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Case Report

Piperacillin-Tazobactam Drug-Induced Thrombocytopenia: Diagnosis Based on Clinical Criteria

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A B S T R A C T

Drug-induced thrombocytopenia (DITP) is an uncommon but well-documented adverse drug reaction. DITP can be diagnosed based on clinical and laboratory criteria. Clinical criteria include severe acute thrombocytopenia (platelet nadir < 20 × 103/μL within 1 week of culprit drug exposure) with bleeding and exclusion of other causes of thrombocytopenia. Antibiotics such as vancomycin, penicillin derivatives, and linezolid have been implicated in DITP. This case report describes a patient who was diagnosed with piperacillin-tazobactam DITP based on clinical criteria with full platelet recovery after piperacillin-tazobactam cessation.

A broad-spectrum bactericidal beta-lactam combination of piperacillin and tazobactam, piperacillin-tazobactam (PTZ), has been used in treating infections caused by gram-negative, gram-positive, and beta-lactamase–producing bacteria associated with complicated nosocomial infections.[1-3] Although considered safe and well tolerated, PTZ has been associated with adverse drug reactions (ADRs) such as thrombocytopenia, often referred to as drug-induced thrombocytopenia (DITP).[1] Because of the complex and multifactorial nature of thrombocytopenia, limitations related to biochemical confirmation of DITP, and nonmandated reporting of DITP, the incidence of DITP has been underestimated to be 10 cases per million annually.[4-6] When caring for patients with sepsis who develop acute, severe thrombocytopenia, maintaining a high index of suspicion while having knowledge of clinical criteria and algorithms is paramount in the early diagnosis and management of DITP.

Case Presentation

This is a case report of a 61-year-old man with a history of sleep apnea, diabetes, atrial fibrillation on apixaban, neurogenic bladder with a chronic urinary catheter requiring multiple exchanges, chronic kidney disease stage 3, and recurrent abdominal wall and left thigh multi–drug-resistant infections being hospitalized for a complicated urinary tract infection (cUTI). He presented to the emergency department for a leaking urinary catheter with flank pain. His urinary catheter was re-exchanged. On presentation, he was found to be lethargic and had hypotension (systolic blood pressure of 70s mm Hg) refractory to fluids, eventually requiring central line placement and vasopressors. His workup included cultures and imaging. His urinalysis was infectious, prompting urine and blood cultures to be collected. The initial laboratory workup showed creatinine of 2.4 mg/dL, a white blood cell count of 10.8 × 10^3/μL, hemoglobin of 9.7 g/dL, and platelets of 255 × 10^3/μL. The medications he received included PTZ, vancomycin, and prophylactic heparin. He was then transferred to the intensive care unit for management.

On day 1, his platelets dropped to 1 × 10^3/μL. Given the concern that it was spurious, it was repeated twice (1 × 10^3/uL and 0 × 10^3/uL). Hematology was consulted, and he underwent extensive workup. Notably, he had no abdominal pain, vascular changes, ecchymosis, or further decline in his mental status. Given the concern for DITP, PTZ, vancomycin, and heparin were all discontinued. His urine culture subsequently grew *Pseudomonas aeruginosa* so he was switched to renal-dose levofloxacin.

On day 2, *P. aeruginosa* showed intermediate resistance to levofloxacin, so the infectious diseases team recommended starting him on meropenem after confirming antimicrobial sensitivities. The patient was then transfused with single-donor platelets (SDPs) to target platelets ≥ 10 × 10^3/μL. Intravenous immunoglobulin (IVIG) was not administered. Because of his cUTI, he also had a computed tomographic scan that showed new left hydronephrosis with an obstructing ureteral stone. Given these findings, he was taken for an emergent cystoscopy with stone extraction and ureteral stent placement by urology. Periprocedurally, he received 3 SDPs, which brought his platelets to 7 × 10^3/μL. Purulent drainage was noted and sent for cultures. Additionally, he developed overt postprocedural hematuria requiring additional SDPs. Despite the hematuria, no IVIG or corticosteroids (CSs) were administered per hematology recommendations.

