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Adverse Drug Reactions and Pattern Use of Cephalosporins: A Retrospective Review of Hospitalized Patients During 5 Years

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Abstract: Cephalosporin drugs are among the most widely prescribed drugs and their utilization can be complicated by the development of adverse drug reactions (ADRs). The aim of this study was to assess the frequency and characteristics of cephalosporin-induced ADRs and to compare the usage pattern of cephalosporin in hospitalized patients in China over a 5-year period, from January 2008 to December 2012. All insured prescriptions which were recorded in hospital information system were retrospectively evaluated for prescriptions included at least one dosage form cephalosporin. All ADRs induced by cephalosporins in the database of Chinese Adverse Drug Reaction Monitoring were analyzed. Of 352,661 inpatients who received cephalosporins, 2046 (0.58%) exhibited ADRs. Cefatriaxone and cefalexin were the drugs most frequently involved in the development of ADRs. The dermatological system (43.50%) was the most commonly affected organ system, with skin rash (30.60%) being the most frequently reported reaction. Cefatriaxone (15.59%) was the most frequently reported individual drug. The most common predisposing factors were polypharmacy and having a history of allergies, which in turn were the main predisposing factors of allergic shock and rash induced by cephalosporins. In conclusion, cephalosporins therapy represents a common cause of ADRs in hospitalised patients the pattern of ADRs reported in the hospitals. The findings offer opportunities for interventions, especially for preventable ADRs, to ensure safer drug use.

Key words: Adverse drug reactions, cephalosporins, pharmacovigilance, drug use pattern

INTRODUCTION

Adverse Drug Reactions (ADRs) are a concern worldwide problem during medication and attack children and adults at varying magnitudes, causing both morbidity and mortality (Lazarou *et al*., 1998; Pirmohamed *et al*., 2004; Oshikoya, 2006). Irrational use of drugs may occur for a variety of reasons, including adverse drug events (ADEs) (Martinez-Mir *et al*., 1999). Pharmacovigilance is traditionally concerned with ADEs, thus contributing to a better understanding of the most important characteristics of ADRs, the pathogenic mechanisms involved and the pattern use of drugs (Lazarou *et al*., 1998; Moore *et al*., 1985). In many developing countries where the medicines market is not adequately regulated, patients may obtain the medicines freely from dispensers without physician's prescription. Thus this irrational use of drugs may be the results of ADE. Although spontaneous reporting is the most widely used method for routinely monitoring ADRs (Rawlins, 1988), it cannot guarantee that a particular adverse event is a true ADR. Therefore, this approach has to be integrated with retrospective data recorded by clinical trials and medical reports to define which ADRs are not time-related or associated with antibiotic drug administration. It can be very useful to improve the health care system in terms of both financial aspects and risk-benefit evaluations conducting retrospective studies on ADRs in hospitalized patients (Brewer and Colditz, 1999).

Cephalosporin drugs are among the most widely used drugs and ADRs may be complicated their usage. In general, they cause few side effects, with the common ones mainly involving the digestive system: mild stomach cramps or upset stomach, nausea, vomiting and diarrhea. These ADRs are usually mild and the symptoms disappeared over time. More severe but rare reactions that can sometimes follow with the use of cephalosporins include black and bloody stools, chest pain, fever, painful or difficult urination, anaphylactic shock and severe colitis. Severe colitis is an infrequent ADR that includes

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severe stomach cramps, severe watery diarrhea (now and then containing blood or mucus), fever and faintness or weakness (Beers, 2003). Few studies have examined the clinical presentation and outcomes of ADRs associated with cephalosporin medications and the pattern use in hospitalized patients in China. Bengbu City has 4 tertiary care teaching hospitals and 13 secondary hospitals, of which the largest hospital is the First Affiliated Hospital of Bengbu Medical College-a 1936-bed tertiary care teaching hospital in the northern region of Anhui Province. Since October 2003, these hospitals have had an ADR spontaneous reporting unit that is coordinated by their department of pharmacy practice. In addition, the ADR reporting unit of the hospitals is among the peripheral centers under the national pharmacovigilance program.

The objectives of this study were to assess the frequency and characteristics of cephalosporin-induced ADRs and to compare the usage pattern of cephalosporin in hospitalized patients in China and to study causes of cephalosporin-induced ADRs with potential risk factors using multiple-factor logistic regression analysis.

