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REVIEW

Carbapenem-Induced Platelet Abnormalities: A Systematic Review Literature Analysis of Platelet Abnormality Caused by Carbapenems

Juan Pan[1,*], Wei Peng[1,*], Chao Ye[2,*], Lingzhi Zhou[1,*], Xu Zhang[1], ZuYi Li[1], Xiaojuan Zhang[1], Qiongliang Yang[1], MingHui Wu[3]

[1]Department of Pharmacy, Liuyang Hospital of Traditional Chinese Medicine, Changsha, Hunan, 410300, People's Republic of China; [2]Department of Pharmacy, Guangdong Provincial Second Hospital of Traditional Chinese Medicine(Guangdong Provincial Engineering Technology Research Institute of Traditional Chinese Medicine), Guangzhou, Guangdong, 510095, People's Republic of China; [3]Department of Oncology and Hematology, Liuyang Hospital of Traditional Chinese Medicine, Changsha, Hunan, 410300, People's Republic of China

*These authors contributed equally to this work

Correspondence: Chao Ye, Department of Pharmacy,Guangdong Provincial Second Hospital of Traditional Chinese Medicine(Guangdong Provincial Engineering Technology Research Institute of Traditional Chinese Medicine), No. 60, Hengfu Road, Guangzhou, Guangdong, 510095, People's Republic of China, Email yechao1234256@163.com; Lingzhi Zhou, Department of Pharmacy, Liuyang Hospital of Traditional Chinese Medicine, Changsha, Hunan, 410300, People's Republic of China, Email 1024482174@qq.com

Objective: To analyze and discuss the clinical characteristics of carbapenem-induced platelet abnormalities.

Methods: The databases of CNKI, Wanfang Data, Chinese VIP, Web of science, PubMed, Embase and Elsevier were searched (up to June 30,2025), and the case reports of carbapenem-induced platelet abnormalities were collected and descriptively analyzed.

Results: A total of 42 patients (21 males and 21 females) were included, with a median age of 64 years (range:0–96 years). Thrombocytosis was observed in 20 patients, while thrombocytopenia occurred in 22 patients. Platelet abnormality most often occurred in patients receiving meropenem (64.3%) followed by imipenem (26.2%). All cases occurred during carbapenem therapy. The median time to platelet count abnormality was 3 days (range 0.125–12), with 79.5% of cases occurring within one week. Specifically, the median time to carbapenem-induced thrombocytopenia was 2.5 days (range 0.125–9), while the median time to carbapenem-induced thrombocytosis was 3 days (range 3–12). The nadir of platelet count was reached at 5 days (range 1–10) after medication, with a median platelet count nadir of 21.5×10^9 /L (range 0–136). The peak of platelet count was reached at 8 days (range 3–18), with a median platelet count peak of 900×10^9 /L (range 570–1,440). Complications occurred in 10 thrombocytopenia cases, all of which were bleeding events. After discontinuation of the drug and symptomatic treatment, all cases showed significant improvement in platelet counts and resolution of complications, except for one patient who died from multiple organ dysfunction syndrome.

Conclusion: Carbapenem-induced platelet abnormalities appear to be more frequent than previously recognized, predominantly occurring within the first week of therapy. This potentially severe adverse drug reaction should be particularly considered in elderly patients receiving meropenem therapy.

Keywords: carbapenem, platelet abnormality, adverse drug reaction, clinical characteristics, systematic review

Introduction

Carbapenem antibiotics are a novel class of β-lactam antibiotics first discovered in 1976. They exhibit broad-spectrum antibacterial activity against Gram-positive, Gram-negative, and anaerobic bacteria, including many multidrug-resistant (MDR) pathogens. At present, there are six varieties of carbapenem antibiotics on the market, including meropenem, imipenem, panipenem, biapenem, ertapenem, and doripenem. Although the prevalence of carbapenem-resistant Enterobacteriaceae (CRE) has been increasing in recent years, and the global spread of these resistant pathogens coupled with their high mortality rates has limited the efficacy of carbapenems against them, carbapenems remain the first-line therapeutic option for severe infections caused by Enterobacteriaceae producing extended-spectrum β-lactamases

