● ● ● **PLATELETS & THROMBOPOIESIS**

DITP causation: 3 methods better than 1?

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In this issue of *Blood*, Reese and colleagues describe 3 different methods to identify drugs that can cause acute—presumably immune-mediated—thrombocytopenia, assembling a list of 2 dozen well-documented culprits, but pointing to many more.[1]

Clinicians evaluating patients with acute thrombocytopenia must consider the possibility of drug-induced immune thrombocytopenia (DITP). Unlike antibody-mediated thrombocytopenia caused by heparin—a relatively common prothrombotic syndrome with platelet-activating antibodies—DITP is rare, usually prohemorrhagic, and caused by non–platelet-activating drug- (or metabolite-) dependent, platelet-reactive antibodies.[2,3] Nevertheless, as thrombocytopenia often occurs in patients receiving numerous drugs, DITP is a common—and vexing— diagnostic consideration: clinicians want to know which drugs are plausible culprits, because indiscriminate discontinuation of all drugs can have serious consequences.

Reese and co-investigators have used 3 approaches to identify drugs that *might* cause DITP: (1) assessment of published case reports using defined clinical criteria; (2) laboratory evaluation for drug-dependent, platelet-reactive antibodies in patients with clinically suspected DITP; and (3) use of a data-mining algorithm to search for drugs within the Food and Drug Administration's Adverse Event Reporting System (AERS) database.[1] Together, these approaches identified 1468 drugs suspected of causing thrombocytopenia; however, only 23 drugs were identified by all 3 methods (see figure).

The first approach (University of Oklahoma) evaluated published cases using defined clinical criteria.[4,5] Drugs were implicated if at least one report merited classifying a drug as having a "definite" causal association, or if 2 or more reports met minimal criteria for a "probable" causal association. Although 253 drugs were thus evaluated, only 87 met the criteria for "definite/probable" causes of DITP.

The second approach used detection of drug-dependent, platelet-reactive antibodies by the Platelet and Neutrophil Immunology Laboratory of the BloodCenter of Wisconsin.
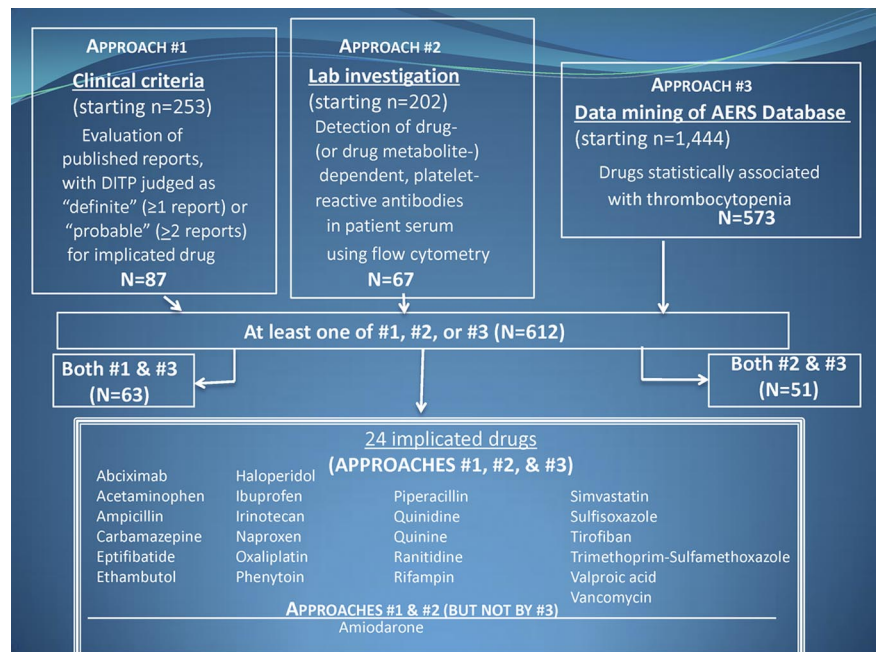
This group, which provides comprehensive referral services for evaluating DITP, recently reported its experience using laboratory detection of drug-dependent antibodies as the key criterion for judging DITP causation.[6] Although 202 different drugs were investigated by the Milwaukee lab, only 67 yielded supportive in vitro data. Combining these complementary clinical and laboratory approaches of the Oklahoma and Wisconsin investigators, 130 drugs had evidence of causality for DITP by either approach, but only 24 drugs were common to both methods (see figure).

