U.S. National Library of Medicine
National Center for Biotechnology Information

NLM Citation: LiverTox: Clinical and Research Information on Drug-Induced Liver Injury [Internet]. Bethesda (MD): National Institute of Diabetes and Digestive and Kidney Diseases; 2012-. Cephalosporins. [Updated 2017 Jan 9].
Bookshelf URL: https://www.ncbi.nlm.nih.gov/books/

Cephalosporins

Updated: January 9, 2017.

OVERVIEW

The cephalosporins are a family of bactericidal antibiotics structurally related to penicillin which were first derived from the fungus, Cephalosporum acremonium. Their basic structure is similar to penicillin with a thiazolidine and beta-lactam ring, which has a variable side chain. Cephalosporins bind to the penicillin-binding proteins on bacteria and inhibit synthesis of the bacterial cell wall, causing cell lysis particularly in rapidly growing organisms. Their differences in activity relate to the range of penicillin-binding proteins that they inhibit. They have a broader activity than the standard penicillins, but are also sensitive to some extent to beta-lactamase. Five generations of cephalosporins have been developed with varying antibacterial activity. Cephalosporins are indicated for infections with susceptible organisms. Cephalosporins have variable oral absorption and many must be given parenterally. In the lists below, formulations that are available in oral and parenteral forms are shown separately.

First generation cephalosporins include cefadroxil, cefazolin, cephalexin, and cephradine, and these are active against many gram-positive cocci, including penicillinase-producing Staphylococcus aureus.

Second generation cephalosporins include cefaclor, cefoxitin, cefprozil, cefonicid, and cefuroxime; these have broader antibacterial activity, and additional sensitive organisms including Citrobacter, Enterobacter, Haemophilus influenzae, Neisseria and Serratia species.

Third generation cephalosporins include cefdinir, cefditoren, cefixime, cefoperazone, cefotaxime, cefpodoxime, ceftazidime, ceftibuten, ceftizoxime, and ceftriaxone, which are less active than first- and second generation drugs against gram-positive bacteria, but more active against gram-negative organisms and have greater stability against beta-lactamases.

Fourth generation cephalosporins include cefepime, which are active against a wide range of both gram-positive and gram-negative organisms.

Fifth generation cephalosporins include ceftaroline and ceftolozane/tazabactam, which are active against a wide range of both gram-positive and gram-negative organisms including methicillin resistant Staphylococcus aureus (MRSA). These agents are sometimes referred to as advanced generation rather than fifth generation cephalosporins.

Cephalosporins have side effects similar to penicillin, and drug-allergy and hypersensitivity are often (but not always) shared. The cephalosporins in general have been associated with little hepatotoxicity and only rare instances of drug induced liver injury due to these agents have been published. A special exception is ceftriaxone, a third generation cephalosporin which, when given parenterally, can cause biliary sludge with

symptoms of cholecystitis and cholestatic jaundice. For these reasons, other than for ceftriaxone, the cephalosporins will be discussed as a general class rather than individual agents, and separately for the intravenous and oral forms.

The cephalosporins are assigned a likelihood score of causing clinically apparent liver injury as a class. Some have been implicated in only a few cases, but in general the liver injury from cephalosporins is similar from case to case. The typical case of liver injury from cephalosporins is a self-limited cholestatic hepatitis with mild if any immunoallergic features that arises 1 to 3 weeks after starting therapy, sometimes occurring after a single parenteral dose.

Oral Cephalosporins

- Cefaclor (2nd)
- Cefadroxil (1st)
- Cefdinir (3rd)
- Cefditoren (3rd)
- Cefixime (3rd)
- Cefpodoxime (3rd)
- Cefprozil (2nd)
- Ceftibuten (1st)
- Cephalexin (1st)
- Cefuroxime (2nd)
- Cephradine (1st)
- Loracarbef (2nd)

Parenteral Cephalosporins

- Cefazolin (1st)
- Cefepime (4th)
- Cefoperazone (3rd)
- Cefotaxime (3rd)
- Cefoxitin (2nd)
- Ceftaroline (5th)
- Ceftazidime (3rd)
- Ceftibuten (3rd)
- Ceftizoxime (3rd)
- Ceftolozane/Tazobactam (5th)
- Cefuroxime (2nd)
- Cephradine (1st)
- Ceftriaxone (3rd)

ANNOTATED BIBLIOGRAPHY

References updated: 09 January 2017

Zimmerman HJ. Cephalosporins. In, Hepatotoxicity: The Adverse Effects of Drugs and Other Chemicals on the Liver. 2nd Ed. Philadelphia: Lippincott, 1999. p. 589-92.

(Expert review of cephalosporins and liver injury published in 1999; mentions that "cephalosporin use has been relatively free of serious hepatic injury" with rare descriptions of cholestatic injury).

Moseley RH. Hepatotoxicity of antimicrobials and antifungal agents. In, Kaplowitz N, DeLeve LD, eds. Drug-induced liver disease. 3rd Edition. Amsterdam: Elsevier, 2013. p. 466.

(Short review of cephalosporin induced liver injury mentions that hepatotoxicity from cephalosporins is rare and usually resembles penicillin induced liver injury).

