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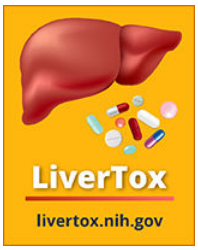


Nafcillin

Updated: October 20, 2020.

OVERVIEW

Introduction

Nafcillin is a parenteral, second generation penicillinase-resistant penicillin antibiotic used largely to treat moderate to severe staphylococcal infections. Nafcillin has been linked to rare occurrences of clinically apparent, idiosyncratic liver injury.

Background

Nafcillin (naf sil' in) is a second generation penicillin that is highly resistant to inactivation by penicillinases and is used to treat moderate-to-severe bacterial infections caused by penicillinase-producing bacteria. Nafcillin was approved for use in the United States in 1970 and is still widely used to treat severe staphylococcal infections. To reduce development of drug-resistant bacteria, nafcillin is recommended to treat or prevent only infections that are proven or suspected to be caused by penicillinase-producing susceptible bacteria. Nafcillin is available in multiple generic forms as solutions or powders for intravenous or intramuscular use in 1 or 2 grams per vial. Oral formulations have been developed and are available in some countries. The recommended dose for parenteral use is 1 to 2 grams every 4 to 6 hours for 5 to 30 days depending upon the type and severity of infection. The oral dose is 500 mg to 1 gram four times daily. Common side effects include nausea, diarrhea, dyspepsia, headache, fatigue, urticaria, skin rash, renal dysfunction, liver enzyme elevations and allergic reactions. Rare potentially severe adverse events include anaphylaxis, Clostridium difficile diarrhea, and severe neutropenia.

Hepatotoxicity

The serum aminotransferase elevations that appear during high dose intravenous therapy with oxacillin do not appear to occur with high doses of nafcillin, and patients who develop elevated serum aminotransferase levels while on high dose oxacillin can be safety switched to intravenous nafcillin or other penicillin antibiotics. Only rare instances of clinically apparent hepatotoxicity have been linked to use of nafcillin. Typically, the injury has been a cholestatic hepatitis that arises 1 to 6 weeks after starting nafcillin and can be prolonged, but ultimately resolves. Rash, fever and eosinophilia are uncommon but can occur (Case 1). The injury is similar to that described with flucloxacillin and cloxacillin but is far less frequent with nafcillin. Autoantibodies are uncommon.

Likelihood score: C (probable rare cause of clinically apparent liver injury).

Mechanism of Injury

The idiosyncratic hepatotoxicity that occurs with nafcillin (and other related penicillins) is sometimes, but not always accompanied by signs of hypersensitivity or allergy, but has some characteristics that suggest such a mechanism, such as the rapid reappearance of injury with reexposure. Too few cases of nafcillin hepatotoxicity have been reported to comment on possible HLA associations, such as the link to HLA-B*5701 which has been made to flucloxacillin.

Outcome and Management

The cholestatic hepatitis due to nafcillin can be symptomatic and prolonged, but has not been linked to acute, liver failure, chronic or permanent injury, or vanishing bile duct syndrome (although these forms of liver injury have been described with the related antibiotic, flucloxacillin). Recovery can be expected in 4 to 12 weeks. Prednisone has been used to treat the cholestatic liver injury when it is symptomatic and prolonged, but its effects are unclear while its side effects can be serious. Patients with clinically apparent liver injury due to nafcillin should be told to avoid reexposure to the penicillinase-resistant penicillins, including dicloxacillin and oxacillin.

Drug Class: Penicillin (Penicillinase-Resistant)

CASE REPORT

Case 1. Cholestatic hepatitis caused by nafcillin.(1)

An elderly lady with septic arthritis was treated with intravenous nafcillin for 3 weeks and developed skin rash and diarrhea (week 2), followed by jaundice and worsening pruritus (week 3). Nafcillin was stopped and ciprofloxacin begun. She had no previous history of jaundice or risk factors for liver disease. Initial laboratory data revealed a serum bilirubin of 5.7 mg/dL, with marked elevations in alkaline phosphatase and modest elevations in serum aminotransferase levels (Table). She had eosinophilia (21%). Tests for viral hepatitis and autoantibodies were negative. Imaging of the abdomen, liver and biliary tree showed no masses or evidence of obstruction. A liver biopsy was compatible with cholestatic hepatitis caused by a medication. Her recovery was slow and she had persistent jaundice and pruritus. Prednisone (20 mg/day) was started, and she recovered clinically and biochemically over the next few weeks allowing prednisone to be discontinued after a total of only 26 days.

Key Points

Medication:	Nafcillin
Pattern:	Cholestatic (R=0.4)
Severity:	3+ (jaundice and hospitalization)
Latency:	Two to three weeks
Recovery:	Complete in 2 months after a course of prednisone
Other medications:	Cefazolin, possibly others

Laboratory Values

Weeks After Starting	Weeks After Stopping	ALT (U/L)	Alk P* (U/L)	Bilirubin* (mg/dL)	Other
0		Normal	Normal	<1.0	Nafcillin started
1			Normal	<1.0	

Table continued from previous page.

