Ceftriaxone-associated side effect findings in children's abdominal ultrasonography

Dr. Sc. Dorina DERVISHI
Faculty of Medical Technical Sciences,
European University of Tirana, Albania
Corresponding author: E-mail: dorina.dervishi@uet.edu.al

MD. Blerina SARACI
Faculty of Medicine,Tirana, Albania /UHC Mother Theresa
Tirana, Albania

MD. Sara ZAVALANI
Aura Clinic, Tirana, Albania

Dr. Sc. Elvana RISTA
Department of Internal Medicine, Hygeia Hospital, Tirana,
Albania

Abstract

Introduction: *Ceftriaxone is a third-generation cephalosporin, which has a broad spectrum of activity against Gram-negative and Gram-positive bacteria. It can sometimes induce biliary sludge or stone formation because of the interaction with Calcium ions.*

The aim of this study is to describe the epidemiology of the side effects after the ceftriaxone therapy in hospitalized pediatric patients and to follow up the group of suspected Ceftriaxone-induced adverse effects.

Methods: *This prospective study was conducted in different Pediatric Services of the University Hospital Center "Mother Theresa", Tirana, during the period October 2021-March 2022. We studied the ultrasonographic data of 80 patients admitted to these services, who had been on Ceftriaxone therapy.*

Results: *All the females aged from 5-10 years old, and males aged from 6-12 years old, underwent ultrasound examination for other reasons and 21.25% of the cases resulted with pseudolithiasis, while 3.75% with nephrolithiasis. According to the total number of cases, 70.6% of them were asymptomatic. Only 29.4 % of the patients referred right upper quadrant pain and 1 of them showed nausea. The symptoms begun from 5th-7th day and last 20 days. The ultrasound imaging performed from 5th- 10thdays after Ceftriaxone administration, showed gallbladder sludge and pseudolithiasis in the symptomatic patients, ranged 8-12 mm, and renal microlithiasis <3mm. These patients were followed with ultrasound exam after 1 month.*

Conclusion: *From all pediatric patients treated with Ceftriaxone and followed with ultrasonography, 21.25% resulted with collateral associated gallbladder pseudolithiasis as side effect from ceftriaxone-therapy, found by ultrasonographic evaluation. None of the cases was complicated with gallbladder hydrops, pancreatitis or hydronephrosis. After the Ceftriaxone therapy was discontinued, the condition resolved spontaneously.*

Key Words: *ceftriaxone, gallbladder pseudolithiasis, nephrolithiasis, ultrasound*

Introduction

Ceftriaxone is a third-generation cephalosporin, which has a broad spectrum of activity against anaerobic and aerobic Gram-negative and Gram-positive bacteria (Richards et. al., 1984).

From 33 to 67% of a ceftriaxone dose is excreted in the urine as unchanged portion while the remainder is secreted in the bile and found in the feces as inactive compounds (www.accessdata.fda.gov/drugsatfda_docs/label/2009/0550585s063lbl.pdf).

It can sometimes induce biliary sludge or stone formation as a Calcium-Ceftriaxone salt, because of the interaction with Calcium ions (Katzung, 2018; Shiffman et al., 1990; Park et al., 1991; Schmutz et al., 2011). Most of the cases affected by this condition are adults and elderly people but also children can develop it (Yoshida et al., 2019; Hotta et al., 2021; Papadopoulou et al., 1999; Prince and Senac, 2003; Ozturk et al., 2005; Araz et al., 2007).

The aim of this study is to describe the distribution, frequency, and pattern of the side effects after the ceftriaxone therapy in hospitalized pediatric patients and to follow up the group of suspected Ceftriaxone-induced adverse effect.