Petri WA Jr. Penicillins, cephalosporins, and other ß-lactam antibiotics. In, Brunton LL, Chabner BA, Knollman BC, eds. Goodman & Gilman's The pharmacological basis of therapeutics, 12th ed. New York: McGraw-Hill, 2011. p. 1477-1504.

(Textbook of pharmacology and therapeutics).

Fung-Herrera CG, Mulvaney WP. Cephalexin nephrotoxicity. Reversible nonoliguric acute renal failure and hepatotoxicity associated with cephalexin therapy. JAMA 1974; 229: 318-9. PubMed PMID: 4406795.

(70 year old man developed nonoliguric renal failure after 8 days of cephalothin-cephalexin with mild jaundice [2.4 mg/dL, AST 85 U/L, Alk P 276 U/L], resolving within a month of stopping).

McArthur JE, Dyment PG. Stevens-Johnson syndrome with hepatitis following therapy with ampicillin and cephalexin. N Z Med J 1975; 81: 390-2. PubMed PMID: 1057088.

(9 month old boy given ampicillin [developing rash 3 days after stopping] and then cephalexin [developing Stevens-Johnson after 3 days], also developed jaundice [bilirubin 13 mg/dL, ALT 460 U/L, Alk P normal], resolving with prednisone; relative role of cephalexin vs ampicillin was unclear).

Schaefer UW, Hackenberg K, Reinwein D. [Cholestatic hepatitis as unusual allergic reaction in cephalothin-treatment] MMW Munch Med Wochenschr 1975; 117: 251-2. German. PubMed PMID: 804105.

(29 year old man developed cholestatic hepatitis [bilirubin 1.7 mg%, ALT 280 U/L, Alk P 404 U/L] after 18 days of intravenous cephalothin therapy; history of penicillin allergy [fever and rash]; hepatitis resolved within 4 weeks of stopping).

Lambert DH. Cephalosporin hepatitis. Anesth Analg 1980; 59: 806-7. PubMed PMID: 7191664.

(Letter arguing that cephalosporins rather than enflurane accounted for hepatitis described by Ona et al.).

Ammann R, Neftel K, Hardmeier T, Reinhardt M. Cephalosporin-induced cholestatic jaundice. Lancet 1982; 2: 337. PubMed PMID: 6124751.

(36 year old woman developed jaundice [bilirubin ~11.7 mg/dL, AST 6 times, Alk P 4 times ULN] after a week of cephalosporin therapy–cefazolin and cefadroxil—with slow resolution of Alk P abnormalities).

Gnann JW Jr, Goetter WE, Elliott AM, Cobbs CG. Ceftriaxone: in vitro studies and clinical evaluation. Antimicrob Agents Chemother 1982; 22: 1-9. PubMed PMID: 6289734.

(Experience in 55 adults given ceftriaxone for severe infections; cure rate of 93%; adverse events in 40%, eosinophilia in 8%, elevated enzymes in 16%, ALT 54-360 U/L, Alk P 151-400 U/L; elevations were transient and resolved with stopping).

Cholestatic jaundice and hematuria due to hypersensitivity to cefaclor in a child. Clin Toxicol 1983; 20: 79. PubMed PMID: 6887302.

(4 year old boy developed hepatitis, fever and gastrointestinal upset after 8 days of oral cefaclor [bilirubin 1.7 mg/dL, ALT 270 U/L, Alk P 677 U/L, no eosinophilia or autoantibodies], which resolved ultimately but specifics on time not given).

Kanetaka T, Oda T. Toxic liver injuries. Acta Pathol Jpn. 1973; 23: 617-27. PubMed PMID: 4800729.

(General review of hepatotoxicity with examples, including case of cephalothin hepatotoxicity, but with few details, other than eosinophilia, fever and hyperglobulinemia; biopsy showed focal necrosis).

Døssing M, Andreasen PB. Drug-induced liver disease in Denmark: an analysis of 572 cases of hepatotoxicity reported to the Danish board of adverse reactions to drugs. Scand J Gastroenterol 1982; 17: 205-11.

PubMed Citation *(Among 572 reports of drug induced liver injury from Denmark between 1968 and 1978, representing 6% of total adverse drug reaction reports and 12% of fatal ones, cephalosporins were not mentioned as a cause).*

Miller WI, Souney PF, Chang JT. Hepatic dysfunction following nafcillin and cephalothin therapy in a patient with a history of oxacillin hepatitis. Clin Pharm 1983; 2: 465-8. PubMed PMID: 6627877.

(Mild ALT elevations found after 13 days of high dose oxacillin [18 g/day], similar increase after nafcillin in an injection drug user. Occurrence after cephalosporin as well, but ALT was raised an outset perhaps due to hepatitis C).

File TM Jr, Tan JS, Salstrom SJ. Clinical evaluation of ceftriaxone. Clin Ther 1984; 6: 653-61. PubMed PMID: 6090021.

(Analysis of 77 patients receiving ceftriaxone for serious infections: 93% efficacy; ALT elevations in 8 [10%, peak levels 92 U/L]).

