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Research Article

Incidence and Risk Factors of Hypersensitivity Reactions to Intravenous Ceftriaxone in Iraqi Hospitals: Nationwide Prospective Study

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Abstract

Background: Ceftriaxone is a widely used cephalosporin in Iraqi hospitals. Despite its broad-spectrum safety profile, hypersensitivity reactions are underreported and poorly characterized in the local setting. ***Objective***: To estimate the incidence of intravenous ceftriaxone-associated hypersensitivity reactions among hospitalized Iraqi patients and identify predictors of risk. ***Methods***: A nationwide, prospective cohort study was conducted from April to July 2024 across ten public hospitals selected for high ceftriaxone use and geographic representation. Inpatients receiving ceftriaxone infusions were actively monitored until discharged. Standardized forms captured demographics, medical history, ceftriaxone dosing, co-medications, and infusion details. Reactions within 12 hours were graded according to the Ring and Messmer scale. Data were audited monthly. Incidence was calculated for predictors of allergic reactions. ***Results***: Of 5,732 patients, 50 experienced hypersensitivities (0.87%; 95% CI 0.65–1.15). Most reactions were mild (Grade I, 70%), followed by Grade II (24%) and Grade III (6%). Rates varied regionally (0–7.3%). Univariate analysis identified prior allergies (OR=3.29), budesonide use (OR=3.04), and fewer ceftriaxone doses (OR 0.80) as risk factors for increased risk. In multivariate models, budesonide use (OR=3.39, p=0.022) and the number of doses (OR=0.78 per additional dose, p=0.036) remained significant. ***Conclusions***: Ceftriaxone-related hypersensitivity in Iraqi public hospitals occurs at a low incidence similar to global reports. Key predictors include underlying atopy (indicated by recent budesonide use) and fewer administered doses. Hypersensitivity reactions mostly occur early in the treatment course. Therefore, active pharmacovigilance and increased clinical monitoring are important during the first few doses of ceftriaxone.

Keywords: Adverse drug reactions; Ceftriaxone hypersensitivity; Pharmacovigilance in Iraq; Prospective cohort study; Risk factors.

حدوث وعوامل خطورة الحساسية المفرطة تجاه السيفترياكسون الوريدي في المستشفيات العراقية: دراسة مستقبلية على مستوى البلد

الخلاصة

الخلفية: يُعدّ سيفترياكسون من سيفالوسبورينات الجيل الثالث واسعة الاستخدام في المستشفيات الحكومية العراقية. ورغم طيفه الواسع وسلامته الجيدة، إلا أن تفاعلات فرط الحساسية لا يتم الإبلاغ عنها بشكل كافٍ وتفتقر إلى التوصيف الدقيق في السياقات المحلية. **الهدف:** تقدير معدل حدوث تفاعلات فرط الحساسية المرتبطة بسيفترياكسون الوريدي لدى المرضى العراقيين الراقدين في المستشفيات، وتحديد العوامل الديموغرافية أو المتعلقة بالعلاج التي تُنبئ بخطر حدوثها. **الطرائق:** أُجريت دراسة جماعية مستقبلية في العراق، خلال الفترة من أبريل إلى يوليو 2024، في عشرة مستشفيات حكومية اختيرت لارتفاع معدل الأستخدام فيها والتوزيع الجغرافي. وتمت مراقبة المرضى الذين يتلقون حقن سيفترياكسون ثلاث مرات أسبوعيًا بشكل دقيق حتى خروجهم من المستشفى. وتم جمع البيانات الديموغرافية والتاريخ الطبي وجرعات سيفترياكسون والأدوية المصاحبة وتفاصيل الحقن باستخدام استمارات موحدة. تم تصنيف ردود الفعل خلال 12 ساعة وفقًا لمقياس رينغ وميسمر. خضعت البيانات للمراجعة الشهرية. حُسب معدل الحدوث مع فترات ثقة 95%، وحدد تحليل الانحدار اللوجستي الثنائي المتغيرات التنبؤية الأحادية والمتعددة لردود الفعل التحسسية. **النتائج:** من بين 5732 مريضًا، عانى 50 مريضًا من فرط الحساسية (0.87%؛ فترة ثقة 95%: 0.65-1.15). كانت معظم ردود الفعل خفيفة (الدرجة الأولى، 70%)، تليها الدرجة الثانية (24%) ثم الدرجة الثالثة (6%). تباينت المعدلات إقليميًا (0-7.3%). حدد التحليل الأحادي وجود حساسية سابقة (نسبة الأرجحية 3.29)، واستخدام بوديزونيد (نسبة الأرجحية 3.04)، وقلة جرعات سيفترياكسون (نسبة الأرجحية 0.80) كعوامل خطر لزيادة احتمالية حدوث رد الفعل التحسسي. في النماذج متعددة المتغيرات، ظل استخدام البوديسونيد وعدد الجرعات لكل جرعة إضافية عاملين مؤثرين بشكلٍ ملحوظ. **الاستنتاجات:** يحدث فرط الحساسية المرتبط بالسيفترياكسون في المستشفيات الحكومية العراقية بنسبة منخفضة مقارنة بالتقارير العالمية. تشمل العوامل الرئيسية المُنبئة للتعرض الحديث للكورتيكوستيرويدات وتكرار جرعاتها. تدعم اليقظة الدوائية الفعّالة والالتزام ببروتوكولات التسريب المعتمدة من وزارة الصحة الاستخدام الآمن للسيفترياكسون.

