsants and sedatives, and the platelet inhibitors tirofiban, eptifibatide, and abciximab. A recent finding of interest is that drugs used in the treatment of cancer, such as platinum-containing compounds, can cause acute, severe, immune thrombocytopenia in addition to their well-known tendency to lower platelet counts by suppressing hematopoiesis [53]. Anecdotal, but well-documented, reports, including some in which thrombocytopenia recurred after challenge, indicate that folk medicines, herbal preparations and even foods occasionally trigger acute thrombocytopenia [54–56], but whether immune mechanisms are responsible is uncertain.

Although the George criteria are useful in defining agents that are capable of causing thrombocytopenia, they do not provide a means of identifying the causative agent in any particular patient, short of carrying out a diagnostic challenge with the suspect drug after recovery. In many, but not all, cases of DITP, it is possible to identify an immunoglobulin in the patient's serum that binds to normal platelets in the presence, but not in the absence, of the implicated drug [20], but there is not universal agreement as to whether detection of such an antibody provides conclusive evidence that the drug for which it is specific actually caused thrombocytopenia. In a recent study of vancomycin-induced thrombocytopenia, von Drygal-

ski *et al.* [57] identified vancomycin-dependent antibodies in 29 patients who satisfied at least three of the four George criteria (Table 2). Comparable antibodies were not found in 500 normal subjects or in 25 patients given vancomycin for at least 1 week who did not experience thrombocytopenia [57]. This study, together with other reports documenting the presence of drug-dependent, platelet-reactive antibodies in patients meeting most of the George criteria [2,20], suggests that detection of a DDAb by an experienced laboratory significantly increases the likelihood that sensitivity to that drug caused or contributed to thrombocytopenia. Table 3 lists drug-dependent antibodies identified using a standard flow cytometric assay [21,53] in patients referred to our laboratory for testing because of a suspicion of DITP over a 10-year span. All positive test results were confirmed by repeat testing. As already noted, detection of a drug-dependent antibody increases the likelihood, but does not prove unequivocally, that a particular drug is the cause of thrombocytopenia.

Clinical presentation

As a rule, patients will have been exposed to the sensitizing medication for at least 1 week before thrombocytopenia becomes clinically evident. As noted, eptifibatide, tirofiban and abciximab are exceptions to this rule, as naturally occurring antibodies specific for these drugs can cause thrombocytopenia within a few hours of the first exposure.

Table 3 Drug-dependent, platelet-reactive antibodies detected in 1998–2008

| Drug category | Number | Individual drugs |
|---------------------------------|--------|---|
| ACE inhibitor | 1–3 | Lisinopril |
| Analgesic | 1–3 | <i>Acetaminophen*</i> , propoxyphene |
| Antibiotic | > 15 | Sulfamethoxazole, vancomycin |
| | 4–15 | Ceftriaxone, levofloxacin, nafcillin, piperacillin, rifampin, trimethoprim |
| | 1–3 | Ampicillin, amoxicillin, cefazolin, cefadroxil, cefepime, cefpodoxime, ceftazidime, ceftizoxime, cefpodoxime, ciprofloxacin, ethambutol, lisinopril, loracarbef, metronidazole, nitrofurantoin, sulfisoxazole |
| Anticonvulsant | > 15 | Carbamazepine |
| | 4–15 | Phenytoin |
| | 1–3 | Lamotrigine, lorazepam, valproic acid |
| Antidepressant, antipsychotic | 1–3 | Amitriptyline, bupropion, haldol, olanzapine, paroxetine, sertraline |
| Antithyroid | 1–3 | Propylthiouracil |
| β-Blocker | 1–3 | Atenolol, propranolol |
| Cardiac | 4–15 | Amiodarone |
| | 1–3 | Dobutamine |
| Chemotherapeutic agent | 4–15 | Oxaliplatin |
| | 1–3 | Geldanamycin, irinotecan, suramin |
| Cinchona alkaloid | > 15 | Quinine, quinidine |
| Diuretic | 4–15 | Furosemide |
| GPIIb–IIIa inhibitor | > 15 | Abciximab, eptifibatide, tirofiban |
| | 4–15 | Orbofiban, xemolifiban |
| Histamine receptor antagonist | 1–3 | Fexofenadine, ranitidine |
| Narcotic | 1–3 | Fentanyl |
| Non-steroidal anti-inflammatory | 4–15 | <i>Naproxen*</i> |
| | 1–3 | Celecoxib, ibuprofen, <i>ibuprofen*</i> , oxaprozin |
| Proton pump inhibitor | 1–3 | Esomeprazole, lansoprazole, pantoprazole |
| Thrombin inhibitor | 1–3 | Argatroban |
| Vasodilator | 1–3 | Papaverine |

ACE, angiotensin-converting enzyme; GP, glycoprotein. *Italics indicate DDABs specific for drug metabolites only.

Once an antibody has been produced, exposure to the sensitizing drug sometimes produces systemic symptoms such as faintness, chills, fever, and nausea [58–60]. Hypotension and even syncope sometimes occur in patients with high-titer antibodies [58,59,61]. Occasional patients present with immune hemolytic anemia or neutropenia in addition to thrombocytopenia [62,63]. In such cases, DDABs specific for red cells or neutrophils can sometimes be detected in addition to platelet-specific antibodies.

