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Identification and Characterization of Cefazolin-induced Liver Injury

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Abstract

Background & Aims—Cephalosporin antibiotics are popular because they have a broad spectrum of activity and are generally well tolerated; cephalosporin-induced liver injury is considered to be rare. We describe a new syndrome associated with a single intravenous dose of cefazolin and the clinical features of cephalosporin-induced liver injury.

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Methods—The drug-induced liver injury (DILI) network collected detailed clinical data on 1212 patients with DILI between 2004 and 2012. We analyzed data from 41 patients in whom cephalosporins were implicated as primary agents of liver disease; 33 were formally adjudicated as having cephalosporin-induced DILI.

Results—Nineteen patients developed clinically apparent DILI after a single intravenous dose of cefazolin. All patients developed self-limited liver injury 3–23 days after receiving cefazolin during surgery—often during a minor outpatient procedure. The latency period was 20 days. Clinical features included itching, jaundice, nausea, fever, and rash. We identified 14 more patients with DILI attributed to other cephalosporins (5 first-, 2 second-, 6 third-, and 1 fourth-generation agents). Although latency and injury patterns were similar for cefazolin and other cephalosporins, the other cephalosporins were associated with more severe courses of injury, including 2 deaths from liver failure.

Conclusions—DILI can develop following a single dose of cefazolin. It is characterized by a latency period of 1–3 weeks after exposure, marked cholestasis, and a self-limited moderate to severe clinical course. Other cephalosporins can cause a similar but more severe injury.

Keywords

hepatotoxicity; DILIN; antibiotic; cephalosporin

Introduction

Cephalosporins are some of the most widely used antibiotics, popular because of their excellent tolerance and broad spectrum of activity^{1–6}. Serious adverse events from cephalosporins are uncommon, and drug-induced liver injury (DILI) is considered to be particularly rare^{7–17}. Indeed, the majority of the literature on cephalosporin induced liver injury consists of single case reports^{8–18}. In prospective registries of DILI, cephalosporins are not prominently mentioned, accounting for only 4 of 461 (0.9%) episodes in a Spanish Registry¹⁸, 1 of 77 (1.2%) in a Swedish study¹⁹ and 1 of 96 (1%) in a recent Icelandic survey²⁰. In contrast, in the ongoing prospective study from the United States known as the Drug-Induced Liver Injury Network (DILIN), cephalosporins were relatively common causes of DILI, and the commonly used, first generation parenteral cephalosporin, cefazolin, was observed to rank highly among implicated single agents. This study describes 19 patients with DILI attributed to cefazolin. These patients had a distinctive clinical phenotype, and cefazolin was frequently overlooked as the putative cause.

Methods

Study Design

The DILIN prospective study is an ongoing, multicenter study of all cases of DILI presenting at 8 geographically diverse medical centers in the US as described^{21, 22}. In brief, patients with a strong clinical suspicion of liver injury caused by a medication or an herbal agent were enrolled. Patients met minimal pre-established criteria for liver injury including the following: (1) aspartate aminotransferase (AST) or alanine aminotransferase (ALT) level > 5 times the upper limit of normal (ULN) or > 5 times baseline levels if pre-treatment

values were known to be abnormal on at least 2 consecutive occasions, or (2) alkaline phosphatase level 2 times the ULN (or baseline level if pre-treatment values were known to be abnormal) on 2 consecutive occasions, or (3) total serum bilirubin level ≥ 2.5 mg/dL accompanied by any elevation in AST, ALT or alkaline phosphatase level, or (4) international normalized ratio (INR) > 1.5 accompanied by any elevations in AST, ALT or alkaline phosphatase level. Patients with acetaminophen toxicity were excluded as were those with bone marrow or liver transplantation. Patients with pre-existing chronic hepatitis C, hepatitis B or nonalcoholic fatty liver disease were eligible; those with autoimmune hepatitis, primary biliary cirrhosis or sclerosing cholangitis were excluded.

