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Original Article

A prospective study of antimicrobial-related adverse drug reactions in hospitalized patients

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Background and Purpose: No previous systematic evaluation of antimicrobial-related adverse drug reactions (ADRs) in Taiwanese patients has been reported. The present study aimed to assess the incidence, risk factors, clinical manifestations, and causative agents of antimicrobial-ADRs in hospitalized patients.

Methods: 299 patients who received antimicrobial treatment during hospitalization in the infection ward of a tertiary hospital for at least two days from October 1, 1999 to February 29, 2000 were prospectively enrolled. Data of patients with parenteral antimicrobial-related ADRs were retrieved for further analysis.

Results: The incidence of antimicrobial-related ADRs (93.1% type B) was 24.1%. Compared with patients without ADRs, patients with antimicrobial-related ADRs were more likely to have a previous history of drug allergy (27.8% vs 16.2%, p=0.035) and had longer duration of hospitalization (28.3 ± 21.0 vs 12.6 ± 9.4 days, p<0.001). The incidence of parenteral antimicrobial-related ADRs in terms of total courses was 16.3% (78/480). Carbapenems (53.8%), amphotericin B (52.9%), and glycopeptides (37.0%) had the highest incidence of associated ADRs. Blood dyscrasias (32.1%), dermatomucosal effects (23.1%), and febrile reactions (17.9%) were the three most common manifestations of ADRs.

Conclusion: Antimicrobial-related ADRs occurred frequently in Taiwanese hospitalized patients.

Key words: Adverse drug reaction reporting systems; Adverse effects; Anti-infective agents; Hospitalization

Introduction

Adverse drug reactions (ADRs) have increased in line with increased drug use. ADRs are associated with prolonged length of hospitalization, increased cost of patient care, and significant morbidity and mortality [1-3]. Previous studies indicated that ADRs account for 5% of all hospital admissions and occur in 10-20% of hospitalized patients [4-7]. Lazarou et al reported an overall incidence of serious and fatal ADRs of 6.7% and 0.32%, respectively, of hospitalized patients [8]. The occurrence of ADRs violates the basic principle of medical practice, *primum non nocere* (first, do no harm), and physicians should evaluate the risk-benefit of any drug treatment.

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Antimicrobial agents are frequently mentioned in studies of ADRs [1,9-12]. Because antimicrobial agents are widely used, being familiar with the clinical manifestations and risk factors of antimicrobial-related ADRs is of great importance for clinicians. To our knowledge, no previous systematic evaluation of antimicrobial-related ADRs in Taiwanese patients has been carried out. The present study aimed to prospectively assess the incidence, risk factors, clinical manifestations and causative agents of parenteral antimicrobial-related ADRs in Taiwanese hospitalized patients.

Methods

All hospitalized patients who received any antimicrobial therapy in the infection ward of National Taiwan University Hospital from October 1, 1999 to February 29, 2000, were prospectively enrolled for ADR evaluation.

Patients were excluded if the duration of stay in the infection ward was less than 2 days. Patients who received antimicrobial therapy during hospitalization were surveyed actively by one investigator who evaluated all patients at risk of ADRs (e.g., due to old age), and detected ADRs actively by patient visiting, chart reading, serum drug level monitoring, checking of laboratory results, and alerting orders searching. Cases were followed until discharge or transfer out of the infection ward.

Age, gender, diagnosis, duration of stay in the infection ward, and history of diabetes mellitus, hypertension or previous food or drug allergy were recorded for all hospitalized patients who received antimicrobial therapy, as were drug name, dosage, route of administration, and duration of medication use. As suspected ADRs were encountered, the investigator would discuss with the primary physician alternative explanation(s) and the possible causative role of medication.

The investigator also applied the ADR probability scale to assess the causative role of the medication. For patients with ADRs, further information was collected, including the onset time of ADRs (duration from start of medication to the occurrence of ADRs); probability, type, and severity of ADRs; clinical manifestations of ADRs; number of concomitant medications used and relevant laboratory data. Episodes caused by parenteral antimicrobial agents were retrieved for further analysis.