Oakes M, MacDonald H, Wilson D. Abnormal laboratory test values during ceftriaxone therapy. Am J Med 1984; 77: 89-96. *(Analysis of laboratory test adverse events among 2,640 children and adults receiving ceftriaxone in prelicensure clinical trials;* PubMed PMID: 6093527.

ALT elevations occurred in 3.3% vs 1.8% receiving comparative agents, but only 4 patients stopped ceftriaxone for liver test abnormalities, one of whom had clinical jaundice).

Moskovitz BL. Clinical adverse effects during ceftriaxone therapy. Am J Med 1984; 77 (4C): 84-8. PubMed PMID: 6093526.

(Review of adverse effects of ceftriaxone from pre-licensure studies; 2640 patients in 153 studies, allergic reactions in 3%; jaundice in 2 patients, both septic and resolved with stopping therapy; no mention of biliary cholic).

Parry MF. Toxic and adverse reactions encountered with new beta-lactam antibiotics. Bull N Y Acad Med 1984; 60: 358-68. PubMed PMID: 6586251.

(Review suggesting that hepatitis occurs in "2-5%" of cephalosporin- and penicillin treated patients).

Jacob LS, Layne P. Cefonicid: an overview of clinical studies in the United States. Rev Infect Dis 1984; 6 (Suppl 4): S791-802. PubMed PMID: 6395272.

(Overview of experience with cefonicid; ALT elevations found in 1.1% of 1118 patients, but no mention of clinically apparent liver injury).

Wolf V, Schomerus A, Berg P. Schwere Leberschadigung als medikamentos-allergische Reaktion auf Cefoperazon. Z Gastroenterologie 1985; 23: 198-202. PubMed PMID: 4060811.

(20 year old man developed fever and jaundice [bilirubin 3.3 mg/dL, ALT 4510 U/L, Alk P 888 U/L] after 23 days of iv therapy with cefoperazone, a 3rd generation cephalosporin with accompanying renal dysfunction and gastrointestinal bleeding, recovery within 2 months of stopping).

Eggleston SM, Belandres MM. Jaundice associated with cephalosporin therapy. Drug Intell Clin Pharmacol 1985; 19: 553. PubMed PMID: 4028960.

(Two patients ages 30 and 69 years developed jaundice 5 and 9 days after starting parenteral cephalosporin [cefamandole and cephapirin] therapy [bilirubin 2.2 and 6.5 mg/dL, ALT ~80 and ~20 U/L, Alk P 85 and 74 U/L]; other possible diagnoses were total parenteral nutrition jaundice, heart failure and sepsis).

Barson WJ, Miller MA, Brady MT, Powell DA. Prospective comparative trial of ceftriaxone vs. conventional therapy for treatment of bacterial meningitis in children. Pediatr Infect Dis 1985; 4: 362-8. PubMed PMID: 3895175.

(Trial comparing ceftriaxone to ampicillin/chloramphenicol for meningitis in 50 children; similar efficacy, more diarrhea with ceftriaxone and 11% had minor ALT elevations, returning to normal during or after therapy).

Norrby SR. Side effects of cephalosporins. Drugs 1987; 34 (Suppl 2): 105-20. PubMed PMID: 3319495.

(Clinical review of side effects of cephalosporins; ALT elevations in 1-8% and rare cases of hepatitis, usually with allergic symptoms; little evidence for cross sensitivity to hepatic damage with penicillins).

Saito A. Cefmetazole postmarketing surveillance in Japan. J Antimicrob Chemother 1989; 23 (Suppl D): 131-9. PubMed PMID: 2722721.

Fekety FR. Safety of parenteral third-generation cephalosporins. Am J Med 1990; 88 (Suppl 4A): 38S-44S. PubMed PMID: 2183609.

(Review article stating that ALT elevations can occur on cephalosporin therapy, but clinically apparent liver disease is rare).

Friis H, Andreasen PB. Drug-induced hepatic injury: an analysis of 1100 cases reported to the Danish Committee on Adverse Drug Reactions between 1978 and 1987. J Intern Med 1992; 232: 133-8. 1506809. PubMed PMID: 1506809.

(Among liver adverse drug reaction reports in Denmark between 1979 and 1987, cephalosporins not mentioned as a cause).

Thompson JW, Jacobs RF. Adverse effects of newer cephalosporins. An update. Drug Safety 1993; 9: 132-42. PubMed PMID: 8397890.

(Review; transient increases in ALT, AST or Alk P occur in 0.7%, 6%, 11% and 28% of prospectively followed patients treated with various cephalosporins; clinically significant biliary sludge occurs with ceftriaxone, particularly in children, not found with other cephalosporins).

Di Martino V, Cadranel J-F, Attali P. [Hepatobiliary complications of the cephalosporins]. Gastroenterol Clin Biol 1994; 18: 839-46. PubMed PMID: 7875391.

(Review; despite widespread use of cephalosporins for more than 15 years, cases of hepatotoxicity are rare, variable in type and rarely severe).

