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REVIEW ARTICLE

Vancomycin-Induced Thrombocytopenia: A Narrative Review

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Abstract Thrombocytopenia has been reported as an adverse reaction of numerous drugs. Vancomycin is often overlooked as a culprit but has been associated with several cases of thrombocytopenia that were not well described in the literature. A literature search was conducted to find reports of thrombocytopenia induced by vancomycin. Biomedical databases including 'PubMed', 'Scopus', and 'Web of Science' were searched using terms 'vancomycin', 'platelet', 'pancytopenia', 'thrombocytopenia', and 'bleeding'. English language articles published before July 2015 were included. Thirty-nine papers including 29 case reports (30 cases), five observational studies, two clinical trials, two letters, and one case series remained for final analysis. The main route of administration was intravenous infusion. This adverse reaction seems to be duration dependent with the mean time to platelet nadir count of 8 days in reported cases. The interval may be significantly shorter in re-exposure to the drug. Platelet nadir counts ranged from 2000 to 100,000/mL in patients who experienced bleeding. Vancomycin-specific antibodies were detected in 13 of 17 patients who were tested in the case reports. Based on the Naranjo Adverse Drug Reaction Probability Scale, reaction was 'definite', 'probable', and 'possible' in 1, 15, and 14 patients, respectively. Among 30 cases, vancomycin was discontinued in 29 patients and platelets returned to normal counts within 5–6 days in 17 of them; in one patient, vancomycin was not discontinued, but platelet count recovered 11 days after the nadir time. Transfusion might be recommended if severe thrombocytopenia and bleeding occurs. Intravenous immunoglobulins, corticosteroids, rituximab, and plasma exchange should be reserved for patients with resistant thrombocytopenia and severe bleeding as mentioned in a number of reports.

Key Points

Vancomycin-induced thrombocytopenia seems to be a duration-dependent reaction.

Diagnosis is often challenging because of concurrent contributing factors and a lack of a definite diagnostic test.

The decision regarding discontinuation of the drug should be made based on a patient's clinical status.

1 Introduction

Drug-induced thrombocytopenia (DIT) has been reported as an adverse reaction of over 300 medications [1, 2]. Nearly ten cases per 1,000,000 patients develop DIT annually. Results of limited epidemiological studies could not identify the probable risk factors for DIT [3]. Whenever an acute thrombocytopenia occurs without a known cause, DIT is a differential diagnosis [4]. Distinction among proposed diagnoses is a complicated and time-consuming process in thrombocytopenic disorders, and DIT is often overlooked. Early diagnosis of DIT is crucial as it leads to timely discontinuation of the offending agent and

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avoidance of unnecessary treatments. For instance, the rate of DIT-related severe and non-severe bleeding was reported to be 6 and 67%, respectively [5]. Therefore, possible DIT complications necessitate a prompt action. Determination of the real cause among different medications that may be used concurrently is a major challenge for the clinicians [6].

Medications may induce thrombocytopenia through non-immune or immune-mediated processes. The myelosuppressive effect of medications such as antineoplastics, antivirals, thiazide diuretics, and tolbutamide is the main non-immune mechanism of DIT through decreased platelet production [5, 7]. A non-immune-mediated increase in platelet destruction can also be a process involved in the pathogenesis of DIT [8]. Immune-mediated drug-dependent destruction of platelets is another mechanism underlying DIT. Various mechanisms have been proposed for this idiosyncratic hypersensitivity reaction and most commonly documented mechanisms are hapten formation (e.g., penicillin, cephalosporin), quinine type (e.g., sulfonamides, non-steroidal anti-inflammatory drugs), fiban type (e.g., glycoprotein IIb/IIIa inhibitors [eptifibatide, tirofiban]), drug-specific antibody formation (e.g., abciximab), autoantibody formation (e.g., procainamide), and immune complex formation (e.g., heparins) [1].

Antibiotics can often induce thrombocytopenia and should be considered as a cause of DIT [8]. Vancomycin, a commonly used glycopeptide antibiotic, has been reported to be a cause of DIT [9]. Vancomycin is used abundantly for the treatment of Gram-positive infections particularly due to methicillin-resistant *Staphylococcus aureus* [10]. Although vancomycin is considered a relatively safe and tolerable medication, serious adverse reactions including hematologic side effects that have been reported infrequently could complicate patient treatment [7, 10]. Hematologic cytopenia is one of the serious adverse drug reactions of vancomycin among which neutropenia has been described well in the literature with an estimated frequency of 2–12% [11].

Vancomycin-induced thrombocytopenia (VIT) is much less explained and its real incidence remains unknown [2, 12]. VIT seems to be under-diagnosed in the clinical settings and probably occurs more frequently than usually expected. VIT was first reported in 1985 and was further explained in the published case reports [12–36]. A case series study on VIT has been published recently in which clinical course, presentation, and serologic findings of 29 patients were described [9]. In this report, the causality of detected vancomycin-dependent antiplatelet antibodies in VIT occurrence was concluded [9]. Although it seems that vancomycin induces thrombocytopenia through immune-mediated mechanisms, mainly the hapten formation, alternative mechanisms remain to be clarified [30]. To the extent of our knowledge, VIT has not been reviewed yet in the literature.

2 Methods

Our purpose was to find all English published reports of thrombocytopenia caused or suspected to be caused by vancomycin. A systematic search was conducted using terms 'vancomycin', 'platelet', 'pancytopenia', 'thrombocytopenia', and 'bleeding'. Biomedical databases comprised PubMed, Scopus, and Web of Science. A general search using the same keywords was also performed with Google Scholar. We applied no time limit on our search. All database searches were completed on July 2015. Eligible publications were observational studies, clinical trials, letters, case reports, and case series with detailed treatment history, so that the evaluation of causality could be performed reliably. Considering other publication types, we excluded conference abstracts, proceedings, dissertations, and book chapters. We also excluded non-English papers and irrelevant articles. Articles in which no data were provided regarding VIT frequency, mechanism, diagnosis, clinical course, presentation, and management were considered to be irrelevant and excluded.

