Hepatic Safety of Common Antibiotics

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- Other relationships in relation to this talk
  - Member of Belgian Antibiotic Policy Coordination Committee
  - Past-member of Belgian Transparency and Drug Reimbursement Committees
  - Testimony (for Industry) and participation (as independent expert) to meetings of the European Medicines Agency (EMA) about antibiotic safety and evaluation of current and novel antibiotics

Drug-induced hepatoxicity: in a nutshell

- important cause of acute liver failure
- underreported and underestimated in many countries
- common classes of drugs include
  - **antibiotics**,
  - antiretrovirals,
  - lipid lowering agents,
  - oral hypoglycemics,
  - psychotropics,
  - Acetaminophen (paracetamol)
  - complementary and alternative medications.
- signature or pattern of liver injury (including liver test abnormalities)
- often important latency of symptom onset,
- immune hypersensitivity may or may not be present
- variable course after drug withdrawal.

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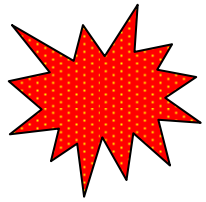
Pugh et al. Drug-induced hepatotoxicity or drug-induced liver injury. Clin Liver Dis. 2009 13:277-94. PMID: 19442919

Drug-induced hepatoxicity: why are antibiotics most frequently involved ?

1. mainly due to their its wide prescription (in terms of number of patients exposed)
2. probably also related to the large doses used compared to many other drugs
   - ➢ 77 % of cases for drugs > 50 mg/day (Swedish registry)



PK/PD may lead lead to dose increases...

3. but the absolute average risk is low (< 5 per 100,000 in general population) with exceptions (see later)

Polson JE. Hepatotoxicity due to antibiotics. Clin Liver Dis 2007; 11:549–61
Robles & Andrade. Hepatotoxicity by antibiotics: update in 2008. Rev Esp Quimioter. 2008:21:224-33
Lammert et al. Relationship between daily dose of oral medications and idiosyncratic drug-induced liver injury: search for signals. Hepatology 2008; 47: 2003–9.

Drug-induced liver injury: what can you see ?

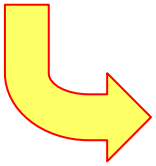
- Acute hepatitis
- Acute cholestasis

- Chronic hepatitis
- Fatty liver/ NASH
- Granulomatous disease
- Fibrosis/ cirrhosis
- Vanishing bile duct
- Veno-occlusive disease, peliosis
- Benign & malignant neoplasia

Fontana RJ Causality Assessment in Drug Induced Liver Injury, FDA, PhRMA, AASLD Symposium January 28, 2005
http://www.fda.gov/downloads/Drugs/ScienceResearch/ResearchAreas/ucm080349.ppt

Drug-induced hepatoxicity: clinical features and significance (in a nutshell)

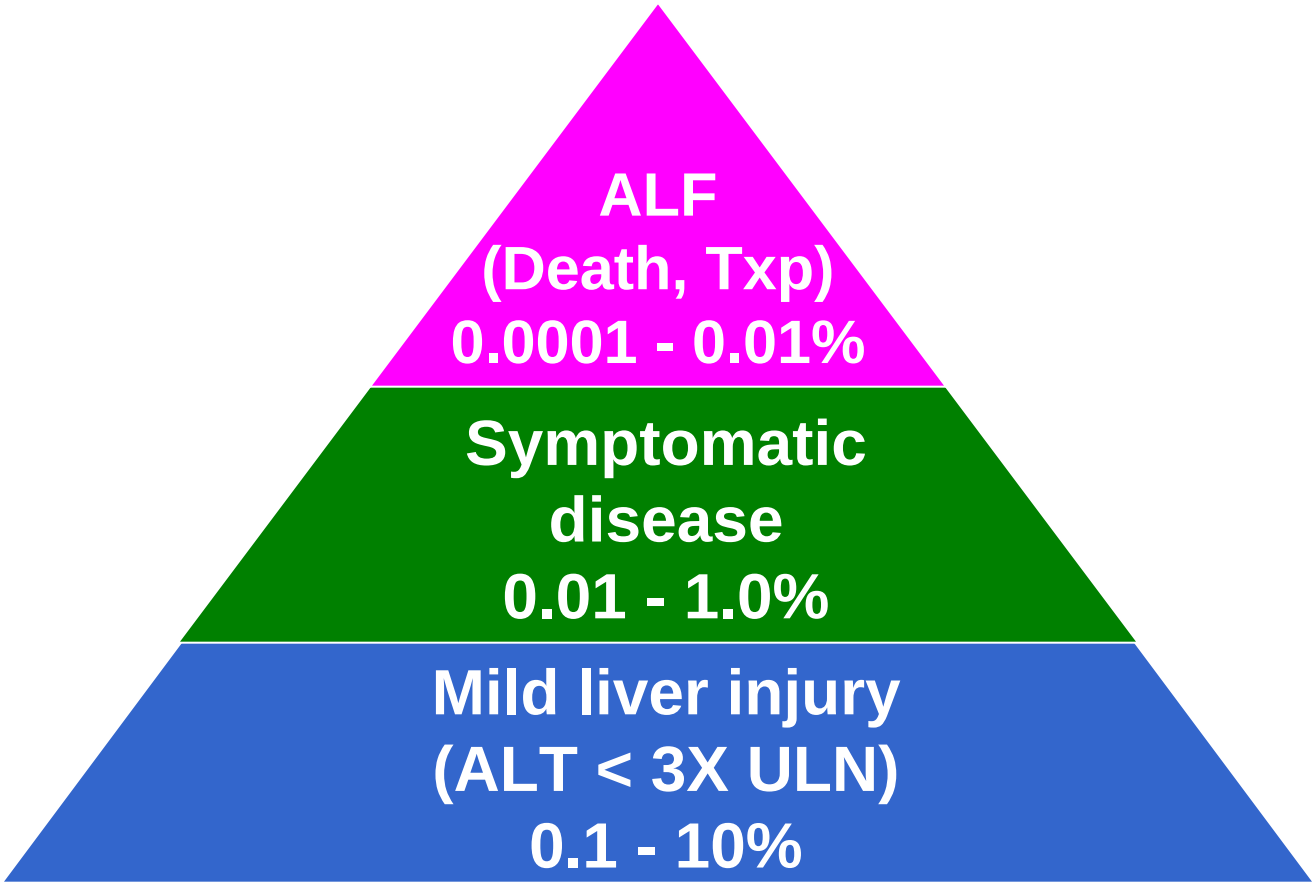
- usually asymptomatic,
- If detected, often transient with only mild hepatic impairment.
- in rare cases, however, may cause
  - significant morbidity
  - need for liver transplantation
  - death from acute liver