MATERIALS AND METHODS

Source of ADR cases: This retrospective, cross-sectional study was conducted in 17 hospitals (4 tertiary care teaching hospitals and 13 secondary hospitals) across Bengbu District, China, based on the ADRs spontaneously reported by various departments of the hospitals to their ADR reporting unit. Documentation of ADRs and mode of reporting in the units are discussed elsewhere in the text. ADRs reported between 1 January 2008 and 31 December 2012 were selected and evaluated in this study. All insured prescriptions which were recorded in hospital information system were retrospectively evaluated for prescriptions included at least one dosage form cephalosporin. All ADRs induced by cephalosporin in the database of Chinese Adverse Drug Reaction Monitoring (CADRM) were analyzed. Extra details on the ADRs were collected for evaluation purposes from the respective case records whenever required. The clinical records of patients who received cephalosporin were consulted and the following data were obtained: sex and age of the patient, history of drug allergy, therapy duration and drug classes involved.

Evaluation of ADR: People's Republic of China Ministry of Health, 2010 published the latest version of Adverse Drug Reaction Reporting and Monitoring Management Approach on 13 December and the provisions thereof have been applied since 1 July 2011. This set of guidelines defines ADR as an untoward clinical manifestation consequent to and caused by the administration of a qualified medicine in normal usage and the amount of drug used, excluding intentional overdose, substance abuse and therapeutic failure (PRCMH, 2010). Drugs involved in the ADRs were codified into various drug classes according to their Anatomical Therapeutic Chemical (ATC) classification based on the World Health Organization (WHO) ATC Index of 2005 (WHO, 2005). The following procedure was used to address the problem of redundant and variable drug nomenclature. The ADR names were coded with WHO Adverse Reaction Terminology (WHO-ART) using preferred terms, which have been developed for more than 30 years to serve as a basis for rational coding of adverse reaction terms (WHO, 2003).

Data collection: Data on the reported ADRs were evaluated to investigate the mode of the ADRs with respect to patient demographics, nature of the reactions, characteristics of the drugs involved and outcomes of the reactions. Causality, severity, preventability and the predisposing factors for the reaction were analyzed. Furthermore, possible relationships between the patient characteristics and the characteristics of the reaction were assessed. Route of administration, indication for cephalosporins use and outcome of reactions were assessed. The study was carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for experiments involving humans.

Data statistics: Data were statistically analyzed using Excel and Stata 11.0. Comparisons between groups were made using student's t-test for continuous variables and χ^2 statistics for noncontinuous data. Logistic regression was also performed to examine the relationship between patient characteristics and ADRs induced by cephalosporin treatment. The $p<0.05$ was considered statistically significant.

RESULTS

During the study period, 1,469,418 hospitalized patients were recorded. Of these patients, 352,661 received cephalosporin. ADR reports implicating cephalosporin (including cefoxitin) which were reviewed represent 19.92% of the total ADR database of 10278 reports for the 5-year period were retrieved from the spontaneously monitoring database and 0.58% of total inpatients who received cephalosporin. Evaluating route of administration in the reported cases revealed that most reactions occurred following intravenous injection of cephalosporin (Table 1). In evaluation of known indications, upper respiratory tract infection was the most

indications for use cephalosporin in reported cases Table 1. Fig. 1 showed that the total number of reports was reduced from 438 cases in 2008 to 295 in 2012. Patients with ADRs induced by cephalosporin did not significantly differ in sex ratio (55.03% men and 44.97% women as well as 53.00% men and 47.00% women, respectively; $\chi^2 = 3.38$, df =1, p> 0.05). Upon evaluation of patient characteristics, more reports of ADRs involved males (55.03%) and patients between 31 and 45 years old (28.05%). Significant differences in the incidence of ADRs were not observed between males (0.60%) and females (0.56%) ($\chi^2 = 3.41$, p>0.05). Table 2 shows that the incidence rates of ADRs among elderly adults were significantly higher than those in the other age groups ($\chi^2 = 163.24$, df = 5, p<0.001).

Of the reactions reported, the organs most commonly affected (according to the WHO-ART) were the skin and appendages disorders (43.50%) and the most frequently reported reaction was rash (30.60%) (Table 3). Third-generation cephalosporins (52.15%) were the drug class most commonly involved, whereas cefatriaxone (15.59%) was the most frequently reported suspected drug in the reactions (Table 4).

