藥品肝損傷之診斷
全球最新趨勢及防治

黃以信

Yi-Shin Huang, MD, FACG

台北榮民總醫院胃腸肝膽科特約主治醫師

振興醫院胃腸肝膽科特約醫師

前陽明交通大學醫學院部定教授

衛福部食藥署藥品安全評估諮議小組委員

衛福部食藥署食品廣告標示諮議會委員

前衛福部藥害救濟審議委員會委員

前衛福部藥品諮詢委員會委員

Outline

- Global trend of drug-induced liver injury (DILI)
- Pathogenesis and diagnosis of DILI
- High-risk drugs to induce liver injury
- High-risk factors of incidence and severity in DILI
- Anti-tuberculosis drug-induced liver injury (ATDILI)
- Pharmacogenetics/pharmacogenomics and DILI
- Prevention and treatment of DILI
- Wrap up

Outline

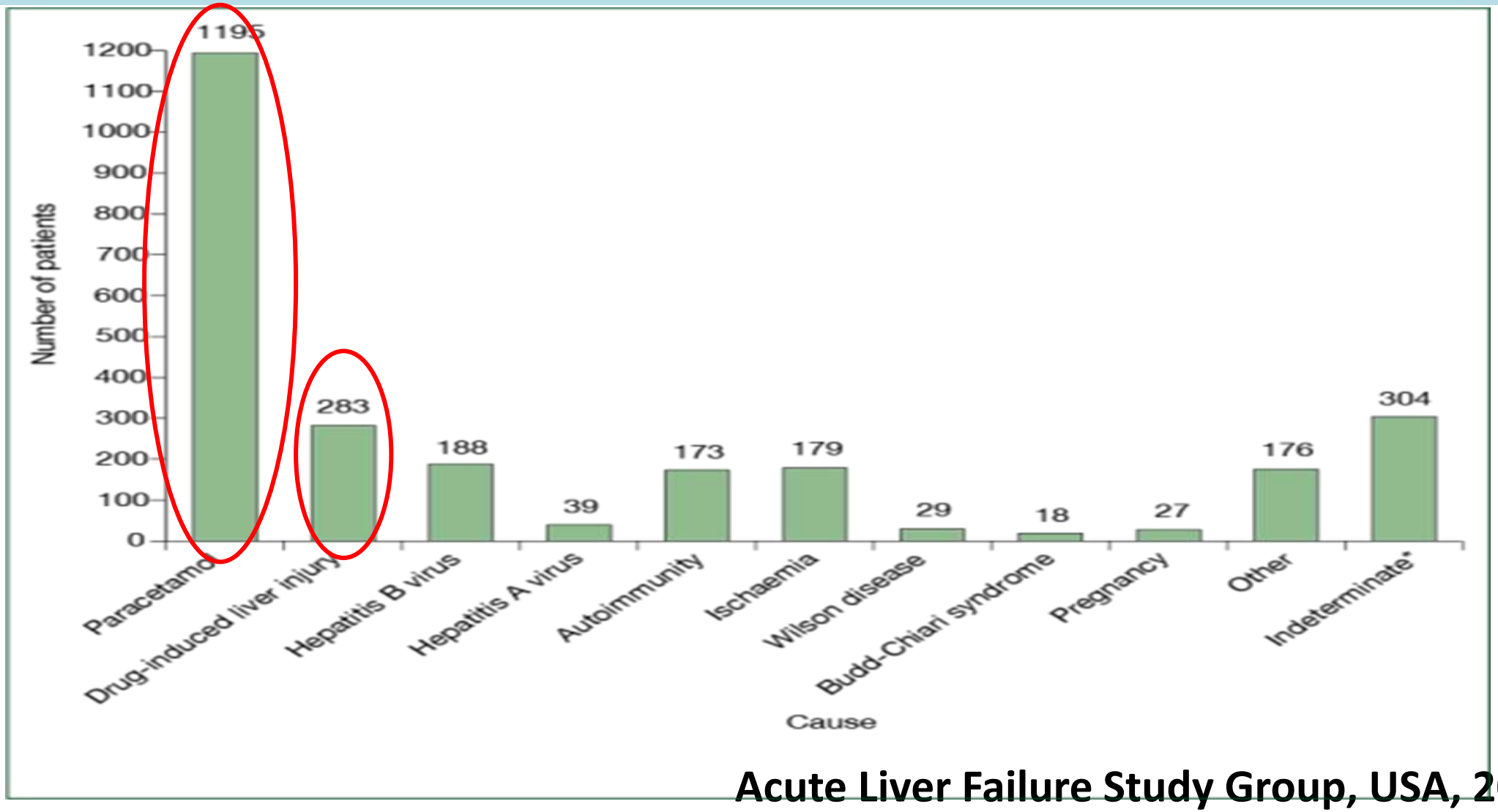
- **Global trend of drug-induced liver injury (DILI)**
- Pathogenesis and diagnosis of DILI
- High-risk drugs to induce liver injury
- High-risk factors of incidence and severity in DILI
- Anti-tuberculosis drug-induced liver injury (ATDILI)
- Pharmacogenetics/pharmacogenomics and DILI
- Prevention and treatment of DILI
- Wrap up

Drug-Induced Liver Injury (DILI)
藥品肝損傷

- DILI may develop ALF and death; is one of the major ADR to withdraw marketed drugs, eg.
  - troglitazone (PPAR for DM)
  - paritaprevir/paritaprevir/ombitasvir (DAA for HCV)
  - ulipristal (progesterone analog for myoma uteri)
  - ketoconazole (anti-fungal)
  - nimesulide (COX-2 NSAID)
- DILI is one of the major cause to stop the trial of developing drugs, eg. ximelagatran (DOAC), bromfenac (NSAID), dilevalol, tasosartan, etc.
- Rare, unpredictable, difficult diagnosis: medical dispute litigation

Acute liver failure in the USA

Drugs were the most common etiologies



Acute Liver Failure Study Group, USA, 2023

Drug-Induced Liver Injury
DILI

- **DILI is the main cause of acute liver failure (ALF) in the US**
- **Viral hepatitis and DILI are the top 2 causes of ALF**
- **There is downward trend of viral hepatitis-induced ALF, and upward trend of drug-induced ALF in most countries**

Jindal A, et al. Liver Int 2022;42:2093–2109

藥害救濟給付案之前五大藥品不良反應統計 (1)

(1999 –2024.3)

*不含預防接種受害救濟案件

不良反應類別	性別		總計	症狀分類	小計
	女	男			
Skin and subcutaneous tissue disorders 皮膚及皮下組織疾患	841	764	1605 (67.21%)	Stevens Johnson Syndrome 史蒂文生氏-強生症候群	830
				Toxic Epidermal Necrolysis 毒性表皮壞死溶解症(包含SJS/TEN overlap)	311
				Drug reaction with Eosinophilia and Systemic Symptoms 藥物疹合併嗜伊紅血症及全身症狀	198
				Other 其他	266
Hepatobiliary disorders 肝膽疾患	86	121	207 (8.67%)	Hepatitis (急性)肝炎	80
				Hepatic failure (急性)肝衰竭	52
				Drug-induced liver injury 藥物性肝傷害	24
				Fulminant Hepatitis 猛爆性肝炎	23
				Other 其他	28
Immune system disorders 免疫系統疾患	89	101	190 (7.96%)	Anaphylactic shock 過敏性休克	147
				Drug hypersensitivity 藥物過敏	26
				Other 其他	17

第1～367次審議會

藥害救濟給付案之可疑藥品前十名 (1999 –2024.3)

排名	藥品成分	案例數
1	Allopurinol	281
2	Phenytoin	159
3	Rifampin/Isoniazid/Pyrazinamide (單方或複方)	151
4	Carbamazepine	144
5	Diclofenac	105
6	Co-trimoxazole	85
7	Ibuprofen	65
8	Lamotrigine	64
9	Sulfasalazine	59
10	Mefenamic acid	58

第1～367次審議會

近年藥害救濟給付案之可疑藥品前十名

2019年~2024年3月 第287～367次審議會

排名	藥品成分	案例數
1	Rifampin/Isoniazid/ Pyrazinamide (單方或複方)	33
2	Sulfasalazine	28
3	Co-trimoxazole	25
4	Allopurinol	24
5	Celecoxib	23
	Diclofenac	23
6	Levofloxacin	20
	Piperacillin/ Tazobactam	20
7	Amoxicillin/ Clavulanate	19
8	Lamotrigine	16
9	Carbamazepine	15
	Ceftriaxone	15
	Etoricoxib	15
	Ibuprofen	15
10	Cephalexin	14

