ANDES PEDIATRICA
REVISTA CHILENA DE PEDIATRÍA
www.scielo.cl

Andes pediatr. 2025;96(5):613-618
DOI: 10.32641/andespediatr.v96i5.5602

ORIGINAL ARTICLE

Incidence, evolution and clinical behavior of pseudocholelithiasis associated with ceftriaxone in children

Incidencia, evolución y comportamiento clínico de la pseudocolelitiasis asociada a ceftriaxona en niños

Diego Andrés Rodríguez Rangel[a,b], **Laura Daniela Arenas Camacho**[b,d], **Nicolas Andres Quiroga Barrera**[b,d], **Angie Daniela Lizarazo**[b,d], **Zully Marley Navas Casas**[b,d], **Hugo Ferreira Traslaviña**[a], **Juan Carlos Uribe Caputi**[c]

[a]Clínica Sanluis. Santander, Colombia
[b]Universidad de Santander. Santander, Colombia.
[c]Universidad Autónoma de Bucaramanga. Grupo de Investigación Observatorio de Salud Pública de Santander. Santander, Colombia.
[d]Residente de Pediatría.

Received: January 28, 2025; Approved: May 15, 2025

What do we know about the subject matter of this study?

Clinical series suggest that ceftriaxone-associated pseudocholelithiasis is a common, underdiagnosed, and underestimated complication that can cause abdominal pain and jaundice and can lead to serious complications such as acute cholangitis.

What does this study contribute to what is already known?

A prospective, protocolized monitoring of pseudocholelithiasis development was conducted on children who were treated with ceftriaxone, with this complication identified in one-third of them. Abdominal pain occurred in almost half of the patients and resolved spontaneously. The main risk factors were age over 5 years, low fluid intake, and overweight and obesity.

Abstract

Ceftriaxone-associated pseudocholelithiasis is common but underdiagnosed in children, occurring in up to half of those receiving ceftriaxone. Although self-limiting, it is frequently accompanied by symptoms. **Objective:** To report the incidence, course, risk factors, and clinical behavior of pseudocholelithiasis in children receiving ceftriaxone. **Patients and Method:** Prospective, descriptive, observational case series study. Patients aged 1 month to 18 years who received ceftriaxone were included. Clinical follow-up and hepatobiliary ultrasound were performed at the start of treatment and every 5 days until complete resolution. Association with risk factors was explored. Statistics used included Pearson's chi-square test and Fisher's exact test. **Results:** Eighty patients were included, 51.2% were male, median age 4.5 years (range 5 months to 17 years). The prevalence of pseudocholelithiasis was

Keywords:
Ceftriaxone;
Pseudocolelithiasis;
Gallbladder;
Bile;
Children

Correspondence:
Diego Andres Rodriguez
drodriguez_rangel@hotmail.com.

Edited by:
Pablo Cruces Romero

How to cite this article: Andes pediatr. 2025;96(5):613-618. DOI: 10.32641/andespediatr.v96i5.5602

35% (28 patients), documented in 6 and 27 patients during the first and second ultrasound (21.4% and 96.4%). Pseudocholelithiasis was significantly more frequent in the age group older than 5 years, those with lower fluid intake, obese, overweight, and very rare in malnourished patients (all $p < 0.05$). Twelve patients presented abdominal pain as a cardinal symptom (42.9%). The mean duration of the stones was 19.1 (5-44) days. **Conclusion:** Ceftriaxone-associated pseudocholelithiasis is common, occurring in 1 out of 3 children who receive it. Its main risk factors were age over 5 years, lower fluid intake, overweight, and obesity. Abdominal pain is frequent, and the progression was self-limited.

Introduction

Ceftriaxone is a third-generation cephalosporin widely used in pediatrics due to its bactericidal action, broad spectrum, long half-life, and good bioavailability[1,2]. About 40% is eliminated by bile, leading to high concentrations in the gallbladder lumen, where it behaves as an anion that promotes the precipitation of calcium salts[2] and affects gallbladder motility, slowing its emptying and promoting precipitation[3]. It is well tolerated, although biliary sludge and pseudocholelithiasis frequently occur in children with its use[2,4,5].

