



Cefodizime: safety profile in patients with comorbidities

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The aim. To evaluate the safety profile of cefodizime in comparison with ceftriaxone and amoxicillin/clavulanic acid based on an analysis of current literature data.

Materials and methods. A literature search was conducted among randomized controlled trials, cohort studies, meta-analyses, and clinical guidelines for the period from 2021 to 2026 in the PubMed database.

Results. The analysis of publications and one clinical guideline revealed that the safety profile of cefodizime in comorbid patients is more favorable compared to ceftriaxone and amoxicillin / clavulanic acid. The use of ceftriaxone is associated with a dose-dependent and duration-dependent risk of developing biliary pseudolithiasis, cholestatic hepatitis, nephrolithiasis, and crystalluria, especially in patients with risk factors such as decompensated comorbidities, dehydration, starvation, and polypharmacy. Amoxicillin / clavulanic acid remains one of the leading causes of drug-induced liver injury, including cholestatic forms, and also demonstrates clinically significant interactions with vitamin K antagonists and direct oral anticoagulants. No convincing data on hepatotoxicity or nephrotoxicity or clinically significant interactions with oral anticoagulants were found for cefodizime, including in patients with hepatobiliary and urinary system pathology. However, the limited volume of clinical studies requires further investigation of its safety in larger cohorts.

Conclusion. Cefodizime, ceftriaxone, and amoxicillin / clavulanic acid are effective in comorbid patients; however, their safety profiles differ. Cefodizime is characterized by a lack of data on hepatotoxicity and nephrotoxicity and does not demonstrate clinically significant drug interactions with oral anticoagulants, unlike ceftriaxone and amoxicillin / clavulanic acid. At the same time, the limited number of clinical studies on cefodizime requires further investigation of its safety profile in larger cohorts of comorbid patients.

Keywords: cefodizime; antibacterial therapy; comorbidities; comorbidity; drug-induced liver injury; nephrotoxicity; oral anticoagulants; drug interactions

Abbreviations: ADR — adverse reaction; ESBLs — extended-spectrum beta-lactamases; PBP — penicillin-binding protein; DILI — drug-induced liver injury; NAFLD — non-alcoholic fatty liver disease; ALD — alcoholic liver disease; HLA — human leukocyte antigen; OACs — oral anticoagulants; DOAC — direct oral anticoagulants; AF — atrial fibrillation; INR — international normalized ratio.

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Цефодизим: профиль безопасности у пациентов с коморбидной патологией

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Цель. Оценить профиль безопасности цефодизима в сравнении с цефтриаксоном и амоксициллин/клавулановой кислотой на основе анализа актуальных литературных данных.

Материалы и методы. Поиск литературы проводили среди рандомизированных контролируемых исследований, когортных исследований, метаанализов и клинических рекомендаций за период с 2021 по 2026 гг. в базе данных PubMed.

Результаты. В результате анализа публикаций и одной клинической рекомендации выявлено, что профиль безопасности цефодизима у коморбидных пациентов более благоприятен по сравнению с цефтриаксоном и амоксициллин/клавулановой кислотой. Применение цефтриаксона сопряжено с дозозависимым и зависящим от длительности терапии риском развития билиарного псевдолитиаза, холестатического гепатита, нефролитиаза и кристаллурии, особенно у пациентов с такими факторами риска, как декомпенсированные сопутствующие заболевания, дегидратация, голодание и полипрагмазия. Амоксициллин/клавулановая кислота остаётся одной из ведущих причин лекарственно-индуцированного поражения печени, включая холестатические формы, а также демонстрирует клинически значимые взаимодействия с антагонистами витамина К и прямыми пероральными антикоагулянтами. Для цефодизима не обнаружено убедительных данных о гепато- и нефротоксичности или клинически значимых взаимодействиях с пероральными антикоагулянтами, в том числе у пациентов с патологией гепатобилиарной и мочевыделительной систем. Вместе с тем ограниченный объём клинических исследований требует дальнейшего изучения его безопасности с участием больших когорт пациентов.

Заключение. Цефодизим, цефтриаксон и амоксициллин/клавулановая кислота эффективны у коморбидных пациентов, однако их профиль безопасности различается. Цефодизим характеризуется отсутствием данных о гепато- и нефротоксичности и не демонстрирует клинически значимых лекарственных взаимодействий с пероральными антикоагулянтами, в отличие от цефтриаксона и амоксициллин/клавулановой кислоты. В то же время ограниченное число клинических исследований цефодизима требует дальнейшего изучения его профиля безопасности в расширенных когортах коморбидных пациентов.

Ключевые слова: цефодизим; антибактериальная терапия; сопутствующие заболевания; коморбидность; лекарственное поражение печени; нефротоксичность; пероральные антикоагулянты; лекарственные взаимодействия

Список сокращений: НР — нежелательные реакции; БЛРС — β-лактамазы расширенного спектра; ПСБ — пенициллин-связывающие белки; ЛИПП — лекарственно-индуцированное поражение печени; НАЖБП — неалкогольная жировая болезнь печени; АБП — алкогольная болезнь печени; HLA — главный комплекс гистосовместимости человека; ФП — фибрилляция предсердий; ОАК — пероральные антикоагулянты; ПОАК — прямые пероральные антикоагулянты; МНО — международное нормализованное отношение.

INTRODUCTION

The increase in patients with polymorbidity and polypharmacy correlates with a higher incidence of adverse drug reactions during antimicrobial therapy. The most vulnerable are elderly patients

and those with chronic diseases of the liver, kidneys, cardiovascular, and respiratory systems, in whom even standard drug doses can be associated with an increased risk of adverse reactions (ARs) and drug interactions [1].

In this regard, the systematization of data on the safety profile of widely used β -lactam antibiotics in comorbid patients is of significant interest for practical healthcare [2].

Cefodizime and ceftriaxone, belonging to third-generation cephalosporins, as well as the combination drug amoxicillin / clavulanic acid, are widely used in the treatment of infections of various localizations in patients of therapeutic profile. Despite accumulated clinical experience, most available studies on the safety profile of these antibiotics were conducted in relatively homogeneous groups, without considering the pronounced comorbidity and polypragmasia characteristic of real clinical practice. This necessitates an analysis and comparison of published data on the frequency and structure of ARs of these drugs in patients with concomitant diseases [3, 4].