- actions of regulatory bodies targeting specific antibiotics
- Increased public awareness

Thiim et al. Hepatotoxicity of antibiotics and antifungals.Clin Liver Dis 2003; 7: 381–99
George & Crawford. Antibacterial-induced hepatotoxicity. Incidence, prevention and management. Drug Saf 1996; 15: 79–85
Andrade et al. Drug-induced liver injury:an analysis of 461 incidences submitted to the Spanish registry over a10-year period. Gastroenterology 2005; 129: 512–21.
Björnsson et al. Fulminant drug-inducedhepatic failure leading to death or liver transplantation in Sweden. Scand J Gastroenterol 2005; 40:1095–101
Björnsson & Olsson Suspected drug-induced liver fatalities reportedto the WHO database. Dig Liver Dis 2006; 38: 33–8

Drug-induced hepatoxicity: finding the real incidence from the tip of the iceberg



Fontana RJ Causality Assessment in Drug Induced Liver Injury, FDA, PhRMA, AASLD Symposium January 28, 2005
http://www.fda.gov/downloads/Drugs/ScienceResearch/ResearchAreas/ucm080349.ppt

Drug-induced hepatoxicity: mechanisms…

- most antibiotic-induced hepatotoxicities are **idiosyncratic**
  - occur in a very small proportion of patients,
  - cannot be predicted either from the drug's pharmacology or from pre-clinical toxicology tests
  - are host dependent.

- mechanisms may be varied and multiple
  - immunological reaction (liver inflammation associated with liver viral or bacterial infection of liver or inflammatory disease)
  - response to hepatotoxic metabolites
  - synergy with inflammatory cytokines signalling

Andrade et al. Idiosyncratic drug hepatotoxicity: a 2008 update. Expert Rev Clin Pharmacol 2008; 1: 261–76
Polson JE. Hepatotoxicity due to antibiotics. Clin Liver Dis 2007; 11:549–61
Uetrecht J. Idiosyncratic drug reactions: current understanding. AnnuRev Pharmacol Toxicol 2007; 47: 513–39
Ganey et al. Adverse hepatic drug reactions: inflammatory episodes as consequence and contributor. Chem Biol Interact 2004; 150: 35–51
Zapater et al. The diagnosis of drug-induced liver disease. Curr Clin Pharmacol 2006; 1: 207–17
Kaplowitz N. Idiosyncratic drug hepatotoxicity. Nat Rev Drug Discov 2005; 4: 489–99

Drug-induced hepatoxicity: symptoms…

- similar to those of other liver diseases,
  - ➢ jaundice,
  - ➢ malaise,
  - ➢ abdominal pain,
  - ➢ unexplained nausea and anorexia.
- mimics other liver diseases
  - ➔ diagnosis of elimination (suspicion / exclusion [viral hepatitis, biliary diseases)
- Clues
  - ➢ “drug allergy” (rash, fever or eosinophilia),
  - ➢ duration of exposure (1–5 weeks)
  - ➢ rapid response following re-administration of the antibiotic

Andrade et al. Idiosyncratic drug hepatotoxicity: a 2008 update. Expert Rev Clin Pharmacol 2008; 1: 261–76
Zapater et al. The diagnosis of drug-induced liver disease. Curr Clin Pharmacol 2006; 1: 207–17
Andrade et al. Causality assessment indrug-induced hepatotoxicity. Expert Opin Drug Saf 2004; 3: 329–44

Drug-induced hepatoxicity: how to ensure early and correct detection …

Anamnesis

- obtain a detailed drug history (➔ drug's hepatotoxic potential)
- look at timing of drug administration vs. emergence of symptoms
- ↗ if previous use of the same antibiotic
- ↘ if concomitant drug use (including herbal medications)