Risk factors include treatment lasting more than 5 days[6], high doses, age under 12 months, prolonged fasting[7], conditions that promote slow emptying of the gallbladder (total parenteral nutrition or major abdominal surgery)[2,8,9], hypercalcemia[10], and impaired renal function since 60% of the drug is eliminated by the kidneys[8]. There are very few cases in the literature that report pseudocholelithiasis due to ceftriaxone in adults[11,12], but they show a similar incidence[12].

The first reports date back to 1986[13], and since 1988, the self-resolving nature of the condition after discontinuing the drug has been described[14,15]. Current publications describe its incidence as 15 to 57%, and in most cases, it is described as asymptomatic and self-resolving[4,6,7,8,15,16,17,18,19] upon discontinuation of the drug[10,20,21]. Complications have been reported[22], such as necrotizing cholecystitis[23], choledocholithiasis[24], and cholangitis[25].

Our objective was to characterize the incidence, evolution, risk factors, and clinical behavior of pseudocholelithiasis in children who received ceftriaxone.

Patients and Methods

Descriptive observational case series study with prospective data collection. Patients aged 1 month to 18 years who received ceftriaxone for a minimum of 5 days at a tertiary health care institution in Bucaramanga, Colombia, were included. The drug was diluted according to the manufacturer's recommendations, with a 1-hour infusion time. The first ultrasound of the bile duct was performed before the second dose of the drug (start of treatment) and then every 5 days until the end of treatment. Exclusion criteria were a diagnosis of cystic fibrosis, hypercholesterolemia, hemolytic disease, a history of bile duct surgery, and discontinuation of ceftriaxone before completing 5 days. Those identified with pseudocholelithiasis were seen weekly with assessments for abdominal symptoms and serial ultrasound monitoring until complete resolution was confirmed.

Ultrasound of the liver and bile ducts was performed by the same pediatric radiologist using Canon Xario® 100G equipment and 3-5 MHz convex transducers and 7-12 MHz linear transducers with 3.5 and 7 MHz transducers. Pseudolithiasis was defined as the presence of biliary sludge, single or multiple stones in the gallbladder[4,5,7].

The response variable was having pseudocholelithiasis, and the exposure variable was receiving ceftriaxone. The following were evaluated as predictor variables: duration of treatment, fasting, ceftriaxone dose, amount of fluids administered, nutritional status, and age. The exposure variable (ceftriaxone treatment) was measured in days and in doses per mg/kg/day, and the response variable (the presence of stones) was measured according to criteria established by the study radiologist. Descriptive statistics were used for data analysis using the Stata v14 software. For the description of quantitative variables, measures of central tendency such as the mean or median were used according to their behavior, and for qualitative variables, frequencies and percentages were used. The variables were described uni- and bivariately with respect to the outcome of interest, presence of stones, using Pearson's chi-square test and Fisher's exact test with a significance level of 5% (0.05).

Written informed consent to participate in the study was requested from parents or guardians, who were informed that they could withdraw at any time. The researchers did not intervene during the antibiotic treatment and limited themselves to informing the treating physician of the ultrasound results. The study was approved by the ethics committee of the *Clínica Sanluis* and the *Universidad de Santander* (UDES).

Results

Eighty-eight children were invited to participate in the study, of whom 80 (90.9%) met the inclusion criteria, with an exclusion rate of 9.1% (change of antibiotic n = 6 and withdrawal from the study n = 2). Of the patients included, 39 were female (48.8%) and 41 were male (51.2%), with a median age of 4.5 years (range 5 months to 17 years). 18.7% of the patients presented malnutrition, 3.7% were overweight or obese, and the remaining 77.5% had age-appropriate anthropometric measurements. Table 1 shows the diagnoses for which they received ceftriaxone. All included patients were followed up completely, with a maximum of nine ultrasounds per patient. Figure 1 shows the flowchart of the study participants.