On day 3, vasopressors were tapered off, and he received another SDP because his platelet count was 6 × 10^3/μL. By day 4, his

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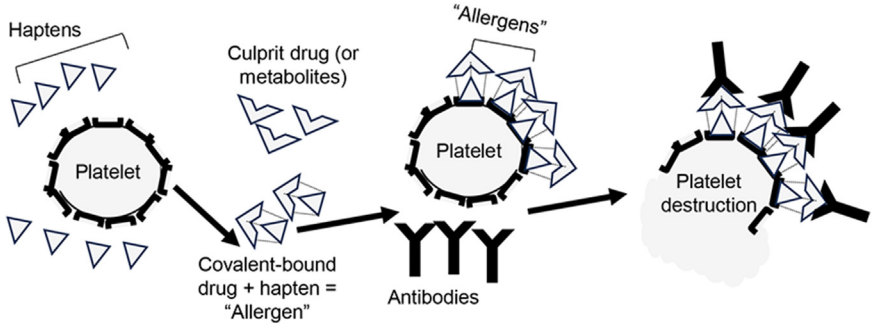

Figure 1. Hapten binding mechanism. This is an image showing how culprit drugs can bind to haptens, leading to the formation of an "allergen"-type complex that binds to platelets triggering antibody-mediated platelet destruction.

platelets increased to 26 $\times$ 10^3/μL with no overt hematuria. On day 5, his platelets continued to improve to 64 $\times$ 10^3/μL, so he had a tunneled central line placed given his poor vasculature and had the original central line removed. He was also placed on prophylactic heparin and downgraded to a telemetry unit. By day 7, he remained stable with his platelets at 193 $\times$ 10^3/μL; he was discharged to a rehabilitation facility with plans to complete a 7-day course of meropenem.

Discussion

Pathophysiology

In order to understand the diagnostic and management principles related to antimicrobial DITP, specifically PTZ DITP, the clinician must have an understanding of the underlying pathophysiologic mechanisms contributing to this disorder. It has been proposed that PTZ DITP mechanisms may be non−immune mediated via myelosuppression or immune mediated via hapten-induced or drug-dependent (or quinine-type) antibodies.[4-7] Although less common, beta-lactams such as piperacillin may cause reversible dose- and duration-dependent thrombocytopenia via suppression of megakaryopoiesis along with neutropenia.[6,8-10]

More commonly, these penicillin derivatives have been implicated in immune-mediated DITP. The first proposed immune-mediated mechanism occurs when haptens form covalent bonds with platelet membrane glycoproteins (GPs).[9-11] Alone, haptens are not immunogenic.[4,12] However, in the presence of a culprit drug or its metabolite, haptens covalently bind to proteins (ie, GPIIb/IIIa) to form a drug-protein complex that acts as an "allergen."[4,9] This allergen then facilitates antibody production and binding to platelets, ultimately leading to hapten-bound platelet destruction.[4,9] Once a preexposed individual has culprit drug reexposure, this "allergen" complex re-forms, providing a target for the antibody facilitating platelet destruction[4] (Figure 1). The second proposed mechanism involves quinine-type or drug-dependent antibodies (DDAbs). Derived from naturally occurring immunoglobulins, DDAbs bind to specific epitopes on platelet surface GPs in the presence of the culprit drug or its metabolite.[4,13] Because they are weakly reactive with low affinity to epitopes on platelet membrane GPs, DDAb binding does not normally result in any reaction.[4,13] However, enhanced affinity and subsequent noncovalent binding may occur with certain sensitizing drugs at certain concentrations.[14,15] Such sensitizing drugs may modify the complementary determining region of the antibody, leading to increased antibody affinity to the platelet epitope and triggering noncovalent binding to platelet GP complexes leading to platelet destruction[4,13] (Figure 2).

Diagnosis

Because of these immune-mediated mechanisms contributing to DITP, diagnostic confirmation often requires biochemical testing looking for the presence of platelet-bound DDAbs in the presence of the culprit drug.[11,16] Although ideal, laboratory testing for DDAbs during thrombocytopenia is often not feasible and fraught with many limitations. These include difficulty in detecting platelet-bound antibodies in the patient's plasma or serum, poor turnaround time (TAT), lack of standardization because of test-related deficiencies, and limited accessibility.[12,15,16]