A third, more novel approach used algorithmic "data mining" of the AERS database. Here, the authors obtained quarterly extracts of AERS data over 4 decades provided in response to a Freedom of Information request.

The authors assessed for different drugs whether the ratio of observed reports exceeded the expected number of reports ("proportional reporting ratio"), using predefined thresholds of "signal of disproportionate reporting." They found 1444 currently approved drugs for which AERS reports of thrombocytopenia existed; 573 of these agents had a statistically significant reporting association with thrombocytopenia.

As mentioned, only 23 drugs appear on all 3 lists (a 24th agent—amiodarone—was found using only the first 2 approaches). There seems little doubt that these 2 dozen drugs cause DITP, although 588 others identified by at least 1 of these 3 approaches remain possible causes of DITP. Most of these additional drugs were identified by data mining, but this method's specificity for DITP is unknown.

Physicians should be cautious about imputing causation simply because any particular drug being given to a thrombocytopenic patient appears on a "list." A patient who really has DITP should exhibit 3 features.[2,7] First, the implicated drug should bear a temporal relationship with thrombocytopenia consistent with an immune-mediated etiology (usually, onset approximately 1 week after beginning a drug for the first time, or more quickly when exposed intermittently). Second, the platelet count nadir should be less than 30×10^9/L,

APPROACH #1	APPROACH #2	APPROACH #3
Clinical criteria (starting n=253) Evaluation of published reports, with DITP judged as "definite" (≥1 report) or "probable" (≥2 reports) for implicated drug **N=87**	**Lab investigation** (starting n=202) Detection of drug- (or drug metabolite-) dependent, platelet-reactive antibodies in patient serum using flow cytometry **N=67**	**Data mining of AERS Database** (starting n=1,444) Drugs statistically associated with thrombocytopenia **N=573**

At least one of #1, #2, or #3 (N=612)

Both #1 & #3 (N=63)

Both #2 & #3 (N=51)

24 implicated drugs (APPROACHES #1, #2, & #3)

Abciximab	Haloperidol		
Acetaminophen	Ibuprofen	Piperacillin	Simvastatin
Ampicillin	Irinotecan	Quinidine	Sulfisoxazole
Carbamazepine	Naproxen	Quinine	Tirofiban
Eptifibatide	Oxaliplatin	Ranitidine	Trimethoprim-Sulfamethoxazole
Ethambutol	Phenytoin	Rifampin	Valproic acid
			Vancomycin

APPROACHES #1 & #2 (BUT NOT BY #3)
Amiodarone

Three different approaches were used to adjudicate drugs as possibly causing DITP. The central box lists the 23 agents identified using all 3 methods (plus 1 drug—amiodarone—implicated by only the first 2 methods). The categories "Both #1 & #3" and "Both #2 and #3" include the 23 patients who were identified using all 3 approaches. The numbers of drugs implicated by only 1 of the 3 approaches were 23, 15, and 482 for approaches #1, #2, and #3, respectively. AERS indicates Adverse Event Reporting System.

and usually less than 20 × 10⁹/L—this is because drug-dependent antibodies usually recognize glycoprotein (GP) IIb/IIIa and/or GPIb/IX antigen targets,[7,8] and these high copy number membrane surface GPs ensure that a high proportion of sensitized platelets are cleared. Finally, there should not be an alternative explanation for thrombocytopenia more highly probable than DITP.