Laboratory findings

- alanine aminotransferase (ALT) > 2 x ULN
- bilirubin ≥2 × ULN) : worse prognosis
  - ➢ if ALT > 3 × ULN) and bilirubin > 2 × ULN ➔ ~ 10 % mortality (Hy's Law)

Bénichou C. Criteria of drug-induced liver disorders. Report of an international consensus meeting. J Hepatol 1990; 11: 272–6.
Danan & Benichou C. Causality assessment of adverse reactions to drugs – I. A novel method based on the conclusions of international consensus meetings: application to drug-induced liver injuries. J Clin Epidemiol 1993; 46: 1323–30
Farrell GC. Drug-induced Liver Disease. Edinburgh: ChurchillLivingstone, 1994

Early and correct detection of drug-induced hepatoxicity: caveats …

Confounding factors

- age
- pre-existing liver disease
- concurrent medications
- excessive alcohol consumption
- acetaminophen (paracetamol) affect biochemical tests
- infection (sepsis) may create liver toxicity (cholestasis)…
- the interval between drug administration and onset of hepatic dysfunction is variable (a few days to several weeks)

Andrade et al. Causality assessment indrug-induced hepatotoxicity. Expert Opin Drug Saf 2004; 3: 329–44
Watkins et al. Using controlled clinical trials to learn more about acute drug-induced liver injury. Hepatology 2008; 48:1680–9

Early and correct detection of drug-induced hepatoxicity: caveats …

Complicating the diagnosis and the reporting…

- increase in transaminases may be transient despite continued treatment unless additional patient's factors
- for most commercialized antibiotics, cases remain rare and have to be balanced with other causes/situations of liver injury including idiopathic liver failure (1 / 1,000,000)
- most diagnoses are the result of retrospective analysis
  - ➢ subjective nature of the approach
  - ➢ potential observer biases.
- the "gold standard" (rechallenge) is difficult to apply (and does not recreate the same environment)

Wilke et al. Identifying genetic risk factors for serious adverse drug reactions: current progress and challenges. Nat Rev Drug Discov 2007; 6: 904–16
Kaplowitz N. Idiosyncratic drug hepatotoxicity. Nat Rev Drug Discov 2005; 4: 489–99
Benichou C, Danan G, Flahault A. Causality assessment of adverse reactions to drugs—II. An original model for validation of drug causality assessment methods: case reports with positive rechallenge. J Clin Epidemiol 1993; 46: 1331–6.

Difficulties with causality assessment…

The so-called “Roussel-Uclaf Causality Assessment Method” has long been the accepted standard instrument …

• **Temporal relationship**	**(0 to 2)**
• **Course**	**(-2 to 3)**
• **Risk factors**	**(0 to 2)**
• **Concomitant drug**	**(0 to -3)**
• **Non-drug causes**	**(-3 to 2)**
• **Prior reports/ information**	**(0 to 2)**
• **Re-challenge**	**(-2 to 3)**
•	
• **Score (-8 to 14)**	

- **Highly probable >8** **Possible 3-5** **Excluded ≤0**
- **Probable 6-8** **Unlikely 1-2**

Bénichou C. Criteria of drug-induced liver disorders. Report of an international consensus meeting. J Hepatol 1990; 11: 272–6.
Danan & Benichou C. Causality assessment of adverse reactions to drugs – I. A novel method based on the conclusions of international consensus meetings: application to drug-induced liver injuries. J Clin Epidemiol 1993; 46: 1323–30
Rochon et al. Drug-Induced Liver Injury Network (DILIN). Reliability of the Roussel Uclaf Causality Assessment Method for assessing causality in drug-induced liver injury. Hepatology. 2008 Oct;48(4):1175-83

Difficulties with causality assessment…

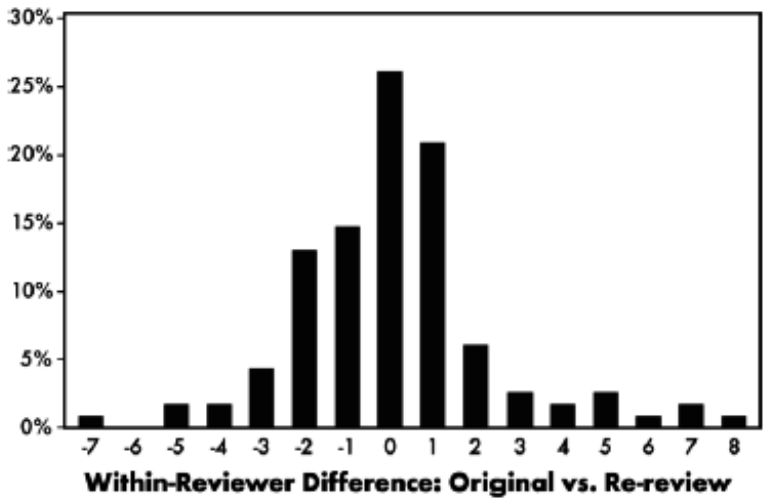
But has been challenged …

Reliability of the Roussel Uclaf Causality Assessment Method for Assessing Causality in Drug-Induced Liver Injury*