Two authors (ZJR and AS) independently performed the searches and imported the records into the bibliographic software EndNote X4 (Thomson Reuters, NYC, USA). They evaluated the records based on the title and abstract. Disagreements were solved by discussion and the full text of the selected articles were reviewed for final inclusion. In the case of unavailability of the full texts, we contacted the authors through their e-mail addresses to provide us with detailed information. We also contacted the authors of case reports if the probability of VIT had not been appraised using a valid tool. In such cases, the probability was determined using th eNaranjo Adverse Drug Reaction Probability Scale [37] and George et al. criteria [38, 39] and the authors confirmed the assessment. Two other colleagues (MM and MTG) engaged in correspondence with authors and data extraction.

3 Results

3.1 Overview

The flow diagram for literature review process and article selection is presented in Fig. 1. The primary search in the mentioned resources yielded 810 records. After removing duplicates and screening the titles, 303 records were selected for further evaluation. Irrelevant articles and conference abstracts were excluded based on abstract

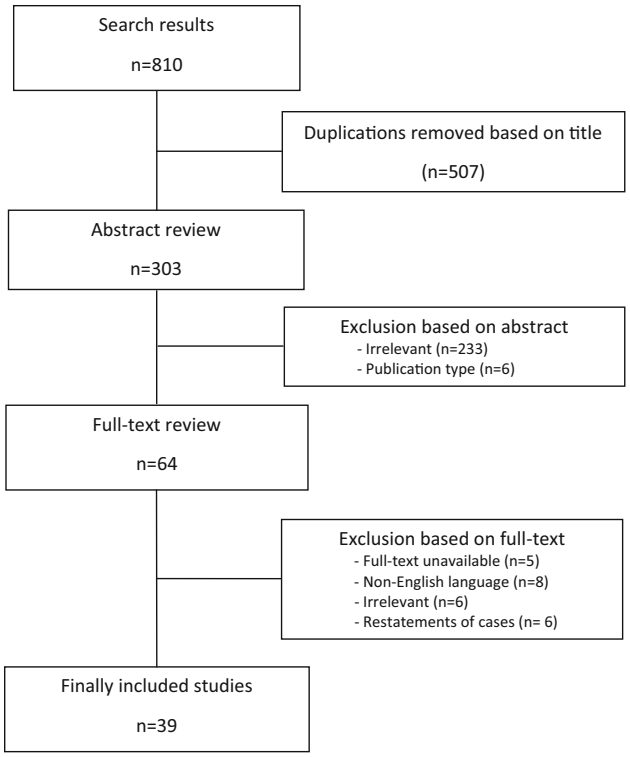

Fig. 1 Summary of literature review process

screening. We found no narrative review, systematic review, and meta-analyses specifically focused on the topic of our review. Two narrative reviews and four systematic reviews and meta-analyses were found in the primary search. However, considering the title and the abstract, none of them covered relevant and valuable information regarding VIT. Therefore, we excluded them from further evaluation. For five of the records including four older studies published between 1985 and 1997, no full texts were found [36, 40–43]. Although the authors were contacted through e-mails, we received no answer. Consequently, we did not consider these records in further evaluations. We also excluded eight records from the literature review because their full texts were not in English. Thirty-nine articles remained for data extraction.

We finally included 29 case reports of VIT, five observational studies, two clinical trials, two letters, and one case series. Demographic characteristics were reported uniformly in all published case reports, but there was not a consistent tendency regarding dose, concurrent medications, transfusion resistance, and signs or symptoms of bleeding. The first reported case of VIT dates back to 1985 and the last was reported in 2015. All case reports are summarized in Table 1. Thirty cases are mentioned in Table 1 because Christie et al. described two patients in their report [18].

Results from publications other than case reports further delineate the correlation between detected vancomycin-specific antibodies and the occurrence of thrombocytopenia. Furthermore, they help to make comparisons of vancomycin and potential alternatives regarding hematologic adverse effects.

3.2 Prevalence/Incidence

As the available information regarding VIT has been mainly derived from published case reports, the real incidence of this adverse reaction remains to be unknown. The incidence of VIT has been stated to be low despite widespread use of the medication. However, the reported prevalence of 5.9 and 7.1% in two retrospective studies was higher than what was expected [49, 50]. Reported values from these studies may be far from the real incidence because the evaluation of causality may not be possible in retrospective studies. However, variations in the thrombocytopenia definition exist among studies.

3.3 Mechanisms/Pathogenesis

Pathogenesis of VIT is not well understood. Although there is some evidence that supports the immune-mediated mechanisms, the process involved in antibody formation and consequent platelet destruction is not well defined [9, 51].

Detection of vancomycin-dependent, platelet-reactive antibodies revealed positive results in more than half of the cases for whom tests were performed [13, 18, 20, 22, 24, 25, 27, 31, 33, 44–46]. Hapten-dependent antibody formation is the most cited mechanism that has been proposed for VIT. It is postulated that vancomycin binding to platelet glycoproteins induces the generation of antibodies. These antibodies are attached to the drug-platelet complex, causing cell lysis [2]. Another proposed mechanism is the increased affinity of drug-dependent antibodies derived from naturally occurring antibodies to the targeted platelet membrane proteins in the presence of the drug [4, 52]. Further investigations regarding the underlying mechanism of VIT in a case series published by Von Drygalski et al. revealed that the detected antibodies reacted with platelets only in the presence of vancomycin, which was consistent with a quinine-type reaction [9]. No vancomycin-dependent antibody was detected in 25 patients who received vancomycin and did not develop thrombocytopenia. Furthermore, an immunoglobulin M vancomycin-dependent antibody was detected in a serum sample of one patient among 451 normal subjects. Consequently, the authors concluded that naturally occurring antibodies may rarely contribute to the development of thrombocytopenia following treatment with vancomycin [9].

