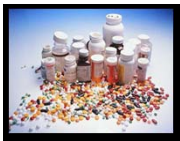
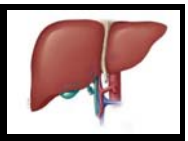




Drug Induced Liver Injury (DILI): Challenges and Opportunities

Robert H. Squires, MD
Professor of Pediatrics
University of Pittsburgh

Overview

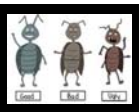
- General aspects of drug-induced liver injury
- Pathogenesis
- Drug-Induced Liver Disease Network
- Examples
  - Minocycline
  - Acetaminophen
  - OxyELITE Pro
- Reporting

LiverTox
Clinical and Research Information on Drug-Induced Liver Injury
www.LiverTox.nih.gov

Scope of the Problem

- Definition is difficult
  - Lack of systematic reporting
  - Unknown denominator of those taking the drug
  - Inconsistent post-marketing testing
  - Lack of consensus of liver test abnormalities
  - Arbitrating the culprit with multiple medications
  - Co-morbidities (e.g., NAFLD)
- Incidence estimated 13—19 / 100,000

Classification



- Intrinsic
  - Predictable, affects everyone
  - Short latency period
  - Dose related
  - Acetaminophen
- Idiosyncratic
  - Unpredictable, susceptible
  - Longer latency period
  - Not dose dependent; >50 mg/d
  - Amoxacillin/clavulanate, isoniazid
- Biochemical pattern
  - Hepatocellular
  - Cholestatic
  - Mixed
- Immune vs non-immune
  - Rash, eosinophilia, systemic
  - Autoimmune markers
  - Latency period
- Histologic features

Histologic Patterns in DILI

Autoimmune Hepatitis	Steatosis / Steatohepatitis	Cholestatic Hepatitis
INH PTU Nitrofurantoin Minocycline Statins Hydralazine Methyldopa	Corticosteroids Antidepressants Amiodarone Methotrexate Valproate Linezolid Zidovudine	Penicillins Cephalosporine Amox/Clavulanate Rifampin Methimazole Many others
Carbamazepine Phenytoin Sulfonomides Interferon INH Mesalamine	Azathioprine Thioguanine Vitamin A Methotrexate Mercaptopurine Didanosine	INH Amox/Clavulanate Phenytoin Statins Green Tea Other Herbals
Granulomatous Hepatitis	Nodular Regenerative Hyperplasia	Acute Hepatitis

Histologic Patterns in DILI

Autoimmune Hepatitis	Steatosis / Steatohepatitis	Cholestatic Hepatitis
INH PTU Nitrofurantoin Minocycline Statins Hydralazine Methyldopa	Corticosteroids Antidepressants Amiodarone Methotrexate Valproate Linezolid Zidovudine	Penicillins Cephalosporine Amox/Clavulanate Rifampin Methimazole Many others
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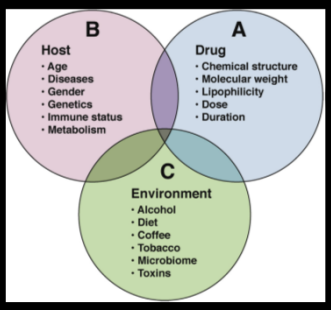
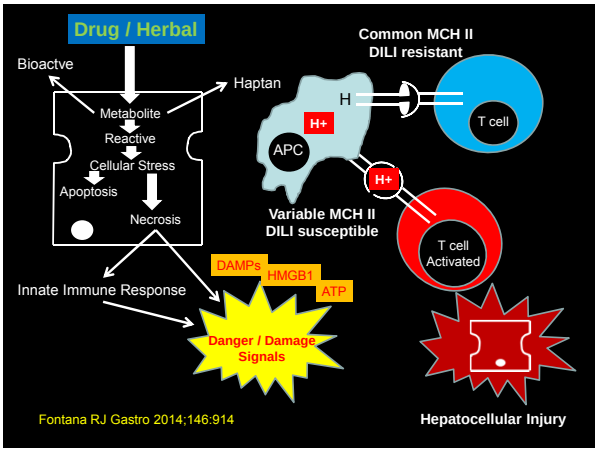
Granulomatous Hepatitis	Nodular Regenerative Hyperplasia	Acute Hepatitis