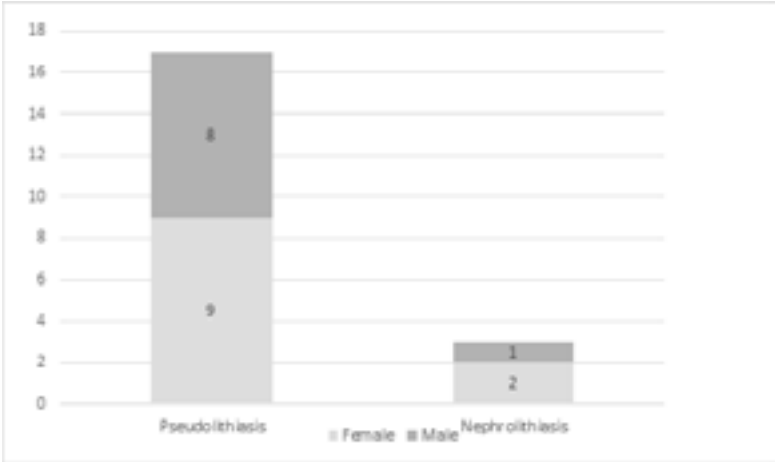
Methods

This is a prospective study, conducted in different Pediatric Services of the University Hospital Center "Mother Theresa", Tirana, during the period October 2021-March 2022. We studied the data of 80 patients admitted to these services for different diagnosis, who had been on Ceftriaxone therapy. During the hospitalization, ceftriaxone was administered intravenously at dosage of 50-100 mg /kg/d, given in 2 doses, in monotherapy (cases with multiple antibiotics therapy were excluded). All the patients underwent ultrasound examination for other reasons. Ultrasonographic evaluations were performed during 4-5th day and 8-10th days after the first dose administration. The patients who resulted with biliary sludge, pseudolithiasis or nephrolithiasis were followed with an ultrasound exam after 1 month.

Results

Female predomination was 43 % of the hospitalized children (n=34) aged 5–10 years old, and 57 % of them were male (n=46) aged 6-12 years old.

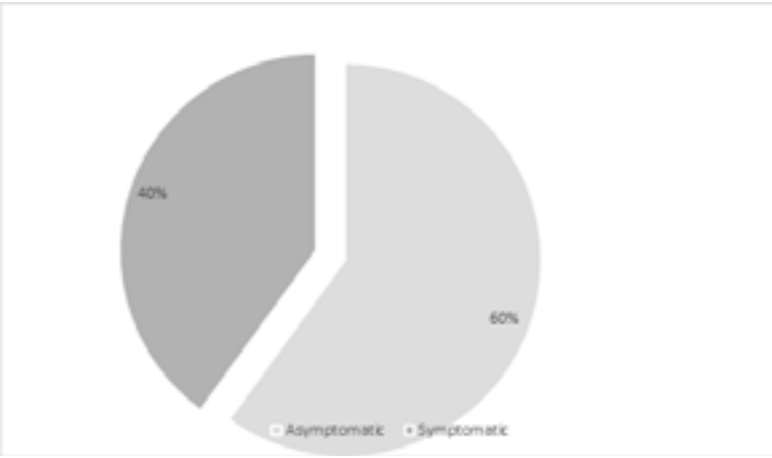
FIGURE 1. Patients number according to diagnosis



According to the total number of cases, 21.25% (n=17, n=9 females, n=8 males) resulted with biliary stone (pseudolithiasis), respectively 53% females and 47% males.

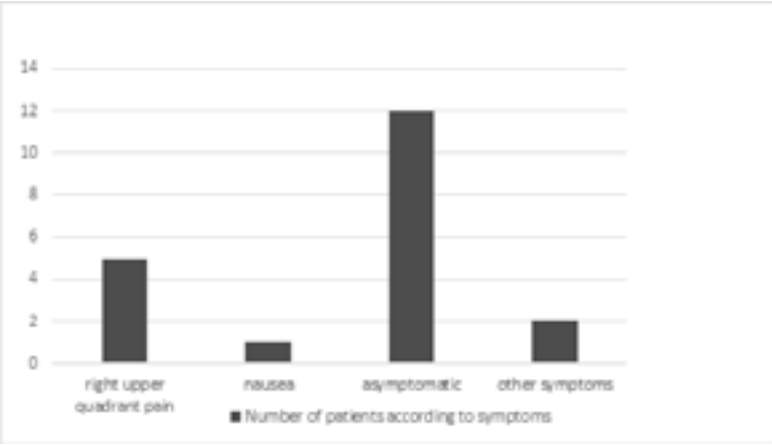
Nephrolithiasis resulted in 3.75% of the patients (n=3, n=2 females, n=1 male), respectively 66,7 % females and 33,3 % males (Figure 1).

FIGURE 2. Patients number according to symptoms



Referring to the studied data (Figure 2) 60% of the patients were asymptomatic (n=12), 40% were symptomatic (n=8).