DILI network and Registry all over the word

- USA: DILIN, NIDDK, FDA, AASLD, PhRMA
- International Severe Adverse Event Consortium (iSAEC): International Drug-Induced Liver Injury Consortium (iDILIC)
- Spain: Spanish DILI Registry
- UK: DILINen
- Sweden: National DILI reporting system
- France: National DILI reporting system
- Denmark: National ADR reporting system
- Japan: National DILI study group
- Korea: Multicenter collaboration study group
- Taiwan: Multicenter collaboration study funded by TFDA
- China: National DILI study group

Global DILI guidelines

Received: 07 July 2022 | Accepted: 07 July 2022
DOI: 10.1002/hep.32689

PRACTICE GUIDANCE

OPEN

AASLD practice guidance on drug, herbal, and dietary supplement–induced liver injury

Robert J. Fontana[1] | Iris Liou[2] | Adrian Reuben[3] | Ayako Suzuki[4] | M. Isabel Fiel[5] | William Lee[6] | Victor Navarro[7]

Hepatology International
https://doi.org/10.1007/s12072-021-10144-3

CONSENSUS

Drug-induced liver injury: Asia Pacific Association of Study of Liver consensus guidelines

878 CLINICAL GUIDELINES

CME

ACG Clinical Guideline: Diagnosis and Management of Idiosyncratic Drug-Induced Liver Injury

Hepatology International (2024) 18:384–419
https://doi.org/10.1007/s12072-023-10633-7

GUIDELINES

Chinese guideline for the diagnosis and treatment of drug-induced liver injury: an update

Clinical Practice Guidelines

JOURNAL OF HEPATOLOGY

EASL Clinical Practice Guidelines: Drug-induced liver injury☆

European Association for the Study of the Liver*

·696·

Chin J Integr Med 2018 Sep;24(9):696-706

Chinese Journal of Integrative Medicine

Available online at link.springer.com/journal/11655
Journal homepage: www.cjim.cn/zxyjhen/zxyjhen/ch/index.aspx
E-mail: cjim_en@cjim.cn

Regulation and Guideline

Guidelines for the Diagnosis and Management of Herb-Induced Liver Injury*

Outline

- Global trend of drug-induced liver injury (DILI)
- **Pathogenesis and diagnosis of DILI**
- High-risk drugs to induce liver injury
- High-risk factors of incidence and severity in DILI
- Anti-tuberculosis drug-induced liver injury (ATDILI)
- Pharmacogenetics/pharmacogenomics and DILI
- Prevention and treatment of DILI
- Wrap up

DILI

Pathogenesis

- **Intrinsic toxicity type**: predictable, dose-related, reproducible

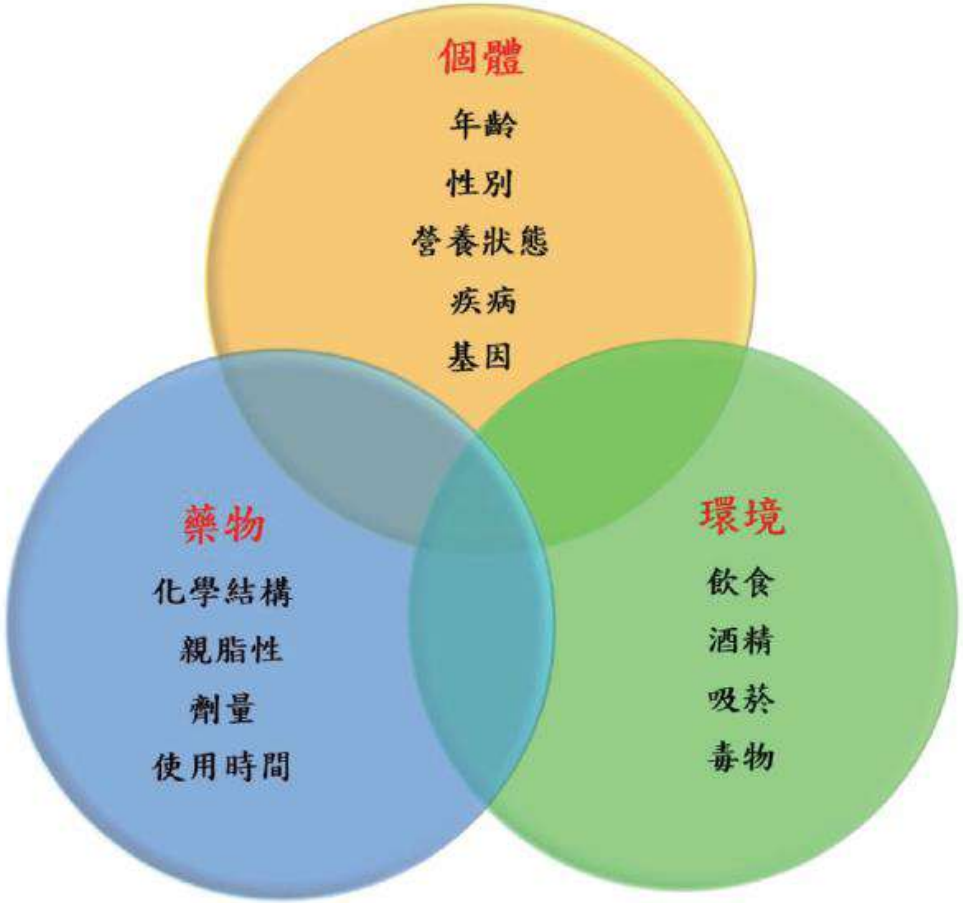
  eg. acetaminophen, methotrexate, bongkrekic acid, CCl_4

- **Idiosyncrasy type**: unpredictable, not dose-dependent, not reproducible: hypersensitivity & metabolic anomaly

  eg. isoniazid, halothane, phenytoin

DILI

Multifactorial



黃以信：藥物性肝損傷：亟需關注的藥物不良反應。台灣醫界2022; 65(2): 79-88

DILI

Clinical types

- **Hepatocellular type**

  ALT > 2X or (X of ALT / X of ALK-P) > 5

  eg. aceteminophen, isoniazid, halothane

- **Cholestatic type**

  ALK-P > 2X or (X of ALT / X of ALK-P) < 2

  eg. chlorpromazine, anabolic steroid

- **Mixed type**

  2 ≤ (X of ALT / X of ALK-P) ≤ 5

  eg. phenytoin, sulfonamide, azathioprine

DILI

Diagnosis (1)

- ALT, ALK-P or Bilirubin > 2X (or ALT > 5X)
- Positive temporal relationship of drug(s) and abnormal LFT: 5-90 days after agent exposure
- Exclusion of viral hepatitis: hepatitis A, B, C, E, EBV, CMV, HSV
- Exclusion of other diseases: alcoholic liver disease, fatty liver, autoimmune hepatitis, primary biliary cholangitis, Wilson disease, hemochromatosis, CHF, shock, hypoxia, sepsis, hepatobiliary stones or tumors

DILI

Diagnosis (2)

- High serum drug level (eg. acetaminophen)
- Liver biopsy may be helpful
- Dechallenge test: decreased ≥ 50% ALT in 30 days
- Rechallenge with caution: doubling ALT
- The Council for International Organizations of Medical Sciences (CIOMS): Roussel Uclaf Causality Assessment Method (RUCAM) (J Clin Epidemiol 1993;46:1323-30)

RUCAM causality assessment of DILI

1. Time to onset — Score

*Before starting drug or more than 15 days after stopping drug	Incompatible Unrelated	
*From the beginning of drug		
5 - 90 days	Suggestive	+2
< 5 or > 90 days	Compatible	+1
*From cessation of drug		
≤ 15 days		+1

RUCAM causality assessment of DILI

2. Course			Score
After cessation of drug, ALT decrease:			
≥ 50%	within 8 days	Highly suggestive	+3
≥ 50%	within 30 days	Suggestive	+2
≥ 50%	after 30 days	Inconclusive	0
< 50%	after 30 days	Against	-2

RUCAM causality assessment of DILI

3. Risk factors	Score
Ethanol	
Presence	+ 1
Absence	0
Age	
≥ 55 years	+ 1
< 55 years	0

RUCAM causality assessment of DILI

4. Concomitant drug(s)	Score
Time to onset incompatible	0
Time to onset compatible but unknown reaction	-1
Time to onset compatible with known reaction	-2
Role proved in this case	-3

