Identifying drugs that cause acute thrombocytopenia:
an analysis using three distinct methods

Jessica A. Reese,1 Xiaoning Li,1 Manfred Hauben,3 Richard H. Aster,4
Daniel W. Bougie,4 Brian R. Curtis,4 James N. George,1,2 Sara K. Vesely,1

1Department of Biostatistics and Epidemiology, College of Public Health, 2Department of
Medicine, College of Medicine,
The University of Oklahoma Health Sciences Center, Oklahoma City, OK
3Pfizer, Inc., New York, NY and Department of Medicine,
New York University School of Medicine, New York, NY; New York Medical College,
Valhalla, NY; Brunel University, West London, UK; University of Maryland College of
Pharmacy, Baltimore, MD
4Department of Medicine, Medical College of Wisconsin and
Blood Research Institute, BloodCenter of Wisconsin, Milwaukee, WI

Short title: Drug-induced thrombocytopenia

Address correspondence to:
Sara K. Vesely, Ph.D.
Department of Biostatistics and Epidemiology, Room CHB 358
The University of Oklahoma Health Sciences Center
P.O. Box 26901
Oklahoma City, OK 73190
Phone: (405) 271-4222, E-mail: sara-vesely@ouhsc.edu
ABSTRACT

Drug-induced immune thrombocytopenia (DITP) is often suspected in patients with acute thrombocytopenia unexplained by other causes, but documenting that a drug is the cause of thrombocytopenia can be challenging. To provide a resource for diagnosis of DITP and also for drug safety surveillance, we analyzed three distinct methods for identifying drugs that may cause thrombocytopenia. [1] Published case reports of DITP have described 253 drugs suspected of causing thrombocytopenia; using defined clinical criteria, 87 (34%) were identified with evidence that the drug caused thrombocytopenia. [2] Serum samples from patients with suspected DITP were tested for 202 drugs; drug-dependent, platelet-reactive antibodies were identified for 67 drugs (33%). [3] The FDA’s Adverse Event Reporting System (AERS) database was searched for drugs associated with thrombocytopenia using data mining algorithms; 1444 drugs had at least one report associated with thrombocytopenia; 573 (40%) drugs demonstrated a statistically distinctive reporting association with thrombocytopenia. Among all 1468 drugs suspected of causing thrombocytopenia, only 102 were evaluated by all three methods and only 23 of these 102 drugs had evidence for an association with thrombocytopenia by all three methods. Multiple methods, each with a distinct perspective, can contribute to the identification of drugs that can cause thrombocytopenia.
INTRODUCTION

Acute immune-mediated thrombocytopenia is a potentially serious adverse reaction to many drugs. Therefore drug-induced immune thrombocytopenia (DITP) should be considered in all patients with acute thrombocytopenia not explained by other causes. It is not uncommon for patients with DITP to be initially diagnosed as having autoimmune thrombocytopenic purpura (ITP). The estimated population incidence of DITP (1-2/100,000/year) is similar to the estimated incidence of ITP in adults (3.3/100,000/year); however the frequency of DITP is much greater in users of specific medications. For example, the estimated incidence of thrombocytopenia among users of trimethoprim-sulfamethoxazole and quinine has been estimated to be 198 and 135/100,000 users/year, respectively. The frequency of DITP may be even greater than these estimates since identification of a drug as the etiology of thrombocytopenia is a difficult problem for clinicians, especially in patients taking multiple medications. The appropriate first step in the evaluation and management of patients with suspected DITP is to discontinue drugs that may be the most likely causes of thrombocytopenia. However current information provides only limited evidence for determining which among a patient’s drugs are most likely to cause thrombocytopenia.
To address this common clinical problem, we used three distinct analytical methods and their corresponding data sets to identify drugs that have evidence for an association with thrombocytopenia. [1] We have performed serial systematic reviews of published case reports of DITP and analyzed the clinical evidence for a causal association of the drug with thrombocytopenia. [2] We analyzed data from diagnostic laboratory testing at the BloodCenter of Wisconsin for drug-dependent, platelet-reactive antibodies. [3] We performed data mining analyses of the United States Food and Drug Administration’s (FDA) Adverse Event Reporting System (AERS) database to identify drugs that had been suspected of causing thrombocytopenia and to determine which among these drugs had a statistically distinctive reporting association with thrombocytopenia. We used the results of these three analyses to develop a comprehensive, current database of drugs associated with thrombocytopenia that we hope will be helpful to clinicians in their evaluation of patients suspected to have DITP and to health professionals involved in drug safety surveillance.
**METHODS**