FIGURE 3. Patients number according to clinical signs



The symptoms began from 5th-7th day and last 20 days. Only 29.4 % of the patients (n=5) referred right upper quadrant pain (2 male and 3 females) and only 1 of them showed nausea (Figure 3).

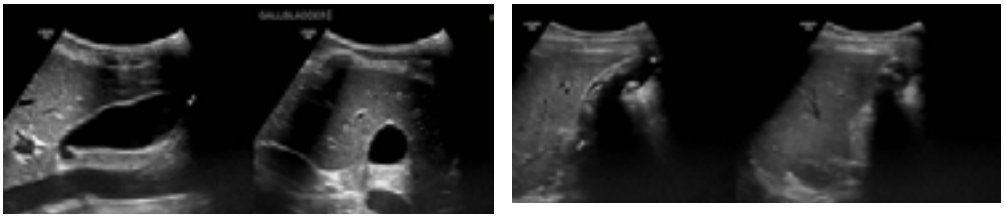
The ultrasound imaging performed from 5th- 10th day after the administration

of Ceftriaxone, showed gallbladder sludge and pseudolithiasis in the symptomatic patients, ranged 8-12 mm, and renal microlithiasis <3mm (Table 1), (Fig.4/b, Fig. 5/a).

TABLE 1. Calculus dimensions in ultrasonography according to the diagnosis

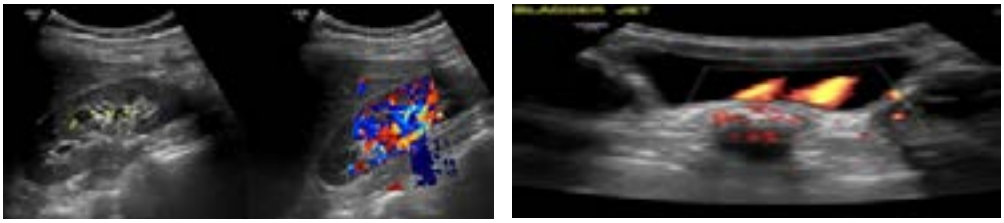
Diagnosis	Calculus dimensions in mm
Pseudolithiasis gallbladder	8-12
Nephrolithiasis	1-3

FIGURE 4. a) Normal gallbladder without calculi, b) Gallbladder calculus (Pseudolithiasis)



a) b)

FIGURE 5. a) Nephrolithiasis, b) Free urinary flow



a) b)

It was suspected to have a Ceftriaxone-induced adverse effect and for this reason ultrasound exam follow up was proposed. The patients who had biliary sludge, pseudolithiasis or nephrolithiasis were followed with ultrasound exam after 1 month. None of the cases was complicated with gallbladder hydrops, pancreatitis or hydronephrosis. The pathological condition resolved spontaneously after Ceftriaxone discontinuation.

Discussion

The World Health Organization (WHO) and US Food Drug Administration (FDA) recommend a dual therapy with ceftriaxone and gentamicin for the

treatment of neonates aged 0–28 days with severe infections (Bartkowska-Śniatkowska et al., 2015; http://www.who.int/selection_medicines/committees/subcommittee/2/Ceftriaxone.pdf.). A dose of 50 mg/kg is recommended for neonates younger than 72 hours and 100 mg/kg for those older than 28 days (Van Reempts et al., 1995). The same doses were used in our study, in patients aged 5-12 years old. Part of a ceftriaxone dose, 33% to 67%, is excreted in the urine as unchanged drug and the residue is secreted in the bile and found in the feces as microbiologically inactive compounds (www.accessdata.fda.gov/drugsatfda_docs/label/2009/0550585s063lbl.pdf). Based on the literature, if the concentration of ceftriaxone in the gallbladder exceeds a specific limit, it can precipitate with calcium ions secreted with the bile acids. Because of this process, biliary sludge as a side effect of ceftriaxone therapy can be composed mainly of calcium-ceftriaxone complexes (Katzung, 2018). This biliary sludge can cause stone formation and may develop into ceftriaxone-induced biliary pseudolithiasis.

