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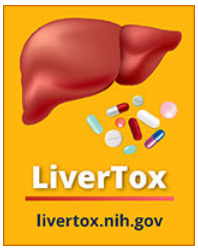


# Macrolide Antibiotics

Updated: August 10, 2017.

## OVERVIEW

The macrolides are bacteriostatic antibiotics with a broad spectrum of activity against many gram-positive bacteria. Currently available macrolides are well tolerated, orally available and widely used to treat mild-to-moderate infections. Several macrolide antibiotics have been linked to liver injury.

Five macrolide antibiotics are currently available for use in the United States: erythromycin, clarithromycin, azithromycin, fidaxomicin and telithromycin, the latter being a related ketolide. Erythromycin was initially isolated in 1952 from Streptomyces erythreus; the other macrolide antibiotics are semisynthetic derivatives. The five macrolide antibiotics have a similar range of activities, being bacteriostatic against many strains of streptococci, staphylococci, clostridia, corynebacteria, listeria, haemophilus sp., moxicella, and Neisseria meningitidis. Clarithromycin and azithromycin are more active than erythromycin against several gram negative bacteria as well as Mycoplasma pneumonia, Helicobacter pylori, Toxoplasma gondii, cryptosporidia and several atypical mycobacteria. Fidaxomicin is not absorbed orally and is used in ten day oral courses to treat Clostridium difficile associated diarrhea. Macrolide antibiotics act by inhibiting protein synthesis of bacteria by binding to the 50S ribosomal element. Resistance occurs by several mechanisms.

Aa low rate of asymptomatic elevation in serum aminotransferase levels that can occur with any of the four orally absorbed macrolide antibiotics, in rates reported to be 1% to 5% of treated patients (depending upon the duration of treatment and intensity of monitoring). These elevations are generally mild-to-moderate in degree, asymptomatic and self-limited and transient in course, rarely requiring dose modification or discontinuation.

More important is clinically apparent liver injury from macrolide antibiotics which has been described for all four of the orally absorbed agents. The liver injury is typically a self-limited cholestatic hepatitis arising within 1 to 3 weeks of starting therapy. Symptoms include fatigue, dark urine and jaundice, often with right upper quadrant pain and fever. The injury is usually self-limited and benign, but in some instances there is prolonged cholestasis and persistence of liver test abnormalities beyond 6 months. Liver histology in these cases generally shows vanishing bile duct syndrome, or at least, some degree of bile ducts loss. A second form of clinically apparent hepatotoxicity from the macrolide antibiotics is an acute hepatocellular injury that usually arises within days of starting therapy, often with re-exposure. This hepatocellular injury with jaundice can lead to acute liver failure and has an appreciable mortality (either death or need for emergent liver transplantation). This hepatocellular pattern occurs most commonly with telithromycin, but is also described with azithromycin and less commonly with clarithromycin and erythromycin.

Fidaxomicin has little systemic absorption and has not been linked to episodes of clinically apparent liver injury. There is likely to be some degree of cross sensitivity to the hepatic injury among the various macrolide antibiotics, but this has not been well defined.

Drug Class: Antiinfective Agents

The following links are to individual drug records.

- Azithromycin
- Clarithromycin
- Erythromycin
- Fidaxomicin
- Telithromycin

## ANNOTATED BIBLIOGRAPHY

References updated: 10 August 2017

Zimmerman HJ. Erythromycins. In, Zimmerman HJ. Hepatotoxicity: the adverse effects of drugs and other chemicals on the liver. 2nd ed. Philadelphia: Lippincott, 1999, pp. 594-5.

*(Expert review of erythromycin induced liver injury published in 1999; erythromycin has been linked most closely with cholestatic hepatitis with onset of 10-20 days on initial exposure and within a week on repeated exposures, presenting with abdominal pain [75%], fever [50%], jaundice [50%], eosinophilia [60%] and pruritus [25%], usually with a self-limiting and benign course).*

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 liver injury attributed to erythromycin, azithromycin and clarithromycin, and that telithromycin has been linked to several instances of severe acute liver injury, some of which have been fatal).*

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 therapeutics).*

Braun P. Hepatotoxicity of erythromycin. J Infect Dis 1969; 119: 300-6. PubMed PMID: 4888905.

*(Thorough review of literature on hepatotoxicity of macrolides up to 1969; by then, 45 published cases reported from erythromycin estolate [none with stearate] presenting within 1-3 weeks with jaundice [67%], abdominal pain, nausea and fever [~50%], as well as eosinophilia [62%], elevations in ALT [100%: average 338 U/L] and Alk P [51%]; 13 rechallenged, invariably followed by rapid recurrence, often severe).*

The erythromycins. A further report from the Australian Drug Evaluation Committee. Med J Aust 1973; 2: 192-3. PubMed PMID: 4741351.

*(As of May 1973, 113 Australian cases of jaundice related to erythromycin [all with estolate] have been reported including patients of all ages, mostly within 14 days of starting drug, but some >21, and injury usually lasting less than 28 days, no deaths).*

Zafrani ES, Ishak KG, Rudzki C. Cholestatic and hepatocellular injury associated with erythromycin esters: report of nine cases. Dig Dis Sci 1979; 24: 385-96. PubMed PMID: 456225.

*(Classic review of histology from 9 cases of erythromycin liver injury from files of the Armed Forces Institute of Pathology, mostly cholestatic or mixed enzyme pattern, all self-limited, ALT 128-560 U/L, Alk P 2-12 times ULN, bilirubin 2.1-12.0 mg/dL; histology showed cholestasis and hepatocellular injury).*

Pessayre D, Larrey D, Funck-Brentano C, Benhamou JP. Drug interactions and hepatitis produced by some macrolide antibiotics. J Antimicrob Chemother 1985; 16 Suppl A: 181-94. PubMed PMID: 3877043.

