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# Penicillins (4th Generation)

Updated: January 16, 2014.

## OVERVIEW

The fourth generation penicillins are semisynthetic modifications of natural penicillin that have the advantage of an extended spectrum of activity particularly against gram negative bacteria including Pseudomonas, Enterobacter, Proteus and Klebsiella species. The first generation penicillins are bactericidal antibiotics naturally derived from the mold, Penicillium chrysogenum. Their basic structure includes a thiazolidine ring connected to a beta-lactam ring with a variable side chain. Penicillins bind to bacterial proteins and inhibit synthesis of the bacterial cell wall, causing cell lysis particularly in rapidly growing organisms. Bacterial resistance to penicillin is usually mediated by beta-lactamase, an enzyme which destroys the beta-lactam ring of penicillin, rendering it inactive.

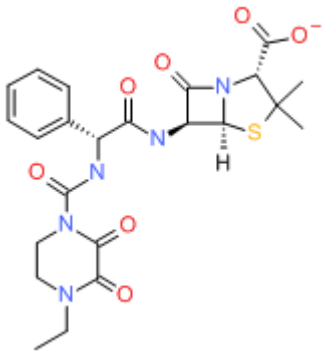
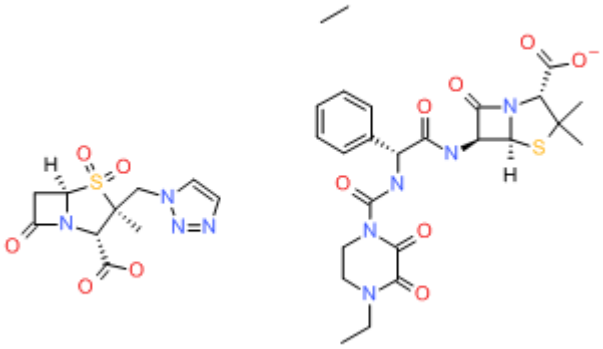
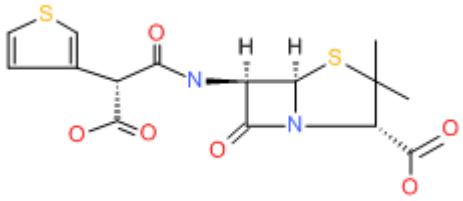
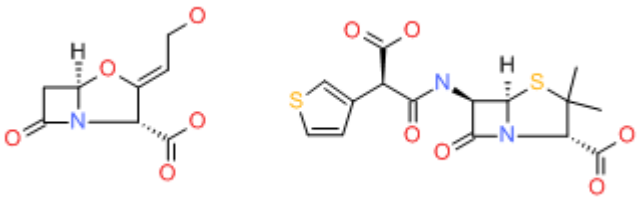
The fourth generation penicillins (sometimes referred to as penicillins with extended spectrum of action) like natural penicillin are susceptible to beta-lactamase. The extended spectrum penicillins are used for therapy of moderate to severe urinary, respiratory, gastrointestinal tract, skin, bone and joint infections. They have activity against Escherichia coli, Hemophilis influenzae, Listeria monocytogenesis, Neisseria gonorrhoeae, Proteus mirabilis, Salmonella, Shigella, Staphylococcus aureus (non-penicillinase producing), Staphylococcus epidermidis, and Streptococcus pneumoniae.

Two fourth generation penicillins are available in the United States: ticarcillin (tye" kar sil' in) and piperacillin (pi" per a sil' in). Several others were used in the United States or Europe, but were abandoned or have been withdrawn (carbenicillin, mezlocillin and azleocillin). Both ticarcillin and piperacillin are also available in combination with beta-lactamase inhibitors such as clavulanate (klav' ue la nate) and tazobactam (taz" oh bak' tam), which provide coverage against penicillinase-resistant bacteria. Ticarcillin and piperacillin are discussed together as they are rare causes of acute liver injury and appear to share a common pattern of associated liver injury. Carbenicillin (kar" ben i sil' in) and mezlocillin (mez" loe sil' in), fourth generation penicillins that have been withdrawn from use, have also been linked to penicillin-like hepatotoxicity. The combination of ticarcillin with clavulanic acid has been associated with injury that resembles the cholestatic hepatitis that follows therapy with amoxicillin/clavulanate.

The following extended-spectrum penicillins are discussed separately with individual clinical cases and references. The following are links to each specific drug record.