Definitions

Incidence

Incidence was expressed in the following ways: (1) the number of patients with antimicrobial-related ADRs per 100 hospitalized patients with antimicrobial use; (2) the number of patients with antimicrobial-related ADRs per 100 parenteral antimicrobial courses; and (3) the number of antimicrobial-related ADR episodes per 100 parenteral antimicrobial courses.

ADRs

According to the definition of the United States Food and Drug Administration (FDA), all noxious and unintended responses to a medicinal product related to any dose should be considered ADRs [13]. ADRs were classified as type A and type B according to the definitions by Rawlins and Tompson [14]. A type A reaction is an over-enhancement of the normal pharmacology of the medication, is predictable and is related to dosage. A type B reaction is a reaction unrelated to the normal pharmacology, is unpredictable and is unrelated to dosage.

The probability of causative agents was assessed by the ADR probability scale designed by Naranjo et al and classified as definite, probable, possible, and suspected [15].

The severity of ADRs was graded as mild (no need to treat or to stop or change medication), moderate (treatment, antidote, admission or prolonged hospitalization from 1 to 6 days required), and severe (ADR treatment for at least 7 days; life-threatening; need for intensive care unit care; disabled; or death due to ADR), according to the study by Seidl et al [16].

Classification of antimicrobial agents and clinical manifestations of ADRs

Antimicrobial agents were classified into 15 different classes, including penicillins, first- and second-generation cephalosporins, third- and fourth-generation cephalosporins, monobactams, carbapenems, macrolides, lincosamides, tetracyclines, aminoglycosides, sulphones and trimethoprim, quinolones, glycopeptides, metronidazole, antifungal agents, and antiviral agents. If several antimicrobial agents were being used at the same time when an ADR developed, the agent most likely to be the cause was identified by the attending physician. If this could not be decided, all agents were regarded as causative agents.

The clinical manifestations of ADR were categorized into allergic reactions, including anaphylactic shock, serum sickness, drug fever, anaphylactoid reaction, etc.; blood dyscrasias, including hemolytic anemia, leucopenia (white blood count $<4000/mm^3$), neutropenia (absolute neutrophil count $<1500/mm^3$), thrombocytopenia (platelet count $<12,000/mm^3$), hypereosinophilia (eosinophil count $>2500/mm^3$), etc.; cardiovascular effects, including arrhythmia, cardiac arrest, conduction disturbance, hypertension, hypotension, etc.; dermatomucosal effects, including angioedema, erythema, pruritis, Stevens-Johnson syndrome, urticaria, etc.; endocrine-metabolic effects, including adrenal insufficiency syndrome, oedema, electrolyte disturbances, gout, hyperglycemia, hypoglycemia, etc.; neurotoxicity, including alteration of consciousness, extrapyramidal syndrome, movement disorders, neuropathy, seizure, sensory disorders, etc.; gastrointestinal (GI) effects, including constipation, diarrhea, GI upset, peptic ulceration with hemorrhage, pseudomembranous colitis, etc.; hemostasis disorders, including bleeding tendency, intravascular clotting, etc.; hepatotoxicity,

including abnormalities of liver function tests, hepatitis, liver injury, etc.; nephrotoxicity, including acidosis, nephrotic syndrome, nephropathy, uremia, etc.; and others. If patients had several clinical manifestations at the same time, each manifestation was counted as a separate episode.

Statistical analysis

Statistical analysis was performed using the Statistical Package for the Social Sciences for Windows (Version 12.0; SPSS, Chicago, IL, USA) software package. Categorical variables were compared by chi-squared or Fisher's exact test. Non-categorical variables were compared by Wilcoxon's rank-sum test. A p value <0.05 was considered significant.