A case with "ceftriaxone pseudolithiasis" was first reported by Schaad in 1986 (Schaad et al., 1986). In this study, the condition resolved spontaneously after ceftriaxone discontinuation. The incidence of ceftriaxone- associated pseudolithiasis in this study was 46.5%, while in the study of Biner et al., (Biner et al., 2006) pseudolithiasis was reported in 10% of the cases, followed by gallbladder sludge with 7% and nephrolithiasis with 0.6%. In the study of Ozturk et al. (Ozturk et al., 2005). [18] 57.57% of the cases resulted with pseudolithiasis and sludge in the gallbladder. In the study of Onlen et al. (Onlen et al., 2007) 32.5% of the cases resulted with biliary sludge and gallstone and 67.5% were normal. In our study pseudolithiasis resulted in 21.25%, followed by nephrolithiasis in 3.75% of the cases. So, biliary pseudolithiasis usually occurs in children receiving high doses of ceftriaxone, while nephrolithiasis is uncommon after ceftriaxone therapy.

These rates may be underestimated because most cases with ceftriaxone therapy are without symptoms, but sometimes it can be associated with abdominal pain in the right upper quadrant or nausea. In the study of Biner et al. 19% of the cases were symptomatic, while in Ozturk et al. all the cases were asymptomatic. In another study of Schaad et al., (Schaad et al., 1988) [20] 18.75% were symptomatic, 6.25% of whom had urolithiasis with renal colic and obstructive pyelectasia. In our study 29.4% of the cases were symptomatic, referring right upper quadrant pain. There is no sex predominance in most studies (Ozturk et al., 2005; Araz et al., 2007; Heim-Duthoy et al., 1990; Al Saidi et al., 2021) while in our study females predominate over males in a 1.1:1 ratio. The symptoms in the symptomatic patients begun from 5^{th}-7^{th} day and last 20 days. There were no complications in these cases. In the study of Biner et al., (Biner et al., 2006) the abnormalities resolved after 10-30 days, while in Schaad et al., (Schaad et al., 1988) ultrasonographic abnormalities resolved after 2-63 days after cessation of the drug.

The major limitations of this study are the low number of cases and the absence of monitoring ceftriaxone concentration in plasma.

Conclusion

In this study were reported 80 cases of pediatric patients treated with Ceftriaxone therapy at a dosage of 50-100 mg /kg/d. From the ultrasonographic imaging performed from 5th to 10th days after Ceftriaxone administration, 20 patients resulted with collateral associated gallbladder pseudolithiasis and nephrolithiasis as side effect from ceftriaxone-therapy, found by ultrasonographic (echographic) evaluation. None of the cases was complicated with gallbladder hydrops, pancreatitis or hydronephrosis. After the Ceftriaxone therapy was discontinued, the condition resolved spontaneously. Since ceftriaxone is increasingly being prescribed, we should be aware of the potential side effects and be more careful when using it in monotherapy or multiple therapies.

References

Al Saidi, D.M., Al Hashmi, D.S., Al Tahir, D.N., & AL Hashami, D.H. (2021). Ceftriaxone-Induced Gallbladder Stones in Children.

Araz, N., Okan, V., Demirci, M., & Araz, M. (2007). Pseudolithiasis due to ceftriaxone treatment for meningitis in children: report of 8 cases. *The Tohoku journal of experimental medicine*, *211*(3), 285–290. https://doi.org/10.1620/tjem.211.285

Bartkowska-Śniatkowska, A., Jończyk-Potoczna, K., Zielińska, M., & Rosada-Kurasińska, J. (2015). Adverse reaction to ceftriaxone in a 28-day-old infant undergoing urgent craniotomy due to epidural hematoma: review of neonatal biliary pseudolithiasis. *Therapeutics and clinical risk management*, *11*, 1035–1041. https://doi.org/10.2147/TCRM.S79419

Biner, B., Oner, N., Celtik, C., Bostancioğlu, M., Tunçbilek, N., Güzel, A., & Karasalihoğlu, S. (2006). Ceftriaxone-associated biliary pseudolithiasis in children. *Journal of clinical ultrasound : JCU*, *34*(5), 217–222. https://doi.org/10.1002/jcu.20228

Heim-Duthoy, K.L., Caperton, E.M., Pollock, R.G., Matzke, G.R., Enthoven, D., & Peterson, P.K. (1990). Apparent biliary pseudolithiasis during ceftriaxone therapy. *Antimicrobial Agents and Chemotherapy, 34*, 1146 - 1149.