*Inclusion criteria for drugs.* Agents described in case reports, laboratory data, and data mining of the AERS database were checked to determine if they were currently approved drugs in worldwide markets, using the Lexi-Comp electronic database,\textsuperscript{14} Micromedex electronic medical database,\textsuperscript{15} and the Martindale Pharmacopoeia.\textsuperscript{16} We used Lexi-Comp as the primary reference database. If an agent was not identified as a currently approved drug using Lexi-Comp, then the Micromedex database was used to determine if the drug was currently approved. If an agent was not identified by either Lexi-Comp or Micromedex, the Martindale Pharmacopoeia was then searched. Drugs not currently approved by regulatory agencies in any country, including investigational drugs, herbal compounds, illegal drugs, and agents that are not used as drugs (for example, pesticides) were excluded. Marrow suppressive drugs that cause predictable, dose-dependent thrombocytopenia were excluded unless the drugs had been identified as the cause of acute immune-mediated thrombocytopenia. Heparin and heparin analogs were excluded from this analysis because heparin-induced thrombocytopenia has a distinct pathogenesis and clinical course manifested predominantly by thrombosis and also because a standardized diagnostic evaluation for heparin-induced thrombocytopenia has been established.\textsuperscript{9,17,18} Some agents were listed in the AERS database individually as well as in
combination with other drugs. Drug combinations were included as separate items when they were documented as distinct approved drugs by one of the resource databases.

**Classification based on case reports of patients with suspected drug-induced thrombocytopenia.** We systematically reviewed all published case reports of drug-induced thrombocytopenia initially in 1998 and we have repeated our systematic reviews every two years, most recently on October 6, 2008. In each review we have used a defined set of clinical criteria to assess the level of evidence for a causal association with thrombocytopenia. Criteria for article identification and selection, data extraction, and assessment of the clinical evidence have been previously described. Four levels of evidence were defined according to the following criteria. [1] “Definite” evidence for a causal association of a drug with thrombocytopenia in a reported patient required four criteria, within the limitations of secondary documentation: [A] the suspected drug was taken before thrombocytopenia occurred and recovery from thrombocytopenia was complete and sustained after the drug was discontinued, [B] the suspected drug was the only drug taken before the onset of thrombocytopenia, or other drugs were continued or re-introduced with a sustained normal platelet count, [C] to the extent possible with secondary documentation, all other potential causes of thrombocytopenia were reasonably excluded, and [D] re-exposure to the
suspected drug resulted in recurrent thrombocytopenia. [2] A “probable”
association required three criteria [A], [B], and [C]. [3] If criterion [A] was
met but both criteria [B] and [C] were not met, the drug was interpreted
as having a “possible” association. [4] If criterion [A] was not met, or if
re-exposure to the suspected drug did not result in recurrent
thrombocytopenia, the drug was interpreted as having an “unlikely”
association. Reasons for failing to meet criterion [A] included reports of
patients with preexisting thrombocytopenia or patients in whom recovery
to a normal platelet count was not described. For this study, drugs were
considered to have a causal association with thrombocytopenia if they
were described in one or more case reports as having “definite” evidence.
However reports describing a rechallenge with the suspected drug are
uncommon. Therefore, in the absence of any case reports with “definite”
evidence, drugs were also considered to have a causal association with
thrombocytopenia if they were described in two or more case reports as
having “probable” evidence. The rationale for this arbitrary rule was that
“probable” was the next highest level of evidence and replicated,
independent findings were considered to provide confirmation of a causal
association. Analysis of tests for drug-dependent antibodies was not
included in these assessments.

Because the goal of the current study was to include all drugs that
had been suspected by a clinician of causing immune-mediated DITP, all
drugs that were identified in published case reports, regardless of their level of evidence, were included in the analysis. Therefore drugs that had been excluded from our previous analyses\textsuperscript{9} because of insufficient data, platelet counts not less than 100,000/\(\mu\)L, and patient age less than 16 years were included in this analysis. Case reports describing the use of an established drug in a non-therapeutic manner (such as an overdose) and that described drug-induced disease that included thrombocytopenia but predominantly involved other organ system abnormalities were excluded from this analysis.