The suspected drug was withdrawn for the management of the ADR in most of the reports (94.62%), whereas additional treatment for the reaction was instituted in 47.60% Table 5. In 98.73% of the reports, the patient recovered from the reaction at the time of the evaluation of the ADR report. An improvement in the adverse reaction was observed in 98.87% of the reports in which dechallenge or dose reduction was performed (Table 5).

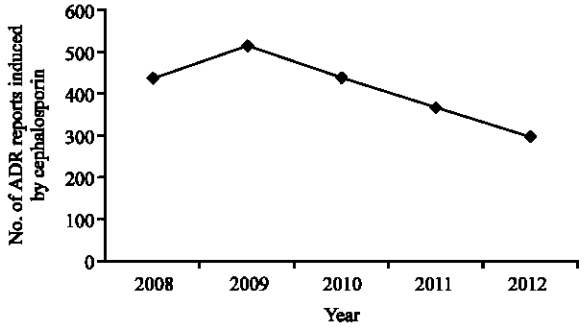

Fig. 1: The trend of cephalosporin induced ADRs from 2008 to 2012

Upon causality assessment, most reports were rated as probable (60.65%), followed by possible (24.10%) (Table 6). Mild and moderate reactions accounted for 51.56 and 47.56% of the reports, respectively and only 0.88% of the reactions were deemed to be severe. In 27.47% of the reports, the reaction was considered to be preventable (definitely or probably preventable).

To evaluate the relationship between patient characteristics and the ADRs of anaphylactic shock and rash induced by cephalosporins, all other ADRs induced by cephalosporins were selected as control. Table 7 shows data on the univariate and multivariate logistic models for the variable presence of two ADRs at hospital admission. Multivariate analysis revealed that none of

Table 1: Route of administration and indication of 2046 ADR cases induced by cephalosporins (including cefoxitin)

Factors	No.	%
Route of administration		
Intravenous injection	1590	77.71
Per oral	456	22.29
Indication		
Upper respiratory tract infection	482	23.56
Bronchitis	317	15.49
Pneumonia	258	12.61
Tonsillitis	195	9.53
Pharyngitis	163	7.97
Nasal sinusitis	104	5.08
Meningitis	86	4.20
Cholecystitis	73	3.57
Wound infection	61	2.98
Diarrhea	58	2.83
Appendicitis	47	2.30
Urethritis	39	1.91
Pelvic inflammation	31	1.52
Mumps	29	1.42
Fever of unknown origin	17	0.83
Other	86	4.20

Table 2: Incidence (%) of ADRs induced by cephalosporins (including cefoxitin) among different age and sex patients

Age group	No. (%) of ARD reports (n)	ADRs induced by Cephalosporins /total number of patients received Cephalosporins (n), Incidence (%)	Gender group (n)	No. (%) of ADR reports (n)	ADRs induced by Cephalosporins / total number of patients received Cephalosporins (n),Incidence (%)
0-15	400(19.55)	400/70179,0.57	Male	1126(55.03)	1126/186910,0.60
16-30	396(19.35)	396/78799,0.50	Female	920	
(44.97)	920/165751,0.56				
31-45	574(28.05)	574/118978,0.48			
46-60	385(18.82)	385/57046,0.67			
61-75	212(10.36)	212/17420,1.22			
?75	79 (3.86)	79/10239,0.77			
Total	2046 (100.00)	2046/352661,0.58		2046(100.00)	2046/352661,0.58

Table 3: Organ systems affected by the 2046 ADR cases induced by cephalosporins (including cefoxitin) and reactions most commonly reported

