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Characteristics of Idiosyncratic Drug-induced Liver Injury in Children: Results From the DILIN Prospective Study

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Abstract

Background—The spectrum and severity of idiosyncratic drug-induced liver injury (DILI) in children are not well established.

Patients and Methods—The DILIN (Drug-Induced Liver Injury Network) Prospective Study is a longitudinal multicenter study designed to determine the etiologies, risk factors, and outcomes of suspected DILI. Between September 2004 and September 2009, 30 children ages 2 to 18 years with suspected DILI who met eligibility criteria were enrolled and studied for at least 6 months.

Results—Mean age was 14 years; 70% were girls. Antimicrobial (50%) and central nervous system agents (40%) were the most commonly implicated drug classes, with minocycline (4), isoniazid (3), azithromycin (3), atomoxetine (3), and lamotrigine (3) the leading agents. Median time from drug initiation to symptom onset was 32 days. Peak (median) liver chemistries were aspartate aminotransferase 503 U/L, alanine aminotransferase 727 U/L, alkaline phosphatase 331 U/L, and total bilirubin 3.9 mg/dL. Autoantibodies were common (64%). Liver injury pattern was hepatocellular 78%, cholestatic 13%, and mixed 9%. The DILI episode was scored: mild 32%, moderate 44%, severe 20%, and fatal (within 6 months) 4%. Causality assessment was definite 36%, very likely 36%, probable 16%, possible 8%, and unlikely 4%. Seven percent had persistent liver test abnormalities at 6-month follow-up suggesting chronic DILI. Liver biopsies from 12 children most frequently demonstrated chronic hepatitis or bile duct injury.

Conclusions—Idiosyncratic DILI in children is most commonly caused by antimicrobial or central nervous system agents and usually presents with a hepatocellular injury pattern. The majority of patients recover, but morbidity and infrequent mortality are seen.

Keywords

drug-induced liver injury; hepatotoxicity; liver biopsy; Roussel Uclaf Causality Assessment Method

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Drug-induced liver injury (DILI) is an underrecognized cause of pediatric liver disease. Nonacetaminophen drugs account for 5% of episodes of acute liver failure in children, and both acute and chronic forms of liver injury from medications have been described in anecdotal reports or small series (1–6). Implicated drugs have included antibiotics, anticonvulsants, psychoactive drugs, and others (7). Most drugs approved before 1998 were tested only in adults, and thus drug hepatotoxicity in children became apparent only during clinical use. Although the 1998 Food and Drug Administration (FDA) Pediatric Rule established the requirement for pediatric testing of all new drugs with potential for use in children, most pediatric and adult clinical trials have not included an adequate number of subjects to detect potential safety signals. Even after approval, only a small proportion of cases of drug toxicity are reported to the FDA Medwatch (8). In the last decade, pemoline, which is used to treat pediatric attention-deficit/hyperactivity disorder (ADHD), was withdrawn from the US market amidst reports of hepatotoxicity. The product labeling of atomoxetine, another widely used drug for ADHD, was changed in 2004 to include a warning regarding potential hepatotoxicity. A National Institutes of Health clinical research workshop in 2008 concluded that additional studies of pediatric DILI were needed because of age-related differences in drug metabolism, implicated drugs, and toxic doses (9).

A number of mechanisms underlying the etiopathogenesis of idiosyncratic DILI have been suggested, including hepatocyte injury secondary to drug binding to protein (protein adducts), injury to canalicular bile transport mechanisms, and biotransformation resulting in immunogenic adducts. Additionally, drugs may influence liver cell apoptosis or mitochondrial function (10). Nonhepatocyte cells such as endothelial cells, stellate cells, or Kupffer cells also may be affected (9). Many of these cellular processes and the ability of the liver to adapt and regenerate may differ in children compared with adults (11). Drug metabolism in children may also differ in terms of absorption, distribution, metabolism, and excretion (12). For example, children have been found to be especially vulnerable to valproate hepatotoxicity but relatively resistant to acetaminophen injury (13,14). Age-related differences in hepatic phase 1 and phase 2 biotransformation have been identified and may contribute to the known variation in susceptibility and outcome of DILI in children compared with adults (11).