The severity of bleeding tends to be inversely related to the platelet count, although patients with profound thrombocytopenia occasionally have no bleeding symptoms.

It is not rare for severely affected individuals (platelets, < 10 000/ μ L) to present with extensive purpuric lesions on the skin and mucosal surfaces, hematuria, and gastrointestinal hemorrhage ('wet purpura'). Those sensitive to quinine sometimes have microangiopathic hemolytic anemia and renal failure typical of the hemolytic uremic syndrome (HUS) [60,64] or thrombotic thrombocytopenic purpura [64]. Rarely, other drugs appear to trigger HUS in association with drug-induced thrombocytopenia [65]. The pathogenesis of renal failure in these cases is not understood [66].

After the sensitizing medication is discontinued, bleeding symptoms usually subside within 1 or 2 days. Platelet counts often return to normal in 4–8 days but, rarely, thrombocytopenia persists for several weeks. Catastrophic bleeding is unusual, but fatal intracranial [67] and intrapulmonary [68] hemorrhage has been described. Patients who present with HUS often require hemodialysis but usually regain normal renal function within a few weeks.

Diagnosis

DITP should be considered in any patient who presents with acute thrombocytopenia of uncertain etiology. A careful history of drug exposure should be taken, and patients should be asked specifically about quinine (still used for the prevention and treatment of nocturnal leg cramps) and sulfonamide antibiotics. It should be kept in mind that quinine present in beverages can trigger DITP [69]. It is not rare for DITP to be diagnosed as acute AITP at the initial presentation. Because the sensitizing medication is usually discontinued when the patient is hospitalized, a rise in platelet count may be attributed to treatment given for AITP, creating the possibility of a recurrence when the patient is re-exposed to the sensitizing drug at a later time. Examples of patients with DITP who were hospitalized for 'recurrent AITP' as many as five times and were subjected to diverse treatments, including splenectomy, before the correct diagnosis was established have been described [58,70]. Because the onset of thrombocytopenia is sometimes associated with chills and fever [58–60], it may initially be assumed that the low platelet count is an indicator of bacterial sepsis [59]. DITP triggered by medications taken surreptitiously has been reported [71].

Detection of an antibody that reacts with normal platelets in the presence of a drug being taken by the patient can be helpful

in diagnosis, although, as noted, the requisite testing is not widely available. A convenient assay for DDABs involves incubation of normal platelets with patient serum in the presence and absence of the implicated drug, followed by washing in the presence of drug and detection of platelet-bound immunoglobulin by flow cytometry [21,72]. Other methods used for DDAB detection include complement fixation [14], platelet lysis [73], induction of platelet procoagulant activity [74], and passive hemagglutination [75]. The relative sensitivity of these techniques for DDAB detection is uncertain. Unfortunately, DDABs cannot always be detected, even in patients in whom DITP is considered to be 'likely' or 'definite' according to the George criteria (Table 2). One reason for this is that many drugs are highly insoluble in aqueous solution and are therefore difficult to work with *in vitro*. Another is that drug metabolites produced *in vivo* can be the sensitizing agents [76,77]. Metabolites shown to be capable of causing sensitization leading to DITP include glucuronide conjugates of non-steroidal anti-inflammatory drugs [76] and acetaminophen [78], as well as acetaminophen sulfate [76,77]. Drug-induced antibodies remain present for at least 1 month after the acute episode, and sometimes persist indefinitely. A diagnostic challenge with the implicated drug following restoration of normal platelet levels can be considered in exceptional cases where DDAB test results are negative and an implicated drug is essential for a patient's medical care. If performed, a challenge should start with very small doses of the medication, that is, 1 or 2 mg, while platelet counts are carefully monitored, as administration of a full dose can produce life-threatening bleeding [79].

Management

A decision on whether to discontinue medication in a patient with possible DITP must be based on clinical considerations, as testing for DDABs requires time and is not widely available. When necessary, pharmacologically equivalent drugs with a different chemical structure can usually be substituted safely for medications essential to a patient's medical care. It is reasonable to give platelet transfusions to severely thrombocytopenic patients who have 'wet purpura', because of their increased risk of intracranial hemorrhage [80]. However, the effectiveness of transfusions has not been formally studied. It is a common practice to administer corticosteroids, but whether they are beneficial in patients with DITP is not established. As most drugs are cleared within a few days, platelet levels often start to increase within a day or two of hospital admission. Rarely, thrombocytopenia and bleeding symptoms persist for several weeks. Such patients have been treated with intravenous IgG [81,82] and even plasma exchange [83], with possible, but not proven, benefit. Although identification of a platelet-reactive DDAB is not useful in acute management, for practical reasons, antibody studies can help to implicate a specific drug as the cause of a thrombocytopenic episode and provide justification for measures taken to prevent future exposure.

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Disclosure of Conflict of Interests

The authors state that they have no conflict of interest.

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