Kojima N, Kumamoto I, Masumoto T, Onji M. A case report of drug-induced allergic hepatitis probably due to the N-methyltetrazolethiol group cephalosporin. Arerugi 1994; 43: 511-4. PubMed PMID: 8198460.

(38 year old woman given cefpiramide for 22 days, developed jaundice 10 days later [bilirubin 13 mg/dL, ALT 920 U/L, GGT 69 U/L], resolving within 2 months of stopping; positive lymphocyte transformation test to cephalosporins with N-methyltetrazolethiol group).

Benyounes M, Horsmans Y, Galand C, Lambert M. [Acute cytolytic hepatitis caused by cefazolin and metronidazole] Gastroenterol Clin Biol 1995; 19: 740-1. French. PubMed PMID: 8522133.

(55 year old woman developed fever, rash and acute liver injury with mild jaundice [ALT 90 times and Alk P 3 times ULN, bilirubin 2.0 mg/dL] after 25 days of combination therapy with iv cephazolin and oral metronidazole, resolving 2 months after stopping).

George DK, Crawford DH. Antibacterial-induced hepatotoxicity. Incidence, prevention and management. Drug Saf 1996; 15: 79-85. PubMed PMID: 8862966.

(Review of hepatotoxicity from antibiotics; liver injury from cephalosporins is extremely rare, although elevations in aminotransferases occur in 0.7-11% of treated patients).

Combe C, Banas B, Zoller WG, Manns MP, Schlöndorff D. [Antibiotic-induced prolonged cholestasis: suspected induction by ceftibuten] Z Gastroenterol 1996; 34: 434-7. German. PubMed PMID: 8928538.

(43 year old woman developed fever followed by prolonged severe cholestatic hepatitis [bilirubin 15.2 mg/dL, ALT 280 U/L, Alk P 2,075 U/L] after 3 days of ceftibuten, but also following 5 days of amoxicillin; died of pseudomonas sepsis with deep jaundice, but without vanishing bile ducts).

Pillans PI. Drug associated hepatic reactions in New Zealand: 21 years' experience. N Z Med J 1996; 109: 315-9. PubMed PMID: 8816722.

(Survey of adverse drug reaction reports found 943 causes of liver injury; cephalosporins not mentioned in the top 20 drugs during the three periods of study).

García Rodríguez LA, Ruigómez A, Jick H. A review of epidemiologic research on drug-induced acute liver injury using the general practice research data base in the United Kingdom. Pharmacotherapy 1997; 17: 721-8. PubMed PMID: 9250549.

(Combined analysis of 8 epidemiologic studies using the UK General Practice Research Database estimated incidence rates of acute liver injury to be highest for isoniazid [400 per 100,000 users] and low for cephalexin [2.0 per 100,000]; only 4 cases identified).

Yossepowitch O, Amir G, Safadi R, Lossos I. Ischemic hepatitis associated with toxic epidermal necrolysis in a cirrhotic patient treated with cefuroxime. Eur J Med Res 1997; 2: 182-4. PubMed PMID: 9110927.

(84 year old woman with HBV related cirrhosis developed toxic epidermal necrolysis after 1 day of cefuroxime [and gentamicin] therapy; 8 days later developed liver failure [bilirubin 7.8 mg/dL, ALT 1155 U/L, INR 2.13], autopsy showed "ischemic" necrosis; no HBV markers given).

Björnsson E, Olsson R. Acute liver injury due to loracarbef. J Hepatol 1997; 26: 739-40. PubMed PMID: 907568.

(Cholestatic hepatitis [bilirubin 19.3 mg/dL, ALT 72 U/L, Alk P 780 U/L] with severe pruritus arising 2 weeks after stopping a 4 week course of loracarbef, an oral cephalosporin, resolving within 3 months of stopping).

Longo F, Hastier P, Buckley MJ, Chichmanian RM, Delmont JP. Acute hepatitis, autoimmune hemolytic anemia, and erythroblastocytopenia induced by ceftriaxone. Am J Gastroenterol 1998; 93: 836-7. PubMed PMID: 9625142.

(80 year old man developed jaundice 3 days after a 12-day course of oral ceftriaxone, [bilirubin 22 times, ALT 11 times and Alk P 6 times ULN], followed by severe hemolytic anemia during recovery requiring prednisone and resolving only by 6 months after stopping).

Famularo G, Bizzarri C, Federico M, et al. Eosinophilic hepatitis associated with cefonicid therapy. Ann Pharmacother 2001; 35: 1669-70. PubMed PMID: 11793641.

(67 year old man developed nausea and abdominal pain 14 days after starting cefonicid therapy [bilirubin normal, ALT 312 U/L, Alk P 563 U/L, eosinophils 22%], resolving within 1-8 weeks of stopping).

Sgro C, Clinard F, Ouazir K, Chanay H, Allard C, Guilleminet C, Lenoir C, et al. Incidence of drug-induced hepatic injuries: a French population-based study. Hepatology 2002; 36: 451-5. PubMed PMID: 12143055.

(All adverse drug reactions from French region from 1997-2000 found 34 cases of liver injury,–2 deaths–for an incidence of 14/100,000, none related to a cephalosporin).