Results

There were 349 Taiwanese patients hospitalized in the infection ward during the study period. Thirty two patients were not included because they did not receive an antimicrobial agent during hospitalization, and 18 patients were excluded due to less than 2 days of stay in the infection ward, leaving a total of 299 patients in the study. ADRs occurred in 108 patients, and comprised 161 episodes. Among them, 101 episodes (62.7%) in 72 patients were related to usage of antimicrobial agents. The incidence of antimicrobial-related ADRs was 24.1% (72/299) in hospitalized patients who received antimicrobial treatment.

Data for patients with ADRs caused by antimicrobial agents and those without any ADR are compared in Table 1. The mean (± standard deviation) duration of hospitalization before the onset of ADR was 10.7 ± 9.6 days. There was no difference in age, gender, history of diabetes mellitus, hypertension, or previous history of food allergy between the 2 groups. Patients with an ADR were more likely to have a previous history of drug allergy (27.8% vs 16.2%, p=0.035) and had a longer length of hospitalization (mean, 28.3 ± 21.0 vs 12.6 ± 9.4 days; p<0.001).

Most ADRs developed in patients aged 66-75 years old (29.2%). However, age distribution was similar in both groups, except that the percentage of patients in the age group 26-35 years was lower in the group with ADRs (2.8% vs 10.5%, p=0.044) [Table 1].

The type, probability, and severity of ADRs caused by antimicrobial agents are shown in Table 2. Most ADRs (93.1%) were classified as type B reactions. The majority (68.3%) of the ADR episodes were judged as probable in causative probability, while 30.7% were judged as possible (30.7%) and 1% as definite. Fifty nine episodes (58.4%) were moderate in severity, 36 episodes (35.6%) were mild, and 6 episodes (5.9%) were severe. Among the 6 episodes of severe severity, most (83.3%) had blood dyscrasias as clinical manifestations and were caused by penicillins (3 episodes), third- and fourth-generation cephalosporins (3), and glycopeptides (2).

Table 1. Comparison of hospitalized patients using antimicrobial agents without adverse drug reactions (ADRs) and patients with antimicrobial-related ADRs

Variable	Without ADRs (n =191) No. (%)	With ADRs caused by antimicrobial agents (n = 72) No. (%)	p
Male/female (n)	98/93	36/36	0.850
Age (years)			
15-25	9 (4.7)	4 (5.6)	
26-35	20 (10.5)	2 (2.8)	
36-45	19 (9.9)	9 (12.5)	
46-55	19 (9.9)	7 (9.7)	
56-65	26 (13.6)	12 (16.7)	
66-75	50 (26.2)	21 (29.2)	
76-85	39 (20.4)	13 (18.1)	
86-95	9 (4.7)	4 (5.6)	
Mean age (years)	60.6 ± 19.2	61.9 ± 17.7	0.629
Duration of hospitalization (days; mean ± SD)	12.6 ± 9.4	28.3 ± 21.0	<0.001
Diabetes mellitus	52 (27.2)	22 (30.6)	0.592
Hypertension	64 (33.5)	19 (26.4)	0.268
Food allergy	4 (2.1)	2 (2.8)	1.000
Drug allergy	31 (16.2)	20 (27.8)	0.035

Abbreviation: SD = standard deviation

Table 2. Type, probability and severity of adverse drug reactions caused by antimicrobial agents

Variable	Episodes of adverse drug reaction No. (%)
Total episodes	101 (100.0)
Type	
Type A	7 (6.9)
Type B	94 (93.1)
Probability	
Definite	1 (1.0)
Probable	69 (68.3)
Possible	31 (30.7)
Severity	
Severe	6 (5.9)
Moderate	59 (58.4)
Mild	36 (35.6)

We retrieved data from patients with parenteral antimicrobial-related ADRs for further analysis. In this analysis, there were 480 courses of parenteral antimicrobial use, and 58 patients had 78 episodes of ADRs. Forty six patients had 1 episode, 8 had 2 episodes, 2 had 3 episodes, 1 had 4 episodes, and 1 had 6 episodes. The median number of concomitant medications was 4 types (range, 4-14).