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INTRODUCTION

Ceftriaxone, a third-generation cephalosporin, is among the most widely used agents in Iraqi hospitals due to its broad antimicrobial spectrum and relatively favorable safety profile [1–3]. It is a first-line treatment for various infections, including respiratory and urinary tract infections, in both community and hospital settings [4–6]. It is a good choice for children because it is easy to take once a day, has a long half-life, and keeps therapeutic levels high [7,8]. On the other hand, ceftriaxone is commonly associated with hypersensitivity reactions ranging from mild skin reactions to full-blown anaphylactic shock [9]. These reactions can be an obstacle for hospitals, particularly when they result from excessive use, as is the case in Iraqi hospitals [3]. There are two types of hypersensitivity reactions to ceftriaxone: immediate and delayed. IgE antibodies are often to blame

for immediate reactions, which can lead to anaphylaxis [10]. Although these severe reactions are rare, they are significant, especially in hospitalized patients who may already be at risk due to preexisting health conditions [11]. The most common side effects of ceftriaxone are skin problems, like maculopapular rashes and urticaria, which affect 1–3% of patients [9]. Delayed reactions, which may involve T-cell mechanisms, can include serious skin conditions like Stevens-Johnson syndrome, toxic epidermal necrolysis, and drug rash with eosinophilia and systemic symptoms [12,13]. Generally, hypersensitivity reactions to ceftriaxone can be attributed to its beta-lactam core, the cephalosporin ring, and the side chain added to the basic structure [14]. It has been found that ceftriaxone is associated with a high rate of overuse and misuse, which contributes to the alarming rise of antimicrobial resistance, as well as an increased risk of unnecessary harm to patients due to allergic reactions of varying severity, thereby complicating the treatment regimen [3,15]. In Iraq, the rate of hypersensitivity reactions to ceftriaxone and its impact on patients are poorly documented in community and hospital settings. However, some local studies have indicated that hypersensitivity reactions are a significant concern in clinical practice [1,3,11,16]. Iraq has maintained an active pharmacovigilance center (IPvC) since it officially joined the WHO's Program for International Drug Monitoring in 2010, becoming part of a global network dedicated to improving medicine safety through effective ADR reporting [17]. Since then, the system has evolved and decentralized to regional centers within each Directorate of Health (DoH) [18]. Recently, pharmacovigilance units have been established within health institutions across the country. These units have direct access to the national ADR database (VigiFlow) [18]. They receive all reports submitted through the national electronic ADR reporting form and delegate them to the regional center at the relevant DoH, which then processes and forwards them to the IPvC. Iraqi pharmacovigilance systems are impacted by widespread underreporting, similar to most global pharmacovigilance systems, which can create gaps in understanding the safety profile of commonly used drugs [19,20]. However, according to the second 2023 pharmacovigilance bulletin issued by the Iraqi Pharmacovigilance Center, covering data collected throughout that year, ceftriaxone was the most frequently reported medication, representing nearly 10% of cases that year, mostly as the suspect drug [21]. Risk assessment of ceftriaxone-associated hypersensitivity in Iraq is limited by two key challenges: the under-reporting of suspected adverse events and the insufficient quality of clinical information documented in spontaneous reports. This lack of proper documentation means the true incidence of ceftriaxone-associated hypersensitivity reactions remains unclear [11]. The pharmacovigilance center noted increasing concern among healthcare professionals regarding the safety profile of ceftriaxone products marketed in Iraq, including those available in public hospitals, which are procured through a centralized system maintained by the MOH. This situation has led to increased, and possibly overreported, ADRs associated with ceftriaxone. Several official letters from healthcare providers raised alarms, claiming that the rate of ADRs is unacceptable. However, no detailed documentation of the cases and their percentages—necessary for assessing the actual incidence—has been provided. In response, the pharmacovigilance center has initiated a nationwide active surveillance study to objectively address public concern over ceftriaxone infusion-associated hypersensitivity reactions. We hypothesize that administering ceftriaxone through IV infusion is linked to a measurable rate of hypersensitivity reactions in hospitalized Iraqi patients. Additionally, this hypothesis suggests that the chance of experiencing a ceftriaxone-induced hypersensitivity reaction is not random but affected by specific patient and treatment-related factors. In particular, patients' demographic characteristics (such as age and sex), the dosage and duration of ceftriaxone therapy, and the conditions of administration (like infusion rate or technique) are expected to significantly correlate with the occurrence of hypersensitivity reactions. In summary, the study aims to estimate the rate of hypersensitivity reactions among hospitalized Iraqi patients receiving ceftriaxone via IV infusion and to identify risk factors that predict which patients are more likely to develop these responses.