RUCAM causality assessment of DILI

5. Non drug causes	Score
Gr I (6 causes): HAV, HBV, HCV, biliary obs, alcoholism, acute hypotension	
Gr II: CMV, EBV, HSV, other underlying diseases	
rule out Gr I & II	+ 2
rule out Gr I	+ 1
rule out 5 or 4 of Gr I	0
rule out <4 of Gr I	- 2
Probable	- 3

RUCAM causality assessment of DILI

6. Previous information of drug	Score
Reaction unknown	0
Reaction published but unlabelled	+ 1
Reaction labelled in the product's characteristics	+ 2

RUCAM causality assessment of DILI

7. Rechallenge		Score
Doubling of ALT with single drug	positive	+ 3
Doubling of ALT with drugs	compatible	+ 1
Increase of ALT but < N	Negative	- 2
or plasma concentration as toxic		+ 3
or validated lab. test: positive		+ 3
negative		- 3

RUCAM causality assessment of DILI

	HEPATOCELLUAR TYPE		CHOLESTATIC OR MIXED TYPE		ASSESSMENT
1. TIME TO ONSET					
Incompatible	Reaction occurred before starting the drug or more than 15 days after stopping the drug (except for slowly metabolized drugs)		Reaction occurred before starting the drug or more than 30 days after stopping the drug (except for slowly metabolized drugs)		UNRELATED
Unknown	When information is not available to calculate time to onset, then the case is				Insufficient data
	Initial Treatment	Subsequent Treatment	Initial Treatment	Subsequent Treatment	Score
From the initiation of the drug					
Suggestive	5 to 90 days	1 to 15 days	5 to 90 days	1 to 90 days	+ 2
Compatible	< 5 or > 90 days	> 15 days	< 5 or > 90 days	> 90 days	+ 1
From cessation of the drug					
Compatible	≤ 15 days	≤ 15 days	≤ 30 days	≤ 30 days	+ 1
2. COURSE	Difference between the peak of ALT and upper limit of normal values		Difference between the peak of alk. phos. (or TB) and upper limit of normal values		
After cessation of the drug					
Highly suggestive	Decrease ≥ 50% within 8 days		Not applicable		+ 3
Suggestive	Decrease ≥ 50% within 30 days		Decrease ≥ 50% within 180 days		+ 2
Compatible	Not applicable		Decrease < 50% within 180 days		+ 1
Inconclusive	No information or decrease ≥ 50%, after the 30th day		Persistance or increase or no information No situation		0
Against the role of the drug	Decrease < 50%, after the 30th day or recurrent increase		Not applicable		- 2
If the drug is continued					
Inconclusive	All situations		All situations		0
3. RISK FACTORS	Ethanol		Ethanol or Pregnancy		
Presence					+ 1
Absence					0
Age of the patient ≥ 55 years					+ 1
Age of the patient < 55 years					0
4. CONCOMITANT DRUG(S)					
None or no information or concomitant drug with incompatible time to onset					0
Concomitant drug with compatible or suggestive time to onset					- 1
Concomitant drug known as hepatotoxin and with compatible or suggestive time to onset					- 2
Concomitant drug with evidence for its role in this case (positive rechallenge or validated test)					- 3
5. SEARCH FOR NON DRUG CAUSES					
Group I (6 causes) = RECENT VIRAL INFECTION WITH HAV (IgM anti-HAV antibody) or HBV (IgM anti-HBc antibody) or HCV (anti-HCV antibody) and circumstantial arguments for non A-non B hepatitis); BILIARY OBSTRUCTION (ultrasonography); ALCOHOLISM (AST/ALT ≥ 2); ACUTE RECENT HYPOTENSION HISTORY (particularly if underlying heart disease)	All causes – groups I and II – reasonably ruled out				+ 2
	The 6 causes of group I ruled out				+ 1
	5 or 4 causes of group I ruled out				0
	Less than 4 causes of group I ruled out				- 2
Group II = Complications of underlying disease(s); Clinical and/or biological context suggesting CMV, EBV or Herpes virus infection	Non drug cause highly probable				- 3
6. PREVIOUS INFORMATION ON HEPATOTOXICITY OF THE DRUG					
Reaction labelled in the product characteristics					+ 2
Reaction published but unlabelled					+ 1
Reaction unknown					0
7. RESPONSE TO READMINISTRATION					
Positive	Doubling of ALT with the drug alone		Doubling of AP (or TB) with the drug alone		+ 3
Compatible	Doubling of ALT with the drugs already given at the time of the 1st reaction		Doubling of AP (or TB) with the drugs already given at the time of the 1st reaction		+ 1
Negative	Increase of ALT but less than N in the same conditions as for the first administration		Increase of AP (or TB) but less than N in the same conditions as for the first administration		- 2
Not done or not interpretable	Other situations		Other situations		0
				TOTAL (add the encircled figures)	

- ≤ 0 excluded
- 1 - 2 unlikely
- 3 - 5 possible
- 6 - 8 probable
- ≥ 9 highly probable

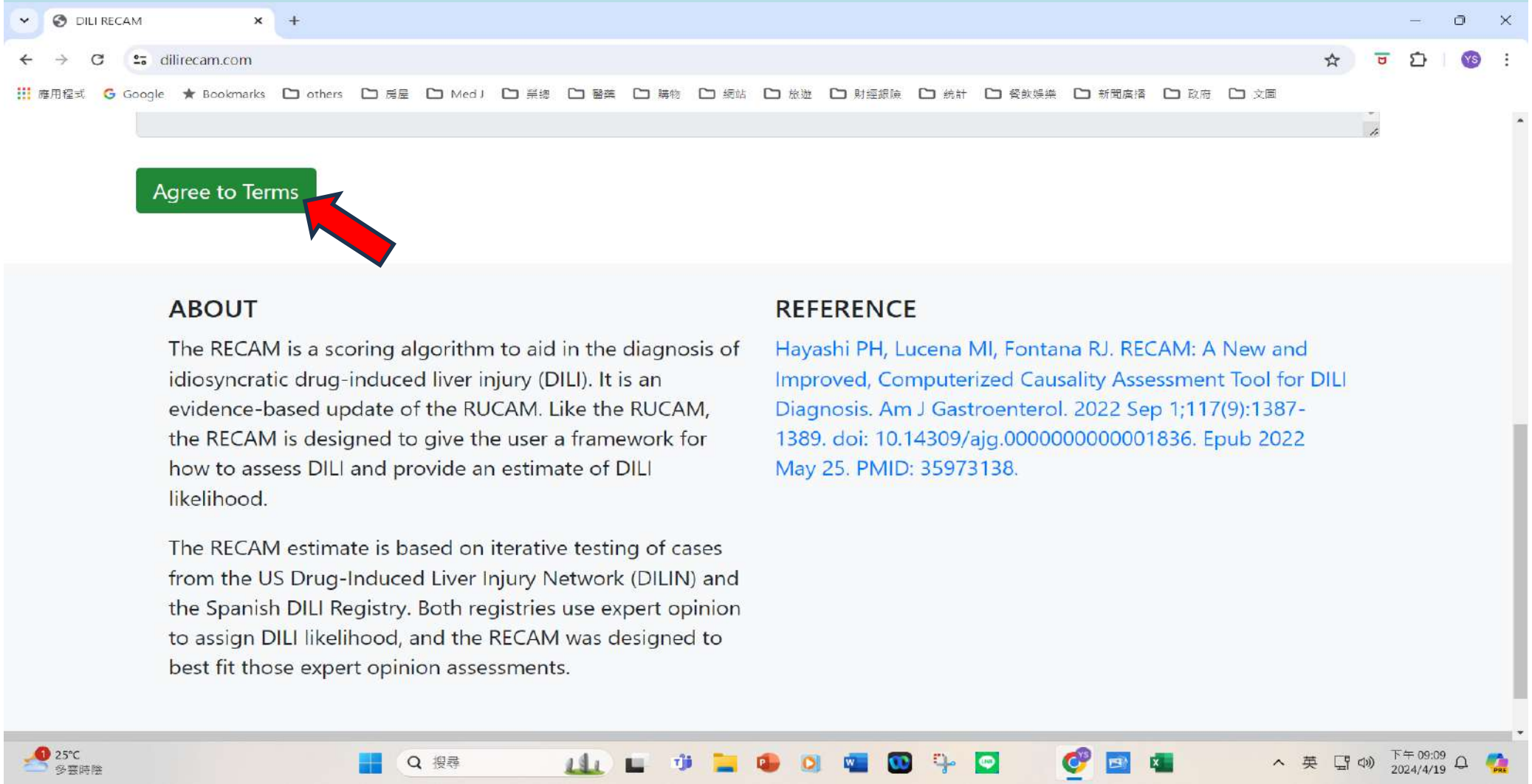
J Clin Epidemiol 1993;46:1323-30

Causality Assessment for DILI

- Naranjo score: good for ADR other than DILI
- RUCAM (Roussel Uclaf Causality Assessment) by CIOMS (Council for International Organizations of Medical Scientists)
- Modified RUCAM from Portugal: Maria and Victorino Clinical Diagnostic Scale (CDS): extrahepatic manifestations: rash, fever, arthralgia, eosinophilia, cytopenia
- Modified RUCAM from Japan: lymphocyte transformation test
- DILIN (Drug-Induced Liver Injury Network) Causality Assessment: expert opinions by experts in US
- RECAM (Revised Electronic Causality Assessment Method): by US DILIN

