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Safety of ceftriaxone in paediatrics: a systematic review

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ABSTRACT

Objective To determine the safety of ceftriaxone in paediatric patients and systematically evaluate the categories and incidences of adverse drug reactions (ADRs) of ceftriaxone in paediatric patients.

Methods We performed a systematic search in Medline, PubMed, Cochrane Central Register of Controlled Trials, EMBASE, CINAHL, International Pharmaceutical Abstracts and bibliographies of relevant articles up to December 2018 for all types of studies that assessed the safety of ceftriaxone in paediatric patients aged ≤18 years.

Results 112 studies met the inclusion criteria involving 5717 paediatric patients who received ceftriaxone and reported 1136 ADRs. The most frequent ADRs reported in prospective studies were gastrointestinal (GI) disorders (37.4 %, 292/780), followed by hepatobiliary disorders (24.6%, 192/780). Serious ADRs leading to withdrawal or discontinuation of ceftriaxone were reported in 86 paediatric patients. Immune haemolytic anaemia (34.9%, 30/86) and biliary pseudolithiasis (26.7%, 23/86) were the two major causes. Haemolytic anaemia following intravenous ceftriaxone led to death in 11 children whose primary disease was sickle cell disease. Almost all biliary pseudolithiasis are reversible. However, the incidence was high affecting one in five paediatric patients (20.7%).

Conclusions GI ADRs are the most common toxicity of ceftriaxone in paediatric patients. Immune haemolytic anaemia and biliary pseudolithiasis are the most serious ADRs and the major reasons for discontinuation of ceftriaxone. Immune haemolytic anaemia is more likely in children with sickle cell disease and may cause death. Ceftriaxone should be used with caution in children with sickle cell disease.

Trial registration number CRD42017055428

What is already known on this topic?

- Ceftriaxone is a broad-spectrum, bactericidal antibiotic with long elimination half-life.
- Ceftriaxone causes biliary pseudolithiasis and urolithiasis in paediatric patients.

What this study adds?

- Diarrhoea and other gastrointestinal adverse drug reactions (ADRs) are the most common ADRs of ceftriaxone in paediatrics patients.
- Biliary pseudolithiasis and cholelithiasis appear to be common ADR affecting one in five paediatric patients, but most of the cases are reversible.
- Haemolytic anaemia is rare but the most serious ADR of ceftriaxone in paediatric patients, and sickle cell disease is a risk factor for haemolytic anaemia.

INTRODUCTION

Ceftriaxone is a parenteral cephalosporin with broad antimicrobial activity and a long elimination half-life of 8 hours.[1] Studies have shown that ceftriaxone is effective for severe acute infections such as meningitis, sepsis and pneumonia.[2 3] Ceftriaxone is widely used in paediatric patients of all ages.[4]

As a consequence of widespread use, adverse drug reactions (ADRs) have increasingly been reported.[5] Concurrent use of intravenous ceftriaxone and calcium-containing solutions in neonates and young infants has been associated with calcium precipitation. Biliary pseudolithiasis and urolithiasis have also been reported in paediatric patients.[6 7] There is a lack of overall assessment of the safety of ceftriaxone, one of the most widely used antibiotics in paediatric patients. This is therefore the reason for performing this systematic review. The aims of this systematic review are: (1) to systematically evaluate the categories and incidences of ADRs in paediatric patients aged from birth to 18 years old; (2) to identify the most common ADRs and the most serious ADRs associated with ceftriaxone in paediatric patients; and (3) to explore the risk factors of serious ADRs.