Pathogenesis of DILI

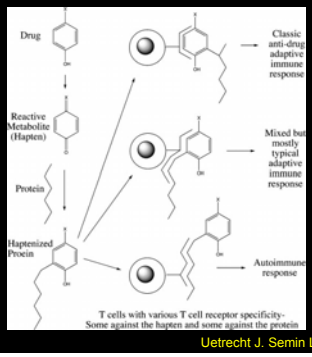


Fontana RJ. Gastroenterology 2014;146:914



Fontana RJ Gastro 2014;146:914

Variability in T-cell Receptor Specificity May Drive Clinical Response



Uetrecht J. Semin Liver Dis. 2009;29:383

DILI with Immune Features

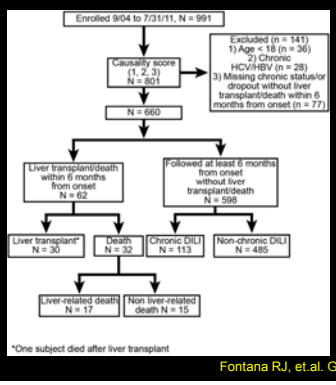
Feature	Immuno-Allergic	Autoimmune
Latency	Short, <30 days	Variable, >3 mo to years
Symptoms	Fever, rash, urticaria, pruritis, arthralgia, Stevens-Johnson, toxic epidermal necrolysis, liver failure	RUQ pain, anorexia, nausea, vomiting, extra-hepatic autoimmune features (joints,GI, renal), liver failure
Laboratory	Eosinophilia	High IgG, (+) autoantibodies
Histology	Lobular and portal inflammation, eos, granuloma, cholestatic/hepatic features	Lobular / portal inflammation, interface hepatitis, lympho-histiocytic and plasma cell infiltrate
History	Allergies-50%	Other autoimmune disease
Outcome	Gradual improvement, chronic DILI is rare, vanishing bile ducts reported	Brisk response to steroids, often weaned within 6 months, no recurrence after weaning
Re-exposure	Rapid; more severe	Gradual, months.
Drugs	Erythromycin, macrolides, PCN, phenytoin, sulfonamides	Statins, minocycline, hydralazine, procainamide

deLemos AS, et.al. Semin Liver Dis. 2014;34:194

New Opportunities for Diagnosis

- Biomarkers
  - Micro RNAs: miR-192, miR-122 Hepatology 2011;54:1767
  - IL-28B genotyping
- Proteomics Aliment Pharmacol Ther. 2012;35:600
  - Apoprotein E
  - Gelsolin, complement C7, amyloid P, age
- Genomics
  - IL-28B for interferon
  - HLA-B*1502 and HLA-A*3101 for carbamazepine
- Protein adducts Hepatology 2011;53:567

DILIN-Adult: Study Population



Fontana RJ, et.al. Gastro 2014;147:96

DILIN Causality Assessment

Score	Likelihood (%)	Description
1 Definite	>95	Injury is typical of drug/herbal
2 Highly likely	75-95	Evidence is clear and convincing; not definite
3 Probable	50-74	Supported by a preponderance of evidence
4 Possible	25-49	Cannot definitely exclude the possibility
5 Unlikely	<25	Highly unlikely base on available information
6 Insufficient	N/A	

Fontana RJ, et.al. Drug Safety 2009;32:55

Roussel Uclaf Causality Assessment Method (RUCAM)

- Type of liver injury
- Time of onset related the first or subsequent exposure
- Duration of exposure to the drug
- Rapidity of ALT decline after stopping drug
- Risk factors
  - Ethanol use
  - Age over 50 years
- Other drug exposures
- Other possible diagnoses
  - Viral hepatitis, biliary obstruction, hypotension, ETOH, biliary obstruction
- Is the drug known to be hepatotoxic
- Was the patient re-exposed to the drug

DILI Experts vs RUCAM

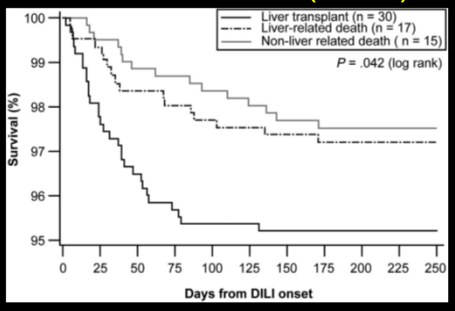
Table 7. Cross-Tabulation of Initial DILIN Causality Scores Against Categorized RUCAM Scores[a]

DILIN Expert Opinion Process	RUCAM: Highly Probable	Probable	Possible	Unlikely	Excluded	Total
Definite	80	72	41	0	0	193
Very Likely	38	100	70	4	0	212
Probable	10	35	33	7	1	86
Possible	2	10	18	8	6	44
Unlikely	2	3	5	3	9	22
Total	132	220	167	22	16	557

[a]This table is restricted to cases in which a single agent was implicated (n = 187 cases). RUCAM scores were missing for 4 reviews, and this resulted in 557 reviews.