Skoog SM, Smyrk TC, Talwalkar JA. Cephalexin-induced cholestatic hepatitis. J Clin Gastroenterol 2004; 38: 833. PubMed PMID: 15365421.

(51 year old man received single infusion of cefazolin preoperatively for Achilles tendon repair, followed 2 weeks later by 10 day course of cephalexin and had onset of dark urine within 3 days eventually developing fever, hives and jaundice [bilirubin 17.9 mg/dL, ALT 87 U/L, Alk P 272 U/L], resolving within 2-3 months of stopping).

Köklü S, Yüksel O, Yolcu OF, Arhan M, Altiparmak E. Cholestatic attack due to ampicillin and cross-reactivity to cefuroxime. Ann Pharmacother 2004; 38: 1539-40. PubMed PMID: 15266040.

(Follow-up on previous report of liver injury from ampicillin, 23 year old man redeveloped liver injury 17 days after starting a 10 day course of oral cefuroxime [bilirubin 0.7 mg/dL, ALT 427 U/L, Alk P 646 U/L], resolving within 2 months; suggesting cross reactivity with ampicillin).

Ravisha MS, Godambe SV. Ceftriaxone induced cholestasis in a neonate: a case report. Indian J Med Sci 2004; 58: 73-4. PubMed PMID: 14993721.

(17 year old boy developed cholestasis after 7 days of iv ceftriaxone; sludge on ultrasound [bilirubin 2.6 mg/dL, ALT 98 U/L, Alk P 1194 U/L], resolving within 3-7 days).

Russo MW, Galanko JA, Shrestha R, Fried MW, Watkins P. Liver transplantation for acute liver failure from drug-induced liver injury in the United States. Liver Transpl 2004; 10: 1018-23. PubMed PMID: 15390328.

(Among ~50,000 liver transplants reported to UNOS between 1990 and 2002, 270 [0.5%] were done for drug induced acute liver failure, but no case was attributed to a cephalosporin).

de Abajo FJ, Montero D, Madurga M, García Rodríguez LA. Acute and clinically relevant drug-induced liver injury: a population based case-control study. Br J Clin Pharmacol 2004; 58: 71-80. PubMed PMID: 15206996.

(Analysis of General Practice Research Database from UK on 1.6 million persons from 1994-2000 found 128 cases of drug induced liver injury (2.4/100,000 person years); 2 occurred in patients receiving cephalosporins, but other agents were being taken and the adjusted odds ratio for risk of hepatotoxicity was not significantly elevated for cephalosporins).

Bjornsson E, Jerlstad P, Bergqvist A, Olsson R. Fulminant drug-induced hepatic failure leading to death or liver transplantation in Sweden. Scand J Gastroenterol 2005; 40: 1095-101. PubMed PMID: 16165719.

(Survey of all cases of DILI with fatal outcome from Swedish Adverse Drug Reporting system from 1966-2002; 103 cases identified as highly probable, probable or possible; no case was attributed to a cephalosporin).

Bell MJ, Stockwell DC, Luban NL, et al. Ceftriaxone-induced hemolytic anemia and hepatitis in an adolescent with hemoglobin SC disease. Pediatr Crit Care Med 2005; 6: 363-6. PubMed PMID: 15857541.

(17 year old boy with sickle cell disease and severe hemolytic anemia given ceftriaxone developed progressive renal and hepatic failure and death; liver failuire likely due to shock).

Rivkin AM. Hepatocellular enzyme elevations in a patient receiving ceftriaxone. Am J Health Syst Pharm 2005; 62: 2006-10. PubMed PMID: 16174837.

(Case report and literature review; seriously ill 31 year old man in ICU had increase in ALT from 9 to 56 to 442 U/L, but normal Alk P and bilirubin and no symptoms, after 7 days of ceftriaxone therapy, with resolution within 2 weeks of switching antibiotics).

Bilici A, Karaduman M, Cankir Z. A rare case of hepatitis associated with cefprozil therapy. Scand J Infect Dis 2007; 39: 190-2. PubMed PMID: 17366046.

(15 year old girl developed jaundice 1 week after finishing a 10 day course of cefprozil [bilirubin 3.5 mg/dL, ALT 543 U/L, Alk P 247 U/L], resolving within 4 weeks).

Pacik PT. Augmentation mammaplasty: postoperative cephalosporin-induced hepatitis. Plast Reconstr Surg 2007; 119: 1136-7. PubMed PMID: 17312549.

(Three patients developed postoperative hepatitis 2-3 weeks after augmentation mammaplasty having received a single dose of cephazolin intraoperatively, no details given).

Talbot GH, Thye D, Das A, Ge Y. Phase 2 study of ceftaroline versus standard therapy in treatment of complicated skin and skin structure infections. Antimicrob Agents Chemother 2007; 51: 3612-6. PubMed Citation (Among 100 patients with complicated skin or skin structure infections treated with intravenous ceftaroline vs vancomycin with or without aztreonam, clinical cure rates and adverse event rates were similar; ALT elevations occurring in 6% vs 12.5% of patients, but no instance of clinically apparent liver injury).