Lower respiratory tract infections are among the leading causes of mortality worldwide. According to the WHO, they rank 7 among the main causes of mortality in upper-middle-income countries and first in low-income countries¹. Urinary tract infections are the second most common pathology among all infectious diseases, affecting over 150 million people worldwide annually [5]. In Russia, 4.1 million medical consultations for urinary tract infections were registered in 2022 [6].

Community-acquired pneumonia, caused by viruses, as well as typical and atypical bacteria, remains one of the leading causes of mortality in patients of different age groups: in high-incidence countries, lethality is 9–17.5% [7]. The presence of concomitant diseases in patients with infectious and inflammatory pathology can affect both the course of the primary and comorbid processes, as well as the efficacy and safety of drug therapy [8].

Comorbidity is defined as the combination in one patient of two or more chronic diseases that are etiopathogenetically linked or coincide in their onset, regardless of the activity of each [9]. With age, the frequency of comorbid diseases increases: in individuals aged 65–74, it reaches 62%, and in patients aged 85 and older, it is 82% [8].

Patients with multiple concomitant diseases appropriately receive several medicines (adequate

polypharmacy). The burden of taking medicines increases the risk of side effects, which is a significant reason for hospitalization and prolonged hospital stays [9].

Cephalosporins are β -lactam antibiotics. Depending on the chronology of drug development and their antimicrobial properties, these antibiotics are divided into different generations, from first to fifth. Structurally, third-generation cephalosporins contain a six-membered dihydrothiazine ring connected to the β -lactam moiety. Substituents at C3, C4, and C7 are key factors in their antimicrobial activity. Furthermore, the carboxyl group at C4 must remain unchanged, and the acylamide side chain at C7 (7-aminocephalosporanic acid nucleus) plays a crucial role in the hydrophilic/hydrophobic properties of these compounds.

Third-generation cephalosporins are the most frequently prescribed group of antibiotics [10]. The first third-generation cephalosporin, cefotaxime, was developed in the late 1970s. Through improvements to the “parent” molecule, ceftriaxone and cefodizime have been created and introduced. These drugs differ from cefotaxime in that they have a longer half-life ($T_{1/2}$), allowing for once or twice daily dosing, which in turn improves patient adherence and reduces therapy costs [11].

These antimicrobial agents are characterized by a broad spectrum of activity, covering both Gram-positive and Gram-negative microorganisms. Their antibacterial effect is more pronounced against Gram-negative flora resistant to first and second-generation cephalosporins [10].

Currently, this advantage has been somewhat diminished due to the spread of extended-spectrum β -lactamase (ESBL)-producing *Enterobacteriaceae* strains, even in community-acquired infections. However, Gram-positive microorganisms and a number of Gram-negative pathogens retain high sensitivity to this class of antibacterial agents, justifying their use in modern clinical practice [11].

Cefodizime belongs to the subclass of amino-2-thiazolyl-methoxyiminocephalosporins and shows significant structural similarity to cefotaxime and ceftriaxone. Several experimental studies have shown that, in addition to its antibacterial action, the drug has a regulatory effect on the inflammatory response

¹ World Health Organization (WHO). The top 10 causes of death. Available from: <https://www.who.int/ru/news-room/fact-sheets/detail/the-top-10-causes-of-death>

and stimulates the functional activity of various components of the immune system, allowing it to be considered a potential immunomodulator in infectious diseases [11, 12].

Being used at therapeutic doses, the pharmacokinetics of cefodizime remain linear. It may be more convenient to use than some other drugs in this class, as it can be administered once or twice daily [13, 14]. Cefodizime has several advantages for use in comorbid patients. This issue will be explored in detail in our article.

THE AIM is to evaluate the safety profile of cefodizime compared to ceftriaxone and amoxicillin / clavulanic acid based on an analysis of current literature data.

MATERIALS AND METHODS

Full-text publications were conducted in the PubMed database. Works studying cefodizime, ceftriaxone, and amoxicillin / clavulanic acid in the treatment of infectious and inflammatory diseases in polymorbid patients with hepatobiliary system pathology, urinary system pathology, or those taking oral anticoagulants from 2021 to 2026 were analyzed using the following keywords: “cefodizime”, “ceftriaxone”, “amoxicillin clavulanate”, “drug-induced liver damage”, “hepatotoxicity”, “cholelithiasis”, “nephrolithiasis”, “crystalluria”, “warfarin”, “direct oral anticoagulants” and their Russian equivalents.

As a result, 3325 sources were found. Works for which full text was not accessible, as well as those not directly related to the review topic, were excluded from the bibliography. Consequently, 58 scientific works were included in this review.

RESULTS AND DISCUSSION

Mechanism of Action of Cephalosporins

Cephalosporins inhibit the synthesis of the bacterial cell wall, specifically peptidoglycan. Peptidoglycans are the exoskeleton of bacteria, providing structural integrity and shape to cells and protecting them from lysis. These structures are cross-linked in the final stage of bacterial cell wall synthesis, forming peptidoglycan polymers with the help of membrane-bound enzymes (i.e., transpeptidases, carboxypeptidases, and endopeptidases), collectively known as penicillin-binding proteins (PBPs) [10].

Most bacteria possess at least one PBP, and they are the target for various β -lactam antibiotics such as cephalosporins, penicillins, carbapenems, and monobactams. The β -lactam ring structure of third-generation cephalosporins mimics the “D-Ala-D-Ala” fragment of the natural PBP substrate. Structural binding of cephalosporin antibiotics to the active site of PBPs in bacterial cell walls leads to the inhibition of their enzymatic activity and disruption of peptidoglycan synthesis, resulting in the inability to build a functional cell wall and subsequent death of bacterial cells due to osmotic lysis [10].

Spectrum of Activity of Cefodizime and Indications for Use

Cefodizime has a broad spectrum of antibacterial activity against Gram-positive and Gram-negative aerobes. Stable sensitivity is noted in *Enterobacteriaceae* (*Escherichia coli*, *Klebsiella pneumoniae*, *Morganella morganii*, *Proteus mirabilis*, *Proteus vulgaris*, *Shigella sonnei*, *Yersinia enterocolitica*, and *Salmonella species*), whereas activity against *Citrobacter* (including *Citrobacter freundii*) and *Serratia marcescens* is noted as weak and variable; against *Enterobacter* spp., the drug, like most third-generation cephalosporins, is ineffective [14].