METHODS

Study design

This observational prospective cohort study was conducted over three months (April 21st to July 21st, 2024) as part of an active surveillance program designed by IPvC at the Iraqi Ministry of Health. The specific ceftriaxone product(s) were provided through centralized procurement processes within the MoH via the state company for drugs and medical appliances. The researchers created a standardized paper data collection form. The form recorded the following data: demographic information (age, sex, pregnancy and lactation status, and weight), medical history and chronic diseases (hypertension, diabetes mellitus, and others), presence of other types of drug or food allergies, and concurrent and chronic medications. Drug information: indication, generic name, batch number, administered dose in mg, number of doses, volume of dilution, duration of infusion, type of diluent, and co-administered medications. Reaction information: occurrence of hypersensitivity, severity grade of hypersensitivity reaction. The Ring and Messmer grading scale (Table 1) was used for classification, ranging from 1 (mild) to 4 (fatal), based on the number and severity of symptoms and involvement of different systems and organs [22,23]. To monitor data collection, IPvC created a live Excel sheet that mirrors the paper form for each study site, to

which all collected cases must be transferred. The DoH of the study site can access the sheet as a viewer only. A detailed ADR form will be sent by the pharmacovigilance unit at the study site via the national VigiFlow database as a "Report from Study" report if a patient experiences adverse reactions within 12 hours post-infusion. This report will then be linked to their corresponding study forms.

Table 1: Ring and Messmer grading scale

Grade	Skin	Abdomen	Respiratory tract	Cardiovascular system
I	Itching, Flushing, Urticaria, Angioedema	No symptoms	No symptoms	No symptoms
II	Itching, Flushing, Urticaria Angioedema	Nausea, Cramps	Rhinorrhea, Hoarseness Dyspnea	Tachycardia (≥20 bpm rise in heart rate), Hypotension (≥20 mmHg falls of SBP), Arrhythmia
III	Itching, Flushing, Urticaria, Angioedema	Vomiting, Defecation	Laryngeal edema (stridor), Bronchospasm, Cyanosis	Circulatory shock
IV	Itching, Flushing, Urticaria, Angioedema	Vomiting Defecation	Respiratory arrest	Circulatory arrest

BPM: beats per minute. SBP: systolic blood pressure.

Study settings

According to the latest official annual report from the Iraqi Ministry of Health, the total number of government hospitals with inpatient facilities (excluding the Kurdistan region) across the country is 222 institutions, with 190 of them having a PV unit. Ten hospitals were ultimately selected as study sites based on the following criteria: 1) Among the highest percentage of ceftriaxone use during the previous year. 2) The PV unit staff members have worked at the hospital for at least six months; 3) Willingness of the institutions; and 4) Geographical distribution of the selected hospitals to include all main regions of the country for a population-representative sample (Figure 1).

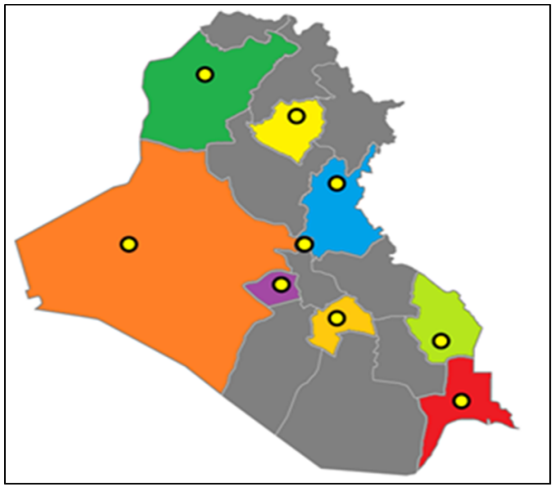

Figure 1: Geographical distribution of the study sites.

Sampling technique and study procedure

The data collection process consisted of consecutive sampling three days a week, consistently conducted for three months at each study site. The aim is to include all eligible patients in sequence to reduce selection bias and to meet the sample size target. This method was chosen because ceftriaxone is prescribed continuously and day-independent. Any inpatient scheduled to receive ceftriaxone during the study day was included and then monitored for allergic reactions for the remainder of their hospital stay. Any patient who could not receive the treatment due to the emergence of an allergy during the pre-administration skin test was excluded, along with duplicated patients and those lacking essential information. All the necessary information was obtained from multiple sources, including patient chart reviews, follow-up with healthcare professionals, interactions with patients, and direct observation, and it was captured within the study data collection form. A period of two weeks was given to data collectors to manually transfer the completed forms to the live Excel sheet.

Sample size calculation

To determine the necessary sample size for a study on ceftriaxone infusion-related allergic reactions, we applied Cochran's formula to estimate the minimum number of participants needed [24]. According to the literature, cephalosporin hypersensitivity has an incidence of approximately 1–3% [9]. We selected the higher end of this range (p=0.03) to ensure our sample size was adequate, with a confidence level of 95% (Z=1.96) and a margin of error of 1% (E=0.01). The resulting minimum sample size was about n=1118 patients. Before beginning the study, each site provided the number of ceftriaxone vials dispensed over the previous three to six months, and all sites exceeded the calculated minimum. Ultimately, we enrolled 5,732 patients, which provided a sufficiently large sample to enhance the accuracy of our incidence estimates, reducing the margin of error to roughly 0.44%.

Roles and responsibilities

IPvC designed the study protocol and the data collection tools. Additionally, IPvC was responsible for recruiting study sites, obtaining official approvals, and overseeing publication. Pharmacovigilance departments at the targeted DoH authorities were responsible for quality assurance and conducted monthly audits at the study sites. The audit's goal was to find any differences from the study protocol, fix them, and see how they might affect the results. The DoH systematically and

retrospectively validated the live Excel spreadsheet, cross-checking it with paper forms. At the study sites, pharmacovigilance units collected data, maintained records, and managed data entry.