The incidence of ADRs caused by parenteral antimicrobial use was 16.3 episodes per 100 courses of parenteral antimicrobial agents. Among all classes of parenteral antimicrobial agents, carbapenems, glycopeptides, and amphotericin B had the highest incidence of ADR development, both in terms of number of patients with ADRs per 100 courses of parenteral antimicrobial agents (38.5%, 37.0%, and 29.4%, respectively) and number of ADR episodes per 100 courses of parenteral antimicrobial agents (53.8%, 37.0%, and 52.9%). The ADR incidence for other antimicrobial agents in terms of number of patients with ADRs per 100 courses of parenteral antimicrobial agents was 21.7%, 17.0%, 16.7%, 12.5%, 9.1%, 7.7%, 6.4% 6.3%, and 0.0% for quinolones, third- and fourth-generation cephalosporins, penicillins, lincosamides, monobactams, antiviral agents, first- and second-generation cephalosporins, metronidazole, and aminoglycosides, respectively.

Blood dyscrasias (32.1%) was the most common clinical manifestation in the parenteral antimicrobial-related ADRs, followed by dermatomucosal effects (23.1%), febrile reactions (17.9%), GI effects (7.7%), hepatotoxicity (6.4%), endocrine-metabolic effects (5.1%), nephrotoxicity (3.8%), neurotoxicity (2.6%), and others (1.3%). The major presentations of blood dyscrasias included leucopenia (76.0%; mean, 2326.3 ± 854.3/mm^3), neutropenia (48.0%; mean, 881.7 ± 501.0/mm^3) and thrombocytopenia (12.0%; mean, 30,000 ± 2645.8/mm^3). Nine patients had leucopenia and neutropenia at the same time. The most common class of parenteral antimicrobial causing blood dyscrasias was glycopeptides, with an incidence of 18.5 episodes per 100 courses of glycopeptide usage, followed by third- and fourth-generation cephalosporins (14.8%) and penicillins (11.1%) [Table 3].

All 25 episodes of blood dyscrasias were type B ADR reactions, and 6 episodes (24.0%) occurred in patients with a previous history of drug allergy. Eight episodes (32.0%) were of mild severity, 12 (48.0%) were of moderate severity, and 5 (20.0%) were severe. The median onset time of blood dyscrasias was 7 days (range, 2-23 days). Most episodes (52.0%) occurred within 1-7 days after the starting of antimicrobial use (Fig. 1).

Dermatomucosal effects were the second most common manifestation of parenteral antimicrobial-related ADRs. Maculopapular rash (33.3%) was most frequently seen, followed by erythematous change (27.8%), pruritis (16.7%) and urticaria (11.1%). The incidence of dermatomucosal effects was higher in patients receiving carbapenems (15.4%) and penicillins (10.0%) [Table 3]. As with blood dyscrasias, all 18 episodes of dermatomucosal ADRs were type B reactions, and a previous drug allergy history was observed in 7 episodes. Two were of mild severity, and 16 were of moderate severity. The median onset time of dermatomucosal ADRs was 4 days (range, 1-24 days). Most episodes (61.1%) occurred within 1-7 days after initiation of medication (Fig. 1).

Among the 14 episodes of febrile reactions associated with parental antimicrobial agents, lincosamides had the highest incidence (12.5%), followed by glycopeptides (11.1%) and monobactams (9.1%) [Table 3]. All of these reactions were also type B, and one affected patient had a prior history of drug allergy. The presentations of GI ADRs included diarrhea (ciprofloxacin [1 episode]), GI upset (cefazolin [1], amphotericin B [1]), and pseudomembranous colitis (ceftazidime [1], imipenem [1], and meropenem [1]). Manifestations of hepatotoxicity included hepatocellular type (imipenem [2], ciprofloxacin [1], ceftriaxone [1]), and combined hepatocellular and cholestatic type (ciprofloxacin [1]).