Weeks After Starting	Weeks After Stopping	ALT (U/L)	Alk P* (U/L)	Bilirubin* (mg/dL)	Other
3	0		Normal	1.5	Nafcillin stopped
4	1		935	5.7	
4.5	1.5	117	1192	9.1	Hospitalized
5	2		1000	11.0	
6	3		1100	13.0	Prednisone started
7	4		350	3.5	
8	5		150	2.0	Prednisone stopped
12	9		Normal	Normal	
Normal Values		**<42**	**<150**	**<1.2**	

* Estimates made from Figure 1.

Comment

The abrupt onset of a cholestatic hepatitis within 3 to 4 weeks of starting nafcillin suggested that the drug was responsible. Liver biopsy confirmed intrahepatic cholestasis compatible with acute drug induced liver disease. While prednisone therapy appeared to have a beneficial effect, most cases of hepatic injury due to penicillinase-resistant penicillins follow a similar course and resolve without prednisone therapy. In this case, the dose and duration of prednisone therapy were kept to a minimum.

PRODUCT INFORMATION

REPRESENTATIVE TRADE NAMES

Nafcillin – Generic

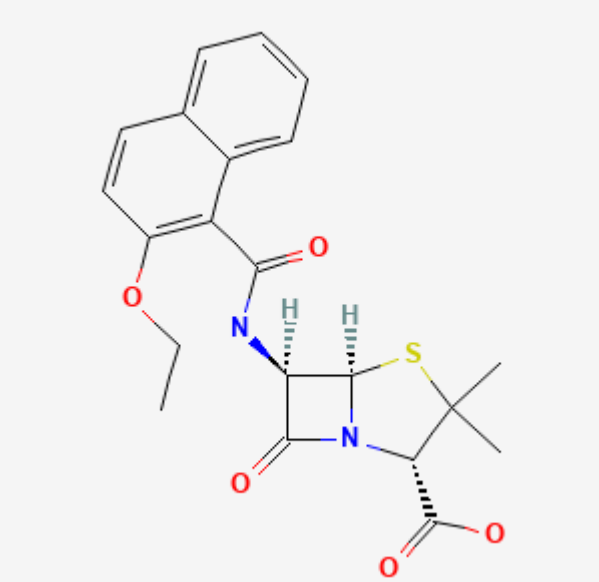
DRUG CLASS

Penicillin (Penicillinase-Resistant)

COMPLETE LABELING

Product labeling at DailyMed, National Library of Medicine, NIH

CHEMICAL FORMULA AND STRUCTURE

DRUG	CAS REGISTRY NUMBER	MOLECULAR FORMULA	STRUCTURE
Nafcillin	147-52-4	C21-H22-N2-O5-S	

CITED REFERENCES

1. Mazuryk H, Kastenberg D, Rubin R, Muñoz SJ. Cholestatic hepatitis associated with the use of nafcillin. Am J Gastroenterol. 1993;88:1960–2. PubMed PMID: 8237951.

ANNOTATED BIBLIOGRAPHY

References updated: 20 October 2020

Zimmerman HJ. Synthetic penicillins. In, Zimmerman HJ. Hepatotoxicity: the adverse effects of drugs and other chemicals on the liver. 2nd ed. Philadelphia: Lippincott, 1999. p. 596-8.

(Expert review of penicillins and liver injury published in 1999).

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 liver injury from the penicillins is very rare, and is usually cholestatic for the oxypenicillins such as dicloxacillin and cloxacillin).

MacDougall C. Penicillins, cephalosporins, and other β-lactam antibiotics. In, Brunton LL, Hilal-Dandan R, Knollman BC, eds. Goodman & Gilman's the pharmacological basis of therapeutics. 13th ed. New York: McGraw-Hill, 2018, pp. 1023-38.

(Textbook of pharmacology and therapeutics).

Nahata MC, DeBolt SL, Powell DA. Adverse effects of methicillin, nafcillin and oxacillin in pediatric patients. Dev Pharmacol Ther. 1982;4:117–23. PubMed PMID: 7172968.

(Prospective study of children treated with intravenous methicillin [28], nafcillin [32] or oxacillin [8]; minimal ALT elevations occurred in 1 on nafcillin and 1 on oxacillin; no jaundice).

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 after 13 days of high dose oxacillin [18 g/day], similar increase after nafcillin and again with cephalosporin in a male injection drug user with probable chronic hepatitis C, which might have accounted for ALT fluctuations).

Lestico MR, Vick KE, Hetsko CM. Hepatic and renal dysfunction following nafcillin administration. Ann Pharmacother. 1992;26:985–90. PubMed PMID: 1504413.