- Piperacillin
- Piperacillin and Tazobactam
- Ticarcillin
- Ticarcillin/Clavulanate

# CHEMICAL FORMULAS AND STRUCTURES

| DRUG | CAS REGISTRY NO | MOLECULAR FORMULA | STRUCTURE |
|---|---|---|---|
| Piperacillin | 59703-84-3 | H26-N5-Na-O7-S |  |
| Piperacillin and Tazobactam | 157044-21-8 | C23-H27-N5-O7-S. C10-H12-N4-O5-S.Na |  |
| Ticarcillin | 34787-01-4 | C15-H16-N2-O6-S2 |  |
| Ticarcillin/ Clavulanic Acid | 86482-18-0 | C15-H16-N2-O6-S2. C8-H9-N-O5 |  |

# ANNOTATED BIBLIOGRAPHY

References updated: 16 January 2014

Zimmerman HJ. Penicillins. In, Hepatotoxicity: The Adverse Effects of Drugs and Other Chemicals on the Liver. 2nd Ed. Philadelphia: Lippincott, 1999. p. 595-6

*(Expert review of penicillins and liver injury published in 1999; piperacillin and ticarcillin are listed as associated with elevations in aminotransferase levels, but without reports of clinically apparent liver injury except with ticarcillin/clavulanate).*

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 there have been few case reports of liver injury due to the extended penicillins).*

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, suggesting that the elevations reflected muscle rather than liver injury).*

Gump DW. Elevated SGOT levels after carbenicillin. N Engl J Med 1970; 282: 1489-90. PubMed PMID: 5419302.

*(26 year old man developed ALT elevations [284-320 U/L] 11 days after starting intravenous carbenicillin without symptoms or jaundice and with rapid resolution upon stopping; a pattern of injury similar to that observed with oxacillin).*

Pines A, Khaja G, Raafat H, Sreedharan KS. Preliminary clinical experience with ticarcillin (BRL 2288) in 101 patients treated for severe respiratory infections. Chemotherapy 1974; 20: 39-44. PubMed PMID: 4210892.

*(Early experience in 101 patients with severe infections given intramuscular ticarcillin; local pain was common and there were minimal and transient elevations in ALT in 4 and Alk P is 5 patients).*

Wilson FM, Belamaric J, Lauter CB, Lerner AM. Anicteric carbenicillin hepatitis. Eight episodes in four patients. JAMA 1975; 232: 818-21. PubMed PMID: 1173185.

*(8 episodes of aminotransferase elevations in 4 patients receiving intravenous carbenicillin, always anicteric, minimally symptomatic and rapidly resolving, positive rechallenge, sometimes with eosinophilia; similar to oxacillin injury).*

Nelson JD, Kusmiesz H, Shelton S, Woodman E. Clinical pharmacology and efficacy of ticarcillin in infants and children. Pediatrics 1978; 61: 858-63. PubMed PMID: 673548.

*(Among 98 children treated with ticarcillin intravenously or intramuscularly, 3 had AST elevations [50-81 U/L] without symptoms or jaundice, and all values decreased during continued treatment).*

Brogden RN, Heel RC, Speight TM, Avery GS. Ticarcillin: a review of its pharmacological properties and therapeutic efficacy. Drugs 1980; 20: 325-52. PubMed PMID: 7002527.

*(Ticarcillin is a semisynthetic penicillin for parenteral administration similar to carbenicillin; adverse events include skin rash, hypokalemia, eosinophilia and platelet dyfunction; ALT elevations and hepatic injury are not mentioned).*

Russo J Jr, Russo ME. Comparative review of two new wide-spectrum penicillins: mezlocillin and piperacillin. Clin Pharm 1982; 1: 207-16. PubMed PMID: 6224627.

*(Review of two extended spectrum penicillins, piperacillin is more active than mezlocillin against Pseudomonas, side effect profiles are similar including ALT elevations that occur with both).*

González MA. Comparison of the efficacy and safety of mezlocillin and ticarcillin in the treatment of patients with serious systemic infections. J Antimicrob Chemother 1982; 9 (Suppl A): 229-30. PubMed PMID: 6210671.

*(Randomized clinical trial of mezlocillin vs ticarcillin in 34 patients with severe infections; no mention of ALT elevations).*

Parry MF, Neu HC. The safety and tolerance of mezlocillin. J Antimicrob Chemother 1982; 9 (Suppl A): 273-80. PubMed PMID: 6210679.

*(Analysis of 1148 patients given intravenous mezlocillin for 1 to 52 days; 3.7% had hypersensitivity reactions, 0.9% elevations in ALT, AST or Alk P, but all were reversible and anicteric. In a direct comparison, AST elevations occurred in 1.5% of mezlocillin vs 7.4% of ticarcillin recipients).*

Ramírez-Ronda CH, Gutiérrez J, Bermúdez RH. Comparative effectiveness, safety and tolerance of mezlocillin and ticarcillin: a prospective randomized trail. J Antimicrob Chemother 1982; 9 (Suppl A): 125-9. PubMed PMID: 6210660.

