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Association Of Gall Bladder Sludge On Ultrasonography In Patients On Ceftriaxone Therapy

Parnit Kalra[1], Vishal Gupta[2], Saurav Bhagat[3*], Ajay Sahni[4], Anukriti Bhardwaj[4]
[1]Senior Resident, Department of Radiology, School of Medical Sciences and Research, Sharda University, Greater Noida, Uttar Pradesh, India
[2]Professor & Head, Department of Radiology, School of Medical Sciences and Research, Sharda University, Greater Noida, Uttar Pradesh, India
[3*]Assistant Professor, Department of Radiology, School of Medical Sciences and Research, Sharda University, Greater Noida, Uttar Pradesh, India.
[4]Post Graduate Resident, Department of Radiology, School of Medical Sciences and Research, Sharda University, Greater Noida, Uttar Pradesh, India

*Corresponding Author:
Saurav Bhagat
E-mail ID: dr.sauravbhagat@gmail.com

Abstract

Introduction

Ceftriaxone, a third-generation cephalosporin antibiotic, can cause gallbladder sludge due to high biliary excretion, leading to potential complications. This study investigates the association between ceftriaxone and gallbladder sludge formation detected by ultrasonography (USG).

Materials And Methods

Conducted in the Department of Radiology at the School of Medical Science and Research, Greater Noida, U.P., this hospital-based cross-sectional study spanned 20 months from August 2022 to March 2024. Fifty-seven patients on ceftriaxone therapy (1 gm BD) underwent baseline and daily USG from day 1 to day 5. Data analysis used SPSS-22, with significance set at $p<0.05$.

Results

Among 57 patients, the mean age was 39.05 years (SD: 14.61), with 63.2% male. By day 5, 29.8% (17 patients) developed gallbladder sludge. Incidence increased from 5.3% on day 3 to 29.8% on day 5. Older patients (>60 years) had a significantly higher incidence (80%) compared to younger patients.

Discussion

The study confirmed a significant association between ceftriaxone therapy and gallbladder sludge, particularly in older patients. Gender did not significantly affect sludge development. Clinicians should monitor patients on ceftriaxone, especially the elderly, for potential biliary complications.

Keywords: *Ceftriaxone, Cephalosporin, Gall bladder, Sludge*

INTRODUCTION

The gallbladder, located on the inferior surface of the liver, is essential for bile storage and excretion. Ceftriaxone, a third-generation cephalosporin antibiotic, can cause gallbladder sludge, potentially leading to gallstones and biliary issues due to its widespread use in treating bacterial infections, especially in hospitalized patients[1]. Ceftriaxone's broad-spectrum activity, easy administration, and safety make it popular, but its high bile excretion causes calcium-ceftriaxone complex precipitation, forming gallbladder sludge[2]. This sludge, often asymptomatic, can progress to gallstone disease, cholecystitis, or pancreatitis[3]. Ultrasonography (USG) is the primary non-invasive method for detecting gallbladder sludge[4].

Studies have shown that gallbladder sludge incidence is significant among patients on ceftriaxone, particularly children and critically ill adults[5]. This sludge formation is dose-dependent and reversible upon stopping the antibiotic[6]. However, the clinical significance of ceftriaxone-induced sludge varies, most patients remain asymptomatic, while few of them develop severe biliary complications requiring intervention[7]. Understanding the risk factors, incidence, and outcomes of sludge formation in ceftriaxone patients is crucial for optimizing care and mitigating complications..This study explores the association between ceftriaxone and gallbladder sludge development as detected by ultrasonography. Given ceftriaxone's frequent inpatient use, understanding its potential adverse biliary effects is vital[8].

MATERIALS AND METHODS

This study aim to investigate the association between ceftriaxone therapy and gall bladder sludge formation observed on ultrasonography (USG). Specifically, it sought to determine the incidence of gall bladder sludge in patients undergoing ceftriaxone treatment and to identify the day of its appearance on USG after starting the therapy.

The research was carried out in the Department of Radiology at the School of Medical Science and Research in Greater Noida, U.P., utilizing a hospital-based cross-sectional design over 20 months from August 2022 to March 2024.

The study involved 57 admitted patients who were given ceftriaxone therapy.

Baseline USG was performed before initiation of ceftriaxone therapy after fasting for 8-10 hours, followed by daily USG from day 1 to day 5 to detect any echogenic content in the gall bladder. Only patients above 18 years with normal gall bladders on the initial USG and on a ceftriaxone dose of 1gm BD were included, while those under 18 or with pre-existing gall bladder disease were excluded. Statistical analysis of the data, entered in a MS Excel spreadsheet and analyzed using SPSS-22, was expressed in percentages to indicate incidence, with results deemed statistically significant at a p-value of <0.05.