Eligible patients had a baseline visit during which extensive clinical history was obtained and laboratory, histologic, and imaging results were documented; pre-established laboratory testing was performed to exclude competing causes of liver injury. All patients were then followed for at least 6 months, and those with evidence of continuing liver injury were asked to return at 12 and 24 months. Chronic liver injury was defined as the presence of liver-related laboratory, radiologic, or histologic abnormalities at least 6 months after onset.

The pattern of liver injury was based upon the ratio (R) of the serum ALT to alkaline phosphatase (both expressed as multiples of the ULN): an R ratio of <2 indicating cholestatic, >5 hepatocellular and 2–5 as mixed cholestatic-hepatocellular injury^{22, 23}. Severity of injury was scored on a 5 point scale: 1 (mild)=serum enzyme elevations without jaundice (bilirubin <2.5 mg/dL), 2 (moderate)=enzyme elevations and jaundice; 3 (moderate hospitalized)=enzyme elevations, jaundice and hospitalization for liver injury; 4 (severe)=jaundice and signs of liver failure (ascites, encephalopathy, INR ≥ 1.5) or other organ failure; 5 (fatal)=death or liver transplantation within 6 months of onset.²³ The study was approved by the Institutional Review Boards (IRBs) of each participating center and all patients provided written informed consent.

Causality

The diagnosis of DILI and the causal relationship between the event and the implicated agent(s) were evaluated in a formal and standardized fashion by the DILIN Causality Committee as described.^{22, 23} This process is based on expert opinion and has been shown to have greater reproducibility, and is better differentiation among levels of causality than the commonly used RUCAM.^{22, 23} Causality was assessed as either definite ($>95\%$ likelihood), highly likely (75%–95% likelihood), probable (50%–74% likelihood), possible (25%–49% likelihood), and unlikely ($<25\%$ likelihood). In cases in which several agents were considered possibly implicated, the overall event was adjudicated for the likelihood that it represented DILI and then each agent was given a separate score, but only one agent was permitted to be considered probable, highly likely or definite.

Statistics

Demographic and clinical data were extracted and analyzed. Descriptive statistics including means, medians, 25th to 75th percentiles, frequencies, and percentages were used to summarize the data. A non-parametric test or chi-square (Fisher's exact test in the case of small sample) was used to compare groups of continuous and categorical variables,

respectively. The LOESS regression model was used to fit smooth curves (and 95% confidence intervals of the curves) of liver tests over time. In the case of multiple peaks of the smoothed curves, smoothed curves were fitted for subgroups as indicated by the data. All P values reported are two-sided; a level of 0.05 was considered statistically significant. All data were analyzed with SAS 9.2.

Results

Cefazolin induced DILI

Among 1212 patients with DILI enrolled into a U.S. prospective database between 2004 and 2012, in which 1019 cases were adjudicated, 19 (2%) were attributed to cefazolin (Supplemental Figure 1). This made cefazolin the 6th most common single agent identified in the entire dataset. Analysis of the course and outcome of these 19 patients revealed distinctive, yet highly consistent clinical features. All 19 patients had undergone surgery and had received a single intravenous dose of cefazolin (1–2 gm) in the perioperative period for prophylaxis against infection. The cefazolin used included different commercial preparations (AncefTM, KefzolTM, and several generic forms). Patients included 11 men and 8 women, all of whom were white and one of whom was Hispanic (Table 1).

All 19 patients developed itching within 3 to 23 days of receiving cefazolin; all but 1 patient was reported to have jaundice (Table 1/2). Symptoms generally lasted for a few days to several weeks and jaundice resolved in all patients within 31 days of onset. Immuno-allergic features were present in 9 patients (fever 9, rash 6, eosinophilia 5) but were generally mild and transient. Two patients had a previous history of jaundice following surgery, which had been attributed to halothane and methimazole, respectively. Importantly, both had also received cefazolin at the time of surgery. The latency from administration of cefazolin exposure to onset during the second episode in these two patients was 3 and 6 days, representing 2 of the 3 cases with latencies of less than one week (implying that the clinical course is more rapid when there has been prior exposure and sensitization). A narrative description of the clinical course of all patients is available in LiverTox (<http://livertox.nih.gov>).

