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-. Penicillins (3rd Generation). [Updated 2016 Mar 30].
Bookshelf URL: https://www.ncbi.nlm.nih.gov/books/

Penicillins (3rd Generation)

Updated: March 30, 2016.

OVERVIEW

The aminopenicillins (sometimes referred to as third generation penicillins) are semisynthetic modifications of natural penicillin that have the advantage of a broader spectrum of activity. Like the natural penicillins, aminopenicillins have a thiazolidine ring structure connected to a beta-lactam ring which makes these agents susceptible to inactivation by beta-lactamase, the usual cause of bacterial resistance to the penicillins. The aminopenicillins, like the natural first generation penicillins, bind to bacterial proteins and inhibit synthesis of the bacterial cell wall, causing cell lysis particularly in rapidly growing organisms. The aminopenicillins are widely used for therapy of mild-to-severe urinary, respiratory, gastrointestinal tract, skin, bone and joint infections. They have activity against Escherichia coli, Hemophilis influenzae, Listeria monocytogenesis, Neisseria gonorrhoeae, Proteus mirabilis, Salmonella, Shigella, Staphylococcus aureus (non-penicillinase producing), Staphyloccocus epidermidis, and Streptococcus pneumoniae.

Two third generation penicillins are available in the United States: ampicillin (am" pi sil' in) and amoxicillin (a mox" i sil' in). Ampicillin is also used as a combination antibiotic with sulbactam (sul bak' tam) sodium which provides coverage against penicillinase-resistant bacteria. The references for ampicillin, amoxicillin and ampicillin/sulbactam are given together at the end of this Overview section, because they are rare causes of acute liver injury and appear to share a common pattern of associated liver injury. Typical hepatotoxicity due to the aminopenicillins resembles that of the first generation penicillins. The typical presentation is a cholestatic hepatitis arising 2 to 4 weeks after starting the antibiotic and sometimes 1 to 2 weeks after stopping a limited course. The injury is usually mild-to-moderate in severity, although fatal cases of acute liver failure have been described, and there have been several reports of vanishing bile duct syndrome or prolonged cholestasis following amoxicillin or ampicillin related cholestatic liver injury.

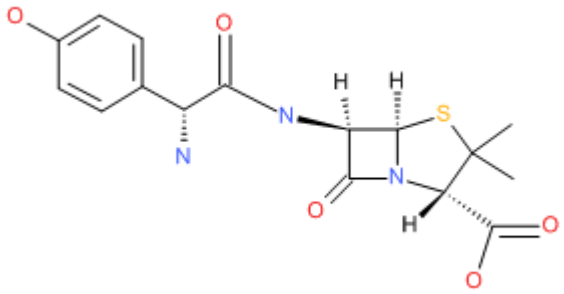
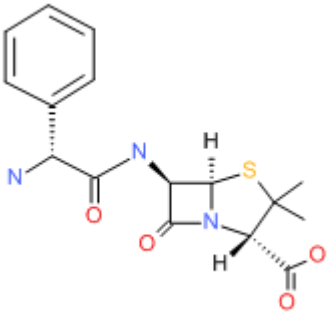
In addition, amoxicillin is commonly used in combination with the beta-lactamase inhibitor clavulanic acid. Amoxicillin/clavulanate is one of the most frequent causes of drug induced liver disease, but the liver injury is usually attributed to the clavulanate rather than the aminopenicillin, and the pattern of injury may be slightly different than that described with penicillin, ampicillin and amoxicillin alone. For these reasons, amoxicillin/clavulanate is discussed separately and references are provided with that discussion.

Bacampicillin and pivampicillin are two aminopenicillins that are not available in the United States. References regarding ampicillin, amoxicillin and ampicillin/sulbactam hepatotoxicity are given below. The following are links to each drug record:

- Amoxicillin
- Amoxicillin-Clavulanate
- Ampicillin
- Ampicillin-Sulbactam

- Bacampicillin
- Pivampicillin

CHEMICAL FORMULAS AND STRUCTURES

DRUG	CAS REGISTRY NO	MOLECULAR FORMULA	STRUCTURE
Amoxicillin	26787-78-0	C16-H19-N3-O5-S	
Ampicillin	69-53-4	C16-H19-N3-O4-S	

ANNOTATED BIBLIOGRAPHY

References updated: 30 March 2016

Zimmerman HJ. Penicillins. In, Hepatotoxicity: the adverse effects of drugs and other chemicals on the liver. 2nd ed. Philadelphia: Lippincott Williams and Wilkins, 1999. p. 595-6.