The Drug-Induced Liver Injury Network (DILIN), established in 2003, is a cooperative agreement among the National Institutes of Health, 5 academic clinical centers (later expanded to 9), and a data coordinating center. The DILIN prospective study is an ongoing observational study of children and adults with suspected DILI with the goal of creating a registry and biosample repository for clinical and mechanistic studies of DILI. The design and development of the DILIN prospective study (15) and the process of causality assessment (16) have been presented recently. In this article, we report the implicated agents, presenting clinical and laboratory characteristics, short-term outcomes, and causality and severity scores of 30 children enrolled during the first 6 years of the DILIN prospective study.

PATIENTS AND METHODS

The DILIN prospective study eligibility criteria, study protocol, and the adjudication of causality and severity scores are described in detail elsewhere (15). Suspect drugs were identified based on compatible timing and evolution in the absence of a competing liver disease diagnosis. Subjects were identified after presenting to 1 of 7 study centers; various approaches including a study Web site, DILI-focused conferences, and local outreach were developed to encourage referrals. Following institutional review board approval at each site, written informed consent was obtained from all of the subjects or parents when appropriate. Patients ages 2 years or older were enrolled if there was a clinical suspicion of drug-induced

hepatotoxicity within 6 months of enrollment and aspartate aminotransferase (AST) or alanine aminotransferase (ALT) >5 times the upper limit of normal (ULN) (or >5 times the predrug average if elevated baseline levels) or alkaline phosphatase >2 times the ULN (or >2 times the predrug average if elevated baseline levels) on 2 consecutive occasions OR serum bilirubin >2.5 mg/dL along with any elevations in AST, ALT, or alkaline phosphatase levels, OR internationalized normal ratio (INR) >1.5 with any elevations in AST, ALT, or alkaline phosphatase levels. Children with known acetaminophen toxicity and/or prior bone marrow or liver transplant were excluded as were those with known primary sclerosing cholangitis, autoimmune hepatitis, or other liver diseases that may confound the diagnosis.

All of the participants were assessed at a baseline visit in which clinical, laboratory, and histologic data were collected. A follow-up study visit was obtained at 6 months, with 12- and 24-month visits scheduled for those with evidence of chronic injury (defined as persistent biochemical, radiographic, histological, or clinical evidence of portal hypertension or chronic liver disease at 6 months after DILI onset).

When available, recuts of liver biopsies were reviewed by the DILIN hepatopathologist (D.E.K.) who was blinded to clinical and demographic information. The pattern of injury was categorized into acute hepatitic, chronic hepatitic, acute cholestatic, cholestatic hepatitis, and other patterns according to standard criteria (17,18). Individual histologic features were also recorded (18). In particular, inflammation and fibrosis were scored according to Ishak et al (19). Ballooning was scored as none, few, or many. Infiltrates of plasma cells, eosinophils, and neutrophils were recorded as either none to rare or noticeably increased. Bile duct injury was recorded as not present, occurring in rare ducts, or occurring in multiple portal triads.

The causal relation between the liver injury event and the implicated agent(s) was systematically evaluated by the DILIN Causality Committee (15). The causality assessment was conducted for each case by both the Roussel Uclaf Causality Assessment Method (RUCAM) (16) and DILIN Causality Assessment (15). The DILIN causality categories include “definite” (>95% likelihood), “highly likely” (75%–95%), “probable” (50%–74%), “possible” (25%–49%), and “unlikely” (<25%). RUCAM values were categorized as “highly probable” (>8), “probable” (6–8), “possible” (3–5), “unlikely” (1–2), or “excluded” (0) (Table 1). In addition, the severity of each DILI episode was categorized as 1 of 5 levels: mild, moderate, moderate-hospitalized, severe, and fatal/transplant, as described elsewhere (15).

Simple descriptive statistics including means, medians, 25th to 75th percentiles, frequencies, and percentages were used to summarize the data. All of the calculations were performed using SAS version 9.2 (SAS Institute Inc, Cary, NC).