*(Randomized clinial trial comparing mezlocillin [n=21] and ticarcillin [n=20]; no ALT elevations occurred).*

Graft DF, Chesney PJ. Use of ticarcillin following carbenicillin-associated hepatotoxicity. J Pediatr. 1982; 100: 497-9. PubMed PMID: 7062188.

*(3 children who developed elevations in serum ALT levels during intravenous therapy with oxacillin or carbenicillin were then treated with ticarcillin without recurrence of liver injury).*

Reed WP, Palmer DL. Comparison of azlocillin and ticarcillin in the treatment of urinary tract infection. J Antimicrob Chemother 1983; 11 (Suppl B): 189-93. PubMed PMID: 6619028.

*(Randomized clinial trial of azlocillin vs ticarcillin in 35 patients with urinary tract infections, both were highly effective; no mention of ALT elevations or hepatic injury).*

Heimbach DM. Cefsulodin therapy for infections due to Pseudomonas aeruginosa in patients with burns. Rev Infect Dis 1984; 6 (Suppl 3): S744-50. PubMed PMID: 6443775.

*(Cefsulodin efficacy vs comparators, one of which was ticarcillin; no information on hepatotoxicity).*

Jackson D, Cockburn A, Cooper DL, Langley PF, Tasker TC, White DJ. Clinical pharmacology and safety evaluation of Timentin. Am J Med 1985; 79(5B): 44-55. PubMed PMID: 4073095.

*(Toxicological studies of ticarcillin and clavulanate in animals and in pharmacologic studies in humans found no evidence of significant liver injury).*

Tasker TC, Cockburn A, Jackson D, Mellows G, White D. Safety of ticarcillin disodium/potassium clavulanate. J Antimicrob Chemother 1986; 17 Suppl C: 225-32. PubMed PMID: 3722044.

*(Preclinical evaluation of ticarcillin found no evidence of significant hepatic injury; early clinical studies found low rate of elevated serum enzymes during therapy, but these may have been due to the underlying illness being treated).*

Tan JS, Wishnow RM, Talan DA, Duncanson FP, Norden CW. Treatment of hospitalized patients with complicated skin and skin structure infections: double-blind, randomized, multicenter study of piperacillin-tazobactam versus ticarcillin-clavulanate. The Piperacillin/Tazobactam Skin and Skin Structure Study Group. Antimicrob Agents Chemother 1993; 37: 1580-6. PubMed PMID: 8215266.

*(Among 251 patients treated with either of 2 fourth generation penicillins, overall rates of response and side effects were similar; no mention of ALT levels of hepatic adverse events).*

Schoonover LL, Occhipinti DJ, Rodvold KA, Danziger LH. Piperacillin/tazobactam: a new beta-lactam/beta-lactamase inhibitor combination. Ann Pharmacother 1995; 29: 501-14. PubMed PMID: 7655135.

*(Review of pharmacology, efficacy and safety of piperacillin/ tazobactam; the most common side effects are diarrhea [8%], nausea, headache, pruritus and rash [1%]; laboratory abnormalities occur in <1% of patients, but can include "transient increases in liver function test results"; no other mention of hepatotoxicity).*

Dietze MA, Martin P, Schaaf-Lafontaine N. [Clinical case of the month. Cholestatic hepatitis after administration of piperacillin]. Rev Med Liege 2002; 57: 571-4. French. PubMed PMID: 12440344.

*(58 year old woman developed cholestatic hepatitis 12 days after starting 10 day course of piperacillin, but also 14 days after finishing a 2 day course of amoxicillin/clavulanate [peak bilirubin 15.0 mg/dL, ALT 624 U/L, Alk P 1730 U/L], resolving within 2 months).*

Yellin AE, Johnson J, Higareda I, Congeni BL, Arrieta AC, Fernsler D, West J, et al. Ertapenem or ticarcillin/ clavulanate for the treatment of intra-abdominal infections or acute pelvic infections in pediatric patients. Am J Surg 2007; 194: 367-74. PubMed PMID: 17693284.

*(Among 105 children in a controlled trial, ALT elevations occurred in 3% on ertapenem vs 4% on ticarcillin/ clavulanate; no details given).*

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, none were attributed to ticarcillin or piperacillin).*

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; none were attributed to an extended spectrum penicillin).*

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, but ticarcillin and piperacillin were not listed in the top 41 causes).*

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, none of which were attributed to an extended spectrum penicillin).*

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, including 15 due to amoxicillin/clavulanate and 1 each to dicloxacillin and phenoxymethylpenicillin, but none to ticarcillin or piperacillin).*