

## Occurrence and Natural Course of Ceftriaxone-associated Pseudocholelithiasis in Indian Children: A Prospective, Observational Study

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### Abstract

**Objective:** To study the occurrence and natural course of ceftriaxone-associated pseudocholelithiasis in Indian children.

**Study design:** Prospective, observational study.

**Participants:** 153 children who received intravenous ceftriaxone during hospitalisation.

**Intervention:** A total of 153 children who received intravenous ceftriaxone during hospitalisation were enrolled in our study. Serial ultrasonography was performed to look for appearance and disappearance of biliary sludge, biliary calculi. Children who developed biliary sludge/calculi were also followed-up for symptoms of acute cholecystitis.

**Results:** The results from our study showed that, in Indian children there was less occurrence. A significant relationship ( $p$  value - 0.01) between the occurrence of pseudocalculi and the age of the patient was observed. Also, we noticed that the occurrence of ceftriaxone associated pseudocalculi and duration of ceftriaxone treatment were related ( $p$  value - 0.05), and took longer time to disappear. All the patients remained asymptomatic.

**Conclusion:** In all cases, ceftriaxone-associated pseudocholelithiasis was asymptomatic and reversible after its discontinuation. The study will create awareness among clinicians regarding its natural course in Indian children and prevent unwanted hasty surgical intervention.

### Introduction

Cholelithiasis, though not uncommon in adult population, is now increasingly being diagnosed in children in recent years due to the widespread availability of ultrasonography. There is not much information from India and no consensus among Indian paediatricians and paediatric surgeons regarding the management of cholelithiasis in children.

The aetiological causes of cholelithiasis in the paediatric age group are haemolytic anaemias (20% - 30%), total parenteral nutrition, ileal disease, congenital biliary disease<sup>1</sup> and drugs (like Ceftriaxone, Octreotide, Frusemide)<sup>2</sup>. Children with gall stones may be asymptomatic (20%) or can present with typical biliary symptoms (50%), non-specific symptoms (25%), or complicated (5% - 10%)<sup>1</sup>.

The global incidence of cholelithiasis in children is 0.13 - 0.3%<sup>3,4</sup>. Whereas in India, the prevalence is 0.35%<sup>5</sup>. Studies on cholelithiasis in children have shown a bimodal distribution, with a small peak in infancy and a steadily increasing incidence from early adolescence onwards<sup>6</sup>. There is a clear female preponderance during adolescence<sup>7</sup>.

Ceftriaxone is one of the most commonly used 3rd generation parenteral cephalosporins because of its wide spectrum of antimicrobial activity, long plasma half-life that allows once daily administration and its potential to penetrate the blood brain barrier. This drug is mainly eliminated in the urine, and to a lesser extent (40%) into bile<sup>8</sup>.

As far as drug induced cholelithiasis is concerned, ceftriaxone associated cholelithiasis is quite common in children, with an occurrence of about 15 - 57%. It occurs as early as the second day of initiation of treatment, is mostly asymptomatic and disappears in less than 2 months after discontinuation of the drug. The typical sonographic appearance of pseudolithiasis is an intense, mobile, echogenic material with acoustic shadow<sup>9-14,17</sup>.

The chemical composition of pseudolithiasis consists of fine lithogenic precipitates, mainly consists of cholesterol monohydrate and calcium bilirubinate. When the solubility product of calcium and unconjugated bilirubin exceeds, calcium bilirubinate precipitates<sup>15</sup>. It has also been observed that high doses of ceftriaxone are more likely to cause pseudolithiasis<sup>16</sup>.

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Ceftriaxone associated pseudolithiasis can be asymptomatic or lead to symptoms including biliary colic, cholecystitis, pancreatitis and cholangitis. Spontaneous resolution has been reported<sup>17</sup>.

At times unnecessary cholecystectomy may be carried-out on patients who are receiving ceftriaxone, due to paucity of data in Indian children. Hence, this prospective observational study was designed to assess occurrence and natural course of pseudocholelithiasis.