Hotta, K., Hashimura, N., Takatsuka, M., Matsuyama, T., Nakagawa, K., Yabusako, T., Hosomi, S., & Fujiwara, Y. (2021). Ceftriaxone-associated Pseudolithiasis in Elderly People: Frequency and Risk Factors. *Internal medicine (Tokyo, Japan)*, *60*(24), 3857–3864. https://doi.org/10.2169/internalmedicine.7611-21 http://www.who.int/selection_medicines/committees/subcommittee/2/Ceftriaxone.pdf.

Katzung BG. (2018) *Basic & Clinical Pharmacology*. 14th ed. Mcgraw-Hill Education; pg 804-805

Onlen, Y., Gali, E., Incecik, F., Deviren, M., & Savaş, L. (2007). Ceftriaxone-Associated Biliary Sludge and Pseudolithiasis in Children. *Infectious Diseases in Clinical Practice, 15*, 167-170.

Ozturk et al., A., Kaya, M., Zeyrek, D., Ozturk, E., Kat, N., & Ziylan, S. Z. (2005). Ultrasonographic findings in ceftriaxone: associated biliary sludge and pseudolithiasis in children. *Acta radiologica (Stockholm, Sweden: 1987)*, *46*(1), 112–116. https://doi.org/10.1080/02841850510015983

Papadopoulou, F., Efremidis, S., Karyda, S., Badouraki, M., Karatza, E., Panteliadis, C., & Malaka, K. (1999). Incidence of ceftriaxone-associated gallbladder pseudolithiasis. *Acta paediatrica (Oslo, Norway: 1992)*, *88*(12), 1352–1355. https://doi.org/10.1080/080352599750030077

Park, H. Z., Lee, S. P., & Schy, A. L. (1991). Ceftriaxone-associated gallbladder sludge. Identification of calcium-ceftriaxone salt as a major component of gallbladder precipitate. *Gastroenterology*, *100*(6), 1665–1670. https://doi.org/10.1016/0016-5085(91)90667-a

Prince, J. S., & Senac, M. O., Jr (2003). Ceftriaxone-associated nephrolithiasis and biliary pseudolithiasis in a child. *Pediatric radiology*, *33*(9), 648–651. https://doi.org/10.1007/s00247-003-0963-0

Richards, D. M., Heel, R. C., Brogden, R. N., Speight, T. M., & Avery, G. S. (1984). Ceftriaxone. A review of its antibacterial activity, pharmacological properties and therapeutic use. *Drugs*, *27*(6), 469–527. https://doi.org/10.2165/00003495-198427060-00001

Schaad, U. B., Tschäppeler, H., & Lentze, M. J. (1986). Transient formation of precipitations in the gallbladder associated with ceftriaxone therapy. *Pediatric infectious disease*, *5*(6), 708–710. https://doi.org/10.1097/00006454-198611000-00026

Schaad, U. B., Wedgwood-Krucko, J., & Tschaeppeler, H. (1988). Reversible ceftriaxone-associated biliary pseudolithiasis in children. *Lancet (London, England)*, *2*(8625), 1411–1413. https://doi.org/10.1016/s0140-6736(88)90596-x

Schmutz, H. R., Detampel, P., Bühler, T., Büttler, A., Gygax, B., & Huwyler, J. (2011). In vitro assessment of the formation of ceftriaxone-calcium precipitates in human plasma. *Journal of pharmaceutical sciences*, *100*(6), 2300–2310. https://doi.org/10.1002/jps.22466

Shiffman, M. L., Keith, F. B., & Moore, E. W. (1990). Pathogenesis of ceftriaxone-associated biliary sludge. In vitro studies of calcium-ceftriaxone binding and solubility. *Gastroenterology*, *99*(6), 1772–1778. https://doi.org/10.1016/0016-5085(90)90486-k

Van Reempts, P. J., Van Overmeire, B., Mahieu, L. M., & Vanacker, K. J. (1995). Clinical experience with ceftriaxone treatment in the neonate. *Chemotherapy*, *41*(4), 316–322. https://doi.org/10.1159/000239361 www.accessdata.fda.gov/drugsatfda_docs/label/2009/0550585s063lbl.pdf

Yoshida, R., Yoshizako, T., Katsube, T., & Kitagaki, H. (2019). Computed tomography findings of ceftriaxone-associated biliary pseudocholelithiasis in adults. *Japanese journal of radiology*, *37*(12), 826–831. https://doi.org/10.1007/s11604-019-00893-5