Table 1 Summary of case reports

No.	Author, year	Age	Sex	Indication	Route	Dose (g/day)/ trough level	Duration of use (days)	Platelet nadir (per mL)	Time to nadir (days)	Time to recovery (days)	Naranjo score	George et al. score	Vancomycin-dependent antibodies	Bleeding sign or symptom
1	Ahmed et al. [44], 2015	63	M	Diabetic foot	IV	NR/16.3	14	2000	15	6–10	Probable	Probable	+	−
2	Anand et al. [13], 2011	54	M	Cellulitis	IV	NR	6	100,000	6	2	Possible	Excluded	+	+
3	Apiwattanakul et al. [14], 2008	16	F	Endocarditis	IV	NR	8	123,000	9	5	Possible	Excluded	Not tested	−
4	Arnold et al. [45], 2013	66	F	Endocarditis	IV	NR	9	4000	9	NR	Probable	Possible	+	+
5	Bay et al. [15], 2006	2	M	Pneumonia	IV	NR	NR	11,000	14	4	Possible	Possible	−	NR
6	Candemir et al., [16] 2012	54	F	Implantable cardioverter defibrillator pocket hematoma	IV	2/NR	15	49,000	12	4	Probable	Excluded	NR	NR
7	Carmichael et al. [17], 1986	42	F	Endocarditis	IV	1/NR	1	82,000	2	9	Possible	Excluded	NR	NR
8	Christie et al. [18], 1990	73	F	Pneumonia	IV	NR	10	14,000	10	2	Probable	Possible	+	NR
9	Christie et al. [18], 1990	31	M	Fever	IV	NR	19	<10,000	8	11 (not discontinued)	Possible	Possible	+	NR
10	Dilli et al. [35], 2008	Neonate	M	Sepsis/pneumonia	IV	NR	10	41,000	10	4	Possible	Possible	−	NR
11	Ganly et al. [12], 2011	67	M	Sepsis	IV	NR/24	6	2000	9	8	Possible	Possible	−	+
12	Govindarajan et al. [19], 1999	72	M	Epidural abscess	IV	NR	28	13,000	18	10	Probable	Possible	NR	NR
13	Kenney et al. [20], 2008	61	M	Gangrene and bacteremia	IV	NR	4	3000	0.5	4	Probable	Possible	+	+
14	Kuruppu et al. [21], 1999	72	F	Endocarditis	IV	NR	6	14,000	7	5	Possible	Possible	−	NR
15	Lee et al. [22], 2009	76	M	Diabetic foot	IV	NR	12	<15,000	11	5	Possible	Possible	+	NR
16	Lobo et al. [46], 2015	67	M	Pneumonia	IV	1/sub-therapeutic	3	2000	4	3	Probable	Possible	+	+
17	Marraffa et al. [23], 2003	50	M	Endocarditis	IV	2/therapeutic window	10	1000	7	5	Probable	Probable	Not tested	+
18	Mizon et al. [24], 1997	71	F	Septicemia	IV	First episode: 1.5/NR Second episode: 2/NR	First: 16 Second: 3	First: < 10,000 Second: 2000	First: 2 Second: 3	First: 3 Second: 4	Probable	Possible	+	+

Table 1 continued

No.	Author, year	Age	Sex	Indication	Route	Dose (g/day)/ trough level	Duration of use (days)	Platelet nadir (per mL)	Time to nadir (days)	Time to recovery (days)	Naranjo score	George et al. score	Vancomycin-dependent antibodies	Bleeding sign or symptom
19	O'Donnell et al. [25], 2007	56	F	Knee prosthesis removal	In cement	4/NR		<10,000	0.16	7	Possible	Possible	+	+
20	Ortin et al. [26], 2008	47	M	Peritonitis	IP	2/NR	1	4000	8	40	Possible	Excluded	−	+
21	Pauldine et al. [27], 2008	60	M	Ventilator-associated pneumonia	IV	NR	1	10,000	3	12	Possible	Possible	+	+
22	Peel et al. [28], 2003	45	M	Peritonitis	IP	2 (on days 1, 3, 7, 10)/10.8, 13.2, 17.6	10	5000	11	7	Probable	Possible	Not tested	+
23	Rocha et al. [29], 2002	38	F	Hip prosthesis infection	IV	2/NR	10	68,000	10	4	Possible	Excluded	NR	NR
24	Rowland et al. [47], 2013	51	M	Acute pancreatitis	IV	2/therapeutic window	8	9000	8	5	Probable	Possible	Not tested	+
25	Ruggero et al. [30], 2012	41	M	First admission: hospital-acquired pneumonia, second admission: sepsis	IV	1/NR	First: 5 Second: 1	First: 15,000 Second: 81,000	First: 5 Second: 1	First: 5 Second: 5	Definite	Possible	−	−
26	Shah et al. [31], 2009	60	M	Shoulder infection	IV	3/14.7	20	6000	20	3	Possible	Possible	+	+
27	Shahar et al. [32], 2000	43	F	Surgery-site infection	IV	NR	14	118,000	NR	4	Probable	Excluded	NR	NR
28	Wetzel et al. [48], 2013	64	F	Sepsis	IV	NR	2	7000	0.3	8	Probable	Possible	NR	−
29	Winteroll et al. [33], 2004	72	M	Sepsis	IV	1/NR	3	3000	6	10	Probable	Possible	+	+
30	Zenon et al. [34], 1991	54	M	Cellulitis	IV	First episode: 2/NR Second episode: 1/NR	First: 3 Second: 1	First: 17,000 Second: 11,000	First: 2 Second: 0.5	First: 6 Second: 7	Probable	Possible	NR	NR

F female, *IP* intraperitoneal, *IV* intravenous, *M* male, *NR* not reported, + indicates yes, − indicates no

Considering different detected pre- and post-exposure vancomycin-dependent anti-platelet antibodies (immunoglobulin G vs. immunoglobulin M) in the case of VIT reported by Kenny et al., the authors proposed two mechanisms for VIT [20]. One mechanism was the development of VIT through the reaction of naturally occurring antibodies with respect to a negative history of vancomycin exposure. Another postulation was a previous immunogenic exposure and pre-existing B cells, which corresponded to the rapid formation of immunoglobulin M and likely re-exposure anamnestic response. Although the patient had no recorded prior exposure to vancomycin, it was not unlikely in view of his past medical history and the authors concluded that the anamnestic response was the more probable underlying mechanism [20].

