

Concomitant Medications Associated with Acute Liver Injury Risk Following Amoxicillin/Clavulanate Exposure Unexplained by Other Causes: Signal Detection Analyses Using Electronic Health Record Data

Authors: Richard Noriega,^{1,2} Jimmy T. Efird,^{3,4} Tim Arnold,^{5,6} Chad A. Dorn,^{1,2} Ruth Reeves,^{1,2} *Ayako Suzuki^{1,7}

1. Health Services Research, Tennessee Valley Healthcare System VA, Nashville, USA
2. Department of Biomedical Informatics, Vanderbilt University Medical Center, Nashville, Tennessee, USA
3. VA Cooperative Studies Program Coordinating Center, Boston VA, Massachusetts, USA
4. School of Medicine, Case Western Reserve University, Cleveland, Ohio, USA
5. Human Systems Integration, Office of Clinical Informatics, Office of Health Informatics, Digital Health Office, Veterans Health Administration, Washington, D.C., USA
6. College of Pharmacy, University of Michigan, Ann Arbor, USA
7. Gastroenterology, Duke University, Durham, North Carolina, USA

*Correspondence to Ayako.suzuki@duke.edu

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BACKGROUND AND AIMS

Drug-induced liver injury (DILI) remains a major adverse drug reaction and a leading cause of drug development failure and post-marketing withdrawal. It significantly impacts patient outcomes and quality of life, and limits therapeutic options. Despite advances, particularly in genetic susceptibility, DILI remains largely unpredictable, with limited understanding of modifiable clinical risk factors. In the context of increasing multimorbidity, ageing populations, and widespread polypharmacy, the role of concomitant medications as potential modifiers of DILI risk has gained increasing attention.

MATERIALS AND METHODS

Leveraging one of the largest unified electronic health record (EHR) systems in the USA from the Department of Veterans Health Administration, the authors applied a previously established framework to identify amoxicillin/clavulanate (AMX/CLAV)-associated acute liver injury (ALI) while excluding competing aetiologies.¹ Using this cohort, the study examined the association between concomitant medication use during AMX/CLAV exposure and AMX/CLAV–ALI events, with ALI attributable to other causes (ALI–OTR) serving as a disease referent for hypothesis generation.

Concomitant medications were defined as those with exposure periods overlapping the AMX/CLAV treatment window, based on the Observational Medical Outcomes Partnership (OMOP) Common Data Model, with combination products disaggregated into individual active ingredients. Multinomial logistic regression models were fitted for each medication, adjusting for demographic

and clinical covariates. Odds ratios were log-transformed and used in clustering analyses to classify medications into three groups: those associated with increased risk of AMX/CLAV–ALI only, ALI–OTR only, or concordant effects on both outcomes.

RESULTS

Among approximately 1.4 million AMX/CLAV-exposed individuals, 1,582 unique concomitant medications were identified. Clustering analysis revealed 32 medications associated with increased odds of AMX/CLAV–ALI only, 79 with ALI–OTR only, and 341 and 45 with increased and decreased odds of both outcomes, respectively. Medications uniquely associated with increased AMX/CLAV–ALI risk only included agents with immunomodulatory or proinflammatory properties, such as anti-androgens and anticholinergics. Bacillus Calmette–Guérin vaccination was also identified, supporting a potential role of immune activation. Additionally, several antivirals, including HIV medications, were identified. In contrast, medications associated with reduced ALI risk, showing concordant effects across outcomes, were predominantly anti-inflammatory, including commonly used agents such as simvastatin, metformin, and lisinopril.

Medications associated with increased risk for both AMX/CLAV–ALI and ALI–OTR included pneumococcal vaccination,

anti-cancer therapies, immunosuppressants, and antimicrobials, suggesting shared or multifactorial mechanisms of liver injury. This group included components of total parenteral nutrition, raising the possibility that nutritional status or lack of enteral intake may contribute to susceptibility of ALI.

CONCLUSION

This large, EHR-based analysis highlights distinct concomitant medications associated with altered risk of AMX/CLAV-related liver injury, many with biologically plausible immunologic mechanisms. These findings underscore the potential of EHR-driven signal detection to identify clinical modifiers of DILI risk and generate testable mechanistic hypotheses. Further work incorporating genomic data; comorbidity burden in joint exposure modelling; sub-analysis by age, sex, and injury types; and targeted hypothesis testing analysis will be important to further refine and validate these associations and ultimately support the development of predictive frameworks for individualised DILI risk assessment.

Reference

1. Noriega R et al. Concomitant medications associated with acute liver injury risk following amoxicillin/clavulanate exposure unexplained by other causes: signal detection analysis using electronic health record data. Abstract SAT-083. EASL Congress, 27–30 May, 2026.