Laboratory documentation of liver injury was first obtained 6 to 31 days after exposure and 2 to 23 days after initial symptoms (Tables 2/3, Figure 1, Supplemental Table 2). Initial abnormalities included elevations in total serum bilirubin and typically a mixed or cholestatic pattern of serum enzyme elevations. Total serum bilirubin rose to greater than 2.5 mg/dL in 18 patients (95%) and to above 10 mg/dL in 7 (37%). Liver test curves revealed two peaks in bilirubin elevation, with each patient fitting into only one of the two peaks occurring either before or after 25 days. The separate LOESS curves for these groups revealed that 7 had a peak in bilirubin level within 15 days (Figure 1A) and 12 with a peak within 30 days (Figure 1B).

The severity of the liver injury was scored as severe (INR rising transiently to 1.5) in 2 patients, moderate (either 2+/3+) in 16, and mild (anicteric) in 1 (Tables 2/3). No patient died or underwent liver transplantation, and none developed clinical evidence of ascites, hepatic encephalopathy or variceal hemorrhage. In follow up, 3 patients had liver test

abnormalities when evaluated 6 months after DILI onset, but serum bilirubin levels were normal and abnormalities were minimal (Supplemental Table 2) and eventually resolved in all patients.

Liver biopsies were performed in 10 patients, 6 of which were available for central review [DEK] (the mean time between onset and biopsy was 30 days). Five patients had a cholestatic pattern of injury (3 had typical cholestatic hepatitis, see Figure 2; one had acute cholestasis and one had chronic cholestasis), and one had a mild acute hepatitis injury pattern. Among the cholestatic injury patients, four had moderate to marked zone 3 cholestasis with varying degrees of parenchymal inflammation while the chronic cholestatic patient had duct injury and pseudoxanthomatous changes without bile accumulation. The sole acute hepatitis case had mild parenchymal injury and inflammation without cholestasis. Finally, 2 of the 6 biopsies had infiltrates of eosinophils.

At the time of initial clinical evaluation, cefazolin was considered to be a potential responsible agent in only 10 of 19 patients, and was often not initially a suspected agent; other drugs initially considered as possibly causative included tramadol, propofol, sevoflurane, azithromycin, clindamycin, oxcarbazepine, ketorolac, chaparral, and oxycodone/acetaminophen in one case each. In some instances, the patient was unaware of having received cefazolin and the information was found only after detailed review of medical records. In the final adjudication by the DILIN Causality Committee for the 19 cases here in which cefazolin was the primary implicated agent, scores were highly likely in all except 3 patients, two of which were considered definite and one probable.

Liver Injury due to other cephalosporins

During the study period, 14 other patients had DILI attributed to non-cefazolin cephalosporins, including both oral and intravenous formulations and agents from all four “generations” of this class of antibiotics (Table 4, Supplemental Figure 1, Supplemental Table 1). One of these cases was scored as definite, 8 as highly likely and 5 as probable. None was administered as a single intravenous injection. All were given for a limited time (2 to 14 days) and clinical symptoms began 1 to 4 weeks (range 4 to 29 days) later. Symptoms included jaundice (79%), itching (64%), nausea (79%), and fever (79%). Immuno-allergic features (fever, rash, eosinophilia) occurred in 36%. Laboratory test abnormalities typically reflected a cholestatic or a mixed cholestatic/hepatocellular injury pattern, similar to those in cefazolin cases (Figure 1). In six of the subjects, liver biopsies were available for central review [DEK]. Five had a cholestatic injury pattern and one had mild acute hepatocellular injury. Finally, 3 of the 6 biopsies had abnormal eosinophilia.