\textbf{Classification based on detection of drug-dependent, platelet-reactive antibodies.} Testing for drug-dependent, platelet-reactive antibodies was performed in the Platelet and Neutrophil Immunology Laboratory of the BloodCenter of Wisconsin (Milwaukee, WI) on samples submitted by clinicians for testing because of a suspicion of drug-induced immune thrombocytopenia from 1995 through December 31, 2008. These data from the BloodCenter of Wisconsin are similar to previously published data from 1998-2008.\textsuperscript{2} Data from this one laboratory were used to provide consistency of the testing procedure and therefore consistent data over 14 years from a laboratory that does referral testing for drug-dependent, platelet-reactive antibodies on a regular basis and on a large scale (about 600 samples per year [excluding heparin], predominantly from the U.S.). Based on extensive inquires, we
believe that the BloodCenter of Wisconsin is the largest resource for drug-dependent, platelet-reactive antibody testing in the United States. Drug-dependent binding of antibodies to intact, normal platelets was demonstrated by flow cytometry as previously described, using methodology that has been standardized across a wide range of drugs.\textsuperscript{11,12} The cut-point defining a positive result is defined by the mean result of a healthy donor population plus 3 standard deviations, providing a confidence level of 99%. All positive reactions were confirmed by an independent repeat assay. For some drugs, such as acetaminophen, ibuprofen, and naproxen, testing required use of drug metabolites since antibodies were specific for metabolites of the drug and did not react with the unmodified drug.\textsuperscript{2} All drugs that met the previously described inclusion criteria for which drug-dependent antibody testing was requested were included in this analysis, whether or not a drug-dependent antibody had been detected.

\textbf{Classification based on data mining of the FDA AERS database.}

The AERS database is coded with the Medical Dictionary for Regulatory Activities (MedDRA), a standardized and widely used adverse event dictionary.\textsuperscript{20} Reporting of adverse drug reactions to the AERS is typically required from pharmaceutical companies; reports are also voluntarily submitted by health care professionals, patients, and others using the MedWatch website.
The principal purpose of the AERS database is to detect signals of possible adverse events that are novel in terms of their clinical nature, frequency, and/or severity. For our analysis we used the quarterly extracts of the AERS data, available from 1968 through June 2009, provided by the FDA in response to a Freedom of Information request. These data extracts contain quantitative information covering all drugs and all events from the core data fields in the form of aggregate reporting frequencies. The clinical narratives of the individual MedWatch forms are not applicable for the data mining techniques used in our analysis and are not included in these quarterly data releases.

Reports of adverse drug reactions to the AERS are numerous and uncensored. Therefore analytic processes (data mining) may be used to quantitatively explore these data, searching for systematic relationships between variables to help safety reviewers identify possible adverse events. Data mining is a screening procedure that identifies an association of drugs with adverse events and provides a possible starting point for further evaluation, if the magnitude of the association is sufficiently large and the clinical context is appropriate. We used previously reported data mining methods\textsuperscript{13,21,22} based on 2x2 contingency tables that classify reports according to the presence or absence of the drug and the presence or absence of the adverse event of
interest, which in this study was thrombocytopenia. We then calculated the number of reports that might be expected if the drug and thrombocytopenia were independently recorded in the database; this expected independent recording of a drug and thrombocytopenia was considered to be a baseline or null level of association. There are various measures of association that may be calculated from 2x2 contingency tables that represent a ratio of observed reports to the expected number of reports. One commonly used measure in drug safety surveillance is described as the proportional reporting ratio (PRR). The greater the ratio of the observed number of reports to the expected number of reports exceeds predefined thresholds, described as disproportionality or a signal of disproportionate reporting (SDR),\textsuperscript{21} the more numerically distinctive is the association between the drug and thrombocytopenia. Disproportionality analysis is a commonly used data mining approach for pharmacovigilance studies.\textsuperscript{13}

data mining algorithms with both frequentist\textsuperscript{13} and Bayesian\textsuperscript{13} methods of analysis. Both methods of analysis were performed on subsets of data grouped by individual years and also by sequential cumulative years (i.e., 1968, 1968-1969, 1968-1970, 1968-1971.....1968-2009). With frequentist analysis of disproportionality, the SDR was significant for a reporting association between a drug and thrombocytopenia if [1] the drug-thrombocytopenia combination was reported three or more times in the analyzed stratum, [2] the PRR (ratio of observed reports to the baseline or expected reports) was equal or greater than two, and [3] Chi-square was greater than four. With Bayesian analysis of disproportionality, the SDR was significant for a reporting association between a drug and thrombocytopenia if [1] the drug-thrombocytopenia combination was reported one or more times in the analyzed stratum and [2] the observed-to-expected number of reports was significantly large as defined by the 5\textsuperscript{th} percentile of the posterior empirical Bayes gamma mixture (EB05) of equal or greater than two, a Bayesian formulation of one of the available association measures for 2x2 tables (the reporting ratio, or RR).\textsuperscript{13} These analyses were performed using Empirica version 7.0 software (Phase Forward, Waltham, MA).
RESULTS