Chen J, Ahmad J. Cefdinir-induced hepatotoxicity: potential hazards of inappropriate antibiotic use. J Gen Intern Med 2008; 23: 1914-6. PubMed PMID: 18752027.

(22 year old man developed jaundice shortly after a 10 day course of cefdinir [bilirubin 15.7 rising to 41.4 mg/dL, ALT 96 U/L, Alk P 175 U/L], slow, but eventual recovery 7 weeks later).

Chalasani N, Fontana RJ, Bonkovsky HL, Watkins PB, Davern T, Serrano J, Yang H, Rochon J; Drug Induced Liver Injury Network (DILIN). Causes, clinical features, and outcomes from a prospective study of drug-induced liver injury in the United States. Gastroenterology 2008; 135: 1924-34. PubMed PMID: 18955056.

(Among 300 cases of drug induced liver disease in the US collected between 2004 and 2008, 5 cases were attributed to cephalosporins with single cases linked to cefaclor, cephalexin, cefazolin cefuroxime and ceftriaxone).

Peker E, Cagan E, Dogan M. Ceftriaxone-induced toxic hepatitis. World J Gastroenterol 2009; 15: 2669-71. PubMed PMID: 19496200.

(12 year old boy developed fatigue after 3 days of ceftriaxone therapy followed by jaundice [bilirubin 4.2 mg/dL, ALT 871 U/L, Alk P 143 U/L, 8% eosinophils], resolving within 10 weeks of stopping).

Ferrajolo C, Capuano A, Verhamme KM, Schuemie M, Rossi F, Stricker BH, Sturkenboom MC. Drug-induced hepatic injury in children: a case/non-case study of suspected adverse drug reactions in VigiBase. Br J Clin Pharmacol 2010; 70: 721-8. PubMed PMID: 21039766.

(Worldwide pharmacovigilance database contained 9036 hepatic adverse drug reactions in children, 104 of which were attributed to ceftriaxone, ranking 10th in frequency and being the only cephalosporin listed).

Reuben A, Koch DG, Lee WM; Acute Liver Failure Study Group. Drug-induced acute liver failure: results of a U.S. multicenter, prospective study. Hepatology 2010; 52: 2065-76. PubMed PMID: 20949552.

(Among 1198 patients with acute liver failure enrolled in a US prospective study between 1998 and 2007, 133 were attributed to drug induced liver injury, one of which was attributed to cefepime, but none to ceftriaxone or other cephalosporins).

Ekiz F, Usküdar O, Simsek Z, Yüksel I, Basar O, Altinbas A, Yüksel O. Cefuroxime axetil-induced liver failure. Ann Hepatol 2010; 9: 306. PubMed Citation (60 year old woman developed jaundice 4 days after a 10 day course of oral cefuroxime [bilirubin 17.9 rising to 30 mg/dL, ALT 1527 U/L, Alk P 1006 U/L], with progressive worsening of INR [1.9] and referral for transplantation, but subsequent full recovery).

Corey GR, Wilcox M, Talbot GH, Friedland HD, Baculik T, Witherell GW, Critchley I, et al. Integrated analysis of CANVAS 1 and 2: phase 3, multicenter, randomized, double-blind studies to evaluate the safety and efficacy of ceftaroline versus vancomycin plus aztreonam in complicated skin and -structure infection. Clin Infect Dis 2010; 5: 641-50. PubMed PMID: 20695801.

(Among 1378 patients with complicated skin or skin structure infections treated with ceftaroline or vancomycin with aztreonam in two large controlled trials, clinical cure rates were similar; no mention of ALT elevations or liver related adverse events).

File TM Jr, Low DE, Eckburg PB, Talbot GH, Friedland HD, Lee J, Llorens L, et al. Integrated analysis of FOCUS 1 and FOCUS 2: randomized, doubled-blinded, multicenter phase 3 trials of the efficacy and safety of ceftaroline fosamil versus ceftriaxone in patients with community-acquired pneumonia. Clin Infect Dis 2010; 51: 1395-405. PubMed PMID: 21067350.

(Among 1228 patients with community acquired bacterial pneumonia treated with ceftaroline or ceftriaxone in two controlled trials, clinical cure rates were similar as were rates of adverse events overall; there were no differences in rates of abnormal laboratory results).

Ceftaroline fosamil (Teflaro) - a new IV cephalosporin. Med Lett Drugs Ther 2011; 53: 5-6. PubMed PMID: 21252841.

(Concise review of the mechanism of action, clinical efficacy, safety and costs of ceftaroline shortly after its approval as therapy of complicated skin and skin structure infections and community acquired pneumonia in the United States, mentions common side effects as being diarrhea, nausea, rash and direct Coombs test positivity, and rare complications of C. difficile infection, but does not mention ALT elevations or hepatotoxicity).

Kaur I, Singh J. Cholestatic hepatitis with intravenous ceftriaxone. Indian J Pharmacol 2011; 43: 474-5. PubMed PMID: 21845011.

(24 year old woman developed dark urine 24 hours after starting ceftriaxone and piroxicam and 3 days later was jaundiced [bilirubin 6.5 mg/dL, ALT 164 U/L, Alk P 580 U/L], resolving within 3 weeks of stopping both drugs).

