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Antibiotics induced thrombocytopenia among hospitalized adult patients: a single center retrospective study

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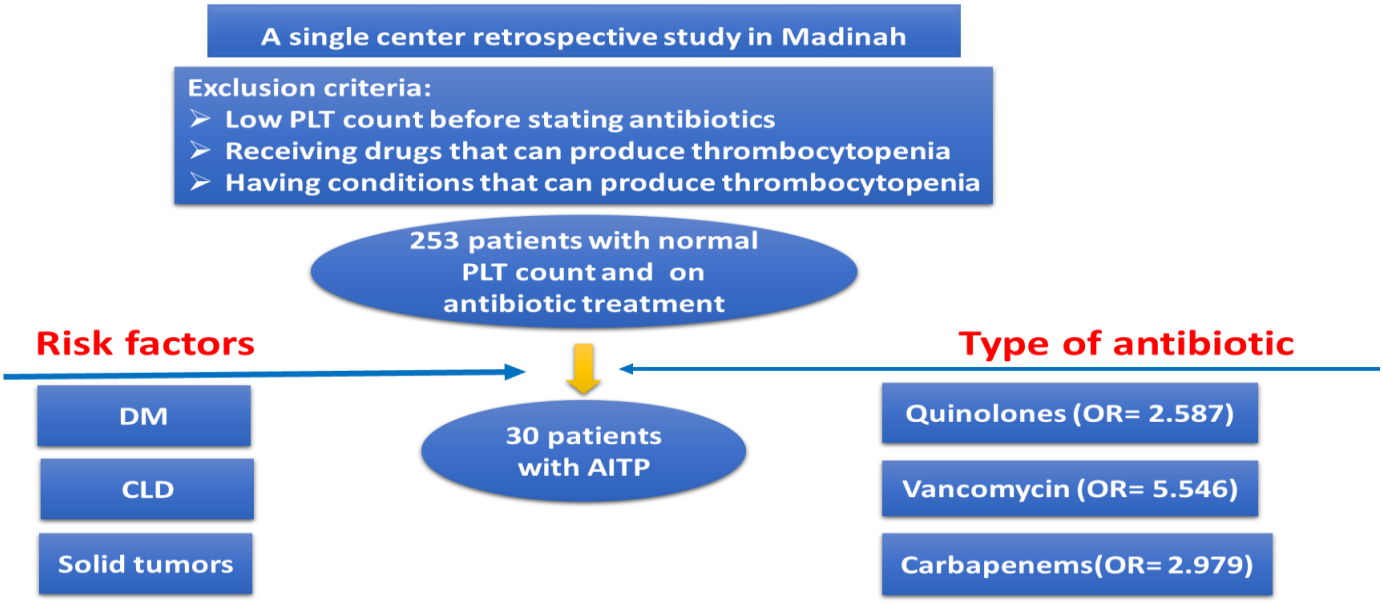
ABSTRACT

Drug induced thrombocytopenia is a common drug side effect which is frequently encountered upon antibiotics use in patients admitted to hospital. It has been associated with various complications related to liability of bleeding.



Clinicians must be aware of the dangers connected with antibiotic therapy in order to maximize patient safety. This study aimed to compare the incidence and the associated risk factors of thrombocytopenia in hospitalized patients receiving different types of antibiotics. After application of inclusion and exclusion criteria, 235 adult patients were included. The patients then were classified into two groups according to the platelet count 5-7 days after starting the antibiotic treatment; patients with platelets (PLT) count > 150 x10^3/ µl and patients with PLT count < 150 x10^3/ µl. The following data were collected from the medical records: age, sex, history of chronic diseases and risk factors, cause of antibiotic treatment, type, dose, duration of antibiotic, co-administrated medications, laboratory data at admission (before starting the antibiotic) and laboratory results 5-7 days after starting antibiotics. We found that quinolones, vancomycin and carbapenems had significantly higher odds of developing thrombocytopenia (OR= 2.587, 95%CI: from 1.156 to 5.789, P= 0.021), (OR= 5.546, 95%CI: from 2.361 to 13.025, P<0.001) and (OR= 2.979, 95%CI: from 1.131 to 7.851, P= 0.027) respectively. Having DM, liver diseases, neurological diseases or solid tumors increased significantly the risk of developing antibiotic induced thrombocytopenia (AITP). AITP is one of the most potentially serious complications of many antimicrobials. PLT should be monitored while on antibiotic therapy for potential thrombocytopenia.