Case reports have described 253 drugs suspected of causing thrombocytopenia. There was evidence for a causal association between the drug and thrombocytopenia for 87 (34%) of these drugs. In patients whose blood samples were submitted to the BloodCenter of Wisconsin for testing for drug-dependent, platelet-reactive antibodies, 202 different drugs were suspected as possible causes of thrombocytopenia. Drug-dependent antibodies were identified for 67 (33%) of these drugs. A total of 351 drugs were described in case reports and/or tested for drug-dependent antibodies; 104 drugs were analyzed by both methods. One hundred thirty (37%) of these 351 drugs had evidence for a causal association with thrombocytopenia either by clinical evidence from case reports, by detection of drug-dependent anti-platelet antibodies, or by both methods. These analyses are summarized in Table 1. Table 2 lists the 24 drugs that had evidence for a causal association with thrombocytopenia by both methods. These 24 drugs included six of the seven drugs that have been described in 10 or more case reports with “definite” or “probable” evidence for a causal association between the drug and thrombocytopenia. Gold has also been identified in 11 case reports having a “probable” association with thrombocytopenia, but no case reports with a “definite” association. Gold has been statistically associated with thrombocytopenia by data mining but has not been
tested for drug-dependent, platelet reactive antibodies at the BloodCenter of Wisconsin since 1995. Previous testing for gold-dependent antibodies at the BloodCenter of Wisconsin was negative (data not shown). These 24 drugs also included 11 of the 12 drugs for which drug-dependent antibodies have been identified in ten or more patients. Ceftriaxone also had evidence for a causal association with thrombocytopenia by detection of drug-dependent, platelet reactive antibodies in ten or more patients. Ceftriaxone has been statistically associated with thrombocytopenia by data mining but has not been reported in any case reports with “definite” or “probable” clinical evidence.

The AERS database contained reports of thrombocytopenia for 2062 agents; 1444 (70%) met our inclusion criteria of currently approved drugs. These 1444 drugs included 327 (93%) of the 351 drugs that were described in case reports and/or tested for drug-dependent antibodies; 24 (7%) of the drugs described in case reports and/or tested for drug-dependent antibodies were not identified in the AERS database. Five hundred seventy-three (40%) of the 1444 drugs were identified as having a statistically significant reporting association with thrombocytopenia; only 91 (16%) of these 573 drugs had been identified with evidence for a causal association with thrombocytopenia by published case reports in the medical literature and/or identification of drug-dependent antibodies. These analyses are summarized Table 3.
Of all 1468 drugs analyzed in this study, only 102 (7%) were evaluated by all three methods (Table 4). Since these drugs were suspected of causing thrombocytopenia and evaluated by all three methods, they may be the most commonly suspected etiologies of DITP. However, of these 102 drugs, only 23 had evidence for a causal association with thrombocytopenia by all three methods; 14 drugs had no evidence for an association by any method; and some drugs were identified only by one method or a combination of two of the methods. Only one drug, amiodarone (Table 2), was identified by both case reports and laboratory testing as having evidence for a causal association with thrombocytopenia that did not have a statistical reporting association with thrombocytopenia detected by data mining, even though it had been reported to the AERS. The results with each of the three methods are summarized in Figure 1.

_Supplement Table S1_ provides a list of all 1468 drugs analyzed in this study with the results of analysis by each of the three methods.

**DISCUSSION**

Acute, immune-mediated thrombocytopenia is a potentially severe adverse reaction to many drugs, therefore the diagnosis of DITP is often
considered in patients with unexpected thrombocytopenia. However there are few data describing the relative risk of individual drugs for causing thrombocytopenia and there are no routine diagnostic procedures for documenting that a drug is the cause of thrombocytopenia. Pharmacoepidemiologic studies have described methods to identify patients with potential DITP and have reported quinine, trimethoprim-sulfamethoxazole, and sulfisoxazole as common causes of DITP. However there is no evidence-based comprehensive database comprising all drugs that have been associated with thrombocytopenia and estimating their relative risk of causing thrombocytopenia. Our goal was to assist the initial evaluation of patients with suspected DITP by identifying drugs that may have a high likelihood of being causative based on the assessment by three distinct methods of analysis.