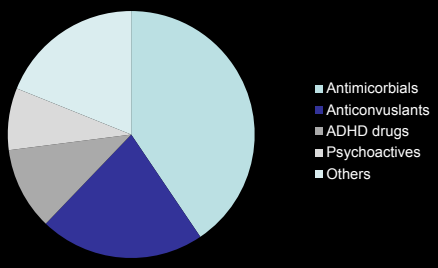
Rockey DC, et.al. Hepatology 2010;51:2117

DILIN-Adult: Adverse Outcomes within 6 months (n=62)



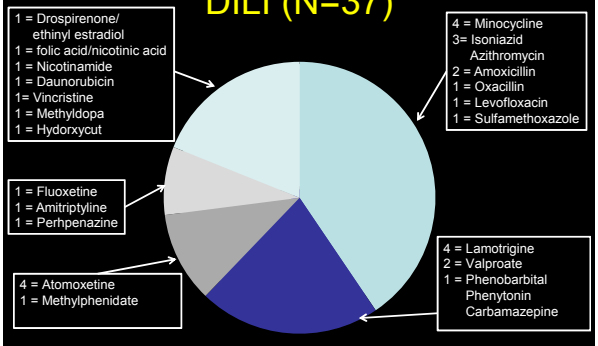
Fontana RJ, et.al. Gastro 2014;147:96

Implicated Agents for Pediatric DILIN (N=37)



Molleston JP, et.al JPGN 2011;53:182

Implicated Agents for Pediatric DILI (N=37)



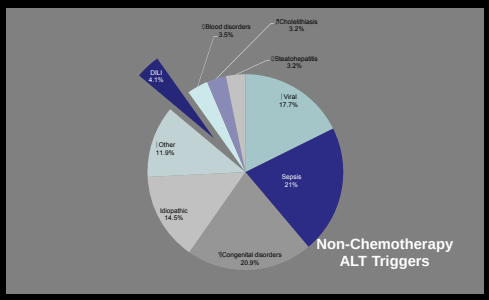
Molleston JP, et.al JPGN 2011;53:182

EMR-based Method to Detect DILI in Children (Abstract #284)

- Drug Safety Service at Children's Mercy Hospital (Kansas City) to detect adverse drug reactions
- Biochemical triggers
  - ALT >5x ULN
  - Total bilirubin > 1.5 x ULN
- Adjudication
  - Staff physician / pharmacologist
    - Drug of known risk of hepatotoxicity
    - Liver injury / recovery in relation to drug exposure / withdrawal
    - No other known cause of liver injury
  - RUCAM

Habiger C, Fischer R, et. al NASPGHAN Abstract #284

Conditions meeting ALT Triggers (excluding chemotherapy agents)



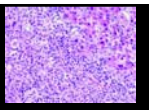
Habiger C, Fischer R, et. al NASPGHAN Abstract #284

DILI: Children's Mercy Hospital

#	Suspected agent	Age (yrs)	Sex	Type	Peak ALT	Peak ALP	Peak Bili	RUCAM
1	Minocycline	15.5	F	Hepatocellular	839	288	1	8
2	Carbamazepine	17.9	F	Hepatocellular	814	66	0.3	6
3	Trimethoprim-sulfamethoxazole	1.4	M	Hepatocellular	944	209	0.2	9
4	Trimethoprim-sulfamethoxazole	14.9	F	Hepatocellular	427	297	5	8
5	Minocycline	14.8	F	Mixed	93	90	0.6	6
6	Doxycycline	17.8	F	Hepatocellular	337	91	0.6	8
7	Oxacillin	6.3	M	Hepatocellular	848	222	0.4	7
8	Cefepime	0.2	M	Hepatocellular	4129	704	4.8	4
9	Methotrexate	5.3	F	Mixed	163	210	0.5	4
10	Aripiprazole	10.9	M	Cholestatic	105	425	0.6	5
11	Sulfasalazine	5.2	F	Hepatocellular	425	193	0.9	7
12	Lamotrigine	17	F	Cholestatic	346	261	5.9	4
13	Minocycline	15.3	F	Hepatocellular	1763	184	3.9	8

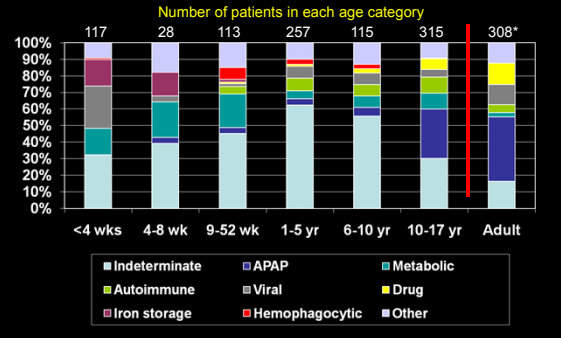
Habiger C, Fischer R, et. al NASPGHAN Abstract #284

Minocycline



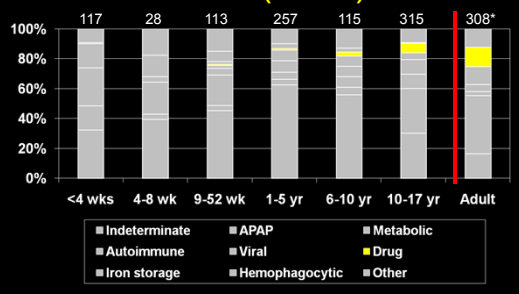
- Age at onset of disease: 16.5 yr (range 13-18)
- Female: 70%
- Duration on minocycline before Sx: 13 mo (range 3-48)
- Duration of Sx before diagnosis: 4.3 mo (range 1-12)
- Cumulative dose: 72 grams (range 18-288)
- Constitutional sx
  - Polyarthralgia, polyarthritis, Raynaud's, a.m. stiffness
- Outcomes (n=27)
  - Transient = 14 (rapid resolution)
  - Intermediate = 6 (resolve within 12 mo)
  - Chronic (active at last f/u)= 7 (31.6 mo; range 13-48)