James Rochon,[1] Petr Protiva,[2] Leonard B. Seeff,[3] Robert J. Fontana,[4] Suthat Liangpunsakul,[5] Paul B. Watkins,[6] Timothy Davern,[7] and John G. McHutchison,[1] for the Drug-Induced Liver Injury Network (DILIN)

Rochon et al. Drug-Induced Liver Injury Network (DILIN). Reliability of the Roussel Uclaf Causality Assessment Method for assessing causality in drug-induced liver injury. Hepatology. 2008 Oct;48(4):1175-83

Difficulties with causality assessment…



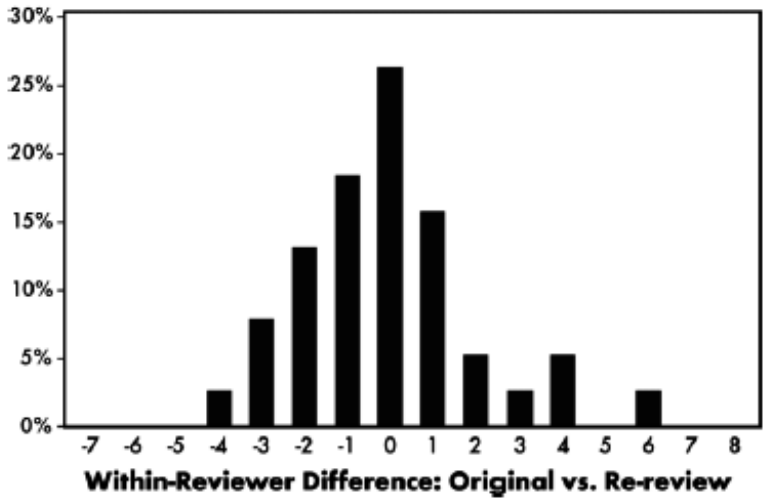


Fig. 1. Histogram of the within-reviewer differences from the first occasion to the second occasion. (A) All reviewers. (B) Site PIs only.

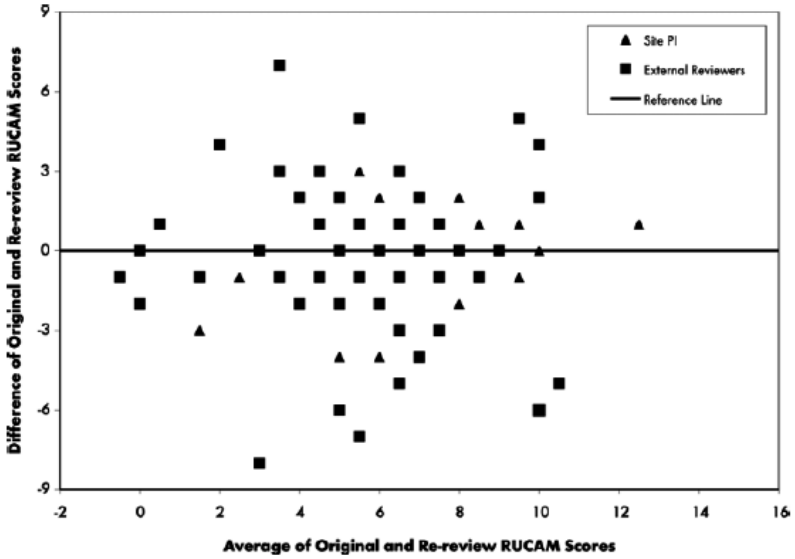


Fig. 2. Bland-Altman plot of test-retest differences versus their mean. The purpose is to determine if the test-retest differences were consistent throughout the range of the RUCAM score. This would be reflected by a constant level of scatter about the reference line. Deviations form this pattern suggests that consistency varies from one place to another in the scale and casts doubt on its overall reliability.

Comparison Between reviewers.

Comparison Between the Two Occasions.

Drug-induced hepatoxicity: elderly are at higher risk

- multi-morbidity
- poly-pharmacy
- drugs more often involved: amoxycilin/clavulanic acid, isoniazide, nitrofurantoin, diclofenac and methotrexate (4 x more than in younger adults)
- causal diagnostic made difficult because simulation of almost all known liver disorders…
- data from clinical trials of little use as most exclude patients >75-80 years of age.

Triantafyllou et al. Gastrointestinal and liver side effects of drugs in elderly patients Best Pract Res Clin Gastroenterol. 2010 Apr;24(2):203-15

Specific drugs: β -lactams and macrolides …

Antibiotic		incidence	main characteristics
β -lactams	oxypenicillins (flucloxacillin)	1.8 / 100,000	• primarily cholestatic hepatitis • rapid and late onset
	amoxyclav	1–17 / 100,000	• hepatocellular, cholestatic or mixed hepatocellular-cholestatic • up 4 weeks after treatment
	ceftriaxone	adults: 25% children: 40%	• cholelithiasis (ceftriaxone–calcium precipitate [“biliary sludge”])
Macrolides	erythromycin clarithromycin	< 4 / 100,000	• cholestatic pattern • portal and bullous inflammation, eosinophilia
	telithromycin		• mild hepatocellular necrosis • hepatocellular and canalicular bile • cholestasis • rapid onset

References: see Andrade & Tulkens. J Antimicrob Chemother. 2011; 66:1431-46. – Table 1

Amoxicillin-clavulanate: incidence …

- clavulanate increases 5-9-fold the risk of hepatotoxicity of amoxicillin. [40,43,55,59,60]
- odd ratios vs non cases of 31.9 with recent use and 94.8 with current use [43]
- responsible for 13%–23% of drug-induced hepatotoxicity cases [7,56,57]
- 9.91 cases of jaundice per 100000 prescriptions [44]
- leading cause of hospitalization for adverse hepatic events [7]

- symptom onset is usually delayed, making early diagnosis difficult [58]

- benign course, with symptoms resolving over several weeks.
- but protracted course, liver failures and deaths have been observed .