Keywords: Thrombocytopenia, Antimicrobials, Vancomycin, Quinolones, Carbapenems.

INTRODUCTION

Thrombocytopenia is a prevalent issue, and it is important to take drug-induced thrombocytopenia (DITP) into account, particularly in hospitalized patients who frequently get new drugs. Hospitalized individuals are more likely to receive new drugs, including antibiotics, and to have a higher incidence to develop DITP [1].

Thrombocytopenia, a platelet (PLT) counts under the lower border of normal (PLT <150 x10^3/ µl), is the most frequently encountered hemostatic abnormality in hospitalized patients especially if critically ill or having chronic diseases [2]. It can lead to various complications related to the threat of bleeding with subsequent lengthy stay in the hospital and increased mortality [3-10]. Different factors can trigger the development of thrombocytopenia including enhanced PLT consumption or degradation, decreased platelet synthesis, and hem dilution [11]. When all other evident causes of thrombocytopenia have been ruled out, DITP should be investigated. 10% to 25% of hospitalized patients with thrombocytopenia had DITP [8, 11-13].

An important medical advancement that significantly decreased the number of infection-related mortality was the development of antibiotic therapy. Currently, at least one antibiotic treatment is administered to 50% of hospitalized patients, which is believed to be unnecessary for 20–30% of these patients [14]. Although antibiotics are frequently used, their potential to have negative consequences is frequently underestimated because most practitioners believe antimicrobial drugs to be relatively innocuous. Patients who are hospitalized to the hospital and given antibiotics frequently develop DITP [15-17]. Clinicians must be aware of the dangers connected with antibiotic therapy in order to maximize patient safety. The purpose of this study was to report the occurrence and assess the risk factors for thrombocytopenia in hospitalized patients due to the most frequently administered antibiotics. To the best of our knowledge, this is the first study to look into the prevalence and risk factors for antibiotics induced thrombocytopenia (AITP) in hospitalized patients in Madinah, Saudi Arabia.

MATERIALS AND METHODS

Patients and Data Collection

The protocol of our retrospective study was evaluated and given the approval by the Institutional Review Board (IRB), General Directorate of Health Affairs in Madinah, Ministry of Health, SAUDI ARABIA (ref. no. 22-083, 10/05/2022).

This was a single center retrospective observational study. A random sample of adult patients admitted in King Fahd hospital, Madinah, SAUDI ARABIA between 2015 and 2022 were included in this study. All patients received antibiotic treatment during their admission period. The inclusion criteria were normal platelet count (>150 x10^3/ µl) before starting the antibiotic treatment.

Age, sex, history of chronic diseases and risk factors, cause of antibiotic treatment, type, dose, duration of antibiotic, co-administrated medications, laboratory data at admission (before starting the antibiotic) and laboratory results 5-7 days after starting antibiotics were all taken from the patient's medical records. Co-administered drugs like tacrolimus, amiodarone, aspirin, digoxin, haloperidol, heparins, and valproic acid that may increase the risk of thrombocytopenia were reviewed. Patients who received co-administrated medication that may cause DITP were excluded from the study. Additionally, patients who have other factors that can contribute to develop thrombocytopenia were excluded from the study, as sepsis, vitamin B12 or folic acid deficiency, leukemia, splenomegaly and immunological disorders as lupus.

Thrombocytopenia was defined as PLT count < 150 x10^3/ µl, Anemia as having a hemoglobin (Hb) <10 g/dL and leukopenia as having a white blood cell count (WBCs) <4,500 cells/µl [1].