We began our effort to document drugs that can cause thrombocytopenia with a systematic analysis of all published case reports of DITP. Analysis of case reports has limitations because [1] it is logical to assume that very few occurrences of DITP are published as case reports; [2] in many published case reports, application and interpretation of the assessment criteria is difficult and the available data presented in the concise reports are often insufficient to determine whether a causal association with thrombocytopenia existed; [3] patients with complex
illnesses who develop possible DITP while being treated with multiple
drugs may be relatively underreported, since clinicians may not be able
to implicate a single, potentially causative drug, and rechallenge with
a suspected drug may not definitely prove causation. While in this study
we have used a reported positive rechallenge as a criterion of a definite
causal association of a drug with thrombocytopenia, a rechallenge is not
necessarily accepted as proof of causation by drug safety surveillance
specialists because the persuasiveness of a reported rechallenge may be
highly situation-dependent.25

A second distinct and informative way to identify drugs that can
cause thrombocytopenia is to identify antibodies that react with platelets
only in the presence of the clinically suspected drug. A positive finding
provides very strong evidence that drug sensitivity is the cause of
thrombocytopenia and can be helpful for understanding the mechanisms
of DITP.26 Because antibody testing is ordered only when a particular
drug is suspected of being a possible cause of thrombocytopenia,
identification of drug-dependent, platelet-reactive antibodies reflects
clinical judgment as well as the laboratory test result. However tests to
identify drug-dependent, platelet-reactive antibodies are performed in few
specialized laboratories and physicians may not be aware of the
availability of these analyses. Even when laboratory analysis for drug-
dependent, platelet-reactive antibodies is performed, tests can be negative in patients with DITP because [1] assay methods may be insufficiently sensitive to detect some antibodies; [2] some drugs are relatively insoluble in water and are difficult to incorporate into *in vitro* assays; and [3] a metabolite of the drug formed *in vivo*, rather than the primary drug, may be responsible for the thrombocytopenia. A limitation of our data may be that we report results from only a single laboratory that primarily tests samples from the U.S.. There are other case reports of drug-induced thrombocytopenia describing drug-dependent antibodies. For example, Kroll, et al. described five patients with drug-induced thrombocytopenia and carbimazole-dependent antibodies. Gold has been reported to induce drug-independent autoantibodies to platelets, resulting in a syndrome similar to ITP. However for our analysis, data from the BloodCenter of Wisconsin, perhaps the largest resource for drug-dependent, platelet-reactive antibody testing in the United States, provided results from many samples submitted from across the United States using consistent methods across 14 years.

When the results of these two distinct methods of drug identification were combined, 351 drugs were identified that were suspected of causing thrombocytopenia. Although 130 (37%) of the 351 drugs had evidence for a causal association with thrombocytopenia by at least one of the two methods, only 104 (30%) drugs had been evaluated
by both methods and only 24 drugs were identified as being causal by both methods.

The third approach used was data mining of the FDA’s AERS database. Because reporting has been simplified by the MedWatch website, the AERS database may provide a more comprehensive list of drugs that can cause thrombocytopenia. The FDA’s quarterly reports of AERS data include all drugs and all adverse events but do not incorporate case level information from the clinical narratives of the individual MedWatch reports. AERS data cannot be used to assess actual risk or incidence because [1] reports are uncontrolled, not peer reviewed and are of uneven quality; [2] they are subject to numerous biases and reporting artifacts that may lead to both under-reporting and over-reporting of drug-event associations; and [3] they do not contain information on the number of persons exposed or at risk. Therefore data mining cannot determine whether a drug is causally associated with thrombocytopenia. Data mining algorithms to search the AERS database are a screening tool of existing data that can identify a statistical reporting association of drugs with thrombocytopenia. Therefore data mining may detect an initial signal that a drug is associated with thrombocytopenia that might be confirmed by subsequent clinical evidence and laboratory detection of drug-dependent antibodies. Also, if a drug had been associated with thrombocytopenia by clinical or
laboratory data, additional detection of a drug's association with thrombocytopenia by data mining may increase the level of suspicion for the drug's risk for causing thrombocytopenia. The sensitivity and/or lack of specificity of data mining was apparent by the identification of a statistically significant reporting association with thrombocytopenia for 482 drugs that did not have evidence for a causal relation with thrombocytopenia by either the clinical or laboratory methods.

The three methods for identifying drugs that can cause thrombocytopenia used in this study each have unique perspectives. No method was inclusive of all drugs that could cause thrombocytopenia and there was relatively little overlap among the drugs identified by each method. A potential limitation of our data was that data from each method were current to a different time in 2008 or 2009. Furthermore, the suspicion of drugs as a cause of thrombocytopenia and the resulting publication of case reports, submission of samples for laboratory testing, and/or reporting to the FDA MedWatch were not systematic, but were only the result of the initiative of individual clinicians. There is no basis for assuming that these data are representative of the U.S. population.