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(ESBLs) or AmpC β-lactamases, owing to their broad antibacterial spectrum and potent bactericidal activity.[1] Moreover, despite the neurotoxicity associated with specific carbapenems such as imipenem and ertapenem, and the nephrotoxicity of imipenem, carbapenems maintain a well-regarded safety profile clinically. This is due to their generally manageable other adverse effects—primarily gastrointestinal disturbances and rash—coupled with a lower incidence of allergic reactions compared to penicillins.[2] Hematological abnormalities involving thrombocytopenia are rare adverse events associated with carbapenems, documented only in sporadic case reports. Consequently, this potential adverse effect may be overlooked in clinical settings. Huang et al[3] studied antibiotic-related thrombocytopenia and noted that 21 of 204 patients (10.3%) with thrombocytopenia were considered to be cases caused by carbapenems. While thrombocytosis associated with carbapenem use has not been reported in the English-language literature, emerging reports from China suggest its occurrence, warranting clinical attention. Since 1986, numerous case reports of platelet count abnormality induced by carbapenems have been published. However, the incidence and the clinical features of carbapenem-induced platelet abnormalities are still unclear. The purpose of this study is to explore the clinical characteristics, diagnosis, and management of carbapenem-induced platelet abnormalities and provide insights to guide its safer clinical use.

Methods

Search Strategy

The systematic literature search was performed in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) framework, adhering to established methodological standards for evidence synthesis studies.[4] We searched the databases of China National Knowledge Infrastructure (CNKI), Wanfang Data, Chinese VIP, Web of science, PubMed, Embase and Elsevier, with no language restrictions. The search terms were (carbapenem OR meropenem OR imipenem OR panipenem OR doripenem OR biapenem OR ertapenem) AND (thrombocytosis OR thrombocythemia OR thrombopenia OR thrombocytopenia OR blood platelet). The completed PRISMA-ScR checklist and the detailed search strategies for all databases are provided in Supplementary Data 1 and Supplementary Data 2, respectively. The search covered all records from database inception to June 30,2025. The present review was unregistered.

Inclusion and Exclusion Criteria

Case reports and case series of carbapenem-induced platelet abnormalities were included as preliminary study.We excluded duplicate literature, reviews, mechanistic studies, animal studies, and studies that only had an abstract with no full text.

Data Extraction

Two investigators independently performed the initial screening of the literature based on the inclusion and exclusion criteria, and extracted data using a standardized data extraction form that had been pilot-tested. Any discrepancies in the extracted data were cross-checked by a third researcher and resolved through group discussion.The following information was collected for each included case using a self-designed data extraction table: region, sex, age, primary disease, accompanying diseases, concomitant medication, carbapenem application,platelet values,occurrence time, clinical manifestation,treatment and prognosis,rechallenge information.

Definition

According to the World Health Organization (WHO) diagnostic criteria for primary thrombocytosis, thrombocytosis is defined as a platelet count exceeding 450×10^9/L.[5] In most studies, the diagnosis of thrombocytopenia is typically based on an absolute platelet count below 150×10^9 /L.[6] With reference to the Common Terminology Criteria for Adverse Events (CTCAE) Version 5.0, the grading criteria are as follows: (1) Grade 1: 75×10^9 /L ≤ platelet count < upper limit of normal; (2) Grade 2: 50×10^9 /L ≤ platelet count < 75×10^9 /L; (3) Grade 3: 25×10^9 /L ≤ platelet count < 50×10^9 /L; (4) Grade 4: platelet count < 25×10^9 /L.[7]

Statistical Analysis

Descriptive analyses were performed on patient characteristics and the features and patterns of ADR, and narrative synthesis was performed on the main outcomes of the included studies. Statistical analysis was performed using SPSS version 26.0 (IBM Corporation, Armonk, NY). The count data are expressed as n (%), and the measurement data are expressed as the median value (minimum, maximum). Normally distributed continuous variables were compared using one-way ANOVA (for comparisons across three or more groups) or independent samples t-tests (for two-group comparisons). Non-normally distributed continuous variables were analyzed using non-parametric alternatives: the Kruskal–Wallis test for multiple groups or the Mann–Whitney *U*-test for two groups. Categorical variables were evaluated using either the Chi-square test or Fisher's exact test, as appropriate. *P* values of less than 0.05 (two-tailed) were considered to indicate statistical significance.

Correlation Evaluation

The Naranjo Adverse Drug Reaction Probability Scale was used to assess the association between carbapenems and abnormal platelet count (see Supplementary Data 3).[8] The application of specific scale items was operationalized as follows: "Rechallenge information" was directly applied to score Item #4 (a score of +2 for a positive rechallenge, −1 for a negative rechallenge, and 0 if the information was unavailable). "Underlying diseases" and "concomitant medications" were systematically evaluated for their contribution to Item #5. A score of −1 was assigned if the event could be entirely explained by an alternative cause. Conversely, a score of +2 was assigned if the alternative cause was deemed unlikely to be the sole explanation and the temporal relationship strongly supported the suspect drug. All assessments were conducted independently by two investigators, with any discrepancies resolved through consensus or by a third arbiter. Probability was assigned via a score termed definite (≥9), probable (5–8), possible (1–4), or doubtful (≤0).