After application of inclusion and exclusion criteria, 235 adult patients were included in this study. The patients were subsequently divided into two groups based on the PLT count 5-7 days after starting the antibiotic treatment; patients with PLT count > 150 x10^3/ µl and patients with PLT count < 150 x10^3/ µl.

Statistical Analysis

The IBM Company, Armonk, NY, USA, used SPSS version

28 to conduct the statistical analysis. The mean and standard deviation (SD) of quantitative parametric data were reported, and an unpaired student t-test was used to examine them. The Mann Whitney-test was used to analyze quantitative non-parametric data, which were provided as the median and interquartile range (IQR). The Chi-square test was used to assess categorical data, which were provided as frequency and percentage (%). To determine the level of correlation between two quantitative variables, the Spearman's rank correlation coefficient was performed. To evaluate the various parameters connected to the prevalence of DITP among the study participants, logistic regression was used. Statistical significance was defined as a two tailed P value 0.05.

RESULTS

Baseline characteristics of the studied patients

The current study comprised 235 adult hospitalized patients, 129 (54.89%) males and 106 (45.11%) females. The patients' ages ranged from 18 to 98 years with a mean age of 51.6± 21.7 years.

Chronic diseases and risk factors were as follows; hypertension 67 (28.51%), Diabetes mellitus (DM) 51 (21.7%), neurological diseases 32 (13.62%), endocrine disorders 12 (5.11%), history of myocardial infarction 14 (5.96%), congestive heart failure 20 (8.51%), peripheral vascular disease (PVD) 22 (9.36%), cerebrovascular accident 15 (6.38%), chronic obstructive pulmonary disease (COPD) 12 (5.11%), peptic ulcer disease 26 (11.06%), liver disease 6 (2.55%), solid tumor 23 (9.79%), lymphoma 3 (1.28%) and Chronic kidney disease (CKD) 9 (3.83%).

The most frequently prescribed antibiotics were cephalosporin's 156 (66.38%), quinolones 54 (22.98%), Beta lactamase inhibitors combinations 51 (21.7%), nitroimidazoles 54 (22.98%), Vancomycin 34 (14.47%) and Carbapenems 26 (11.06%). 5-7 after starting antibiotic treatment, 205 patients were found to have normal PLT count > 150 $x10^3$/ µl and 30 patients developed PLT count < 150 $x10^3$/ µl.

Relation between Patients' Demographics and Development of Thrombocytopenia

Table 1: Relation between patients' demographics and development of AITP

		Platelet count after 5-7 days of antibiotic treatment ($x10^3$/µl)		P value
		PLT count > 150 (n=205)	AITP (n=30)	
Age (years)	Median	51	68	**0.022**
	IQR	33 - 68	38.5 – 75.25	
Sex	Male	113 (55.1%)	16 (53.3%)	0.854
	Female	92 (44.9%)	14 (46.7%)	

Data are presented as frequency (%) unless otherwise stated, Statistical significance at P<0.05

Table 1 shows that patients who developed thrombocytopenia were significantly older than participants with PLT count >150 $x10^3$/ µl after treatment (P value= 0.022) with no statistically significant difference in the sex distribution between the two groups.

Relation between different types of Antibiotic and Occurrence of Thrombocytopenia

By studying the relation between antibiotic type and the incidence of thrombocytopenia after antibiotic treatment; quinolones, Vancomycin and Carbapenems were administered at significantly higher rates in participants who developed thrombocytopenia when compared to those with PLT >150 $x10^3$cells/µl (P= 0.018, <0.001, 0.031 respectively). Contrariwise, there was no significant correlation between PLT level after treatment and cephalosporin's, Beta lactamase inhibitor combinations or nitroimidazoles administration Table 2.