RESULTS

Thirty children ages 2 to 18 years with suspected DILI that met predefined eligibility criteria were enrolled between September 2004 and September 2009. Data available as of September 14, 2009 were analyzed.

Implicated Drugs

Antimicrobials and central nervous system (CNS) agents were the 2 drug classes that were most commonly implicated (Table 2). Minocycline was the single most commonly implicated agent (n = 4); other antimicrobials included isoniazid (n = 3), azithromycin (n = 3), amoxicillin (n = 2), and 1 case each of oxacillin, levofloxacin, and sulfamethoxazole. Among the CNS agents, atomoxetine (n = 3) and lamotrigine (n = 3) were the most common

agents. In 5 children, there were 2 suspected drugs and in a sixth child there were 3 suspected drugs. Nearly half the children had been exposed to 5 or more concomitant drugs in the 2 months before DILI onset.

Clinical Presentations

Most children with DILI were in early adolescence, with mean and median ages of 12 and 14 years, respectively, and 70% were girls. Prior drug allergies were reported in 43%, whereas alcohol use was rare (3.3%) and no child reported cigarette smoking. Although only 1 of the children had a history of preexisting liver disease (biliary atresia with native liver), underlying neuropsychiatric, pulmonary, or cardiac conditions were common (Table 3). By history, DILI signs and symptoms were apparent at a mean of 140 and median of 32 days after drug initiation. Biochemical evidence of liver injury was recorded at a mean 196 and median 45 days after starting the implicated agent. A particularly prolonged latency was noted in the minocycline cases (median 569 days, range 196–647) and with atomoxetine (median 510 days, range 117–699). Common symptoms included jaundice, abdominal pain, pruritus, nausea, rash, and fever. In 2 patients, Stevens-Johnson syndrome was seen at presentation and in 1, thrombocytopenia (Table 3).

Biochemical Abnormalities

Based on serum enzyme elevations, the pattern of liver injury was considered hepatocellular in 78%, cholestatic in 13%, and mixed in 9%. The median (25%, 75%) ALT and AST at onset were 405 (234, 1437) U/L and 528 (164, 1379) U/L, respectively, with higher values in the hepatocellular group (median ALT 891 U/L and AST 1206 U/L) than in the cholestatic group (ALT 70 U/L and AST 47 U/L). The median peak alkaline phosphatase (Alk P) for the overall group was 331 (169, 479) U/L, whereas it was 495 U/L for the cholestatic group; alkaline phosphatase levels were not adjusted for age. The median total bilirubin (25%, 75% limits) was 3.7 (1.6, 4.4) mg/dL at onset and at peak was 3.9 (1.0, 14.5) mg/dL in the overall group with a similar peak of 5.3 (1.0, 23.0) mg/dL in the cholestatic group. The mean and median eosinophil counts were 196/ μ L and 140/ μ L, with only 1 child having an eosinophil count of more than 500/ μ L. In 64% of children with DILI, autoantibodies were detected: anti-nuclear antibody (ANA) was positive in 46%, smooth muscle antibody (SMA) was positive in 42%, either was positive in 64%, and both were positive in 23%. Among those who were ANA positive, the titer was 1:160 in 46%. The median immunoglobulin G (IgG; not adjusted for age) was 1270 (857.0–1850.0) mg/dL (Table 3). The drugs associated with autoantibodies were minocycline (4), atomoxetine (3), lamotrigine (2), azithromycin (2), amoxicillin (2), and, in single cases, isoniazid, sulfamethoxazole, amitriptyline, oxacillin, and methyl dopa.