(Expert review of penicillins and liver injury published in 1999; the penicillins commonly lead to hypersensitivity reactions but rarely to liver injury).

Moseley RH. Hepatotoxicity of antimicrobials and antifungal agents. In, Kaplowitz N, DeLeve LD, eds. Drug-induced liver disease. 3rd ed. Amsterdam: Elsevier, 2013, pp. 463-82.

(Review of hepatotoxicity of antibiotics mentions that penicillins rarely cause liver injury and both hepatocellular and cholestatic patterns of injury have been described).

Petri WA Jr. Penicillins, cephalosporins, and other β-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, pp. 1477-1504.

(Textbook of pharmacology and therapeutics).

Knirsch AK, Gralla EJ. Abnormal serum transaminase levels after parenteral ampicillin and carbenicillin administration. N Engl J Med 1970; 282: 1081-2. PubMed PMID: 5438429.

(Elevations in AST and CPK, but not ALT, occurred after intramuscular injections of ampicillin and carbenicillin, but not after cephalosporins or saline; thus, the elevations probably reflected muscle rather than liver injury).

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

(Stevens-Johnson syndrome developed in a 9 month old child given ampicillin (rash) and cephalexin, with subsequent hepatocellular injury [bilirubin 13 mg/dL], resolving with prednisone therapy).

Tamarkina AD, Dement'eva ES, Krylova NI, Minasova GS, Kuleshova EE. [Enzymological evaluation of the hepatotoxicity of ampicillin and its therapeutic form, roscillin, in the treatment of pyelonephritis in pregnancy] Antibiot Med Biotekhnol 1985; 30: 62-4. Russian. PubMed PMID: 3994343.

(Prospective analysis of serum enzyme levels in 12 patients receiving ampicillin found no changes during 12 days of therapy, although minor changes occurred when it was stopped).

Lees L, Milson JA, Knirsch AK, Greenhalgh K. Sulbactam plus ampicillin: interim review of efficacy and safety for therapeutic and prophylactic use. Rev Infect Dis 1986; 8 (Suppl 5): S644-S650. PubMed PMID: 3026019.

(Review of 45 studies of ampicillin/sulbactam in 899 patients found successful outcome in 92%; ALT elevations in 6.9%, AST in 6.2%, but all resolved with stopping and similar rates were reported with use of comparative agents).

Galante D, Esposito S, Barba D, Ruffilli MP. Clinical efficacy and safety of sulbactam/ampicillin in patients suffering from chronic liver disease. J Antimicro Chemother 1987; 19: 527-32. PubMed PMID: 3034850.

(41 patients with advanced liver disease were given sulbactam/ampicillin: there was no worsening of liver disease or enzyme elevations attributed to medication).

Cavanzo FJ, Garcia CF, Botero RC. Chronic cholestasis, paucity of bile ducts, red cell aplasia, and the Stevens-Johnson syndrome. An ampicillin-associated case. Gastroenterology 1990; 99: 854-6. PubMed PMID: 2116345.

(A 35 year old woman developed Stevens-Johnson syndrome with cholestatic hepatitis and red cell aplasia 4 days after starting oral ampicillin and subsequently developed vanishing bile duct syndrome and prolonged cholestasis, but with gradual ultimate improvement after several years).

Davies MH, Harrison RF, Elias E, Hübscher SG. Antibiotic-associated acute vanishing bile duct syndrome: a pattern associated with severe, prolonged, intrahepatic cholestasis. J Hepatol 1994; 20: 112-6. PubMed PMID: 8201211.

(Two cases of vanishing bile duct syndrome, one with toxic epidermolysis developing in a 37 year old woman a day after starting amoxicillin with persistent sclerosing cholangitis-like syndrome and severe jaundice documented by four liver biopsies; second case in a 42 year old woman treated with flucloxacillin who developed cholestatic hepatitis followed by persistent Alk P elevations who underwent five liver biopsies).