First, it may be difficult detecting platelet-bound antibodies in the patient's plasma or serum. One theory is that DDAbs may lead to less circulating platelets and thus less detectable platelet-bound DDAbs.[12] Second, because of inefficient TAT, results are not readily available.[14,16] Although testing for DITP can still be performed up to 3 weeks after the acute event, even if the thrombocytopenia is

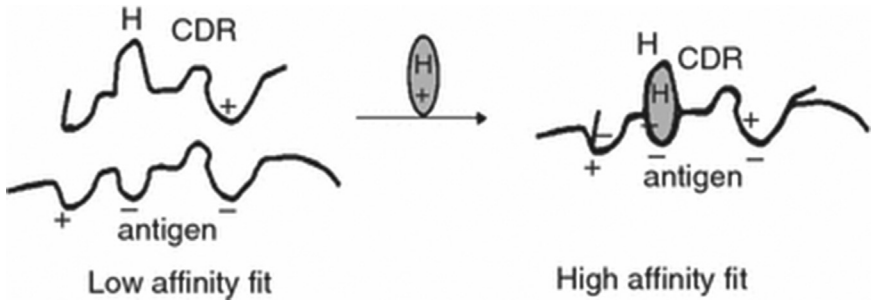

Figure 2. DDAbs binding mechanism. This is an image showing how sensitizing drugs (H+) can enhance affinity between the complementary determining region (CDR) of the DDAbs and platelet epitopes (ie, antigenic determinant), leading to platelet destruction.
Reprinted with permission from Aster et al.[4]

Table 1
Naranjo Adverse Drug Reaction Probability Scale

Question	Yes	No	Do Not Know	Score
1. Are there any previous *conclusive* reports on this reaction?				
2. Did the adverse event appear after the suspected drug was administered?				
3. Did the adverse reaction improve when the drug was discontinued or a *specific* antagonist was administered?				
4. Did the adverse event reappear when the drug was re-administered?				
5. Are there alternative causes (other than the drug) that could on their own have caused the reaction?				
6. Did the reaction reappear when a placebo was given?				
7. Was the drug detected in blood (or other fluids) in concentrations known to be toxic?				
8. Was the reaction more severe when the dose was increased or less severe when the dose was decreased?				
9. Did the patient have a similar reaction to the same or similar drugs in any previous exposure?				
10. Was the adverse event confirmed by any objective evidence?				

This table provides a 10-point questionnaire to evaluate the likelihood of an adverse drug reaction occurring.
Adapted with permission from Naranjo et al.[18]

resolving or has resolved, it is possible that this delay may result in decreased sensitivity or failure to detect DDAbs.[5,17]

Third, there is a lack of standardization in laboratory techniques and validation across a range of drugs contributing to test-related deficiencies.[11,15,17] First, the drug metabolite, rather than the primary drug itself, may trigger DITP.[14] This may be problematic if assays cannot detect these drug metabolites or if these metabolites are not available for use as test reagents.[14,16] Second, because each laboratory defines its own cutoff values for confirming ADRs, there is a lack of consensus with optimal drug concentrations in vitro.[12,16] Third, specific assays or testing requirements may be incompatible with the culprit drug's particular chemical properties (ie, low drug solubility or drug insolubility), leading to testing interference.[12,16]

Fourth, although existing assays have good specificity, they have poor sensitivity in DDAb detection.[12,14,17] Generally, patients with positive tests should be advised to avoid future drug reexposures.[17] However, because of the aforementioned limitations described along with low sensitivity in DDAb detection, negative results may be obtained in patients with a high clinical probability of DITP.[11,14] For example, if the sample was not collected promptly, the DDAb titer may be too low to be detectable, resulting in a false negative despite meeting the clinical criteria.[12,17] Therefore, a negative result does not definitively rule out DITP.[12,14,17]

Lastly, although flow cytometry is most commonly used, no single method has been universally accepted as the gold standard for the laboratory diagnosis of DITP.[11] Additionally, given the complexity and uncertainties associated with these assays, they are only performed in specialized laboratories in platelet immunology.[12] Consequently, these tests are not readily accessible for use.[11]