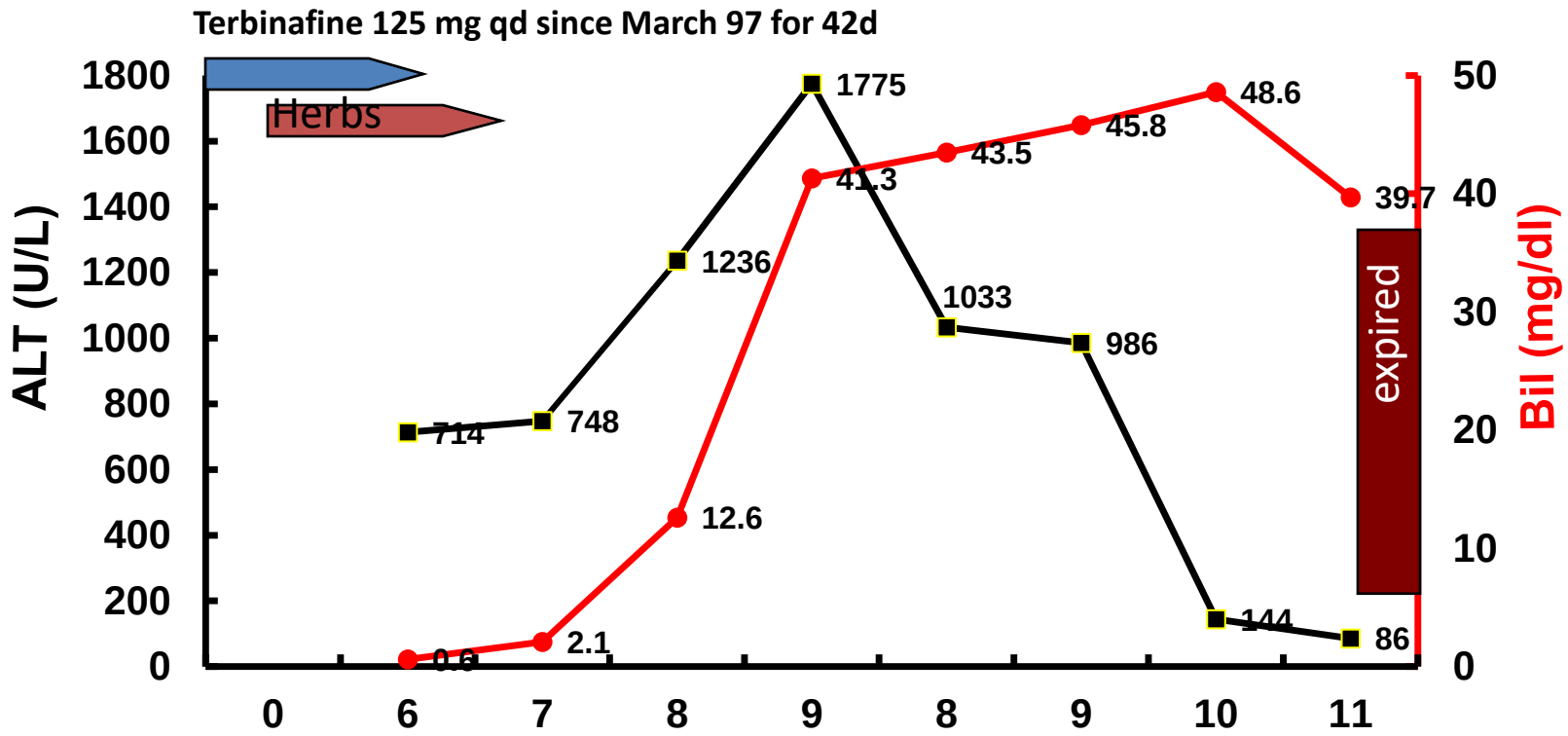
RECAM

Revised Electronic Causality Assessment Method



Anti-fungal drug, terbinafine-induced liver injury mortality case in 1997

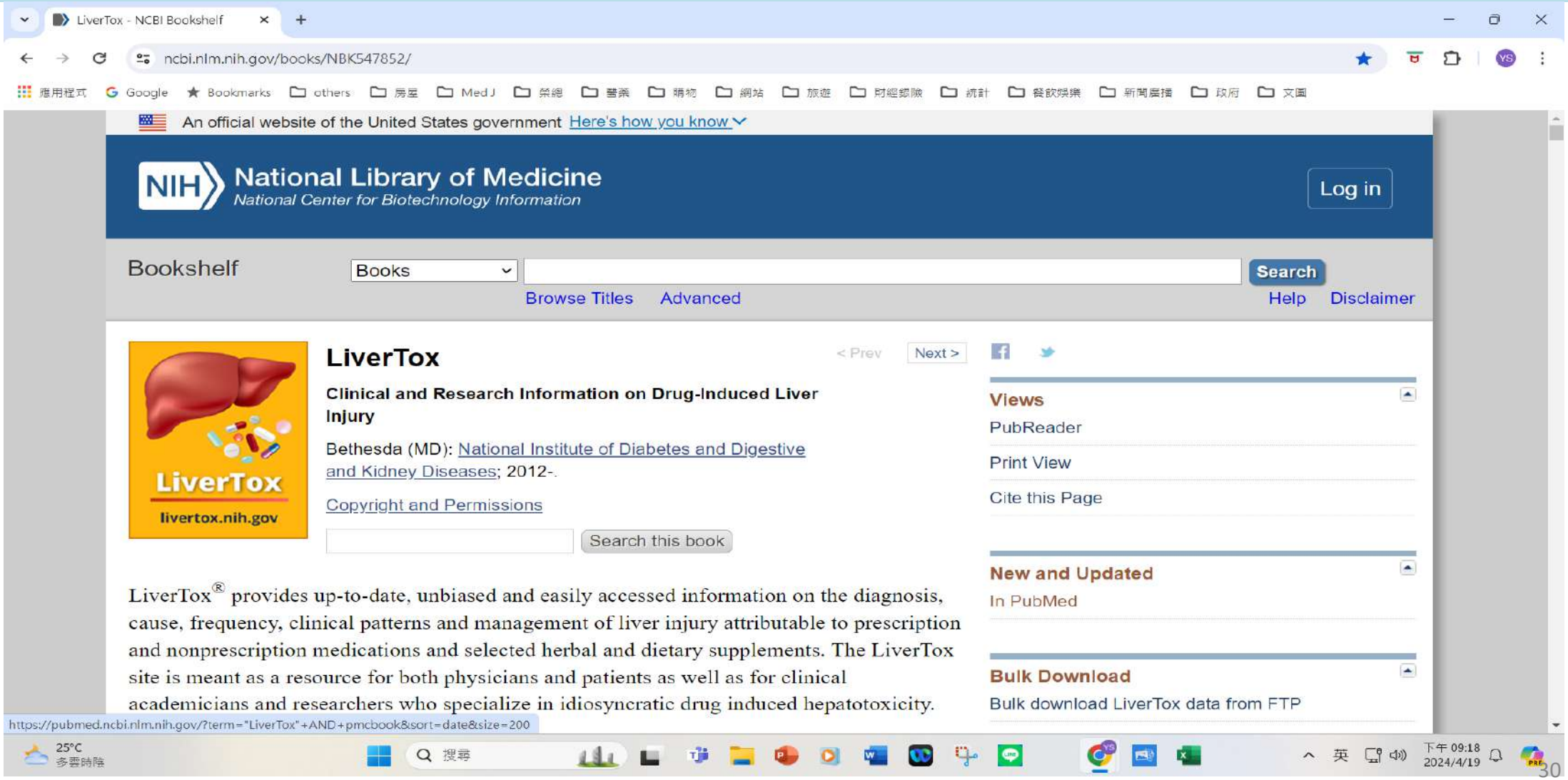
Mr.洪, 40 y/o, tinea pedis



Anti-fungal drug, terbinafine-induced liver injury mortality case in 1997

- HBsAg(+), HBeAg(-), anti-HBe(+), antiHA-IgM (-),
- Anti-HCV(-), anti-EBV-IgM(-), anti-CMV-IgM(-)
- Died of hepatic failure in June 1997
- 家屬向陳市議員陳情訴諸媒體
- 衛生署藥政處召開專家鑑定會議六次
- Final diagnosis: fulminant hepatitis, may be related to Hepatitis B; terbinafine-induced hepatitis is unlikely, according to RUCAM score: 2 --HBV(+), herbs(+)
- 推促台灣藥害救濟制度之成立