Training and pilot study

IPvC conducted multiple online training and discussion sessions with the study team before beginning data collection. A one-week pilot phase was initially planned to test the data collection procedures and electronic data entry process. A follow-up meeting was then held to gather feedback from the pilot phase. The final protocol and study tools were subsequently refined. Additionally, a WhatsApp group was created for the entire study team to facilitate ongoing support, real-time troubleshooting, and communication.

Ethical considerations

The study was conducted in accordance with the principles of the Declaration of Helsinki and the guidelines of Good Clinical Practice. Data collection relied on secondary data extracted from existing patient records and hospital documentation. However, verbal consent was obtained from patients. Patient confidentiality and data protection were maintained throughout the study. The Directorate of Technical Affairs has officially approved the study (Number 204, Dated 2/1/2024) as part of IPvC's main roles and responsibilities, as well as the approved ministerial study projects for 2024. Each study site has officially nominated itself to take part in the study through its PV unit.

Statistical analysis

All analyses were conducted using GraphPad Prism (version 10.4). Continuous variables are presented as medians and interquartile ranges, while categorical variables are expressed as counts and percentages. Univariate binary logistic regression analysis was initially performed, using allergic reaction development as the dependent variable, to identify potential predictors and confounders, including patient demographics and concomitant medications. To find independent predictors while avoiding statistical overfitting, we employed a parsimonious approach for our final model. Specifically, only variables with a statistically significant association ($p< 0.05$) in the univariate screening were included in the multivariate binary logistic regression model. Considering the total number of outcome events (n=50), limiting the multivariate model to these significant predictors—such as the number of ceftriaxone doses, budesonide use, and a history of allergy—ensured the model met the standard events-per-variable biostatistical threshold for stability. The *p*-value was deemed significant if it was less than 0.05.

RESULTS

No critical or major findings were identified during the audit that would require excluding the study site. The study included 5,732 patients; 50 experienced allergic reactions, resulting in a cumulative incidence of 0.87% (95% CI: 0.65 – 1.15%). Most patients (39.1%) were under 10 years old (median age: 2 years) and weighed 44 kg. Table 2 presents the characteristics of the examined patients.

Table 2: Sociodemographic and patient characteristics of the patients involved in the study

Variables	Value	Variables	Value
Age (year)	2.0(0.8-5.0)	Antihistamines within 3 days	252(4.4)
≤10	2241(39.1)	Corticosteroids within a week	933(16.3)
11 – 19	657(11.5)	Hydrocortisone	433(7.6)
20 – 29	766(13.4)	Dexamethasone	652(11.4)
30 – 39	572(10)	Betamethasone	4(0.1)
40 – 49	378(6.6)	Prednisolone	33(0.6)
50 – 59	328(5.7)	Budesonide	175(3.1)
≥60	753(13.1)	Previous exposure	646(11.3)
Unknown	37(0.6)	Was an allergy test done?	4496(78.4)
Weight (kg)	44(10-75)	Dose number	2(2 – 3)
Sex		Dose (mg)	1000(750 – 1000)
Female	3160(55.1)	Dosing frequency	2(1–2)
Male	2572(44.9)	Infusion time (min)	30(30 – 30)
Positive medical history	1565(27.3)	Dilution volume	100(100 –100)
Diabetic mellitus	611(10.7)	*Solution*	
Hypertension	824(14.4)	NS	4441(77.5)
History of allergy	111(1.9)	GS	940(16.4)
Concomitant Medicinal Products	5615(98)	GW	351(6.1)
		Simultaneous IV medicines	5359(93.5)

Values are presented as median (interquartile range), frequency, and percentage. NS (Normal Saline), GS (Glucose Saline), and GW (Glucose Water).

As shown in Figure 2, most allergic reactions were grade I (70%), followed by grade II (24%) and grade III (6%) (Figure 2). Diyala had the most allergic reactions (7.3%), followed by Basra (2.9%) and Nineveh (2.1%). There were no cases in Diwaniyah. Further analysis indicated that most centers had a lower risk of allergic reactions compared to Diyala, as demonstrated in Table 3. Previous allergy history (OR, 95% CI: 3.294, 1.01 - 10.749) and use of budesonide (OR, 95% CI: 3.043, 1.078 - 8.592) were associated with an increased risk of allergic

reactions, while a higher number of ceftriaxone doses (OR, 95% CI: 0.796, 0.643 - 0.985) was linked to a reduced risk, as shown in Figure 3.

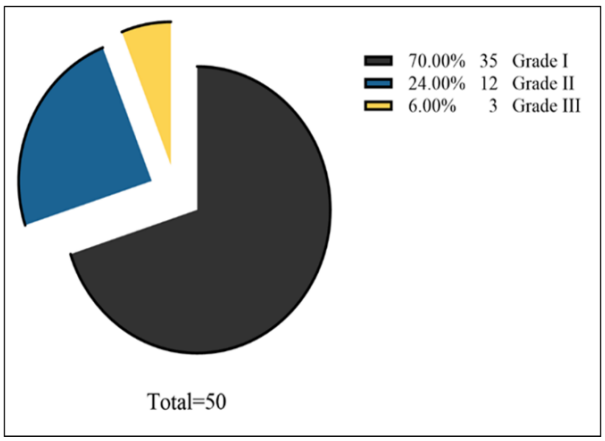

Figure 2: Grading of allergic reaction.