RESULTS

A total of 57 patients were included in the study from Aug 2022 to March 2024. The mean age of the patients were 39.05 years (SD: 14.61). The age wise distribution has been mentioned in Table 1.

Table 1: Age wise distribution in study subjects (n=57)

Age group	No.	%
18-30 years	19	33.3
31-45 years	22	38.6
46-60 years	11	19.3
>60 years	5	8.8

Thirty-six (63.2%) study subjects were male and 21 (36.8%) were female. (Table 2)

Table 2: Gender distribution in study subjects (n=57)

Gender	No.	%
Male	36	63.2
Female	21	36.8

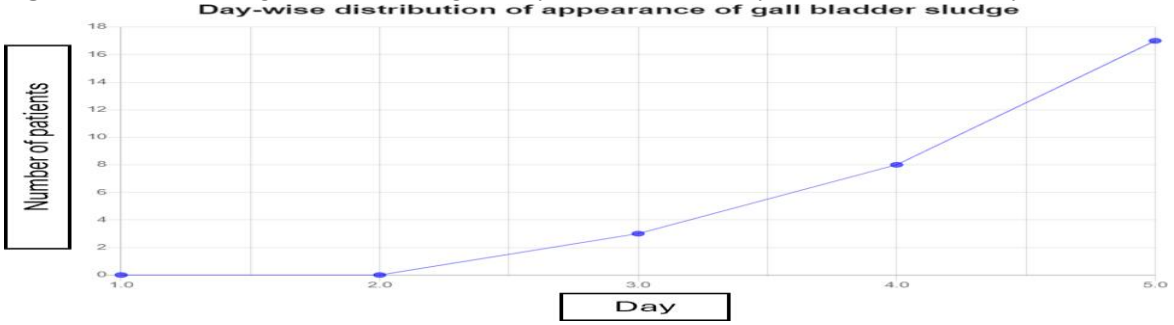
Proportion of patients who developed gall bladder sludge by day 5 was 29.8% (17 patients, 95% CI 18.4%-43.4%). (Table 3)

Table 3: Proportion of patients with gladder bladder sludge by day 5 (n=57)

Gall bladder Sludge	No.	%
Present	17	29.8
Absent	40	70.2

The median day for appearance of gall bladder sludge was 5 (IQR: 4-5). Three patients developed it on. Day 3, five patients on Day 8 and nine patients developed it on Day 5. (Figure 1)

Figure 1 Incidence of gall bladder sludge at day 3 was 5.3%, at day 4 was 14% and at day 5 was 29.8%.



(Table 4)

Table 4: Gall bladder Sludge at different time interval (n=57)

Gall bladder Sludge	No.	%
At day 3	3	5.3
At day 4	8	14.0
At Day 5	17	29.8

Proportion of male subjects who developed gall bladder sludge were 38.9% (14 subjects) as compared to 14.3% females (3 subjects). There was no significant difference between the two groups (p=0.17). The day wise distribution of development of sludge also showed no significant difference between males and females. (Table 5)

Table 5: Gall bladder Sludge at different time interval in male and female (n=57)

Gall bladder Sludge	Female (n=21)	Male (n=36)	p value
At day 3	0	3 (8.3%)	0.28
At day 4	1 (4.8%)	7 (19.4%)	0.23
At Day 5	3 (14.3%)	14 (38.9%)	0.17

Incidence of gall bladder sludge in males at day 3 was 8.3%, at day 4 was 19.4% and at day 5 was 38.9% while in females, incidence of gall bladder sludge at day 3 was 0%, at day 4 was 4.8% and at day 5 was 14.3%.

Eighty percent of patients >60years developed gall bladder sludge while none of the patients less than 30years developed gall bladder sludge. Incidence of gall bladder sludge was significantly higher in the older age group compared to younger age at all days (p value <0.01). (Table 6).