## Material and methods

This was a prospective, observational study conducted after ethics clearance, in the department of Paediatrics and Radiodiagnosis in a tertiary care teaching hospital in New Delhi, India, from November 2017 to March 2019. Any child admitted to this hospital with suspected or definite bacterial infection was eligible for the study, if the physicians in charge of the case had decided to start ceftriaxone therapy. A total of 153 patients who received intravenous ceftriaxone during hospitalisation were enrolled in our study. According to previous research, incidence of ceftriaxone associated pseudocalculi was between 10% to 47%. It was used to statistically arrive at sample size of 153.

Ultrasonography was done to assess biliary sludge, biliary calculi size on D0, D3, D7, D21 and further follow-up by ultrasound was done on D45, D60 till the findings disappeared.

Criteria for positive gallstones in ultrasound were the presence of mobile, gravity dependent, echogenic material accompanied by clear acoustic shadowing and sludge was diagnosed when hyperechogenic bile showed no acoustic shadowing. Patients who developed biliary sludge/calculi were followed-up for symptoms of acute cholecystitis like fever, vomiting, right hypochondrial pain. The respective days of appearance and disappearance of sludge and calculi were noted. Persistence of either stone or sludge beyond 60 days was to be followed-up to 6 months or disappearance whichever is earlier.

## Statistical analysis

Descriptive statistics was analysed with SPSS version 17.0 software. Continuous variables were presented as mean  $\pm$  SD. Categorical variables was expressed as frequencies and percentages. The Pearson's chi-square test or the chi-square test of association was used to determine if there was a relationship between two categorical variables.

P value less than 0.05 was considered to be statistically significant.

## Results

Among 153 cases taken for the study, 52.9% of the cases were male and 47.1% were female and gender was not a risk factor for ceftriaxone associated occurrence of biliary calculi. The pseudocalculi were seen in 32 (20.9%) cases. The mean duration of onset of occurrence of pseudocalculi was  $10.12 \pm 3.93$  days (with a range of 4 - 19 days).

The occurrence of calculi was significantly higher ( $p < 0.05$ ) in cases with age 3 - 6 years (26.8%), 6 - 9 years (21.2%) and more than 9 years (34.3%) compared to the cases with age less than 3 years (4.5%). We observed that there was an increase in occurrence of calculi with age.

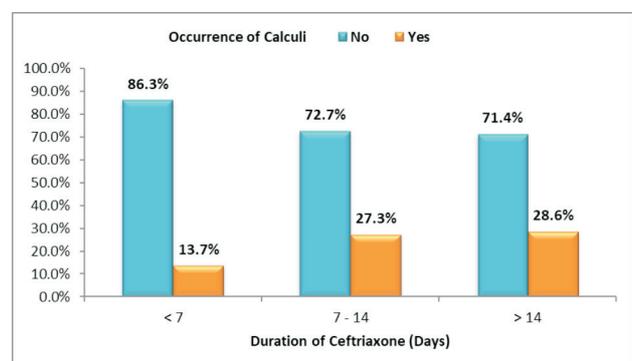
It was observed that the occurrence of calculi was higher (but not significant) in cases with ceftriaxone dose of 1,000 - 2,000 mg (18.3%), 2,000 - 3,000 mg (30.0%) and 3,000 - 4,000 mg (30.8%) compared to the cases with dose less than 1,000 mg (5.6%) (Table I).

**Table I: Relationship between occurrence of calculi and dose of ceftriaxone.**

Occurrence of Calculi	Mean (mg)	SD	Median	Mean rank	p value
No	1807	731.3	1700	71.86	0.005
Yes	2216	747.1	2050	96.45	

Also, there was a significant relationship between occurrence of calculi and duration of ceftriaxone. The occurrence of calculi was significantly higher in cases with duration 7 - 14 days (27.3%) compared to the cases with duration less than 7 days (13.7%). Further, the occurrence of calculi was higher (but not significant) in cases with duration more than 14 days (28.6%) compared to the cases with duration less than 7 days. Occurrence of pseudocalculi was seen as early as day 3 of ceftriaxone treatment in our study.