Etiology of PALF (N = 945)



* Lee, WM Sem Liv Dis. 2003;23:217

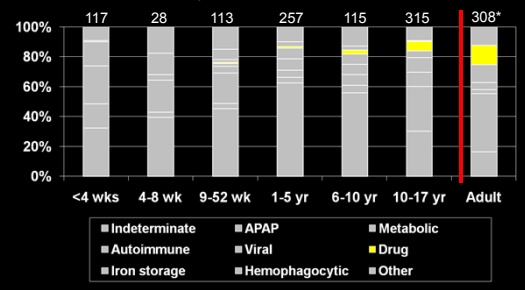
Non-APAP Drug Induced 27/945 (2.9%)



< 12 years

Valproate = 3
Isoniazid = 2
Dilantin = 1
Chemotherpy = 1

L-asparaginase = 1
Trileptal = 1
Methotrexate = 1
Multiple = 1



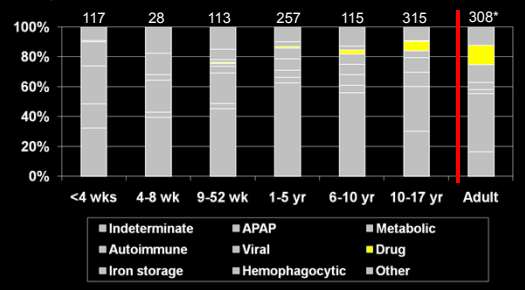
13 – 17 years

Isoniazid = 3
Bactrim = 2
Iron = 2
Ecstasy = 1

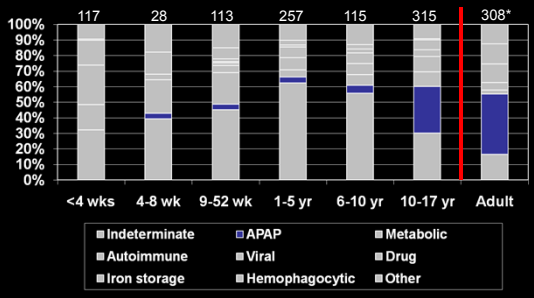
Pemoline (Cylert) = 1
Cytoxin/Dilantin = 1
Dilantin = 1
Anesthetic = 1

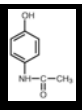
Methamphetamine = 1
Minocycline = 1
Niacin/ETOH = 1
Pravastatin = 1

PTU = 1

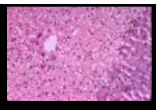


Acetaminophen = 115 (12.2%)

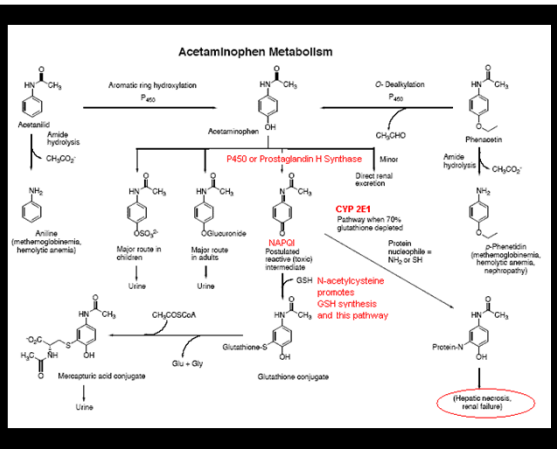




Para-aceTYLaminophENOL
PARA-aCETylAMinophenOL



- First introduced in 1893
- Exposure
  - ~200,000 million people/yr take acetaminophen (APAP)
  - In 2005: US consumers purchased **28 billion doses** of APAP products
  - Maximum daily dose (Adult: 325 or 500 mg/tab; Child: 80 or 160 mg tab or 160 mg/5ml)
    - Adult = 4 gm/d
    - Child = 10-15 mg/kg/dose; 75 mg/kg/d
- Mechanism of action in not well defined
  - Weak inhibitor of cyclooxygenase
- Toxicity
  - Estimated 500 deaths / year from acute ingestion (50% unintentional)
  - Median acute dose is 24 gm; as low as 2.5 gm / day



Chronic APAP Exposure in PALF

- Widely available
- Safe dose: 10-15mg/kg (single), ≤ 5 times per day, 75 mg/kg/d
- ALF in adults with unintentional overdose following exposure to >4-6 gm/day (8-12 extra-strength APAP)
- 895 children grouped by APAP exposure history
  - 83: Chronic Exposure: multiple doses ≥ 2 days
  - 85: Single dose exposure
  - 498: No exposure: No history, measured and undetectable APAP level, final dx that is not APAP toxicity
  - 229: Criteria not met: History of exposure w/o documentation
- Single dose and total daily dose per day recorded