Cefodizime inhibited *Haemophilus influenzae* (ampicillin-sensitive and resistant), *Moraxella catarrhalis*, *Neisseria gonorrhoeae* (β -lactamase-producing and non-producing), and *Neisseria meningitidis*, but is inactive against *Pseudomonas aeruginosa* and *Xanthomonas maltophilia*. *Methicillin-sensitive strains of Staphylococcus aureus* are sensitive to the drug, whereas *Staphylococcus epidermidis* and *MRSA* remained resistant. *In vitro*, cefodizime effectively inhibited *Streptococcus agalactiae*, *S. pneumoniae*, and *S. pyogenes*, demonstrating activity comparable to first and second-generation cephalosporins [14].

In adult patients, the drug can be used for bacterial infections caused by susceptible microorganisms. Its use is of greatest clinical significance in patients with weakened body condition and/or reduced immune defense. The spectrum of indications includes uncomplicated lower urinary tract infections in women, other urinary tract infections, lower respiratory tract infections, and gonorrhea.

Dosage adjustment is necessary only in elderly patients with impaired renal function.

Side Effects

Cephalosporins are generally well-tolerated, but individuals with penicillin allergy may have an increased risk of allergic reactions due to the common β -lactam ring [15].

Generally, a higher frequency of cross-reactivity is observed with first-generation cephalosporins [15].

Ceftriaxone, while maintaining high clinical efficacy, is characterized by a more pronounced risk of drug-induced liver injury (DILI), including cholestatic forms and the development of biliary pseudolithiasis / cholelithiasis, as well as nephrotoxic complications manifesting as nephrolithiasis and crystalluria in predisposed patients. Concurrently, rare but clinically significant cases of severe cutaneous and systemic reactions (Stevens-Johnson syndrome, toxic epidermal necrolysis) and ceftriaxone-associated neurotoxicity in the form of encephalopathy have been described [10].

Cefodizime, in contrast, demonstrates a more favorable safety profile: according to available clinical data, the drug is generally well-tolerated upon parenteral administration, with no convincing evidence of clinically significant hepato- and nephrotoxicity, which allows it to be considered a preferred option in patients with an increased risk of hepatobiliary and renal complications of antibacterial therapy [14].

Comorbid Patients with Impaired Liver and Pancreatic Function

Pancreatitis, including both acute and chronic forms, is a primary cause of gastrointestinal morbidity and hospitalization [16].

Acute pancreatitis is a critical condition with high mortality, ranging from 20% to 40%, mainly due to systemic complications such as sepsis and multiple organ failure [17].

The global standardized incidence rate of pancreatitis in 2021 was 52.64 (95% CI: 45.57–60.42) per 100,000 people. The lowest incidence rate in individual countries was observed in Zambia (23.76, 95% CI: 19.15–29.79), and the highest in the Russian Federation (173.44, 95% CI: 142.20–204.01) [16].

It is estimated that in 2024, there were approximately 240 million people worldwide with

chronic hepatitis B virus infection, corresponding to 2.9% of the global population, as well as about 68 million people infected with hepatitis C virus².

According to available data, in 2024, approximately 1.1 million deaths from cirrhosis and liver cancer associated with hepatitis B virus were registered worldwide, which is 17% higher than in 2015: 240,000 people died from liver cirrhosis and liver cancer caused by hepatitis C virus (95% CI: 160,000–370,000), which is 12% less compared to 2015³.

It is estimated that hepatic steatosis affects 1.7 billion people worldwide and is one of the fastest-growing causes of chronic liver disease globally⁴.

According to the results of a meta-analysis conducted in 2023, the global prevalence of non-alcoholic fatty liver disease (NAFLD) has increased by 50.4% over the past 20 years. In the Russian clinical epidemiological study DIGER, the authors also note a significant increase in the frequency of NAFLD among the Russian population (+38.1% over 7 years of observation) [18].

Approximately 26% of individuals with alcohol abuse and up to 55% of patients with alcohol use disorder develop one of the clinical forms of alcoholic liver disease (ALD) [19].

About 10–20% of people with ALD develop liver cirrhosis. Thus, the prevalence of alcohol-related liver cirrhosis is estimated at approximately 0.3% in the general population, but increases to 12.9% in individuals with alcohol use disorder [20].

In 2023, according to available data, 3.15 million people suffered from alcoholic liver cirrhosis. 419,429 new cases were registered: despite the overall increase in disease prevalence, the age-standardized prevalence was 34.6 per 100,000 people, reflecting demographic shifts [21].

The epidemiology of chronic cholecystitis largely coincides with the epidemiology of gallstone disease. It is estimated that 10% to 20% of the world's population develops gallstone disease during their lifetime, with approximately 80% of cases remaining clinically asymptomatic [22].

² World Health Organization (WHO). Global hepatitis report 2026. Geneva; 2026. Available from: <https://whodc.mednet.ru/en/main-publications/infekzionnye-bolezni-i-borba-s-nimi/virusnyj-gepatit/4478/visit.html>

³ Ibid.

⁴ Seventy-ninth World Health Assembly — Daily update: 21 May 2026. World Health Organization; 2026. Available from: <https://www.who.int/news/item/21-05-2026-seventy-ninth-world-health-assembly---daily-update--21-may-2026> (accessed 21.05.2026).

Untreated acute cholecystitis is associated with a significant risk of complications and mortality, especially in the elderly patient group.

Gallbladder perforation, a potential complication of untreated cholecystitis, has a mortality rate of 30% [23].

Given the high prevalence of liver and biliary tract pathology in the population, it is crucial to assess the risk of hepatotoxic ARs when prescribing drug therapy.