Table 6: Gall bladder Sludge at different time interval in different age group (n=57)

Gall bladder Sludge	18-30 years (n=19)	31-45 years (n=22)	46-60 years (n=11)	>60 years (n=5)	p value
At day 3	0	0	1 (9.1%)	2 (40%)	**<0.01**
At day 4	0	3 (13.6%)	1 (9.1%)	4 (80%)	**<0.01**
At Day 5	0	9 (40.9%)	4 (36.4%)	4 (80%)	**0.001**

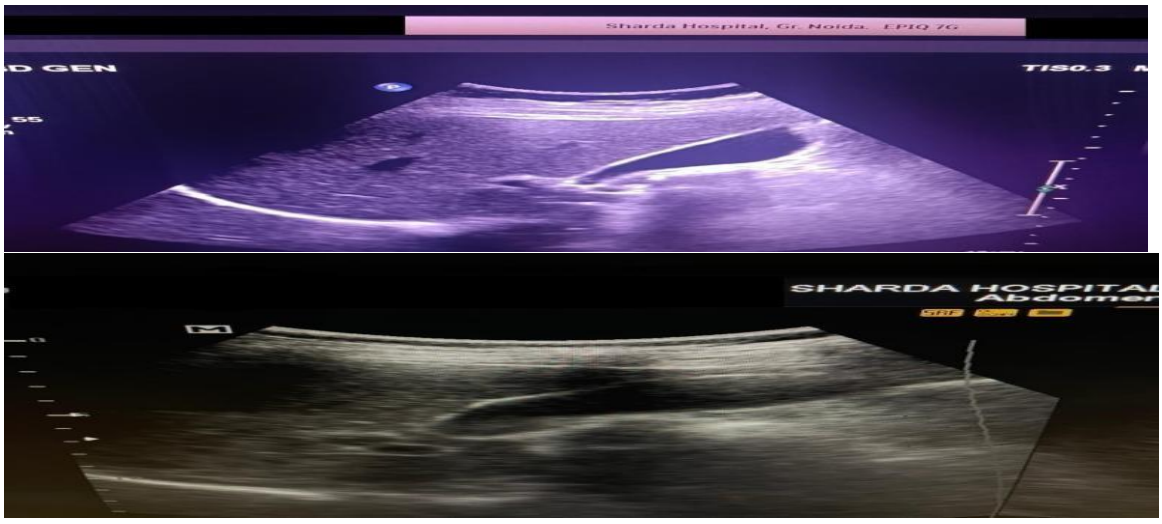


Figure 2 : Ultrasound image of gall bladder showing no sludge on initiation of ceftriaxone therapy .

Figure 3 : Ultrasound image of gall bladder showing sludge on Day 3 of ceftriaxone therapy in the similar patient as depicted in Figure 2.

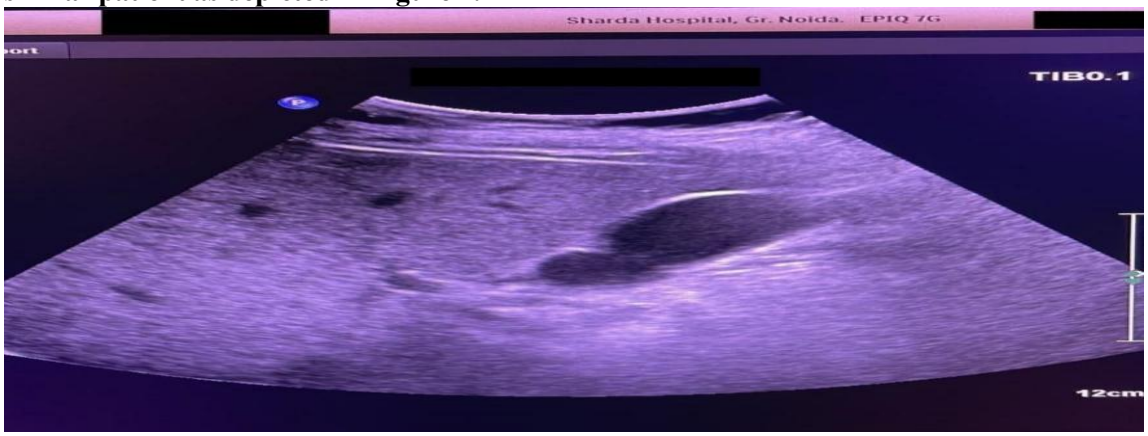


Figure 4 : Ultrasound image of gall bladder showing no sludge on initiation of ceftriaxone therapy .