In contrast to patients with cefazolin-induced DILI, patients with DILI due to the other cephalosporins had a more severe course. Two patients died, 1 other patient was considered to have severe liver injury, 9 moderate and 2 mild. The majority (64%) of patients required hospitalization and the mortality rate was 14%. One patient developed Stevens Johnson Syndrome (i.e., severe skin injury, multi-organ failure) and died of liver and multisystem organ failure. One death was in a patient with underlying cirrhosis due to alpha-1-antitrypsin disease, who developed a severe immuno-allergic syndrome, including a rash (without desquamation) and eosinophilia and died of liver and multisystem organ failure. In follow

up, 3 patients had liver test abnormalities 6 months after DILI onset, but serum bilirubin levels were normal and the enzyme elevations were mild (Supplemental Table 2).

Discussion

While the cephalosporins have been thought to be a rare cause of idiosyncratic DILI, this has not been the experience in an ongoing study from the US. Among 1019 patients with DILI collected between 2004 and 2012 and undergoing careful causality assessment, 19 were attributed to cefazolin and 14 more to other cephalosporins. This made cefazolin the 6th most commonly identified specific agent responsible for DILI, and likewise, the cephalosporins, the 6th most common drug class to cause DILI. For cefazolin, the clinical presentation or “signature” was cholestatic or mixed hepatocellular-cholestatic injury arising 1 to 3 weeks after a single intravenous injection of the antibiotic given at the time of surgery, often unknown to the patient. Jaundice (95%) and pruritus (100%) were the most prominent signs or symptoms. The course was usually self-limited. Notably, because of confusion about the specific diagnosis, patients underwent substantial diagnostic testing (including multiple CT scans, MRI’s, ERCPs, liver biopsies, and others), which was often unnecessary and/or led to severe complications.

The findings reported here have several important clinical implications. First, cefazolin was often overlooked as a cause of DILI. In our experience, many patients were not aware that they had received cefazolin during outpatient procedures, and further, clinicians and often even DILIN investigators often did not initially consider or recognize cefazolin as a cause of DILI. For example, by definition, DILIN enrolls only patients recruited because of a high suspicion of DILI; even given this scenario, cefazolin was implicated only in retrospect after careful review of the medical record in 53% of patients. For these reasons, we speculate that cefazolin is and has been underappreciated as a cause of DILI. The appearance of jaundice and pruritus 1 to 3 weeks after minor surgery should lead to a search of operative records and medications that might have been given during surgery. These results also imply that the merits of routine use of cefazolin at the time of uncomplicated surgery should be carefully reconsidered ^{1, 24, 25}.

Reports of delayed DILI after a single intravenous dose of medication are rare, but have been reported sporadically ²⁶. A search of the FDA Adverse Event Reporting system (<http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Surveillance/AdverseDrugEffects/>) failed to reveal a report of DILI after a single intravenous dose of medication. Notwithstanding, the most common drugs associated with a single “dose” of medications include the halogenated anesthetics which are given during anesthesia, including halothane, isoflurane, enflurane, desflurane, and sevoflurane. While they are not given intravenously, the inhaled route is likely similar from a pharmacologic delivery standpoint. Although infrequently currently used, halothane’s pattern of liver injury is assumed to be typical for the other halogenated anesthetics; it is well described to cause an acute and often fulminant DILI picture, in a primary hepatocellular pattern, occurring shortly after exposure ^{27,28}. Since the halogenated anesthetics are often given during surgeries in which cefazolin may also be given prophylactically, it is important to consider each of these agents as potential causes of DILI in patients having orthopedic type surgeries

for which cefazolin is used prophylactically to prevent infection. Based on the data from our study, several points are noteworthy. First, the timing of injury for the halogenated anesthetics is typically more acute than what we have reported here for cefazolin, the former occurring within hours or days of exposure²⁹. Additionally, the injury pattern for the halogenated anesthetics is typically hepatocellular, rather than mixed or cholestatic as is typical for cefazolin (Table 2). Finally, in our cohort, a distinct minority of patients (2 sevoflurane, 1 desflurane) received halogenated anesthetics, making it highly unlikely that these agents confounded causality assessment in our patients.