References: see Andrade & Tulkens. J Antimicrob Chemother. 2011; 66:1431-46

Amoxicillin-clavulanate: pathology and risk factors …

- delayed cholestatic or mixed hepatocellular-cholestatic injury [40,59,61]
- younger patients are more likely to develop hepatocellular injury than cholestatic or mixed injury [56]

- Risk factors: [40,56]
  - prolonged/repeated courses
  - > 65 y
  - if both : 1 case/1,000 prescription
- significant association between DRB1*1501-DRB5*0101-DQB1*0602 haplotype and cholestatic hepatitis[62]

References: see Andrade & Tulkens. J Antimicrob Chemother. 2011; 66:1431-46

Erythromycin / Clarithromycin …

Incidence

- documented for all ester derivatives [4,5,70]
- elevation of serum aminotransferases 15% of cases / hepatitis in ~2% of patients if > 2 weeks [71,72]
- UK: cholestatic hepatitis in 3.6 cases / 100000 users.[73]
- rare need of hospitalization (US: 2.28 / 1 million patients)[75]

Pathology

- combination of intrinsic hepatotoxic effects and hypersensitivity reactions
- cholestatic pattern but cases with hepatocellular injury.[72]
- potential aggravation of hepatotoxicity of other drugs trough impairment of their metabolism
- resolves most often within 2–5 weeks of treatment discontinuation

References: see Andrade & Tulkens. J Antimicrob Chemother. 2011; 66:1431-46

Telithromycin…

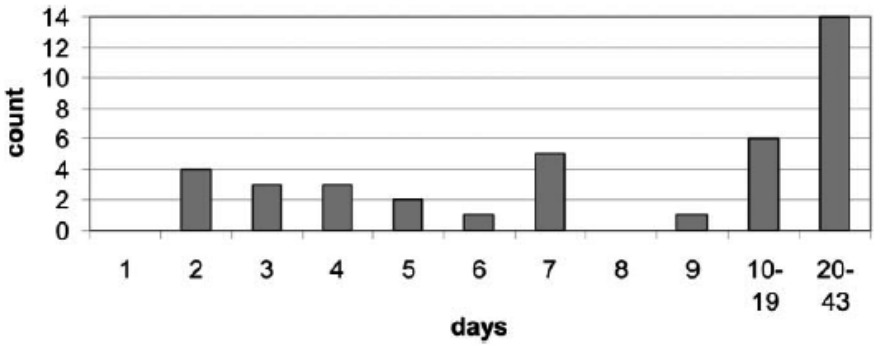
Telithromycin-Associated Hepatotoxicity: Clinical Spectrum and Causality Assessment of 42 Cases

Allen D. Brinker,[1] Ronald T. Wassel,[1] Jenna Lyndly,[1] Jose Serrano,[2] Mark Avigan,[1] William M. Lee,[3] and Leonard B. Seeff[2]

- unusual form of rare hepatotoxicity characterized by
  - short latency,
  - systemic symptoms and signs,
  - in some cases, significant ascites
- Difficulties with the “classical” causality assessment instruments due to the unusual form

Brinker et al. Hepatology 2009;49:250-257

Telithromycin…



rapid onset

Fig. 1. Distribution of days between initiation of telithromycin and onset of symptomatic illness for 39 cases of telithromycin-associated liver injury.

Table 2. Correlation of Disease Severity with Probability/ Causality

Causality DILIN Severity*	Possible	Probable	Very likely	Totals
1	4	4	0	8
2	1	2	1	4
3	5	8	3	16
4	3	3	3	9
5	3	1	1	5
Totals	16	18	8	42

*Numbers indicate degree of severity ranging from 1 (least severe) to 5 (most severe) as defined by the Drug-Induced Liver Injury Network (see text for details).

only 8 cases "very likely"