Leonis MA, et.al Pediatrics. 2013;131:e740-e746

APAP Characteristics and Diagnoses

	Chronic Exposure N=83	Acute Exposure N=85	No Exposure N=498
Age (years)			
N	83	85	498
Median	3.5	15.2	3.2
(25th , 75th)	(1.2, 10.1)	(14.3, 16.3)	(0.1, 10.1)
Sex			
Male	45 (54.2%)	15 (17.6%)	278 (55.8%)
Female	38 (45.8%)	70 (82.4%)	220 (44.2%)
Ethnicity			
Not Hispanic or Latino	62 (74.7%)	79 (92.9%)	398 (79.9%)
Hispanic or Latino	21 (25.3%)	6 (7.1%)	100 (20.1%)
Encephalopathy at study entry			
Missing	5 (-)	2 (-)	36 (-)
Grade 0	30 (38.5%)	51 (61.4%)	247 (53.5%)
Grade I	27 (34.6%)	16 (19.3%)	119 (25.8%)
Grade II	9 (11.5%)	5 (6.0%)	46 (10.0%)
Grade III	7 (9.0%)	6 (7.2%)	33 (7.1%)
Grade IV	5 (6.4%)	5 (6.0%)	17 (3.7%)

APAP Characteristics and Diagnoses

	Chronic Exposure N=83	Acute Exposure N=85	No Exposure N=498
Reported APAP dose (mg/kg/d)			
N	63	70	N/A
Median	30.8	258.1	
(25th, 75th)	(15.1, 52.4)	(135.9, 378.4)	
Exposure to other APAP-containing Meds			
n (%)	54 (65.1%)	30 (35.3%)	N/A
Serum APAP Level			
Missing	52 (-)	38 (-)	N/A
< 10 mg/L	10 (32.3%)	16 (34.0%)	
≥ 10 mg/L	21 (67.7%)	31 (66.0%)	
Final Diagnosis			
APAP Overdose	18 (21.7%)	82 (96.5%)	0 (0.0%)
Metabolic	4 (4.8%)	0 (0.0%)	72 (14.5%)
Autoimmune	6 (7.2%)	0 (0.0%)	34 (6.8%)
Infection	7 (8.4%)	0 (0.0%)	51 (10.2%)
Indeterminate	31 (37.3%)	3 (3.5%)	234 (47.0%)
Other	17 (20.5%)	0 (0.0%)	107 (21.5%)

Biochemical Characteristics

	Chronic Exposure N=83	Acute Exposure N=85	No Exposure N=498
INR			
N	72	79	389
Median	2.6	2.2	2.7
(25th, 75th)	(2-4)	(1.7, 3.3)	(2.1, 3.8)
Total bilirubin (mg/dl)			
N	76	75	420
Median	3.2	2.0	13.1
(25th, 75th)	(1.6, 12.8)	(1.1, 3.5)	(5.7, 19.7)
ALT (IU/L)			
N	77	75	363
Median	2384.0	5140.0	855.0
(25th, 75th)	(1038, 4344)	(2600, 7050)	(149, 2067)

21-day Outcome: Chronic APAP Exposure

	Chronic Exposure N=83	Acute Exposure N=85	No Exposure N=498
Death w/o transplantation	10 (12.0%)	2 (2.4%)	78 (15.7%)
Transplantation	17 (20.5%)	5 (5.9%)	174 (34.9%)
Alive w/o transplantation	56 (67.5%)	78 (91.8%)	246 (49.4%)

Leonis MA, et.al Pediatrics. 2013;131:e740-e746

APAP Chronic Exposure in PALF

- Children with CE
  - Dose history revealed doses within the usual daily dose
  - Had lower bilirubin and higher ALT than NE; similar to SE
  - APAP levels were elevated in 67%; 3 were >100 mg/L
  - Clinical outcomes were worse than SE, but better than NE
- Obtaining the dose and frequency of APAP exposure is important
- Characterizing the pharmacokinetics of APAP in the setting of CE in ill children is necessary

Leonis MA, et.al Pediatrics. 2013;131:e740-e746

1,3 dimethylamylamine (DMAA) toxicity

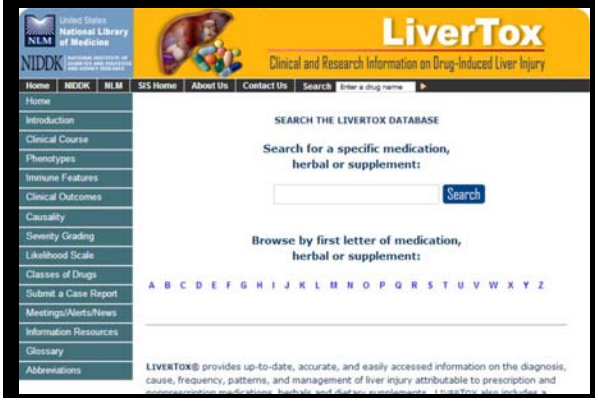
- DMAA banned by FDA
- Sept 2013 Hawaii DOH
  - 7 cases acute liver injury
- National advisory 10/13
- Feb 2013 FDA reported
  - 97 cases
  - 47 hospitalizations
  - 3 liver transplants
  - 1 death