METHODS

This study has been registered with the international prospective register of systematic reviews. We reported the methods of the systematic review in a previously published protocol.[8] In brief, a comprehensive search was performed using Medline (Ovid), PubMed, Cochrane Central Register of Controlled Trials, EMBASE, CINAHL and International Pharmaceutical Abstracts for relevant articles up to December 2018. We included all types of studies including randomised controlled trials (RCTs), cohort studies, case–control studies, cross-sectional studies, case series and case reports that assessed the safety of ceftriaxone in paediatric patients aged from birth to 18 years old. There was no restriction on language. We excluded editorials, conference abstracts, studies that evaluated the safety of ceftriaxone during pregnancy and studies that included both paediatric and adult patients but did not report the ADRs separately for paediatric

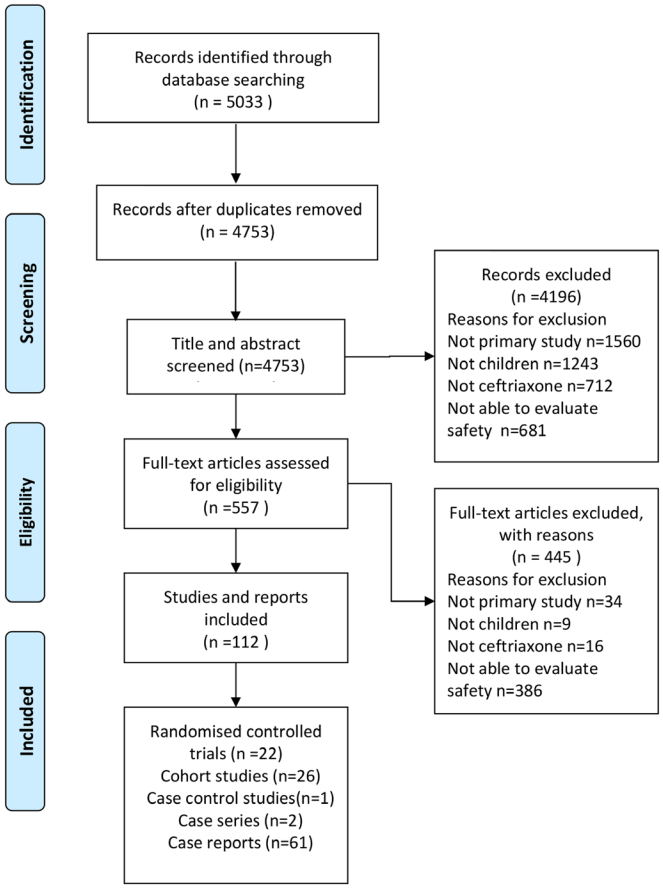

Figure 1 PRISMA 2009 flow diagram from: Moher D, Liberati A, Tetzlaff J, Altman dG, the PRISMA group (2009). Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. PLoS Med 6 (7): e1000097. PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses.

patients. We used the Cochrane risk of bias tool to assess risk of bias in RCTs, Newcastle-Ottawa Scale for case–control study and cohort studies and relevant tools for other types of studies.[9 10] We recorded the number of ADR as zero when the study explicitly reported zero event of a particular ADR, or when the study had the capacity to detect the particular ADR but did not report any event. We calculated the pooled incidence of a particular ADR associated with ceftriaxone based on RCTs and prospective cohort studies. Pooled incidence of a particular ADR per 100 patients=(number of events associated with ceftriaxone/number of patients in ceftriaxone group) × 100. For ADRs that required specific investigations (eg, biliary), the denominator was the number of patients in the ceftriaxone group of studies that performed the specific investigation. Otherwise, the denominator was the number of patients in ceftriaxone group of all RCTs and prospective cohort studies. We conducted meta-analysis of RCTs to assess the comparative safety of ceftriaxone in relation to placebo or other antibiotics by random effect model in Revman 5.3.[11] We used risk difference (RD) as the pooled effect measurement instead of relative risk (RR) or OR as planed in the protocol. Because when the number of events is zero in either group, we cannot use inverse variance methods to calculate RR or OR but can still use RD in the presence of zero events.[12] We did not perform subgroup analysis or meta-regression, because most studies enrolled patients in the same age group (24 months–11 years) and used a similar dose of ceftriaxone (50–100 mg/kg/day).

Table 1 Summary of all articles

Study type	No. of studies	No. of ADRs, n (%)	No. of patients, n (%)
RCTs	22	423 (37.2)	2462 (43.1)
Prospective cohort studies	19	357 (31.4)	2397 (41.9)
Retrospective cohort studies	7	75 (6.6)	730 (12.8)
Case–control	1	3 (0.3)	40 (0.7)
Case series	2	23 (2.0)	23 (0.4)
Case report	61	255 (22.5)	65 (1.1)
Total	112	1136	5717

ADRs, adverse drug reactions; RCT, randomised controlled trial.