Histology

Liver biopsies were performed in 47% of the children. Of these, 12 had been reviewed by the study pathologist at the time of this analysis (Table 4). Necroinflammatory activity was a common finding, with grade 3 to 4 interface hepatitis in 6 (50%) and grade 3 to 4 lobular inflammation in 7 (58%). Two biopsies (16.4%) revealed bridging necrosis or multiacinar collapse. Eosinophils were increased in 5 (42%), but plasma cells were noted in only 2 of the biopsies. Canalicular cholestasis was seen in 5 cases (42%) and 3 biopsies (25%) demonstrated injury in multiple bile ducts. Only 1 biopsy showed moderate (grade 3) steatosis, with the remaining cases showing at most mild steatosis. Moderate fibrosis, grade 2 to 4, was seen in 6 (50%) biopsies, but none had cirrhosis. Primary implicated drugs in the biopsied children included minocycline (3), atomoxetine (3), azithromycin (2), and 1 case each of lamotrigine, trimethoprim-sulfamethoxazole, amitriptyline, and drospirenone/ethinyl estradiol. In 1 case, 2 drugs were implicated (nicotinic acid and amitriptyline). Of note, all of the cases attributed to minocycline showed a chronic hepatitic pattern, typical for this agent

(Fig. 1A). The atomoxetine cases showed both hepatitic (acute and chronic) and cholestatic hepatitis patterns. The case associated with the oral contraceptive drospirenone/ethinyl estradiol showed cholestatic hepatitis with prominent canalicular cholestasis (Fig. 1B). The case attributed to lamotrigine showed acute hepatitis, whereas 1 azithromycin case showed acute intrahepatic cholestasis with duct paucity (Fig. 1C).

Outcomes

The mean (median) time to normalize ALT was 119 (78.5) days and the mean (median) time to normalize bilirubin was 44 (34) days (Table 3). Sixty-three percent of the children were hospitalized or had their hospitalization prolonged by DILI. Forty percent of the children were treated with corticosteroids. Two children demonstrated evidence of chronic liver disease at 6 months. In the first case, a 16-year-old had been treated with minocycline for mild acne for 2.5 years, at which time the drug was stopped because of joint symptoms, malaise, and elevated liver enzymes. Liver biopsy 6 months later revealed chronic hepatitis with interface changes and bridging fibrosis; 1 year after minocycline was stopped, liver enzymes remained elevated. In the second case, a previously healthy 12-year-old white girl presented with cholestatic hepatitis and Stevens-Johnson syndrome attributed to azithromycin. A liver biopsy 3 months after onset demonstrated vanishing bile ducts that further progressed during follow-up into worsening ductopenia and neochoangiogenesis on biopsy. After the data collection period for this study, she developed progressive respiratory insufficiency from bronchiolitis obliterans that was refractory to corticosteroids and died of pneumonia and liver failure with a bilirubin of 17 mg/dL, 22 months after DILI onset. A child with congenital heart disease died of multiorgan failure (with prominent liver involvement). None of the children were eligible for liver transplants.

Adjudication of Causality and Severity

The DILIN causality scores were definite in 36.0%, very likely in 36%, probable in 16%, possible in 8%, and unlikely in 4%. The latter 3 cases were attributed to sulfamethoxazole/trimethoprim, isoniazid, and valproic acid. The RUCAM causality scores were “highly probable” or “probable” in 58% and “possible” in 29%; 4% were “excluded.” Interestingly, in 2 cases with “unlikely” RUCAM score, DILIN clinical score was “probable” or “very likely.” The DILIN severity scores were mild in 32%, moderate in 20%, moderate-hospitalized in 24%, severe in 20%, and fatal (within 6 months) in 4% (summarized in the online-only supplemental table available at <http://links.lww.com/MPG/A47>).

DISCUSSION

DILI is a rare cause of liver injury in children. Both hepatocellular and cholestatic patterns have been reported, as have chronic injury patterns (20–24). DILI has been reported as a cause of acute liver failure, with acetaminophen accounting for 14% of cases and other drugs accounting for 5% in the largest reported series from the Pediatric Acute Liver Failure Study Group (2,25). The majority of reported cases involved antibiotics or anticonvulsants. Data are limited, however, on the spectrum of DILI in children. The prospective, detailed, and carefully adjudicated pediatric data contained within the DILIN Prospective Study provides a unique opportunity to study the clinical spectrum and outcomes of DILI in children.