This study has a number of strengths. First, data were collected in a standardized and prospective fashion; this allowed for collection of important clinical data as well as those focused on outcome. An important part of this data collection was the regular review of all medical records by trained personnel. Additionally, the causality process used was robust, and has been shown to be superior to conventional instruments such as RUCAM²³. The assignment of causality to cefazolin was strengthened by finding a typical clinical signature and the absence of competing diagnoses or exposures to agents that cause cholestatic, self-limited, injury. Other commonly implicated drugs were generally considered to lack a hepatotoxicity signature (propofol, tramadol, oxycodone), or cause a very different pattern of hepatic injury (acetaminophen, sevoflurane, oxcarbamazepine, and azithromycin). This further suggests that the cases included in this study are *bona fide* cases of cephalosporin induced DILI. In this context, we were surprised to find that, heretofore, cephalosporin-induced DILI has rarely been reported. In fact, there appear to be no more than a total of 10 previously reported cephalosporin-induced DILI cases^{8–17}.

Cephalosporin-induced liver injury appears to resemble that associated with amoxicillin/clavulanic acid³⁰. As with amoxicillin/clavulanate-induced liver injury, clinical symptoms arose 1 to 3 weeks after initial exposure and well after the antibiotic was stopped. Immuno-allergic features were often present but usually transient and mild, with full blown “drug reaction with eosinophilia and systemic symptoms” (DRESS) syndrome being uncommon³¹. More rapid recurrence upon re-exposure was also common. Furthermore, the injury signature was usually cholestatic with jaundice and itching, features also typical of amoxicillin/clavulanic acid-induced liver injury. We speculate that, because cephalosporins share the beta lactam structure of penicillins and clavulanic acid, a common mechanism of injury may be an immuno-allergic reaction to a structural component of the beta lactam 4-ring molecule.

It was notable that 2 patients receiving non-cefazolin cephalosporins died, and an additional patient had severe injury. However, in each of the fatal cases, patients had a complicated clinical course, with severe hypersensitivity reaction on top of an underlying liver disease. Therefore, we urge caution in concluding that non-cefazolin cephalosporin-induced DILI may be severe or fatal. Since cephalosporins are commonly used in clinical practice, it is likely that the overall mortality rate associated with cephalosporin use is low, but not nil, and it may be more likely in patients with underlying disorders.

In conclusion, cephalosporins appear to be a relatively common cause of antibiotic associated liver injury. The latency period is typically 1 to 3 weeks after exposure, and

patients may not become symptomatic until after the antibiotic is stopped – this is particularly true in the unique clinical syndrome in which a single infusion of cefazolin leads to DILI. The course of cephalosporin-induced DILI is usually one of a mild-to-moderate, self-limited cholestatic injury, particularly when associated with a single cefazolin infusion. However, severe and even fatal, DILI may occur in a small number of patients, and some cases may be followed by evidence of chronic injury.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1. Liver test abnormalities

The liver test abnormalities in 19 patients with cefazolin induced DILI are depicted. In (A) are shown patients falling into the early peak abnormality group, and in (B), the later peak group. Values on the X axis include bilirubin (mg/dL) or fold elevations over the upper limit of normal (ULN) in international units.

Figure 2. Cefazolin induced DILI - histology

In (A) is shown the liver test profile of a patient with typical cholestasis from cefazolin induced DILI. Values on the X-axis include bilirubin (mg/dL) or fold elevations over the upper limit of normal (ULN) in international units (IU). In (B-C) are shown photomicrographs of the liver biopsy specimen taken 30 days after exposure to cefazolin in a representative patient. In (B), the image depicts cholestatic hepatitis with mild portal and lobular inflammation (H&E, 200x). In (C), high magnification of zone 3 revealed prominent canalicular cholestasis (arrowheads), which was demonstrated more clearly on the iron stain (inset) (H&E, 600x). In (D), is depicted prominent canalicular cholestasis (arrowhead) in a different patient with cefazolin induced DILI (H&E, 400x) in a different patient.