RESULTS

Study characteristics

After systematic literature search, we identified a total of 112 studies with reports on the toxicity of ceftriaxone from 28 countries, including 22 RCTs, 19 prospective and 7 retrospective cohort studies, 1 case–control study, 2 case series and 61 case reports (figure 1). The 112 studies included 5717 paediatric patients who received ceftriaxone and documented 1136 ADRs in total (online supplementary appendix 1). Nearly 40% of the ADRs (423/1136) were from RCTs and 31.4% (357/1136) from prospective cohort studies (table 1). The age of patients was from 1 month to 18 years. The daily dosage and duration of ceftriaxone ranged from 30 to 120 mg/kg/day and 2–50 days (online supplementary appendix 1). Lack of allocation concealment (3/22, 14%) or unclear reporting regarding allocation concealment (14/22, 64%) was the major source of risk of bias in RCTs. Lack of comparability was the major concern in cohort studies. Online supplementary appendix 2 presents the risk of bias for each individual study. Only one study had a high risk of bias in four domains (Cannavino *et al*) and one in three domains (Biner *et al*).[13 14]

Prospective studies

More than one-third of ADRs reported from RCTs and prospective cohort studies were gastrointestinal (GI) disorders (37.4 %, 292/780), followed by hepatobiliary disorders (24.6%, 192/780), and general disorders and administration site conditions (22.3%, 174/780). Diarrhoea was the most common ADR affecting 3.0% paediatric patients (table 2).

Among studies detecting certain ADRs that required specific investigations, six studies looking for biliary pseudolithiasis detected 89 ADRs in 430 paediatric patients, giving an incidence of 20.7%. Five studies looking for cholelithiasis detected 62 cases in 329 paediatric patients, giving an incidence of 18.8%. The most common laboratory change was thrombocytosis with an incidence of 31.2% (table 3).

Compared with placebo, ceftriaxone showed no statistically significant difference in the incidences of nausea and vomiting, abdominal pain and fever.[15] Similar results were found when ceftriaxone was compared with penicillins, chloramphenicol by meta-analyses (online supplementary appendix 3) and compared with quinolones and carbapenems by RCTs.[16 17] Ceftriaxone showed an increased risk of rash (RD 0.03, 95% CI 0.00 to 0.07, p=0.05) and a decreased risk of nausea and vomiting (RD −0.02, 95% CI −0.05 to 0.00, p=0.05) compared with macrolides (online supplementary appendix 3).

Table 2 Risk of ADRs from RCTs and prospective cohort studies

ADRs	No. of events	Pooled incidence of ADRs per 100 patients*
Gastrointestinal disorders		
Diarrhoea	150	3.0
Nausea and vomiting	84	1.7
Abdominal pain	42	0.8
Stomachache	16	0.3
Subtotal	**292**	
General disorders and administration site conditions		
Fever	85	1.7
Pain in injection site	74	1.5
Localised pain	4	0.1
Thrombophelibitis	10	0.2
Arthralgia	1	<0.1
Subtotal	**174**	
Skin and subcutaneous tissue disorders		
Rash	57	1.2
Itching	4	0.1
Infusion site erythema	2	<0.1
Subtotal	**63**	
Others		
Stomatitis	7	0.1
Anorexia	6	0.1
Persistent hearing deficiencies	2	<0.1
Otitis media	1	<0.1
Subtotal	**16**	
Total	**545**	

*The total number of patients is 4928.
ADRs, adverse drug reactions; RCTs, randomised controlled trials.