	ADRs			ADRs	
Organ system	No.	(%)	Reaction	No.	(%)
Skin and appendages disorders	890	43.50	Rash	626	30.60
			Pruritus	89	4.35
			Urticaria	78	3.81
			Rash maculo-papular	43	2.10
			Rash erythematous	35	1.71
			Sweating increased	11	0.54
			Dermatitis	5	0.24
			Vesicular rash	3	0.15
Body as a whole-general disorders	444	21.70	Anaphylactoid reaction	314	15.35
			Fever	59	2.88
			Hyperpyrexia	37	1.81
			Headache	13	0.64
			Malaise	11	0.54
			Anaphylactic shock	8	0.39
			Alcohol intolerance	2	0.10
Gastro-intestinal system disorders	429	20.97	Nausea and vomiting	248	12.12
			Increased stool urgency	93	4.55
			Flatulence	50	2.44
			Abdominal pain	34	1.66
			Stomatitis ulcerative	4	0.20
Respiratory system disorders	91	4.45	Dyspnoea	87	4.25
			Pharyngitis	4	0.20
Central and peripheral nervous system disorders	69	3.37	Dizziness	60	2.93
			Anaesthesia local	4	0.20
			Tetany	3	0.15
			Dysphonia	2	0.10
Heart rate and rhythm disorders	40	1.96	Palpitation	35	1.71
			Arrhythmia	5	0.24
Vascular (Extracardiac) disorders	20	0.98	Flushing	20	0.98
Application site disorders	20	0.98	Injection site reaction	20	0.98
Hearing and visibular disorders	12	0.59	Tinnitus	12	0.59
Cardiovascular disorders, general	12	0.59	Hypotension	4	0.20
			Oedema periorbital	4	0.20
			Pallor	4	0.20
Urinary system disorders	5	0.24	Haematuria	5	0.24
Live and biliary system disorders	5	0.24	Hepatic fnnction abnormal	5	0.24
White cell and res disorders	4	0.20	Leucopenia	4	0.20
Resistance mechanism disorders	3	0.15	Infection fungal	3	0.15
Musculo-skeletal system disorders	2	0.10	Arthralgla	2	0.10

the sociodemographic and health habit variables considered was associated with the outcomes. On the other hand, univariate analysis showed that history of allergies and polypharmacy variables were clearly significant for anaphylactic shock, whereas gender, history of allergies and polypharmacy variables were clearly significant for rash ($p<0.05$). Age (OR = 2.009; 95% CI = 0.577-7.002), gender (OR = 0.799; 95% CI = 0.442-1.446), genetic or family history (OR = 2.517; 95% CI = 0.297-21.344), as well as multiple and intercurrent disease (OR = 1.038; 95% CI = 0.527-2.047) were associated with a lower relation of anaphylactic shock induced by cephalosporins at hospital admission. Moreover, age (OR = 0.915; 95% CI = 0.750-1.116), genetic or family history (OR = 1.155; 95% CI = 0.672-1.987), as well as multiple and intercurrent disease (OR = 1.016; 95% CI = 0.911-1.132) were associated with a lower relation of rash at hospital admission.

DISCUSSION

ADRs are one of the most common causes behind the withdrawal of certain drugs from the market, with consequent considerable financial implications for the pharmaceutical industry (Lasser *et al*., 2002). Most clinically relevant ADRs occur at a rate of 1/10,000 or less. Statisticians have reported that approximately 10,000-20,000 patients need to be monitored during clinical trials to identify ADRs at a rate of 1/3000 or 1/6000. The safety of new agents cannot be fully assessed until a drug has been in the market for many years (Ingelman-Sundberg, 2001). Therefore, as the most severe drug-induced reactions cannot be uncovered before licensing, efficient post-marketing surveillance is needed (Gruchalla, 2000). Furthermore, periodic evaluation of ADR data for incidence and pattern is essential. Dissemination of this information to health care professionals helps in promoting drug safety in institutions.

Table 4: Drug classes and individual drugs most commonly associated with 2046 ADRs cephalosporins (including cefoxitin)

Drug class (ATC code)	ADRs No.	ADRs %	Drug	ADRs No.	ADRs %
First generation cephalosporin(J01DB)	536	26.20	Cefalexin	263	12.85
			Cefradine	96	4.69
			cefathiamidine	89	4.35
			cefazolin	55	2.69
			ceftezole	33	1.62
Second generation cephalosporin(J01DC)	407	19.89	cefuroxime	134	6.55
			Cefoxitin[a]	104	5.08
			cefotiam	87	4.25
			cefaclor	31	1.52
			Cefmetazole	25	1.22
			cefamandole	17	0.83
			Cefprozi	8	0.39
			cefonicid	1	0.05
Third generation cephalosporin(J01DD)	1067	52.15	cefatriaxone	319	15.59
			Cefoperazone and sulbactam	204	9.97
			cefoperazone	190	9.28
			ceftazidime	129	6.30
			cefotaxime	50	2.44
			cefixime	44	2.15
			ceftizoxime	42	2.05
			cefmenoxime	24	1.17
			cefpiramide	23	1.12
			cefodizime	17	0.83
			cefetamet	14	0.68
			Cefdinir	11	0.54
The fourth generation cephalosporin(J01DE)	36	1.76	cefepime	35	1.71
			cefpirome	1	0.05