Even among the 102 drugs tested by all three methods, there was little overlap among the drugs identified by each method. Some drugs had evidence for an association with thrombocytopenia by one method but
not others, by only two of the methods, or by all three methods, or by none of the three methods. However the combined use of all three methods and their data sets to identify drugs with evidence for an association with thrombocytopenia provides the most complete useful current information for evaluation and management of patients with suspected DITP. The 612 drugs identified as being associated with thrombocytopenia by any of the three methods should be considered as possible causes of thrombocytopenia, provided that the associated clinical features, such as timing of the onset of thrombocytopenia in relation to drug administration, are also consistent with a diagnosis of DITP for the drug in question (Supplement Table S1). Perhaps important for patient evaluations, the 23 drugs found to be associated with thrombocytopenia by all three methods should be considered to be a likely cause of otherwise unexplained thrombocytopenia in any patient receiving them (Table 2). This interpretation is supported by the observation that six of the seven drugs that have been described in 10 or more case reports with “definite” or “probable” evidence for a causal association between the drug and thrombocytopenia and 11 of the 12 drugs for which drug-dependent, platelet-reactive antibodies have been identified in 10 or more patients are included among these 23 drugs.

However data obtained by the three methods are insufficient to accurately rank drugs against each other according to their relative risk
for causing thrombocytopenia. Future research may incorporate more quantitative information and epidemiologic analyses to develop algorithms that can inform physicians about the relative risks for thrombocytopenia with individual drugs. Improvement in causality assessment algorithms may be supported by future research to determine the risk of thrombocytopenia associated with each drug, related to the number of patients exposed to the drug. Since drug-dependent, platelet-reactive antibodies typically develop within one-two weeks after beginning a new drug (or over a longer period when a drug is taken intermittently) the number of patients who have been exposed to each drug is the important observation, rather than the duration of exposure to the drug. Currently, only limited data have been reported from population surveillance and case control studies. With wider use of electronic medical records, it may be possible for future studies to estimate these data.

The limited overlap among these three methods for identifying drugs that can cause thrombocytopenia and the difficulty of establishing an unequivocal diagnosis of DITP emphasizes the responsibility of clinicians to carefully consider possible drug etiologies in their evaluation of patients with thrombocytopenia. Careful clinical evaluation should include explicit questions about drug use, including the occasional use of over-the-counter drugs, quinine-containing beverages, and other non-
prescription remedies.30 The evaluation should also document the clinical criteria that are required to establish evidence for a causal association of the suspected drug with thrombocytopenia.9 If clinical evidence is not definite, or if a positive test for drug-dependent, platelet reactive antibodies has not been previously documented, consideration should be given to testing the patient for the presence of drug-dependent antibodies.11;12

If there is evidence that a drug caused thrombocytopenia, the physician should report his experience to the FDA MedWatch website (https://www.accessdata.fda.gov/scripts/medwatch/) for inclusion in the AERS database and also to the drug's manufacturers. Finally, if there are few case reports describing definite or probable clinical evidence for the drug's association with thrombocytopenia, it is important to publish this experience. The data derived from increased effort to document drugs as the cause of thrombocytopenia will help to develop causality assessment algorithms; these algorithms can then provide clinicians with more accurate information about which drugs are most likely to cause thrombocytopenia. Accurate information about drugs that can cause DITP will strengthen the ability of clinicians to assess future patients with suspected DITP as well as support the efforts of health professionals to provide drug safety surveillance.
ACKNOWLEDGEMENTS

We thank Ms. Shari C. Clifton, MLIS, AHIP, Professor/Head, Reference & Instructional Services, Robert M. Bird Health Sciences Library, University of Oklahoma Health Sciences Center, for her assistance with identifying resources for identification of drugs that are currently approved worldwide.

Support: This project was supported in part by The National Institutes of Health (HL-13629 and HL-44612, Drs. Aster and Bougie)

Authorship and Conflict of Interest Statements

Authorship: All authors designed the research, analyzed the data, and wrote the paper. RHA, DWB, and BRC performed tests for drug-dependent antibodies. MH performed the data mining. JAR, XL, JNG, and SKV synthesized the data.

