Therapeutic management of idiosyncratic drug-induced liver injury and acetaminophen hepatotoxicity in the paediatric population: a systematic review

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Hao Niu[1,2,3*], Edmond Atallah[4,5*], Ismael Alvarez-Alvarez[1,2,3*], Inmaculada Medina-Caliz[1], Guruprasad P Aithal[4,5], Cigdem Arikan[6,7], Raul J Andrade[1,2†], M Isabel Lucena[1,2,3†]

1. Servicios de Aparato Digestivo y Farmacología Clínica, Hospital Universitario Virgen de la Victoria, Instituto de Investigación Biomédica de Málaga-IBIMA, Universidad de Málaga, Málaga, Spain

2. Biomedical Research Network Center for Hepatic and Digestive Diseases (CIBERehd), Carlos III Health Institute, Madrid, Spain

3. Platform for Clinical Research and Clinical Trials IBIMA, Plataforma Isciii De Investigación Clínica, Madrid, Spain

4. School of Medicine, Nottingham Digestive Diseases Centre, University of Nottingham, Nottingham, United Kingdom

5. National Institute for Health Research (NIHR) Nottingham Biomedical Research Centre, Nottingham University Hospitals NHS Trust and the University of Nottingham, Nottingham, United Kingdom

6. Koç University, Pediatric Gastroenterology-Hepatology/Liver Transplantation Center, Istanbul, Turkey

7. Koç University Research Center for Translational Medicine (KUTTAM)-Liver Immunology Lab, Istanbul, Turkey

[*] HN, EA and IA-A equally contributed as first authors.

[†] RJA and MIL equally contributed as senior authors.

Correspondence to:

M Isabel Lucena, MD, PhD, Professor

Departamento de Farmacología, Facultad de Medicina,

Universidad de Málaga

Boulevard Louis Pasteur 32, 29071, Málaga, Spain.

Tel.: +34-952-131572

Fax: +34-952-131568

lucena@uma.es

Table S1. Characteristics and outcome of drug-induced liver injury in the paediatric population.

Culprit drug	Median age (range)	Sex		Drug start to DILI onset (median)	Severity of DILI at recognition (n)	DILI pattern (n)	Outcome (n)
		Boy	Girl				
Preterm newborn neonates (from day of birth through the expected date of delivery plus 27 days)							
Acetaminophen (N=1)	35 days	1	-	5 days	Severe	Hepatocellular	Recovery
Term and post-term neonates (from day of birth plus 27 days)							
Acetaminophen (N=1)	4 days	1	-	1 day	Severe	NA	Recovery
Infants (or toddlers) (from 1 month [28 days] to 23 months)							
Acetaminophen (N=7)	6 months (58 days – 18 months)	5	2	1 day	Severe (2) ALF (2) NA (3)	Hepatocellular (2) NA (5)	Recovery (6) Death (1)
Children (from 2 years to 11 years)							
Acetaminophen (N=13)	NA[a]	4	6	1 day (N=3)	Mild (1) Moderate (2) ALF (10)	NA (13)	Recovery (13)
TMP-SMZ (N=4)	6 years (2 – 8 years)	2	2	25 days	Severe (1) NA (3)	Hepatocellular (1) Cholestatic (1) NA (2)	Recovery (3) LTx (1)
Valproic acid (N=15)	4.9 years (1.1 – 8.8 years)	11	4	NA	ALF (1) NA (14)	Hepatocellular (14) NA (1)	Death (14) LTx (1)
Amoxicillin-clavulanate (N=1)	2 years 9 months	1	-	24 days	NA	Cholestatic	LTx
Adolescents (from 12 years to less than 18 years)							
Acetaminophen (N=2)	15.5 years (14 – 17 years)	1	1	10 hours (N=1)	ALF (1) NA (1)	NA (2)	Recovery (1) LTx (1)
Valproic acid (N=2)	15 years (12 – 17 years)	1	1	NA	NA (2)	Hepatocellular (2)	Death (2)
TMP-SMZ (N=1)	17 years	1	-	28 days	Moderate	Hepatocellular	Recovery

ALF: acute liver failure; DILI: drug-induced liver injury; LTx: liver transplantation; NA: Not available; TMP-SMZ: trimethoprim-sulfamethoxazole.

[a] One child was two years old, six children were aged a median of 2.2 years old, one child was four years old, three children aged ≤5 years, one child was six years old, and the remaining child was aged nine years.

Table S2. Prospective and retrospective studies on idiosyncratic drug-induced liver injury in the paediatric population.

	United States (n=57)[a] [46]	**Spain (n=33)**[b] [47]	**India (n=39)**[c] [48]	**China (n=69)**[c] [49]
Age, years (median, range)	14.3 (1.7-17.9)	2.7 (0.1-16)	16 (2.6-17)	8 (0.2-14)
Female, %	67	47	44	33
Jaundice, %	53	-	79	59
Fever, %	37	-	41	32
Rash, %	25	-	41	22
Hospitalization, %	63	-	82	100[e]
Duration of therapy (median) (days)	55	9.5	30	-
Liver injury pattern, %				
Hepatocelular	82	56	54	90
Cholestatic	8	19	26	2.9
Mixed	10	25	21	7.2
Major culprit drugs, %				
	Minocycline (19); valproate (11); azithromycin, isoniazid, trimethoprim-sulfamethoxazole (7.0)	Amoxicillin-clavulanate (31); ibuprofen, isoniazid (8.3)	Anti-tuberculous drugs (22); phenytoin (10); carbamazepine (5)	Chinese herbal medicines (22); anti-tuberculosis agents, macrolides (8.7)
Causality assessment method	CIOMS/RUCAM	CIOMS/RUCAM	CIOMS/RUCAM	CIOMS/RUCAM
Liver parameters at DILI recognition, median (range)				
Aspartate aminotransferase (IU/L)	380 (26-3,400)	-	258 (25-1,857)	434 (145-968)[f]
Alanine aminotransferase (IU/L)	411 (33-4,185)	-	323 (12-5,647)	649 (215-1,125)[f]
Alkaline phosphatase (IU/L)	203 (62-1,177)	-	258 (81-1,695)	287 (224-419)[f]
Total bilirubin (mg/dL)	3.3 (0.2-34)	-	5.1 (0.7-31)	4.1 (0.5-14.8)[f]
INR	1.2 (0.9-3.9)		1.5 (0.8-12)	-
Severity, %				
Mild	35		-	-
Moderate	41[d]		-	-
Severe	19	5.6	-	-
Fatal/liver transplant	5	2.8	31	8.7
Liver-related death, n (%)	0 (0)	1 (2.8)	12 (31)	2 (2.9)
Liver transplantation, n (%)	3 (5)	1 (2.8)	0 (0)	0 (0)

Anti-tuberculosis drugs: isoniazid, rifampicin, pyrazinamide and ethambutol; CIOMS/RUCAM: Council for International Organizations of Medical Sciences / Roussel Uclaf Causality Assessment Method; INR: International Normalized Ratio; macrolides: azithromycin, roxithromycin.

[a] Data from the Drug Induced Liver Injury Network (DILIN).

[b] There were 36 DILI episodes. Three episodes were accidental re-exposure. Percentages are based on the number of DILI episodes.

[c] Data from single-center studies.

[d] Severity of DILI in 18% of cases was moderate, and for the 23% of cases were moderate-hospitalized.

[e] Data collected from hospitalized patients.

[f] Peak values. Data are presented as median and interquartile range.