3.4 Clinical Presentation

Generally, it can be said that a period of at least 6 days is needed after drug exposure to mount an immune response and reach the platelet nadir count [9]. The mean time to platelet nadir count was about 8 days after the first exposure in reported cases. It is compatible with the 5- to 10-day time frame that has been described for classic DIT occurrence [45]. It should be noted that the interval may be significantly shorter in the case of re-exposure to the drug, so that in one patient thrombocytopenia occurred only after 4 h of re-exposure to vancomycin [25]. In those patients who developed two episodes of VIT, the time to the second nadir count was also significantly short, in order that it occurred after 0.5, 1, and 3 days of treatment for three patients in second episodes of suspected VIT [24, 30, 34]. Although it remains unknown why some patients experienced too rapid a fall in platelet counts, the presence of naturally occurring antibodies to vancomycin in healthy people may justify the rapid decline in the platelet counts of some patients even after a single dose of vancomycin [9].

Bleeding with various degrees of severity was reported for about half of the cases. Because the bleeding status was not reported for the remaining half of the cases, the true incidence of bleeding remains to be clarified. Seven out of 14 patients in whom bleeding was reported experienced mild to moderate bleeding defined as petechia or ecchymoses [13, 20, 26–28, 31, 45]. Platelet nadir count in these cases ranged from 2000 to 10,000/mL, except for one patient [13] who had a platelet count of 100,000/mL. Seven patients had severe bleeding episodes manifested as wet purpura or active bleeding from a site [12, 23–25, 33, 46, 47]. Platelet nadir counts for these patients ranged from less than 1000 to 10,000/mL. In three patients with platelet nadirs of 2000, 7000, and 15,000/mL, no bleeding occurred [30, 44, 48].

In the study by Von Drygalski et al., platelet count dropped to about 7% of baseline counts and reached a mean number of 13,600/mL in about 8 days after vancomycin initiation. In this study, one third of the patients experienced severe bleeding with a mean platelet count of 8400/mL, while the mean platelet count was 35,000/mL in asymptomatic patients. Therefore, based on available data, the association between nadir count and severity of bleeding cannot be concluded. However, it has been noted that in similar platelet counts, the severity of bleeding is higher in VIT compared with thrombocytopenia induced by other causes [9].

Concomitant pancytopenia was reported in five cases [14, 17, 29, 32, 44]. Eight patients experienced signs or symptoms of hypersensitivity reactions at the time of vancomycin administration [14, 16, 17, 22, 26, 29, 32, 47]. These included but were not limited to rash and fever. Red man syndrome was reported in two cases [17, 32].

3.5 Vancomycin Serum Concentration

Trough levels were reported in seven papers [12, 23, 28, 31, 44, 46, 47]. Five figures were within the therapeutic window of 10–20 mcg/L, one figure was subtherapeutic, and the last one was 24 mcg/L. In a study by Patel and coworkers, there was a straight association between the highest trough level of vancomycin in the first 7 days of treatment and the risk of at least a 50% decrease in the platelet count [53]. Although the reaction can occur at concentrations usually achieved in clinical practice, it must be emphasized that achieving the proposed trough levels is mandatory to prevent unnecessary supratherapeutic serum levels with subsequent thrombocytopenia [54]. However, it is not clear which pharmacokinetic parameter of vancomycin (i.e., trough, peak, or area under the concentration-time curve) is associated with thrombocytopenia and could be considered as a predictive factor.

3.6 Vancomycin Dose and Route of Administration

A daily or cumulative dose of vancomycin was not reported consistently in reported cases. In one case, only a single dose of medication precipitated the reaction [17]. The reported daily doses varied between 1 and 4 g. The minimum reported cumulative dose of vancomycin prior to the occurrence of thrombocytopenia was 1 g [17, 30, 34] and the maximum was 60 g [31]. With respect to the observed variation, it seems that VIT is not a function of cumulative doses, and other factors such as duration of use may play a more important role in the occurrence of VIT.

In one case, vancomycin was loaded in an orthopedic cement [25]. Intraperitoneal administration was performed for two patients undergoing continuous ambulatory peritoneal dialysis [26, 28]. All remaining patients received vancomycin by intravenous infusion.

3.7 Diagnosis

True diagnosis of VIT is quite challenging because the contribution of other suspected causes of thrombocytopenia must be ruled out before considering vancomycin as the causative factor. Primary immune thrombocytopenia, disseminated intravascular coagulation, heparin-induced thrombocytopenia, and concomitant use of other medications are among the most commonly encountered conditions that may contribute to the development of thrombocytopenia. For some patients, the underlying disease itself may be the precipitating factor.

Possible contributors to thrombocytopenia were reported for the majority of cases. Other drugs with thrombocytopenia-inducing potential were also used simultaneously with vancomycin. Concurrent medications included piperacillin in four cases [13, 22, 30, 48], gentamicin in three cases [35, 45, 46], penicillin [14, 15], cefepime [29, 48], and ciprofloxacin [28, 31] each for two patients, and ceftazidime [20], fusidic acid [24], teicoplanin [26], linezolid [27], imipenem/cilastatin [29], carbamazepine, phenytoin, ranitidine, and digoxin [45] each in one case.

Considering Heparin induced thrombocytopenia (HIT), one of two patients who had no history of prior heparin use [23, 25] was positive for the heparin-specific antibody [23]. Among nine patients with reported heparin use, seven cases were negative for antibodies [12, 13, 24, 27, 30, 31, 33]. No data regarding the history of heparin use and performed tests for antibody detection were provided in other case reports. The contribution of disseminated intravascular coagulation (DIC) was ruled out in 12 patients [13, 15, 16, 24, 26–28, 30, 31, 35, 46, 47]. For other patients, it was not reported whether a DIC assessment had been carried out. The presence of platelet-reactive antibodies against concurrent medications was also assessed as appropriate for clinical suspicion in some cases [20, 22–24, 27, 30, 31, 33].