Endocrine-metabolic ADRs comprised hypokalemia (potassium <3.5 mEq/L) caused by amphotericin B (4 episodes). Nephrotoxicity with elevation

Table 3. Number and incidence[a] of clinical manifestations of adverse drug reactions (ADRs) according to class of parenteral antimicrobial agents

Class of antimicrobial agents	BD	DE	FR	HE	GI	EM	NE	NR	Other	Total episodes	Total courses
Penicillins (n) [%]	10 (11.1)	9 (10.0)	1 (1.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	20 (22.2)	90
Oxacillin (n)	3	6	0	0	0	0	0	0	0	9	
Ampicillin (n)	4	3	0	0	0	0	0	0	0	7	
Amoxicillin (n)	2	0	0	0	0	0	0	0	0	2	
Ticarcillin (n)	1	0	1	0	0	0	0	0	0	2	
First- and second-generation cephalosporins (n) [%]	3 (2.7)	2 (1.8)	2 (1.8)	0 (0.0)	1 (0.9)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	8 (7.3)	110
Cefazolin (n)	2	0	1	0	1	0	0	0	0	4	
Cefoxitin (n)	1	0	1	0	0	0	0	0	0	2	
Cefotiam (n)	0	1	0	0	0	0	0	0	0	1	
Cefuroxime (n)	0	1	0	0	0	0	0	0	0	3	
Third- and fourth-generation cephalosporins (n) [%]	13 (14.8)	4 (4.5)	4 (4.5)	1 (1.1)	1 (1.1)	0 (0.0)	0 (0.0)	1 (1.1)	0 (0.0)	24 (27.3)	88
Cefotaxime (n)	4	2	1	0	0	0	0	1	0	8	
Ceftriaxone (n)	3	2	1	1	0	0	0	0	0	7	
Ceftazidime (n)	4	1	2	0	1	0	0	0	0	8	
Cefepime (n)	2	0	0	0	0	0	0	0	0	2	
Monobactams (n) [%]	0 (0.0)	0 (0.0)	1 (9.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (9.1)	11
Aztreonam (n)	0	0	1	0	0	0	0	0	0	1	
Carbapenems (n) [%]	1 (7.7)	2 (15.4)	0 (0.0)	2 (15.4)	2 (15.4)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	7 (53.8)	13
Imipenem (n)	1	2	0	2	1	0	0	0	0	6	
Meropenem (n)	0	0	0	0	1	0	0	0	0	1	
Lincosamides (n) [%]	0 (0.0)	0 (0.0)	1 (12.5)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (12.5)	8
Clindamycin (n)	0	0	1	0	0	0	0	0	0	1	
Aminoglycosides (n) [%]	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	64
Quinolones (n) [%]	0 (0.0)	1 (4.3)	1 (4.3)	2 (8.7)	1 (4.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	5 (21.7)	23
Ofloxacin (n)	0	0	0	2	1	0	0	0	0	3	
Ciprofloxacin (n)	0	1	1	0	0	0	0	0	0	2	
Glycopeptides (n) [%]	5 (18.5)	1 (3.7)	3 (11.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (3.7)	0 (0.0)	10 (37.0)	27
Vancomycin (n)	4	1	3	0	0	0	0	1	0	9	
Teicoplanin (n)	1	0	0	0	0	0	0	0	0	1	
Metronidazole (n) [%]	0 (0.0)	1 (6.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (6.3)	16
Amphotericin B (n) [%]	0 (0.0)	0 (0.0)	1 (5.9)	0 (0.0)	1 (5.9)	4 (23.5)	2 (11.8)	0 (0.0)	1 (5.9)	9 (52.9)	17
Acyclovir (n) [%]	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (7.7)	0 (0.0)	0 (0.0)	1 (7.7)	13

Abbreviations: BD = blood dyscrasias; DE = dermatomucosal effects; FR = febrile reactions; HE = hepatic; GI = gastrointestinal effects; EM = endocrine-metabolic effects; NE = nephrotoxicity; NR = neurotoxicity

[a]Incidence is expressed as the number of ADR episodes divided by the total courses of each class of antimicrobial agents (%).

of serum creatinine level (>1 mg/dL) was observed with amphotericin B (2) and acyclovir (1) use. Neurotoxicity comprised one episode of seizure associated with cefotaxime use, and one of ototoxicity associated with vancomycin use. One episode of infusion-related reaction was caused by amphotericin B.