Conflicts of interest: Ms. Li, Ms. Reese, Dr. Vesely, and Dr. George have no conflict of interest with the topic or data of this report. Dr. Aster and Mr. Curtis are partially supported by the BloodCenter of Wisconsin and its Laboratory of Platelet Immunology. Dr. Hauben is Medical Director of Risk Management Strategy for Pfizer, Inc., owns stock and stock options
in Pfizer, Inc., and owns stock in other pharmaceutical companies that may market drugs mentioned in this article or competing drugs from the same pharmacological/therapeutic classes as drugs mentioned in this article.
Reference List


TABLE LEGENDS

Table 1. Comparison of analyses of 351 drugs that were suspected causes of thrombocytopenia by clinical criteria in published case reports and/or by laboratory identification of drug-dependent, platelet-reactive antibodies. The symbol [+1] indicates evidence for a causal association with thrombocytopenia by clinical evidence and/or by detection of drug-dependent antibodies; [-] indicates drugs described in case reports that did not provide evidence for a causal association with thrombocytopenia, and/or were submitted for laboratory testing for drug-dependent antibodies but none were identified; [0] indicates drugs not described in case reports and/or not submitted for laboratory testing. The 253 drugs evaluated by case reports are represented in the first (left) two columns. The 202 drugs evaluated by laboratory testing are represented in the top two rows (lines). The 351 drugs evaluated by both case reports and laboratory testing are represented by the sum of all three lines and columns. The 24 drugs that had evidence for a causal association with thrombocytopenia by both case reports and detection of drug-dependent antibodies are represented in the top left cell. In addition to these 24 drugs, 106 drugs (22 + 21 in the top row [line] and 19 + 44 in the first [left] column) had evidence for causal association with thrombocytopenia by either published case reports or detection of drug-dependent platelet reactive antibodies. Therefore, 130 drugs (24 + 106) had evidence for
causal association by either cause reports and/or detection of drug-dependent antibodies.

**Table 2.** Twenty-four drugs with evidence for a causal association with thrombocytopenia by both clinical data from published case reports and by identification of drug-dependent, platelet-reactive antibodies are listed. Twenty-three of these drugs also had a statistically significant reporting association with thrombocytopenia by data mining of the AERS database.

These six drugs had clinical evidence for a causal association with thrombocytopenia in ten or more case reports and have been identified by the presence of drug-dependent, platelet reactive antibodies in ten or more patients.

†These 11 drugs had evidence for a causal association with thrombocytopenia by detection of drug-dependent, platelet reactive antibodies in ten or more patients.

‡For acetaminophen and naproxen, drug-dependent antibodies have only been identified for metabolites and do not react with the unmodified drug. For ibuprofen, drug-dependent antibodies that reacted with the unmodified drug have been identified in some patients; in other patients drug-dependent antibodies only reacted with metabolites of ibuprofen.
Table 3. Data mining analysis of the FDA AERS database compared to the results of analysis by clinical criteria in published case reports and by identification of drug-dependent platelet-reactive antibodies for 1468 drugs that were suspected causes of thrombocytopenia. The symbol [+\(\cdot\)] indicates a statistically significant reporting association with thrombocytopenia by data mining or evidence for a causal association with thrombocytopenia by clinical evidence and/or by detection of drug-dependent antibodies; [-\(\cdot\)] indicates the absence of a statistically significant reporting association with thrombocytopenia or the absence of clinical and laboratory evidence for a causal association with thrombocytopenia; [0\(\cdot\)] indicates drugs not reported to the AERS database in association with thrombocytopenia, not described in case reports, or not submitted for laboratory testing. 130 drugs had evidence for causal association with thrombocytopenia by either published case reports and/or detection of drug-dependent platelet reactive antibodies (first, left column). 573 drugs had a statistically significant reporting association with thrombocytopenia by data mining (top row [line]). 91 drugs had evidence for causal association by case reports and/or laboratory analysis and data mining (top left cell). In addition to these 91 drugs, 521 drugs (112 + 370 in the top row [line] and 30 + 9 in the first [left] column) had evidence for a causal association with thrombocytopenia by either published case reports and/or detection of drug-dependent platelet reactive antibodies or by data mining. Therefore, a total of 612 drugs (91
had evidence for causal association by one or more of the three methods.

Table 4. The results of analysis by each method and each combination of methods for the 102 drugs that were tested by all three methods.
Table 1. Comparison of analyses by clinical criteria in published case reports and by laboratory identification of drug-dependent, platelet-reactive antibodies of 351 drugs that were suspected of causing thrombocytopenia.

<table>
<thead>
<tr>
<th>Laboratory (n=202)</th>
<th>Clinical Criteria (n=253)</th>
<th>(n=98) 0 (not reported)</th>
<th>TOTAL</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>+</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>(n=149)</td>
<td>24</td>
<td>22</td>
<td>67</td>
</tr>
<tr>
<td></td>
<td>19</td>
<td>39</td>
<td>135</td>
</tr>
<tr>
<td></td>
<td>44</td>
<td>105</td>
<td>149</td>
</tr>
<tr>
<td>TOTAL</td>
<td>87</td>
<td>166</td>
<td>351</td>
</tr>
</tbody>
</table>
Table 2. Drugs with evidence for association with thrombocytopenia by clinical data in published case reports, identification of drug-dependent, platelet-reactive antibodies, and data mining of the AERS database.