Brinker et al. Hepatology 2009;49:250-257

Telithromycin…

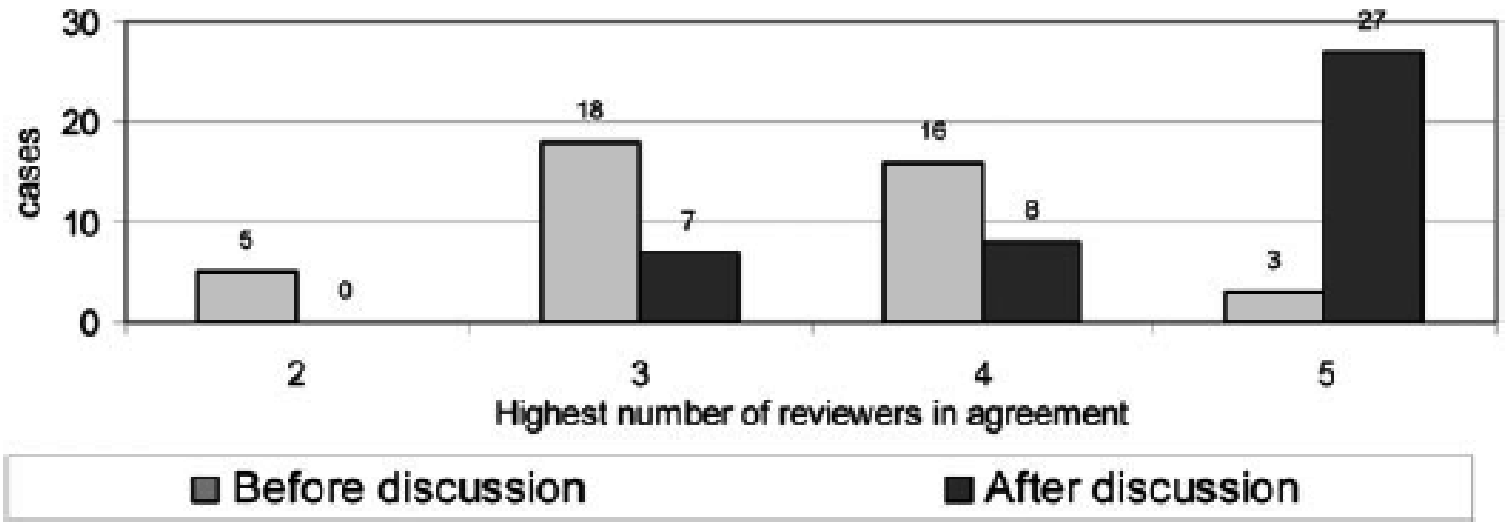


Fig. 2. Level of agreement among five reviewers assessing the likelihood of causal association between hepatotoxicity and telithromycin exposure in 42 spontaneously reported cases.

agreement on likelihood not easy to reach …

Brinker et al. Hepatology 2009;49:250-257

Specific drugs: fluoroquinlones …

Antibiotic		incidence	main characteristics
fluoroquinolones	ciprofloxacin	isolated cases	•hepatocellular and cholestatic hepatitis •fatalities reported
	levofloxacin	< 1 case / 5 millions prescriptions	•hepatocellular and cholestatic hepatitis •fatalities reported
	moxifloxacin	isolated cases	•hepatocellular and cholestatic hepatitis •fatalities reported •rapid and late onsets reported
	trovafloxacin	145 cases / 2.5 millions users	•hepatic necrosis leading to liver failure •variable onset •possibly related to difluorophenyl and/or cyclopropylamine moieties

References: see Andrade & Tulkens. J Antimicrob Chemother. 2011; 66:1431-46. – Table 1

Ciprofloxacine / Levofloxacin …

Ciprofloxacin

- literature remains scanty…
- incidence is considered as very low [4,5] but unexpectely severe and fatal cases have been documented[100,101]
- hepatocellular injury and cholestatic hepatitis [102,103]

Levofloxacin

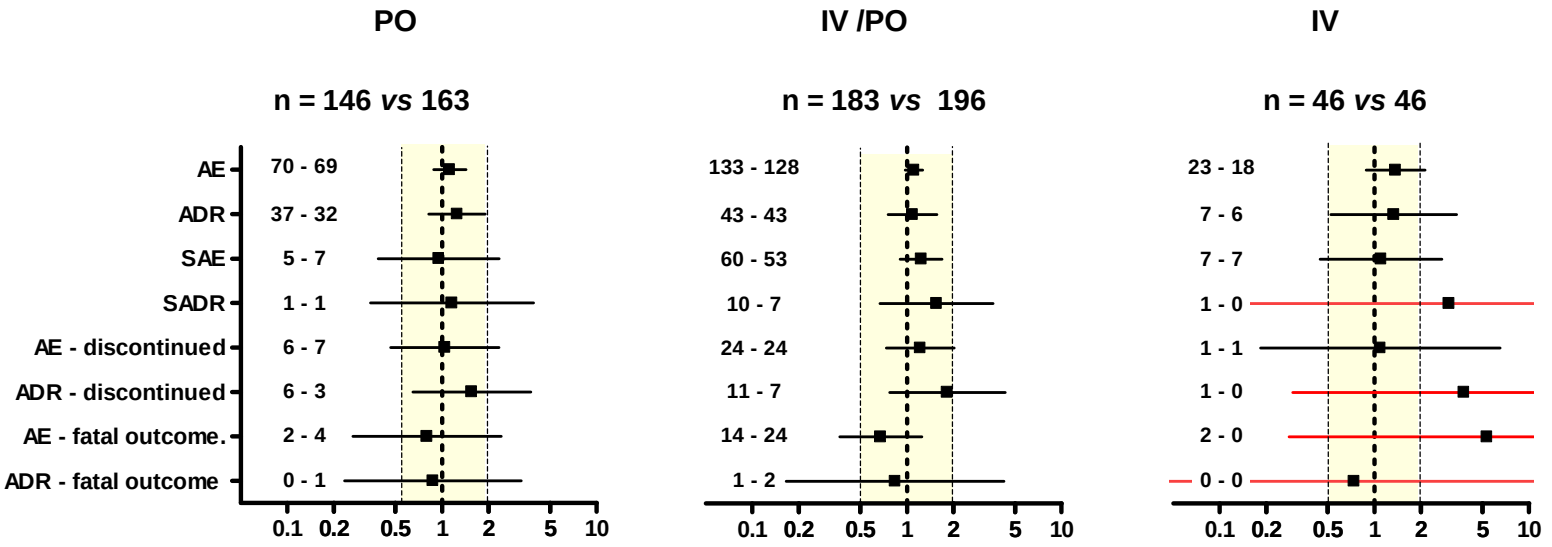
- incidence is also low with abnormal liver function in <1% in clinical trials [106]
- post-marketing surveillance shows cases in <1 for 5 million prescriptions [107]
- Hhepatic failure have been reported[108–113] and the US prescribing information mentions severe, and sometimes fatal, hepatotoxicity