In light of these limitations to biochemical confirmation of DITP, clinicians can still implement clinical tools to aid with DITP diagnosis. First, diagnosis of PTZ DITP can be evaluated using a tool with concurrent, content, and consensual validity—the Naranjo ADR Probability Scale.[18] This tool determines the probability that a drug caused an ADR based on points totaled after answering 10 questions.[18] Depending on the points totaled, ADR probability due to the identified drug would then be classified as definite (≥ 9), probable (5-8), possible (1-4), or doubtful (≤ 0)[18] (Table 1). The second tool that can be used evaluates the likelihood that the cause of the thrombocytopenia was related to that specific drug based on 4 criteria.[4,9,13-16] Then, depending on which and how many of these criteria were met, DITP probability due to the identified drug would then be classified as definite, probable, possible, unlikely, or not evaluable (Table 2). The last tool that can be applied is the algorithm by Arnold et al.[11] This algorithm can help distinguish from other causes of thrombocytopenia by evaluating the severity and temporal pattern of thrombocytopenia, the presence of bleeding, and the culprit drug's prior implication in DITP[11] (Figure 3).

Management

The main management principle of antimicrobial DITP requires cessation of all potential culprit drugs in those who develop acute, severe thrombocytopenia.[11,14] In general, platelet transfusions are ineffective, especially if the drug or its metabolite are present in the plasma.[6,14] Nonetheless, they may be necessary in those with severe thrombocytopenia and overt bleeding.[4,11] Other supportive measures such as IVIG and CSs may also be considered in those with severe thrombocytopenia, an existing or high risk of bleeding, or if DITP is difficult to distinguish from immune thrombocytopenia

Table 2
Drug-Induced Thrombocytopenia (DITP) Criteria and Level of Probability

DITP Criteria	
1. Thrombocytopenia must occur post–drug exposure; recovery from thrombocytopenia must be complete and sustained after the drug has been discontinued.	
2. Other drugs administered before thrombocytopenia were continued or reintroduced after discontinuation of the suspected drug.	
3. Other causes of thrombocytopenia, including other drugs, must be excluded.	
4. Drug rechallenge (if done) must result in recurrence of the thrombocytopenia.	
Level of Probability	
Definite	All 4 criteria met
Probable	Criteria 1-3 met
Possible	Criterion 1 met
Unlikely	Criterion 1 not met
Data not evaluable	Insufficient patient data in report; platelet count not $< 100 \times 10^3/\mu L$; cytotoxic drug, marrow suppression; nontherapeutic agent or used in nontherapeutic manner; drug-induced disease in addition to thrombocytopenia; patient age < 16 years

This table depicts the likelihood that the cause of the patient's thrombocytopenia was related to the suspected drug based on 4 criteria with classification identifying the level of probability the patient has DITP.
Adapted with permission from George et al.[13]

