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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-. Clarithromycin. [Updated 2017 Aug 10].
Bookshelf URL: https://www.ncbi.nlm.nih.gov/books/

Clarithromycin

Updated: August 10, 2017.

OVERVIEW

Introduction

Clarithromycin is a semisynthetic macrolide antibiotic used for a wide variety of mild-to-moderate bacterial infections. Clarithromycin has been linked to rare instances of acute liver injury that can be severe and even fatal.

Background

Clarithromycin (kla rith" roe mye' sin) is a semisynthetic macrolide antibiotic used widely to treat mild-to-moderate bacterial infections caused by sensitive agents. Clarithromycin, like other macrolide antibiotics such such as eythromycin and azithromycin, is bacteriostatic against many gram positive bacteria including many strains of streptococci, staphylococci, clostridia, corynebacteria, listeria, haemophilus sp., moxicella, and Neisseria meningitidis. Clarithromycin is also active against Chlamydia pneumoniae, Helicobacter pylori, and several atypical mycobacteria. Macrolide antibiotics act by inhibiting protein synthesis of bacteria by binding to the 50S ribosomal element. Resistance occurs by several mechanisms. Clarithromycin was approved for use in the United States in 1993, and currently more than 3 million prescriptions are filled yearly. Typical indications are for upper respiratory infections, bronchitis, sinusitis, community acquired pneumonia, and skin and tissue infections. Clarithromycin is also used for infections caused by Chlamydia pneumoniae, Helicobacter pylori and atypical mycobacteria. Clarithromycin is available in tablets of 250 and 500 mg generically under several commercial names including Biaxin, Claripen and Clacid. Extended release formulations are also available. The typical course is 250 to 500 mg twice daily (or 1000 mg extended release tablets once daily) for 7 to 14 days. Clarithromycin is given chronically in some situations such as prophylaxis against mycobacterium avium complex in patients with HIV infection. Clarithromycin is generally well tolerated, but side effects can include nausea, abdominal pain, diarrhea, dyspepsia, headache, dizziness, angioedema and rash.

Hepatotoxicity

Clarithromycin, like other macrolide antibiotics, has been linked to a low rate of acute, transient and usually asymptomatic elevations in serum aminotransferase levels which occur in 1% to 2% of patients treated for short periods and a somewhat higher proportion of patients given clarithromycin long term. Asymptomatic elevations in serum enzymes are particularly common among elderly patients given higher doses of clarithromycin.

Clarithromycin can also cause acute, clinically apparent liver injury with jaundice, which is estimated to occur in 3.8 per 100,000 prescriptions. The liver injury usually appears within the first 1 to 3 weeks after initiation of treatment and can arise after clarithromycin is stopped. The pattern of liver enzyme elevations varies, but the resulting hepatitis is often cholestatic and can be prolonged (Case 1). Allergic signs and symptoms have not been

consistently reported. While cholestatic hepatitis is most typical of clarithromycin induced liver injury, rare cases with hepatocellular injury and abrupt onset have been described. These hepatocellular cases are more likely to be severe and can result in acute liver failure. However, in most instances, recovery occurs within 4 to 8 weeks of withdrawal of the medication. The typical latency, clinical pattern and course of the cholestatic hepatitis due to clarithromycin resembles that of the other macrolide antibiotics.

Likelihood score: B (highly likely cause of clinically apparent liver injury).

Mechanism of Liver Injury

The cause of the idiosyncratic liver injury due to clarithromycin is unknown, but the rapidity of onset and prompt recurrence upon rechallenge suggests hypersensitivity. Clarithromycin is extensively metabolized by the microsomal cytochrome P450 system and is a potent inhibitor of CYP 3A4, for which reason it can cause serious drug-drug interactions with agents that are metabolized by CYP 3A4 such as siapride, terfenadine, ergotamine, colchicine, amlodipine, diltiazem and many statins and benzodiazepines. Thus, in some situations, clarithromycin may lead to liver injury from a concurrent medication because of a decrease in its metabolism and increased blood levels.

Outcome and Management

The minor serum aminotransferase elevations that appear during therapy with clarithromycin are usually benign, asymptomatic and resolve rapidly whether or not clarithromycin is stopped. The acute hepatic injury with jaundice, however, can be prolonged and troublesome and lead to loss of intrahepatic bile ducts and vanishing bile duct syndrome. Rare instances of fatality from clarithromycin induced liver disease have been reported. It is unclear whether there is cross sensivity to hepatic injury about the different macrolide antibiotics, but after severe injury from one macrolide, it is prudent to avoid use of the others.

