

Clinical and HLA Correlates in Cephalosporin Induced Liver Injury



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Abstract **Background:** Cephalosporins (CS) are among the most used antibiotics in clinical practice and are notable for their efficacy and safety profile. Acute, idiosyncratic liver injury from CS occurs, but is rare and typically mild to moderate in severity and self-limited in course. **Aims:** We sought to characterize the clinical, biochemical features and HLA associations of liver injury attributed CS in the DILIN prospective study. **Results:** Between 2004 and Nov 2, 2022, a total of 2347 cases of drug-induced liver injury (DILI) were enrolled in the prospective DILIN study and had 6 months of follow up and formal adjudication. 1854 cases were scored as being probable, highly likely or definite DILI, 58 of which (3%) were attributed to different CS, including cefazolin (n=40), cephalixin (n=4), ceftriaxone (n=3), cefdinir (n=3), cefuroxime (n=3) and 5 others with one each. Characteristic clinical features of CS DILI were a self-limited, mixed or cholestatic hepatitis arising 1 to 4 weeks after starting and often several weeks after stopping the antibiotic (Table 1). Most striking was the phenotype of cefazolin and other parenteral cephalosporins given as a single dose with onset of jaundice, fatigue and itching 1 to 3 weeks later. HLA sequencing performed on 57 CS cases revealed a significant association with HLA-A*02:01, an allele also found to be linked to amoxicillin and amoxicillin/clavulanate [A/C] DILI (PMID: 36496055). The association was strongest with cefazolin with an allele frequency [AF] 51% and carriage frequency [CF] 78% compared to population-based AF of 23% and CF of 39%. Other A/C related HLA and genetic variants (HLA-B*15:18, DRB1*15:01, ERAP2 [rs1363907] and PTPN22 [rs2476601]) were not increased in frequency with CS liver injury. The HLA-A*02:01 association found with cefazolin was not found in the 17 other CS cases [AF 0.31]. The clinical features of cefazolin cases with and without HLA-A*02:01 were similar, although the cases with the allele tended to be more severe (81% vs. 44% with either moderate-hospitalized or severe by DILIN). **Conclusions:** The cephalosporins are rare causes of liver injury and have a self-limited, mixed/cholestatic hepatitis that arises after a short course of therapy. Most cases are due to cefazolin which has an HLA association similar but not identical to amoxicillin and A/C.

Background Cephalosporins (CS) are among the most used antibiotics in clinical practice and are notable for their efficacy and safety profile (Figure 1). Acute, idiosyncratic liver injury from CS occurs, but is rare and typically mild to moderate in severity and self-limited in course.

Table 1. Select demographic, clinical and biochemical features of Cefazolin vs. other cephalosporins (CS). Results are shown as median [range] or as number [%] of subjects.

Feature*	Cefazolin N=40	Other CS N=18	p
Age (years)	52.8 (19-82)	42.8 (4-85)	0.10
Male Sex	22 (55%)	9 (50%)	0.72
Race			0.03
White	38 (95%)	14 (78%)	
Black	1 (2.5%)	4 (22%)	
Asian	0	0	
Other	1 (2.5%)	0	
Hispanic	1 (2.5%)	1 (6%)	0.53
Duration of therapy (days)	1.0 (1-2)	7.5 (1-15)	< 0.001
Time to onset (days)	20.5 (6-33)	15.0 (6-48)	0.47
BMI (kg/m ²)	24.6 (12.2-43.7)	24.8 (16.4, 46.1)	0.86
Causality Score			0.06
Definite	0 (0%)	0 (0%)	
Highly Likely	26 (65%)	7 (39%)	
Probable	14 (35%)	11 (61%)	
History of Drug Allergies	18 (45%)	9 (50%)	0.72
Alcohol use (any)	23 (61%)	7 (39%)	0.13
Symptoms			
Jaundice	36 (90%)	15 (83%)	0.67
Rash	10 (25%)	3 (17%)	0.74
Fever	14 (35%)	7 (39%)	0.78

Results

- Between 2004 and Nov 2, 2022, a total of 2347 cases of drug-induced liver injury (DILI) were enrolled in the prospective DILIN study and had 6 months of follow up and formal adjudication. 1854 cases were scored as being probable, highly likely or definite DILI, 58 of which (3%) were attributed to different CS, including cefazolin (n=40), cephalixin (n=4), ceftriaxone (n=3), cefdinir (n=3), cefuroxime (n=3) and 5 others with one each.
- Characteristic clinical features of CS DILI were a self-limited, mixed or cholestatic hepatitis arising 1 to 4 weeks after starting and often several weeks after stopping the antibiotic (Table 1).
- Most striking was the phenotype of cefazolin and other parenteral cephalosporins given as a single dose with onset of jaundice, fatigue and itching 1 to 3 weeks later.**

Table 2. Select biochemical features, severity of illness, clinical outcomes and allele frequency (AF) of Cefazolin vs. other cephalosporins (CS). Results are shown as median [range] or as number [%] of subjects.