Choi YY, Jung YH, Choi SM, Lee CS, Kim D, Hur KY. Gallbladder pseudolithiasis caused by ceftriaxone in young adult. J Korean Surg Soc 2011; 81: 423-6. PubMed PMID: 22200045.

(Two men, ages 21 and 22 years, developed gallstones found by CT scan 5 and 17 days after starting ceftriaxone without symptoms or laboratory abnormalities, resolving within 1 month of stopping).

Kwon H, Lee SH, Kim SE, Lee JH, Jee YK, Kang HR, Park BJ, et al. Spontaneously reported hepatic adverse drug events in Korea: multicenter study. J Korean Med Sci 2012; 27: 268-73. PubMed PMID: 22379337.

(Summary of 2 years of adverse event reporting in Korea; of 9360 reports, 567 were liver related, including 54 [9.5%] attributed to cephalosporins, but no details provided).

Björnsson ES, Bergmann OM, Björnsson HK, Kvaran RB, Olafsson S. Incidence, presentation and outcomes in patients with drug-induced liver injury in the general population of Iceland. Gastroenterology 2013; 114: 1419-25. PubMed PMID: 23419359.

(In a population based study of drug induced liver injury from Iceland, 96 cases were identified over a 2 year period, of which 2 were attributed to cephalosporins, one with jaundice to cephalexin and one with enzyme elevations only to ceftazidime).

Rodríguez Rangel DA, Pinilla Orejarena AP, Bustacara Diaz M, Henao García L, López Cadena A, Montoya Camargo R, Moreno LA. [Gallstones in association with the use of ceftriaxone in children.]. An Pediatr (Barc) 2014; 80 (2): 77-80. Spanish. PubMed PMID: 23759541.

(Prospective study in 73 children receiving ceftriaxone, identified sludge or gallstones [4-14 mm in diameter] by ultrasound in 31 [43%], of whom 7 had symptoms, all resolving within 2 months of stopping, but one requiring surgery).

Tomoda T, Ueki T, Saito S, Tatsukawa M, Nawa T, Hamamoto H, Endo H, Yabushita K, Shimoe T, Sakaguchi K. [A case of ceftriaxone-associated pseudolithiasis in an adult patient that disappeared after the discontinuation of ceftriaxone]. Nihon Shokakibyo Gakkai Zasshi 2013; 110: 1481-6. Japanese. PubMed PMID: 23912008.

(47 year old woman found to have developed biliary stones and sludge on CT scan after 8 days of intravenous ceftriaxone, which disappeared within 6 days).

von Martels JZ, Van de Meeberg EK, Holman M, Ligtenberg JJ, Ter Maaten JC. Pseudolithiasis after recent use of ceftriaxone: an unexpected diagnosis in a child with abdominal pain. Am J Emerg Med 2013; 31: 1294. e5-6. PubMed PMID: 23809091.

(14 year old boy treated for Lyme disease with a 2 week course of iv ceftriaxone presented 4 days later with abdominal pain and biliary stones by ultrasound and ERCP [bilirubin 4.2 mg/dL, ALT 187 U/L, Alk P 398, GGT 291 U/L], resolving with conservative management within a few days and no stones found on follow-up ultrasound 4 weeks later).

Hernández N, Bessone F, Sánchez A, di Pace M, Brahm J, Zapata R, A Chirino R, et al. Profile of idiosyncratic drug induced liver injury in Latin America. An analysis of published reports. Ann Hepatol 2014; 13: 231-9. PubMed PMID: 24552865.

(Systematic review of literature of drug induced liver injury in Latin American countries published from 1996 to 2012 identified 176 cases, but none were attributed to a cephalosporin).

Alemayehu H, Desai AA, Thomas P, Sharp SW, St Peter SD. Ceftriaxone-induced pseudolithiasis in children treated for perforated appendicitis. Pediatr Surg Int 2014; 30: 323-6. PubMed PMID: 24464035.

(Among 71 children treated with iv ceftriaxone for perforated appendicitis, 10 [14%] developed gallbladder stones or sludge, one of whom developed symptoms and underwent cholecystectomy).

Lucasti C, Hershberger E, Miller B, Yankelev S, Steenbergen J, Friedland I, Solomkin J. Multicenter, double-blind, randomized, phase II trial to assess the safety and efficacy of ceftolozane-tazobactam plus metronidazole compared with meropenem in adult patients with complicated intra-abdominal infections. Antimicrob Agents Chemother 2014; 58: 5350-7. PubMed PMID: 24982069.

(Among 121 patients with complicated intra-abdominal infections enrolled in a controlled trial, clinical cure rates were lower with ceftolozane with tazobactam [84%] than meropenem [96%], but adverse event rates were similar [50% vs 49%], ALT elevations occurring in no patient on ceftolozane but 8% on meropenem).

Casapao AM, Davis SL, Barr VO, Klinker KP, Goff DA, Barber KE, Kaye KS, et al. Large retrospective evaluation of the effectiveness and safety of ceftaroline fosamil therapy. Antimicrob Agents Chemother 2014; 58: 2541-6. PubMed PMID: 24550331.