Specifically, among the 50 patients who experienced hypersensitivity, reactions mostly occurred early in treatment: 25 cases (50%) during the first dose, 17 (34%) during the second, 3 (6%) during the third, and 5 (10%) at the fourth dose or later. In multivariate analysis, dose number and budesonide use were independent predictors of allergic reactions, as indicated in Table 4.

DISCUSSION

This marks the first time the Iraqi Pharmacovigilance Center has conducted a nationwide, multi-center active surveillance activity. It aimed to assess and understand the risk of hypersensitivity reactions associated with intravenous ceftriaxone infusions. Ongoing concerns regarding serious hypersensitivity reactions have previously prompted the Iraqi Ministry of Health to mandate that intravenous ceftriaxone be administered through infusion over at least 30 minutes, using appropriately diluted solutions—that is, after performing a dermal sensitivity test [15,25,26]. This policy has been strictly enforced within public hospital settings.

Table 3: Regional variations of the reported allergic reaction according to the reporting center

Center location	All cases n(%)	Allergic reaction n(%)	OR (95%CI)	*p*-value
Anbar	653(11.4)	2(0.3)	0.04(0.01-0.18)	<0.001
Basrah	105(1.8)	3(2.9)	0.37(0.10-1.37)	0.136
Diwaniyah	226(3.9)	0(0.0)	-	-
Baghdad	1311(22.9)	12(0.9)	0.12(0.05-0.27)	<0.001
Karbala	999(17.4)	3(0.3)	0.04(0.01-0.14)	<0.001
Kirkuk	1282(22.4)	9(0.7)	0.09(0.04-0.22)	<0.001
Maysan	720(12.6)	4(0.6)	0.07(0.02-0.22)	<0.001
Nineveh	286(5.0)	6(2.1)	0.27(0.10-0.75)	0.012
Diyala	150(2.6)	11(7.3)	Reference	-

OR: Odds Ratio, CI: confidence interval, in the logistic regression analysis, Diyala was chosen as the reference for comparison to calculate the odd ratio.

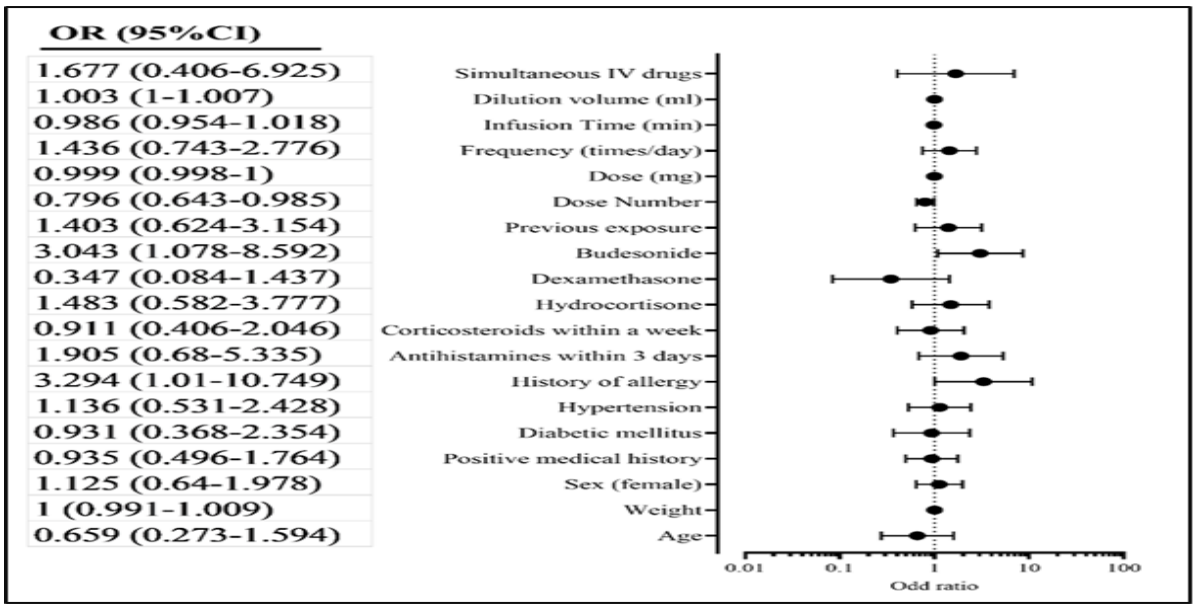

Figure 3: Forest plot illustrates the assessment of predictors for ceftriaxone-induced allergic reactions. Data are presented as Odds Ratios (ORs) with their corresponding 95% Confidence Intervals (CIs) derived from univariate binary logistic regression analyses. The vertical dotted line at OR = 1 represents the no-effect line. Solid black circles indicate the point estimate of the OR for each variable, and the horizontal bars represent the 95% CI. Variables with a 95% CI entirely above 1 indicate a statistically significant increased risk of hypersensitivity, whereas variables with a 95% CI entirely below 1 indicate a statistically significant decreased risk.

Table 4: Multivariate analysis of the risk of developing an allergic reaction

Variables	OR (95%CI)	*p*-value
The number of ceftriaxone doses	0.779(0.617-0.984)	0.036
Budesonide use	3.385(1.188-9.641)	0.022
History of allergy	1.1(0.148-8.2)	0.926

OR: odd ratio, CI: confidence interval.