Results

Patients' Information

After retrieval and screening, forty-two patients from 41 studies were included in this analysis.[9–49] The literature search process is outlined in Figure 1. There are 21 males (50.0%) and 21 females (50.0%). The median age of these patients was 64 years (range 0–96). Patients aged >60 and >75 years accounted for 54.8% and 38.1% of the study population, respectively. Among these patients, 37 patients were from Asia (People's Republic of China, N = 33;India, N = 3; Pakistan, N = 1), 3 patients were from Europe (Spain, N = 1; Serbia, N = 1; Malta, N = 1), 2 patients were from North America (United States of America, N = 2). Among the carbapenems, meropenem was associated with the highest incidence, accounting for 64.3% (N = 27), followed by imipenem (N = 11, 26.2%),ertapenem (N = 2, 4.8%) and biapenem (N = 1, 2.4%).No relevant literature reports were found for panipenem and doripenem. Additionally, one patient developed thrombocytopenia after switching from biapenem to meropenem. Carbapenems were prescribed mainly for pulmonary infection (N=20,47.6%),abdominal infection (N=10,23.8%),sepsis (N=7,16.7%).Urinary tract infection (N=2,4.8%),shoulder joint infection (N=1,2.4%),renal cyst infection (N=1,2.4%) and intracranial infection (N=1,2.4%) were also common indications. The most common bacterial species involved were *Klebsiella pneumoniae* and *Escherichia coli*. Thirty patients (71.4%) had underlying disease, including hypertension (12 cases),diabetes (9 cases), cerebral infarction (6 cases),coronary heart disease (4 cases) and renal insufficiency (4 cases). Two patients had a history of smoking.Details are shown in Table 1.

Administration of Carbapenems

The dose of carbapenems was available on 40 cases. The daily dosage of carbapenem for all patients did not exceed the maximum daily dose specified in the drug instructions. After carbapenems administration, the median time to onset of abnormal platelet count was 3 days (range 0.125–12).The time of carbapenem-induced thrombocytopenia and thrombocytosis were 2.5 days (range 0.125–9) and 3 days (range 1–12), respectively. Abnormal platelet count occurred in 2 cases (4.8%) after rechallenging with carbapenems, and the the median time to abnormal platelet count occurrence of rechallenge patients was 3.5 days (range 3–4), which was no significant difference with the time of the first occurrence.