The disappearance of pseudo calculi was monitored. In our



**Fig. 1: Relationship between occurrence of calculi and duration of ceftriaxone.**

study, fourteen cases showed disappearance of pseudocalculi after D21 and D45, each. 1 case showed disappearance of pseudocalculi after D60. Two cases showed disappearance of pseudo calculi after D7. The mean duration of disappearance of pseudocalculi was 30 days.

The mean value of serum alkaline phosphatase at which occurrence of pseudocalculi was seen was in a range of 144 IU/L to 402 IU/L with a mean of  $253.25 \pm 74.17$  IU/L and it was not statistically significant. All the cases remained asymptomatic.

Out of the 153 cases in our study, 23 patients showed occurrence of ceftriaxone associated biliary sludge (15%), with both the genders equally affected. A significant relationship between occurrence of sludge and age was seen, there was a significantly higher occurrence of sludge in cases with age 3 - 6 years (26.8%) compared to the cases with age less than 3 years (6.8%). Similar to the occurrence of pseudocalculi and its relationship with dosage of ceftriaxone, there was no relationship between occurrence of sludge and pseudocalculi with weight, height and dose of ceftriaxone.

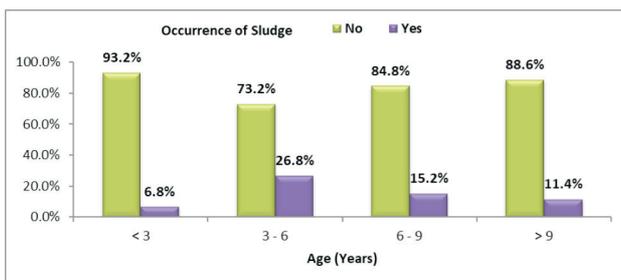


Fig. 2: Relationship between occurrence of biliary sludge and age.

Table II: Relationship between occurrence of sludge and duration of ceftriaxone.

Duration of ceftriaxone (Days)	Occurrence of sludge		Total	p value
	No	Yes		
< 7	67 (91.8%)	6 (8.2%)	73	-
7 - 14	53 (80.3%)	13 (19.7%)	66	0.056
> 14	10 (71.4%)	4 (28.6%)	14	0.040
Total	130 (85.0%)	23 (15.0%)	153	-

The occurrence of sludge was significantly higher in cases with duration more than 14 days (28.6%) compared to the cases with duration less than 7 days (8.2%). Further, the occurrence of sludge was slightly higher, but not significant in cases with duration 7 - 14 days (19.7%) compared to the cases with duration less than 7 days.

In our study, out of the 13 cases who developed ceftriaxone associated biliary sludge, 11 cases showed disappearance

of sludge by D21, 7 cases showed disappearance of sludge by D7 and 5 cases showed disappearance of sludge by D45 (mean of disappearance was 38 days).

## Discussion

An assessment of ceftriaxone-induced pseudolithiasis as per age, dosage, duration onset and disappearance was done in 153 patients.

The age distribution of pseudocalculi in our study was similar to the study by Schaad *et al* in 1988<sup>18</sup>. We too have reported an increase in occurrence of calculi with age, however occurrence was on the lower side, i.e., 20.9% versus 40% by Schaad *et al*<sup>18</sup>.

The correlation between dosage and occurrence was not dissimilar to the study by Schaad *et al* who reported a reversible ceftriaxone associated gallstone in 40% children following high doses of ceftriaxone<sup>19</sup>. In our study it was observed that the occurrence of pseudocalculi was higher (but not significant, may be due to lack of samples in the group < 1,000 mg) in cases with dose 1,000 - 2,000 mg (18.3%), 2,000 - 3,000 mg (30.0%) and 3,000 - 4,000 mg (30.8%) compared to the cases with dose less than 1,000 mg (5.6%).

In a study by Soysal *et al*, it was observed that probability of ceftriaxone associated pseudolithiasis increases if the duration of ceftriaxone is over five days<sup>10</sup>. We also found that there was a significant relationship between occurrence of pseudocalculi and duration of ceftriaxone as per results. The occurrence of calculi was significantly higher in cases with duration 7 - 14 days (27.3%) compared to the cases with duration less than 7 days (13.7%). Further, the occurrence of calculi was higher (but not significant, may be due to lack of samples in the group > 14 days) in cases with duration more than 14 days (28.6%) compared to the cases with duration less than 7 days.