(Four cases of elevations in creatinine, BUN and bilirubin within 4 days of starting iv nafcillin, but most patients had abnormal liver tests before therapy; minimal change in AST and Alk P and all patients were septic and also received rifampin and/or gentamicin).

Mazuryk H, Kastenberg D, Rubin R, Muñoz SJ. Cholestatic hepatitis associated with the use of nafcillin. Am J Gastroenterol. 1993;88:1960–2. PubMed PMID: 8237951.

(80 year old developed pruritus and rash after 2 weeks of intravenous nafcillin [8 g/day], with subsequent jaundice [bilirubin rising from 5.7 to 15 mg/dL, ALT 117 U/L, Alk P 1,102 U/L]; after month of jaundice, prednisone was started with prompt improvement).

Presti ME, Janney CG, Neuschwander-Tetri BA. Nafcillin-associated hepatotoxicity. Report of a case and review of the literature. Dig Dis Sci. 1996;41:180–4. PubMed PMID: 8565754.

(63 year old developed jaundice after 5 days of intravenous nafcillin [bilirubin rising to 40 mg/dL, ALT ~210 U/L, Alk P ~375 U/L], lasting 2 months, previous history of dicloxacillin allergy-rash).

Ibáñez L, Pérez E, Vidal X, Laporte JR. Grup d'Estudi Multicènteric d'Hepatotoxicitat Aguda de Barcelona (GEMHAB). Prospective surveillance of acute serious liver disease unrelated to infectious, obstructive, or metabolic diseases: epidemiological and clinical features, and exposure to drugs. J Hepatol. 2002;37:592–600. PubMed PMID: 12399224.

(Survey of 107 cases of acute serious liver disease, not due to viruses, found no instances of drug induced liver injury due to penicillinase-resistant penicillins).

Maraqa NF, Gomez MM, Rathore MH, Alvarez AM. Higher occurrence of hepatotoxicity and rash in patients treated with oxacillin, compared with those treated with nafcillin and other commonly used antimicrobials. Clin Infect Dis. 2002;34:50–4. PubMed PMID: 11731945.

(Retrospective analysis of laboratory tests from 222 children receiving outpatient parenteral oxacillin, nafcillin, clindamycin or other antibiotics found 12 cases of anicteric and self-limited hepatotoxicity, 9 [22%] from oxacillin, all hepatocellular with normal bilirubin, onset in 6-43 days, resolution in 1-3 weeks; none to nafcillin; 1 clindamycin, 1 ceftriaxone and 1 ampicillin/sulbactam/gentamicin).

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

(A population based study identified 34 cases of acute drug induced liver injury over a 3 year period, including 10 [25%] due to antibiotics; one was due to cloxacillin with a 5 day latency, mixed serum enzyme pattern and recovery within 2 weeks of stopping).

Björnsson 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.

(Analysis of all fatal adverse drug event reports of liver injury in Sweden between 1966 and 2002, found 103 cases; most common causes were halothane [n=16], acetaminophen [14], flucloxacillin [9], and TMP-SMZ [6]).

Hussaini SH, O'Brien CS, Despott EJ, Dalton HR. Antibiotic therapy: a major cause of drug-induced jaundice in southwest England. Eur J Gastroenterol Hepatol. 2007;19:15–20. PubMed PMID: 17206072.

(Review of causes of non-obstructive jaundice in 347 patients presenting between 1998 and 2004 at a single UK center, 28 were thought to be drug induced liver injury [8.1%] and antibiotics were the most common cause, 32% amoxicillin/clavulanate, 25% flucloxacillin, 18% other).

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, antimicrobials accounted for 45% of cases with 23 single agent cases due to amoxicillin/clavulanate, 13 nitrofurantoin, 10 fluoroquinolones, 9 macrolides, 9 sulfonamides, 5 cephalosporins, 3 oxacillin, 2 doxycycline, 2 amoxicillin, and one each for gentamicin, imipenem, and clindamycin, but none from dicloxacillin or nafcillin).

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; leading causes were antituberculosis agents [58%], anticonvulsants [11%] and NSAIDs [2%]; specific antibiotic agents included sulfamethoxazole/ trimethoprim [2%] and amoxicillin-clavulanate [1%]; no mention of 2nd generation penicillins).

Ferrajolo C, Capuano A, Verhamme KMC, Schuemie M, Rossi F, Stricker BH, Sturkenboom CJM. 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.

(Among 624,673 adverse drug reports in children in a worldwide pharmacovigilance database, 6595 [1%] were for hepatic injury and antibacterials accounted for 11%, those with the highest adjusted odds ratios being aztreonam, erythromycin, ceftriaxone and minocycline; no mention of penicillins).

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, but none were attributed to a penicillinase-resistant penicillin).