. References: see Andrade & Tulkens. J Antimicrob Chemother. 2011; 66:1431-46
Licata et alFluoroquinolone-induced liver injury: three new cases and a review of the literature. Eur J Clin Pharmacol. 2012; 68:525-32
Alan et al. Unexpected severe hepatotoxicity of ciprofloxacine: two case reports.Drug Chem Toxicol. 2011; 34:189-91

Moxifloxacin …

- clinical trials and post-marketing surveillance shows minimal incidence of hepatic injury
- liver tests may be abnormal in ~1%–5% of patients.[115,116]
- spontaneous reports including on 9 deaths (association posssibe)[119,120]

Incidence of adverse events in clinical studies of patients with hepatic impairment and treated with moxifloxacin or a comparator



. References: see Andrade & Tulkens. J Antimicrob Chemother. 2011; 66:1431-46
Tulkens et al. Moxifloxacin safety: an analysis of 14 years of clinical data. Drugs R D. 2012; 12:71-100

Moxifloxacin / Levofloxacin: a debate …

Early release, published at www.cmaj.ca on August 13, 2012. Subject to revision.

CMAJ RESEARCH

Fluoroquinolone therapy and idiosyncratic acute liver injury: a population-based study

J. Michael Paterson MSc, Muhammad M. Mamdani PharmD MPH, Michael Manno MSc, David N. Juurlink MD PhD; for the Canadian Drug Safety and Effectiveness Research Network

- case–control study in a cohort of outpatients ≥ 66 y having received antibiotic(s) frequently used to treat respiratory tract infections
- cases: admission within 30 days after receiving the antibiotic with a diagnosis of toxic liver disease (with hepatitis, hepatic necrosis or unspecified or acute/subacute or unspecified hepatic failure (n=746)
- Potential confounding factors: alcohol dependence, diabetes mellitus, recent use of other hepatotoxic drugs (phenytoin, isoniazid, amoxicillin/clavulanate and valproicacid)
- Exclusion of patients multiple drugs during the 30-day window, diagnosis or procedure related to liver disease in the preceding 5 years
- final selection: n=144 [1409 matched controls])

Moxifloxacin / Levofloxacin: a debate …

Table 3: Crude incidence of admission to hospital for acute liver injury within 30 days of exposure to an antibiotic agent

Antibiotic agent	No. of exposures	Admission to hospital for acute liver injury within 30 d of dispensing	Rate per 100 000 exposures
Clarithromycin (reference)	910 817	36	3.95
Cefuroxime axetil	248 458	16	6.44
Ciprofloxacin	1 051 959	67	6.37
Levofloxacin	324 660	28	8.62
Moxifloxacin	325 920	26	7.98

UK: cholestatic hepatitis in 3.6 cases / 100000 users for erythromycin (see slide 20)

This crude incidence rate is 6 x larger than previously published values…

- differences in definitions of outcomes,
- incomplete reporting of adverse events in previous studies
- the older age of study's participants

Moxifloxacin / Levofloxacin: a debate …

Table 2: Association between admission to hospital for acute liver injury and recent use of antibiotic agents

Antibiotic agent	Crude OR (95% CI)	Adjusted OR* (95% CI)	*p* value†
Clarithromycin (reference)	1.00	1.00	
Cefuroxime axetil	1.65 (0.84–3.24)	1.43 (0.72–2.83)	0.3
Ciprofloxacin	1.83 (1.12–2.98)	1.56 (0.95–2.58)	0.08
Levofloxacin	2.06 (1.14–3.73)	1.85 (1.01–3.39)	0.046
Moxifloxacin	2.44 (1.37–4.36)	2.20 (1.21–3.98)	0.009

Note: CI = confidence interval, OR = odds ratio
*Model includes neighbourhood income quintile, number of prescription drugs received in the preceding year, number of outpatient visits to a physician in the preceding year, diabetes mellitus, receipt of sulfamethoxazole and trimethoprim in the 90 days before admission, and receipt of isoniazid, phenytoin, amoxicillin/clavulanate or valproate in the 90 days before admission.
†Wald χ^2.