[a]Cefoxitin that its parent nucleus is similar with cephalosporins belongs to cephalosporin C and is usually accustomed to the second generation cephalosporins

Table 5: Management and outcomes of the 2046 ADRs associated with 2046 ADRs cephalosporins (including cefoxitin)

	ADRs No.	ADRs %
Management[a]		
Drug withdrawn	1936	94.62
Dose altered	87	4.25
Additional treatment given	974	47.60
No change in drug regimen and no additional treatment	93	4.55
Outcome		
After dechallenge/dose alteration	2023	98.87
Improved	1907	93.21
Not improved	29	1.42
Unknown[b]	87	4.25
After rechallenge	87	4.25
Recurrence of symptoms	23	1.12
No recurrence of symptoms	29	1.42
Unknown	35	1.71
Final outcome		
Fatal	8	0.39
Recovered[c]	2020	98.73
Continuing[d]	12	0.59
Unknown[b]	6	0.29

[a]Total is different from the total number of ADR reports as the drug was withdrawn, the dose was altered, or additional treatment was given in many cases, [b]Final outcome of the event is unknown due to missed follow-up, [c]Patient recovered during hospitalization or during subsequent follow-up, [d]Reaction continuing during discharge and subsequent follow-up

Table 6: Analysis of 2046 ADRs induced by cephalosporins (including cefoxitin) for causality, severity and preventable

Parameters	ADRs No.	ADRs %
Causality		
Definite	295	14.42
Probable	1241	60.65
Possible	493	24.10
Doubtful	17	0.83
Severity		
Mild	1055	51.56
Moderate	973	47.56
Severe	18	0.88
Definitely preventable		
Definitely preventable	168	8.21
Probably preventable	394	19.26
Not preventable	1484	72.53

Table 7: Logistic regression analysis of patient characteristics and anaphylactic shock and rash induced by cephalosporins

Dependent variable(s)	Independent variable(s)	Odds Ratio	95%CI	p-value
Anaphylactic shock	Age	2.009	0.577~7.002	0.273
	Gender	0.799	0.442~1.446	0.459
	Genetic or family history	2.517	0.297~21.344	0.397
	Allergic history	3.615	1.045~12.508	0.042
	Multiple and intercurrent disease	1.038	0.527~2.047	0.916
	Polypharmacy	6.438	1.405~29.502	0.016
Rash	Age	0.915	0.750~1.116	0.380
	Gender	1.297	1.192~1.411	0.000
	Genetic or family history	1.155	0.672~1.987	0.602
	Allergic history	0.781	0.631~0.968	0.024
	Multiple and intercurrent disease	1.016	0.911~1.132	0.781
	Polypharmacy	0.311	0.225~0.430	0.000

This observational retrospective study based on the clinical medical records of inpatients found those cephalosporins were widely used in various departments of the hospitals that were investigated (4 tertiary care teaching hospitals and 13 secondary hospitals from Bengbu District). Other studies have reported that common ADRs (≥1% of patients) associated with cephalosporin therapy include diarrhea, nausea, rash, electrolyte disturbances and/or pain and inflammation at the injection site, as well as that infrequent ADRs (0.1%-1% of patients) include vomiting, headache, dizziness, oral and vaginal candidiasis, pseudomembranous colitis, superinfection, eosinophilia and/or fever. Effective comparisons of the incidence rate obtained with data from other studies could not be performed because most studies focused on the incidence of ADRs in hospitalized patients or outpatients and were based on a prospective surveillance methodology (Jose and Rao, 2006). In the

study, the overall incidence of ADRs induced by cephalosporins in hospitalized patients was 0.58%, which is low compared with published data indicating that 1.0% of hospitalized patients developed an ADR. The major reason for this low number is the fact that our data were based on spontaneous reporting, whereas incidence rates reported in the literature were mainly based on prospective surveillance studies. In the study conducted by Bennett and Lipman (Impicciatore *et al*., 2001), the incidence of ADRs by spontaneous reporting was only 0.08% compared with the rate of 7.2% that they identified by prospective surveillance under the same study conditions, which can be attributed to the fact that the ADRs in their patients were more likely to be mild and hence less likely to be reported. Patients with reactions of higher severity are admitted in the hospital and hence will be reported as inpatients.