*(Review of hepatic effects of macrolides including 55 cases of hepatitis from erythromycin estolate, 10 from ethylsuccinate, and 3 from propionate; "mixed" enzyme pattern was common, fever in 59%, eosinophilia in 45%, "outcome is always favorable").*

Bojarska-Dahlig H. Hepatotoxicity of macrolide antibiotics. J Antimicrob Chemother 1990; 25: 475-7. PubMed PMID: 2338425.

*(Discussion of relative rates of liver injury in rats based upon molecular weight and erythromycin equivalents).*

Carson JL, Strom BL, Duff A, Gupta A, Shaw M, Lundin FE, Das Kl. Acute liver disease associated with erythromycins, sulfonamides, and tetracyclines. Ann Intern Med 1993; 119 (7 Pt 1): 576-83. PubMed PMID: 8363168.

*(In Medicaid records between 1980-87, 107 patients were hospitalized for acute hepatitis of unknown cause, 5 [4.7%] of whom had received erythromycins compared to 0.9% of controls; no case received estolate form).*

Derby LE, Jick H, Henry DA, Dean AD. Erythromycin-associated cholestatic hepatitis. Med J Aust 1993; 158: 600-2. PubMed PMID: 8479375.

*(Retrospective cohort study of 366,064 people who received erythromycin in UK database, found 13 cases of cholestatic hepatitis of uncertain cause within 45 days of prescription: risk=3.6/100,000 similar for ethylsuccinate and base preparations [estolate and stearate rarely used]: risk increased with age, independent of sex).*

Pérez Gutthann S, García Rodríguez LA. The increased risk of hospitalizations for acute liver injury in a population with exposure to multiple drugs. Epidemiology 1993; 4: 496-501. PubMed PMID: 8268277.

*(Case control study from Canadian Health Plan records between 1982-6, risk of hospitalization for liver injury was 1/100,000 for NSAIDs and 14/100,000 for erythromycin estolate [no case related to other types of erythromycin] and risk increased if multiple known causes of hepatotoxicity were used).*

Periti P, Mazzei T, Mini E, Novelli A. Adverse effects of macrolide antibacterials. Drug Saf 1993; 9: 346-64. PubMed PMID: 8280403.

*(Extensive review of literature on adverse events reported with macrolide antibiotics).*

Hautekeete ML. Hepatotoxicity of antibiotics. Acta Gastroenterol Belg 1995; 58: 290-6. PubMed PMID: 7491842.

*(Review of hepatotoxicity associated with antibiotics including the erythromycins, well known causes of cholestatic hepatitis).*

von Rosensteil NA, Adam D. Macrolide antibacterials. Drug interactions of clinical significance. Drug Saf 1995; 13: 105-22. PubMed PMID: 7576262.

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

*(Erythromycin ranked first as a cause of liver adverse drug reaction in New Zealand from 1974 to 1995, accounting for ~12% of cases).*

Viluksela M, Vainio PJ, Tuominen RK. Cytotoxicity of macrolide antibiotics in a cultured human liver cell line. J Antimicrob Chemother 1996; 38: 465-73. PubMed PMID: 8889721.

*(In vitro study of cytotoxicity of macrolides).*

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

Chitturi S, Farrell GC. Drug-induced cholestasis. Semin Gastrointest Dis 2001; 12: 113-24. PubMed PMID: 11352118.

*(Review of cholestatic forms of drug induced liver disease with a case report of prolonged jaundice and pruritus starting 8 weeks after a 1-week course of erythromycin base).*

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.

*(All fatal adverse drug event reports of liver injury in Sweden between 1966 and 2002, found 103 cases, only one due to erythromycin).*

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]).*

Chang CY, Schiano TD. Drug hepatotoxicity. Aliment Pharmacol Ther 2007; 25: 1135-51. PubMed PMID: 17451560.

*(Review article summarizing large cohort studies in which erythromycin or the macrolides were often among the most common causes of liver injury).*

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).*

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 included 63 cases attributed to azithromycin, 60 to erythromycin and 35 to 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).*

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 only one due to macrolides [clarithromycin] and none to telithromycin).*

Andrade RJ, Tulkens PM. Hepatic safety of antibiotics used in primary care. J Antimicrob Chemother 2011; 66: 1431-46. PubMed PMID: 21586591.

*(Review: short description of the clinical and histologic features of hepatotoxicity associated with erythromycin, clarithromycin, azithromycin and telithromycin).*

Gagne JJ, Glynn RJ, Rassen JA, Walker AM, Daniel GW, Sridhar G, Schneeweiss S. Active safety monitoring of newly marketed medications in a distributed data network: application of a semi-automated monitoring system. Clin Pharmacol Ther 2012; 92: 80-6. PubMed PMID: 22588606.

*(Description of results of a semiautomated, sequential propensity score with a matched cohort approach for drug safety monitoring based upon electronic databases; among 106,658 new users of telithromycin and a similar number of users of azithromycin identified over a 5 year period, 41 cases of hepatitis were found, 23 due to telithromycin for a risk rate of 2 per 10,000 users, not appreciably greater than with azithromycin).*

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 Feb 15. [Epub ahead of print] 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 28 due to an antibiotic, but none were attributed to azithromycin or other macrolides).*

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.

*(Among 176 reports of drug induced liver injury from Latin America published between 1996 and 2012, only one was attributed to a macrolide antibiotic: clarithromycin).*

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, 233 [36%] were attributed to antibiotics including 29 [3.2%] from macrolide anitbiotics: 18 due to azithromycin, 2 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 a specific aOR for azithromycin of 2.4).*

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 both of whom developed evidence for chronic liver injury suggestive of vanishing bile duct syndrome).*