

# Severe, Refractory Thrombocytopenia in a Critically Ill Patient Caused by Vancomycin Induced Antibodies

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Received date: December 03, 2016; Accepted date: December 26, 2016; Published date: January 02, 2017

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Citation: Holden VK, Varonin D, Robinett KS. Severe, Refractory Thrombocytopenia in a Critically Ill Patient Caused by Vancomycin Induced Antibodies. J Clin Med Ther. 2017, 2:1.

## Abstract

The differential diagnosis for isolated thrombocytopenia in critically ill patients is broad and includes sepsis, disseminated intravascular coagulation and thrombotic thrombocytopenic purpura and medication effects. Vancomycin, a commonly used antibiotic for hospital-acquired infections, can cause severe, refractory thrombocytopenia due to antibody-mediated platelet destruction. This was first described in 2007 based on 12 case reports of vancomycin-associated thrombocytopenia. The study looked at 29 patients and demonstrated that the thrombocytopenia was immune mediated. We describe a unique case of severe vancomycin induced thrombocytopenia with a lower nadir and longer effect duration than previously described. Our patient is a 70-year-old man who presented with upper respiratory symptoms and was diagnosed with post-influenza pneumonia. Twelve days after completing a course of vancomycin and piperacillin/tazobactam, he developed another episode of sepsis and was resumed on antibiotics. After receiving a dose of vancomycin, the patient's platelet count decreased from 197,000/ $\mu$ L to 1,000/ $\mu$ L. This case illustrates the importance of awareness of vancomycin induced thrombocytopenia. The platelet destruction is caused by a platelet-specific drug-dependent antibody formation. Blood samples should be tested for the antibodies using immunofluorescence by flow cytometry; however, the results may be falsely negative if they were obtained after the patient has received platelet transfusions. This presents a diagnostic challenge and requires maintaining a high index of suspicion as treatment interventions include avoiding drug exposure.

**Keywords:** Platelets; Thrombocytopenia; Vancomycin; Immunofluorescence

## Introduction

The differential diagnosis for isolated thrombocytopenia in critically ill patients is broad and includes sepsis, disseminated intravascular coagulation, and thrombotic and medication effects [1,2]. Vancomycin, a commonly used antibiotic for hospital-acquired infections, can cause severe, refractory thrombocytopenia due to antibody-mediated platelet destruction. We describe a unique case of severe vancomycin induced thrombocytopenia with a lower nadir and longer effect duration than previously described.

## Case Presentation

A 70-year-old man presented with a fall, altered mental status and an upper respiratory infection, found to have a subarachnoid and intraventricular hemorrhage. He was not a candidate for neurosurgical intervention and was transferred to the medical intensive care unit for management of respiratory failure. Initially, he was diagnosed with influenza A and pneumonia for which he was treated empirically with a 7 day course of intravenous vancomycin and piperacillin/tazobactam. His hospital course was complicated by ischemic acute tubular necrosis requiring continuous renal replacement therapy with transition to intermittent hemodialysis. Twelve days after completing antibiotics, he developed septic shock requiring vasopressors and was started empirically on vancomycin, meropenem, and micafungin. Within 6 hours of receiving vancomycin, the patient's platelet count decreased from 197,000/ $\mu$ L to 1,000/ $\mu$ L, confirmed by a citrated platelet count and lack of platelet clumping. Heparin-induced thrombocytopenia antibody was negative. Lab tests were not consistent with disseminated intravascular coagulation, and our suspicion for immune thrombocytopenic purpura was low. Antibiotics were subsequently deescalated to cefepime.

With the drop in the platelet count, the patient developed coffee-ground secretions from his gastric tube associated with a decrease in hemoglobin from 7.5 g/dL to 6.3 g/dL. He was transfused a total of twelve units of platelets and 3 units of

packed red blood cells over the following 4 days. A vancomycin-dependent platelet antibody test was obtained after the patient received his sixth unit of platelets. He remained refractory to platelet transfusions, and the platelet count recovered to  $>150,000/\mu\text{L}$  after eleven days. The vancomycin-dependent antibody test (performed by Blood Center of Wisconsin) returned positive for IgG platelet antibody in the patient's serum without the drug. Both the IgM and IgG platelet antibody in the patient's serum with vancomycin were negative. The test result returned 8 days after sending the blood sample, and vancomycin was subsequently added to the patient's list of medication allergies.

## Discussion

Vancomycin is a widely used glycopeptide antibiotic. It is an established cause of immune-mediated thrombocytopenia, first reported in 1985. Features of drug-induced immune thrombocytopenia include a platelet nadir  $<20,000/\mu\text{L}$ , bleeding complications, and onset 5-10 days after beginning daily drug exposure or within hours of subsequent exposure [3]. A platelet-specific drug-dependent antibody formation results in platelet destruction [4]. Blood samples should be tested for the antibodies using immunofluorescence by flow cytometry, the most sensitive method for detecting drug-dependent antibodies [2]. A positive lab test demonstrating the antibodies can confirm the diagnosis, but a negative test does not rule it out [3]. In the largest available case series, about 55% of patients had only IgG antibodies, 10% had only IgM, and 35% had both classes present [1]. The targets of the antibodies are often on platelet GPIIb/IIIa or GPIb/IX [3,5].

A drug re-challenge resulting in thrombocytopenia recurrence is also diagnostic but impractical [3]. In one case, vancomycin-dependent antibodies were not detected due to the timing of the serum sampling after massive platelet transfusions [6]. Although the antibody testing is not useful in the acute management, it can be helpful in pinpointing a specific drug as the cause of thrombocytopenia as the drug sensitivity can persist for many years to indefinitely; therefore, it is important to counsel patients on drug avoidance [2,3,5].

In a case series of patients with vancomycin-dependent antibodies, the nadir platelet count, a mean of  $13,600/\mu\text{L}$ , was reached about 8 days after initiation of vancomycin. The median time required for the platelet level to return to at least  $150,000/\mu\text{L}$  after vancomycin was stopped was 7.5 days. Severe thrombocytopenia (platelet count  $<20,000/\mu\text{L}$ ) persisted for 7-8 days after vancomycin was discontinued in 2 dialysis patients. Ten of the 29 patients (34%) had severe bleeding-gross hematuria, gastrointestinal hemorrhages requiring transfusion, intrapulmonary hemorrhages, and excessive bleeding from venipuncture sites [1].

Acute vancomycin-induced thrombocytopenia can occur rapidly as an amnestic response, especially in patients with pre-existing IgG class vancomycin-dependent antibodies from prior exposure, such as our patient [1,2,4,7]. The thrombocytopenia is also refractory to platelet transfusions [4,5] patients received 10 units of platelets in some cases [7-8]. Management consists of stopping the medication, and the platelet count usually returns to normal within a week [2]. Treatment with intravenous immunoglobulin and/or steroids can be considered in some cases of severe thrombocytopenia or significant mucosal bleeding [1-3,5,7,8].

## Conclusion

Critically ill patients may have several reasons for thrombocytopenia, but physicians must have a high index of clinical suspicion for immune-mediated thrombocytopenia. Vancomycin antibody induced thrombocytopenia is a severe disease that is refractory to treatment. It can increase the risk of bleeding and does not respond to platelet transfusions. Testing for drug-dependent antibodies takes time; thus, it is imperative to avoid susceptible medication exposure during the work-up. Vancomycin is a widely used antibiotic and can cause significant morbidity through this mechanism if left unrecognized.

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