LiverTox NIH US

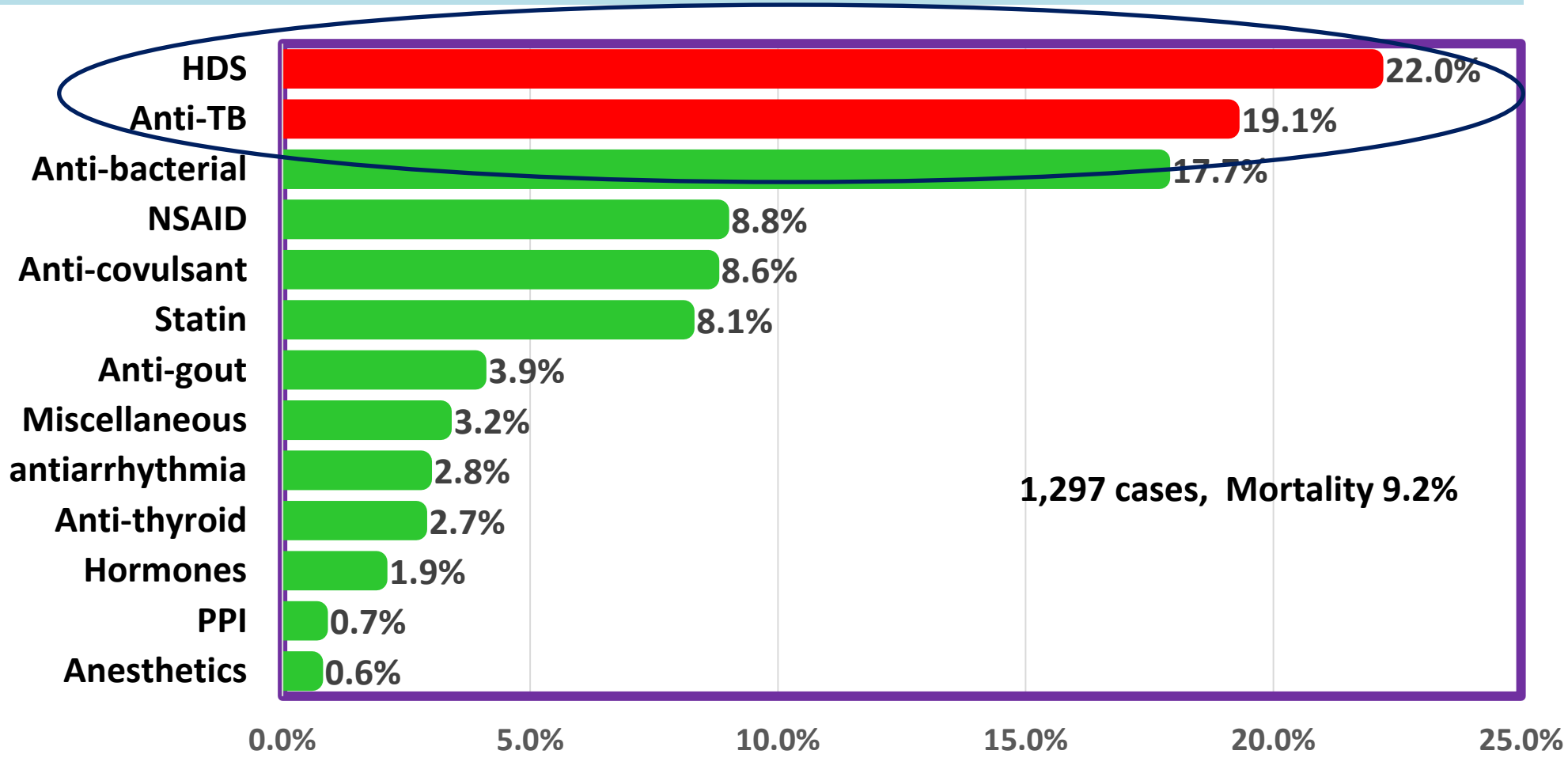


Outline

- Global trend of drug-induced liver injury (DILI)
- Pathogenesis and diagnosis of DILI
- **High-risk drugs to induce liver injury**
- High-risk factors of incidence and severity in DILI
- Anti-tuberculosis drug-induced liver injury (ATDILI)
- Pharmacogenetics/pharmacogenomics and DILI
- Prevention and treatment of DILI
- Wrap up

DILI in Taiwan: a multiple centers study

Herbal and dietary supplements (HDS) & anti-TB



Huang YS, et al. Hepatol Int 2021; 15: 1456-1465

Culprit conventional (Western) drugs of DILI in Taiwan
a multiple centers study

1. Antimicrobials	**481 (47.4%)**
1.1 Antituberculosis agents	257 (25.3%)
isoniazid/rifampicin/pyrazinamide	257
1.2 Antibacterial agents	187 (18.4%)
sulfamethoxazole-trimethoprim	42
amoxicillin-clavulanate	31
minocycline	18
cephalexin	15
others	
1.3 Antifungal agents	33 (3.3%)
ketoconazole	15
terbinafine	12
itraconazole	6
2. Non-steroidal anti-inflammatory drugs	**118 (11.6%)**
diclofenac	43
mefenamic acid	20
ibuprofen	18
others	

3. Anticonvulsants	**112 (11.1%)**
phenytoin	32
carbamazepine	27
valproic acid	23
others	
4. Statins	**105 (10.4%)**
rosuvastatin	20
fluvastain	19
others	
5. Anti-gout agents	**50 (4.9%)**
allopurinol	47
febuxostat	3
6. Anti-arrhythmia agents	**35 (3.5%)**
amiodarone	29
dronedarone	6
7. Anti-thyroid agents	**34 (3.4%)**
propylthiouracil	21
carbimazole	13

Huang YS, et al. JCMA 2022; 85: 286-94
Huang YS, et al. Hepatol Int 2021; 15:1456-65

Prospective study of DILI in Japan 2010-2018

Therapeutic class	No. of cases	Percentage
Anti-inflammatory drugs	62	11
Antimicrobial drugs	59	11
Anticancer drugs	55	10
Dietary supplements	50	9
Drugs for the gastrointestinal system	49	9
Drugs for psychiatric and neurological systems	43	8
Chinese herbal medicines	34	6
Drugs for the cardiovascular system	34	6
Anti-allergy drugs	27	5
Hematopoietic and anticoagulant drugs	23	4
Antilipidemic drugs	21	4
Others	89	16

HDS
15% (84/546)