Table 3 Risk of ADRs that need specific investigations from RCTs and prospective cohort studies

ADRs	No. of events	No. of studies	No. of patients	Pooled incidence of ADRs per 100 patients
Hepatobiliary disorders				
Biliary pseudolithiasis	89	6	430	20.7
Cholelithiasis	62	5	329	18.8
Biliary sludge	32	6	441	7.3
Serum bilirubin rise	7	1	170	4.1
Transient elevation of glutamic oxaloacetic	1	1	33	3.0
Impaired liver function	1	1	106	0.9
Subtotal	**192**			
Blood and lymphatic disorders				
Thrombocytosis	19	2	61	31.2
Neutropaenia	14	5	255	5.5
Eosinophilia	2	1	34	5.9
Subtotal	**35**			
Renal and urinary disorders				
Nephrolithiasis or kidney stone	5	2	370	1.4
Urinary sludge	1	1	35	2.9
Ureteral calculi	1	1	53	1.9
Microscopic haematuria	1	1	106	0.9
Subtotal	**8**			
Total	**235**			

ADRs, adverse drug reactions; RCTs, randomised controlled trials.

Only one RCT and one prospective cohort study assessed the comparative risk of biliary pseudolithiasis between ceftriaxone and other cephalosporins.[2 6] Both studies found ceftriaxone increased the risk of biliary pseudolithiasis (RD 0.30, 95% CI 0.18 to 0.43, p<0.01; RD 0.15, 95% CI 0.07 to 0.23, p<0.01).[2 6] Meta-analyses comparing long-course ceftriaxone with short-course ceftriaxone found no statistical significant difference in terms of diarrhoea, rash, fever and stomatitis (online supplementary appendix 3).

The categories of 356 ADRs reported from retrospective studies were almost consistent with those from prospective studies. Biliary sludge and cholelithiasis were the most common ADRs reported in retrospective studies (24.1%, 86/356). The ADR of immune haemolytic anaemia was only reported by retrospective studies (table 4).

Serious ADRs leading to withdrawal or discontinuation of ceftriaxone were reported in 86 paediatric patients (table 5). Immune haemolytic anaemia (34.9%, 30/86) and biliary pseudolithiasis (26.7%, 23/86) were the two major causes. Eleven patients aged from 2 to 17 years old died due to haemolytic anaemia following intravenous ceftriaxone (table 5).[18]

Biliary or urinary precipitations

A total of 269 events of biliary pseudolithiasis, cholelithiasis or biliary sludge were reported (183 from prospective studies and 86 from retrospective studies). Children who suffered from biliary pseudolithiasis, cholelithiasis or biliary sludge were aged from 1.5 to 16 years old. The daily dose of ceftriaxone ranged from 100 mg/kg/day to 2 g/day. The detection of biliary pseudolithiasis, cholelithiasis or biliary sludge was 3–18 days after the use of ceftriaxone by ultrasound. Forty-one patients (15.2%) were reported having GI symptoms including abdominal pain, nausea or vomiting. Forty patients had to discontinue ceftriaxone. Only five studies reported the combination use of medicines, one of which reported the combined use of calcium in

Table 4 ADRs reported from retrospective studies

ADRs	No. of events*
Lithiasis	
Cholelithiasis	56
Biliary pseudolithiasis	20
Biliary sludge or cholelithiasis	10
Urolithiasis	16
Nephrolithiasis	7
Others	
Immune haemolytic anaemia	30
Abdominal pain	14
Nausea or vomiting	13
Renal failure	11
Rash	9
Back pain	6
Unresponsive	6
Fever	6
Hypotension	5
Hypercalciuria increase	5
Liver function worsen	5
Total	**219**

*We only presented ADRs when the number of events is ≥5.
.ADRs, adverse drug reactions.

Table 5 Summary of serious ADRs causing death, necessitating withdrawal or discontinuation of therapy

ADRs	No. of death	No. of withdrawal or discontinuation *
RCTs and prospective cohort studies		
Biliary pseudolithiasis	0	23
Cholelithiasis	0	2
Neutropaenia	0	2
Rash	0	1
Retrospective cohort studies		
Immune haemolytic anaemia	11	30
Leukocytoclastic vasculitis	0	1
X-linked agammaglobulinaemia	0	1
Biliary pseudolithiasis	0	12
Cholelithiasis	0	2
Choledocholithiasis	0	1
Cholestasis	0	1
Hepatic toxicities (liver injury)	0	1
Toxic hepatitis	0	1
Rash	0	3
Anaphylactic	0	3
Vitamin K deficiency	0	1
Non-convulsive status epilepticus	0	1
Total	**11**	**86**

*When the patients died after withdrawal or discontinuation of ceftriaxone, we counted it both as a case of 'death', and as a case of 'withdrawal or discontinuation'.
ADRs, adverse drug reactions; RCTs, randomised controlled trials.

two cases.[19] Most cases of biliary pseudolithiasis and cholelithiasis were self-resolving after cessation of ceftriaxone.