Of the 78 episodes of parenteral antimicrobial-related ADRs, third- and fourth-generation cephalosporins (30.8%), penicillins (25.6%), glycopeptides (12.8%), amphotericin B (11.5%), and first- and second-generation cephalosporins (10.3%) were the most common causative agents (Table 4). Blood dyscrasias (54.2%), dermatomucosal effects (16.7%), and febrile reactions (16.7%) were the common clinical manifestations in ADRs from third- and fourth-generation cephalosporins.

The most frequent ADRs with penicillins were blood dyscrasias (50.0%), dermatomucosal toxicity (45.0%) and febrile reactions (5.0%). The ADRs caused by glycopeptides included blood dyscrasias (50.0%), febrile reactions (30.0%), dermatomucosal effects (10.0%), and neurotoxicity (10.0%). The most common ADRs caused by amphotericin B were hypokalemia (44.4%) and nephrotoxicity (22.2%).

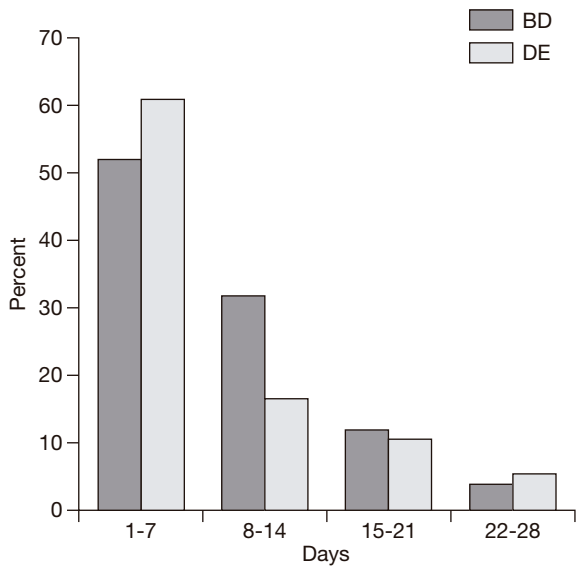

Fig. 1. Episode distribution of antimicrobial-related blood dyscrasias (BD) and dermatomucosal effects (DE) according to onset time after starting of antimicrobial treatment.

As with third- and fourth-generation cephalosporins, blood dyscrasias (37.5%), dermatomucosal effects (25.0%), and febrile reactions (25.0%) were commonly seen in ADRs of first- and second-generation cephalosporins. The usual presentations of ADRs associated with carbapenems were dermatomucosal effects (28.6%), hepatotoxicity (28.6%) and GI effects (28.6%). Among episodes of quinolone-related ADRs, hepatotoxicity (40.0%) was the most frequently seen, followed by dermatomucosal effects (20.0%), febrile reactions (20.0%) and GI effects (20.0%). Only one ADR episode occurred with monobactams, lincosamide, metronidazole and antiviral agents, respectively. No ADR was observed with aminoglycosides, which might be attributed to their short-term use and adherence to dosage guidelines in clinical practice.

Discussion

Because of differences in study design, data collection, and definition of ADRs, the diversity of drugs used, and the heterogeneity of the investigated populations, the reported incidence of ADRs varies greatly in the literature. The present study showed an incidence of 24.1% for antimicrobial-related ADRs in hospitalized patients treated with antimicrobials, or 16.3 episodes per 100 courses of parenteral antimicrobial use. As compared with the reported incidence of 3.0-4.9 antimicrobial-related ADR episodes per 100 antimicrobial users [10,17], our results demonstrate a very high rate in the Taiwanese population. The discrepancy between this study and others might be attributed to the prospective and active surveillance study design, or to racial differences. Though the mechanism was not clear, a higher incidence of hepatotoxicity was observed in Asian people undergoing antituberculosis therapy [18-22] than in western counterparts [23]. This implies that genetic factors might contribute to the high ADR incidence in our study. Our patient population (inpatients at a tertiary hospital) and definition of ADRs (the definition of the