Aiso M, et al. Hepatol Res 2019; 49: 105–110

HDS was the principal cause of DILI in Korea

Table 2. Classification of causative agents

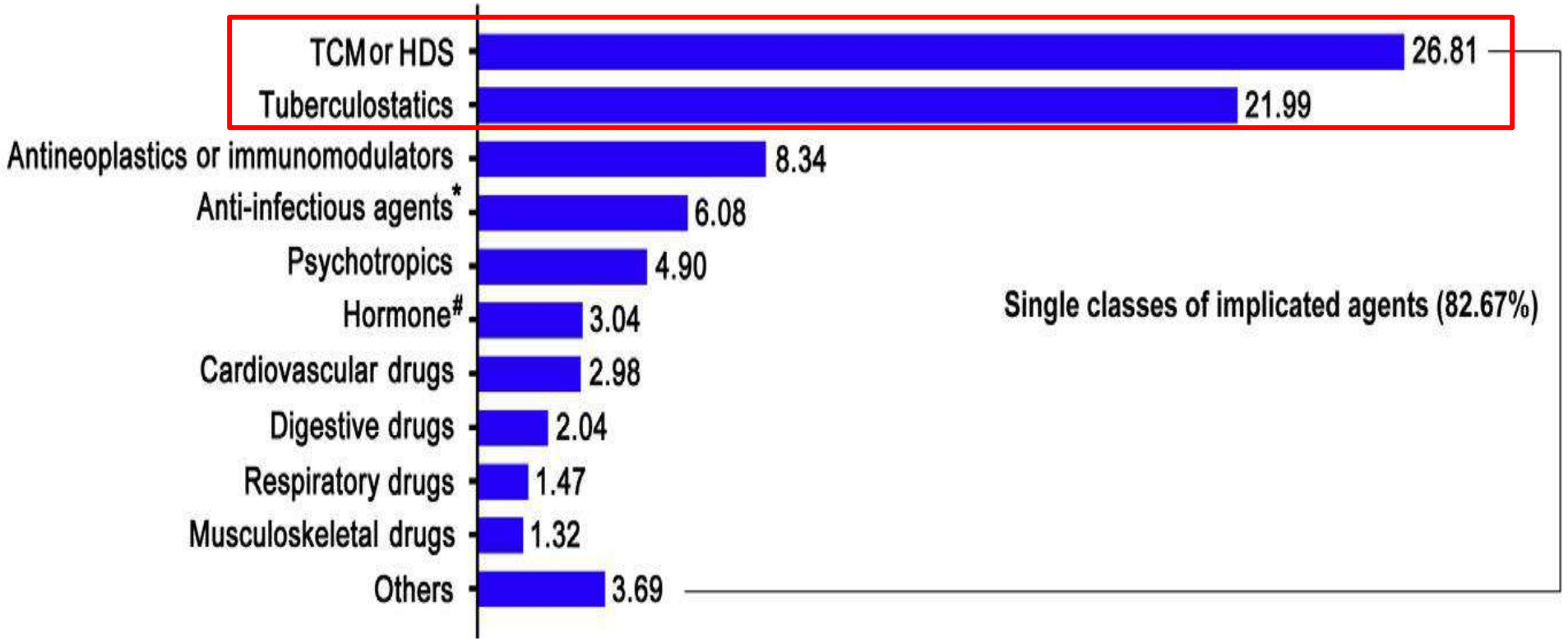
Etiology		*N* (%)
"Medications"	"Prescription medications"	77 (20.8)
	"Non-prescription medications"	24 (6.5)
"Herbs"	"Herbal medications"	102 (27.5)
	"Herbal preparations"	12 (3.2)
	"Medicinal herbs or plants"	35 (9.4)
"Health foods or dietary supplements"		51 (13.7)
"Folk remedies"		32 (8.6)
"Combined"		30 (8.1)
Others		8 (2.2)

N, number.

62.5% (232/371)

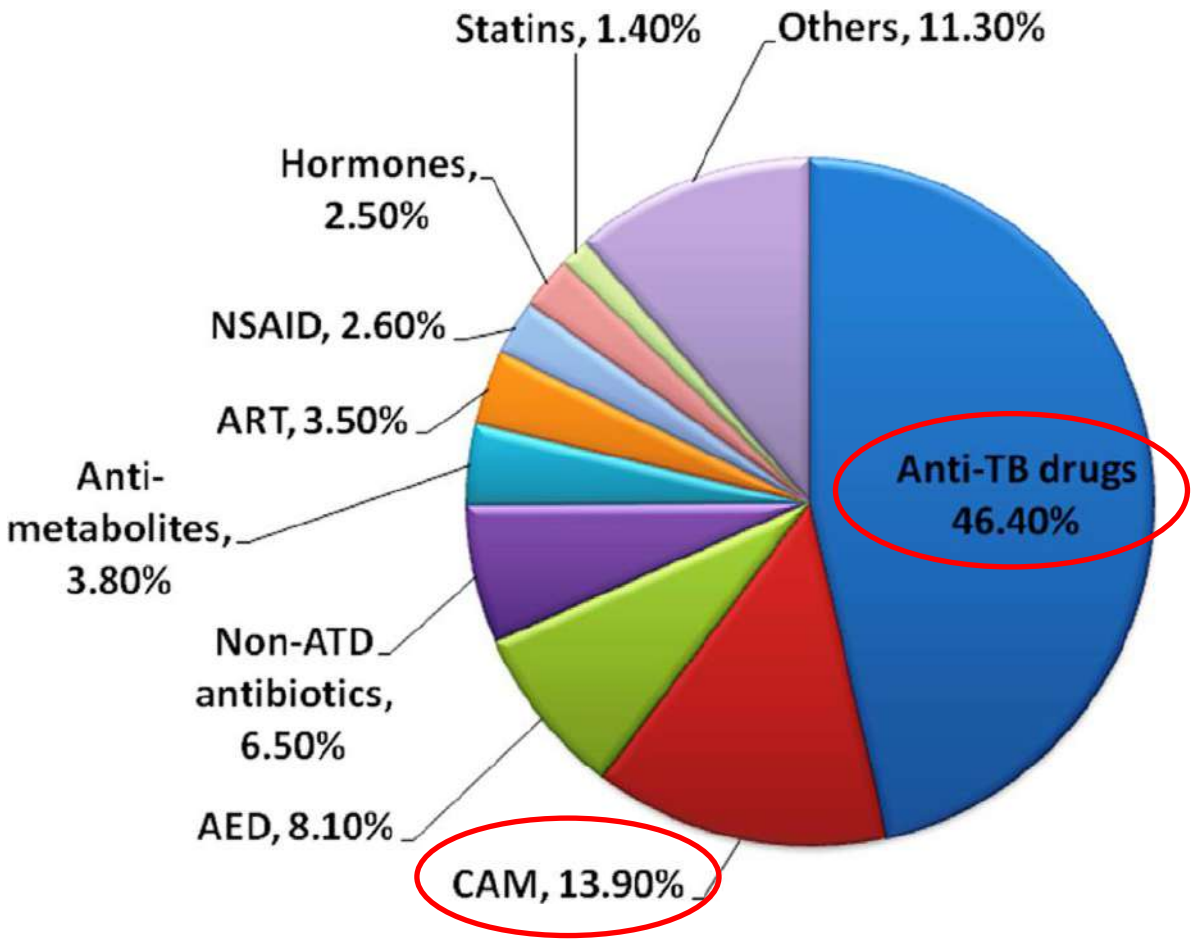
Suk KT, et al. Am J Gastroenterol 2012; 107:1380–1387

