

# Severe Hypoalbuminemia Increases the Risk of Thrombocytopenia in Critically Ill Adult Patients Receiving Teicoplanin

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**ABSTRACT:** Teicoplanin is a drug of choice for treating infections by gram positive microorganisms. Teicoplanin-induced thrombocytopenia is an adverse drug reaction found in critically ill patients receiving teicoplanin. The aim of this observational study was to analyze the increased risk of occurring teicoplanin-induced thrombocytopenia in patients with severe hypoalbuminemia than the patients having normal blood-albumin level. A 5-month long study was conducted in an adult-ICU department on 42 critically ill adult patients. In this study, 17 (40.48%, n=42) patients developed teicoplanin-induced thrombocytopenia and among them, 14 patients (60.87%, n=23) were suffering from severe hypoalbuminemia during the initiation of teicoplanin therapy. All the events were normalized within 48 hours after discontinuing the teicoplanin. In this study, we found that teicoplanin-induced thrombocytopenia is one of the most common adverse drug reaction developed in critically ill adult patients and concurrent severe hypoalbuminemia may enormously increase the risk of this adverse drug reaction.

**Key words:** Teicoplanin; Thrombocytopenia; Severe hypoalbuminemia; Adverse drug reaction

## INTRODUCTION

Teicoplanin, discovered in 1976, is a highly protein bound glycoside antibiotic with similar antibacterial properties to vancomycin and active against a variety of gram positive microorganisms.<sup>1</sup> Thrombocytopenia is a disorder where the count of one of the blood components thrombocytes, also known as platelet is reduced below 1.5 lacs/Cumm of blood.<sup>2</sup> Drug-induced thrombocytopenia is a common type of adverse drug events (ADE) in the Intensive Care Unit's (ICU) critically ill patients and antibiotic associated thrombocytopenia is one of the most common incidence among these events, globally.<sup>3</sup>

Study found that among all the teicoplanin-induced adverse events, 14% cases are teicoplanin-induced thrombocytopenia (TIT) in critically ill patients of ICU where development of acute thrombocytopenia is closely related to the serum teicoplanin concentration.<sup>1</sup> Protein bound drugs including teicoplanin bind with the albumin of blood, and the ratio of albumin-bound form and the free-active form of these drugs is highly regulated by the present level of albumin in blood. In severe hypoalbuminemia (SHA), a condition where serum albumin level goes down below 2.5 g/dL, the free-active concentration of these drugs is greatly varied, accordingly.<sup>4</sup> In this study, we analyzed the relationship between TIT and SHA in ICU's critically ill patients with normal kidney function.

## MATERIALS AND METHODS

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We conducted this observational study in the adult-ICU department of Square hospital, a tertiary level hospital in the capital Dhaka of Bangladesh. The ICU has twenty well equipped beds and this is country's one of the best ICU care facilities. The study was started on February, 2018 and ended on June, 2018. During this period, 1917 different aged critically ill patients were admitted in that ICU and among those patients, 42 adult patients (25 to 45 years old) with normal kidney function were selected for the study purpose. Hospital Acquired Pneumonia (HAP) by coagulase-negative staphylococci was common in all patients of this study and teicoplanin was the chosen antibiotic therapy for all study-patients according to the microbiological culture-sensitivity reports. Among them, 23 patients were suffering from SHA (albumin level: below 2.5 g/dL) during the initiation of teicoplanin therapy. Before starting teicoplanin therapy (loading dose: 400 mg intravenously, every 12-hours for 3-doses; and maintenance dose: 400 mg intravenously, every 24-hours), the platelet count was normal (above 1.5 lacs/Cumm of blood) in every study patient. No patient had any low platelet count history before initiating teicoplanin therapy at their ICU staying time at that hospital. All types of adverse drug reactions (ADR) happened among those patients during this study period were recorded and among

those ADRs, specific TIT events were considered for the study. Every TIT event was analyzed with the level of albumin in the blood of those patients during that study period and the correction time of the TIT events were recorded after discontinuing the teicoplanin therapy. During the study period, renal function of all the study patients was normal (serum creatinine level: 0.8-1.4 mg/dL).