The demographic characteristics of our study population showed that female gender had no predominance over males, which is in agreement with previous research (Arulmani *et al*., 2008). Studies have shown that a higher percentage of ADRs was found in geriatric and pediatric populations, which is not similar to our results (Gonzalez-Martin *et al*., 1998; Somers *et al*., 2003). In the study, puber patients (28.05%) experienced a higher percentage of ADRs than did other populations. The high difficulty in judging an ADR induced by a certain medicine can be ascribed to the fact that most pediatric and geriatric patients had a multiple and intercurrent disease and received polypharmacy in tertiary care teaching or secondary hospitals. Second, there were more puber and wrinkly patients who received cephalosporins.

The most common systems associated with ADRs in this study were the skin and appendages involving general disorders. This finding is consistent with many studies that have reported high percentages of dermatological manifestations (Jose and Rao, 2006). The gastrointestinal system has also been reported to be involved in most ADRs induced by cephalosporins (Chinese National Formulary, 2010). In our retrospective evaluation, cefatriaxone, cefalexin and cefoperazone and sulbactam turned out to be the most frequently involved cephalosporins in ADRs (15.59, 12.85 and 9.97% of cases, respectively). Research has shown that patients with a history of reaction have a six fold higher risk of experiencing further reactions on subsequent exposure compared with those without any such history (Da Fonseca, 2000). The most important risk factors for drug hypersensitivity are related to the chemical properties of drugs. This observation is consistent with the natural history of drug allergies and it is worth noting that hypersensitivity reactions to cephalosporins depend on the presence of preformed antibodies (Svensson *et al*., 2001). Moreover, the results indicate that another important risk factor for the development of ADRs is represented by the number of drugs in prescribed therapies. In fact, in agreement with the literature, the observations confirmed that the use of multiple drugs is more related to ADRs than the presence of concomitant diseases.

Another feature of ADRs refers to their severity and it has demonstrated that 0.88% of the reported ADRs could be classified as severe. Such a finding may indeed depend on the frequent occurrence in hospitalized patients of several concomitant diseases that require numerous medications as part of their daily treatments. Therefore, hospital practice seems to predispose patients to a higher incidence of adverse effects and interactions related to antibiotic agents, thus possibly being associated with an increased risk of severe ADRs. A retrospective study (Pichichero, 2006) suggested a 1-3% incidence of immune or anaphylactic shock to cephalosporin independent of any history of penicillin/amoxicillin allergy. Anaphylactic shock from cephalosporins is extremely rare, with the risk estimated to be between 0.0001 and 0.1% only. A seminal study reported that approximately 0.004-0.015% of treatment courses with penicillin resulted in anaphylaxis. Several studies have demonstrated that cephalosporin-induced anaphylaxis does not occur more frequently in patients with known penicillin allergy compared with those without such an allergy. In the retrospective analysis, anaphylactic shock was recognized as a severe ADR induced by cephalosporins. This event could be related to history of drug allergies and multiple drugs and its incidence was estimated as 0.002%, which is consistent with the literature.

Drug withdrawal or dose reduction is usually the first step used in the management of an ADR. In the study, the suspected drug was withdrawn or the dose thereof was reduced after the ADR was identified in 98.87% of the reports. No change in therapy or additional treatment was instituted in 4.55% of cases. The fact that most reactions (51.56%) were mild in severity might have contributed to these values. Drug rechallenge was performed in only 4.25% of reports. The presence of a safer alternative drug and the fact that many of the reactions were hypersensitive where rechallenge was not a wise option resulted in this low number. In most reactions (98.73%), the patient recovered completely, a finding similar to that reported by Soleymani *et al*. (2011) in their study of hospitalized patients (Pichichero, 2006).

This study is not without limitations, however. The most important limitation is the underreporting of suspected ADRs. In fact, the medical personnels seemed unaware of the need to report well-known severe reactions and for further guidance on what to report. Underreporting may have also occurred because the medical personnels were under the misconception that they should be absolutely confident in the cause-effect relationship between a drug and its presumed adverse reactions before reporting it.

CONCLUSION

In conclusion, the results indicate that cephalosporins represent a common cause of ADRs in hospitalized patients and that drug surveillance can successfully identify targeted adverse events. Moreover, the findings highlight the importance of retrospective analysis for all types of ADR-related research studies.

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