Culprit drug categories of retrospective DILI study in China



Shen T, et al. Gastroenterology 2019;156:2230–2241

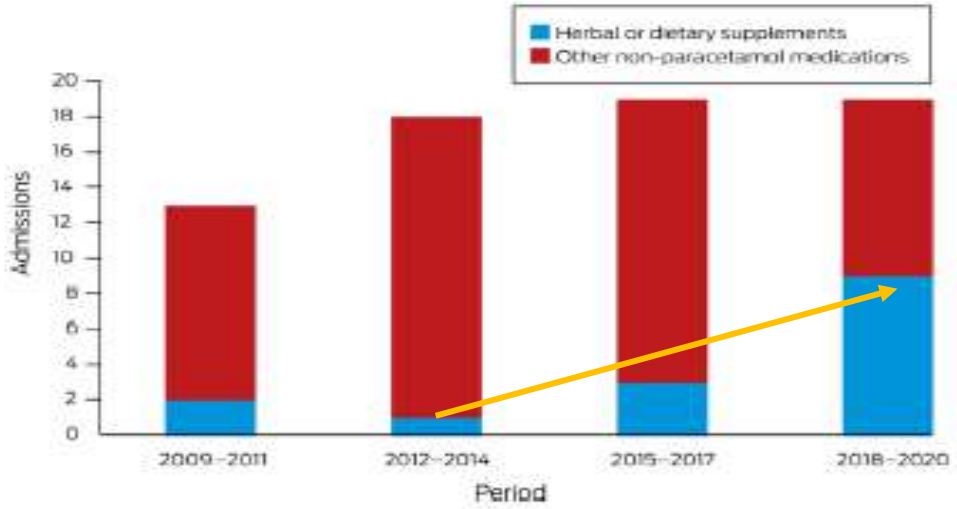
The Indian Network of DILI



Devarbhavi H, et al. J Clin Exp Hepatol 2021; 11: 288–298

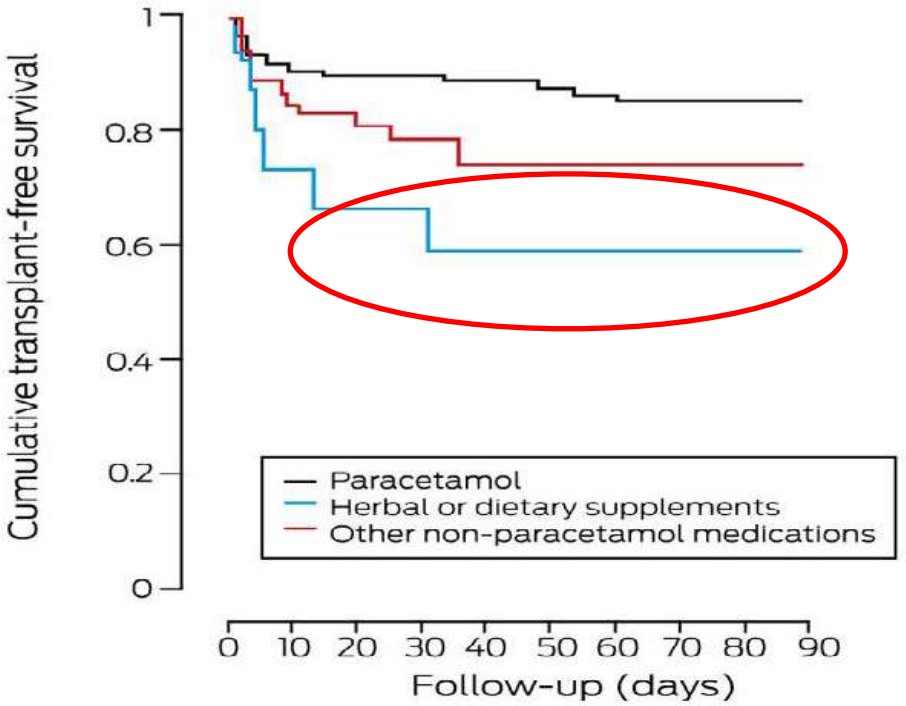
DILI in Australia, 2009–2020:
Secular trend of increasing proportion of HDS

- **HILI** has **increased** since 2009



- Almost half the patients with **HILI** had **non-European** ethnic backgrounds

- **HILI** had lower survival rate than **CILI**



Nash E, et al. Med J Aust 2021; 215: 261-268

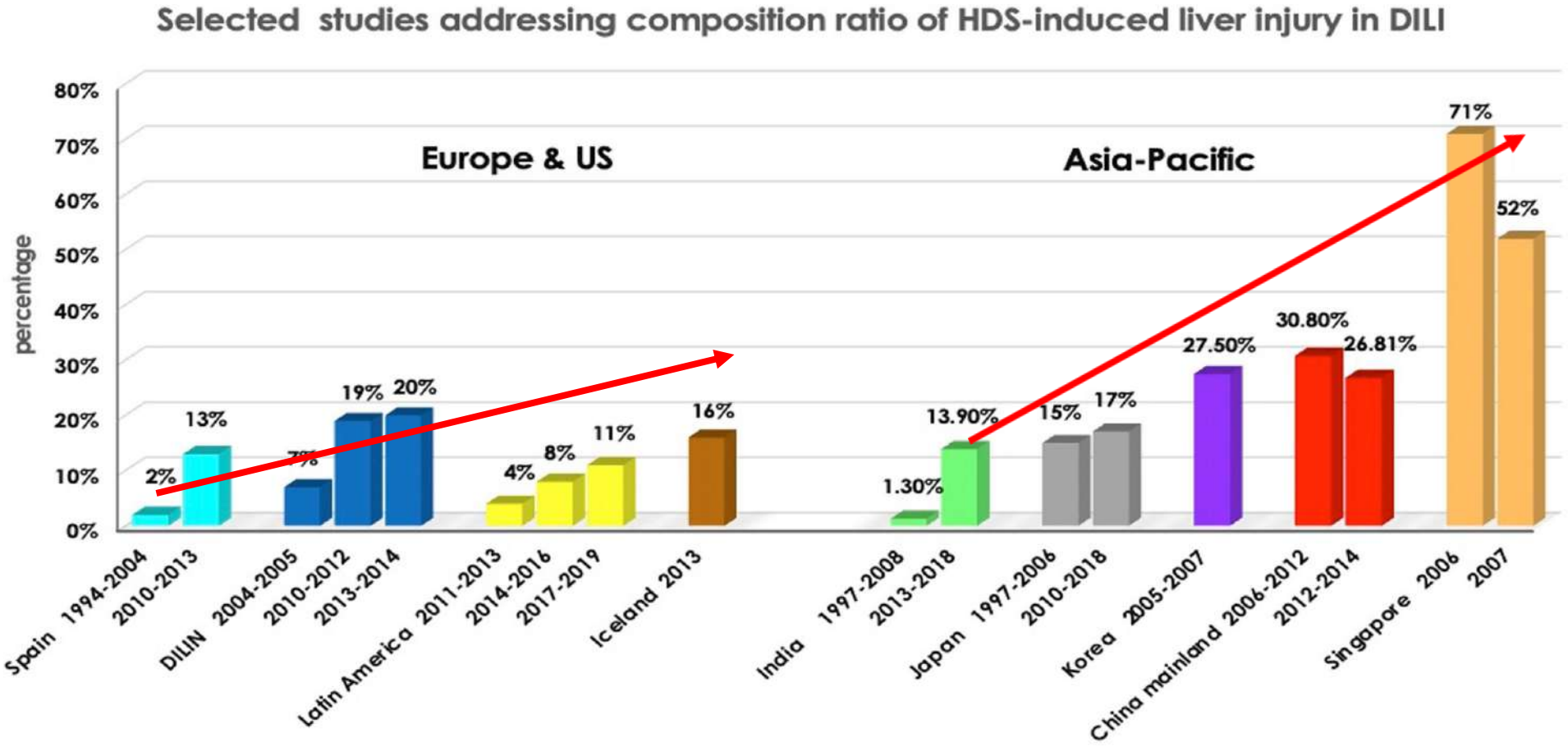
Drug-induced acute-on-chronic liver failure (ACLF) study in Asian Patients

APASL ACLF working party

- Drugs were important causes of ACLF in Asia-Pacific, predominantly from HDS, followed by anti-TB drugs
- Patients with drug-induced ACLF had poorer liver function and higher mortality (46.5%) than non-drug-induced ACLF (38.8%) (*P* = 0.007)

Devarbhavi, H, et al. Am J Gastroenterol 2019;114:929–937

Secular increasing percentage of HDS-induced liver injury (HILI) in DILI worldwide, esp. in Asia-Pacific



Li X, et al. Liver Int 2022; 42: 1999-2014

Top 10 Therapeutic Classes and Individual Agents to Cause DILI in US DILIN

	Therapeutic classes	n		Individual agents[a]	n
1	Antimicrobials	408	1	Amoxicillin-clavulanate	91
2	Herbal and dietary supplements	145	2	Isoniazid	48
3	Cardiovascular agents	88	3	Nitrofurantoin	42
4	Central nervous system agents	82	4	Sulfamethoxazole/ trimethoprim	31
5	Anti-neoplastic agents	49	5	Minocycline	28
6	Analgesics	33	6	Cefazolin	20
7	Immunomodulatory	27	7	Azithromycin	18
8	Endocrine	20	8	Ciprofloxacin	16
9	Rheumatologic	13	9	Levofloxacin	13
10	Gastrointestinal	12	10	Diclofenac	12

[a]Herbal and dietary supplements are not included. Also, in cases of multiple implicated agents, the primary implicated agent was considered for this analysis.