Table 2: Relation between antibiotic type and development of thrombocytopenia

	Platelet count after 5-7 days of antibiotic treatment ($x10^3$/µl)		P value
	PLT count > 150 (n=205)	PLT count < 150 (n=30)	
Cephalosporin's	134 (65.4%)	18 (60%)	0.566
Quinolones	42 (20.5%)	12 (40%)	0.018
Beta lactamase inhibitor combinations	45 (22%)	6 (20%)	0.809
Nitroimidazoles	48 (23.4%)	6 (20%)	0.678
Vancomycin	22 (10.7%)	12 (40%)	<0.001
Carbapenems	19 (9.3%)	7 (23.3%)	0.031

Relation between Chronic Diseases and Risk Factors and Occurrence of Thrombocytopenia

Table 3: Relation between history of chronic diseases and development of thrombocytopenia among the studied participants

	Platelet count after 5-7 days of antibiotic treatment ($x10^3$/µl)		P value
	PLT count > 150 (n=205)	PLT count < 150 (n=30)	
Hypertension	55 (26.8%)	12 (40%)	0.136
Diabetes mellitus	40 (19.5%)	11 (36.7%)	**0.033**
Neurological disease	23 (11.2%)	9 (30%)	**0.010**
Endocrine disorder	10 (4.9%)	2 (6.7%)	0.655
History of myocardial infarction	12 (5.9%)	2 (6.7%)	0.596
Congestive heart failure	17 (8.3%)	3 (10.3%)	0.722
Peripheral vascular disease	18 (8.8%)	4 (13.3%)	0.497
Cerebrovascular accident	12 (5.9%)	3 (10%)	0.416
COPD	10 (4.9%)	2 (6.7%)	0.655
Peptic ulcer disease	22 (10.7%)	4 (13.3%)	0.754
Liver disease	1 (0.5%)	5 (16.7%)	**<0.001**
Solid Tumor	16 (7.8%)	7 (23.3%)	**0.015**
Lymphoma	3 (1.5%)	0 (0%)	>0.999
Chronic kidney disease	9 (4.7%)	0 (0%)	0.602

The relation between risk factors and the incidence of thrombocytopenia after antibiotic treatment is demonstrated in Table As patients with thrombocytopenia suffered from neurological, liver diseases, DM and solid tumors at significantly higher rates when compared to participants with PLT count >150 $x10^3$ cells/µl as

P value = 0.01, <0.001, 0.033, 0.015 respectively.

Relation between Complete Blood Count (CBC) Results and the Development of Thrombocytopenia

Before antibiotic administration, the studied participants had comparable CBC, while 5-7 days after antibiotic administration, patients with thrombocytopenia had significantly lower hemoglobin (Hb), red blood cells (RBCs) count, hematocrit (Ht) with higher incidence rate to develop leukopenia and anemia compared to participants with PLT count >150 x103 cells/µl (P<0.05) as shown in Table **.**

Table 4: Relation between CBC and the development of thrombocytopenia

	Days	Platelet count after 5-7 days of antibiotic treatment (x10^3/µl)		P value
		PLT count > 150 (n=205)	PLT count < 150 (n=30)	
Hb (g/dL)	Before	10.63 ± 2.5	10.7 ± 2.81	0.825
	7 days	10.3 ± 2.24	8.81 ± 2.23	<0.001
Anemia (Hb<10 g/dL) after treatment	N (%)	91 (44.4%)	22 (73.3%)	0.003
RBCs (x10^3 cells/µl)	Before	4.06 ± 1.01	3.89 ± 1.01	0.604
	7 days	3.89 ± 0.88	3.15 ± 0.76	<0.001
Ht (%)	Before	33.42 ± 7.67	32.82 ± 7.64	0.826
	7 days	32.78 ± 7	27.86 ± 6.35	<0.001
WBCs	Before	11.39 (7.96 – 17)	13.27 (8.85 – 17.96)	0.439
	7 days	9.41 (7.38 – 13.12)	9.95 (5.75 – 11.51)	0.239
Leukopenia (WBCs<4500 cells/µL) after treatment	N (%)	5 (2.4%)	5 (16.7%)	0.004

Data are presented as mean ± SD, median (IQR) unless otherwise mentioned, Statistical significance at P<0.05