Impact of Comorbidity on the Safety of β -Lactam Antibiotic Therapy

Numerous observational cohort studies confirm a direct correlation between the cumulative burden of chronic diseases and the frequency of ARs during β -lactam antibiotic therapy. In particular, an analysis of the North American population demonstrated a statistically significant association between high scores on the Charlson Comorbidity Index (CCI) and the probability of developing both typical (Type A) and idiosyncratic (Type B) ARs. Notably, the CCI comorbidity index has become part of the panel of independent predictors of ARs, alongside polypharmacy, geriatric status of the patient, and gender. Antibacterial agents were second only to anticoagulants in the hierarchy of pharmacological classes most frequently inducing ARs.

The most vulnerable cohort regarding drug-induced acute kidney injury when prescribing antimicrobial drugs are individuals of geriatric profile with pre-existing multimorbidity. Basic risk determinants include diabetes mellitus, essential arterial hypertension, systolic myocardial dysfunction, and chronic kidney disease. This risk is potentiated by concomitant therapy with drugs that modify the renin-angiotensin-aldosterone system (ACE inhibitors, angiotensin II receptor blockers) and diuretics. Dehydration acts as an additional trigger, exacerbating the prerenal vasoconstrictor component of nephrotoxicity [8].

Safety of Cefodizime, Ceftriaxone, and Amoxicillin / Clavulanic Acid in Patients with Hepatobiliary System Pathology

Parenteral administration of ceftriaxone causes biliary sludge (pseudolithiasis) in 3–46% of patients⁵ [24].

⁵ LiverTox: clinical and research information on drug-induced liver injury [Internet]. Bethesda (MD): National Institute of Diabetes and Digestive and Kidney Diseases; 2012–. Ceftriaxone. Updated 20 Dec 2021. Available from: <https://www.ncbi.nlm.nih.gov/books/NBK548258/> (accessed 24.05.2026).

In most cases, it is asymptomatic and spontaneously resolves after discontinuation of the drug, but in rare cases, it leads to severe pancreatitis or cholecystitis requiring surgical intervention. In children, the risk is higher with high doses of ceftriaxone, prolonged therapy, fasting, and dehydration.

The mechanism involves the binding of the drug to calcium ions, leading to the formation of insoluble crystals in bile and urine. Interaction with calcium phosphate forms stable stone aggregates. Very rarely, idiosyncratic cholestatic hepatitis develops.

Clinical Trial Results and Patient Management Strategies

In most described cases, recovery was rapid, within 1–2 weeks, but some patients required cholecystectomy during the acute illness, and stones or sediment could persist for several months. The immunoallergic form of cholestatic hepatitis usually resolves quickly and is not associated with acute liver failure or chronic liver damage.

Probability Assessment: B (ceftriaxone is a highly probable cause of clinically significant liver injury and can also lead to the formation of bile sediment and “pseudolithiasis” caused by ceftriaxone crystallization in bile present in the gallbladder or biliary tract)⁶.

Bile acids and ceftriaxone may use the same transport pathway, so ceftriaxone secretion with bile can inhibit bile acid secretion. While ceftriaxone is 85–95% bound to albumin in blood, 45% is excreted unchanged in bile; therefore, the concentration of ceftriaxone in bile is 20–150 times higher than in serum [25, 26].

When the concentration of ceftriaxone in the gallbladder exceeds a threshold value, it is known to precipitate by binding to calcium ions secreted along with bile acids. Subsequently, the precipitated drug forms stones and can ultimately lead to ceftriaxone-induced biliary pseudolithiasis. The formation of this calcium-ceftriaxone complex is detected by ultrasound as a gallstone or bile sediment. Pseudobiliary stones are considered structurally unstable; therefore, they are easily excreted with bile [26].

T. Yassen et al. presented the results of a prospective study on the incidence and clinical outcomes of biliary pseudolithiasis associated with

⁶ Ibid.

ceftriaxone use. The study included 60 patients. In 11 of them, ultrasound revealed cholelithiasis (18.3%) [26]. In univariate analysis, cholelithiasis developed more frequently in patients requiring fasting and bed rest ($p < 0.001$). In multivariate analysis, the duration of fasting (OR, 4.44; 95% CI: 2.04–14.64; $p < 0.0001$) and the duration of bed rest (OR, 2.21; 95% CI: 1.25–4.26; $p = 0.008$) were significantly associated with pseudolithiasis and independent of each other. Furthermore, cholelithiasis appeared relatively early during the period of fasting and bed rest [26].

When studying potential risk factors using the FAERS database, data on 764 adverse events (AEs) related to the formation of stones in the hepatobiliary system during ceftriaxone therapy were analyzed to assess potential risk factors: age group, sex, dose. Sex was not identified as a risk factor for the development of ceftriaxone-induced hepatobiliary stones. However, male infants (under 1 year), boys, girls, male adolescents, and elderly women were potential risk factors for the development of ceftriaxone-induced hepatobiliary stones, based on $ROR_{025} > 1$ and $IC_{025} > 0$ criteria [26].

In a retrospective study involving 634 adult patients with common infectious diseases treated with ceftriaxone in a general hospital in Qatar, it was found that the use of ceftriaxone in combination with other drugs metabolized in the liver was associated with a significantly higher incidence of liver damage (19.7%) compared to data from other similar studies [27–29]. The inclusion criteria were as follows: a) hospitalized patients aged ≥ 18 years from January 2019 to December 2019 in an inpatient setting; b) patients who received intravenous ceftriaxone at a dose of ≥ 2 g/day for ≥ 2 consecutive days.

A retrospective analysis of hospitalized patients aged ≥ 65 years who received ceftriaxone at Innoshima-Ishikai Hospital between May 2022 and April 2025, conducted by T. Tagashira et al. [30], revealed that in patients aged ≥ 65 years, baseline ALT levels (≥ 11 U/L) and CRP levels (≥ 5.9 mg/dL) were associated with an increased risk of drug-induced liver injury during ceftriaxone use. Therefore, careful monitoring of liver function during and after ceftriaxone administration was recommended in this patient group. The study compared two groups: patients with and without liver dysfunction. Liver dysfunction developed in 19

patients, accounting for 18.1% (19/105). In the liver dysfunction group, ALT levels significantly increased after ceftriaxone administration. The median time to the onset of liver dysfunction was 8 days ([Q1–Q3] = 6.5–9.5 days). Furthermore, liver dysfunction developed within 8 days in 58% of patients. No significant differences were observed between the groups in terms of age, sex, duration of ceftriaxone administration, cumulative ceftriaxone dose, or concomitant medication use. The daily dose of ceftriaxone was 2 g/day in 101 patients (96% of the cohort). Significant differences were noted in ALT ($p = 0.001$), AST ($p = 0.046$), and CRP ($p = 0.009$) levels between the groups, while other laboratory parameters did not differ significantly [30].