Drug Class: Antiinfective Agents, Macrolide Antibiotics

CASE REPORT

Case 1. Cholestatic hepatitis after clarithromycin.

[Modified from: Sousa C, Correia J, Santos J, Silvestre F, Bernardo A. [Cholestatic hepatitis probably induced by clarithromycin] Gastroenterol Clin Biol 1997; 21: 632-3. French. PubMed Citation]

A 74 year old man with acute bronchitis was treated with a 10 day course of clarithromycin (500 mg daily) and developed nausea and jaundice by day 7. Because of itching and worsening symptoms, he sought medical advice and was hospitalized. He was jaundiced and had right upper quadrant tenderness over the liver, but was not febrile. He denied a history of alcohol intake and had no risk factors for viral hepatitis. Laboratory tests showed marked elevations in alkaline phosphatase and bilirubin levels with moderate increases in ALT and AST levels. He tested negative for markers of hepatitis A, B and C, had low levels of antinuclear and anti-smooth muscle antibody, and liver ultrasound was normal. A liver biopsy showed intrahepatic cholestasis with centrolobular ballooning degeneration, portal inflammation with a prominence of eosinophils, and ductular proliferation. His other medications that he took chronically were stopped at the same time. He recovered over the next few weeks and all liver tests were normal in follow up 3 months later.

Key Points

Medication:	Clarithromycin (500 mg daily for 10 days)
Pattern:	Cholestatic (R=0.6)
Severity:	3+ (jaundice and hospitalization)

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Medication:	Clarithromycin (500 mg daily for 10 days)
Latency:	1 week
Recovery:	Complete within three months
Other medications:	Digoxin, captopril, nitropaste, aminophylline, salbutamol, and budesonide (by inhalation) for several years

Laboratory Values

Time After Starting	Time After Stopping	AST (U/L)	Alk P (U/L)	Bilirubin* (mg/dL)	Other
Nausea and jaundice arose on day 7 of a 10 day course of clarithromycin					
2 weeks	5 days	520	3090	25.1	Admission
3 weeks	11 days	256	2477	30.4	Liver Biopsy
4 weeks	18 days	155	1108	8.5	
5 weeks	27 days	84	445	4.0	
3 months	3 months	19	117	0.8	
Normal Values		**<33**	**<117**	**<1.2**	

* Converted from µmol (1.0 mg/dL = 17.1 µmol).

Comment

A convincing history for drug induced liver disease and the only new medication taken was clarithromycin. The latency was short (one week) as is typical for macrolide induced hepatotoxicity, and the pattern of liver enzyme elevations was cholestatic which also is typical. Despite the patient's age and depth of jaundice, recovery was complete, taking somewhat longer than usual for this form of drug induced liver injury probably because of the height of the bilirubin and alkaline phosphatase elevations.

CASE REPORTS SUBMITTED TO LIVERTOX

Clinical cases of drug-induced liver injury that have been submitted to LiverTox ("Submit a Case Report") are available for review. Most of these reference cases are from the Drug-Induced Liver Injury Network, but others are from users of LiverTox who have submitted data from an actual clinical case. All cases have been reviewed and cleared of personal identifiers and a brief comment added by the LiverTox editors. Click on the following link to view the submitted case reports that have been made publically available.

Submitted Cases on Clarithromycin

PRODUCT INFORMATION

REPRESENTATIVE TRADE NAMES

Clarithromycin — Generic, Biaxin®

DRUG CLASS

Antiinfective Agents

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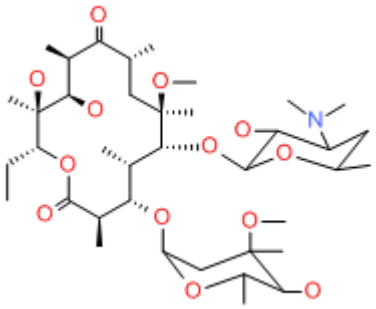
COMPLETE LABELING

Product labeling at DailyMed, National Library of Medicine, NIH

CHEMICAL FORMULA AND STRUCTURE

DRUG	CAS REGISTRY NUMBER	MOLECULAR FORMULA	STRUCTURE
Clarithromycin	81103-11-9	C38-H69-N-O13	

ANNOTATED BIBLIOGRAPHY

References updated: 10 August 2017

Moseley RH. Macrolide antibiotics. Hepatotoxicity of antimicrobials and antifungal agents. In, Kaplowitz N, DeLeve LD, eds. Drug-induced Liver Disease. 3rd ed. Amsterdam: Elsevier, 2013, pp. 466-7.

(Expert review of macrolide antibiotic induced liver injury mentions that clarithromycin has been implicated in cases of cholestatic hepatitis, particularly in elderly patients on high doses).

