

# Biliary pseudolithiasis induced by Ceftriaxone in pediatric patient treated in Cape Verde: case presentation

## Summary

**Introduction:** Ceftriaxone, a third generation cephalosporin, has become a frequently used antibiotic in pediatric patients with severe infections due to its pharmacological characteristics: broad spectrum, but in known its association with the occurrence of vesicular pseudolithiasis. The objective of this article is to present a case of Ceftriaxone-induced biliary pseudolithiasis in a pediatric patient with a diagnostic approach that takes into consideration the combination of clinical-imaging methods.

**Case presentation:** We present a clinical case of a healthy 9-year-old school boy who experienced non-specific abdominal pain for 11 days and was evaluated at Batista de Sousa Hospital. São Vicente Island, Cape Verde. The mother refers that she has presented unquantified febrile sensation. The clinical-imaging findings suggest appendicular plastron, for which an antibiotic plan with Ceftriaxone is decided. On the 14th day of the administration of Ceftriaxone she added constant pain in the right hypochondrium, so a diagnosis of Ceftriaxone-induced biliary pseudolithiasis was made.

**Conclusion:** The combination of the clinical-imaging methods pave the way for an accurate diagnosis of Ceftriaxone-induced biliary lithiasis disease in children under the premise that this drug should be used with caution.

**Keywords:** ceftriaxone, biliary pseudolithiasis; biliary lithiasis, imaging

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## Introduction

Ceftriaxone, a third generation cephalosporin, has become a frequently used antibiotic in pediatric patients with severe infections due to its pharmacological characteristics: broad spectrum, administration interval and good penetration into the cerebrospinal fluid. Approximately 10% of patients taking this antibiotic have experienced side effects, requiring discontinuation in only 2%. The most common adverse effects include eosinophilia, thrombocytosis and leukopenia, hypersensitivity reactions and gastrointestinal problems; it is common to present biliary mud in pediatric patients receiving this substance.<sup>1</sup> Consistent with the above, the insoluble components of bile form gallstones. Bilirubin, bile salts, phospholipids and cholesterol are the main organic solutes. Gallstones are divided into two categories: cholesterol stones and pigment stones. The former are the ones that occur most frequently in gallbladder and biliary tract disorders. Pigments with a lower proportion are further classified into black or brown pigment stones. As opposed to a diet rich in fats, pregnancy, obesity, use of some medications such as Ceftriaxone.<sup>2</sup>

In this vein, cholelithiasis, a condition in which stones form in the gallbladder or bile ducts, is much less common in children than in adults. Ceftriaxone is 40% eliminated by the biliary route and, because of its affinity for calcium, it can precipitate and cause gallstones. It has been shown that as early as the second day of treatment, 12-45% of patients receiving Ceftriaxone develop ultrasound images of biliary lithiasis. It has been observed in recent years that pediatric patients receiving this substance develop biliary mud, which could resemble a real clinical cholelithiasis, for this reason we present the case of a pediatric patient who develops vesicular pseudolithiasis during antibiotic treatment with Ceftriaxone for an appendicular plastron.<sup>3</sup>

The subject of Ceftriaxone-induced biliary pseudolithiasis in pediatric patients has been addressed by numerous foreign and national researchers, the analysis of many of their works is based on clinical case reports, however, their objectives do not transcend the diagnostic approach that gives merit to the use and combination of clinical-imaging methods aimed at a logical process for a better diagnostic approach. Therefore, the aim of this article is to present a case of Ceftriaxone-induced biliary pseudolithiasis in a pediatric patient with a diagnostic approach that takes into consideration the combination of clinical-imaging methods.

## Clinical picture

### Patient information

A healthy 9-year-old schoolboy experienced non-specific abdominal pain for 11 days and was evaluated at the Batista de Sousa Hospital. San Vicente Island, Cape Verde Country. The mother refers that she has presented unquantified febrile sensation, accompanied by nausea in the last 48 hours prior to the consultation. During the physical examination she showed a painful mass with signs of peritoneal irritation, a soft abdomen, depressible, painful on superficial palpation mainly in the right iliac fossa (RIF) and decreased hydro-aerial sounds. Axillary temperature of 38.8°C. Laboratory test results indicated a high white blood cell count of 19,000 cells/mm<sup>3</sup> with a preponderance of neutrophilic (85.2%) and a CRP concentration of 9.7 mg/dl. A B and D mode multifrequency transducer grayscale abdominal ultrasound was performed: it showed a heterogeneous, hyperechoic area surrounding the cecum that appeared thickened. Also found adjacent to the same small amount of free fluid. The above findings strongly suggest the existence of appendiceal plastron. After

evaluation, surgery was performed and an antibiotic plan was decided with Ceftriaxone at a dose of 100 mg/kg/day, divided into 3 times a day, infused for 30 minutes diluted with physiological saline solution. On the 14th day of the administration of Ceftriaxone, she added constant pain in the right hypochondrium.