Table 4. Frequency of clinical manifestations of adverse drug reactions (ADRs) according to class of parenteral antimicrobial agents

Class of antimicrobial agents	BD No. (%)	DE No. (%)	FR No. (%)	HE No. (%)	GI No. (%)	EM No. (%)	NE No. (%)	NR No. (%)	Other No. (%)	Total episodes (n = 78) No. (%)
Penicillins	10 (50.0)	9 (45.0)	1 (5.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	20 (25.6)
First- and second-generation cephalosporins	3 (37.5)	2 (25.0)	2 (25.0)	0 (0.0)	1 (12.5)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	8 (10.3)
Third- and fourth-generation cephalosporins	13 (54.2)	4 (16.7)	4 (16.7)	1 (4.2)	1 (4.2)	0 (0.0)	0 (0.0)	1 (4.2)	0 (0.0)	24 (30.8)
Monobactams	0 (0.0)	0 (0.0)	1 (100.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.3)
Carbapenems	1 (14.3)	2 (28.6)	0 (0.0)	2 (28.6)	2 (28.6)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	7 (9.0)
Lincosamides	0 (0.0)	0 (0.0)	1 (100.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.3)
Aminoglycosides	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Quinolones	0 (0.0)	1 (20.0)	1 (20.0)	2 (40.0)	1 (20.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	5 (6.4)
Glycopeptides	5 (50.0)	1 (10.0)	3 (30.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (10.0)	0 (0.0)	10 (12.8)
Metronidazole	0 (0.0)	1 (100.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.3)
Amphotericin B	0 (0.0)	0 (0.0)	1 (11.1)	0 (0.0)	1 (11.1)	4 (44.4)	2 (22.2)	0 (0.0)	1 (11.1)	9 (11.5)
Acyclovir	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (100.0)	0 (0.0)	0 (0.0)	1 (1.3)

Abbreviations: BD = blood dyscrasias; DE = dermatomucosal effects; FR = febrile reactions; HE = hepatic; GI = gastrointestinal effects; EM = endocrine-metabolic effects; NE = nephrotoxicity; NR = neurotoxicity

United States FDA [13], which regards all noxious and unintended responses to medicinal products related to "any dose" as ADRs) were other possible explanations for the high incidence of ADRs in the present study.

In previous studies, antimicrobial agents were the most common or the second most common drugs causing ADRs in patients of different settings [1,9-12], and other commonly implicated agents included cardiovascular, antineoplastic, antihypertensive, non-steroidal anti-inflammatory drugs and antidepressant agents. The present study is consistent with previous reports in finding antimicrobial agents as the predominant cause of ADRs. This re-affirms the importance of clinicians being familiar with the manifestations of antimicrobial-related ADRs in daily practice, since their occurrence might mimic other diseases, result in unnecessary investigations, and delay proper management.

In the analysis of antimicrobial-related ADRs, we found most episodes were type B (93.1%), and more patients with such ADRs had a previous history of drug allergy than those without ADRs (27.8% vs 16.2%, p=0.035). This observation differs from the traditional concept that type A reactions are more common than type B reactions [5,17]. It is difficult to explain why type B reactions were more commonly seen in our patients, but this finding might explain why age was not a risk factor for ADR development in the present study. Because type B reactions are unrelated to pharmacology and are idiosyncratic, it is extremely important to record agents causing such reactions in patients' charts to avoid treatment with the same agents and re-occurrence of the ADR.

Prolonged length of hospitalization (28.3 ± 21.0 vs 12.6 ± 9.4 days, p<0.001) was noted in patients with ADRs compared with those without ADRs. This finding might be the cause or effect of ADR development. Comparing the duration of hospitalization before the onset of ADRs with the duration of hospitalization in patients without ADRs shows no significant difference (10.7 ± 9.6 vs 12.6 ± 9.4 days, p=0.14). Therefore, our findings are consistent with ADR occurrence complicating the course of infection and prolonging hospitalization.