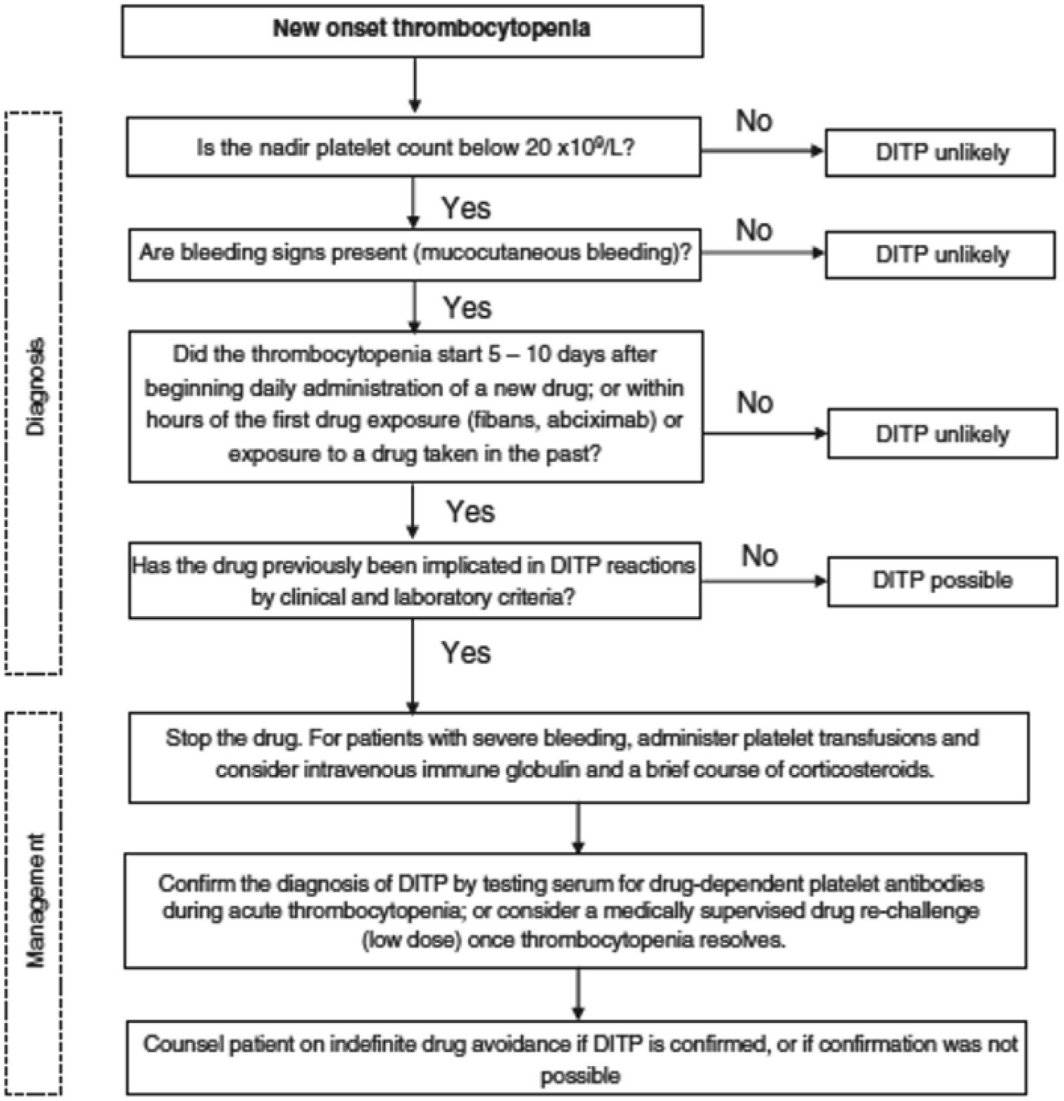

Figure 3. Diagnosis and management of DITP: Arnold et al[11] criteria. This figure shows a diagnostic and management algorithm for a patient with new-onset severe and acute thrombocytopenia suspicious for DITP evaluating the severity and temporal pattern of thrombocytopenia, the presence of bleeding, and the culprit drug's prior implication in DITP. *Reprinted with permission from Arnold et al.*[11]

(ITP).[11,15,19] After all, high-dose CSs and IVIG have been associated with decreasing or slowing down platelet consumption or destruction.[9,19,20] Nonetheless, CSs and IVIG are not highly recommended because their use is based on case reports.[9,14] Moreover, platelet count recovery only occurred once the culprit drug was discontinued regardless of other interventions.[6,9,15]

Patient Diagnosis and Management

Clinical diagnosis of PTZ DITP was determined based on the prior clinical criteria described. First, using the Naranjo ADR Probability Scale, PTZ ADR was deemed probable after scoring a 6.

- Are there previous conclusive reports for this reaction? (Yes, +1)
- Did the adverse event appear after the suspected drug was administered? (Yes, +2)
- Did the adverse reaction improve when the drug was discontinued or a specific antagonist was administered? (Yes, +1)
- Are there alternative causes that could on their own have caused the reaction? (No, +2)

To substantiate this finding, the DITP criteria and level of probability tool were implemented. Based on this, this patient met criteria 1 to 3, suggesting that PTZ DITP was probable. Criterion 1 was met because thrombocytopenia occurred post-PTZ with complete and sustained platelet recovery once PTZ was discontinued (Table 3). Criterion 2 involved the reintroduction of other drugs also implicated in DITP after discontinuation of the suspected drug. Therefore, heparin and vancomycin, 2 drugs commonly implicated in DITP, were evaluated.