Leitner JM, Graninger W, Thalhammer F. Hepatotoxicity of antibacterials: pathomechanisms and clinical data. Infection. 2010;38:3–11. PubMed PMID: 20107858.

(Review of hepatotoxicity of antibiotics, mentions that cholestatic hepatitis has been reported with many beta-lactams and beta-lactamases inhibitors).

Alam MB, Kadoura A, Sathaiah M. A fatal case of nafcillin-induced hepatotoxicity: a case report and the literature review. Case Rep Med. 2012;2012:953714. PubMed PMID: 22844299.

(53 year old woman developed jaundice 15 days after starting intravenous nafcillin for osteomyelitis [bilirubin 9.6 mg/dL, ALT 24 U/L, Alk P 388 U/L], with worsening despite stopping nafcillin [bilirubin 28.7 mg/dL, ALT 24 U/L, Alk P >1884 U/L], and death from multiorgan failure 2 months later).

Monshi MM, Faulkner L, Gibson A, Jenkins RE, Farrell J, Earnshaw CJ, Alfirevic A, et al. Human leukocyte antigen (HLA)-B*57:01-restricted activation of drug-specific T cells provides the immunological basis for flucloxacillin-induced liver injury. Hepatology. 2013;57:727–39. PubMed PMID: 22987284.

(*T cells from persons with HLA-B*57:01 were activated when exposed to dendritic cells presenting flucloxacillin bound to albumin, and were similarly activated by oxacillin, cloxacillin and dicloxacillin).*

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, 1 to dicloxacillin [2nd generation] and 1 to phenoxymethylpenicillin [1st generation], the latter two cases being anicteric).

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 36 [37%] due to antibiotics and specifically dicloxacillin in 1 of 22,320 patients treated and cloxacillin in 1 of 3659 patients treated).

Wuillemin N, Terracciano L, Beltraminelli H, Schlapbach C, Fontana S, Krähenbühl S, Pichler WJ, et al. T cells infiltrate the liver and kill hepatocytes in HLA-B(*)57:01-associated floxacillin-induced liver injury. Am J Pathol. 2014;184:1677–82. PubMed PMID: 24731753.

*(Analysis of T cells from HLA-B*57:01 positive, healthy, non-flucloxacillin exposed controls demonstrated cytotoxicity of their CD8 cells by exposure to increasing concentrations of flucloxacillin with HLA-linked target cells).*

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 from Latin American countries published between 1996 and 2012 identified 176 cases, of which 37 [19%] were attributed to antimicrobials, but none to penicillinase resistant penicillins such as oxacillin, nafcillin or dicloxacillin).

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.e7. PubMed PMID: 25754159.

(Among 899 cases of drug induced liver injury enrolled in a US prospective study between 2004 and 2013, 323 cases [36%] were attributed to antibiotics 3 of which were due to oxacillin, all being self-limited episodes of aminotransferase elevations without jaundice; no instances of dicloxacillin or nafcillin associated liver injury).

Usui T, Naisbitt DJ. Human leukocyte antigen and idiosyncratic adverse drug reactions. Drug Metab Pharmacokinet. 2017;32:21–30. PubMed PMID: 28017537.

*(Review of the association of specific forms of idiosyncratic drug reactions and HLA alleles focusing on class I alleles linked with abacavir [B*57:01], allopurinol [B*58:01], carbamazepine [B*15:02], amoxicillin/clavulanate [A*02:01], and flucloxacillin [B*57:01]).*

Rao Q, Schuster I, Seoud T, Zarrabi K, Goolsarran N. A patient with nafcillin-associated drug-induced liver failure. Case Rep Gastroenterol. 2017;11:564–8. PubMed PMID: 29033779.

(68 year old man with osteomyelitis developed jaundice 4 weeks after starting intravenous nafcillin, 2 g every 4 hours [bilirubin 9.4 rising to 14.1 mg/dL, ALT 127 U/L, Alk P 311 U/L, INR 1.6, eosinophils 21%], worsening for 7 days after stopping, but then resolving and 6 months later had normal liver tests).

Cirulli ET, Nicoletti P, Abramson K, Andrade RJ, Bjornsson ES, Chalasani N, Fontana RJ, et al; Drug-Induced Liver Injury Network (DILIN) investigators. International DILI consortium (iDILIC). A missense variant in PTPN22 is a risk factor for drug-induced liver injury. Gastroenterology. 2019;156:1707–1716.e2. PubMed PMID: 30664875.

(Genome-wide association studies on 2048 patients with drug induced liver injury and 12,439 controls identified a variant in PTPN22 which was highly associated with liver injury, allele frequency being 0.12 among cases and 0.08 among controls with highest association in Northern Europeans and in cases of amoxicillin clavulanate, PTPN22 being a cellular kinase involved in modulation of immune reactions).