Table 1

Clinical and causality characteristics of cefazolin induced liver injury (n = 19)

Feature	No (%)
Age (median-years)	53
Female	8 (42%)
BMI (median-kg/m ²)	26
Prior history of any drug allergy	9 (47)
Heavy alcohol use*	12 (63)
Diabetes mellitus	5 (26)
Hepatitis C (HCV RNA positive)	1 (5)
Time from administration to symptom onset	
< 1 week	3 (16)
2–4 weeks	13 (68)
> 4 weeks	3 (16)
Time to first laboratory abnormality	
< 1 week	1
1–2 weeks	5
3–4 weeks	13
Jaundice	18 (95)
Itching	19 (100)
Nausea	15 (79)
Abdominal pain	5 (26)
Rash	6 (32)
Fever	9 (47)
Eosinophilia	5 (26)
Hospitalization	11(69)
Severity	
Mild	1 (5)
Moderate	6 (32)
Moderate & hospitalized	10 (53)
Severe	2 (11)
Fatal	0
Causality	

Feature	No (%)
Probable	1(5)
Highly likely	16 (84)
Definite	2 (11)
Persistent abnormal liver tests more than 6 months	3 (16)

BMI, body mass index

*
>2 drinks/day in men and >1 drink/day women

Table 2

Detailed clinical features of cefazolin induced DILI

N	Age	Prior Drug Allergies	Days from Drug Start to DILI Onset	Nausea	Fever	Rash	Itching	Liver Biopsy Performed at Screen Visit	At Onset-ALT	At Onset-AST	At Onset-ALP	At Onset-Total Bili	Peak Values from DILI Onset to Month 6 Visit-ALT	Peak Values from DILI Onset to Month 6 Visit-AST	Peak Values from DILI Onset to Month 6 Visit-ALP	Peak Values from DILI Onset to Month 6 Visit-Total Bili	Patient was hospitalized	DILI Causality Score	DILI Severity Score
1	28	Yes	18	Yes	Yes	No	Yes	Yes	558	286	390	6.2	558	286	390	6.2	No	Definite	Moderate
2	53	No	21	Yes	Yes	No	Yes	No	401	151	432	6.5	401	151	521	10.6	Yes	Very likely	Severe
3	51	No	23	No	Yes	No	Yes	Yes	751	246	170	4.7	1233	472	266	9.8	Yes	Very likely	Moderate-H
4	67	Yes	20	Yes	No	No	Yes	Yes	639	623	1407	2.7	659	654	1527	18.1	Yes	Very likely	Moderate-H
5	56	Yes	20	No	Yes	No	Yes	No	614	281	508	2.2	614	281	564	2.8	No	Very likely	Moderate
6	45	Yes	20	Yes	No	No	Yes	Yes	377	280	689	2.9	468	280	781	18.8	Yes	Very likely	Moderate-H
7	49	No	24	Yes	No	No	Yes	Yes	618	238	328	4	945	414	406	5.1	No	Very likely	Moderate
8	60	Yes	3	Yes	No	No	Yes	No	194	109	309	5.7	194	135	385	5.7	Yes	Very likely	Moderate-H
9	72	No	23	Yes	No	No	Yes	Yes	135	134	354	6.4	135	155	441	11.1	Yes	Very likely	Moderate-H
10	83	No	29	No	Yes	No	Yes	No	197	159	443	10.7	200	159	513	11.4	Yes	Very likely	Moderate-H
11	57	Yes	28	Yes	Yes	Yes	Yes	No	303	201	448	1.2	378	212	889	1.9	Yes	Very likely	Mild
12	53	Yes	15	Yes	Yes	Yes	Yes	Yes	170	65	224	4.3	170	65	227	7.6	Yes	Very likely	Moderate-H
13	68	No	4	Yes	Yes	Yes	Yes	No	155	76	357	6.9	155	82	435	13	No	Very likely	Moderate
14	59	No	26	Yes	No	No	Yes	Yes	380	136	329	5.3	409	191	370	6.4	Yes	Very likely	Severe
15	45	No	21	Yes	No	No	Yes	Yes	769	143	305	5.3	769	143	305	9.3	Yes	Probable	Moderate-H
16	76	Yes	29	Yes	Yes	Yes	Yes	No	496	194	1457	7.9	496	194	1457	10.9	No	Very likely	Moderate
17	31	No	6	No	No	No	Yes	Yes	168	47	340	5	168	76	397	8.7	No	Very likely	Moderate
18	19	Yes	24	Yes	No	Yes	Yes	Yes	515	189	360	13.5	515	189	360	14.2	Yes	Very likely	Moderate-H
19	47	No	12	Yes	No	Yes	Yes	Yes	293	359	1332	14.9	390	415	1489	14.9	Yes	Definite	Moderate-H