MacDougall C, Chambers HF. Macrolides and ketolides. In, Brunton LL, Chabner BA, Knollman BC, eds. Goodman & Gilman's the pharmacological basis of therapeutics. 12th ed. New York: McGraw-Hill, 2011, pp. 1529-34. *(Textbook of pharmacology and therapeutic*

s).

Wallace RJ Jr, Brown BA, Griffith DE. Drug intolerance to high-dose clarithromycin among elderly patients. Diagn Microbiol Infect Dis 1993; 16: 215-21. PubMed PMID: 8477575.

(Elevations of Alk P and GGT occurred in 5 of 14 elderly patients receiving clarithromycin in high doses [2 g/day] after 1 to 6 weeks of therapy, resolving slowly; no jaundice and few symptoms).

Yew WW, Chau CH, Lee J, Leung CW. Cholestatic hepatitis in a patient who received clarithromycin therapy for a Mycobacterium chelonae lung infection. Clin Infect Dis 1994; 18: 1025-6. PubMed PMID: 8086541.

(62 year old man with atypical mycobacterial disease received high doses of clarithromycin [2 g/day] and developed rising Alk P [110 to 447 U/L], bilirubin [0.5 to 2.2 mg/dL] and ALT [18 to 46 U/L] during 2 months of therapy, resolving slowly once drug was stopped).

Brown BA, Wallace RJ Jr, Griffith DE, Girard W. Clarithromycin-induced hepatotoxicity. Clin Infect Dis 1995; 20: 1073-4. PubMed PMID: 7795060.

(Letter in response to Yew et al. pointing out similarity of details in case to those from their study [Wallace 1993] and adding two further cases of marked Alk P and GGT elevations during high dose clarithromycin therapy, particularly in elderly and frail patients, resolving slowly over 1 to >3 months; not seen with lower doses).

Cadranel JF, Bachmeyer C, Pras V, Bouraya D, Pourvillain S, Biour M, Mougeot-Martin M. [Acute symptomatic cytolytic hepatitis probably related to clarithromycin] Gastroenterol Clin Biol 1996; 20: 1034-5. French. PubMed PMID: 9119179.

(41 year old woman developed acute abdominal pain after 3 days of clarithromycin therapy [bilirubin 0.7 mg/dL, ALT 10 times ULN, Alk P normal], resolving with a month of stopping).

Shaheen N, Grimm IS. Fulminant hepatic failure associated with clarithromycin. Am J Gastroenterol 1996; 91: 394-5. PubMed PMID: 8607519.

(25 year old man developed jaundice and abdominal pain after 9 days of clarithromycin [bilirubin 12.6 rising to 32 mg/dL, ALT 4790 U/L, Alk P 225 U/L], with subsequent signs of liver failure leading to transplant 11 days after admission; patient died postoperatively).

Sousa C, Correia J, Santos J, Silvestre F, Bernardo A. [Cholestatic hepatitis probably induced by clarithromycin] Gastroenterol Clin Biol 1997; 21: 632-3. French. PubMed PMID: 9587506.

(74 year old man developed jaundice after 7th day of 10-day course of clarithromycin [bilirubin 25.1 mg/dL, ALT 498 U/L, Alk P 3148 U/L], resolving fully within 3 months of stopping: Case 1).

Vial T, Biour M, Descotes J, Trepo C. Antibiotic-associated hepatitis: update from 1990. Ann Pharmacother 1997; 31: 204-20. PubMed PMID: 9034423.

(Extensive review including discussion of 3 macrolides [erythromycin, clarithromycin and azithromycin], ALT elevations occurred in 0.4-1.2% of patients treated, but similar rates found in placebo controls; rare instances of cholestatic hepatitis have been reported with all three).

Baylor P, Williams K. Interstitial nephritis, thrombocytopenia, hepatitis, and elevated serum amylase levels in a patient receiving clarithromycin therapy. Clin Infect Dis 1999; 29: 1350-1. PubMed PMID: 10525003.

(77 year old man developed acute interstitial nephritis and thrombocytopenia with mild increases in AST and CPK without jaundice after 5 days of clarithromycin therapy, but also 5 days after a 7 day course of trimethoprim/sulfamethoxazole; all abnormalities subsequently resolved).

Fox JC, Szyjkowski RS, Sanderson SO, Levine RA. Progressive cholestatic liver disease associated with clarithromycin treatment. J Clin Pharmacol 2002; 42: 676-80. PubMed PMID: 12043957.

(59 year old woman developed jaundice a few days after stopping a 3 day course of clarithromycin [bilirubin 17 mg/dL, ALT 428 U/L, Alk P 2831 U/L], eventually leading to liver and renal failure and death 3 weeks later).