The average number of days of treatment was 9.6 days (5 to 18 days), and the average dose was 94.7 mg/kg/day (range 25 to 118 mg/kg/day; 70.1% received doses of 100 mg/kg/day) (Table 2). Pseudolithiasis was observed in 28 cases, corresponding to a prevalence of 35%. There was a tendency toward a higher prevalence in females (41% vs. 29.2%; RR 0.71, CI 0.38-1.3; p = 0.27). The first ultrasound (day 5 of treatment) showed 21.4% of pseudocholelithia-

Table 1. Diagnoses for which ceftriaxone was prescribed

Acute sinusitis	Frequency (%)
Acute mastoiditis	33.8% (27)
Pneumonia	26.3% (21)
Urinary tract infection	25% (20)
Acute bacterial diarrhea	10% (8)
Acute meningitis	3.8% (3)
Meningitis aguda	1.3% (1)

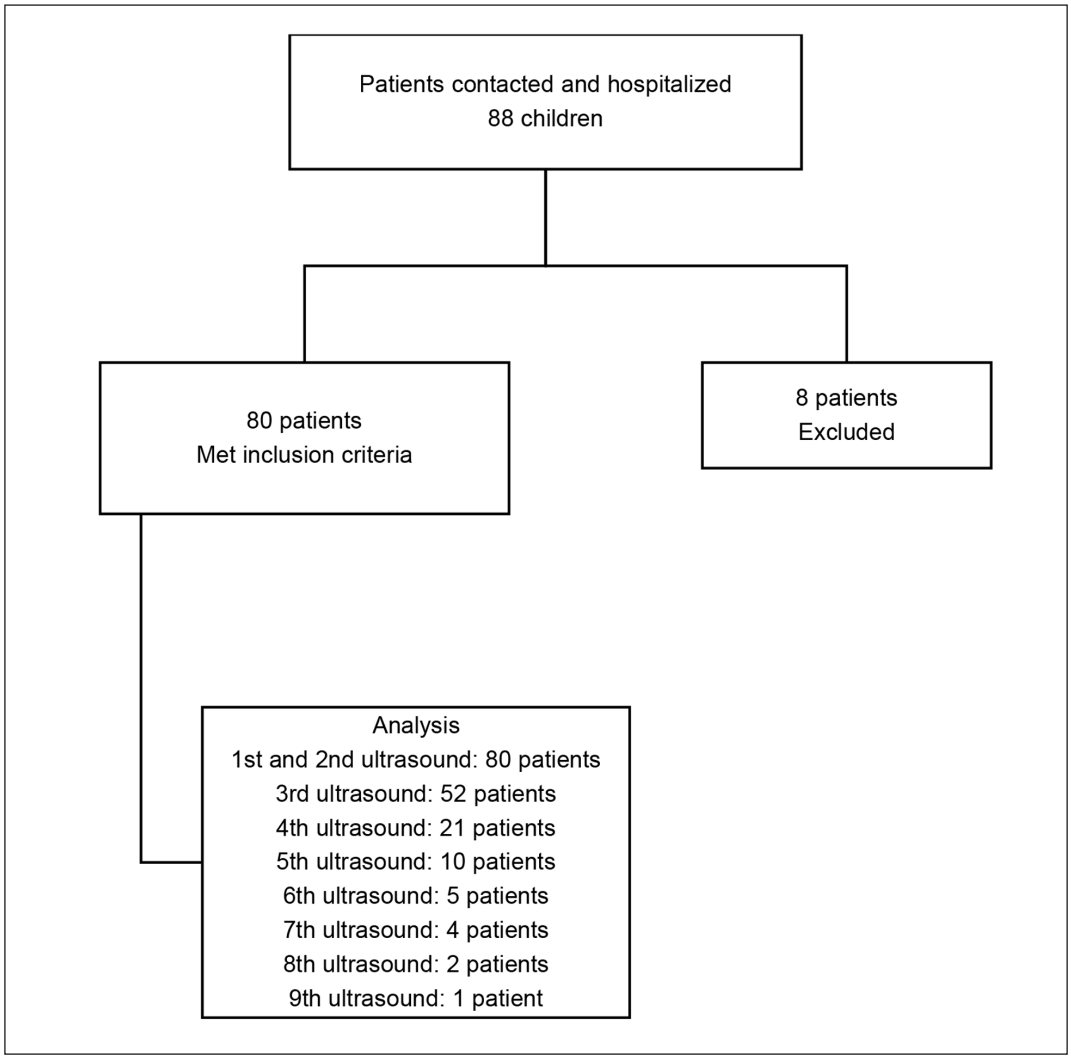

Figure 1. Follow-up patient's flowchart received ceftriaxone

Table 2. General characteristics of patients who received ceftriaxone

Demographic and clinical variables of the participants	
Age range	
Under 2 years old	N: 11 (13.7%)
From 2 to 5 years old	N: 33 (41.2%)
Over 5 years old	N: 36 (45%)
Gender	
Female	N: 39 (48.7%)
Male	N: 41 (51.2%)
Nutritional classification	
Malnutrition	N: 15 (18.7%)
Eutrophic	N: 62 (77.5%)
Overweight	N: 2 (2.5%
Obesity	N: 1 (1.25%)
Fluid therapy	
Saline solution 0.9%	N: 73 (91.2%)
Ringer's lactate	N: 5 (6.2%)
SSN dextrose	N: 2 (2.5%)
Amount of fluids administered	
Basal fluids (oral and venous)	N: 66 (82.5%)
Fluids greater than basal	N: 14 (17.5%)
Treatment days	Minimum value 4 days Maximum 18 days Average 9.56 days
Ceftriaxone dose range	
Less than 75 mg/kg/day	N: 10 (12.5%)
From 75 to 100 mg/kg/day	N: 67 (83.75%)