The Ministry of Health's recommendations ensured that all cases included in this study, conducted solely in public hospital settings, received ceftriaxone. The current findings indicate that among 5,732 patients, 50 experienced allergic reactions. This yields an estimated incidence of ceftriaxone-associated hypersensitivity reactions in public hospitals of 0.87%, similar to the 0.349% incidence reported in a multi-center Chinese study [27]. This rate falls within the lower range of the worldwide reported incidences, which vary between 1% and 3% [9,28–30]. The high reporting rate could partly be due to increased use of the drug and the lack of a standardized grading method, which may cause misconceptions and over-reporting, leading to a perception that ceftriaxone is more dangerous than it actually is. Seventy percent of the reported reactions were mild (Grade 1), and twenty-four percent were moderate (Grade 2). In contrast to an Iranian study that reported 30% of ceftriaxone reactions as severe [31], only 6% of cases in this study were classified as severe (Grade 3), with no fatalities. The severe cases were mainly treated with immediate intravenous hydrocortisone and diphenhydramine, while the most serious and life-threatening reactions also received intramuscular adrenaline injections. Rates of allergic reactions varied significantly between centers: one site reported a 7.3% rate, two sites reported around 2%, and all other sites recorded rates below 1%. Since the patient profiles at the high-reporting center closely resembled those at other sites, these differences likely reflect variations in hospital protocols, population characteristics, or reporting practices. The centers with the largest patient cohorts had the lowest reaction rates. Among the variables studied, allergic history to ceftriaxone (OR: 3.294) and lower ceftriaxone doses (OR: 0.796) were significantly associated with increased risk, emphasizing the importance of a thorough patient history before administering ceftriaxone. Studies have shown that cross-reactivity is possible in patients with allergy history and is mainly driven by identical or similar side chains between β-lactam antibiotics rather than the β-lactam ring alone [32,33]. This inverse relationship—where the odds of a reaction decrease as the number of tolerated doses increases—is a key clinical finding. It shows that ceftriaxone hypersensitivity reactions mainly occur early in treatment. This aligns with the expected immune mechanism of immediate, IgE-mediated responses upon re-exposure or cross-sensitization. Clinically, this study highlights the importance of increased vigilance and close patient monitoring, especially during the first and second doses, as the risk drops significantly after initial tolerance is achieved [34]. The multivariate model independently and significantly linked the use of budesonide to a higher risk of hypersensitivity among the analyzed medications. Although it is unlikely that inhaled budesonide directly causes systemic ceftriaxone hypersensitivity, its use probably indicates the presence of underlying atopic diseases, such as asthma or hyper-reactive airway disease. Patients with pre-existing atopic conditions tend to have a hyper-responsive immune system and are more likely to develop drug-induced allergic reactions. Therefore, the association with budesonide emphasizes the need to consider underlying respiratory atopy as a general risk factor when administering intravenous antibiotics [33]. In contrast, other variables such as age, sex, weight, medical history, and additional factors did not show statistically significant correlations. Although sex was not significantly associated with allergic outcomes, 30 cases (60%) of documented allergic reactions were female, as reported in another study [30]. Unlike a study by Yang et al. (2024), which found that a low body mass index increases the risk of cephalosporin allergy [27], weight did not significantly correlate with allergy risk in our study. This highlights the complexity and multifactorial characteristics of drug hypersensitivity, indicating that a targeted approach may be more effective for risk management strategies than a generalized one. A significant result of this study is the implicit validation of the MOH-mandated administration protocol, which corresponds with prior research identifying infusion rate as a critical risk factor [31]. The relatively low incidence and absence of fatal cases support the ongoing enforcement of standardized infusion guidelines across both public and private healthcare sectors. Educating healthcare staff on early detection and management of allergic reactions is also recommended. Skin testing with cephalosporins has variable sensitivity (31%–72%), limiting its clinical usefulness. Additionally, negative skin tests do not reliably exclude immediate hypersensitivity [28]. Penicillin-specific IgE antibody levels decline over time [35]. In our study, negative skin test results did not eliminate all cases of immediate hypersensitivity risk. However, they may have contributed to reducing its incidence. Despite allergy testing being part of mandated practice, our data showed inconsistent implementation across institutions, which may lead to increased risks of allergic reactions in patients who are not adequately tested. Emphasizing routine allergy testing, particularly in patients with a history of allergies or autoimmune diseases, could further reduce reaction risks. This study also confirms that ceftriaxone products used in the public health sector have a favorable safety profile, and adherence to administration protocols should minimize allergic adverse events to the lowest possible level. The study employed a standardized data collection method, continuously evaluated through monthly quality

assurance audits to ensure adherence to the study protocol, thereby strengthening the validity of the results.

Study limitations

Some limitations were shared by multiple centers, including inaccurate or missing data (particularly patient weights), incomplete or incorrect patient medication histories due to poor patient recall, and inadequate health literacy. Other notable challenges were limited staff availability and workload. The geographical distribution of the participating hospitals could be considered purposive, non-random hospital selection, which may impact the generalizability of the results. Moreover, the study did not include the private health sector's experience with ceftriaxone infusions, which should be addressed in future research. Additionally, while we captured a general 'history of allergy' (primarily previous drug/food reactions), our data collection did not explicitly isolate systemic atopic diseases like asthma, meaning we had to rely on proxy indicators (such as budesonide use) to infer the impact of underlying atopy on hypersensitivity risk.