Feature*	Cefazolin N = 40	Other CS N = 18	p
Enzyme Pattern			0.77
Hepatocellular (R ≥ 5)	6 (15%)	4 (22%)	
Mixed (R >2 to <5)	16 (40%)	6 (33%)	
Cholestatic (R ≤ 2)	18 (45%)	8 (44%)	
Severity Assessment			0.25
Mild (Anicteric)	3 (8%)	1 (6%)	
Moderate (Jaundiced)	8 (20%)	6 (33%)	
Moderate & Hospitalized	27 (18%)	8 (44%)	
Severe (Decompensation)	2 (5%)	2 (11%)	
Fatal (Death or Transplant)	0	1 (6%)	
Hospitalization	29 (73%)	13 (72%)	0.99
Liver Transplant	0	0	NA
Death	0	1 (6%)	0.32
Chronic Injury	5 (14%)	3 (18%)	0.70
Liver Biopsy	19 (48%)	8 (44%)	0.83
HLA-A*02:01 Carriage Rate	31 (78%)	9 (53%)	0.11
HLA-A*02:01 Allele Frequency	0.50	0.29 (n=17)	0.06

Results (Continued)

- HLA sequencing performed on 57 CS cases revealed a significant association with HLA-A*02:01, an allele also found to be linked to amoxicillin and amoxicillin/clavulanate [A/C] DILI.
- The association was strongest with cefazolin with an allele frequency [AF] 51% and carriage frequency [CF] 78% compared to population-based AF of 23% and CF of 39%.**
- Other A/C related HLA and genetic variants (HLA-B*15:18, DRB1*15:01, ERAP2 [rs1363907] and PTPN22 [rs2476601]) were not increased in frequency with CS liver injury.
- The HLA-A*02:01 association found with cefazolin was not found in the 17 other CS cases [AF 0.31].
- The clinical features of cefazolin cases with and without HLA-A*02:01 were similar, although the cases with the allele tended to be more severe (81% vs. 44% with either moderate-hospitalized or severe by DILIN).

Conclusion

The cephalosporins are rare causes of liver injury and have a self-limited, mixed/cholestatic hepatitis that arises after a short course of therapy. Most cases are due to cefazolin which has an HLA association similar but not identical to amoxicillin and A/C.

Figure 1. Commonly prescribed cephalosporins

First generation	Second generation	Third generation	Fourth generation	Fifth generation
Effective against many Gram-positive and some gram-negative bacteria	Expanded activity against Gram-negative bacteria	Broader activity against Gram-negative but less effective against Gram-positive bacteria	Broad spectrum against Gram-positive and Gram-negative bacteria	Extended spectrum of activity against Gram-positive and Gram-negative bacteria
Simple structure with a six-membered dihydrothiazine ring. Contains a methyl group at the 7-position	Similar to first-generation cephalosporins but with added side chains.	Introduction of a methoxymethyl group at position 7 of the cephalosporin nucleus.	Contains a pyridinium group.	Most structurally distinct group. Contains an oxime side chain and an aminothiazole side chain.
Cefazolin (Kefzol, Kefzol), Cephalixin (Keflex)	Cefuroxime (Zinacef), Cefuroxime (Zinacef), Loracarbef (Lorabid)	Ceftriaxone (Rocephin), Cefotaxime (Ceforan), Cefazidime (Fortaz, Tazicef), Cefepime (Suprax), Cefepime (Varentin), Cefibuten (Cedax)	Cefepime (Maxipime)	Ceftaroline (Teflaro), Cefepime (Zentax, Mavelon)

Please note that this table provides a general overview of commonly known cephalosporins. There may be additional formulations, brand names, or variations available in different regions or due to ongoing pharmaceutical developments.

Aim We sought to characterize the clinical, biochemical features and HLA associations of liver injury attributed CS in the Drug-Induced Liver Injury Network (DILIN) prospective study.

Methods Patients with liver injury attributed with high confidence (DILIN causality assessed as definite, highly likely, and probable) to CS were identified from the DILIN database and included in the current analysis. HLA typing was performed using an Illumina MiSeq platform. In addition to descriptive statistics and clinical outcomes, analysis of HLA alleles was performed by Fisher's exact test to compare allele frequency (AF) in CS DILI cases and population controls assembled from five dbGaP GWAS datasets.