## RESULTS

All 42 patients received teicoplanin with the recommended loading and maintenance doses, and no renal-dose adjustment was required during the study period. Among those 42 patients, 17 patients (40.48%, n = 42) developed TIT event and 25 patients (59.52%, n = 42) developed no types adverse event including TIT during the study period (Table 1).

During the study period, among 42 patients, 23 patients had SHA and their level of serum albumin was found below 2.5 g/dL (Table 2). In comparison to the reported total number of TIT events in patients (17, n = 42), 14 TIT events (60.87%, n = 42) were found in patients suffering from SHA and only 3 patients developed TIT without having SHA during the study period (Table 2).

**Table 1. Development of teicoplanin-induced thrombocytopenia among critically ill patients**

Number of patients (n)	Number of patients developed TIT event (n=42)	Percentage (%) of patients developed TIT event	Number of patients developed no TIT event (n=42)	Percentage (%) of patients developed no ADR event including TIT
42	17	40.48	25	59.52

**Table 2. Co-relation between severe hypoalbuminemia and development of teicoplanin-induced thrombocytopenia.**

Number of patients had SHA (n=42)	Number of patients had SHA and developed TIT (%) (n=17)	Number of patients had no SHA and developed TIT event (n=17)	NPC <sup>a</sup> in patients within 48 hrs after discontinuing the therapy (n=17)	NPC in patients within 72 hrs after discontinuing the therapy (n=17)
23	14 (60.87)	3	15	2

NPC<sup>a</sup>: Normalized platelet count

To normalize the platelet count after justifiably detecting the ADR events associated with teicoplanin therapy in patients during the study time, the therapy was then discontinued immediately and switched to

another suitable alternate antibiotic therapy. After discontinuing the teicoplanin therapy, platelet count was normalized in 15 patients within 48 hrs and 2 patients were normalized within 72 hrs (table 2).

## DISCUSSION

In certain countries of Asia, infections with gram-positive microorganisms like, coagulase-negative staphylococci is one of the major causes of morbidity as well as mortality among ICU's patients, and 33 to 55% mortality rate was recorded in patients with methicillin-resistant *Staphylococcus aureus* (MRSA) pneumonia.<sup>3</sup>

Teicoplanin is a complex-structured antibiotic consists of five closely related glycoside antibiotics and has once daily dosing advantage over vancomycin. Teicoplanin can be administered intravenously and intramuscularly without changing any fluctuation in the plasma-drug concentration. It is a first-line drug of choice of many physicians because of its significant effectiveness against most listeria, enterococci and staphylococci, including methicillin-resistant strains and also vancomycin-resistant *Staphylococcus aureus* (VRSA). It shows its bactericidal activity through inhibiting bacterial cell wall synthesis by strongly binding with the D-Alanyl-D-alanine terminus of cell wall precursor units. Teicoplanin has a long elimination half-life (up to 100 hours in patients with normal renal function) with large distribution volume. 90 to 95% teicoplanin is bound to plasma protein and its protein binding directly affects its bactericidal activity.<sup>1</sup>

Among the ICU's seriously ill patients, 19 to 63% incidences of thrombocytopenia reported, globally and drugs like, heparin and some antibiotics are mostly found to develop acute thrombocytopenia.<sup>3</sup> Drug-induced thrombocytopenia was first reported in 19<sup>th</sup> century.<sup>5</sup> Study found that among the critically ill patients, 25% patients develop drug-induced thrombocytopenia and in a year, at least 10 incidences of drug-induced thrombocytopenia reported per million populations.<sup>6</sup> Drug-induced thrombocytopenia is an acutely developable event, and may cause sudden bleeding and death. In ICU's critically ill patients, sometimes a culprit drug-induced thrombocytopenia is misdiagnosed with either sepsis like complications, or with immune thrombocytopenic purpura (ITP). In some cases, unknown etiology of multiple prescribed drugs takes