As one of the leading causes of DITP, heparin-induced thrombocytopenia (HIT) was a differential diagnosis. Although the severity of thrombocytopenia is typically moderate (nadir ~ $50 \times 10^3/\mu L$) in (immune) HIT, complicated cases with superimposed sepsis or DIC may result in severe thrombocytopenia $< 20 \times 10^3/\mu L$.[14] Therefore, his 4T score was calculated to be a 4 with an intermediate probability of HIT (~14%) (platelet nadir $< 10 \times 10^3/\mu L$ [0 points], platelet count fall ≤ 1 day with prior heparin exposure within 30 days [2 points], nonnecrotizing skin lesions without suspicion for thrombosis [1 point], and other causes such as nonheparin DITP and sepsis [1 point]).[21] Thus, an enzyme immunoassay to detect anti-PF4/H antibodies was

Table 3
Platelet Count and Medication Timeline

Labs	Reference Range	Day 0	Day 1 (#1)	Day 1 (#2)	Day 1 (#3)	Day 2 (AM)	Day 2 (PM)	Day 3	Day 4	Day 5	Day 6	Day 7
WBC	4-10 10 × 3/μL	10.8	9.8	9.1		8.2	28.4	19	9.5	8.5	5.8	8.7
Hgb/Hct	11.6-15.0 g/dL 35.5%-44.9%	9.7/29.4	8.9/26.6	8.9/26.6		8.8/27.8	9.0/26.5	8.2/24.5	7.8/24.0	7.7/24.2	10.4/32.9	8.1/24.8
Platelet	140-400 10 × 3/μL	255	1	1	0	3	7	6	26	64	93	193
PT/INR	9.8-13.1 s/≤ 5.01		16.1/1.37	15.4/1.32				17.9/1.52		15.6/1.33		
PTT	26-38 s			24								
FDP				5-20								
fibrinogen	187-420 mg/dL			775								
D-dimer				5648								
haptoglobin				321								
Bilirubin total	0.10-1.20 mg/dL			0.3		0.2		0.3	0.3	0.2	0.3	
Reticulocyte count	0.60%-2.71%			1.08								
Medications												
Vancomycin 1.5 g IVPB ×1 dose (vancomycin trough levels)			15			6						
Piperacillin-tazobactam 4.45 g IVPB		×2 doses	×1 dose									
Levaquin 750 mg IVPB			×1 dose									
Meropenem 500 mg every 8 h IVPB					×2 doses	×3 doses		×3 doses	×3 doses	X3 doses	X3 doses	X3 doses
Heparin 5,000 U SQ every 8 h										X2 doses	X3 doses	X3 doses

Labs	Reference Range	Day 32	Day 33	Day 34	Day 35	Day 36	Day 37	Day 38	Day 39	Day 40	Day 41
WBC	4-10 10 × 3/μL	12.07	11.17	10.02		6.80	6.88	6.88	7.34	7.87	8.02
Hgb/Hct	11.6-15.0 g/dL 35.5%-44.9%	7.6/24.6	7.5/24.6	7.5/24.2		7.8/25.7	7.1/23.8	6.7/22.3	8.5/27.0	9.2/29.7	8.1/26.0
Platelet	140-400 10 × 3/μL	332	340	285		255	242	246	274	323	339
Medications											
Aspirin 81 mg PO daily		×1 dose	×1 dose	×1 dose	×1 dose	×1 dose	×1 dose	×1 dose	×1 dose	X1 dose	X1 dose
Atorvastatin 40 mg PO nightly											
Heparin 5,000 SQ every 8 h		×3 doses	×3 doses	×3 doses	×3 doses	×3 doses	×3 doses	×3 doses	×3 doses	X3 doses	X3 doses
Iron polysaccharides 150 mg PO daily											
Meropenem 1 g IVPB every 8 h		×3 doses	×3 doses	×3 doses	×3 doses	×3 doses	×3 doses	×3 doses	×3 doses	X3 doses	X3 doses
Vancomycin 2 g IVPB load then redosed based on trough levels				15.2	24.4	19.9	18.1	20.1	15.2	17.5	16.8
Protonix 40 mg PO daily		×1 dose	×1 dose	×1 dose	×1 dose	×1 dose	×1 dose	×1 dose	×1 dose	X1 dose	X1 dose
Saccharomyces boulardii 250 mg PO daily											
Oxycodone 10 mg every 6 h PRN moderate pain											
Ondansetron 4 mg IVP every 6 h PRN nausea, vomiting											
Acetaminophen 650 mg PO every 4 h PRN mild pain											