More than 100 mg/kg/day	N: 3 (3.75%)
Fasting for more than 24 hours	N = 10 (12.5%)

SSN: Isotonic Normal Saline Solution.

sis (6 patients), the second one (day 10 of treatment) showed 96.4% (27 patients out of 28 positive), and the third one (day 15 of treatment) showed 100% of pseudocholelithiasis. Positive patients were followed up for up to 44 days after the start of treatment, and the mean duration of pseudocholelithiasis was 19.1 (5-44) days. 12 patients with pseudocholelithiasis (42.9%) presented with abdominal pain, while 4 and 2 presented with nausea and 2 with abdominal distension as an additional symptom. In three cases, it was necessary to discontinue ceftriaxone treatment due to pain, and one case required management in the emergency department due to suspected cholangitis, receiving analgesics and intravenous antibiotics.

Statistical analysis of the factors associated with pseudocholelithiasis showed that it was more prevalent in children over 5 years of age than in those between 2 and 5 years of age (42.2% vs. 33.3%, respectively; p = 0.01), with no cases identified in children under 2 years of age. It was also more prevalent in patients who received less total fluid intake than their baseline requirements (40.9% vs. 7.1%; p = 0.016) and in obese and overweight patients, and was very rare in patients with malnutrition (66.7% vs. 6.7%; p = 0.013). No relationship was found between pseudocolelithiasis and the type of intravenous fluids received or fasting periods, with a tendency toward higher frequency with doses > 100 mg/kg/day (p = 0.41).