The lack of a clear explanation regarding ruling out other causes of thrombocytopenia was a major pitfall in nearly half of the reports [12, 14, 17–23, 25, 29, 32–34, 45]. Moreover, concurrent use and relatively simultaneous discontinuation of other medications with vancomycin made the definite diagnosis of VIT questionable in some of the cases [14, 15, 29, 30, 45, 48].

Among 17 cases in whom the presence of vancomycin-dependent platelet-reactive antibodies was assessed and reported, 13 patients revealed positive results [13, 18, 20, 22, 24, 25, 27, 31, 33, 44–46]. In the case series of VIT reported by Von Drygalski et al., platelet-reactive antibodies were identified in 34 patients [9]. Detected vancomycin-dependent platelet reactive antibodies among 29 patients with follow-up information were of immunoglobulin G class in 16 patients, immunoglobulin M class in three patients, and both classes in ten patients [9].

The detection of reactive antibodies can help with the diagnosis, but it bears some limitations. First, it is not widely available. Second, the true sensitivity of these tests is not clear. Third, the testing for antibodies is a time-consuming process that may be detrimental in some situations. Finally, the test results may become negative even in some cases graded as ‘definite’ according to the scoring tools [1]. The Naranjo Adverse Drug Reaction Probability Scale [37] and George et al. criteria [38, 39] together with the detection of reacting antibodies may assist clinicians with the VIT diagnosis.

The likelihood of vancomycin contribution to the observed thrombocytopenia, either reported by the authors or calculated based on the presented history, is described in Table 1. In 6 out of 30 cases, the Naranjo Adverse Drug Reaction Probability Scale was reported by the authors [23, 28, 30, 32, 46, 47]. George et al. criteria was reported for one patient by the author [33]. Among authors to whom emails were sent to confirm the calculated probability scales, only five authors replied [16, 21, 35, 44]. One case of definite VIT was reported based on the Naranjo Adverse Drug Reaction Probability Scale [30] and none were definitely caused by vancomycin according to George et al. criteria. Seven patients were excluded for evaluation by this criteria [13, 14, 16, 17, 26, 29, 32].

The Naranjo Adverse Drug Reaction Probability Scale was developed in 1991 to standardize the assessment of causality for adverse drug reactions [37]. It is the most widely accepted instrument for evaluating the probability of adverse drug reactions because of its validity and simplicity. Using the questionnaire containing ten queries, probability is assigned via a score termed as ‘definite’, ‘probable’, ‘possible’ or ‘doubtful’.

Considering the Naranjo Adverse Drug Reaction Probability Scale, vancomycin was a possible cause of thrombocytopenia in nearly half of the patients. It seems that the Naranjo Adverse Drug Reaction Probability Scale could not perform well in the causality assessment of reported cases owing to the presence of various alternative causes and the impossibility of a re-challenge in most of the clinical situations.

In 1998, George et al. used clinical criteria to evaluate each case of DIT and to establish the causality of the culprit medication [39]. Using the mentioned criteria, they identified many medications that induced thrombocytopenia and developed a list that has been updated regularly and is available online (http://www.ouhsc.edu/platelets) [38, 45].

Exclusion of other potentially implicated drugs and re-administration of the suspicious medication are usually impossible in clinical practice. Similar to the pitfalls

mentioned for the Naranjo Adverse Drug Reaction Probability Scale, these limitations could be attributed to the George et al. criteria. According to the criteria, insufficient clinical data for the causality assessment and platelet count of 100,000/mL or more are two items based upon cases that should be excluded from further evaluation. Consequently, seven reported cases in our review were excluded from evaluation by George et al. criteria [39].

Currently, there is not a universally accepted gold standard test for the diagnosis of DIT including vancomycin. It seems that the ultimate decision must be made based on clinical suspicion. Experts have proposed a clinical approach to the diagnosis and management of a patient with new-onset thrombocytopenia in whom drug-induced immune thrombocytopenia is suspected [45]. This systematic approach combined clinical and laboratory criteria to identify the culprit medication.

3.8 Management

In nearly all patients in the included case reports, whenever VIT was suspected, treatment with vancomycin was discontinued. Vancomycin was replaced with appropriate antibiotics based on an indication in 15 patients [14–16, 19–23, 27, 29–31, 34, 44, 45]. In other cases, discontinuation of the drug with close monitoring of the patient was implemented. Vancomycin was not discontinued in one case, but platelet count recovered 11 days after the nadir time [18]. The vancomycin-loaded cement was removed from the knee of a patient with suspected VIT [25]. In the only reported case series, vancomycin was discontinued in 14 of 29 patients suspected to have VIT [9]. In the remaining 15 cases, thrombocytopenia was initially attributed to other causes and vancomycin was continued for 1–14 days [9].

The critical step after suspicion of VIT is to decide whether to continue or discontinue the medication. Most of the bleeding episodes were reported in patients with platelet nadirs less than 10,000/mL. However, it might be potentially life threatening to wait for the mentioned platelet counts before discontinuing vancomycin. A case of platelet restoration from very low counts without bleeding despite continued vancomycin use has been reported [18]. The benefits of continued therapy vs. the risk of severe bleeding should be balanced in making a decision in cases that vancomycin is believed to be critical for treating the underlying infection and no proper alternative exists. Another factor that should be monitored closely is the trend of a fall in platelet counts. Too rapid falling necessitates vigilant continuation of vancomycin because the extent of a fall cannot be estimated accurately and discontinuing the medication in higher counts should be taken into consideration.

Restoration of platelet count after the discontinuation of vancomycin is a function of the degree of renal insufficiency. A mean of 7.2 days was required for platelet count recovery to 150,000/mL after vancomycin discontinuation in the study by Von Drygalski et al. while three of patients with impaired renal function remained extremely thrombocytopenic for 7–8 days [9]. In patients with severe renal insufficiency, it may take several weeks to reach normal platelet counts because vancomycin circulates in the body for a long time because of slow clearance [55]. In the case reported by Ortin et al., thrombocytopenia resolved after 40 days in a patient undergoing peritoneal dialysis [26], while the mean time for the restoration of platelet counts was about 6 days in reported cases with normal renal function.