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

PubMed Citation (Adverse drug reaction reports identified 943 liver injuries over 21 years in New Zealand; amoxicillin listed in top 20 drugs over several periods).

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. *PubMed Citation*

(Adverse drug reaction reports in Denmark from 1978 to 1987; no mention of aminopenicillins).

Bolzan H, Spatola J, Castelletto R, Curciarello J. [Intrahepatic cholestasis induced by amoxicillin alone] Gastroenterol Hepatol 2000; 23: 237-9. Spanish. PubMed PMID: 10902278.

(24 year old woman developed weakness after 5 days and dark urine after 7 days of amoxicillin therapy, but continued it for 10 days developing deep jaundice and pruritus [bilirubin 10.5 rising to 23.3 mg/dL, ALT 30 U/L, Alk P 314-546 U/L], resolving within 2 months of stopping).

Schwarze C, Schmitz V, Fischer HP, Sauerbruch T, Spengler U. Vanishing bile duct syndrome associated with elevated pancreatic enzymes after short-term administration of amoxicillin. Eur J Gastroenterol Hepatol 2002; 14: 1275-7. PubMed PMID: 12439126.

(45 year old woman developed progressive cholestasis and vanishing bile duct syndrome 2 months after a 6 day course of amoxicillin; progressive cholestasis evolved into chronic liver failure and death 18 months later).

Heluwaert F, Roblin X, Duffournet V, Capony P, Martin D, Roblin X. [Hepatitis related to amoxicillin or levofloxacin: a case report] Rev Med Interne 2003; 24: 841-3. French. PubMed PMID: 14656650.

(34 year old woman developed nausea followed by jaundice 2 weeks after starting 6 day course of amoxicillin and 1 week after starting a 5 day course of levofloxacillin [bilirubin 6.6 rising to 12.6 mg/dL, ALT 8.7 times and Alk P 2.1 times ULN]: case most compatible with levofloxacin hepatotoxicity with abrupt onset and hepatocellular pattern of serum enzymes).

Köklü S, Yüksel O, Filik L, Usküdar O, Altundag K, Altiparmak E. Recurrent cholestasis due to ampicillin. Ann Pharmacother 2003; 37: 395-7. PubMed PMID: 12639171.

(23 year old man had recurrent bouts of liver injury 12, 8, and 5 days after starting three 7 day courses of ampicillin; last episode marked by bilirubin 2.1 mg/dL, ALT 265 U/L, and Alk P 455 U/L, resolving within 10 days 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 23 year old man in previous report, who redeveloped liver injury 17 days after starting a 10 day course of cefuroxime [bilirubin 0.7 mg/dL, ALT 427 U/L, Alk P 646 U/L], resovling within 2 months, suggesting cross sensitivity to hepatic injury between cephalosporins and ampicillin).

Köklü S, Köksal AS, Asil M, Kiyici H, Coban S, Arhan M. Probable sulbactam/ampicillin-associated prolonged cholestasis. Ann Pharmacother 2004; 38: 2055-8. PubMed PMID: 15494387.

(74 year old developed cholestatic hepatitis arising 1 week after 7 day course of ampicillin/sulbactam with prolonged jaundice [bilirubin 31 mg/dL, ALT 33 U/L, Alk P 519 U/L], resolving after 7 months, except mild GGT elevations).

Romney R, Biour M, Belloula D, Elbaz D, Carriere J, Cadranel JF. [Amoxicillin induced acute hepatitis] Gastroenterol Clin Biol 2004; 28: 505-6. French. PubMed PMID: 15243334.

(27 year old developed acute hepatitis 3 days after starting amoxicillin [bilirubin 7.9 mg/dL, ALT 84 times, Alk P normal], resolving within 1 month; patient also took acetaminophen).

de Abajo FJ, Montero D, Madurga M, Rodriguez LAG. Acute and clinically relevant drug-induced liver injury: a population based case-control study. Brit J Clin Pharm 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); amoxicillin was associated with a minimal increase in risk).