According to our study, 14 cases showed disappearance of pseudocalculi after D21 and D45, each. One case showed disappearance of pseudocalculi after D60, 2 cases showed disappearance of pseudocalculi after D7. The mean duration of disappearance of pseudocalculi was 30 days. Our findings are in agreement with the study conducted by Schaad *et al*, in which the biliary precipitates had completely resolved 2 to 63 days (mean 15 days) after the end of treatment<sup>10</sup>.

All the patients who developed pseudocalculi in our study were asymptomatic. This aspect is in contrast to the study done by Schaad *et al* in which 3 out of the 16 patients with gallbladder calculi (19%) had unequivocal biliary symptoms (colicky upper abdominal pain, nausea, and vomiting); ceftriaxone was therefore discontinued and symptoms resolved after 2, 3, and 5 days<sup>1</sup>.

Occurrence of sludge in our study (15 %), with both the genders equally affected was nearly similar to the study by Avci *et al*, in which the incidence of sludge was 10 - 25%<sup>20</sup>.

There was a significantly higher occurrence of sludge in cases with age 3 - 6 years (26.8%) compared to the cases with age less than 3 years (6.8%). In a study conducted by Soysal *et al* biliary sludge was found to be more common among younger patients<sup>10</sup>. There was no relationship between occurrence of sludge and dose of ceftriaxone in the present study.

The sludging of bile was correlated with the duration of ceftriaxone. This is in accordance with a study which showed that Ceftriaxone is crystallised with free calcium in dose- and time-dependent manner<sup>21</sup>.

In general, the formation of biliary sludge can be expected to take 3 to 22 days after beginning ceftriaxone therapy and it may be reversible upon discontinuation of the drug with a range of 2 to 63 days after the end of treatment<sup>17</sup>. In our study the mean duration of appearance was  $6.3 \pm 5.0$  days and disappearance of sludge was 38 days.

**Table III: Comparison between occurrence of ceftriaxone-associated biliary pseudocalculi and sludge.**

	Biliary pseudocalculi	Biliary sludge
Occurrence	32 (20.9%)	23 (15.0%)
Age (Years)	$7.7 \pm 3.2$	$6.5 \pm 3.0$
Male: Female ratio	1:1	11:12
Weight (Kg)	$22.0 \pm 7.3$	$19.78 \pm 7.0$
Height (cm)	$117.4 \pm 18.24$	$110.6 \pm 17.38$
BMI (Kg/m <sup>2</sup> )	$15.50 \pm 1.607$	$15.59 \pm 1.599$
Relation with dosage	Yes	No
Duration of onset of appearance (Days)	$12 \pm 3.9$	$6.3 \pm 5.0$
Mean duration of disappearance (Days)	30	38
Symptoms	No symptoms of cholangitis/ cholecystitis/ pancreatitis	No symptoms of cholangitis/ cholecystitis/ pancreatitis

There are many unreported cases of surgical intervention in such pseudocholelithiasis and awareness of ceftriaxone induced cholelithiasis by the physician can certainly avert such eventualities, and patient can be managed conservatively.

It is concluded that ceftriaxone induced pseudolithiasis is not uncommon in Indian children and the paediatrician/physician must be aware of regular follow-ups to establish

its disappearance with due course of time. The study sensitizes the treating physician and will prevent medicolegal implications. The study opens up more research opportunities to closely monitor other cephalosporin treated patients regarding possible cholelithiasis.

### Key messages

The incidence of ceftriaxone-induced pseudocholelithiasis in paediatric age group is (10 - 40%) which may be symptomatic. No study has been conducted in Indian children. As per this study, the occurrence of ceftriaxone associated pseudocholelithiasis in Indian children is lesser (20.9%), asymptomatic and takes longer duration to resolve and has strong correlation with increasing age and duration of therapy. A watchful expectancy, rather than surgery, is advisable in such type of patients who are treated with ceftriaxone.

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