Conclusions

The observed incidence of hypersensitivity reactions secondary to intravenous ceftriaxone among patients in Iraqi public hospitals is 0.87%, as shown by this prospective cohort study. Ceftriaxone is confirmed to have a favorable safety profile when administered in accordance with the Ministry of Health's standardized protocols. Although variability occurs within regions as well as mild manufacturer-related variability, no deviations were noted as being of critical concern to patient safety. A history of allergy, lower dose numbers, and budesonide use as a proxy indicator were identified as significant predictors of hypersensitivity reactions. The study highlights the effectiveness of active pharmacovigilance initiatives in addressing potential signals generated by spontaneous reporting and strengthening medication risk management in resource-limited healthcare settings. Future pharmacovigilance training initiatives should focus on accurately describing and classifying hypersensitivity reactions during spontaneous reporting.

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Conflict of interests

The authors declared no conflict of interest.

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Data sharing statement

De-identified participant data that supports the findings of this study, along with the study protocol and statistical analysis plan, will be made available from the corresponding author upon reasonable request. Requests should specify the intended use, analysis plan, and measures to protect confidentiality.

REFERENCES

1. Naqid IA, Balatay AA, Hussein NR, Ahmed HA, Saeed KA, Abdi SA. Bacterial strains and antimicrobial susceptibility patterns in male urinary tract infections in Duhok province, Iraq. *Middle East J Rehabil Health Stud*. 2020;7(3):e103529. doi: 10.5812/mejrh.103529.
2. Fadheel QJ, Naser RT. Evaluation of Antibiotics Activity among Hospitalized Patients in Iraq. *J Pharm Res Int*. 2021;33(20B):30-43. doi: 10.9734/jpri/2021/v33i20B31356.
3. AL-Biati HA, Abdulkareem AH, Abood MK. Clinical pharmacist intervention in prescription of ceftriaxone use in community pharmacy. *Indian J Forensic Med Toxicol*. 2021;15(3):4670-4679. doi: 10.37506/ijfmt.v15i3.16191.
4. Mandell LA, Wunderink RG, Anzueto A, Bartlett JG, Campbell GD, Dean NC, *et al*. Infectious Diseases Society of America/American Thoracic Society consensus guidelines on the management of community-acquired pneumonia in adults. *Clin Infect Dis*. 2007;44(Suppl 2):S27-72. doi: 10.1086/511159.
5. Jackson CD, Burroughs-Ray DC, Summers NA. Clinical guideline highlights for the hospitalist: 2019 American Thoracic Society/Infectious Diseases Society of America Update on Community-Acquired Pneumonia. *J Hosp Med*. 2020;15(12):743-745. doi: 10.12788/jhm.3444.
6. Lupia T, Corcione S, Mornese Pinna S, De Rosa FG. New cephalosporins for the treatment of pneumonia in internal medicine wards. *J Thorac Dis*. 2020;12(7):3747-3763. doi: 10.21037/jtd-20-417.
7. Al-Anbari H, Al-Hilali K, Sughair MH. Comparable efficacy of azithromycin versus ceftriaxone in eradicating *H. influenzae* of pediatric nasal carriers in Iraq. *J Basic Appl Res Biomed*. 2019;5(1):49-54.
8. Al-Saedi HFS, Hadi SI, Younis WK, Musa IH. Comparing the effects and adherence to azithromycin versus ceftriaxone in treatment of acute otitis media in pediatric patients in Karbala city. *Nat Volatiles Essent Oils*. 2021;8(4):3793-3803.
9. Moreno E, Macías E, Dávila I, Laffond E, Ruiz A, Lorente F. Hypersensitivity reactions to cephalosporins. *Expert Opin Drug Saf*. 2008;7(3):295-304. doi: 10.1517/14740338.7.3.295.
10. Maker JH, Stroup CM, Huang V, James SF. Antibiotic hypersensitivity mechanisms. *Pharmacy (Basel)*. 2019;7(3):122. doi: 10.3390/pharmacy7030122.
11. Allela O. Explore adverse drug reactions (ADRs) reporting by clinical and community pharmacists in Duhok, Kurdistan region-Iraq: hampered and perspective. *Pharmacia*. 2022;69(4):1057-1062. doi; 10.3897/pharmacia.69.e95691.
12. Mori F, Liccioli G, Piccorossi A, Sarti L, Barni S, Giovannini M, et al. The diagnosis of ceftriaxone hypersensitivity in a paediatric population. *Int Arch Allergy Immunol*. 2019;178(3):272-276. doi: 10.1159/000495302.
13. Zyryanov S, Asetskaya I, Butranova O, Terekhina E, Polivanov V, Yudin A, et al. Stevens-Johnson syndrome and toxic epidermal necrolysis: Analysis of the russian database of spontaneous reports. *Pharmaceuticals (Basel)*. 2024;17(6):675. doi: 10.3390/ph17060675.
14. Al-Ansari RY, Almuhaish LA, Hassan KA, Fadoul T, Woodman A. A Saudi woman with ceftriaxone induced fixed drug eruption.