Logistic Regression

Age was substantially linked with the occurrence of AITP, according to the findings of Univariate logistic regression analysis (OR= 1.022, 95%CI: from 1.003 to 1.042, P= 0.025). Similarly, number of antibiotics was substantially correlated with the incidence of development of thrombocytopenia after treatment as patients on five antibiotics had higher odds of experiencing thrombocytopenia compared to those on one antibiotic (OR= 9.75, 95%CI: from 2.316 to 41.045, P= 0.002). Regarding type of antibiotics, participants on quinolones (OR= 2.587, 95%CI: from 1.156 to 5.789, P= 0.021), Vancomycin (OR= 5.546, 95%CI: from 2.361 to 13.025, P<0.001) and Carbapenems (OR= 2.979, 95%CI: from 1.131 to 7.851, P= 0.027) had considerably larger chances of developing thrombocytopenia than those who weren't.

Patients with DM (OR= 2.388, 95%CI: from 1.053 to 5.417, P= 0.037), Neurological diseases (OR= 3.391, 95%CI: from 1.388 to 8.285, P= 0.007), liver disease (OR= 40.8, 95%CI: from 4.581 to 363.419, P<0.001) and solid tumours (OR= 3.595, 95%CI: from 1.339 to 9.657, P=0.011) had noticeably larger chances of having AITP than the healthy ones.

Anemic patients (OR= 3.455, 95%CI: from 1.465 to 8.099, P=0.005) and those with leukopenia (OR= 8, 95%CI: from 2.16 to 29.57, P=0.002) had considerably higher probabilities of developing AITP than the healthy ones

Table 5: Univariate logistic regression of characteristics associated with the incidence of developing thrombocytopenia

	uOR	P-value	95% CI	
			LL	UL
Age (years)	1.022	0.025	1.003	1.042
Sex				
Male	Ref			
Female	1.075	0.854	0.499	2.317
Number of antibiotics				
One antibiotic	Ref			
Two antibiotics	0.989	0.984	0.341	2.869
Three antibiotics	1.551	0.426	0.527	4.566
Four antibiotics	3.25	0.122	0.728	14.502
Five antibiotics	9.75	0.002	2.316	41.045
Type of antibiotics				
Cephalosporin's	0.795	0.566	0.363	1.743
Quinolones	2.587	0.021	1.156	5.789
Beta lactamase inhibitor combinations	0.889	0.809	0.343	2.307
Nitroimidazoles	0.818	0.678	0.316	2.117
Vancomycin	5.546	<0.001	2.361	13.025
Carbapenems	2.979	0.027	1.131	7.851
Positive risk factors				
DM	2.388	0.037	1.053	5.417
Neurological disease	3.391	0.007	1.388	8.285
Liver disease	40.8	<0.001	4.581	363.419
Solid tumor	3.595	0.011	1.339	9.657
Starting anemia (Hb<10 g/dL)	3.445	0.005	1.465	8.099
Starting leukopenia (WBCs<4500 cells/µL)	8	0.002	2.164	29.57

UOR: unadjusted odds ratio, CI: confidence interval, Statistical significance at P<0.05

DISCUSSION

Drug-induced PLT-reactive antibodies, bone marrow suppression, and reduced platelet synthesis are just a few of the ways that medications can cause thrombocytopenia [18]. Drug-induced thrombocytopenia typically develops 5 to 7 days after exposure [19, 20]. Since most hospitalized patients are taking many drugs and have comorbid conditions that might also cause thrombocytopenia, a diagnosis of DITP is typically difficult. The primary course of treatment is discontinuation of the offending medication, therefore after 4 to 5 half-lives of the offending agent or its metabolite, the PLT count often begins to recover [21].

The results of the current study showed that quinolones, Vancomycin and Carbapenems were the antibiotic classes with a statistically significant connection with thrombocytopenia. Patients who developed thrombocytopenia tended to be older than patients with normal PLT count. Having DM, liver diseases, neurological diseases or solid tumors increased significantly the risk of developing AITP. Additionally, patients who have anemia and/or leukopenia before starting treatment showed significant higher risk to develop the thrombocytopenia after antibiotic treatment. Moreover, our results showed that patients who developed thrombocytopenia also had significantly higher rate to develop anemia and/or leukopenia.