The clinician should also be aware that many drugs beyond the 2 dozen listed do cause DITP. For example, the Milwaukee laboratory has identified at least 10 patients with suspected DITP as having ceftriaxone-dependent platelet-reactive antibodies,[1,6] a causal relationship also supported by data mining.[1] Inexplicably, however, no individual case reports of ceftriaxone-induced DITP exist.[4,5]

Another example: 4 years ago, the authors of this Inside *Blood* commentary jointly observed a 39-year-old male burn victim in whom acute, severe thrombocytopenia (platelet count nadir, 12 × 10⁹/L) began 1 week after beginning a course of mirtazapine (tetracyclic antidepressant), and in whom no other convincing explanation was found; the thrombocytopenia quickly resolved after stopping mirtazapine. A PubMed search ("mirtazapine" and "thrombocytopenia") yielded a single report[9] of mirtazapine-induced DITP, and in which mirtazapine-dependent GPIIb/IIIa-reactive antibodies were identified. The existence of this single published report, in our view, strongly supported the plausibility of a diagnosis of mirtazapine-induced DITP in our patient, even though we could not detect mirtazapine-dependent antibodies in our patient's serum by flow cytometry (in vitro testing for drug-dependent antibodies is relatively specific, but, unfortunately, not always very sensitive[7]). However, as only one ("probable") report of mirtazapine-induced DITP currently exists,[9] and as no such case has undergone serologic verification by the Milwaukee laboratory,[6] mirtazapine failed on 2 counts to meet the authors' criteria for inclusion within the list of 24 drugs.[1] Encouragingly, AERS data mining did identify mirtazapine as a possible cause of DITP.[1]

Between these 2 extremes of putative DITP due to ceftriaxone and mirtazapine—the former almost attaining the top tier and the latter meeting only the novel data-mining category—there undoubtedly exist many other drugs that cause DITP. The strongest candidates are those for which laboratory evidence of drug-dependent antibodies exist,[6] followed by those for which reasonably convincing clinical evidence has been tabulated.[4,5] By these standards, 106 drugs (beyond those 24 listed) meet this level of culpability.[1] The contribution of Reese et al—including the searchable online data supplement—is a valuable "one-stop" resource for clinicians. Their 3-pronged approach of careful evaluation of clinical observations,[4,5] laboratory detection of drug-dependent antibodies,[6] and, now, data mining of spontaneously generated AERS reports,[1] will help focus attention on those drugs that really cause DITP.

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● ● ● **THROMBOSIS & HEMOSTASIS**

Comment on Feys et al, page 2005

ADAMTS13 Alone

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Whether ADAMTS13 deficiency alone is sufficient to cause an acute episode of TTP or whether additional prothrombotic conditions are also required has been uncertain— until now.

The discovery of the plasma protease, ADAMTS13, and its function to cleave the newly synthesized, ultra-large multimers of von Willebrand factor (VWF) changed the landscape of thrombotic thrombocytopenic purpura (TTP), providing insights for etiology and pathogenesis.[1] Severe ADAMTS13 deficiency can be acquired, caused by an autoantibody that inhibits ADAMTS13 function, or very rarely it can be caused by a mutation of the *ADAMTS13* gene. A severe deficiency of ADAMTS13 activity, either acquired or congenital, is strongly associated with acute episodes of TTP. However, there are multiple observations that people can have severe ADAMTS13 deficiency, either acquired or congenital, without clinical signs of TTP.

Acquired severe ADAMTS13 deficiency can be documented in approximately one-third of patients diagnosed with TTP.[2] Some of these patients may continue to have severe ADAMTS13 deficiency after an apparent complete recovery with no clinical signs of TTP. Whether persistent ADAMTS13 deficiency during remission predicts a subsequent relapse remains uncertain.[2] In some patients, acute episodes of TTP are apparently preceded (perhaps "triggered"?) by an inflammatory condition (such as pregnancy, pancreatitis, or an infection) but whether "trigger" conditions precede acute episodes of TTP occasionally, often, or always is unknown.

The occurrence of acute episodes of TTP in patients with congenital severe ADAMTS13 deficiency may also be unpredictable. Some patients present with manifestations of TTP in infancy while others, even in the same family with the same genetic abnormality, may not have clinical signs of TTP until they are adults, or may never have clinical manifestations of TTP.[3]

It was predicted based on clinical observations, that mice with deletions of the *ADAMTS13* gene would manifest the clinical features of TTP, but they did not.[4,5] Additional stresses, such as Shiga toxin,[4] a procoagulant infusion,[5] or use of a mouse strain with