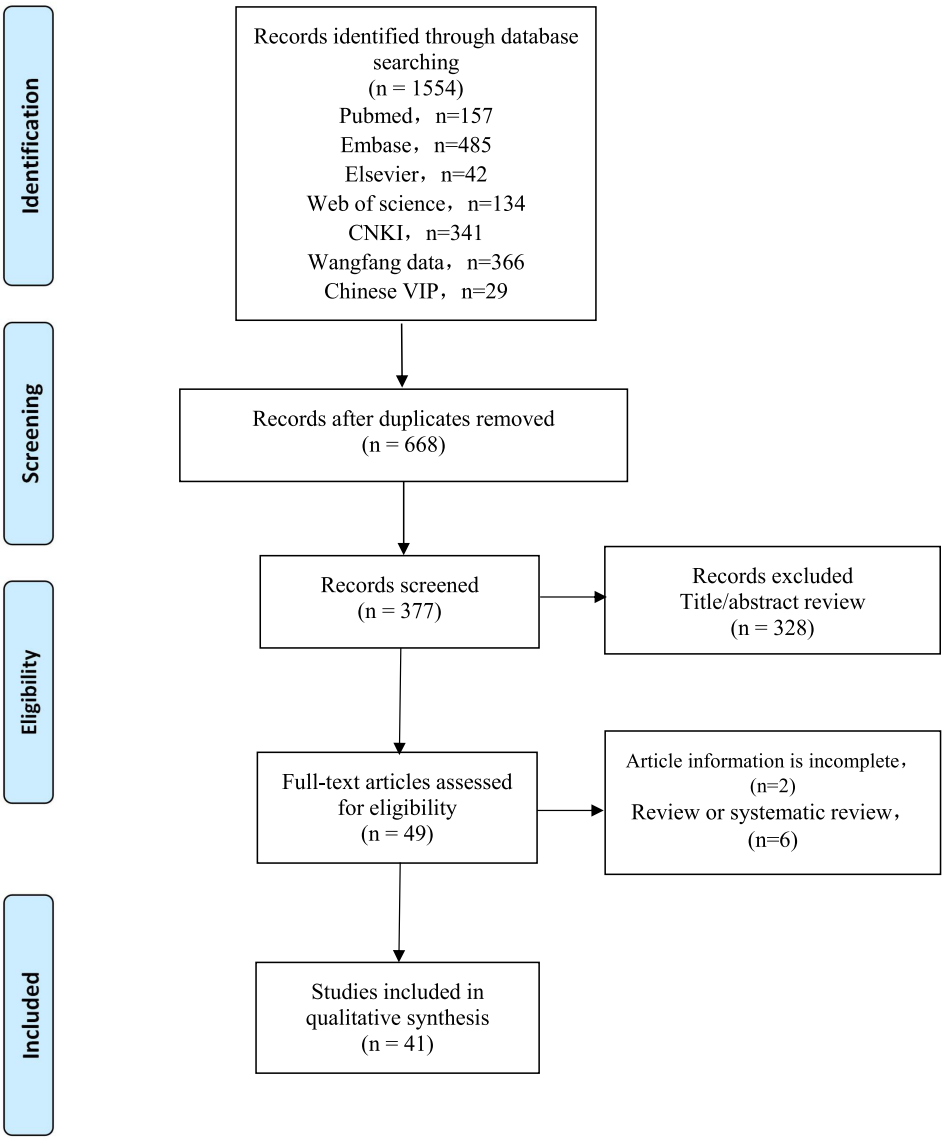

Figure 1 Flowchart of literature screening.

Laboratory Tests, Treatment and Outcome

The laboratory findings, treatments, and outcomes of the 42 patients are summarized in Tables 2 and 3. Among them, 20 patients (47.6%) developed carbapenem-induced thrombocytosis, including 8 cases of extreme thrombocytosis (platelet count > 1,000 × 10^9 /L). Conversely, 22 patients (52.4%) developed carbapenem-induced thrombocytopenia, which was graded as follows: Grade 1 in 2 patients, Grade 2 in 1 patients, Grade 3 in 7 patients, and Grade 4 in 12 patients. Bleeding complications occurred in 10 patients (23.8%) with platelet count abnormalities. In the 20 patients of thrombocytosis caused by carbapenems, the median time of carbapenem use was 8 days (range 4–18). The median time to platelet count increase was 3 days (range 1–12), with a median time to peak of 8 days (range 3–18). The peak platelet count reached 900×10^9 /L (range 570–1,440). Six patients received aspirin therapy, five patients were given heparin / low molecular weight heparin,two patients were treated with dipyridamole, and 1 patient required rivaroxaban. After drug withdrawal and symptomatic treatment, all patients showed platelet count recovery or improvement with a median time of 13 days (range 1–26). While meropenem was associated with a longer platelet recovery time compared to other carbapenems (p<0.05), Dunn's post hoc analysis did not reveal any statistically discernible differences between the groups. The decrease of platelet count in 22 patients occurred during the use of carbapenems, and the median time of carbapenems

Table 1 Characteristics of the 42 Included Patients

Parameter		Value
Sex (42)[a]	Male	21(50.0%)
	Female	21(50.0%)
Age (42)[a]	Years	64(0,96)[b]
	>60 years	23(54.8%)
	>75 years	16(38.1%)
Region (42)[a]	China	33(78.6%)
	India	3(7.1%)
	The United States	2(4.8%)
	Pakistan	1(2.4%)
	Spain	1(2.4%)
	Serbia	1(2.4%)
	Malta	1(2.4%)
Carbapenem (42)[a]	Meropenem	27(64.3%)
	Imipenem	11(26.2%)
	Ertapenem	2(4.8%)
	Biapenem	1(2.4%)
	Biapenem switch to Meropenem	1(2.4%)
Indication (42)[a]	Pulmonary infection	20(47.6%)
	Abdominal infection	10(23.8%)
	Sepsis	7(16.7%)
	Urinary tract infection	2(4.8%)
	Shoulder joint infection	1(2.4%)
	Renal cyst infection	1(2.4%)
	Intracranial infection	1(2.4%)
Bacteriumb (16)[a]	*Klebsiella pneumoniae*	5(31.2%)
	Escherichia coli	5(31.2%)
	Burkholderia cepacia	1(6.2%)
	Providencia rettgeri	1(6.2%)
	Enterobacter cloacae	1(6.2%)
	Pseudomonas aeruginosa	1(6.2%)
	Multi-drug resistant bacteria	1(6.2%)
	G-*bacteria*	1(6.2%)
Time of abnormal platelet count onset during the first carbapenem administration(39)[a]	Days	3 (0.125–12)[b]
	Abnormal platelet count onset within 1 week	31(79.5%)
Abnormal platelet count occurs in two consecutive carbapenem(2)[a] administrations(2)[a]	Days	3.5(3–4)[b]
Time to hospitalization(33)[a]	Days	20(6,48)[b]
Accompanying diseases (30)[a]	Hypertension	12(40.0%)
	Diabetes	9(30.0%)
	Cerebral infarction	6(20.0%)
	Coronary heart disease	4(13.3%)
	Renal insufficiency	4(13.3%)
	Acute kidney injury	3(10%)
	Chronic kidney disease	2(6.7%)
	Alzheimer disease	2(6.7%)
	Subarachnoid hemorrhage	1(3.3%)
	Ileus	1(3.3%)
	Chronic obstructive pulmonary disease	1(3.3%)
History of smoking		2(4.8%)