Cephalosporins can cause self-limiting mixed / cholestatic hepatitis, occurring after a short course of therapy with a latency period of up to 3 weeks.

From January 1, 2004, to November 2, 2022, a total of 2347 cases of DILI were included in the DILIN study, of which 1854 were classified as probable, highly probable, or definite. Human leukocyte antigen (HLA) sequencing was performed, and its association with the risk of DILI was studied. As a result, 58 cases (3%) were associated with the use of various cephalosporins, including cefazolin ($n = 40$), cephalexin ($n = 4$), ceftriaxone ($n = 3$), cefdinir ($n = 3$), cefuroxime ($n = 3$), and five other individual drugs. Clinical manifestations included a self-limiting course with a mixed or cholestatic biochemical pattern without signs of hypersensitivity, occurring within 1–4 weeks. In the overall cohort, HLA-A*02:01 was significantly associated with an increased risk of cephalosporin-induced liver injury (OR: ~ 2.5 – 2.7 , $p < 0.0001$). The strongest association was observed with cefazolin, where the carriage rate was 85% compared to 38% in individuals with DILI caused by other drugs [15].

Results of a retrospective case-control study involving 185 children showed that the occurrence of pseudocholelithiasis (PL) was not significantly associated with ceftriaxone dosage. Furthermore, the rate of metabolism and excretion of ceftriaxone may play a key role in the development of PL. Serum analysis revealed distinct markers of liver and kidney function in the PL group, including lower levels

of total bile acids (PL(+)=1.8 (0.85–3.79) $\mu\text{mol/L}$ vs. PL(-)=3.9 (2.18–7.00) $\mu\text{mol/L}$, $p=0.000$), adenosine deaminase (PL(+)=14 (12–21) U/L vs. PL(-)=19 (15–27) U/L, $p=0.003$), and lactate dehydrogenase (PL(+)=195 (180.5–268) U/L vs. PL(-)=256 (207–313) U/L, $p=0.003$), as well as higher creatinine levels (PL(+)=57 (51.85–66.3) $\mu\text{mol/L}$ vs. PL(-)=50.7 (39–62), $p=0.021$) [31].

According to the VigiAccess resource⁷, ceftriaxone caused hepatobiliary system disorders, accounting for 1% of all AEs, with 4,596 cases reported, including: cholelithiasis—953 reports, cholestasis—360 reports, pseudocholelithiasis—219 reports, cholestatic hepatitis—160 reports, cholecystitis—146 reports, bile duct stones—57 reports, cholestatic liver injury—56 reports, acute cholecystitis—51 reports, biliary colic—47 reports, cholangitis—39 reports, biliary obstruction—10 reports.

Amoxicillin, both as monotherapy and in combination with the β -lactamase inhibitor clavulanic acid, is the most widely prescribed penicillin in Europe and many other countries [32, 33].

Amoxicillin is prescribed for infectious processes caused by microorganisms that do not produce β -lactamases. In clinical practice, the drug is used to treat respiratory tract diseases (upper and lower), urinary tract infections, *Helicobacter pylori* eradication, and bacterial infections of the skin and soft tissues.

Amoxicillin and amoxicillin / clavulanic acid are generally considered well-tolerated medicines with an established safety profile based on widespread global clinical use. However, amoxicillin / clavulanic acid combination should be prescribed with caution to patients with hepatic dysfunction and is not recommended for patients with a history of cholestatic jaundice / hepatic dysfunction [32].

ARs of the hepatobiliary system are an important issue in drug safety and pharmacovigilance, as they are a major cause of acute liver failure. Amoxicillin, both as monotherapy and in combination with clavulanic acid, has previously been described as a hepatotoxic agent in pediatrics [32].

In two previous population studies conducted in adult patients with DILI, the authors indicated that the amoxicillin / clavulanic acid combination demonstrates a higher risk of acute liver injury compared to the use of amoxicillin alone [34, 35].

The odds ratio (OR) for reports of serious “Hepatobiliary Disorders” for the combination drug amoxicillin / clavulanic acid compared to amoxicillin in the European Economic Area and the United Kingdom from 2020–2024 was 2.78 (95% CI 2.41–3.24) [32].

The hepatotoxic effect of amoxicillin is not a direct pharmacological effect but primarily an immunoallergic one [32]. This immune-mediated hypersensitivity leads to damage that is more often cholestatic or less commonly hepatocellular.

Polymorphism of *HLA* class I and II genes is considered a risk factor for the development of amoxicillin / clavulanate-induced liver injury, confirming the key role of the adaptive immune response in the pathogenesis of this complication [32].

A retrospective study analyzing AE reports in the global pharmacovigilance database VigiBase, registered in Switzerland from 2010 to 2020, showed that the amoxicillin / clavulanic acid combination was one of the most frequently suspected drugs in the development of severe drug-induced liver dysfunction (134—mention frequency of amoxicillin / clavulanic acid; 3.1%—of drugs; 6.6%—of individual AE reports). A total of 2042 individual AE reports were analyzed, including 10,646 drugs and 6,436 AEs.

Analysis using EudraVigilance data confirmed that the combination of amoxicillin and clavulanic acid is less safe than amoxicillin monotherapy, as the comparison of warnings about “hepatobiliary disorders” with the combination showed (OR = 2.78, 95% CI: 2.41–3.24) a stronger association between liver diseases and the use of amoxicillin and clavulanic acid-based drugs [32].

Data from a retrospective analysis of disproportionately using FAERS data for the period January 2010 to December 2023 showed that amoxicillin / clavulanic acid exhibited the most pronounced hepatotoxicity (OR = 4.56, 95% CI 4.12–5.03). The types of hepatotoxicity varied depending on the drug: cholestatic hepatitis was most common with amoxicillin / clavulanic acid [36].