Blood dyscrasias were the most common clinical manifestation of parenteral antimicrobial-related ADRs, followed by dermatomucosal effects, febrile reactions, and GI effects. However, in other reports, the order was dermatomucosal effects, blood dyscrasias, nephrotoxicity, and GI effects [17,24]. Differences in study populations (inpatients vs outpatients), drug use, administration route (oral vs intravenous), and definition of manifestations of ADRs might contribute to such variation.

Leucopenia (76.0%) and neutropenia (48.0%) were the most commonly seen presentations of blood dyscrasias from our observations, and most episodes occurred within 1-7 days after initiation of medication. The incidence of blood dyscrasias was high in patients treated with glycopeptides (18.5 episodes per 100 courses of parenteral antimicrobials), third- and fourth-generation cephalosporins (14.8), and penicillins (11.1) in our patients. This contrasts with an incidence of neutropenia of around 0-5% in patients receiving vancomycin (leucopenia, 13%), and only around 3-8% in patients receiving beta-lactam agents in the studies by Hoffman-Terry et al [24] and Olaison et al [25]. The high incidence of ADRs found in our study was probably due to the active surveillance study design, and differences in racial characteristics and clinical settings (hospitalized patients vs outpatients).

Furthermore, Olaison et al reported that neutropenia mostly developed after antimicrobial use for 3 to 4 weeks [25]. The inconsistency in onset time between that study and ours could be partly explained by the fact that some patients (8 episodes) received other beta-lactams in other hospitals prior to enrollment in our study. Since the number of cases in our study is limited and some episodes developed without previous beta-lactam exposure, further investigation is needed to explore these inconsistent results.

Parenteral carbapenems (15.4%) and penicillins (10.0%) had the highest incidence of development of dermatomucosal ADRs, and most episodes occurred within 7 days after prescription. The incidence in our study was much higher than that reported by van der Linden et al, who found that trimethoprim-sulfamethoxazole (2.1%), fluoroquinolones (1.6%), and penicillins (1.1%) were the most common agents causing dermatomucosal ADRs [26]. Since most of our episodes developed quickly after prescription, we suspect that previous exposure, with resulting preformed antibodies, or idiosyncratic reactions might have influenced our findings. However, we do not have any data to support this hypothesis.

Few studies have compared the incidence of ADRs between classes of antimicrobial agents. Our observations offer useful information to clinical physicians prescribing antimicrobial agents to patients. However, some limitations exist in the present study. First, the severity of the patients' infectious diseases, detailed underlying conditions, and previous drug history were

not recorded. Because ADRs might mimic other diseases, and vice versa, the lack of sufficient information might affect the interpretation of study results. Furthermore, prior exposure of antimicrobial agents before enrollment might also have affected our results. Second, the study period is short and the number of cases is limited, which might have biased our observations. Therefore, some data need to be interpreted cautiously, such as the high incidence of drug fever (12.5%) with clindamycin, comprising only one episode. In addition, whether high ADR incidence with carbapenems (53.8%), and third- and fourth-generation cephalosporins (27.3%) — which were often used as last resorts for management of infection — was caused by prior antimicrobial agent use requires further investigation to validate our findings. Third, we did not evaluate the outcome of the ADRs in terms of cost. Fourth, few comparable studies are reported in the literature, making it difficult to make valid comparisons between ours and others.

In conclusion, the use of antimicrobial agents caused a higher incidence of ADRs in Taiwanese hospitalized patients than in those from western countries. Blood dyscrasias, dermatomucosal effects, and febrile reactions were the most common manifestations. When prescribing drugs in daily practice, clinicians should take antimicrobial-related ADRs into consideration, especially when patients receiving antimicrobial therapy have new clinical manifestations after initiation of antimicrobial therapy.

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