too much time to find out the responsible drug for an acute thrombocytopenic event.<sup>7</sup> A number of studies found that drug-induced thrombocytopenia is an idiosyncratic immune-mediated reaction. Drug-dependent antibodies are developed in response to a specific drug-therapy and these unusual types of antibodies specifically bind to epitopes on platelet surface glycoproteins. These antibodies are very much specific to the respective drug's structure. These drug-specific antibodies may be generated from naturally occurring pool of immunoglobulins.<sup>7,8,9</sup> Drug-dependent antiplatelet antibodies are generally evolved after initiating a specific drug therapy and in some cases, after using a specific drug therapy for a long time, intermittently. In most of the cases, platelets are more targeted by antiplatelet antibodies than white blood or red blood cells and thrombocytopenia-like event is frequently developed.<sup>7</sup>

Study found teicoplanin-dependent platelet autoantibodies (TDPA) in patients with thrombocytopenia when the patients are existed on teicoplanin therapy. In that study, researchers identified GPIIb/IIIa as the target antigen for TDPA which may ultimately cause destruction of platelet cells in the plasma and this adverse drug event is diminished when teicoplanin therapy is discontinued. Study also found that patients on teicoplanin therapy may produce TDPA without hampering the normal platelet count at that time and in that case, the presence of these antibodies is very difficult to predict. As a result, these unusual kinds of autoantibodies may cause thrombocytopenia.<sup>10</sup>

In our study, we found that patients (n=42) with normal platelet count developed thrombocytopenia when teicoplanin therapy was started and TIT may be developed due to synthesis of teicoplanin-dependent platelet autoantibodies.

Severe hypoalbuminemia (serum albumin level: <2.5 g/dL) significantly affects the pharmacokinetics of high plasma bound drugs like, teicoplanin, and free teicoplanin concentration in the blood is increased with the increased tissue distribution and reduced therapeutic half-life.<sup>11,12</sup> Study showed that

when concentration of drugs is increased in blood or tissue level beyond the drug-specific therapeutic window, then chances of adverse drug reaction is raised and in case of high plasma bound drugs, concomitant presence of SHA enhances the possibility of happening unexpected adverse drug event.<sup>12,13</sup> Therapeutic drug monitoring (TDM) is an useful tool for monitoring serum-teicoplanin concentration accurately which may ensure the minimum inhibitory concentration (MIC) of teicoplanin without having excessive free drug accumulation in the blood.<sup>14</sup>

In our study, TIT was observed more frequently in patients with SHA (60.87%, n=42) than the patients with normal blood-albumin level. After discontinuing the teicoplanin therapy, most of the patients (15, n= 17) recovered from TIT within 48 hours and rest of the patients recovered within 72 hours. Except thrombocytopenia, no other teicoplanin-induced adverse drug event was observed during the study period. So, the possibility of teicoplanin-induced adverse drug event like, thrombocytopenia was enhanced through the production of TDPA, when patients were suffering from severe hypoalbuminemia. In case of mild reduction in serum-albumin level (2.5 to 3.0 g/dL), no thrombocytopenia event was observed during the study period.

## CONCLUSION

Teicoplanin-induced thrombocytopenia is an unwanted and sentinel event which may cause unexpected death of the patient. Platelet autoantibodies are the major factor behind this TIT event. Severe hypoalbuminemia is the clinical condition where free plasma-teicoplanin level is significantly increased with the increased chance of Platelet autoantibodies-induced thrombocytopenia. Immediate correction of SHA as well as continuous adverse drug reaction monitoring in the critical areas like, ICU are very necessary to identify and to efficiently manage this ADE without too much delay. Discontinuation of the therapy is the ideal tool to overcome the event. Further study is necessary to

identify other possible factors behind TIT event and in-depth correlations between SHA and TIT.

## CONFLICT OF INTEREST

There is no conflict of interest regarding this study.

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