This table depicts a timeline of medication administered relative to the temporal pattern of the patient's platelet count (and other relevant laboratory values) during his hospitalization.
FDP = fibrin degradation products ; Hct = hematocrit; Hgb = hemoglobin; INR = international normalized ratio; IVPB = intravenous piggyback; PO = by mouth; PRN = as needed; PT = prothrombin time; PTT = partial thromboplastin time; SQ = subcutaneous; WBC = white blood cell.

sent, which was negative. Because this assay has a high negative predictive value, especially in patients with low or intermediate pretest probability, it was unlikely that this patient had HIT.[14,15] Moreover, he was introduced to prophylactic heparin on day 5 and upon rehospitalization on day 32 without any drop in his platelet count (Table 3).

Deemed one of the most commonly implicated drugs in quinine-type DITP, vancomycin was also considered.[9,19] Vancomycin-induced thrombocytopenia results in severe thrombocytopenia (nadir 20 $\times$ $10^3/\mu L$) within 6 to 12 days of treatment but may occur more precipitously upon reexposure.[9,15] VIT was less likely because he was treated with a 14-day course of vancomycin beginning his rehospitalization on day 32 for *Staphylococcus epidermidis* bacteremia thought to be (tunneled) catheter associated while sustaining normal platelets ($>$ 150 $\times$ $10^3/\mu L$). Therefore, he met criterion 2 because he had sustained normal platelet counts despite drug rechallenge with heparin and vancomycin.

Criterion 3 involves excluding other causes of thrombocytopenia. The following were evaluated: reversible causes, spurious thrombocytopenia and pseudothrombocytopenia, sepsis, disseminated intravascular coagulopathy (DIC), and (primary) ITP. He had no hepatosplenomegaly on imaging, making platelet sequestration unlikely. There were no ringed sideroblasts on the differential, making vitamin deficiencies (eg, vitamin B6) unlikely. Spurious thrombocytopenia and pseudothrombocytopenia were also less likely because 3 sequential platelet counts were $<$ 5 $\times$ $10^3/\mu L$ with testing avoiding the use of EDTA.[22,23] Sepsis was considered because it can induce increased consumption or decreased production of platelets via pathogen, endotoxin-mediated, or immune complex−mediated mechanisms.[22,23] In fact, studies reported that platelet indexes such as the platelet count and the mean platelet volume have prognostic value in predicting mortality in septic patients.[23,24] Even so, median and nadir counts of patients with thrombocytopenia associated strictly with sepsis are often not $<$ 20 $\times$ $10^3/\mu L$.[23,24] Thus, sepsis-induced DIC was considered. Based on the International Society on Thrombosis and Hemostasis DIC criteria, the patient scored 5 points (platelet $<$ 50 $\times$ $10^3/uL$ = 2 points and elevated fibrin-related markers [eg, D-dimer and fibrin degradation products] = 3 points).[25] However, DIC was less likely given his normal fibrinogen and prothrombin time and his lack of hemolytic markers. ITP was also considered because DITP is often misdiagnosed as the former.[11] Even so, ITP was unlikely because platelet recovery in ITP only occurs posttreatment with CSs and IVIG.[20] Additionally, this patient did not receive either, and he still had platelet recovery upon cessation of PTZ without recurrence of thrombocytopenia. Because these causes were ruled out, this patient also met criterion 3.

When concerned about DITP, potential culprit agents are often discontinued simultaneously because laboratory results are often unavailable or negative despite meeting the clinical criteria.[14,17] To address this diagnostic uncertainty, reintroduction of the culprit drug or a drug rechallenge to provoke thrombocytopenia has been proposed as the fourth criterion.[11,17] In the case of PTZ DITP, case reports highlighted drug rechallenge with inadvertent PTZ reexposure causing acute thrombocytopenia (nadir 3-40 $\times$ $10^3/\mu L$) with recovery within 7 days post-PTZ discontinuation.[7,10] Even so, drug rechallenge was not done because it is impractical and risky, potentially subjecting this patient to recurrent thrombocytopenia and bleeding.[11,12] Nevertheless, he had a high probability of having PTZ DITP based on the clinical criteria.