Masiá M, Gutiérrez F, Jimeno A, Navarro A, Borrás J, Matarredona J, Martín-Hidalgo A. Fulminant hepatitis and fatal toxic epidermal necrolysis (Lyell disease) coincident with clarithromycin administration in an alcoholic patient receiving disulfiram therapy. Arch Intern Med 2002; 162: 474-6. PubMed PMID: 11863483.

(47 year old man developed severe rash 1 month after starting disulfiram and 1 week after starting clarithromycin [bilirubin 15.3 mg/dL, ALT 2603 U/L, Alk P 240 U/L], with subsequent liver failure and death; authors hypothesized that there were drug interactions with combined inhibition of CYP 3A4 and 2E1 by the 2 agents).

Christopher K, Hyatt PA, Horkan C, Yodice PC. Clarithromycin use preceding fulminant hepatic failure. Am J Gastroenterol 2002; 97: 489-90. PubMed PMID: 11866297.

(40 year old woman developed nausea, abdominal pain and fever at the end of a 7 day course of clarithromycin, with subsequent jaundice and hepatic failure [bilirubin 33.4 mg/dL, ALT 1974 U/L, Alk P 1095 U/L, protime 21 seconds], dying 13 days after presentation).

Tietz A, Heim MH, Eriksson U, Marsch S, Teracciano L, Krähenbühl S. Fulminant liver failure associated with clarithromycin. Ann Pharmacother 2003; 37: 57-60. PubMed PMID: 12503933.

(58 year old woman with heart disease developed jaundice after 4 days of clarithromycin treatment [bilirubin 4.6 mg/dL, ALT 13,853 U/L, Alk P 258 U/L, prothrombin index 10%], recovering within 2 weeks; possibly due to ischemic hepatitis).

Sopena N, Martínez-Vázquez C, Rodríguez-Suárez JR, Segura F, Valencia A, Sabrià M. Comparative study of the efficacy and tolerance of azithromycin versus clarithromycin in the treatment of community-acquired pneumonia in adults. J Chemother 2004; 16: 102-3. PubMed PMID: 15078008.

(Comparison of 3 day azithromycin vs 10-14 day clarithromycin course in 70 adult patients with pneumonia showing similar efficacy [>90%] and frequency of side effects [26.5% vs 25%], with no mention of hepatic injury).

Peters TS. Do preclinical testing strategies help predict human hepatotoxic potentials? Toxicol Pathol 2005; 33: 146-54. PubMed PMID: 15805066.

(FDA scientist review of discrepancies between preclinical testing and toxicity identified when agent becomes generally available; clarithromycin is used as an example).

Björnsson E, Olsson R. Suspected drug-induced liver fatalities reported to the WHO database. Dig Liver Dis 2006; 38: 33-8. PubMed PMID: 16054882.

(Among 4690 reports of drug induced liver injury with fatal outcome reported to WHO, clarithromycin was among the top 20 agents implicated [51 cases]).

Giannattasio A, D'Ambrosi M, Volpicelli M, Iorio R. Steroid therapy for a case of severe drug-induced cholestasis. Ann Pharmacother 2006; 40: 1196-9. PubMed PMID: 16720710.

(Adolescent girl developed jaundice 1 week after 15 day course of clarithromycin and nimesulide [ALT 69 U/L, GGT normal and bilirubin 10.6 mg/dL]; prolonged jaundice led to use of prednisone [starting at 1 mg/kg/day] with rapid improvement, stopped after 12 weeks, ultimately complete recovery).

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, 5 cases were attributed to telithromycin and 3 to azithromycin as single agents, but none to erythromycin or clarithromycin).

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

(Review; the macrolide antibiotics may cause cholestatic hepatitis at an estimated rate of 3.6 for erythromycin, 3.8 for clarithromycin, and 5.5 cases per 100,000 prescriptions for telithromycin, compared to 10 for sulfonamides and 2000 per 100,000 for isoniazid).

Caramaschi P, Mahamid H, Bambara LM, Biasi D. Liver impairment after concomitant administration of bosentan and clarithromycin in systemic sclerosis. Joint Bone Spine 2010; 77: 81-2. PubMed PMID: 20022782.

(Two cases, 47 and 69 year old women with systemic sclerosis were treated with bosentan without difficulty, but developed ALT elevations [peak 503 and 94 U/L, Alk P 263 and 293 U/L] without jaundice within 5-7 days of starting clarithromycin, which resolved with stopping both or either, attributed to drug-drug interactions).