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 done in the US between 1990 and 2002, 270 [0.5%] were done for drug induced acute liver failure; one case was attributed to amoxicillin/clavulanate, but none to penicillin, ampicillin or amoxicillin alone).

Fontana RJ, Shakil AO, Greenson JK, Boyd I, Lee WM. Acute liver failure due to amoxicillin and amoxicillin/clavulanate. Dig Dis Sci 2005; 50: 1785-90. PubMed PMID: 16187174.

(Two case reports, one of acute liver failure arising 1 month after 6 day course of oral amoxicillin for dental work [bilirubin 23.0 mg/dL, ALT 521 U/L, GGT 89 U/L], progressing to liver failure and liver transplant; second case attributed to amoxicillin/clavulanate).

Andrade RJ, Lucena MI, Kaplowitz N, Garcia-Munoz B, Borraz Y, Pachkoria K, Garcia-Cortes M, et al. Outcome of acute idiosyncratic drug-induced liver injury: Long-term follow-up in a hepatotoxicity registry. Hepatology 2006; 44: 1581-8. PubMed PMID: 17133470.

(Clinical description of 28 patients with "chronic" outcome of drug induced liver injury included one case attributed to amoxicillin with jaundice arising 5 days after a 1 day course with severe hypersensitivity; 6 months later, only evidence of chronic injury was an elevated GGT ~1.4 times ULN).

Madroñero AB, Porcel JM, Bielsa S. [Hepatotoxicity induced by amoxicillin] Rev Esp Enferm Dig 2007; 99: 173-4. Spanish. PubMed PMID: 17516833.

(76 year old woman developed acute cholestatic hepatitis 2 weeks after starting 6 days of amoxicillin [bilirubin 9.4 mg/dL, ALT 54 U/L, Alk P 339 U/L], resolving within 1 month of stopping).

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 from 2004 to 2008, 23 cases were attributed to amoxicillin/clavulanate, 2 cases to amoxicillin, but none to ampicillin).

Björnsson E, Davidsdottir L. The long-term follow-up after idiosyncratic drug-induced liver injury with jaundice. J Hepatol 2009; 50: 511-7. PubMed Citation

(Among 685 patients identified an average of 10 years after an episode of drug induced liver injury, 23 [3.4%] had continuing liver disease, 8 with cirrhosis. One patient who died of cirrhosis had ampicillin-attributed liver injury 3 years previously).

Treudler R, Grunewald S, Gebhardt C, Simon JC. Prolonged course of acute generalized exanthematous pustulosis with liver involvement due to sensitization to amoxicillin and paracetamol. Acta Derm Venereo 2009; 89: 314-5. PubMed PMID: 19479138.

(48 year old man treated with amoxicillin for 3 days and acetaminophen for 5 days developed generalized pustular rash with fever and later had ALT elevations [3 times ULN] and hepatomegaly that arose after initiation of high dose methylprednisolone therapy).

Devarbhavi H, Dierkhising R, Kremers WK, Sandeep MS, Karanth D, Adarsh CK. Single-center experience with drug-induced liver injury from India: causes, outcome, prognosis, and predictors of mortality. Am J Gastroenterol 2010; 105: 2396-404. PubMed PMID: 20648003.

(313 cases of drug induced liver injury were seen over a 12 year period at a large hospital in Bangalore, India; 3 [1%] were attributed to the combination of amoxicillin and clavulanate, but none were attributed to ampicillin or amoxicillin alone].

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 including 66 due to antimicrobial agents, including two attributed to amoxicillin but none to ampicillin; no details given).

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, amoxicillin/clavulanate accounted for 38 cases [0.4%] for an adjusted odds ratio of 1.7, whereas neither amoxicillin or ampicillin alone were listed among the 41 most common causes [linked to at least 30 cases]).

Kim JS, Jang YR, Lee JW, Kim JY, Jung YK, Chung DH, Kwon OS, Kim YS, Choi DJ, Kim JH. A case of amoxicillin-induced hepatocellular liver injury with bile-duct damage. Korean J Hepatol 2011; 17: 229-32. PubMed PMID: 22102391.