The results from the first 300 subjects enrolled in DILIN were recently published (26). Nearly half of the episodes of liver injury in those 300 subjects were associated with antimicrobials, 15% with CNS drugs, and 10% with dietary or herbal supplements. The most common single implicated drugs were amoxicillin-clavulanate, nitrofurantoin, isoniazid, and trimethoprim-sulfamethoxazole. Four adult patients were found to have acute hepatitis C

instead of DILI. Chronic DILI was observed in 14%, the mortality rate was 8%, and 2% had received transplants. The present study reports results for a subset of pediatric patients ages 2 to 18 years enrolled in the DILIN study, which includes both adults and children.

Several unique features of DILI in children are illustrated in the present report. The frequency of comorbidities, although not entirely unexpected in children receiving medications, suggests an increased vulnerability in chronically ill children. Twenty percent of the children were exposed to 2 or more implicated drugs, similar to the adult cohort but more than the 9% reported in a similar study from Spain (27). Nearly half of the children had been exposed to 5 or more drugs other than the implicated drugs in the 2 months before DILI onset. The history of drug allergies in 43% is notable and may help the clinician identify children at risk. Only 1 enrolled child reported exposure to toxins such as alcohol and no unsuspected underlying liver disease was found at presentation or during follow-up.

The classes of agents associated with DILI in children were similar to those reported in adults (28,29). Antimicrobials were the most commonly implicated drug class, reported in a proportion (50%) similar to that found in the overall (mostly adult) DILIN cohort. Minocycline, prescribed for acne in 4 adolescents, was the single most commonly implicated drug, reported in 13% of pediatric DILI episodes compared to only 1% of the first 300 subjects reported in the DILIN cohort (26). Other antibacterial and antimycobacterial agents were implicated in 11 cases or 37%. Interestingly, amoxicillin-clavulanate, the most commonly implicated drug in the adult cohort of DILIN, was not reported in any of the 30 children. CNS drugs were implicated in 40% of cases of pediatric DILI: anticonvulsants given for seizures or psychiatric problems in 20%, drugs for ADHD in 13%, and antidepressants in 7%. In comparison to the entire DILIN group, more than twice as many pediatric cases involved psychoactive drugs than in the overall cohort. Importantly, herbal and dietary supplements were implicated in only 1 case of pediatric DILI (3%), in contrast to almost 10% in the overall DILIN study presumably resulting from the lower frequency of use of these products in children.

A number of clinical features of pediatric DILI are illustrated in this group of 30 children. Although the most common presenting symptoms were jaundice, abdominal pain, nausea, and itching, it is important to note that 40% of the children were not jaundiced. Only one-third displayed rash and 2 of the 30 children had concomitant Stevens-Johnson syndrome. The liver injury pattern in the children with DILI was most often hepatocellular, likely related to the implicated drugs. The median peak bilirubin of 3.9 mg/dL suggests a significant impairment in excretory function. Importantly, 4 of the children demonstrated impairment of hepatic synthetic function manifested by an INR >2. This, accompanied by the fact that 63% of the children were hospitalized (or had prolongation of hospitalization), demonstrates the potential severity of pediatric DILI. Our data suggest that although symptoms and clinical evidence of hepatotoxicity often occur within 1 or 2 months of exposure to the inciting drug, presentation of DILI may be delayed by months. In particular, subjects with minocycline and atomoxetine hepatotoxicity only presented after taking these medications for many months, which is consistent with prior reports featuring these agents (3,5). Similarly, biochemical normalization may take 1 to several months. Therefore, follow-up monitoring after drug discontinuation should reflect this potential for slow improvement, along with awareness of the potential for the development of severe or chronic liver disease (30,31). Finally, the unusual case of fatal bronchiolitis obliterans along with ductopenia demonstrates the potential for prominent extrahepatic manifestations of adverse drug reactions in some patients with DILI. It is notable that this child also had Stevens-Johnson syndrome, which recently has been reported to be associated with cholestatic liver disease and severe lung disease in a teenager treated with ciprofloxacin (32). Stevens-Johnson may identify DILI cases associated with an increased risk of serious extrahepatic complications.