(*Continued*)

Table 1 (Continued).

Parameter		Value
Concomitant medications	Tigecycline,voriconazole,polymyxin,fluconazole,cefoperazone and sulbactam,teicoplanin,linezolid,vancomycin,Rivaroxaban, esomeprazole,acarbose,ibuprofen,thrombopoietin,lansoprazole, Hydroclopidogrel,atorvastatin calcium,Insulin, nifedipine, metoprolol, Acetylcysteine, terbutaline, budesonide,tamsulosin, pantoprazole,prednisone,Omeprazole,Nadroparin,tiotropium, aspirin,isosorbide mononitrate, ambroxol,Doxofylline, ulinastatin, magnesium isoglycyrrhizinate injection,low molecular heparin,aminophylline	29(69.0%)
Concomitant antibacterial medication		9
	Vancomycin	3(33.3%)
	Linezolid	2(22.2%)
	Cefoperazone and sulbactam	2(22.2%)
	Tigecycline	1(11.1%)
	Voriconazole	1(11.1%)
	Polymyxin	1(11.1%)
	Fluconazole	1(11.1%)
	Teicoplanin	1(11.1%)

Notes: [a]Represents the number of patients out of 42 in whom information regarding this particular parameter was provided. [b]Median (minimum-maximum).

Table 2 Clinical Characteristics, Treatment and Outcome of Carbapenem-Induced Thrombocytosis

Parameter	Meropenem	Imipenem	Ertapenem	Biapenem	Total	*P* value
Number of cases	12	5	2	1	20	/
Male:Female	7:5	1:4	2:0	1:0	11:9	0.129[b]
Age(Years)	50(0.5,80)[a]	40(2.83,65)[a]	65(62,68)[a]	51	51(0.5,80)[a]	0.264[c]
Duration of carbapenem use(Days)	11.5(4,18)[a]	7(7,16)[a]	6(6,6)[a]	8	8(4,18)[a]	0.149[c]
Time to onset of platelet count increase(Days)	5(1,12)[a]	3.5(3,10)[a]	1.5(1,2)[a]	3	3(1,12)[a]	0.242[c]
Time to peak platelet count(Days)	10(4,18)[a]	7(3,16)[a]	5.5(5,6)[a]	8	8(3–18) [a]	0.203[c]
The peak of platelet count(L^{-1})	876(666,1440)[a]	1058(570,1349)[a]	631(610,652)[a]	905	900(570,1440)[a]	0.099[c]
Time to platelet count recovery/improvement(Days)	15(8,26)[a]	6(1,15)[a]	1.25(1,1.5)[a]	7	13(1,26)[a]	0.017[c†]
Time to hospitalization (Days)	20(13,33)[a]	22(13,24)[a]	9.5(9,10)[a]	7	20(6,48)[a]	0.072[c]
Recovered/improved cases	12	5	2	1	20	/

Notes: [a]Median (minimum-maximum). [b]Chi-square tests was used. [c]Due to an insufficient sample size (n=1), biapenem was excluded from the dataset prior to the calculation of the *P* value using the Kruskal–Wallis test. † Despite a statistically significant difference in the time to platelet recovery/improvement among carbapenem groups detected by the Kruskal–Wallis test ($p = 0.017$), subsequent Dunn's post hoc tests with Bonferroni correction failed to identify any statistically significant pairwise comparisons (all adjusted *p*-values > 0.05).