Among 30 patients that were described in case reports, the transfusion of platelets was considered for the management of 20 patients with various success rates [12, 16, 18–20, 22–28, 31, 33, 34, 44–46, 48]. Twelve patients were reported to be transfusion resistant [16, 18–20, 22–24, 27, 33, 46, 48]. However, the exact definition of 'transfusion resistance' was not stated in these reports. It was reported in the case series published by Von Drygalski and colleagues that platelet counts did not rise significantly in 78% of patients during 6–24 h after platelet transfusions [9]. Platelet transfusion was considered for the management of 14 patients in this study and failed to raise platelet counts in 11 cases. The responses of the other three patients could not be determined [9]. The survival time of infused platelets is reduced significantly in drug-induced immune thrombocytopenia and the transfusion of platelets does not always result in expected increases in platelet counts of affected patients [3]. Nevertheless, given the life-threatening potential, transfusion should be considered in cases of severe thrombocytopenia (platelet count less than 20,000/mL) and bleeding.

Besides transfusion, other measures such as corticosteroids (e.g., prednisolone 1–2 mg/kg/day for 2–4 weeks), intravenous immunoglobulins (1 g/kg/day for 2 days), rituximab (375 mg/m^2 weekly for 4 weeks), and plasma exchange have been used with varying success, but none has been reported to be consistently effective [3, 4]. Among patients in case reports, eight, seven, and three patients received intravenous immunoglobulin, corticosteroids, and both, respectively [12, 18, 20, 23, 25–28, 45, 46]. One patient with refractory thrombocytopenia responded to treatment with rituximab [26]. In the study by Von Drygalski et al., additional interventions included administration of corticosteroids in five cases, intravenous immunoglobulins in three cases, anti-Rh immunoglobulin in one case, and plasma exchange for one patient; all with suspicion of autoimmune thrombocytopenia or post-transfusion purpura [9].

Current data seem inconclusive regarding the most appropriate action when the discontinuation of vancomycin does not result in a rapid return of the platelet count, and especially when existing bleeding does not respond well to transfusions. Because a combination of these interventions has been tried in some cases of VIT [12, 23, 26, 46], the relative contribution of each single intervention cannot be determined. Von Drygalski et al. concluded that the intervention did not lead to a significant rise in platelet counts in half of the study patients who underwent these treatments [9]. The efficacy of the abovementioned interventions has not been evaluated thoroughly; therefore, choosing the next most appropriate intervention could be dependent on a trial-and-error method.

Finally, using alternative agents to vancomycin appears inevitable in almost all patients. Reviewing alternatives to vancomycin for the treatment of resistant Gram-positive bacteria is beyond the scope of this article and is discussed elsewhere [11]. There are two points to consider when switching of the antibiotic is anticipated. First, thrombocytopenia has been reported with some of the alternative medications at equal or even higher rates than those reported for vancomycin [53, 56, 57]. For example, in a randomized trial on patients with methicillin-resistant staphylococcal infection, the prevalence of thrombocytopenia was 19% in the linezolid group vs. only 2% in the vancomycin group [57, 58], although this has not been always the case [50, 58, 59]. Nevertheless, the possibility of continued or the reappearance of thrombocytopenia after antibiotic switch does not precludes judicious use of these agents, but necessitates continued close monitoring of the platelet count. Second, there is concern about the possible cross-sensitivity between vancomycin and some of new agents. Hsiao and colleagues evaluated the outcome of 14 patients intolerant to vancomycin who were switched later to teicoplanin [60]. The rate of hypersensitivity reactions to teicoplanin was unexpectedly high for these patients, so that 58.3% of them developed reactions, which were hematologic in 71.4% of the incidents. The authors argued that although the overall prevalence of adverse effects seems to be lower for teicoplanin, this may not apply to those previously demonstrated to be vancomycin intolerant. Similar findings were also observed in the study by Rao et al. [61]. In this prospective study on patients with orthopedic bacterial infections, similar hematologic adverse reactions were observed for linezolid and vancomycin. Interestingly, a higher incidence of thrombocytopenia was only noted in the linezolid-treated patients who were recently switched from vancomycin [61]. Pre-emptive testing for vancomycin-induced antibodies has been proposed as a safer alternative to vancomycin in patients susceptible to repeated infections [20].

4 Conclusion

VIT appears to be duration dependent and monitoring platelet counts is recommended at least once weekly and more frequently in patients who develop thrombocytopenia or bleeding. The reaction can occur precipitously in subsequent exposures to the drug. Abrupt discontinuation of the offending medication was reported as the only effective approach in the treatment of DIT including VIT. In patients with a strong clinical suspicion of VIT, who presented with nadir platelet counts less than 20,000/mL and signs or symptoms of bleeding, vancomycin should be stopped immediately. Transfusion is recommended if severe thrombocytopenia and bleeding occurs. Discontinuation of vancomycin led to the resolution of thrombocytopenia after a mean time of 5–6 days. If thrombocytopenia persists longer or is accompanied by signs and symptoms of bleeding, treatment with corticosteroids, intravenous immunoglobulins, or even plasma exchange may be considered. In cases with confirmed VIT, the patients should be counseled to avoid future exposures.