The high frequency of autoantibodies in these children (total 64%; ANA 46%, SMA 42%) was notable, with significant titers in almost half of those with positive ANA; 35% of the overall DILIN cohort (mostly adults) were ANA positive and 25% were SMA positive (26,33). Two commonly implicated drugs in this series, minocycline and atomoxetine, have been associated with autoimmune hepatitis (3,5). As reported with other drugs that present with an autoimmune phenotype, a prolonged latency period with both of these agents was noted. Lamotrigine, associated with 2 pediatric DILI episodes, was recently the subject of an FDA drug safety communication regarding the association of aseptic meningitis with its use; hepatic involvement was noted in some cases and underlying autoimmune disease in a few (34). Forty years ago, methyldopa was recognized as causing an autoimmune hepatitis phenotype (35) with subsequent reports of autoantibodies accompanying DILI (36). Immunoallergic mechanisms are suspected in many other drugs (37,38). Autoimmunity may play a role in a significant number of pediatric DILI cases. Corticosteroids were used in almost half of the children in the group, suggesting the clinical suspicion of an autoimmune (or at least hypersensitivity) mechanism, although peripheral eosinophilia was not seen in any child at baseline. It is not possible to assess response to corticosteroids in this uncontrolled observational study, and the role of corticosteroids in managing patients with DILI remains controversial because of the lack of large, prospective studies (5,6,10).

The 12 liver biopsies reported in this study represent a relatively large number of carefully studied tissue samples correlated with clinical information from children with DILI. Less than half of the biopsies showed tissue eosinophilia, emphasizing the fact that eosinophilia is not always seen in drug-induced hepatitis. Interface hepatitis was seen in half of the children, consistent with the marked elevations in serum aminotransferase levels, whereas bile duct damage was seen in 25%; however, it was apparent that a wide range of histologic abnormalities can be seen in pediatric DILI, generally similar to adult abnormalities reported (17). Notably, fibrosis was common in this pediatric group. The observed injury patterns in some of the cases correlated well with reported patterns of injury for these agents, but additional analyses from the DILIN database are needed.

The study was limited by potential selection bias because children were recruited by large pediatric academic centers with a special interest in DILI. The small number of subjects recruited more than 5 years raises the possibility that some DILI cases were not identified and that the spectrum and frequency of DILI in children may not be accurately represented in this study. It is likely that more severe cases of DILI were included in this study than are encountered in the general population. It is possible that children with chronic illness had more frequent monitoring of serum biochemistries. To exclude competing etiologies of liver injury, each enrolled child underwent a comprehensive, standardized evaluation and an objective causality assessment was applied to all of the cases. Furthermore, 88% of the cases were scored as probable, very likely, or definite. In addition, all of the participants were studied for 6 months to exclude other competing causes of liver injury. The small number of children enrolled precluded analysis of prognostic factors.

In summary, the clinical spectrum of DILI in children is broad, ranging from asymptomatic biochemical hepatitis to acute liver failure. It is important for clinicians to recognize the potential for commonly used antimicrobial or neurotropic drugs in children to cause serious liver injury, carefully weigh the risk–benefit ratio, and evaluate potential symptoms and signs promptly. Data from this study showing slow resolution of liver injury can also inform the monitoring of the pediatric patient during the recovery phase. The accurate characterization of potential DILI cases is crucial to improving our understanding of its pathogenesis and treatment. Further study into the role of autoimmunity in pediatric DILI and the potential role of corticosteroids and other targeted therapies (eg, carnitine for valproate hepatotoxicity) is needed (39). Future studies including larger numbers of children

and a wider spectrum of DILI will enable us to better identify and manage children at risk for this potentially life-threatening cause of liver disease. Furthermore, analysis of the biological samples collected in this prospective study may provide insights into the mechanisms, risk factors, and outcomes of pediatric DILI, with the ultimate goal of preventing future cases of this rare but potential severe adverse drug reaction.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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FIGURE 1.