Discussion

In this study, we conducted a prospective clinical and ultrasound follow-up in a cohort of pediatric patients who received ceftriaxone, and our main findings were consistent with those reported in a Colombian study more than 10 years ago[26]. It occurs in approximately 1 in 3 exposed children, is self-resolving, and frequently causes symptoms, although in the current study, compared to the previous one, the frequency of symptoms was much higher (42% vs. 22%). This contrasts with some publications that describe it as oligosymptomatic[17,18]. Regarding its prevalence, there are few studies in Latin America on ceftriaxone-associated pseudocolelithiasis[26,27]. An incidence of 42.5% is described in a group of 73 children in Bogotá[26], its onset was 5 days after receiving the drug, and 25% had some associated symptoms.

Regarding the risk factors, it has been reported that prolonged treatment[12] and high doses in children under 12 months of age and fasting[13] promote the precipitation of calcium salts of ceftriaxone[2] and the onset of pseudocholelithiasis. However, we did not observe any relationship with treatment duration or dose, and, contrary to what has been published, there were no cases in children under 2 years of age. Multivariate analyses were performed to find an explanation for this association that goes beyond what is described in the literature. No relationship was found with the dose of the medication, which could be the most likely hypothesis; but there was a relationship with a higher volume of fluids administered in the group of children under 5 years of age, which could have "protected" them from developing pseudocholelithiasis. However, this association was not statistically significant. In the two series of Colombian children, it was less frequent in those who received a higher intake of intravenous fluids, suggesting that maintaining adequate hydration

is a protective factor, considering that 60% of the drug is eliminated in urine[2,12].

Pseudolithiasis caused by ceftriaxone occurs early, with only 5 days of treatment. 21.4% of the patients presented it, which is less than what was observed in the previous series, where more than 90% presented it after 5 days, and is consistent with a prospective study that evaluated 44 children, finding a prevalence of 25%, and 54.5% developed it in the first 3 days of treatment[15]. Obesity and overweight are described and accepted risk factors for cholelithiasis; in our case, a higher prevalence of ceftriaxone-associated pseudocholelithiasis was documented in obese and overweight children, which is not described in the literature[6,10] and is probably related to the increased risk of gallstone formation determined by excess weight and associated metabolic alterations.

Regarding the clinical course, ceftriaxone-associated pseudocholelithiasis in children is a condition that resolves spontaneously when the drug is discontinued[6,13], which has been observed in both series. However, there are reports in the literature of severe cases such as necrotizing cholecystitis[19] or cholangitis[25]. It is unclear whether the medication should be discontinued once pseudocholelithiasis is identified or if it is possible to complete the initially planned course of treatment. Considering that stone resolution usually occurs between 5 and 44 days after treatment ends, the most reasonable recommendation seems to be that this decision should be guided by symptoms or associated complications.

In general, the prognosis for ceftriaxone-associated pseudocholelithiasis is good, and, although its management is still controversial[27,28,29], the trend is toward conservative management, with local experiences showing that 100% of stones have resolved 55 days after discontinuing treatment[26]. It has been suggested that improving the hydration status of patients receiving ceftriaxone could have an impact on reducing its incidence[30], especially in patients with impaired renal function[31,32] and in those receiving higher doses for longer periods[33], as well as modifying its use in patients with prolonged fasting[29].

A limitation of this study is that it does not have a control group of patients with similar baseline conditions receiving other types of treatment or antibiotics, in whom the risk of pseudocholelithiasis associated with or increased by other interventions is evaluated.

In conclusion, a high incidence of ceftriaxone-associated pseudocholelithiasis is observed. Overweight, obesity, and age over 5 years were identified as risk factors, while better hydration appeared to be protective. Although the course was generally self-limiting, a significant proportion of patients presented symptoms. It is important that children receiving ceftriaxone follow administration protocols that ensure adequate fluid intake, clinical monitoring of symptoms, and consideration of hepatobiliary ultrasound in cases where clinical suspicion or symptoms warrant it, or in the identified risk groups.

Ethical Responsibilities

Human Beings and animals protection: Disclosure the authors state that the procedures were followed according to the Declaration of Helsinki and the World Medical Association regarding human experimentation developed for the medical community.

