

# Antibiotics and Liver Injury in Paediatric Primary Care: a Case-Control Study using Healthcare Database Network

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Antibiotics have been associated with hepatotoxicity<sup>[1-2]</sup> but the comparative risk of liver injury among antibiotics needs to be better in the pediatric population.

To assess the association between antibiotic use and liver injury in children and adolescents.

We performed a population-based case-control study combining three European electronic primary care databases over the years 2000-2008: The Integrated Primary Care Information database (Netherlands), and PEDIANET and Health Search/CSD Longitudinal Patient Database (Italy) covering overall 450,000 children and adolescents (<18 years old). Cases of liver injury in this paediatric population were identified according to CIOMS criteria and validated in each database, retaining only idiopathic events. Up to 100 controls were matched to each case by age, sex and index date. Antibiotic exposure was classified as current if a prescription for the antibiotic of interest lasted until index date or ended within 15 days prior to the index date. Odds Ratios (OR, plus 95% of Confidential Interval, CI) of liver injury following antibiotic use were estimated using conditional logistic regression.

Overall, 938 liver injury cases were matched to 103,306 controls. Current use of any antibiotic was associated with an increased risk for hepatotoxicity compared to past use [OR adj. 2.8 (95% CI, 2.3 to 3.6)]. In comparison to past use of antibiotics, statistically significant ( $p < 0.05$ ) associations were identified for current use of the following agents: rokitamycin (16.6, 6.9 to 39.9) and clarithromycin (3.5, 2.0 to 6.4) among macrolides; ceftriaxone (14.9, 6.1 to 36.7), cefaclor (3.9, 1.8 to 8.1), and cefixime (3.6, 1.7 to 7.7) among cephalosporins; co-trimoxazole (12.6, 5.5 to 28.6); amoxicillin/clavulanic acid (2.5, 1.6 to 4.0) and amoxicillin (1.9, 1.1 to 3.1), among penicillins. When restricting the analysis to the cases diagnosed by specialists, the associations remained for all of these antibiotics, except for rokitamycin and amoxicillin. When using current use of amoxicillin as comparator, the risk of liver injury increased only for current use of rokitamycin, ceftriaxone, and co-trimoxazole.

The risk of liver injury in children and adolescents is three-times higher for current users of antibiotics as compared to those who were previously exposed. Among antibiotics belonging to different therapeutic subclasses, heterogeneity of the associations was observed ranging from 16.6 for rokitamycin to 1.9 for amoxicillin. Several analyses were applied to control for confounding factors, although some residual confounders due to unmeasurable covariates, such as severity of infection, cannot be ruled out.

## References

1. Chalasani N, et al. Causes, clinical features, and outcomes from a prospective study of drug-induced liver injury in the United States. *Gastroenterology* 2008; 135: 1924-34.
2. Ferrajolo C, et al. 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.