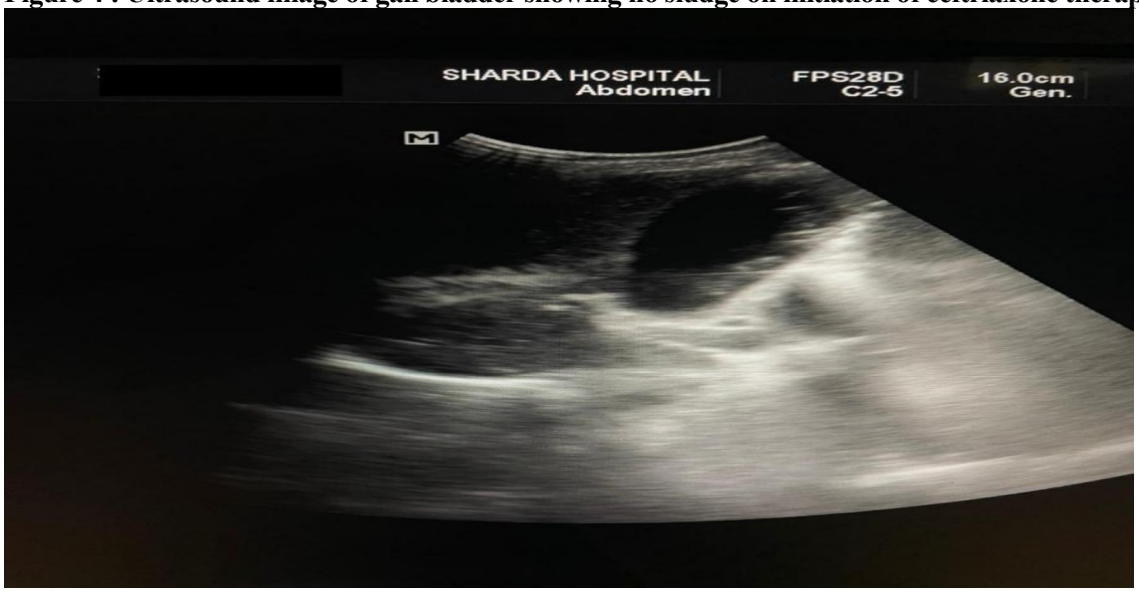


Figure 5 : Ultrasound image of gall bladder showing sludge on Day 4 of ceftriaxone therapy in the similar patient depicted in Figure 4.

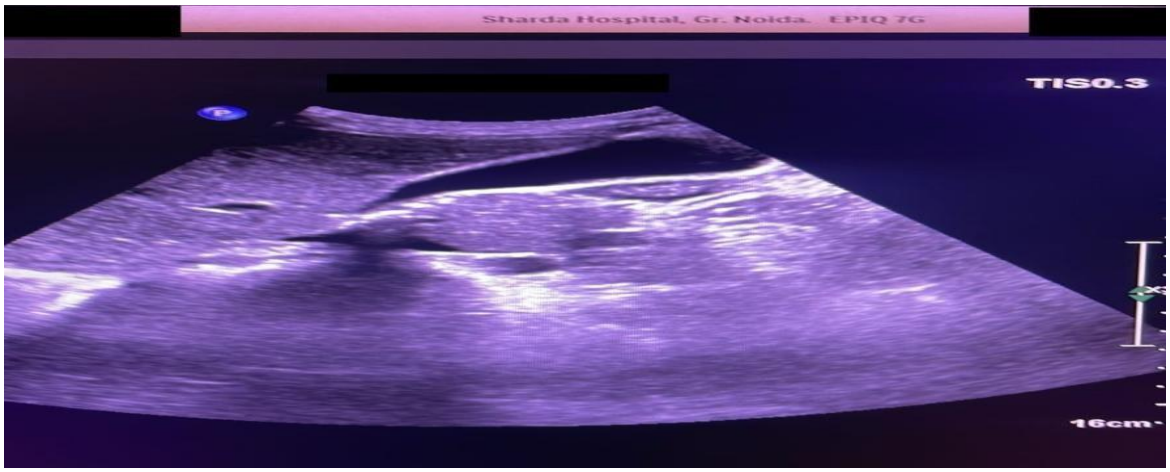


Figure 6 : Ultrasound image of gall bladder showing no sludge on initiation of ceftriaxone therapy .