use was 7.5 days (range 1–27), which was shorter than the thrombocytosis group. The median time of platelet count reduction was 2.5 days (range 0.125–9). The valley time was 5 days (range 1–10), and the valley value of platelet count was 21.5×10^9 /L(range 0–136).Bleeding complications occurred in 10 of the 22 patients, including melena, skin ecchymosis, hematuria, oral mucosal bleeding, gingival bleeding and purpura. All patients immediately stopped carbapenems when thrombocytopenia occurred. Nine patients received platelet transfusion therapy, 2 patients was given hormone therapy, and 1 patient received red blood cell transfusion. All but one patient, who died of multiple organ dysfunction syndrome secondary to septic shock,[21] showed a significant improvement in platelet count and resolution of complications following drug withdrawal and symptomatic treatment.The median time of improvement was 8 days (range 2–26).Unlike carbapenem-induced thrombocytosis, imipenem demonstrated the longest median latency to symptom presentation and hematological recovery in carbapenem-associated thrombocytopenia cases.

Table 3 Clinical Characteristics, Treatment and Outcome of Carbapenem-Induced Thrombocytopenia

Parameter	Meropenem	Imipenem	Biapenem	Total	*P* value[c]
Number of cases	16[b]	6	1[b]	22	/
Male:Female	8:8	4:2	0:1	12:10	0.417[d]
Age(Years)	82.5(0,96)[a]	80.5(76,94)[a]	83	82(0,96)[a]	0.693[e]
Duration of carbapenem use(Days)	6(2,16)[a]	9(1,13)[a]	6	6.5(1,16)[a]	0.590[e]
Time to onset of platelet count decline(Days)	2.5(1,8)[a]	7.5(1,13)[a]	2	2.5(0.125,9)[a]	0.197[f]
Time to valley platelet count(Days)	5(3,10)[a]	1.06(0.125,2)[a]	10	5(1,10)[a]	0.519[e]
The valley of platelet count(L^{-1})	25(2,136)[a]	7.5(1,9)[a]	5	21.5(0,136)[a]	0.315[f]
Number of cases of complications	8	2	0	10	/
Time to platelet count recovery/improvement(Days)	8(2,21)[a]	8.5(2,26)[a]	/	8(2,26)[a]	0.850[e]
Time to hospitalization (Days)	20(6,48)[a]	20.5(13,34)[a]	17	20(9,33)[a]	0.871[e]
Recovered/improved cases	14[b]	6	1[b]	21	/

Notes: [a]Median (minimum-maximum). [b]Include the patient data of the case that initially used biapenem and then switched to meropenem. [c]Due to an insufficient sample size (n=1), biapenem was excluded from the analysis prior to the calculation of the *P* value. [d]Fisher's exact test was used. [e]Mann–Whitney *U*-test was employed. [f]Independent samples t-tests was used.

Concomitant Medication Analysis

Among the 22 cases of carbapenem-induced thrombocytopenia, 17 involved concomitant medications. Of these, 15 patients received drugs known to potentially cause thrombocytopenia (eg, heparins, proton pump inhibitors, vancomycin). Importantly, the causal attribution to carbapenems remained unequivocal in all but 5 cases, where the influence of concomitant medications could not be entirely ruled out. Similarly, among the 20 cases of carbapenem-induced thrombocytosis, 12 patients were on concomitant therapy, with only 2 exposed to agents associated with thrombocytosis (eg, prednisone, low-molecular-weight heparin). A confounding effect from co-medications was considered possible in just a single case of thrombocytosis.

Relevance Evaluation

Of all 42 cases,32 patients (57.1%) were assessed as probable carbapenem-induced platelet abnormalities, of which 57.1% (n=24) received a score of 8, 16.7% (n=7) were rated as 7, and 2.4% (n=1) received a score of 5 using the Naranjo algorithm for estimating the probability of ADRs. Seven patients with a score of 4 and 1 patient with a score of 2 could be considered to have possible abnormal platelet count. Two patients (4.8%) were classified as definite with a score of 9.

Discussion

Among the 42 cases included in this study, the age range of the patients with carbapenem-induced platelet abnormalities was wide. 54.8% of patients were ≥60 years old and 38.1% were ≥75 years old, which aligns with the recognized increased risk of adverse drug reactions in elderly patients.[3,50] It may be related to many basic diseases, tissue and organ function degradation, slow drug metabolism, easy to produce drug accumulation and other factors in elderly patients.