A, A 17-year-old white male taking minocycline for 2 years developed severe hepatitis. Minocycline was discontinued but then later resumed after normalization of liver biochemistries. Liver biopsy 2 months after rechallenge (ALT 628) showed moderate portal inflammation (P), interface hepatitis and scattered foci of lobular inflammation and apoptosis (arrows) (original magnification $\times 400$). Liver dysfunction resolved with steroids. B, A 16-year-old white female developed cholestatic hepatitis 2 weeks after starting drospirenone/ethinyl estradiol birth control pills. Biopsy 4 weeks after DILI onset showed prominent canalicular cholestasis (arrows) near the central vein (V) with lobular inflammation (L) and rare apoptotic cells. Portal inflammation was also present (not shown) (original magnification $\times 400$). C, A 10-year-old female with vanishing bile duct syndrome caused by azithromycin. Biopsy 2 weeks after DILI onset showed minimal inflammation, but most portal areas lacked bile ducts. A representative duct-less portal area is shown with portal vein (V) and hepatic artery (A) indicated (original magnification $\times 600$).

TABLE 1

Causality and severity scores: DILIN adjudication

Causality		Severity	
RUCAM score			
Highly probable	13	Mild	32
Probable	46	Moderate	20
Possible	29	Moderate/hospitalized	24
Unlikely	8	Severe *	20
Excluded	4	Fatal	4
DILIN score			
Definite	36		
Very likely	36		
Probable	16		
Possible	8		
Unlikely	4		

DILIN = Drug-Induced Liver Injury Network; RUCAM = Roussel Uclaf Causality Assessment Method. Data represented in percentages.

* One child who was initially adjudicated to have severe DILI at the time of data analysis later died at 22 months after DILI onset of respiratory and liver failure; this child's death is not included here.

TABLE 2

Implicated agents for pediatric drug-induced liver injury

Antimicrobials (N = 15)	15
Minocycline	4**
Isoniazid	3
Azithromycin	3
Amoxicillin	2
Oxacillin	1
Levofloxacin	1#
Sulfamethoxazole	1
ADHD drugs (N = 4)	4
Atomoxetine	3
Methylphenidate	1
Anticonvulsants (N = 8)	8
Lamotrigine	3^^
Valproate	2^^
Phenobarbital	1#
Phenytoin	1#
Carbamazepine	1@
Psychoactives (N = 3)	3
Fluoxetine	1
Amitriptyline	1^
Perphenazine	1@
Others (N = 7)	8
Folic acid/nicotinamide/zinc	1**
Nicotinamide	1^
Daunorubicin	1~
Vincristine	1~
Methyldopa	1
Drospirenone/ethinyl estradiol	1
Hydroxycut	1

Each different symbol denotes 1 of the 6 children in whom multiple drugs were implicated and marks the implicated drugs. ADHD = attention-deficit/hyperactivity disorder.

TABLE 3

Selected demographic and clinical characteristics of children with DILI

Age, median (25th, 75th) y	13.7 (7.8, 17.1)
Gender, male/female, %	30/70
Race, white/black/other, %	80/7/13
Other medical conditions, %	
Drug allergies	43
Alcohol use	3
Endocrine	7
Neurologic	27
Cardiac	17
Renal	3
Pulmonary	23
Intestinal	13
Malignancy	3
Liver disease	3
Clinical presentation: median times (25%–75%)	
Days from drug start to symptoms	32 (10, 132)
Days from drug start to DILI onset	45 (19, 501)
Days from onset to peak bilirubin *	7 (3, 14)
Days from onset to peak ALT †	6 (2, 21)
Clinical resolution: median times (25%–75%)	
Days from onset to bilirubin <2.5 *	34 (12, 75)
Days from onset to ALT < ULN †	79 (55–166)
Clinical signs and symptoms, %	
Jaundice	60
Nausea	43
Fever	33
Abdominal pain	53
Rash	30
Stevens-Johnson	7
Itching	37
Neutropenia	3
Thrombocytopenia	3
Biochemical values: median (25%, 75%)	
Peak ALT	727 (262, 1787)
Peak AST	503 (195, 1521)
Peak alkaline phosphatase	331 (169, 479)
Peak bilirubin total	3.9 (1, 14.5)
Peak INR	1.2 (1.1, 1.7)
Absolute eosinophils at baseline	140 (56, 242)
IgG	1270 (857, 1850)

ANA positive, %	46
Anti-SMA positive, %	42

ALT = alanine aminotransferase; ANA = anti-nuclear antibody; AST = aspartate aminotransferase; DILI = drug-induced liver injury; IgG = immunoglobulin G; INR = international normalized ratio; SMA = smooth muscle antibody.