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 containing 9036 hepatic adverse drug reactions in children includes 63 cases attributed to azithromycin, 60 to erythromycin and 35 to clarithromycin).

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. (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, of which 31 were due to antibiotics, one of which was attributed to clarithromycin). PubMed PMID: 20949552.

Hydzik P, Gawlikowski T, Groszek B. [Drug-induced erythrodermia complicated by multiorgan failure--case report]. Przegl Lek 2011; 68: 503-5. Polish. PubMed PMID: 22010450.

(23 year old young woman developed toxic epidermal necrolysis with liver, lung and renal injury two weeks after starting a course of clarithromycin, ibuprofen and acetaminophen [bilirubin 10.7 mg/dL, ALT 915 U/L, GGT 252 U/L, INR 1.7], with ultimate complete resolution).

Kwon H, Lee SH, Kim SE, Lee JH, Jee YK, Kang HR, Park BJ, Park JW, Hong CS. 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 6 [1.1%] attributed to macrolide antibiotics).

Maggi P, Solarino B, Cassano P, Tattoli L, Leone A, Maselli E, Angarano G. Fatal fulminant hepatitis following administration of clarithromycin in a patient chronically treated with antipsycotic drugs. Immunopharmacol Immunotoxicol. 2013; 35: 191-4. PubMed PMID: 22804484.

(23 year old man developed nausea, diarrhea and fever within 3 days of starting a 5 day course of clarithromycin, with subsequent jaundice [bilirubin 9.6 mg/dL, ALT 4065 U/L] followed by hepatic failure, coagulopathy, intracerebral hemorrhage and death).

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 large, electronic healthcare databases identified 785 cases of acute liver injury of unknown cause, 110 of which occurred in relationship to a prescription, the highest relative risk [RR] being associated with clarithromycin [RR=25.9], amoxicillin/ clavulanate [RR=18.6] and amoxicillin [RR=6.0]).

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, none of which were attributed to clarithromycin or other macrolide antibiotics).

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, one of which was attributed to clarithromycin [acute liver failure], but none were attributed to other macrolide antibiotics).

Ferrajolo C, Coloma PM, Verhamme KM, Schuemie MJ, de Bie S, Gini R, Herings R, et al.; EU-ADR consortium. Signal detection of potentially drug-induced acute liver injury in children using a multi-country healthcare database network. Drug Saf 2014; 37: 99-108. PubMed PMID: 24446276.

(Analyses of large spontaneous reporting databases from 3 European countries between 1995 and 2010 identified 125 drugs with at least one exposed case of unexplained acute liver injury in children, 20 of which had a statistically significant association, including clarithromycin [5 cases] and erythromycin [4 cases]).

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 nested case control analysis of a health care network database of persons between 2001 and 2009, 8 selected antibiotics were assessed for association with risk of hospitalization for liver injury, adjusted relative risks being significantly elevated for levofloxacin [3.2], moxifloxacin [2.3], doxycycline [2.5], amoxicllin/clavulanate [2.5] and amoxicillin [2.3], but not for clarithromycin [1.8], telithromycin [1.7] or cefuroxime [0.9]).

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 [36%] were attributed to antibiotics including 29 [3.2%] due to marolides of which 18 were linked to azithromycin, 2 to clarithromycin, 2 erythromycin and 7 telithromycin).

Ferrajolo C, Verhamme KM, Trifirò G, 't Jong GW, Picelli G, Giaquinto C, Mazzaglia G, et al. Antibiotic-induced liver injury in paediatric outpatients: a case-control study in primary care databases. Drug Saf 2017; 40: 305-15. PubMed PMID: 28025733.

(In a health care database of 429,772 children in Italy and the Netherlands followed between 2008 and 2010, 938 cases of liver injury of uncertain cause were identified, the rate being higher in those with current use of antibiotics [12% vs 3.6%] for an adjusted odds rate ratio [aOR] of 3.2; specific antibiotics most commonly implicated were fluoroquinolones [19.0], cephalosporins [4.5], macrolides [3.5] and penicillins [2.6], and specific aOR for clarithromycin of 5.6 [12 cases]).

Bonkovsky HL, Kleiner DE, Gu J, Odin JA, Russo MW, Navarro VM, Fontana RJ, et al.; U.S. Drug Induced Liver Injury Network Investigators. Clinical presentations and outcomes of bile duct loss caused by drugs and herbal and dietary supplements. Hepatology 2017; 65: 1267-77. PubMed PMID: 27981596.

(Among 363 patients with drug induced liver injury who underwent liver biopsy, 26 [7%] had bile duct loss, including 2 cases attributed to azithromycin, but none to clarithromycin or other macrolides).