### Diagnostic evaluation

On physical examination the patient presented constant pain in the right hypochondrium, nausea and palpable gallbladder. Examination showed no left shift and normal liver function tests. An abdominal ultrasound revealed a normal liver and biliary tract of normal caliber with a dilated and enlarged gallbladder, with thin walls, dense and heterogeneous internal content towards declining portions as well as the existence of biliary mud, also coalescing with the same, calcium-like echorefringence of approximately 7 mm with posterior acoustic shadow in projection to the neck (Figure 1). This finding was not specified in the initial ultrasound at admission, which led to raise the possibility of pseudolithiasis due to Ceftriaxone.



**Figure 1** Calcific echorefringence in relation to pseudolithiasis due to Ceftriaxone.

### Therapeutic intervention

Given the findings and the suspicion of a link between the lithiasis and Ceftriaxone, the drug was discontinued. Over the next 48 hours, the patient's abdominal pain improved significantly and the gallbladder was not palpable on physical examination. Follow-up abdominal ultrasound showed a significant decrease in biliary mud with persistent lithiasis. Abdominal ultrasound 30 days after treatment of acute abdominal pathology showed persistent lithiasis with a diameter of less than 5 mm and a normal-sized gallbladder. Due to persistent ultrasound abnormalities, a third abdominal ultrasound was performed 60 days after the acute episode. The scan revealed a normal-sized gallbladder with no stones inside (Figure 2). In this patient, the main cause of vesicular lithiasis was the administration of Ceftriaxone, which was prolonged and at high doses, having disappeared after discontinuation of the drug.



**Figure 2** Gallbladder of normal size and without lithiasis in its interior.

### Discussion

Currently, advances in diagnostic ultrasound make it possible to detect biliary lithiasis so early, and in asymptomatic patients as an ultrasound finding, which would explain, in part, the increase in the clinical incidence of this pathology in pediatrics. Although the natural history of this disease and the therapeutic behaviors are relatively well established in adults, there are limitations in the natural history of cholelithiasis in children and, therefore, the medical behaviors to follow.

The appearance of pseudolithiasis, which occurs in 25-55% of patients according to different series studied, is generally asymptomatic but a not negligible percentage of patients present pain in the right hypochondrium, nausea and vomiting. Cases of pancreatitis secondary to biliary obstruction and choledocholithiasis that required surgical management have also been reported. It has even been reported the appearance of nephrolithiasis associated to vesicular lithiasis in a 7 year old patient 3 days after treatment with Ceftriaxone.<sup>4</sup>

Sienra MC and collaborators state that vesicular lithiasis associated with the use of Ceftriaxone in children is relatively frequent, occurring in 15 to 57% of all patients administered the drug. Most cases are asymptomatic and self-resolving. It is described that lithiasis disappears between the 2nd day after the beginning of administration and the 63rd day after drug discontinuation.<sup>5</sup>

Prolonged treatment more than 5 days with Ceftriaxone, at high doses (doses equal to or higher than 100 mg/kg/kg/day) per day), as well as prolonged fasting or any condition leading to a slow emptying of the gallbladder to which nutrition infusion therapy is added.<sup>6,7</sup>

Naranjo-Cardenas et al. report that there is a direct association between the use of Ceftriaxone and the formation of gallstones in almost 57% of the cases, which is confirmed by numerous studies showing that the use of Ceftriaxone as an antibiotic, since the drug has an affinity for calcium. Gallstone disease or pseudolithiasis of the bile duct may develop. However, it does not cause serious complications because it disappears after discontinuation of the antibiotic.<sup>8</sup>

The use of Ceftriaxone has increased due to its excellent antibacterial spectrum. Its use requires knowledge of symptom recognition and ultrasound detection of biliary tract complications, so it should be used with caution in patients with dietary restrictions or in other diseases with risk of stone formation such as pediatric patients receiving parenteral nutrition. In addition, it is necessary to know the natural history of this pathology, which in most cases is characterized by spontaneous resolution after discontinuation of the drug, favoring conservative treatment and wait-and-see methods.

**Novelty** of this article aims to highlight the importance of an accurate diagnostic approach in Ceftriaxone-induced biliary pseudolithiasis in pediatric patient that has been, is and will always be an intellectual challenge for physicians, due to the increasing number of Ceftriaxone prescriptions in our community, it is important to report this side effect, if it occurs, to the National Institute of Drug Information and Pharmacovigilance of the National Institute of Public Health and to understand its true proportions as a complication in children.

### Conclusion

The diagnostic approach of the presented case study assumes that a good physician-patient relationship, a thorough medical history and a detailed physical examination are the basis for all diagnostic considerations, but the real value is reflected in the application and

combination of these methods and imaging techniques, which pave the way for an accurate diagnosis of Ceftriaxone-induced gallstone disease in children, helping to improve the quality of patient care.

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## Conflicts of interest

The authors declare that there are no conflicts of interest.

## Declarations

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