<table>
<thead>
<tr>
<th>Drugs associated with thrombocytopenia by all 3 methods</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abciximab†</td>
</tr>
<tr>
<td>Acetaminophen‡</td>
</tr>
<tr>
<td>Ampicillin</td>
</tr>
<tr>
<td>Carbamazepine¢†</td>
</tr>
<tr>
<td>Eptifibatide†</td>
</tr>
<tr>
<td>Ethambutol</td>
</tr>
<tr>
<td>Haloperidol</td>
</tr>
<tr>
<td>Ibuprofen‡</td>
</tr>
<tr>
<td>Irinotecan</td>
</tr>
<tr>
<td>Naproxen‡</td>
</tr>
<tr>
<td>Oxaliplatin</td>
</tr>
<tr>
<td>Phenytoin†</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Drug associated with thrombocytopenia by case reports and laboratory testing but not significant by data mining</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amiodarone</td>
</tr>
</tbody>
</table>

For personal use only.
Table 3. Comparison of analyses by data mining of the FDA AERS database to the results of analysis by clinical criteria in published case reports and by identification of drug-dependent, platelet-reactive antibodies for 1468 drugs that were suspected causes of thrombocytopenia.

<table>
<thead>
<tr>
<th>Data Mining</th>
<th>Clinical and/or Laboratory (n=351)</th>
<th>Laboratory (n=1117)</th>
<th>TOTAL</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>+</td>
<td>-</td>
<td>0 (not reported/tested)</td>
</tr>
<tr>
<td>(n=1444)</td>
<td>91</td>
<td>112</td>
<td>370</td>
</tr>
<tr>
<td></td>
<td>-</td>
<td>30</td>
<td>94</td>
</tr>
<tr>
<td>(n=24)</td>
<td>9</td>
<td>15</td>
<td>0</td>
</tr>
<tr>
<td>TOTAL</td>
<td>130</td>
<td>221</td>
<td>1117</td>
</tr>
</tbody>
</table>
Table 4. Evidence for a causal association with thrombocytopenia among the 102 drugs analyzed by all three methods: case reports, laboratory identification of drug-dependent, platelet-reactive antibodies, and data mining of the FDA AERS database

<table>
<thead>
<tr>
<th>Result</th>
<th>No. of Drugs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Evidence by all 3 methods</td>
<td>23</td>
</tr>
<tr>
<td>Evidence by case reports and laboratory</td>
<td>1</td>
</tr>
<tr>
<td>Evidence by case reports and AERS</td>
<td>16</td>
</tr>
<tr>
<td>Evidence by laboratory and AERS</td>
<td>15</td>
</tr>
<tr>
<td>Evidence only by case reports</td>
<td>3</td>
</tr>
<tr>
<td>Evidence only by laboratory</td>
<td>5</td>
</tr>
<tr>
<td>Evidence only by AERS</td>
<td>25</td>
</tr>
<tr>
<td>No evidence by any method</td>
<td>14</td>
</tr>
<tr>
<td><strong>Total drugs analyzed</strong></td>
<td><strong>102</strong></td>
</tr>
</tbody>
</table>
FIGURE LEGEND

Figure 1A illustrates the results of analysis by published case reports, and the relation of the results to analysis by the other two methods. Not all of the 87 drugs with evidence in case reports were also analyzed by the other two methods. Figure 1B illustrates the results of analysis by laboratory detection of drug-dependent, platelet-reactive antibodies, and the relation of the results to analysis by the other two methods. Not all of the 67 drugs with evidence by documentation of drug-dependent antibodies were also analyzed by the other two methods. Figure 1C illustrates the results of analysis by data mining of the AERS database, and the relation of the results to analysis by the other two methods. Not all of the 573 drugs with evidence in the AERS database were also analyzed by the other two methods.
Figure 1C

1468 Drugs evaluated

24 Drugs not reported to AERS database

1444 Drugs reported to AERS database

871 Drugs with no evidence in AERS database

573 Drugs with evidence in AERS database

482 Drugs with evidence only by AERS

40 Drugs with evidence also by case reports

28 Drugs with evidence also by laboratory

23 Drugs with evidence by all three methods
Identifying drugs that cause acute thrombocytopenia: an analysis using three distinct methods

Jessica A. Reese, Xiaoning Li, Manfred Hauben, Richard H. Aster, Daniel W. Bougie, Brian R. Curtis, James N. George and Sara K. Vesely