Collectively, the available data suggest that elderly and senile patients exhibit increased vulnerability to DILI, largely attributed to age-associated decreases in hepatic blood flow, as well as changes in enzyme system activity and the clearance of drugs metabolized by the liver⁸. From a clinical-practical standpoint, age

⁷ VigiAccess. WHO global database of individual case safety reports. Available from: <https://www.vigiaccess.org/> (accessed 10.06.2026).

⁸ Clinical Guidelines. Medicinal liver damage; 2025. Available from: https://cr.minzdrav.gov.ru/view-cr/747_2. Russian

is a significant risk factor influencing the likelihood of developing drug-induced liver injury, as well as its type and phenotypic manifestation. Elderly patients predominantly experience cholestatic forms of DILI, along with a higher frequency of chronic progression compared to younger and middle-aged individuals.

Publications have described cases of DILI in elderly patients receiving ceftriaxone therapy [37, 38].

Direct randomized clinical trials specifically comparing cefodizime and ceftriaxone regarding the risk of biliary sludge / pseudolithiasis and hepatotoxicity in the PubMed database were not found; the available data only allow for indirect comparison of safety profiles based on clinical studies and review articles on cefodizime and ceftriaxone. Nevertheless, the totality of clinical and pharmacoepidemiological data indicates a higher risk of ceftriaxone-associated biliary complications and drug-induced liver injury compared to cefodizime, for which the hepato- and biliary safety profile appears more favorable.

Safety Profile of Cefodizime, Ceftriaxone, and Amoxicillin / Clavulanic Acid in Patients with Diseases of the Urinary System

A number of drugs can induce the development of nephrolithiasis and crystalline nephropathy; drug-induced stones account for 1% to 2% of all cases of urolithiasis [39].

Ceftriaxone is a poorly soluble drug with high urinary excretion, which promotes crystallization [39, 40].

T. Kimata et al. [41] conducted a case-control study involving 83 children with bacterial pneumonia aged 3 months to 8.9 years. The children were divided into two groups: 43 children receiving ceftriaxone (Group A) and 40 children receiving amoxicillin (Group B). Paired serum and urine samples were collected from patients in each group before and after treatment. No significant differences in demographic characteristics or blood biochemical parameters were found between the groups. However, the mean urinary calcium to creatinine ratio (uCa / Cr, mg/mg) was significantly higher in Group A patients than in Group B patients after treatment (0.19 vs. 0.09, $p < 0.001$), and analysis of paired urine samples showed that uCa / Cr significantly increased after treatment only in Group A

patients ($p < 0.001$). A weak, statistically insignificant correlation was found between ceftriaxone dose and uCa/Cr in Group A ($p = 0.10$, $r = 0.24$). The obtained results demonstrate that ceftriaxone can potentially significantly increase urinary calcium excretion, which, in turn, may be associated with ceftriaxone-associated urolithiasis or precipitate formation [41].

It should also be noted that transient hypercalciuria and increased excretion of oxalic and uric acids have been identified [42]; however, studies exist that confirm crystal formation with normal urinary calcium levels or other salts [43].

A. Louta et al. conducted a systematic review [39] that included 33 studies. Of these, 12 were case reports, 11 were prospective studies, 9 were retrospective studies, and only 1 was a randomized controlled trial. The systematic review aimed to analyze the known effects of ceftriaxone use in hospitalized pediatric patients, including an assessment of the likelihood of precipitate and stone formation in the biliary and urinary tracts, as well as an examination of the link with maternal history during pregnancy. The study results were analyzed to understand side effects and identify any predisposing factors.

According to the obtained results, the formation of urinary crystals after ceftriaxone administration is influenced by various risk factors, such as urinary stasis, family history, metabolic disorders (e.g., hypercalciuria), changes in urine pH, infection, environmental factors (e.g., high temperature), low urine output, high drug dosage, prolonged treatment, high urinary drug excretion, and concomitant therapy. The most common manifestation was kidney stone formation [43].

Although litholysis occurred early (by the end of the first week), cases of stone dissolution were noted to occur after 7 months [43].

The results of a systematic review and meta-analysis of 8 clinical studies ($n = 760$), which provided a pooled estimate of the incidence of ceftriaxone-induced urolithiasis in children, showed that the incidence of ceftriaxone-induced urolithiasis was 7% (95% CI 2–12%), with significant variability observed due to study design and diagnostic approach [25].

According to the Vigibase Database⁹, 2424 ARs related to kidney and urinary tract disorders

⁹ Vigibase. WHO global database of individual case safety reports.

have been reported with ceftriaxone use, accounting for 1% of all reported ARs. The structure of ARs related to kidney and urinary tract disorders includes: nephrolithiasis—129 reports, crystalluria—31 reports, ureterolithiasis—24 reports, urinary stone—18 reports, bladder stone—13 reports, ureteral obstruction—6 reports, crystalline nephropathy—4 reports, urinary tract obstruction—4 reports, urethral stone—2 reports, urethral obstruction—2 reports, bladder obstruction—1 report.

Summary information on patients with urological pathology who have transurethral or ureteral catheters is presented in Table 2.

Ceftriaxone therapy can induce precipitation of the drug's calcium salts in the urinary tract. This phenomenon is predominantly observed in the pediatric population when high daily dosages (≥ 80 mg/kg) or cumulative doses exceeding 10 g are administered, especially in the presence of dehydration and immobilization. Microlithogenesis can be subclinical or manifest as ureteral obstruction with subsequent development of postrenal acute kidney injury. The phenomenon is fully reversible: crystal excretion and restoration of urodynamics occur after discontinuation of the antibiotic¹⁰.

Drug Interactions with Anticoagulants

Warfarin is the most widely used oral anticoagulant worldwide [44]. It is a vitamin K antagonist with a narrow therapeutic range, influenced by genetic polymorphism, drug interactions, and diet. Indications for the use of vitamin K antagonists include the following [45]: atrial fibrillation, acute coronary syndrome, heart failure, prosthetic heart valve, stroke, venous thromboembolism (VTE), pulmonary embolism, antiphospholipid syndrome.

Atrial fibrillation (AF) is the most common type of arrhythmia in adults, affecting approximately 59.7 million people worldwide as of 2019, an 111% increase since 1990 [46].