OxyELITE Pro© associated liver injury

Age	Sex	Duration	Total bili (mg/dl)	ALT (IU/ml)	INR	ENC	Outcome
45	F	2 yr	26.4	1,980	3.8	Yes	LTx
28	M	8 wk	32	2,379	3.4	Yes	LTx
19	M	3 yr	1.2	189	1.3	No	Resolved
28	F	4 wk	6.7	1,162	1.2	No	Resolved
23	M	2 yr	17.5	194	--	No	Resolved
23	M	1 wk	6.3	176	0.9	No	Resolved
24	F	1 yr	8	3,348	--	No	Resolved

Diges Dis Sci. 2014

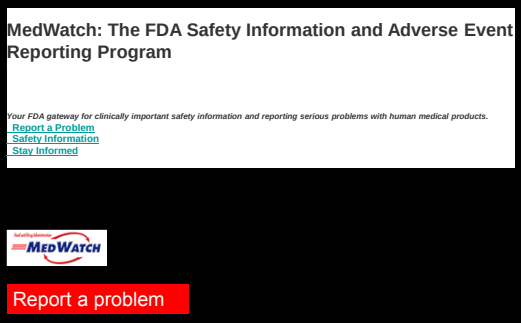
Google "livertox"-- http://livertox.nlm.nih.gov

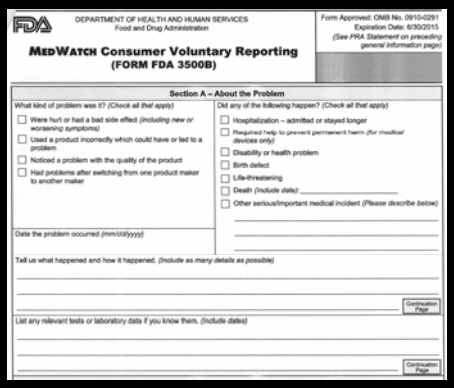


Minocycline

- Overview
- Hepatotoxicity
- Mechanism of injury
- Outcome and Management
- Illustrative case reports
- Product information
- Chemical formula and structure
- Links
  - Recent references on PubMed
  - ClinicalTrials.gov (165 studies)
  - Toxline citations:

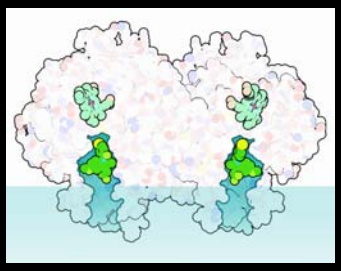
www.fda.gov/saftey/medwatch





Evaluation and Assessment

- Careful drug and supplement use history
- Timing of exposure
- Characterize injury pattern
- Evaluate for alternative liver disease
- Remove the drug
- Monitor response
- Report to MedWatch



Section B – About the Products

Name of the product as it appears on the box, bottle, or package *(Include as many names as you see)*

Name of the company that makes the product

Expiration date *(mm/dd/yyyy)*	Lot number	NDC number

Strength *(for example, 250 mg per 500 mL or 1 g)*	Quantity *(for example, 2 pills, 2 puffs, or 1 teaspoon, etc.)*	Frequency *(for example, twice daily or at bedtime)*	How was it taken or used *(for example, by mouth, by injection, or on the skin)*?

Date the person first started taking or using the product *(mm/dd/yyyy)*: _____

Date the person stopped taking or using the product *(mm/dd/yyyy)*: _____

Why was the person using the product *(such as, what condition was it supposed to treat?)*

Did the problem stop after the person reduced the dose or stopped taking or using the product? ☐ Yes ☐ No

Did the problem return if the person started taking or using the product again? ☐ Yes ☐ No ☐ Didn't restart

Do you still have the product in case we need to evaluate it? *(Do not send the product to FDA. We will contact you directly if we need it.)* ☐ Yes ☐ No

Go to Section D (Skip Section C)

Section D – About the Person Who Had the Problem

Person's Initials	Sex ☐ Female ☐ Male	Age *(at time the problem occurred)* or Birth Date	Weight *(Specify lbs or kg)*	Race

List known medical conditions *(such as diabetes, high blood pressure, cancer, heart disease, or others)*

Please list all allergies *(such as to drugs, foods, pollen, or others)*.