*
For cases with peak total bilirubin >2.5 mg/dL.

*
For cases with peak ALT >5 times ULN.

TABLE 4

Selected clinical characteristics of children with DILI who had liver biopsy performed

Drug	Age, y	Sex	Injury	Peak ALT, U/L	Peak ALP, U/L	Peak T Bil, mg/dL	AutoAb	Days to onset	Days onset to biopsy	Causality	Severity	Histology
Atomoxetine	11.5	F	HC	732	222	1.6	ANA SMA	117	29	3	1	Severe acute hepatitis, multiacinar necrosis; plasma cells in portal areas. Bridging fibrosis present.
Atomoxetine	12.8	F	HC	2999	296	11.5	ANA	510	15	1	3	Cholestatic hepatitis with extensive interface hepatitis, eosinophils in portal areas, duct injury, small lipid vacuoles, periportal fibrosis.
Atomoxetine	7.8	M	HC	781	321	1.1	ANA SMA	699	91	2	1	Mild chronic hepatitis with eosinophils, no cholestasis.
Minocycline	17.1	M	HC	1233	135	1	ANA SMA	569	144	1	2	Marked chronic hepatitis, with microgranulomas; eosinophils and few plasma cells. Poulsson-like duct lesions; perivenular and periportal fibrosis.
Minocycline	17.9	F	HC	1826	158	1	ANA SMA	714	22	2	1	Chronic hepatitis, extensive interface hepatitis, lobular inflammation, focal bridging necrosis/fibrosis.
Minocycline	15.7	F	HC	343	92	0.6	ANA	196	101	2	1	Chronic hepatitis, moderate interface hepatitis, periportal fibrosis.
Azithromycin*	10.9	F	HC	418	1112	13	Neg	64	15	3	4	Marked intrahepatic cholestasis, mild inflammation. Bile duct loss/injury.
Azithromycin	13.5	M	CS	262	395	5.3	SMA	14	39	N/A	N/A	Intrahepatic cholestasis, minimal inflammation, glycogenosis.
Lamotrigine	12	F	HC	862	846	12	ANA	34	15	1	3	Acute hepatitis, zone 3 ballooning, lobular inflammation, bile duct injury, mild fibrosis.
Sulfamethoxazole	16.2	F	CS	82	495	23	ANA	1	11	5	3	Cholestatic hepatitis, portal and lobular inflammation with eosinophils seen. Mild fibrosis.
Amitriptyline	16.4	F	HC	2411	130	3.2	SMA	5	40	2	4	Mild nonspecific changes, minimal portal inflammation, limited biopsy.

Drug	Age, y	Sex	Injury	Peak ALT, U/L	Peak ALP, U/L	Peak T Bil, mg/dL	AutoAb	Days to onset	Days onset to biopsy	Causality	Severity	Histology
Drosiprenone	16.3	F	Mixed	256	335	14.9	Neg	38	N/A	2	3	Cholestatic hepatitis with mild lobular inflammation, mild fibrosis.

Causality clinical assessment scores: definite (1), very likely (2), probable (3), possible (4), and unlikely (5). Severity scores: mild (1), moderate (2), moderate and requiring hospitalization (3), severe (4), and fatal (5). ALP = alkaline phosphatase; ALT = alanine aminotransferase; ANA = anti-nuclear antibody; AutoAb = autoantibody; Bili = bilirubin; CS = cholestatic; HC = hepatocellular pattern of injury; N/A = not available; Neg = autoantibody negative; SMA = anti-smooth muscle antibody; T = total.

* This child was assessed to have severe DILI (score 4) when the causality and severity were adjudicated; however, at 22 months after the DILI onset she died from respiratory and liver failure.