Compliance with Ethical Standards

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References

1. Aster RH, Curtis BR, McFarland JG, Bougie DW. Drug-induced immune thrombocytopenia: pathogenesis, diagnosis, and management. J Thromb Haemost. 2009;7(6):911–8. doi:10.1111/j.1538-7836.2009.03360.x.
2. Rondina MT, Walker A, Pendleton RC. Drug-induced thrombocytopenia for the hospitalist physician with a focus on heparin-induced thrombocytopenia. Hosp Pract (1995). 2010;38(2):19–28.
3. van den Bemt PM, Meyboom RH, Egberts AC. Drug-induced immune thrombocytopenia. Drug Saf. 2004;27(15):1243–52. doi:10.2165/00002018-200427150-00007.
4. Aster RH, Bougie DW. Drug-induced immune thrombocytopenia. N Engl J Med. 2007;357(6):580–7. doi:10.1056/NEJMra066469.
5. Kenney B, Stack G. Drug-induced thrombocytopenia. Arch Pathol Lab Med. 2009;133(2):309–14. doi:10.1043/1543-2165-133.2.309.
6. Arnold DM, Kukaswadia S, Nazi I, et al. A systematic evaluation of laboratory testing for drug-induced immune thrombocytopenia. J Thromb Haemost. 2013;11(1):169–76. doi:10.1111/jth.12052.
7. Priziola JL, Smythe MA, Dager WE. Drug-induced thrombocytopenia in critically ill patients. Crit Care Med. 2010;38(6 Suppl.):S145–54. doi:10.1097/CCM.0b013e3181de0b88.
8. Patnode NM, Gandhi PJ. Drug-induced thrombocytopenia in the coronary care unit. J Thromb Thrombolysis. 2000;10(2):155–67.

9. Von Drygalski A, Curtis BR, Bougie DW, et al. Vancomycin-induced immune thrombocytopenia. N Engl J Med. 2007;356(9):904–10. doi:10.1056/NEJMoa065066.
10. Levine DP. Vancomycin: understanding its past and preserving its future. South Med J. 2008;101(3):284–91. doi:10.1097/SMJ.0b013e3181647037.
11. Black E, Lau TT, Ensom MH. Vancomycin-induced neutropenia: is it dose- or duration-related? Ann Pharmacother. 2011;45(5):629–38. doi:10.1345/aph.1P583.
12. Ganly P, Downing J, Stiven P, et al. Clinical and serological diagnoses of a patient with vancomycin-induced thrombocytopenia. Transfus Med. 2011;21(2):137–9.
13. Anand A, Chauhan HK. Piperacillin and vancomycin induced severe thrombocytopenia in a hospitalized patient. Platelets. 2011;22(4):294–301. doi:10.3109/09537104.2010.549973.
14. Apiwattanakul N, Wanitkun S, Chongtrakool P, Sirinavin S. A patient with penicillin-resistant viridans group streptococcal endocarditis and unusual reactions to vancomycin. Southeast Asian J Trop Med Public Health. 2008;39(6):1088–91.
15. Bay A, Oner AF, Dogan M, Çaksen H. A child with vancomycin-induced thrombocytopenia. J Emerg Med. 2006;30(1):99–100.
16. Candemir B, Aribuca A, Koca C, et al. An unusual case of vancomycin-related systemic reaction accompanied with severe thrombocytopenia mimicking pacemaker-related infective endocarditis: a case report and review of literature. J Interv Card Electrophysiol. 2013;38(2):143–5. doi:10.1007/s10840-012-9738-6.
17. Carmichael A, Al-Zahawi M. Drug points: pancytopenia associated with vancomycin. BMJ. 1986;293(6554):1103.
18. Christie DJ, van Buren N, Lennon SS, Putnam JL. Vancomycin-dependent antibodies associated with thrombocytopenia and refractoriness to platelet transfusion in patients with leukemia. Blood. 1990;75(2):518–23.
19. Govindarajan R, Baxter D, Wilson C, Zent C. Vancomycin-induced thrombocytopenia. Am J Hematol. 1999;62(2):122–3.
20. Kenney B, Tormey CA. Acute vancomycin-dependent immune thrombocytopenia as an anamnestic response. Platelets. 2008;19(5):379–83. doi:10.1080/09537100802082280.
21. Kuruppu JC, Le TP, Tuazon CU. Vancomycin-associated thrombocytopenia: case report and review of the literature. Am J Hematol. 1999;60(3):249–50.
22. Lee JH, Kim DS, Lee HS, et al. A case of vancomycin-induced thrombocytopenia. Korean J Hematol. 2009;44(4):294–7.
23. Marraffa J, Guharoy R, Duggan D, et al. Vancomycin-induced thrombocytopenia: a case proven with rechallenge. Pharmacotherapy. 2003;23(9):1195–8.
24. Mizon P, Kiefel V, Mannessier L, et al. Thrombocytopenia induced by vancomycin-dependent platelet antibody. Vox Sang. 1997;73(1):49–51.
25. O'Donnell E, Shepherd C, Neff A. Immune thrombocytopenia from vancomycin in orthopedic cement. Am J Hematol. 2007;82(12):1122.
26. Ortín BP, Solis MA, Ramos VB, et al. Thrombocytopenia in a patient on peritoneal dialysis. Nefrologia. 2008;28(4):453–5.
27. Pauldine R, Pustavoitau A. Case report: vancomycin-induced thrombocytopenia in a burn patient. Eplasty. 2008;8:e39.
28. Peel RK, Sykes A, Ashmore S, et al. A case of immune thrombocytopenic purpura from intraperitoneal vancomycin use. Perit Dial Int. 2003;23(5):506–8.
29. Rocha JL, Kondo W, Baptista MI, et al. Uncommon vancomycin-induced side effects. Braz J Infect Dis. 2002;6(4):196–200.
30. Ruggero MA, Abdelghany O, Topal JE. Vancomycin-induced thrombocytopenia without isolation of a drug-dependent antibody. Pharmacotherapy. 2012;32(11):e321–5. doi:10.1002/phar.1132.
31. Shah RA, Musthaq A, Khardori N. Vancomycin-induced thrombocytopenia in a 60-year-old man: a case report. J Med Case Rep. 2009;3:7290. doi:10.4076/1752-1947-3-7290.
32. Shahar A, Berner Y, Levi S. Fever, rash, and pancytopenia following vancomycin rechallenge in the presence of ceftazidime. Ann Pharmacother. 2000;34(2):263–4.
33. Winteroll S, Kerowgan M, Vahl C-F, Leo A. Vancomycin-mediated drug-induced immune thrombocytopenia. Transfus Med Hemother. 2004;32(1):20–3.
34. Zenon GJ, Cadle RM, Hamill RJ. Vancomycin-induced thrombocytopenia. Arch Intern Med. 1991;151(5):995–6.
35. Dilli D, Oguz SS, Dilmen U. A newborn with vancomycin-induced thrombocytopenia. Pharmacology. 2008;82(4):285–6. doi:10.1159/000163099.
36. Walker RW, Heaton A. Thrombocytopenia due to vancomycin. Lancet. 1985;1(8434):932.
37. Naranjo CA, Busto U, Sellers EM, et al. A method for estimating the probability of adverse drug reactions. Clin Pharmacol Ther. 1981;30(2):239–45. doi:10.1038/clpt.1981.154.
38. George JN, Aster RH. Drug-induced thrombocytopenia: pathogenesis, evaluation, and management. Hematol Am Soc Hematol Educ Program. 2009:153–8. doi:10.1182/asheducation-2009.1.153.
39. George J, Raskob G, Shah S, et al. Drug-induced thrombocytopenia: a systematic review of published case reports. Ann Intern Med. 1998;129(11):886–90.
40. Bonfiglio MF, Traeger SM, Kier KL, et al. Thrombocytopenia in intensive care patients: a comprehensive analysis of risk factors in 314 patients. Ann Pharmacother. 1995;29(9):835–42.
41. Howard CE, Adams LA, Admire JL, et al. Vancomycin-induced thrombocytopenia: a challenge and rechallenge. Ann Pharmacother. 1997;31(3):315–8.
42. Linder N, Edwards R, MeClead R, et al. Safety of vancomycin with or without gentamicin in neonates. Neonatal Netw. 1993;12(8):27–30.
43. Wood MJ. Comparative safety of teicoplanin and vancomycin. J Chemother. 2000;12(Suppl. 5):21–5.
44. Ahmed Y, Sartin C, Umer I, et al. Vancomycin-induced severe asymptomatic immune thrombocytopenia; a rare cause. Southwest Respir Crit Care Chronicles. 2015;3(9):42–5.
45. Arnold DM, Nazi I, Warkentin TE, et al. Approach to the diagnosis and management of drug-induced immune thrombocytopenia. Transfus Med Rev. 2013;27(3):137–45. doi:10.1016/j.tmrv.2013.05.005.
46. Lobo N, Ejiofor K, Thurairaja R, Khan MS. Life-threatening haematuria caused by vancomycin-induced thrombocytopenia. BMJ Case Rep. 2015;2015. doi:10.1136/bcr-2014-208192.
47. Rowland SP, Rankin I, Sheth H. Vancomycin-induced thrombocytopaenia in a patient with severe pancreatitis. BMJ Case Rep. 2013;2013. doi:10.1136/bcr-2013-200830.
48. Wetzel DR, Njathi CW, Telesz BJ, et al. Thrombocytopenia of unusual etiology in the intensive care unit. J Med Cases. 2013;4(12):792.
49. Marinho DS, Huf G, Ferreira BL, et al. The study of vancomycin use and its adverse reactions associated to patients of a Brazilian university hospital. BMC Res Notes. 2011;4:236. doi:10.1186/1756-0500-4-236.
50. Moenster RP, Linneman TW, Finnegan PM, McDonald JR. Daptomycin compared to vancomycin for the treatment of osteomyelitis: a single-center, retrospective cohort study. Clin Ther. 2012;34(7):1521–7. doi:10.1016/j.clinthera.2012.06.013.
51. Domen RE. Vancomycin-induced cytopenias. Arch Intern Med. 1992;152(2):413–4.
52. Bougie DW, Wilker PR, Aster RH. Patients with quinine-induced immune thrombocytopenia have both "drug-dependent" and "drug-specific" antibodies. Blood. 2006;108(3):922–7. doi:10.1182/blood-2006-01-009803.
53. Patel N, VanDeWall H, Tristani L, et al. A comparative evaluation of adverse platelet outcomes among Veterans' Affairs

