Alcohol use as a risk factor for drug-induced liver injury with amoxicillin-clavulanate in the *All of Us* Research Program

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Purpose

Drug-induced liver injury (DILI) is one of the leading causes of acute liver failure in the U.S.[1] In general, DILI events are rare (occurring in approximately 1 in 10,000 patients exposed), but these events have the potential to be lethal. Identifying demographic factors and relevant clinical covariates associated with DILI may help physicians risk-stratify patients for experiencing this adverse drug reaction.[2]

Antibiotics, such as amoxicillin-clavulanate (trade name Augmentin), are a known cause of DILI. Previous studies conducted by the DILI Network (DILIN), an academic consortium investigating all aspects of DILI in adults and children, have identified antibiotics as the most common causative class of DILI, with Augmentin as the most implicated drug.[1,3] As a result, there is great interest in identifying genetic and environmental risk determinants that could be used to avoid DILI with Augmentin.[4]

Alcohol consumption, BMI, and age are three clinical covariates that may influence a patient's risk of experiencing DILI with Augmentin. Previous studies have not found a significant relationship between alcohol consumption and DILI severity or chronicity.[5,6] The relationship between a patient's BMI and DILI susceptibility remains unclear. Obesity may place some patients at risk for developing DILI through the presence of non-alcoholic steatohepatitis (NASH)[7]; however more work is needed to characterize this relationship because associations between BMI and DILI could be confounded by the presence of polypharmacy in obese patients.[8] Similarly, increased comorbidities and medication use as people grow older (> 65 years) may alter susceptibility to the development of DILI in older populations.[9] Further studies into alcohol consumption, BMI, and age will help clarify their role as risk determinants.

Phenotyping Algorithm

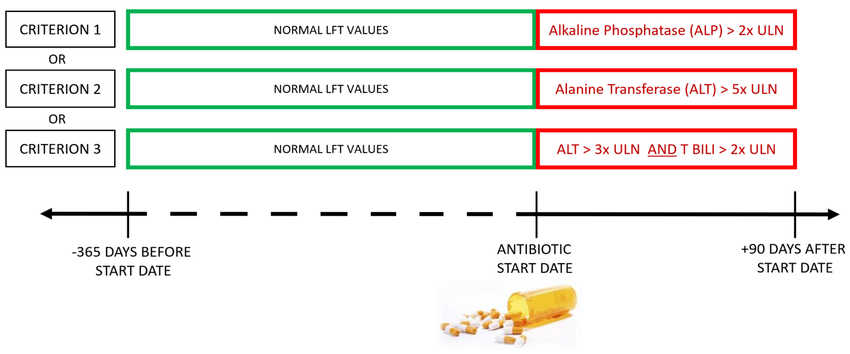

Figure 1. Initial screening for potential drug-induced liver injury (DILI) cases. Approach to identifying DILI case patients in All of Us, based on criteria established by an expert working group[10].

Methods

- Retrospective observational cohort
- De-identified longitudinal clinical data
- EMR-linked biobank based at NIH in Washington, DC
- Phenotyping algorithm previously published by Expert Working Group[10]
- Exclusion Criteria = infectious hepatitis or alcohol-related hepatic cirrhosis
- Additional Exclusion Criteria based on Phenome Scanning = ischemic liver injury or liver cancer
- Assessment of clinical covariates (alcohol use, BMI, age) comparing means of DILI cases vs. Non-DILI controls