Questions:
- representativeness of the population
- outcome (admission) and causality (beyond use of antibiotic within 30 days)

Other specific drugs …

Antibiotic		incidence	main characteristics
sulfonamides	sulfasalazine	1 per 1000 prescriptions	• cholestatic or mixed hepatocellular-cholestatic injury • within first 4 weeks
	trimethoprim/ sulfamethoxazole	< 2 per 10000 prescriptions	• cholestatic or mixed hepatocellular-cholestatic injury
Tetracyclines	tetracycline	1 per 18 million daily doses	• microvesicular steatosis (acute fatty liver); • cholestatic with ductopenia • long latency period • **most cases related to high doses**
oxazolidinones	linezolid	isolated cases	• severe liver failure with lactic acidosis • microvesicular steatosis • related to mitochondrial dysfunction (?)

References: see Andrade & Tulkens. J Antimicrob Chemother. 2011; 66:1431-46. – Table 1

Linezolid

J. Med. Toxicol. (2010) 6:322–326
DOI 10.1007/s13181-010-0047-0

TOXICOLOGY OBSERVATION

Severe Drug-induced Liver Injury Associated with Prolonged Use of Linezolid

Liesbet De Bus · Pieter Depuydt · Louis Libbrecht · Linos Vandekerckhove · Joke Nollet · Dominique Benoit · Dirk Vogelaers · Hans Van Vlierberghe

Microvesicular steatosis with associated bile duct damage coupled with fullminant course of liver dysfunction;

Treatment of 50 days

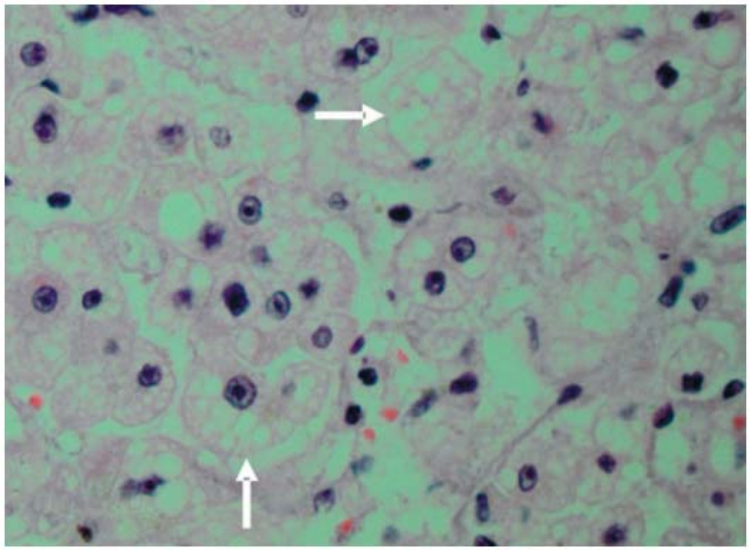


Fig. 1 The parenchyma shows diffuse microvesicular steatosis (*arrows*). (Original magnification ×400)

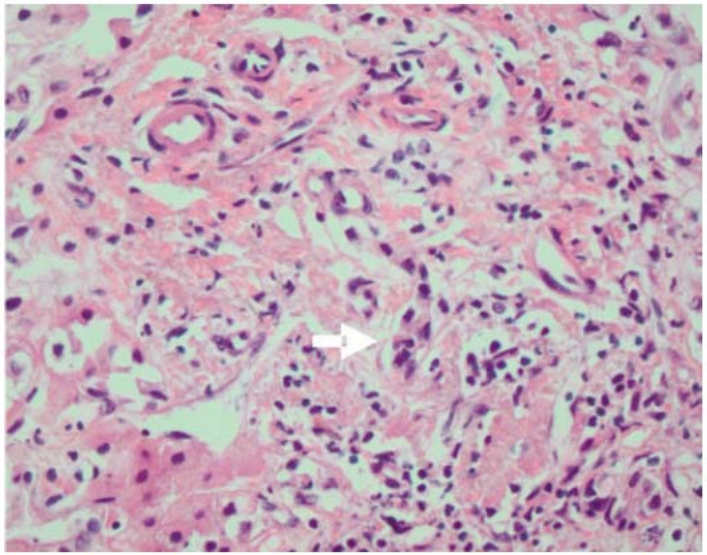


Fig. 2 Portal tract with a mildly increased mononuclear infiltrate and a bile duct with damaged, degenerated epithelium containing a lymphocyte (*arrow*). (Original magnification ×400)

Conclusions and food for thought

- Drung-induced liver injury has been associated with the use of nearly all antibiotics and may mimic various forms of acute and chronic hepatobiliary disease
- Diagnosis is always one of increasing probability, as conclusive proof is often lacking
- With the exception of antibiotics that have been withdrawn (telithromycin, trovafloxacin) and of clavulanic acid, incidences are very low (~ 1 to 10/100,000) and must be balanced with the benefit expected from the treatment
- Both physicians and patients need to be aware of, and monitor for, potential symptoms and take prompt action if signs of hepatotoxicity emerge, as this is, for now, the only effective action

William ML Drug-induced hepatotoxicity. N Engl J Med 2003; 349:474–485
Abboud & Kaplowitz Drug-induced liver injury. Drug Saf 2007; 30:277–294
Andrade & Tulkens Hepatic safety of antibiotics used in primary care J Antimicrob Chemother. 2011; 66:1431-46