List any other important information about the person *(such as smoking, pregnancy, alcohol use, etc.)*

List all current prescription medications and medical devices being used. Continuation Page

List all over-the-counter medications and any vitamins, minerals, supplements, and herbal remedies being used. Continuation Page

Go to Section E

Characteristics for those with APAP adducts tested and those without

	Participants with APAP adduct tested (n=84) N (%)	Participants without APAP adduct tested (n=100) N (%)	p-value
Age at randomization			0.08
Less than 2 years	24 (28.6)	41 (41.0)	
At least 2 years	60 (71.4)	59 (59.0)	
Coma grade at randomization			0.16
0-1	65 (77.4)	68 (68.0)	
2-4	19 (22.6)	32 (32.0)	
Sex			0.35
Male	43 (51.2)	58 (58.0)	
Female	41 (48.8)	42 (42.0)	
Race			0.95
White	61 (72.6)	72 (72.0)	
African American	13 (15.5)	17 (17.0)	
Other	10 (11.9)	11 (11.0)	
Final diagnosis			0.47
Indeterminate	48 (57.1)	61 (61.0)	
Autoimmune	9 (10.7)	10 (10.0)	
Metabolic	6 (7.1)	12 (12.0)	
Infection	8 (9.5)	6 (6.0)	
Other	13 (15.5)	11 (11.0)	

Drug Induced Liver Injury Network (Adult and Pediatric)

- Inclusion
  - Five Sites: UConnecticut, UCSF, Indiana, UMichigan, UNoCarolinia
  - Over 2 years of age
  - Enrolled within 6 mo of liver injury
  - AST/ALT >5 x ULN or >5 x pre-drug average
  - Total bilirubin >2.5 mg/dl + elevated AST, ALT or SAP
  - INR >1.5 with + elevated AST, ALT or SAP
- Exclusion
  - Acetaminophen toxicity
  - Pre-existing liver disease (e.g., PBC, PSC, AIH, or biliary disease)
  - Liver / bone marrow transplant
  - Identifiable competing cause of liver injury other than HIV, HBV, HCV, unexplained abnormal liver tests

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1-year overall survival, spontaneous survival and transplantation rate for death as a competing risk between those with APAP adducts tested and those without

	Participants with APAP adduct tested		Participants without APAP adduct tested		
	N	Cum. %*	N	Cum. %*	p-value &
1y overall survival	84	78%	100	78%	0.998
1y spont survival	84	45%	100	43%	0.64
1y transplant rate (death as a competing risk event)	84	36%	100	43%	0.39

Note: * Cum. %.= Cumulative percent for survival of 1 year after randomization
+ Cum. Inc.= Cumulative percent of incidence of transplantation within 1 year after randomization for death as a competing risk
& From Log-rank test
# From Chi-square test

Children surviving 1 year tested for APAP adducts

APAP Adduct* (nmol/ml)	NAC (N=68)			Placebo (N=76)		
	Total	No LTx	LTx	Total	No LTx	LTx
Missing	33	16	17	45	24	18
<1	32	16	16	24	16	9
≥ 1	3	1	2	6	6	0

* = APAP adducts levels ≥1 nmol/ml are considered (+)

There were no children who died by 1 year who tested positive for APAP adducts

DILIN Severity Index

Score	Grade	Definition
1	Mild	Elevated ALT/SAP; TB <2.5; INR <1.5
2	Moderate	Elevated ALT/SAP; either TB or INR elevated
3	Mod-Severe	Elevated ALT/SAP; either TB or INR elevated; hospitalized
4	Severe	Elevated ALT/SAP; TB <2.5; + Liver failure or other organ failure due to DILI event
5	Fatal	Death or Liver Transplant
With / without Symptoms: nausea, vomiting, rash, itching, fatigue, weight loss		

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Characteristics for those with APAP adducts tested and those without enrolled in NAC trial

	Participants with APAP adduct tested (n=84) N (%)	Participants without APAP adduct tested (n=100) N (%)	p-value
Age at randomization			0.08
Less than 2 years	24 (28.6)	41 (41.0)	
At least 2 years	60 (71.4)	59 (59.0)	
Coma grade at randomization			0.16
0-1	65 (77.4)	68 (68.0)	
2-4	19 (22.6)	32 (32.0)	
Sex			0.35
Male	43 (51.2)	58 (58.0)	
Female	41 (48.8)	42 (42.0)	
Race			0.95
White	61 (72.6)	72 (72.0)	
African American	13 (15.5)	17 (17.0)	
Other	10 (11.9)	11 (11.0)	
Final diagnosis			0.47
Indeterminate	48 (57.1)	61 (61.0)	
Autoimmune	9 (10.7)	10 (10.0)	
Metabolic	6 (7.1)	12 (12.0)	
Infection	8 (9.5)	6 (6.0)	
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1-year overall survival, spontaneous survival and transplantation rate for death as a competing risk between those with APAP adducts tested and those without

	Participants with APAP adduct tested		Participants without APAP adduct tested		
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1y overall survival	84	78%	100	78%	0.998
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1y transplant rate (death as a competing risk event)	84	36%	100	43%	0.39