Data confidentiality: The authors state that they have followed the protocols of their Center and Local regulations on the publication of patient data.

Rights to privacy and informed consent: The authors have obtained the informed consent of the patients and/or subjects referred to in the article. This document is in the possession of the correspondence author.

Conflicts of Interest

Authors declare no conflict of interest regarding the present study.

Financial Disclosure

Authors state that no economic support has been associated with the present study.

References

1. Chadwick EG, Connor E, Shulman S, Yogev R. Efficacy of ceftriaxona in treatment of serious childhood infections. J Pediatr. 1983;103:141-5.
2. Stevens R, Rodman P, Rodman J. Pharmacokinetics of antimicrobial therapy. Semin Pediatr Infect Dis. 1998;4:273-80.
3. Arpacık M, Ceran C, Kaya T, Karadas B, Sarac B, Koyluoğlu G. Effects of ceftriaxone sodium on in vitro gallbladder contractility in guinea pigs. J Surg Res. 2004; 122:157-61.
4. Olóndriz O. Seudolitiasis vesicular transitoria (barro biliar) como complicación del tratamiento con ceftriaxona. Bol. S. Vasco-Nav. Pediatr. 2002; 36:38-9.
5. Araz N, Okan V, Demirci M, Araz M. Pseudolithiasis due to ceftriaxone treatment for meningitis in children: Report of 8 cases. Tohoku J. Exp. Med. 2007; 211:285-90.
6. Soysal A, Eraşov K, Akpınar I, Bakır M. Biliary precipitation during ceftriaxone therapy: Frequency and risk factors. Turk J Pediatr. 2007;49:404-7.
7. Ozturk A, Kaya M, Zeyrek D, Ozturk E, Kat N, Ziylan Z. Ultrasonographic findings in ceftriaxone: Associated biliary sludge and pseudolithiasis in children. Acta Radiol. 2005; 46(1):112-6.
8. Bor O, Dinleyici E, Kebapci M, Aydogdu D. Ceftriaxone-associated biliary sludge and pseudocholelithiasis during childhood: A prospective study. Pediatr Int. 2004; 46:322-4.
9. Cerana C, Oztoprakb I, Cankorkmaza L, Gumuşb C, Yildiza T, Koyluoglu G. Ceftriaxone-associated biliary pseudolithiasis in paediatric surgical patients. J Antimicrob Agents. 2005; 225(3):256-9.
10. Zaki SA, Shanbag P. Biliary pseudolithiasis secondary to ceftriaxone therapy. Indian J Pharmacol. 2010; 42(3):193-4.
11. Bickford C, Spencer A, Spencer P. Biliary sludge and hyperbilirubinemia associated with ceftriaxone in an adult: Case report and review of the literature. Pharmacotherapy. 2005; 25(10):1389-95.
12. Heim-Duthoy K, Caperton E, Pollock R, Matzke G, Enthoven D, Peterson PK. Apparent biliary pseudolithiasis during ceftriaxone therapy. Antimicrob Agents Chemother. 1990; 34:1146-9.
13. Schaad UB, Tschäppeler H, Lentze MJ. Transient formation of precipitations in the gallbladder associated with ceftriaxone therapy. Pediatr Infect Dis. 1986;5(6):708-10.
14. Schaad UB, Wedgwood-Krucko J, Tschaeppeler H. Reversible ceftriaxone-associated biliary pseudolithiasis in children. Lancet. 1988;17(8625):1411-3.
15. Papadopoulou F, Efremidis S, Karyda S, et al. Incidence of ceftriaxone-associated gallbladder pseudolithiasis. Acta Pediatr. 1999; 88: 1352-5.
16. Alehossein M, Nasoohi S, AkhtarKhavari H. Ceftriaxone Induced Biliary Pseudolithiasis in children: Report of 14 Cases. Iran J Pediatr. 2008; 18:31-7.