Four prospective studies and eight retrospective studies reported 30 cases of nephrolithiasis, ureteral calculi and urinary sludge. Five of the 30 cases (16.7%) occurred alongside biliary precipitations. Eighteen cases (60%) reported clinical symptoms including anuria, oliguria, lumbar pain or GI symptoms (eg, abdominal pain, vomiting and diarrhoea). However, none of the studies reported renal function of patients before receiving ceftriaxone. Among the cases with prognosis reported, half of them were self-resolving. Three prospective cohort studies with a sample size of >100 patients assessed the risk of biliary or urinary precipitations and are described below.

Soyal *et al*[20] enrolled 114 patients who received ceftriaxone, and detected biliary sludge or cholelithiasis with biliary ultrasonography before the treatment of ceftriaxone and on the 5th, 10th day and the end of treatment. If biliary sludge or cholelithiasis was detected, sonographic examination was performed until the biliary precipitation disappeared. This study found that high daily dose (>2 g) and longer duration of treatment (>5 days) were the risk factors of biliary precipitation (OR 10.4, 95% CI 3.73 to 29.72; OR 3.4, 95% CI 1.31 to 9.83).[20] The radiologist who performed the ultrasonography did not know the route of ceftriaxone but probably knew that the patients received ceftriaxone. The diagnostic criteria of biliary sludge and cholelithiasis were not reported.

Palanduz *et al*[21] enrolled 118 patients given ceftriaxone for severe infection. Blood urea nitrogen and creatinine levels were measured in all patients when they entered the study and at the end of the antibiotic treatment. Serial sonograms of the gallbladder were obtained on days 1, 5–7 and 10–14 of ceftriaxone treatment and on the day after the treatment ended if the treatment lasted more than 2 weeks. Patients with abnormal ultrasounds were evaluated every 3 days until the abnormalities resolved. This study found 17% children (20/118), all asymptomatic, demonstrated sonographic abnormalities: 8 had gallbladder sludge, defined as echogenic material without associated acoustic shadowing, and 12 had pseudolithiasis, defined as echogenic material with acoustic shadowing. Whether the radiologists who performed the ultrasonography were blinded were not reported.

Mohkam *et al*[22] enrolled 284 patients given ceftriaxone for pyelonephritis. All patients had normal blood urea nitrogen, creatinine at enrolment. Renal ultrasound examination was performed before and between the 9th and 10th days of treatment. The third ultrasound examination was carried 3 months after discontinuation of ceftriaxone when patients were on hydration protocol (usage of at least 150 mL/kg of fluid per day). This study found renal stones in 1.4% children (4/284). The diagnostic criteria of nephrolithiasis and whether the radiologists who performed the ultrasonography were blinded were not reported.

Immune haemolytic anaemia

Thirty cases of immune haemolytic anaemia associated with ceftriaxone were all reported from case reports. These patients were aged from 0.7 to 17 years old. The doses of ceftriaxone were from 50 mg/kg/day to 4 g/day. Immune haemolytic anaemia was detected after a few minutes to 7 days of the first dose of ceftriaxone. Ten of the 30 patients had sickle cell disease as primary disease.

DISCUSSION

Our review found that GI ADRs were the most common toxicity of ceftriaxone in paediatric patients followed by hepatobiliary toxicity. Diarrhoea, nausea and vomiting were the most common ADRs among GI system, while biliary pseudolithiasis, cholelithiasis and biliary sludge were the most common among hepatobiliary system. Biliary precipitations and immune haemolytic anaemia were the most serious ADRs and most frequent reasons for discontinuation of ceftriaxone in paediatric patients.