Definite - Greater than 95%; Very likely - 75-95%; Probable 50-75%

H = hospitalized

DILI onset has been defined previously as the time at which the patient met study entry criteria, which is based on liver test abnormalities (see Fontana RJ, Watkins PB, Bonkovsky HL, et al. Drug-Induced Liver Injury Network (DILIN) prospective study: rationale, design and conduct. Drug Saf 2009;32:55-68).

Table 3

Laboratory features of cefazolin induced liver injury

Feature	Median	Range
Time from administration to laboratory abnormalities (days)	21	6–29
ALT (U/L), initial	380	135–769
AST (U/L), initial	189	47–623
Alkaline phosphatase (U/L), initial	360	170–1457
Bilirubin (mg/dL), initial	5.3	1.2 – 14.9
INR, initial	1.0	0.8–1.2
R value, initial	1.8	0.4 – 8.8
ALT (U/L), peak	409	135–1233
AST (U/L), peak	191	65–654
Alkaline phosphatase (U/L), peak	435	227–1527
Bilirubin (mg/dL), peak	9.8	1.9–18.8
INR, peak	1.1	1.0–2.0
Eosinophilia (no, % and count/ μ L)	5 (26%)	533 – 3400

R value = ratio of the serum ALT to alkaline phosphatase (both expressed as multiples of the ULN)

Table 4

DILI caused by cephalosporins

Drug	No Cases	Generation	Route	Duration of treatment (range, days)	Latency (range, days)	Initial ALT (U/L) (mean $\pm$ SD and median)	Initial Alk P (U/L) (mean $\pm$ SD and median)	Initial Bilirubin (mg/dL) (mean $\pm$ SD and median)	Severe (n, %)
Cefazolin	19	1 st	IV	1	6–29	407 $\pm$ 211 380	536 $\pm$ 399 360	6.1 $\pm$ 3.6 5.3	2/19 (11%)
Cephalexin	3	1 st	Oral	2–14	11–20	378 $\pm$ 365 316	313 $\pm$ 179 397	2.3 $\pm$ 3.4 0.4	1/3 (33%) * fatal
Cefadroxil	2	1 st	Oral	14	27	486 $\pm$ 381 486	234 $\pm$ 79 234	19.6 $\pm$ 20.0 19.6	0 (0%)
Cefuroxime	1	2 nd	IV	11	56	268	651	8.4	0 (0%)
Cefaclor	1	2 nd	Oral	2	6	64	104	4.1	0 (0%)
Ceftriaxone	4	3 rd	IV	3–13	4–29	292 $\pm$ 181 227	362 $\pm$ 191 412	1.8 $\pm$ 1.9 1.1	1/4(25%)
Cefdinir	1	3 rd	Oral	9	12	232	409	4.7	0 (0%)
Cefotaxime	1	3 rd	IV	4	1	23	127	2.3	1/1 (100%) * fatal
Cefipime	1	4	IV	7	20	205	62	11.3	0(0%)

Severe = proportion scored as severe or fatal

Cholestatic = proportion with jaundice, itching and cholestatic or mixed pattern of serum enzyme elevations (R value <5) Typical signature - The signature of cefazolin hepatotoxicity is defined as symptomatic liver injury with jaundice and pruritus, cholestatic or mixed aminotransferase elevations, and an onset of 1 to 4 weeks after exposure.

* Denotes 1 fatal case