(39 year old woman developed liver injury 8 weeks after starting amoxicillin [2 g daily] for actinomycosis [bilirubin rising to 2.9 mg/dL, ALT 157-216 U/L, Alk P 100-199 U/L], liver biopsy showing bile duct damage and loss, and persistence of mild liver test abnormalities during follow up).

Ruiz Rebollo ML, Aller De La Fuente R, Macho Conesa A, Salado Valdivieso I, Sainz Gil M, Carvajal A, Manuel González J. [Amoxicillin-induced cholestatic hepatitis]. Gastroenterol Hepatol 2011; 34: 474-7. Spanish. PubMed PMID: 21783281.

(87 year old man developed jaundice 2 weels after a 10 day course of amoxicillin [bilirubbin 15.5 mg/dL, ALT 292 U/L, Alk P 295 U/L], resolving within 2 months of presentation).

Chaabane NB, Safer L, Njim L, Zakhama A, Saffar H. Cholestatic hepatitis related to amoxicillin. Drug Chem Toxicol 2011; 34: 357-8. PubMed PMID: 21714770.

(34 year old woman developed pruritis followed by jaundice 1 week after stopping a 10 day course of amoxicillin [bilirubin 30.5 mg/dL, ALT 56 U/L, Alk P 647 U/L], resolving within 8 weeks, but redeveloping jaundice after a 3 day course of amoxicillin 6 months later).

Oxlund J, Ferguson AH. [Amoxicillin-induced hepatitis]. Ugeskr Laeger 2011; 173: 1885-6. Danish. PubMed PMID: 21712012.

(61 year old man developed jaundice 20 days after starting amoxicillin without clavulanate [bilirubin 5.6 mg/dL, ALT 709 U/L, Alk P 316 U/L], resolving within 4 weeks of stopping).

Lucena MI, Molokhia M, Shen Y, Urban TJ, Aithal GP, Andrade RJ, Day CP, et al; Spanish DILI Registry; EUDRAGENE; DILIN; DILIGEN; International SAEC. Susceptibility to amoxicillin-clavulanate-induced liver injury is influenced by multiple HLA class I and II alleles. Gastroenterology 2011 Jul; 141: 338-47. PubMed PMID: 21570397.

*(A genome wide association study [GWAS] on 201 European and U.S. cases of amoxicillin/clavulanate hepatotoxicity and 532 population controls identified two strong HLA associations, one in the class II [DRB1*1501-DQB1*0602] and one in the class I region [A*0201]).*

Köksal AS, Yildiz H, Onder O, Avci S, Kayaåetin E. Sulbactam/ampicillin associated hepatocellular type liver injury. Acta Gastroenterol Belg 2012; 75: 66-7. PubMed PMID: 22567755.

(47 year old woman developed jaundice 8 days after a 4 day course of ampicillin/sulbactam [bilirubin 18.9 mg/dL, ALT 1344 U/L, Alk P 208 U/L], resolving within 10 weeks of stopping).

Studniarz M, Czubkowski P, Cielecka-Kuszyk J, Jankowska I, Teisseyre M, Kamińska D, Markiewicz M, et al. Amoxicillin/clavulanic acid-induced cholestatic liver injury after pediatric liver transplantation. Ann Transplant 2012; 17: 128-31. PubMed PMID: 22466919.

(8 year old boy, 4 years after a liver transplant for biliary atresia, developed jaundice 2 days after finishing a 2 week course of amoxicillin/clavulanate [bilirubin 6.9 mg/dL, ALT 227 U/L, Alk P not given], resolving within 12 weeks).

Bollaert M, Jeulin H, Waton J, Gastin I, Tréchot P, Rabaud C, Schmutz JL, Barbaud A. [Six cases of spring DRESS]. Ann Dermatol Venereol 2012; 139: 15-22. PubMed PMID: 22225738.

(Among 6 patients who developed DRESS syndrome and presented to a single medical center within a one month period, all had herpes virus in blood [EBV, HSV, or HHV-6] and had received medications starting within 3-6 weeks of onset including one case each attributed amoxicillin, allopurinol, carbamazepine and TMP/SMZ, and another 2 cases associated with multiple agents including vancomycin).