The last algorithm implemented for the clinical diagnosis and management of this patient's DITP was Arnold et al's algorithm.[11] One of the first clinical manifestations suggestive of DITP is severe thrombocytopenia, with nadir platelet counts often $\leq$ 20 $\times$ $10^3/\mu L$.[11,14] The patient developed severe thrombocytopenia (nadir 0 $\times$ $10^3/\mu L$) within 24 hours of PTZ exposure, thus making PTZ DITP possible.

Given the severity of thrombocytopenia, most patients with DITP will have bleeding complications, with the incidence of fatal and major bleeding at 0.8% and 9%, respectively.[14,15] Mild symptoms include mucocutaneous manifestations, such as ecchymosis, petechiae, or "wet purpura" and even naso-oropharyngeal bleeding.[4,12] However, others may develop major intracranial, gastrointestinal, or genitourinary bleeding, resulting in blood loss anemia.[12,15] Initially, this patient did not have overt hematuria until he underwent genitourinary procedures resulting in hematuria.

Temporal associations, specifically how they relate to platelet count decline and recovery, can help determine the underlying cause of thrombocytopenia and its likely mechanism. Immune-mediated DITP occurs 5 to 14 days after the initiation of a new drug or more precipitously (eg, within 2 days) after reexposure with a single dose or with specific drugs such as GPIIb/IIIa inhibitors.[9,15] Additionally, recovery from immune-mediated DITP begins 1 to 2 days after drug cessation with bleeding resolution and, subsequently, a return to baseline platelet counts within 1 week.[11,15] His drop in platelets within 24 hours of PTZ exposure with recovery (29 $\times$ $10^3/\mu L$) by day 4 and normalization (193 $\times$ $10^3/\mu L$) by day 7 is highly suggestive of immune-mediated DITP triggered by preexisting DDAbs. Typically, the platelet count is expected to recover upon discontinuation of the culprit drug or elimination of drug metabolites 4 to 5 half-lives after.[14] However, hepatically metabolized and/or renally cleared drugs implicated in DITP may result in prolonged thrombocytopenia in patients with hepatic and/or renal dysfunction.[9,26] Because of his chronic renal dysfunction, he may have had prolongation of DDAbs, leading to a slightly protracted platelet recovery.

If the patient meets criteria related to severity, bleeding, and temporal association, then DITP is possible. If not, then it is unlikely that the thrombocytopenia is caused by DITP. The last of the criteria involves being a drug implicated with DITP.[11] Thus, if the suspected culprit drug has been previously shown to be associated with DITP, then the diagnosis is more likely.[11] Piperacillin and even PTZ have been implicated as causes of DITP based on published reports, reports in the Adverse Event Report System, and the presence of DDAbs.[6,11,17] Therefore, based on Arnold et al's algorithm,[11] the diagnosis of PTZ DITP was possible for this patient.

Adhering to this algorithm from a DITP management standpoint, PTZ and other potential culprit drugs (ie, vancomycin and heparin) were discontinued. Given his *Pseudomonas* cUTI with intermediate resistance to levofloxacin and high concern for PTZ DITP, he was switched to meropenem. For this patient, SDPs were transfused to maintain platelets $>$ 10 $\times$ $10^3/\mu L$. Even so, his counts were transiently and minimally responsive. IVIG and CSs were not administered. By day 4, his platelet counts were recovering (29 $\times$ $10^3/\mu L$) and were normalized (193 $\times$ $10^3/\mu L$) by day 7.

Conclusion

When caring for a patient with sepsis and acute, severe, isolated thrombocytopenia, early recognition of DITP will prompt early discontinuation of culprit drugs (ie, antimicrobials) and, if needed, substitution with alternative agents. Although confirmatory biochemical assays in detecting the presence of DDAbs can provide a definitive diagnosis, standardization and clinical application may be prohibited by limited accessibility, test-related deficiencies leading to poor sensitivity, and poor TAT. Therefore, knowledge and implementation of existing clinical criteria may be acceptable alternatives to DDAb detection because they will not only prevent unintended re-exposure and associated sequelae but also unnecessary diagnostic testing and interventions.

CRediT Author Statement

Al Aguilar: Writing – review & editing, Writing – original draft, Visualization, Validation, Conceptualization.

Declaration of Competing Interest

In compliance with standard ethical guidelines, the author reports no relationships with business or industry that may pose a conflict of interest.

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