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Drug-Induced Liver Injury (DILI) in a National Cohort of Hospitalized Patients treated with Aztreonam and Ceftazidime

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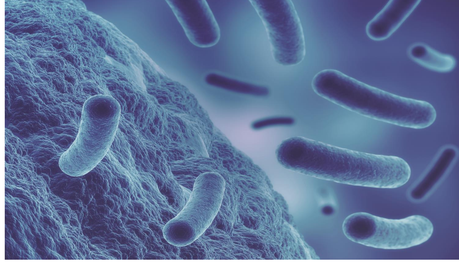


BACKGROUND

- Drug-induced liver injury (DILI) can be a severe and even fatal complication of antibiotic use
- Cephalosporins such as ceftazidime (CAZ) are rare causes of clinically apparent DILI, while data regarding DILI associated with the monobactam aztreonam (ATM) are sparse (https://livertox.nlm.nih.gov/)
- ATM and CAZ are both partnered with novel beta-lactamase inhibitors (i.e. avibactam, AVI) as therapy for MDR infections (CAZ-AVI and ATM-AVI) .
- Using a nationwide cohort of patients hospitalized within the Veterans Health Administration (VHA) we examined the rates, severity, and injury patterns of DILI among patients receiving ATM and compared them to CAZ as a benchmark agent

Table 1: Definitions, type and severity of liver injury

Term	Clinical chemistry definitions
DILI	ALT ≥ 5xULN or ALP ≥ 2xULN or ALT ≥ 3xULN with Tbili ≥ 2xULN
Injury pattern	R ≥ 5: Hepatocellular pattern 2 < R < 5: Mixed pattern R ≤ 2: Cholestatic pattern
Severity	Mild: TBili < 2xULN Moderate: DILI present plus Tbili ≥ 2xULN Severe: DILI present plus Tbili ≥ 2xULN + - INR ≥ 1.5 - Ascites or encephalopathy - Other organ failure Fatal or transplantation

ALT: Alanine aminotransferase; ALP: Alkaline phosphatase; INR: International normalized ratio; Tbili: Total bilirubin; ULN: Upper limit of normal; R = (ALT/ULN)/(ALP/ULN)

METHODS

From patients hospitalized in the VHA in fiscal years 2012-2017, we:

- Identified patients with 1 episode of treatment with ATM or CAZ for 3 or more consecutive days, and with liver function tests (LFTs) measured during or within 7 days of stopping treatment
- Excluded patients with abnormal LFTs in the year prior, with more than one episode of treatment with either antibiotic
- Compared characteristics of patients treated with ATM and CAZ
- Calculated DILI rates, severity & injury pattern (Table 1) and compared them according to antibiotic received
- Analyzed the subset of patients with bacteremia, defined as any positive blood culture < 7 days prior to ATM/CAZ
- Estimated logistic models predicting DILI and moderate/severe DILI based on patient characteristics and antibiotic received

RESULTS

- 10,061 patients treated with ATM and 8,752 with CAZ
- 3,530 ATM and 2,801 CAZ patients met inclusion criteria
- Similar age, comorbidities and rates of alcoholism and liver disease in patients treated with ATM and CAZ; both overall and in subset with bacteremia (Table 2)
- Significantly higher rate of DILI observed in ATM patients, p<0.01
- Rates of moderate/severe DILI were not significantly different (Figure 1 and Table 3, p > 0.05 both overall and in bacteremia)
- Among DILI cases in ATM patients, 49% were cholestatic and 37% were hepatocellular vs. 62% and 25% for CAZ (Figure 2)
- All results were more pronounced in patients with bacteremia

Logistic regression models predicting DILI:

- Significant effects of age, bacteremia, ATM/CAZ treatment days
- Difference in DILI between ATM vs. CAZ present after adjusting for other variables, ATM vs. CAZ OR = 1.6, 95% CI = (1.3,1.9)

Logistic regression model predicting moderate/severe DILI:

- Significant effects of alcoholism, bacteremia, liver disease
- No significant difference between ATM and CAZ

Table 2: Characteristics of analyzed patients treated with ATM and CAZ

	ATM (n = 3,530)	CAZ (n = 2,801)	ATM + bact (n = 598)	CAZ + bact (n = 443)
Age – mean(sd)	70 (12)	69 (12)	70 (12)	69 (12)
Charlson– mean(sd)	4.5 (2.8)	4.8 (2.8)	4.6 (2.8)	4.9 (2.8)
Alcoholism– #(%)	752 (21%)	587 (21%)	138 (23%)	102 (23%)
Liver disease–#(%)	540 (15%)	410 (15%)	91 (15%)	72 (16%)
Drug days– median (IQR)	5 (4,8)	6 (4,9)	5 (4,8)	5 (4,9)

Table 3: Prevalence of DILI (%, 95% CI) in patients treated with ATM or CAZ

	ATM	CAZ	ATM + bact	CAZ + bact
DILI, overall	5.9 (5.2,6.8)	3.4 (2.8,4.1)	8.9 (6.7,11.4)	3.8 (2.3,6.1)
Mod/severe DILI	2.0 (1.6, 2.5)	1.5 (1.1, 2.0)	3.0 (1.8,4.7)	2.3 (1.1, 4.1)

Figure 1: DILI by drug & severity

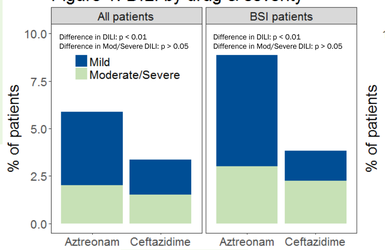
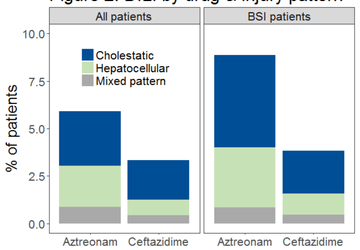


Figure 2: DILI by drug & injury pattern



CONCLUSIONS

- In a cohort of hospitalized VHA patients, ATM treatment is associated with increased risk of mild liver injury, but a causal relationship cannot be determined from this data
- DILI rates observed similar to those in smaller prior studies
- Observations are limited by availability of LFTs, non-random treatment selection, and other unmeasured confounders
- Further analyses of this cohort, including antibiotic dosing, severity of illness, and hepatotoxic medications, are underway

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