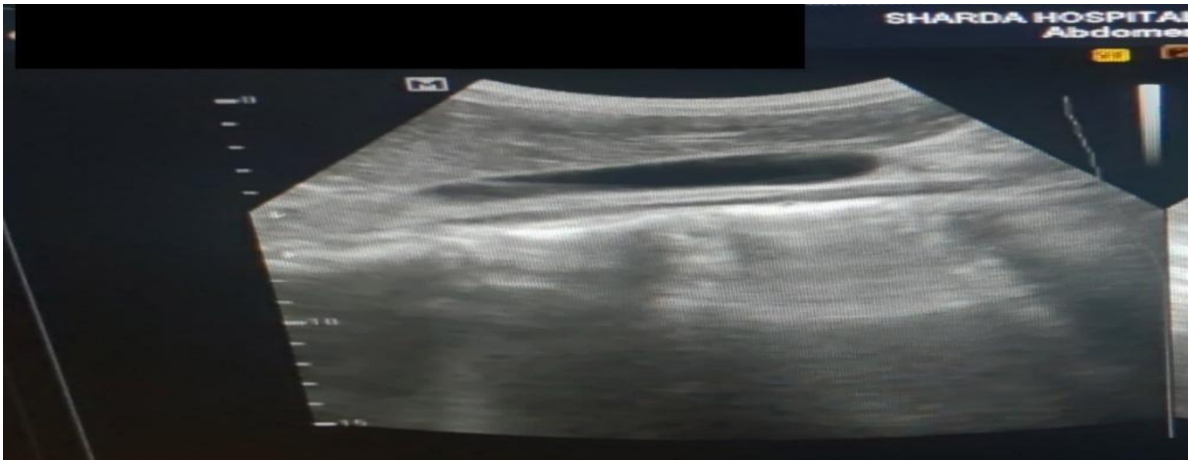


Figure 7 : **Ultrasound image of gall bladder showing sludge on Day 5 of ceftriaxone therapy in the similar patient depicted in Figure 6 .**

DISCUSSION

We conducted a prospective study to calculate the incidence of biliary sludge formation on ultrasonography among patients receiving ceftriaxone therapy. A total of 57 patientswere recruited with majority of them being males. Ceftriaxone therapy has been associated with the development of biliary sludge previously. The postulated mechanism is related to the higher concentrations of Ceftriaxone in bile (up to 150 times of serum) which precipitates with calcium. Although most of these patients are asymptomatic, rarely they can develop acute cholecystitis or biliary colic. Consideringthe vast number of patients receiving ceftriaxone therapy daily worldwide, even these rare complications can have significant health care impacts.

The findings of this study provide valuable insights into the potential association between ceftriaxone therapy and the development of gall bladder sludge. This association raises important considerations regarding the clinical management of patients receiving ceftriaxone, particularly in terms of monitoring for gall bladder- related complications.

In this study, the demographic profile of patients and the incidence of gall bladder sludge were investigated. Firstly, the mean age of patients, calculated at 39.05 years with a standard deviation of 14.61, was found to be consistent with prior research conducted by Heim-Duthoy KL et al.[10] This alignment suggests a certain demographicconsistency across studies. However, it contrasts with an earlier study by Cometta et al.[11] in 1990, indicating potential shifts in patient demographics over time or variationsacross different populations.

Gender distribution among participants was also noted, with a notable difference observed between this study and that of Pigrau C and colleagues. While Pigrau C et al.[12] reported a higher proportion of female participants, the current investigation found male patients outnumbering females. This difference in gender distribution prompts further exploration into potential factors influencing patient recruitment or underlying population demographics.

The incidence of gall bladder sludge among patients in our study at day 5 was 29.8%. This is higher than the rates reported previously. The incidences reported by Cometta et al.[11], Heim Duthoy KL et al.[10], and Pigrau C et al.[12] was lower at 5%, 21%, and 25%respectively. All the studies had less sample size and had included 40, 28 and 20 patientsrespectively. The mean daily dosage of Ceftriaxone was like our study at 2gm/day. More data is available on the association of Ceftriaxone therapy with biliary sludge formation in children. The incidence in pediatric populations, can vary from 11% as reported by Acun C et al.[13] and 15% by Bonnet et al.[14], to 25% and 43% as reported byPapadopoulou F et al.[15] and Schaad UB et al.[16] respectively.

The median day of development of gall bladder sludge in our study was 5 days. Three out of the seventeen patients who developed gall bladder sludge had it by day 3 whereasalmost half (eight out of seventeen patients) had it by day 4. While the detection occurred within 3-5 days in the current investigation,

earlier studies, including one published in Lancet in 1989, reported a wider range of 4-17 days.[10] Similarly, a separatestudy focusing on pediatric patients by Schaad UB et al.[16] observed sludge within 3-10days. These variations in detection timelines highlight the need for standardized protocols and further investigation into factors influencing sludge formation and detection.