Case Rep Dermatol Med. 2024;2024:9975455. doi: 10.1155/2024/9975455.
15. Kurmanji JM, See OG, Al-Jumaili AA, Younus MM. Quality indicators of antimicrobials prescribing in Iraq: A scoping review. *Al-Rafidain J Med Sci*. 2024;7(1):221-226. doi: 10.54133/ajms.v7i1.1227.
16. Nassr OA, Abd Alridha AM, Naser RA, Abbas RS. Antibiotic prescribing in the acute care in Iraq. *Int J Pharmacol Pharm Sci*. 2018;12(10):485-489.
17. Younus MM, Ibrahim IR. Pharmacovigilance for Herbal Medicines in Iraq. In: Barnes J, (Editor), Pharmacovigilance for Herbal and Traditional Medicines: Advances, Challenges and International Perspectives. Cham: Springer International Publishing; 2022. p. 385-394. doi: 10.1016/B978-0-323-85542-6.00001-9.
18. Younus M, AlShimran B. Expansion of VigiFlow network to a third level for post-marketing surveillance of COVID-19 vaccines in Iraq. *Drug Saf*. 2022;45:1224. doi: 10.1007/s40264-022-01219-7.
19. Vargas F, Ringel JB, Yum B, Levitan EB, Mangal S, Steinman MA, et al. Implications of under-reporting medication side effects: Beta-blockers in heart failure as a case example. *Drugs Aging*. 2023;40(3):285-291. doi: 10.1007/s40266-023-01007-7.
20. Al-Jumaili AA, Younus MM, Kannan YJA, Nooruldeen ZE, Al-Nuseirat A. Pharmaceutical regulations in Iraq: from medicine approval to postmarketing. *East Mediterr Health J*. 2021;27(10):1007-1015. doi: 10.26719/emhj.21.025.
21. Iraqi Pharmacovigilance Center. Iraqi Ministry of Health Pharmacovigilance Bulletin. 2023;1(2):1-14. Available at: https://storage.moh.gov.iq/2025/02/20/2025_02_20_12180339206_8606373221452472.pdf.
22. Ring J, Messmer K. Incidence and severity of anaphylactoid reactions to colloid volume substitutes. *Lancet*. 1977;1(8009):466-469. doi: 10.1016/s0140-6736(77)91953-5.
23. Mueller HL. Further experiences with severe allergic reactions to insect stings. *N Engl J Med*. 1959;261:374-377. doi: 10.1056/NEJM195908202610803.
24. Cochran WG. Sampling Techniques. 3rd Edition, John Wiley & Sons, New York; 1977. Available at: https://www.scirp.org/reference/ReferencesPapers?ReferenceID=1390266
25. Al-Jumaili AA, Ahmed KK, Mawla ES, Majeed IM, Al-Rekabi MD. Irrational use of antibiotics in Iraqi public hospitals. *Latin Am J Pharm*. 2023;42(S1):178-183.
26. Salih NT. Kadhim D. Adherence to American Society of Health-System Pharmacists Surgical Antibiotic Prophylaxis Guideline in Medical City Teaching Hospitals/Baghdad. *Iraqi J Pharm Sci*. 2017;25(2):40-45. doi: 10.31351/vol25iss2pp40-45.
27. Yang P, Dai D, Li Q, Zhan H, Li X, Lu X, et al. A multicenter clinical study on the incidence and influencing factors of cephalosporin-induced anaphylaxis. *Zhejiang Da Xue Xue Bao Yi Xue Ban*. 2024;53(5):615-622. doi: 10.3724/zdxbyxb-2024-0100.
28. Dickson SD, Salazar KC. Diagnosis and management of immediate hypersensitivity reactions to cephalosporins. *Clin Rev Allergy Immunol*. 2013;45(1):131-142. doi: 10.1007/s12016-013-8367-x.
29. D'Errico S, Frati P, Zanon M, Valentinuz E, Manetti F, Scopetti M, et al. Cephalosporins' cross-reactivity and the high degree of required knowledge. Case report and review of the literature. *Antibiotics (Basel)*. 2020;9(5):209. doi: 10.3390/antibiotics9050209.
30. Macy E, Poon KYT. Self-reported antibiotic allergy incidence and prevalence: age and sex effects. *Am J Med*. 2009;122(8):778.e1-7. doi: 10.1016/j.amjmed.2009.01.034.
31. Shalviri G, Yousefian S, Gholami K. Adverse events induced by ceftriaxone: a 10-year review of reported cases to Iranian Pharmacovigilance Centre. *J Clin Pharm Ther*. 2012;37(4):448-451. doi: 10.1111/j.1365-2710.2011.01321.x.
32. Caruso C, Valluzzi RL, Colantuono S, Gaeta F, Romano A. β-lactam allergy and cross-reactivity: A clinician's guide to selecting an alternative antibiotic. *J Asthma Allergy*. 2021;14:31-46. doi: 10.2147/JAA.S242061.
33. Mahlab-Guri K, Asher I, Sthoeger Z. Immediate and delayed hypersensitivity reactions to corticosteroids - prevalence, diagnosis and treatment. *Swiss Med Wkly*. 2023;153:40025. doi: 10.57187/smw.2023.40025.
34. Touati N, Cardoso B, Delpuech M, Bazire R, El Kara N, Ouali D, et al. Cephalosporin hypersensitivity: Descriptive analysis, cross-reactivity, and risk factors. *J Allergy Clin Immunol Pract*. 2021;9(11):4181. doi: 10.1016/j.jaip.2021.09.001.
35. Finke SR, Grieco MH, Connell JT, Smith EC, Sherman WB. Results of comparative skin tests with penixilloyl-polylysine and penicillin in patients with penicillin allergy. *Am J Med*. 1965;38:71-82. doi: 10.1016/0002-9343(65)90161-0.