According to our findings, people taking quinolones had noticeably increased probabilities of getting thrombocytopenia than those not taking them. Our results are consistent with earlier reports that identified instances of thrombocytopenia linked to the use of quinolones [22-25]. Some reports have been documented that the drug-induced platelet-reactive antibodies that cause complement-mediated PLT degradation are the cause of this connection. This immune mechanism is also supported by the rapid onset and recurrence with reexposure to quinolones [25]. Quinolones have structural similarity to quinine which can explain its ability to induce platelet-reactive antibodies [13].

Vancomycin is widely used, however it is unclear how frequently Vancomycin-induced thrombocytopenia occurs. This condition is frequently regarded to be a rare cause of immunological thrombocytopenia. According to our findings, Vancomycin users had noticeably increased probabilities of developing thrombocytopenia than non-users. Similarly, according to earlier research, Vancomycin-induced thrombocytopenia was observed to have a prevalence of 5.9–7.1% [26-28]. Additionally, some previous reports highlighted that Vancomycin may cause thrombocytopenia at greater rates, comparable to linezolid, a common cause of antibiotic induced thrombocytopenia [29-31].

Vancomycin-dependent PLT-reactive antibodies has been determined to be the most likely reason of thrombocytopenia [32]. Curiously, one retrospective investigation reported a linear exposure-response association between the highest Vancomycin trough concentrations and a 50% drop in PLT from baseline, which may point to a different no immune-mediated mechanism of thrombocytopenia [29].

According to our findings, people taking Carbapenems had a noticeably increased chance of developing thrombocytopenia than people not taking them. Meropenem or other Carbapenems have been shown in some case studies and series to produce severe thrombocytopenia [33-35]. Huang and his colleagues in their case report detected PLT antibodies and proved that the binding location of the Meropenem-induced PLT antibodies was glycoprotein IIb/IIIa [36].

Some drugs are able to induce pancytopenia, not only thrombocytopenia, by decreasing bone marrow cell density or by impairing cell maturation within bone marrow [37, 38]. Antibiotics such as Vancomycin and linezolid can directly damage the bone marrow, which can also cause thrombocytopenia [39, 40]. The results of the current study showed that patients who developed thrombocytopenia also had significantly lower Hb and WBCs and higher rate to develop anemia and/or leukopenia.

The present study showed that starting anemia and the history of chronic liver disease (CLD) was correlated with the incidence of the antibiotic induced thrombocytopenia. Our results are consistent with a previous report [25] where they showed quinolones were found to be significantly associated with anemia and CLD in inducing thrombocytopenia in CLD patients. Higher levels of autoantibodies to platelet surface antigens in CLD patients can speed up the removal of platelets by the splenic and hepatic reticuloendothelial system, causing fast platelet death and helping to explain, in part, the development of thrombocytopenia [41-43].

To the best of our Knowledge, this is the first study in Madinah, SAUDI ARABIA to investigate the incidence and the risk factors to develop antibiotics induced thrombocytopenia (AITP) in hospitalized patients. However, the limitations of the study that the period needed for thrombocytopenia to heal after stopping the antibiotics were not evaluated in all patients. This can be evaluated in a multicenter future study in Madinah.

CONCLUSION

Among the several causes of thrombocytopenia, AITP is a relatively uncommon disorder. To quickly stop using and replace the harmful substance, as well as to prevent further exposure, it is crucial to identify it. Clinicians need to be on the lookout for any negative side effects from using antimicrobial drugs. The onset of thrombocytopenia is one of the most severe potential side effects of several antibiotics. A higher risk of haemorrhage might result in higher morbidity and mortality due to thrombocytopenia. Physicians should emphasize the risk factors that can raise the likelihood of developing

thrombocytopenia before choosing the antimicrobial medication, and PLT count should be regularly checked while on therapy for possible thrombocytopenia.

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