Biliary pseudolithiasis and cholelithiasis are different stages of forming gallstones with approximately one in five children in prospective studies being affected. The incidence of urinary tract precipitations (stone or calculi) is lower than the incidence of biliary precipitations (pseudolithiasis or cholelithiasis) with approximately 15 in 1000 in prospective studies being affected. Our review found that most of the biliary precipitations were self-resolving after cessation of ceftriaxone. The limitations of the primary studies that assessed the risk of biliary or urinary tract precipitations are: first, the diagnostic criteria are unclear, and the terminology used for describing precipitations varied between studies. Second, the time point when examinations were performed varies. Third, the blinding of outcome assessors was poorly reported. Despite this, the fact that prospective studies suggest one in five children will develop biliary pseudolithiasis or cholelithiasis is of concern. A large prospective cohort study with clear diagnostic criteria and blinding of assessors would help establish the clinical significance of lithiasis following ceftriaxone.

Another serious ADR is haemolytic anaemia. The fact that it has only been reported in case reports suggests that it is uncommon. A systematic review of ceftriaxone-induced immune haemolytic anaemia in adults and children included 37 cases, of which 70% were children.[23] Mortality was 30% in all age groups and 64% in children. Seventy per cent of patients had an underlying condition, of which sickle cell disease was most commonly

reported. Previous ceftriaxone exposure was reported in 65% of the cases.[23] Sickle cell disease is associated with streptococcal infection, which is usually sensitive to benzylpenicillin.[24 25] The choice of ceftriaxone, a broad-spectrum antibiotic, is therefore an example of irrational prescribing. The predisposition of children with sickle cell disease to haemolytic anaemia following ceftriaxone suggests that this antibiotic should be avoided in children with sickle cell disease.

Our systematic review is the first review that systematically evaluated all categories of suspected ADRs associated with ceftriaxone in paediatric patients. We note several limitations of our review. First, since the assessment of safety was usually not the first objective in prospective studies, the pooled incidence of ADRs in our review might be underestimated for ADRs that do not need specified investigation (eg, nausea). However, the incidence of ADRs that need specified investigations (eg, biliary) might be overestimated. When the outcome assessors knew the treatment, they might over diagnose the ADRs (eg, biliary pseudolithiasis and cholelithiasis) that were reported by previous studies. Moreover, for ADRs that were only monitored in a few studies (eg, thrombocytosis), the incidence of ADRs calculated by our study must be viewed with caution. Second, we did not perform the subgroup analysis of different age groups because ADRs were not reported separately according to children's age groups in studies that enrolled patients of more than one age groups. We did not perform the subgroup analysis of different dosage because most patients received a dosage of 50–100 mg/kg/day. Third, we searched but finally did not include the reports from spontaneous ADR reporting databases as planned in the protocol, because the data from these databases failed to explicitly provide information on type of ADRs and characteristics of patients. We think these data gave limited information to our readers.

Ceftriaxone is a valuable broad-spectrum antibiotic in the management of severe sepsis. It is, however, one of many broad-spectrum antibiotics. The high risk of biliary pseudolithiasis and cholelithiasis, even if it appears to be reversible, is of concern. Further well-designed prospective studies evaluating the risk of lithiasis in comparison with other broad-spectrum antibiotics are needed.

In conclusion, our review found that GI ADRs were the most common toxicity of ceftriaxone in children. Diarrhoea, nausea and vomiting were the most common ADRs among GI system. Biliary pseudolithiasis and immune haemolytic anaemia were the most serious ADRs and the major reasons for discontinuation of ceftriaxone in children. Almost all biliary pseudolithiasis were reversible. Immune haemolytic anaemia was more likely in children with sickle cell disease and may cause death. Ceftriaxone should, therefore, be used with caution in children with sickle cell disease.

Contributors LNZ, IC and LLZ drafted the initial protocol; CW, MJ, KC, HZ, ZC and LH screened the literature and abstracted the data; LNZ and HL solved the discrepancy from the literature screening and data abstraction; LNZ drafted the initial paper; IC and LLZ revised the paper; and all the authors approved the final version.

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