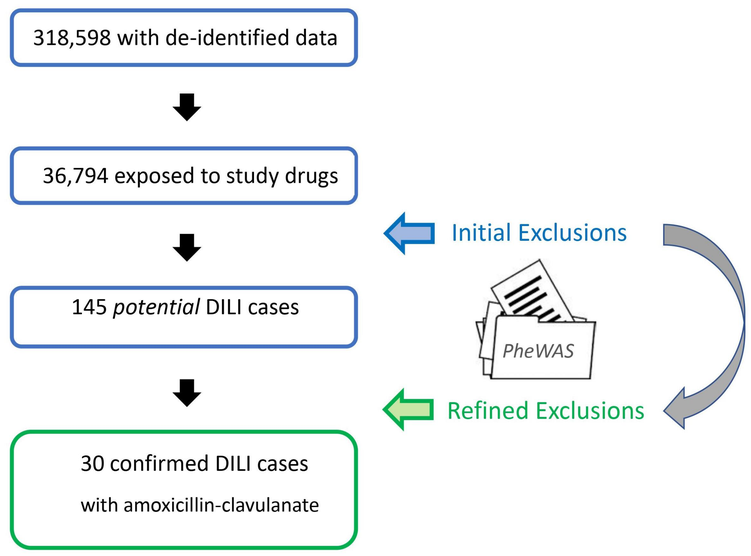

Figure 2. Study design. Flowchart summarizing overall study cohort, phenotyping steps, and final case counts. DILI, drug-induced liver injury; PheWAS, phenome-wide association study.

Table 1. Exclusion criteria (applied if found ever within a patient's EMR).

Alcohol-Related Liver Disease
Viral Hepatitis (HAV,HBV,HCV)
Malignant neoplasm of small intestine
Malignant neoplasm of liver
Malignant neoplasm of gallbladder
Malignant neoplasm of retroperitoneum
Neuroendocrine tumors
Hypersplenism
Follicular lymphoma
Non-follicular lymphoma
MALT lymphoma
Lymphoid leukemia

Table 2. Exclusion criteria (applied within 3 months of drug start date).

Viral pneumonia
Acute respiratory failure
ARDS
Coma
Hypoxemia
Hypotension
Hypovolemia
Cholelithiasis
Cholecystitis
Cholangitis
Sepsis
Shock

Results

- 145 potential DILI cases, mostly cholestatic
- 30 confirmed DILI cases
- Trend toward higher mean alcohol intake in DILI cases with Augmentin
- Neither BMI nor age were found to be associated with case status

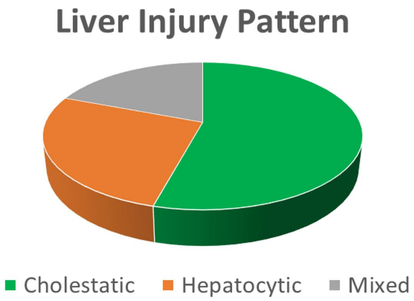

Figure 3. Liver injury pattern for preliminary DILI cases.

Table 3. Preliminary DILI case counts for amoxicillin-clavulanate.

	potential DILI cases *n*	cholestatic injury *R ratio < 2* *n (%)*	mixed injury *R= 2 to 5* *n (%)*	hepatocytic injury *R ratio > 5* *n (%)*
Augmentin	146	**79 (54.1)**	28 (19.1)	39 (26.7)

* We required potential cases to have at least one ALT and at least one ALP in the 0-90 day window.
* Potential case numbers include patients meeting **any** of the criteria in Figure 1.
* Initial injury pattern was determined by calculating an R ratio ([peak ALT/ULN]/[peak ALP/ULN]).

Table 4. Final DILI case counts for amoxicillin-clavulanate with age and BMI assessment.

	counts *n*	age (years) mean (S.D.)	age (years) median	BMI (kg/m²) mean (S.D.)	BMI (kg/m²) median
cases	30	47.3 (19.5)	48	29.5 (8.3)	28.8
controls	28,539	50.7 (15.3)	52	31.0 (7.6)	29.8

Table 5. Alcohol use distribution in *potential* DILI cases versus controls.

	counts *n*	No Alcohol	Monthly or Less	2 to 4 Per Month	2 to 3 Per Week	4 or More Per Week
cases	124	41	43	15	14	11
controls	32,295	6,965	11,293	6,440	4,043	3,554

Table 6. Mean alcohol use in confirmed DILI cases versus controls.

	counts *n*	Mean Alcohol Use (drinks per month)
cases	30	**4.6**
controls	28,539	**3.9**

Conclusion

Data from the EHR-linked research cohorts can be efficiently mined to identify DILI cases related to antibiotic use. In All of Us, analysis of clinical covariates revealed a higher mean alcohol intake in acute DILI cases compared to controls. This suggests that reducing alcohol use may favorably modify the risk for DILI with amoxicillin-clavulanate.

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