(Among 527 patients treated with ceftaroline in a retrospective survey from 5 medical centers, clinical response rates were high [88%] and adverse events were uncommon and usually mild, only one patient [<1%] having had a transient ALT elevation).

Chalasani N, Bonkovsky HL, Fontana R, Lee W, Stolz A, Talwalkar J, Reddy KR, et al.; United States Drug Induced Liver Injury Network. Features and outcomes of 899 patients with drug-induced liver injury: the DILIN prospective study. Gastroenterology 2015; 148: 1340-52. PubMed PMID: 25754159.

(Among 899 cases of drug induced liver injury seen over a ten year period at 8 U.S. medical centers, 323 [36%] were attributed to antibiotics of which 36 [4%] were cephalosporins including cefazolin [21], ceftriaxone [4], cefalexin [3], cefadroxil [2] and cefuroxime [2] and four others [1 case each]).

Alqahtani SA, Kleiner DE, Ghabril M, Gu J, Hoofnagle JH, Rockey DC; Drug-Induced Liver Injury Network (DILIN) Study Investigators. Identification and characterization of cefazolin-induced liver injury. Clin Gastroenterol Hepatol 2015; 13: 1328-36. PubMed PMID: 25528012.

(Among 1019 patients enrolled in a US database of drug induced liver injury between 2004 and 2012, 33 [3%] were due to cephalosporins, of which 19 presented 6-29 days after a single iv injection of cefazolin exhibiting a cholestatic pattern of injury, mild immunoallergic features, moderate severity and invariably a self-limited course).

Wagenlehner FM, Umeh O, Steenbergen J, Yuan G, Darouiche RO. Ceftolozane-tazobactam compared with levofloxacin in the treatment of complicated urinary-tract infections, including pyelonephritis: a randomised, double-blind, phase 3 trial (ASPECT-cUTI). Lancet 2015; 385 (9981): 1949-56. PubMed PMID: 25931244.

(Among 1083 patients with complicated urinary tract infections treated with intravenous ceftolozane with tazobactam or levofloxacin for 7 days, clinical cure rates were higher with ceftolozane [77% vs 68%], while overall adverse event rates were similar [35% vs 34%] and ALT elevations occurred in 1.7% vs 0.9%, but there were no liver related serious adverse events or discontinuations).

Solomkin J, Hershberger E, Miller B, Popejoy M, Friedland I, Steenbergen J, Yoon M, et al. Ceftolozane/tazobactam plus metronidazole for complicated intra-abdominal infections in an era of multidrug resistance: results from a randomized, double-blind, phase 3 trial (ASPECT-cIAI). Clin Infect Dis 2015; 60: 1462-71. PubMed PMID: 25670823.

(Among 596 patients with complicated intra-abdominal infections treated with ceftolozane/tazobactam or meropenem with metronidazole, clinical cure rates were similar [83% vs 87%], as were overall adverse events rates [44% vs 43%] with ALT elevations in 2.5% of patients; no mention of liver related serious adverse events).

Ceftolozane/Tazobactam (Zerbaxa)--a new intravenous antibiotic. Med Lett Drugs Ther 2015; 57 (1463): 31-3. PubMed PMID: 25719997.

(Concise summary of the mechanism of action, clinical efficacy, side effects and costs of ceftolozane with tazobactam shortly after its approval for complicated urinary tract or intrabdominal infections in the US; mentions common side effects as being diarrhea, nausea, headache and feve,r and rare but serious adverse events of C. difficile colitis and hypersensitivity reactions; no mention of ALT elevations or hepatotoxicity).

Dryden M, Zhang Y, Wilson D, Iaconis JP, Gonzalez J. A Phase III, randomized, controlled, non-inferiority trial of ceftaroline fosamil 600 mg every 8 h versus vancomycin plus aztreonam in patients with complicated skin and soft tissue infection with systemic inflammatory response or underlying comorbidities. J Antimicrob Chemother 2016; 71: 3575-84. PubMed PMID: 27585969.

(Among 761 patients with complicated skin and skin structure infections treated with intravenous ceftaroline or vancomycin with aztreonam, clinical cure rates were similar [78% vs 79%] as were adverse event rates which included ALT elevations in 1.2% vs 1.6%, but no liver related serious adverse events).

Korczowski B, Antadze T, Giorgobiani M, Stryjewski ME, Jandourek A, Smith A, O'Neal T, et al. A multicenter, randomized, observer-blinded, active-controlled study to evaluate the safety and efficacy of ceftaroline versus comparator in pediatric patients with acute bacterial skin and skin structure infection. Pediatr Infect Dis J 2016; 35: e239-47. PubMed PMID: 27164462.

(Among 159 children with acute bacterial skin and skin structure infections treated with intravenous ceftaroline or comparator antibiotics, clinical cure rates were similar as were adverse events including clinical chemistry abnormalities; ALT elevations above 3 times ULN occurred in 1% on ceftaroline and 2% on comparator agents [1 patient in each group]).