In this study, all patients who experienced abnormal platelet counts were administered within the maximum daily dosage range specified in the drug instructions. Since most of the original data in this study did not provide information on renal function, it was impossible to determine whether the dosage was adjusted based on creatinine clearance, and thus the relationship between dosage and abnormal platelet counts could not be evaluated. However, Khan found that the adverse reactions of meropenem increased linearly with the deterioration of renal function, and thrombocytopenia was the most common adverse reaction (37.81%).[51] Therefore, physicians should adjust the dosage or prolong the interval of administration according to the patient 's creatinine clearance rate when prescribing carbapenems.

In our study, all 42 cases of platelet count abnormality induced by carbapenems occurred during the medication period, with no delayed-onset cases observed. Moreover, 79.5% of the cases occurred within 7 days of administration, which is consistent with previous literature reports on antimicrobial-induced thrombocytopenia.[3] However, there are currently no comprehensive reviews on the median time of antimicrobial-induced thrombocytosis. It is recommended that it's necessary to strengthen platelet count monitoring within the first week of carbapenem use.This research also showed

that meropenem demonstrates the greatest propensity to cause platelet count disorders within the carbapenem class, a phenomenon that may be attributed to its higher utilization rates in clinical practice.[52]

Among the 20 patients with thrombocytosis included in this study, all exhibited only elevated platelet counts without complications such as thromboembolism or abnormal bleeding. This suggests that carbapenem-induced thrombocytosis is relatively insidious and further supports the finding that secondary thrombocytosis carries a lower risk of thrombosis and abnormal bleeding.[53,54] Of the 22 patients with thrombocytopenia, 10 presented with bleeding symptoms such as melena, skin petechiae, or hematuria, among whom 9 had severe or extremely severe thrombocytopenia, and 70% were elderly patients. This indicates a certain correlation between bleeding symptoms and platelet counts in carbapenem-induced thrombocytopenia. Additionally, for elderly patients receiving carbapenems, close monitoring for clinical bleeding manifestations and dynamic changes in platelet levels within 7 days is essential.

Once abnormal platelet counts are detected, the medication should be promptly discontinued. For patients who meet the criteria for extreme thrombocytosis (platelet count exceeds $1,000 \times 10^9$ /L) or have cardiovascular risk factors or a history of thrombosis, anticoagulant or antiplatelet therapy such as aspirin or clopidogrel may be administered. When the platelet count exceeds $1,500 \times 10^9$ /L, plateletpheresis can be employed to rapidly and effectively reduce platelet levels.[55] For severe cases of thrombocytopenia, symptomatic and supportive treatments such as intravenous glucocorticoids, intravenous immunoglobulin, and transfusions of plasma or platelet suspensions may be used. In this study, all included cases suspected of carbapenem-induced platelet abnormalities discontinued the sensitizing drug and received appropriate treatment. Except for one patient who died of multiple organ dysfunction, the median recovery or improvement time for platelet counts in the remaining patients was within one platelet cycle, indicating a favorable prognosis.

At present, the mechanism of carbapenem-induced platelet abnormality is still unclear. The possible mechanisms of carbapenem-induced thrombocytosis are as follows: (1) As broad-spectrum antibiotics,long-term use of carbapenem depletes the gut microbiota,thereby inhibiting signal transducer and activator of transcription 1 (STAT1) signaling in the intestine and affecting the cell cycle activity of normal hematopoietic progenitor cell populations.[56] (2) Consumption of regulatory T cells (Tregs), resulting in bone marrow suppression.[57]

The pathogenesis of drug-induced thrombocytopenia is mainly immune thrombocytopenia and non-immune thrombocytopenia, in which immune thrombocytopenia is the main cause of drug-induced thrombocytopenia.[58] Drug-induced thrombocytopenia mediated by immune mechanism is often accompanied by a high risk of bleeding. Thrombocytopenia usually occurs after 5–10 days of drug exposure. Drug-induced thrombocytopenia mediated by non-immune mechanisms is usually dose-and time-dependent, and thrombocytopenia gradually occurs after several weeks of medication. Among the 22 patients with thrombocytopenia included in this study, thrombocytopenia occurred rapidly, and one of them was treated with anti-platelet. Platelet antibody was detected and had positive results.[28] Combined with the characteristics of immune mechanism-mediated drug-induced thrombocytopenia and non-immune mechanism-mediated drug-induced thrombocytopenia, it is speculated that the mechanism of carbapenem-induced drug-induced thrombocytopenia may be immune thrombocytopenia.