17. Palanduz A, Yalçin I, Tonguç E, et al. Sonographic assessment of ceftriaxone-associated biliary pseudolithiasis in children. J Clin Ultrasound.. 2000; 28(4):166-8.
18. Bustos R, Barrientos L, Fernández P. Pseudolitiasis biliar inducida por ceftriaxona. Rev chil pediatr. 2001; 72:40-4 .
19. Azarkar G, Mahi Birjand M, Ehsanbakhsh A, Bijari B, Reza Abedini M, Ziaee M. Ceftriaxone-associated nephrolithiasis and gallstone in adults. Drug Healthc Patient Saf. 2018;10:103-8.
20. Kutuya N, Ozaki Y. A symptomatic child with ceftriaxone-associated biliary pseudolithiasis. J Med Ultrasonics. 2008;35:125-8.
21. Reyes-Hernández D, Reyes-Hernández U, Reyes-Gómez U, et al. Dos casos de pseudolitiasis biliar en niños asociada a la ceftriaxone. Rev Mex Pediatr. 2012; 79(5):236-9.
22. Sienra MC, Pereira Núñez D, Pacheco H, Juambeltz C. Complicaciones por pseudolitiasis vesicular y nefrolitiasis asociada a ceftriaxona. Reporte de caso. Cir Pediatr. 2020;33:149-52.
23. Kathleen S, Puder G. Acute necrotizing cholecystitis: a rare complication of ceftriaxone-associated pseudolithiasis. Pediatr Surg Int. 2006;22:562-4.
24. Yamabe A, Irisawa A, Wakabayashi H, Tsunoda T, Tominaga K. Ceftriaxone-associated Pseudolithiasis in the Gallbladder and Bile Duct of an Elderly Patient. Intern Med. 2020; 59: 2725-8.
25. Rodríguez DA, Bustacara M, Pinilla AP, Henao L. Coledocolitiasis y colangitis como complicación del uso de ceftriaxona en niños: reporte de caso. Infectio. 2012;16(3):187-90.
26. Rodríguez Rangel DA, Pinilla Orejarena AP, Bustacara Diaz M, et al. Cálculos biliares asociados al uso de ceftriaxona en niños. An Pediatr (Barc). 2014;80(2):77-80.
27. Teixeira Brandt C, Santos Cavalcanti M, Naara M, Soares M, Bandin Cruz D. Biliary Lithiasis Associated with the Use of Ceftriaxone for Gastroenteritis in Children: Case Report and Literature Review. Clin Surg. 2017; 2: 1455-9.
28. Biner B, Oner N, Celtik C, et al. Ceftriaxone-associated biliary pseudolithiasis in children. J Clin Ultrasound. 2006; 34:217-22.
29. Oggiano AM; Clemente M, Cuzzolin L, Locci C, Piredda CM, Schwarz K, Antonucci R. Pharmacological treatment of ceftriaxone-related cholelithiasis in children: is it worthwhile?. J Ped Neo Individ Med. 2019;8(1):e080108.
30. Fan L, Lau P, Kapur J, Krishnan S, Karthik V. Ceftriaxone-induced pseudolithiasis: not just a theoretical risk. Singapore Med. J 2017; 58(11):676-7.
31. Yamada S, Takesako M, Nakano T, Tsuruya K, Kitazono T. Rapid formation of large pseudostones and acute cholangitis caused by ceftriaxone treatment for bacterial pneumonia in a patient on kidney transplantation: potential risk of ceftriaxone use in patients with decreased kidney function. CEN Case Reports. 2020, 9:87-8.
32. Oyama Y, Iwafuchi Y, Narita I. Ceftriaxone-associated pseudolithiasis in hemodialysis patients: a case series study. Renal Replacement Therapy. 2021, 7(6); 3-8.
33. Young Choi Y, Hwa Jung Y, Mun Choi S, Seung Lee C, Kim D, Yul Hur K. Gallbladder pseudolithiasis caused by ceftriaxone in young adult. J Korean Surg Soc. 2011;81:423-6.