Sánchez-Ruiz-Granados E, Bejarano-García A, Uceda-Torres E. Recurrent cholestasis by amoxicillin-clavulanic acid: the importance of a correct diagnosis of hepatotoxicity. Rev Esp Enferm Dig 2012; 104: 616-7. PubMed PMID: 23368660.

(62 year old man with a hepatic hydatid cyst and previous episode of unexplained jaundice, redeveloped jaundice and pruritus 20 days after starting amoxicillin/clavulanate [bilirubin 12 mg/dL, ALT and Alk P normal]).

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; 144: 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, the most commonly implicated agent being amoxicillin with clavulanate [15 cases]; none were attributed to amoxicillin or ampicillin alone).

Sistanizad M, Peterson GM. Drug-induced liver injury in the Australian setting. J Clin Pharm Ther 2013; 38: 115-20. PubMed PMID: 23350857.

(Among 17 cases of suspected drug induced liver injury seen at a single referral hospital in Tasmania over a 12 month period, 11 were due to antibiotics including flucloxacillin in 4, amoxicillin in 2, amoxicillin/clavulanate in 2, and rifampin, moxifloxacin and ciprofloxacin in 1 each).

Beraldo DO, Melo JF, Bonfim AV, Teixeira AA, Teixeira RA, Duarte AL. Acute cholestatic hepatitis caused by amoxicillin/clavulanate. World J Gastroenterol 2013; 19: 8789-92. PubMed PMID: 24379601.

(63 year old man developed jaundice and pruritus arising 45 days after a course of amoxicillin/clavulanate [bilirubin 8.3 mg/dL, ALT 200 U/L, Alk P 60 U/L], with severe course, but ultimate recovery).

Girelli F, Bernardi S, Gardelli L, Bassi B, Parente G, Dubini A, Serra L, Nizzoli M. A New Case of DRESS Syndrome Induced by Sulfasalazine and Triggered by Amoxicillin. Case Rep Rheumatol 2013; 2013: 409152. PubMed PMID: 23936716.

Stephens C, López-Nevot MÁ, Ruiz-Cabello F, Ulzurrun E, Soriano G, Romero-Gómez M, Moreno-Casares A, et al. HLA alleles influence the clinical signature of amoxicillin-clavulanate hepatotoxicity. PLoS One 2013; 8: e68111. PubMed PMID: 23874514.

(Analysis of HLA alleles in 75 cases of amoxicillin/clavulanate hepatotoxicity found various associations of some alleles with clinical features).

Ferrajolo C, Verhamme KM, Trifirò G, 't Jong GW, Giaquinto C, Picelli G, Oteri A, et al. Idiopathic acute liver injury in paediatric outpatients: incidence and signal detection in two European countries. Drug Saf 2013; 36: 1007-16. PubMed PMID: 23591830.

(Analysis of 3 electronic healthcare databases from Italy and the Netherlands from 2000-2008 identified 785 cases of unexplained acute liver injury in children, linked to 110 possible medications, with increased adjusted relative risk [RR] of recent exposure to amoxicillin/clavulanate [RR=18.6] and amoxicillin [RR=7.5]).

Devarbhavi H, Andrade RJ. Drug-induced liver injury due to antimicrobials, central nervous system agents, and nonsteroidal anti-inflammatory drugs. Semin Liver Dis. 2014; 34: 145-61. PubMed PMID: 24879980.

(Review of drug induced liver injury from various classes of agents, mentions that amoxicillin/clavulanate is the leading cause of drug induced liver injury, marked by a latency of several days to weeks, often after stopping the antibiotic, the injury varying from cholestatic to hepatocellular and the mortality rate being as high as 7%).

Björnsson ES. Epidemiology and risk factors for idiosyncratic drug-induced liver injury. Semin Liver Dis 2014; 34: 115-22. PubMed PMID: 24879977.

(Estimates of the incidence of drug induced liver injury have ranged from 2 to 19 case per 100,000 inhabitants, probably because of variation in medication use, definitions used and rigor of capturing all patients in a population; in recent studies, amoxicillin/clavulanate has been the most frequently implicated drug).