Note: * Cum. %.= Cumulative percent for survival of 1 year after randomization
+ Cum. Inc.= Cumulative percent of incidence of transplantation within 1 year after randomization for death as a competing risk
& From Log-rank test
# From Chi-square test

Children who tested positive for APAP adducts in NAC trial

9 / 84 tested positive
All 9 survived to 1 year

6 Placebo
- All with native liver

Diagnosis
- 3 indeterminate
- 1 viral hepatitis
- 1 sepsis

3 NAC
- 2 received LT
- 1 native liver

Diagnosis
- All indeterminate

APAP adducts in PALF participants with indeterminate etiology

	Adduct positive = 20 n(%)	Adduct negative = 169 n(%)	p-value
Hepatic Encephalopathy at Enrollment*			<0.0001
Grade 2 or less	11 (61.1)	154 (91.1)	
Grade 3 or 4	7 (38.9)	12 (8.9)	
Maximum Hepatic Encephalopathy**			0.01
Grade 2 or less	10 (52.6)	128 (77.1)	
Grade 3 or 4	9 (47.4)	38 (22.9)	
Laboratory Value Median (IQR)			
ALT IU/L	5112(3760-8004)	1634(704-2779)	<0.0001
AST IU/L	4608(2136-8120)	1843(713-3415)	0.0007
Total Bilirubin mg/dL	3.7(2.7-4.8)	15.7(8.7-20.7)	<0.0001
Direct Bilirubin mg/dL	1.9(1.2-2.6)	10.9(5.1-14.5)	<0.0001
INR	3.8(2.7-5.9)	2.7(2.2-4.0)	0.02
Creatinine mg/dL	0.8(0.5-1.1)	0.4(0.3-0.7)	0.004
21 day Outcome			
Death without Transplantation	1(5.0%)	18(10.7%)	0.03
Transplantation	4(20.0%)	76(45.0%)	
Spontaneous Survival	15(75.0%)	75(44.4%)	

Outcomes of Participants with Specific Non-APAP Diagnoses

	Adduct Positive N=9	Adduct Negative N=138	
Hepatic Encephalopathy at Enrollment*			0.55
Grade 2 or less	7	118	
Grade 3 or 4	2	15	
Maximum Hepatic Encephalopathy**			0.57
Grade 2 or less	7	105	
Grade 3 or 4	2	25	
Laboratory Value Median (IQR)			
ALT IU/L	2926 (1486-3900)	658 (123-2210)	**0.04**
AST IU/L	3559 (690-4530)	937 (214-2831)	**0.02**
Total Bilirubin mg/dL	3.0 (2.1-3.7)	8.4 (4.1-16.0)	**0.01**
Direct Bilirubin mg/dL	1.6 (0.9-2.0)	4.5 (1.8-9.8)	**0.04**
INR	2.5 (2.0-4.0)	2.6 (2.1-3.3)	0.82
Creatinine mg/dL	0.5 (0.3-1.2)	0.5 (0.4-0.7)	0.71
21 day Outcome			0.61
Death without Transplantation	1	22	
Transplantation	1	31	
Spontaneous Survival	7	85	

Prolonged NAC treatment delays recovery from APAP toxicity in mice

- Treatement group A
  - Saline or APAP (350 mg/kg) by IP injection
  - After 2 hrs, randomized to saline or NAC (100mg/kg/dose) every 12 hrs for 72 hrs
- Treatment group B
  - Randomized to treatment for 24 hrs
- Control group
  - Saline injected but not randomized the treatment
- Outcome
  - All animals sacrificed at 72 hrs
  - Measured AST/ALT, histology, cyclin D1

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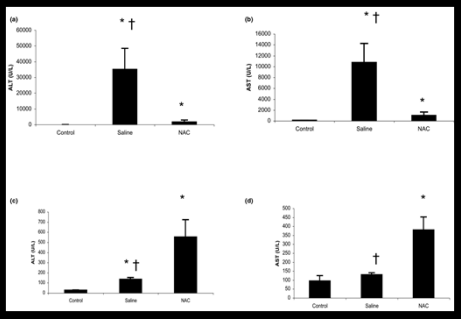
AST/ALT levels after 24 (top) or 72 hrs (bottom) of NAC



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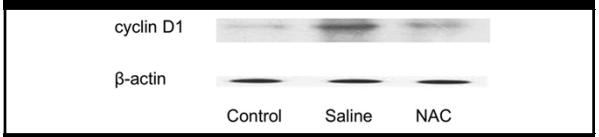
Western blot of liver tissue to assess protein levels of Cyclin D1 after 72 hrs of NAC



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Challenges

- Definition of biochemical profile for DILI
- Multiple medication exposures
- Pathogenesis is multifactorial; "personalized"
- Confounding features (e.g., NAFLD, preexisting condition)
- Lack of systematic reporting

Findings of APAP challenged mice receiving prolonged NAC treatment

- Increased serum ALT/AST
- Increased hepatocyte vacuolation
- Delayed hepatocyte regeneration