Over the past 20 years, the prevalence of AF has increased by 33%, and it is projected to increase by more than 60% by 2050. Age plays a crucial role in the factors contributing to AF development. Its prevalence is low (0.1%) in adults younger than 55 years, but increases to 5.9% in individuals aged 65 years and

older and to 9.0% in individuals aged 80 years and older [46].

AF is associated with an increased risk of stroke, so patients with AF are recommended to take oral anticoagulants (OACs) to reduce this risk [47].

The global prevalence and use of OACs increased from 42% in 2010 to 78% in 2018, respectively. Following the introduction of direct oral anticoagulants (DOACs), the proportion of OAC users worldwide nearly doubled [48]. Given the high prevalence of OAC use, it is important to assess the presence of clinically significant interactions between OACs and the antibacterial drugs being studied.

Numerous studies have convincingly confirmed an increased risk of serious bleeding in patients concurrently receiving antibiotics and warfarin [44, 49–51]. Cephalosporins and amoxicillin / clavulanic acid, despite not affecting the cytochrome P450 system, have shown a positive correlation with increased INR values.

However, one of the common complications associated with warfarin therapy is an increased risk of serious bleeding, especially when used concurrently with drugs that can affect its metabolism [44].

Specifically, antibiotics can influence the anticoagulant effect of warfarin through various mechanisms. Antibacterial drugs can induce or inhibit the activity of the CYP2C9 isoenzyme, which is crucial for warfarin metabolism. Furthermore, some antibiotics can disrupt the population of vitamin K-producing bacteria in the gut, further modulating warfarin's pharmacological response. As a result, these drug interactions can either enhance or weaken warfarin's efficacy, which can have potential clinical consequences [44].

Numerous cases have been described in the literature of the simultaneous use of amoxicillin or amoxicillin / clavulanic acid and warfarin, demonstrating an increase in the international normalized ratio (INR) and/or bleeding from 7 days after the start of amoxicillin to 9 days after discontinuation of amoxicillin therapy [44, 52, 53].

A prospective cross-sectional observational study conducted by M.I. Abdel-Aziz et al. [49] involving 120 patients investigated the effect of polypharmacy and high doses of amoxicillin / clavulanate on the intensity of the anticoagulant effect of warfarin in

¹⁰ Global hepatitis report 2026. Geneva: World Health Organization; 2026.

hospitalized patients. Potentially interacting drugs were classified according to their propensity to increase INR or bleeding risk. In 87.5% of patients receiving high doses of amoxicillin / clavulanic acid (10–12 g per day), INR values reached ≥ 4 , compared to 28.9% of patients receiving standard doses (up to 3.6 g per day) during hospitalization ($p \leq 0.001$). An increase in the number of potentially interacting drugs known to increase INR was a significant predictor of INR values ≥ 4 (OR = 2.5; 95% CI 1.3–4.7), and an increase in the number of potentially interacting drugs that increase bleeding risk was a significant predictor of bleeding episodes (OR = 3.1; 95% CI 1.3–7.3). This is likely due to the fact that most penicillins (with the exception of nafcillin and dicloxacillin) suppress intestinal microflora. This leads to a decrease in the population of vitamin K-producing bacteria, a deficiency of the latter, and consequently, an enhanced anticoagulant effect of warfarin [54].

A smaller number of intestinal bacteria producing vitamin K likely leads to a decrease in the amount of vitamin K-dependent plasma clotting

factors, enhancing the anticoagulant effect of warfarin [44].

Cephalosporins have been found to interact with warfarin, increasing the risk of hypoprothrombinemia, inhibiting P-glycoprotein, and altering gastrointestinal microflora [44].

A clinical case of hemarthrosis in an 85-year-old female patient with phlegmon during therapy with cephalosporin (ceftazoline) and warfarin, due to developed hypoprothrombinemia, has been described [55].

The mechanism of interaction between ceftriaxone and warfarin is currently not well understood. However, it is known that antibiotics can disrupt normal intestinal flora, which produces a significant amount of vitamin K. A small study in healthy volunteers showed that intestinal bacteria produce approximately 1.6 mg of menaquinones (bacterially synthesized vitamin K) [56].

Table 1 — Frequency of adverse reactions associated with impaired liver, biliary tract, and pancreatic function with the use of amoxicillin / clavulanic acid, ceftriaxone, cefodizime

Adverse Reaction	Amoxicillin / clavulanic acid ¹¹	Ceftriaxone ¹²	Cefodizime ¹³
ALP	uncommon	common	Rare
ALT	uncommon	common	rare
AST	uncommon	common	rare
Hepatitis	very rare	not identified	not identified
Cholestatic jaundice	very rare	not identified	not identified
Pancreatitis	Frequency unknown	The use of ceftriaxone is associated with rare episodes of pancreatitis, the pathogenesis of which may be due to the phenomenon of biliary pseudolithiasis obstruction. Although the initial patient cohort was characterized by high comorbidity and the presence of pre-existing risk factors for cholestasis (including parenteral nutrition), the trigger role of precipitates, consisting of calcium-ceftriaxone conglomerates, in the lumen of the bile ducts cannot be completely excluded.	not identified

Note: ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase.

¹¹ Register of OHLP and LV of the EAEU. Amoxicillin+[Clavulanic acid] powder for solution preparation for intravenous administration, 500 mg+100 mg, 1000 mg+200 mg (vials), LP-No.(002949)-(RG-RU) dated Aug 07, 2023. Available from: https://lk.regmed.ru/Register/EAEU_SmPC

¹² Register of OHLP and LV of the EAEU. Ceftriaxone powder for solution preparation for intravenous and intramuscular administration, 1.0 g (vials) LP-No.(005496)-(RG-RU) dated May 17, 2024. Available from: https://lk.regmed.ru/Register/EAEU_SmPC

¹³ Register of OHLP and LV of the EAEU. Mizida-AG (Cefodizim) powder for solution preparation for intravenous and intramuscular administration, 2000 mg, LP-No.(010400)-(RG-RU) dated June 02, 2025. Available from: https://lk.regmed.ru/Register/EAEU_SmPC

Table 2 — Patients with urological pathology having transurethral or ureteral catheters