In our study older age was significantly associated with the development of biliary sludge while on ceftriaxone therapy. Almost 80% of the patients aged >60years developed sludge by day 5 whereas no patient below the age of 30years had biliary sludge formation. None of the previous studies done in adults have looked at this association possibly due to the lower number of patients recruited.

Data from studies done in children and few case reports in adults have implicated prolonged duration of therapy, higher dosage, dehydration, renal impairment, fasting and immobilisation as risk factors for development of biliary sludge. A study done Murata et al.[17] in children showed that fasting status and bed rest was positively associated with biliary sludge formation on ceftriaxone therapy with a OR of 4.44 and

2.21 respectively. Another study done by Ubakta et al.[18] among adults identified fastingas a risk factor with OR of 4.65. The half-life of Ceftriaxone is 7-8hours in healthy adults but increases to 13.5hr in the elderly and can further increase to 21.4hrs in patients with renal dysfunction. Moreover, in patients with renal impairment, the biliary elimination of Ceftriaxone is increased leading to greater risk of ceftriaxone associated pseudolithiasis. The study done by Ubakta et al showed CKD and hemodialysis to be associated with sludge formation with OR of 1.83 and 5.18 respectively.

The higher incidence of gall bladder sludge among the elderly in our study could be possibly due to the higher likelihood of immobilisation, renal impairment and reduced oral intake in older patients compared to young adults. Further studies with more robustdata collection are needed to confirm our findings.

Female sex is an established risk factor for gall stone disease. This is primarily becauseof oestrogen on biliary cholesterol secretion leading to supersaturation of bile. As ceftriaxone associated pseudolithiasis is unrelated to cholesterol metabolism the same risk does not apply. In our study gender did not confer any additional risk for formationof ceftriaxone associated biliary sludge. Although males had higher incidence of biliarysludge (38.9% vs 14.3%), it was not statistically significant and could be due to the underlying diagnosis, age, or weight difference between the patients. This is in line withprevious studies which also did not show any gender predilection for Ceftriaxone associated pseudolithiasis.

It is important to note that while our findings demonstrate a significant association between ceftriaxone therapy and gall bladder sludge, the exact clinical implications ofthis association warrant further investigation. Although gall bladder sludge is often considered a benign condition, it can predispose individuals to more serious complications such as acute cholecystitis, biliary colic, and even the formation of gallstones. Therefore, clinicians should exercise caution when prescribing ceftriaxone, particularly in patients with pre-existing risk factors for gall bladder disease. Before treating the biliary sludge the clinicians should emphasize on previous treatment history as most of the ceftriaxone associated sludge resolves by itself .

Also, there has been a greater emphasis on researching the pediatric populationcompared to adults, indicating a higher prevalence of the condition among children.

There are several limitations to our study. The study period was limited to 5 days due to logistical reasons which can lead to underestimation of the true incidence ofceftriaxone associated biliary sludge. Data regarding other variables like weight,diagnosis, fasting, immobilisation, renal dysfunction could not be collected thereby limiting our potential to identify other potential risk factors. Another limitation of our study is the lack of long-term follow-up data to assess the progression of gall bladder sludge to symptomatic disease in patients receiving ceftriaxone therapy as well as the resolution of gall bladder sludge after cessation of Ceftriaxone. Future research endeavours should aim to address this limitation by conducting prospective studies withextended follow-up periods to evaluate the clinical outcomes associated with ceftriaxone-induced gall bladder sludge. Additionally, the potential role of other risk factors such as concurrent medication use, underlying comorbidities, and geneticpredispositions should be explored to better understand the multifactorial nature of gallbladder disease in patients undergoing ceftriaxone therapy.

CONCLUSION

This study provides significant insights into the association between ceftriaxone therapy and the development of gall bladder sludge, as detected by ultrasonography. The findings reveal a notable incidence of gall bladder sludge, particularly in older patients, with a median appearance on the fifth day of therapy. Despite the higher incidence in males, the gender difference was not statistically significant. These results highlight the need for careful monitoring of patients, especially the elderly, undergoing ceftriaxone treatment to prevent potential complications such as acute cholecystitis and biliary colic.

Given the considerable number of patients receiving ceftriaxone worldwide, these findings underscore the importance of considering gall bladder-related side effects in clinical decision-making. Further research with larger sample sizes, extended follow-up periods, and comprehensive data on potential risk factors is essential to enhance understanding and management of ceftriaxone-associated gall bladder sludge. This study advocates for the development of clinical guidelines to optimize patient care and antibiotic stewardship, minimizing adverse biliary outcomes in patients undergoing ceftriaxone therapy

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