Despite the limited case series in our study, the findings gain strong support from large-scale pharmacovigilance data. A query of the US FDA Adverse Event Reporting System (FAERS) identified a substantial number of spontaneous reports associating carbapenems with platelet disorders. Specifically, we found 186 reports of thrombocytopenia and decreased platelet counts linked to meropenem, 115 linked to imipenem, and multiple cases associated with ertapenem and doripenem. This external validation indicates that the signal detected in our case series reflects a broader, real-world phenomenon. The convergence of evidence suggests that carbapenem-induced platelet abnormalities may be more common than previously recognized and underscores the critical importance of proactive monitoring in clinical practice.

Differentiating carbapenem-induced platelet abnormalities from the well-documented hematological manifestations of sepsis poses a significant challenge. Sepsis is a common cause of thrombocytopenia, which results from a combination of decreased platelet production, sequestration, and increased consumption.[59] Conversely,reactive thrombocytosis during the recovery phase is largely attributed to mechanisms like enhanced thrombopoiesis mediated by IL-6 and increased thrombopoietin production.[60] To address this confounding factor, our causality assessment rigorously evaluated the temporal relationship between platelet count changes and the clinical course of the infection. Nevertheless, we acknowledge that in a retrospective study of critically ill patients, completely distinguishing drug effects from the underlying

disease remains inherently difficult, which constitutes a limitation of our study. Therefore, our findings underscore a significant association that warrants further prospective investigation with stringent monitoring of infection biomarkers to establish causality.

This study represents a secondary analysis and synthesis of reported cases of carbapenem-associated platelet abnormalities, which inherently carries several limitations. First, incomplete documentation of key clinical parameters across heterogeneous case reports may introduce potential bias into our conclusions. Second, the majority of source literature lacked standardized microbiological susceptibility data and resistance patterns, making it difficult to assess the appropriateness of antibiotic therapy. It is particularly important to note that infections caused by carbapenem-resistant organisms are associated with higher rates of treatment failure and mortality.[61] Thrombocytopenia, a recognized hematologic complication of severe infection, may be primarily caused by treatment failure due to carbapenem-resistant pathogens and the resulting persistent sepsis, rather than by the drug itself. Consequently, attributing thrombocytopenia solely to the drug in this context risks overestimating the incidence of drug-induced events. Additionally, the unfavorable prognosis typically associated with drug-resistant infections must be distinguished from outcomes directly attributable to the pharmacological agent. Finally, the rarity of these adverse events resulted in a limited sample size. Future prospective studies investigating this association would greatly benefit from systematic collection of pathogen susceptibility data, which would help elucidate these complex interactions and provide independent validation of our findings.

Conclusions

Carbapenem-associated platelet abnormalities may occur more frequently than previously recognized, representing a potential safety signal that warrants enhanced clinical vigilance. It is recommended to strengthen the monitoring of platelet counts in patients within the first week of carbapenem use, especially in elderly patients who receiving meropenem treatment.If any abnormalities are detected, the monitoring frequency should be increased appropriately, and discontinuation of the drug or symptomatic treatment should be considered when necessary to reduce the risk of thrombotic or bleeding events.

Future Direction

The challenge of differentiating carbapenem-induced adverse events from the sequelae of untreated resistant infections, underscores the need for innovative diagnostic and therapeutic approaches. Looking forward, emerging technologies hold significant promise.Advanced nanomedicine strategies, such as drug-conjugated magnetic nanoparticles, could revolutionize the rapid detection and isolation of pathogens in clinical samples, thereby providing clearer microbiological context for adverse event assessment.[62] Furthermore, CRISPR-based gene-editing platforms are being explored not only as therapeutic tools to directly counteract resistance genes but also as highly sensitive diagnostic systems.[63,] The integration of such cutting-edge tools into future pharmacovigilance and clinical study designs could greatly enhance our ability to accurately attribute toxicities and develop more targeted therapeutic interventions against multidrug-resistant organisms.

Data Sharing Statement

Data sharing is not applicable to this article as no datasets were generated or analysed.

Ethics Approval and Informed Consent

This study is a systematic review and analysis of de-identified, publicly available data from previously published case reports. As the research exclusively utilized secondary data from open-access databases (CNKI, Wanfang, VIP, PubMed, Elsevier, Springer Link, Wiley, OVID, and Web of Science) without any direct involvement of human subjects, primary data collection, or access to private health records, it does not require ethical committee approval in accordance with international guidelines for systematic reviews (eg, Cochrane Handbook) and institutional policies for non-interventional research.

Authors'contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors declare that they have no competing interests in this work.

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