Pathology	Amoxicillin / clavulanic acid	Ceftriaxone	Cefodizime
Hematuria	very rare	rare	not identified
Glucosuria	not identified	rare	not identified
Precipitates in the urinary tract	In individuals with impaired renal excretion, the formation of crystals and the development of obstructive uropathy are observed extremely rarely, including acute renal failure.	The accumulation of crystalline conglomerates in the lumen of the urinary tract can initiate their obturation with subsequent development of postrenal acute renal failure.	not identified

Table 3 — Drug interactions of cefodizime, ceftriaxone, and amoxicillin / clavulanic acid with oral anticoagulants (vitamin K antagonists)

Interaction	Amoxicillin / clavulanic acid	Ceftriaxone	Cefodizime
Leukopenia	rare	common	frequency unknown
Thrombocytopenia	rare	common	frequency unknown
Coagulopathy	In patients receiving a combination of amoxicillin with clavulanic acid along with indirect anticoagulants, an increase in prothrombin time (increase in INR) has been reported in rare cases.	uncommon	frequency unknown
Interaction with anticoagulants (vitamin K antagonists)	Rare cases of increased International Normalized Ratio (INR) have been described in the literature in patients when acenocoumarol or warfarin was used concurrently with amoxicillin. When indirect (oral) anticoagulants are prescribed concurrently with a combination of amoxicillin and clavulanic acid, monitoring of relevant parameters is necessary, and a dose adjustment of anticoagulants may be required.	The risk of bleeding increases when vitamin K antagonists are used during ceftriaxone therapy. Blood coagulation parameters should be constantly monitored, and the dose of vitamin K antagonists should be adjusted if necessary.	not described

Note: INR, International Normalized Ratio.

Ceftriaxone is excreted in bile by approximately 33–67%, forming relatively high concentrations in the intestine¹⁴. This pharmacokinetic characteristic allows ceftriaxone to disrupt normal intestinal flora to a greater extent than other antibiotics primarily excreted by the kidneys, thereby causing a greater reduction in vitamin K synthesis.

In a retrospective study by L.M. Saum et al. [56], the increase in INR from baseline was compared in patients ($n = 120$) receiving long-term warfarin therapy and diagnosed with urinary tract infections, who were treated with ceftriaxone, a first-generation cephalosporin (cefazolin or cephalexin), or a penicillin (ampicillin / sulbactam, amoxicillin / clavulanic acid, piperacillin/tazobactam). It was found that the ceftriaxone group ($n = 27$) showed a statistically significantly higher peak INR compared to all other antibiotics studied (ceftriaxone—3.56, first-

generation cephalosporins—2.66, penicillins—2.98, ciprofloxacin—2.3; $p = 0.004$), as well as a statistically significantly greater degree of INR change (+1.19, +0.66, +0.8, +0.275; $p = 0.006$), and a statistically significantly greater percentage change in INR compared to ciprofloxacin (54.4% vs. 12.7%; $p = 0.037$) [56].

Ceftriaxone interacts with warfarin, increasing the INR in patients more than other commonly prescribed antibiotics for the treatment of urinary tract infections.

A summary of drug interactions between cefodizime, ceftriaxone, and amoxicillin / clavulanic acid with oral anticoagulants (vitamin K antagonists) is presented in Table 3.

A study conducted at Tikur Anbessa Hospital [57] found a moderate drug interaction between ceftriaxone and heparin (22.6%) and warfarin (6.7%). Bleeding or elevated INR was observed in 6 patients (1.9%), with one patient dying from bleeding.

Similar results were obtained in another retrospective study conducted in hospitals in Eastern

¹⁴ Register of OHLP and LV of the EAEU. Ceftriaxone powder for solution preparation for intravenous and intramuscular administration, 1.0 g (vials) LP-No.(005496)-(RG-RU) dated May 17, 2024.

Ethiopia [58], which analyzed the medical records of 271 patients. A total of 71 drugs were prescribed concurrently with ceftriaxone, most commonly metronidazole and tramadol. Ceftriaxone was most frequently used for postoperative prophylaxis ($n = 80$, 27.5%) and for the treatment of pneumonia ($n = 62$, 21.3%). Moderate drug interactions between ceftriaxone and unfractionated heparin ($n = 6$), warfarin ($n = 5$), and enoxaparin ($n = 1$) were found among concurrently prescribed drugs.

Review Limitations

The work performed has several important limitations that may affect the interpretation and generalization of the results.

Limitation of Design and Methodology. The authors conducted a non-systematic review, which is a major limitation of this study. Although the database we used is the most widely used in medicine, it does not fully cover all available information.

A significant number of studies were retrospective and had small patient samples. Large pharmacoepidemiological studies evaluating the long-term safety of cefodizime are lacking, and we also did not find studies that directly compared the safety profiles of the drugs studied.

CONCLUSION

It has been established that cefodizime, ceftriaxone, and amoxicillin / clavulanic acid are effective antibacterial drugs for the treatment of infections in patients with comorbid pathology. However, their safety profiles differ and should be considered when choosing therapy in high-risk patients.

Cefodizime demonstrated a favorable tolerability profile: no signals of hepatotoxicity or nephrotoxicity were noted in available clinical data, and no clinically significant drug interactions with oral anticoagulants were identified, unlike ceftriaxone and amoxicillin / clavulanic acid. These features make cefodizime a potentially preferred option in comorbid patients receiving anticoagulant therapy and/or having risk factors for VTE and kidney disease.

However, the volume of available clinical studies on cefodizime remains limited, which does not allow for a definitive determination of its place in the therapy of comorbid patients compared to the more studied ceftriaxone and amoxicillin / clavulanic acid. Further prospective randomized and observational studies, including patients with polymorbidity and polypharmacy, are needed for a more detailed assessment of the safety profile and confirmation of the obtained results.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

AUTHORS' CONTRIBUTION

Sergey K. Zyryanov — conceptualization, formal analysis, writing—original draft, writing—review & editing; Elena I. Kondratyeva — investigation, writing—review & editing; Elena A. Baibulatova — visualization, writing—original draft. All authors confirm that their authorship meets the international ICMJE criteria (all authors made a significant contribution to the development of the concept, conduct of the study and preparation of the article, read and approved of the final version before the publication).

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