Kaye JA, Castellsague J, Bui CL, Calingaert B, McQuay LJ, Riera-Guardia N, Saltus CW, et al. Risk of acute liver injury associated with the use of moxifloxacin and other oral antimicrobials: a retrospective, population-based cohort study. Pharmacotherapy 2014; 34: 336-49. PubMed PMID: 24865821.

(In a US healthcare database with 1.3 million antimicrobial users, there were 607 cases of liver injury and 11 cases of liver failure, the highest relative risk for current single use being 3.2 for levofloxacin, 2.5 for amoxicillin/clavulanate, 2.5 for doxycycline, 2.3 for moxifloxacin and 2.3 for amoxicillin).

Fontana RJ. Pathogenesis of idiosyncratic drug-induced liver injury and clinical perspectives. Gastroenterology 2014; 146: 914-28. (Review of clinical phenotypes and pathogenesis of different forms of drug induced liver injury including antibiotics and amoxicillin/clavualanate). PubMed PMID: 24389305.

Leise MD, Poterucha JJ, Talwalkar JA. Drug-induced liver injury. Mayo Clin Proc 2014; 89: 95-106. PubMed PMID: 24388027.

(Review of drug induced liver injury mentions that antibiotics are the most common cause and amoxicillin/clavulanate the most common single cause in Europe and the US, accounting for 8-22% of cases).

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: 1340-1352.e7. PubMed PMID: 25754159.

(Among 899 cases of drug induced liver injury enrolled in a US prospective study between 2004 and 2013, 91 [12%] were attributed to amoxicillin/clavulanate [ranking first], 6 [0.7%] to amoxicillin alone [ranking 27th], but none to ampicillin).

Guéant JL, Romano A, Cornejo-Garcia JA, Oussalah A, Chery C, Blanca-López N, Guéant-Rodriguez RM, et al. HLA-DRA variants predict penicillin allergy in genome-wide fine-mapping genotyping. J Allergy Clin Immunol 2015; 135: 253-9. PubMed PMID: 25224099.

(In a genome wide association study of 387 patients with immeidate allergic reactions to beta-lactam antibiotics, several class 2 HLA associations [HLA-DRA regions] were found for penicillin responses, but they did not apply to cephalosporin cases).

Björnsson ES. Drug-induced liver injury: an overview over the most critical compounds. Arch Toxicol 2015; 89: 327-34. PubMed PMID: 25618544.

(Review of the most common causes of drug induced liver injury in 3 recent surveys, all of which listed amoxicillin/clavulanate as the most frequent cause).

Kim SH, Saide K, Farrell J, Faulkner L, Tailor A, Ogese M, Daly AK, et al. Characterization of amoxicillin- and clavulanic acid-specific T cells in patients with amoxicillin-clavulanate-induced liver injury. Hepatology 2015; 62: 887-99. PubMed PMID: 25998949.

(Lymphocytes from 6 of 7 patients with a history of amoxicillin-clavulanate induced liver injury showed significant proliferation or cytokine release in response to amoxicillin or clavulanate alone in vitro; T cell clones responding to each drug were produced that were HLA resisted but not cross reactive).

Björnsson ES. Hepatotoxicity by Drugs: The Most Common Implicated Agents. Int J Mol Sci 2016; 17. PubMed PMID: 26861310.

(Review of the most common causes of drug-induced liver injury based upon categorization from LiverTox).

deLemos AS, Ghabril M, Rockey DC, Gu J, Barnhart HX, Fontana RJ, Kleiner DE, et al; Drug-Induced Liver Injury Network (DILIN). Amoxicillin-clavulanate-induced liver injury. Dig Dis Sci. 2016 Mar 22. [Epub ahead of print] PubMed PMID: 27003146.

(Among 1038 cases of drug induced liver injury enrolled in a US database between 2004 and 2014, 117 were attributed to amoxicillin/clavulanate [9%]; mean age 60 years, 62% men, mean latency 29 days, mostly jaundiced and cholestatic [meidan bilirubin 6 mg/dL, ALT 362 U/L, Alk P 288 U/L, R value 2.7], 3 underwent liver transplant with resolution in almost all cases, although sometimes delayed).