patients receiving linezolid or vancomycin. J Antimicrob Chemother. 2012;67(3):727–35. doi:10.1093/jac/dkr522.
54. Rybak M, Lomaestro B, Rotschafer JC, et al. Therapeutic monitoring of vancomycin in adult patients: a consensus review of the American Society of Health-System Pharmacists, the Infectious Diseases Society of America, and the Society of Infectious Diseases Pharmacists. Am J Health Syst Pharm. 2009;66(1):82–98. doi:10.2146/ajhp080434.
55. Vandecasteele SJ, De Vriese AS. Recent changes in vancomycin use in renal failure. Kidney Int. 2010;77(9):760–4. doi:10.1038/ki.2010.35.
56. Wilson AP. Comparative safety of teicoplanin and vancomycin. Int J Antimicrob Agents. 1998;10(2):143–52.
57. Jaksic B, Martinelli G, Perez-Oteyza J, et al. Efficacy and safety of linezolid compared with vancomycin in a randomized, double-blind study of febrile neutropenic patients with cancer. Clin Infect Dis. 2006;42(5):597–607. doi:10.1086/500139.
58. Kohno S, Yamaguchi K, Aikawa N, et al. Linezolid versus vancomycin for the treatment of infections caused by methicillin-resistant *Staphylococcus aureus* in Japan. J Antimicrob Chemother. 2007;60(6):1361–9. doi:10.1093/jac/dkm369.
59. Young LS. Hematologic effects of linezolid versus vancomycin. Clin Infect Dis. 2004;38(8):1065–6. doi:10.1086/382364.
60. Hsiao SH, Chou CH, Lin WL, et al. High risk of cross-reactivity between vancomycin and sequential teicoplanin therapy. J Clin Pharm Ther. 2012;37(3):296–300. doi:10.1111/j.1365-2710.2011.01291.x.
61. Rao N, Ziran BH, Wagener MM, et al. Similar hematologic effects of long-term linezolid and vancomycin therapy in a prospective observational study of patients with orthopedic infections. Clin Infect Dis. 2004;38(8):1058–64. doi:10.1086/382356.