Gastroenterology 2015;148:1340–1352

The prospective multi-national European DILI study (n = 246)

J (Anti-infective for systemic use)	74 (37%)
J01 (Antibacterials for systemic use)	66 (89%)
J04 (Antimycobacterials)	7 (9.5%)
J05 (Antivirals for systemic use)	1 (1.4%)
L (Antineoplastic and immunomodulating agents)	50 (25%)
L01 (Antineoplastic agents)	33 (66%)
L04 (Immunosuppressants)	17 (34%)
M (Musculo-skeletal system)	9 (4.5%)
N (Nervous system)	14 (7.0%)
N01 (Anaesthetics)	1 (7.1%)
N02 (Analgesics)	3 (21%)
N03 (Antiepileptics)	4 (29%)
N06 (Psychoanaleptics)	2 (14%)
N07 (Other nervous system drugs)	4 (29%)
P (Antiparasitic products, insecticides and repellents)	1 (0.5%)
R (Respiratory system)	1 (0.5%)
- (Herbal and dietary supplements, including anabolic androgenic steroids)	12 (6.0%)

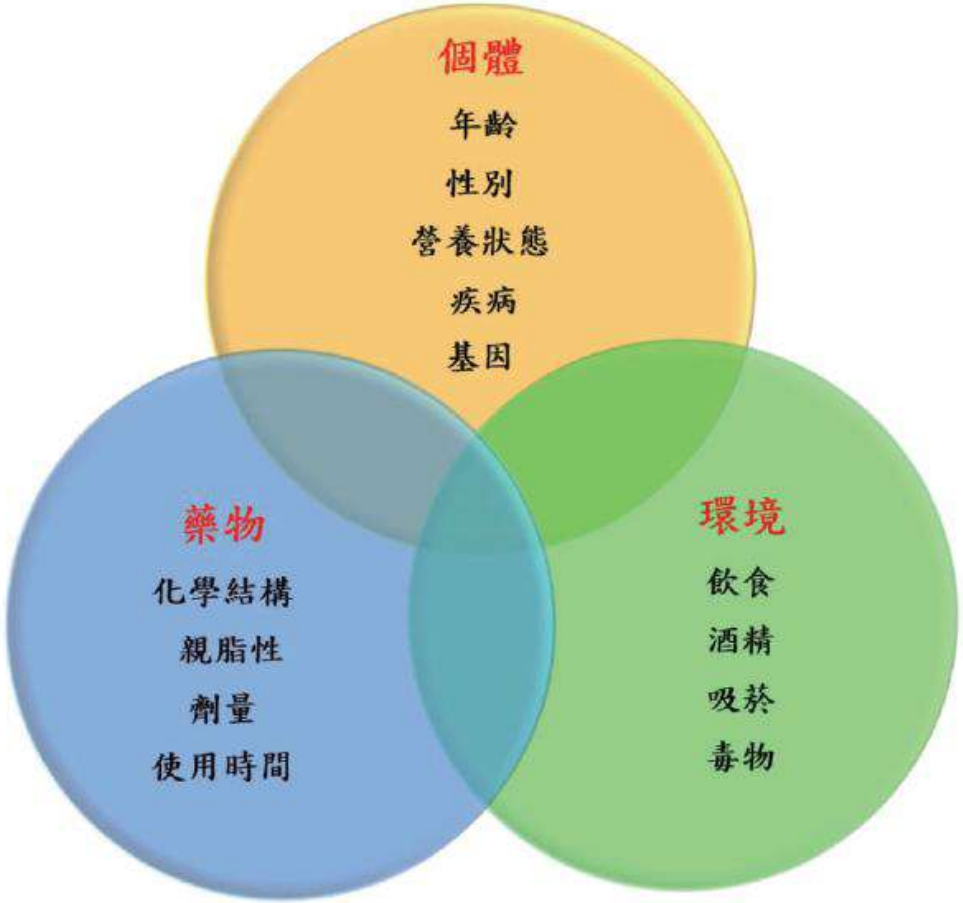
Björnsson ES, et al. Liver Int 2023; 43: 115-126

Outline

- Global trend of drug-induced liver injury (DILI)
- Pathogenesis and diagnosis of DILI
- High-risk drugs to induce liver injury
- **High-risk factors of incidence and severity in DILI**
- Anti-tuberculosis drug-induced liver injury (ATDILI)
- Pharmacogenetics/pharmacogenomics and DILI
- Prevention and treatment of DILI
- Wrap up

Drug-induced Liver Injury (DILI)

Multifactorial



黃以信：藥物性肝損傷：亟需關注的藥物不良反應。台灣醫界2022; 65(2): 79-88

Risk factors of Susceptibility to DILI

- **Elderly:** anti-TB
- **Female:** old age
- **Pregnancy:** anti-TB
- **Ethnicity:** Asian-anti-TB, Caucasian-amoxicillin/clavulanic acid, African American-sulfa drugs
- **Alcoholic** consumption
- **Chronic viral hepatitis:** HBV, HCV
- **Fatty liver:** tamoxifen, MTX
- Underlying **liver diseases**
- **AIDS:** anti-TB
- **Malnutrition**
- **Polypharmacy**: anti-TB
- **Lipophilicity** of drugs
- **Genetics:** HLA, drug-metabolizing enzyme, transporter

Risk factors of severe outcome in DILI

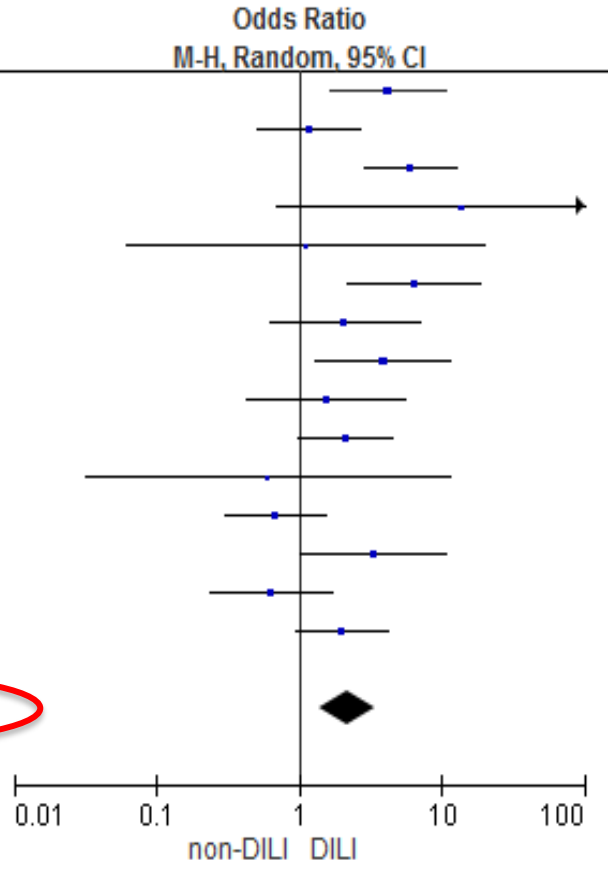
- Elderly: anti-TB
- Alcoholic consumption
- Chronic viral hepatitis: HBV, HCV
- Underlying liver diseases
- Malnutrition
- Polypharmacy: anti-TB
- Severe cutaneous adverse reaction (SCAR)
- Acute kidney injury (AKI)
- Anti-TB drugs
- Herbal and dietary supplements (HDS)
- Jaundice
- Genetics: HLA, drug-metabolizing enzymes, transporters

Chronic hepatitis B infection increases the risk of anti-TB DILI: a meta-analysis

Study or Subgroup	DILI Events	DILI Total	Control Events	Control Total	Weight	Odds Ratio M-H, Random, 95% CI	Year
McGlynn 1986	9	20	59	361	8.1%	4.19 [1.66, 10.55]	1986
Hwang 1997	9	63	22	177	8.7%	1.17 [0.51, 2.71]	1997
Wong 2000	15	41	28	319	9.3%	6.00 [2.85, 12.62]	2000
Patel 2002	3	3	52	155	1.8%	13.80 [0.70, 272.16]	2002
Fernandez-Villar 2003	0	20	8	394	1.9%	1.11 [0.06, 19.89]	2003
Pan 2005	19	53	5	62	7.2%	6.37 [2.18, 18.62]	2005
Lee 2005	9	13	101	194	6.4%	2.07 [0.62, 6.95]	2005
Sun 2009	6	42	9	219	7.1%	3.89 [1.31, 11.59]	2009
Chien 2010	3	25	22	270	6.0%	1.54 [0.43, 5.54]	2010
Wang 2011	11	53	31	283	9.2%	2.13 [0.99, 4.56]	2011
Chan 2012	0	5	18	140	1.9%	0.60 [0.03, 11.34]	2012
Shu 2013	7	111	73	815	8.9%	0.68 [0.31, 1.53]	2013
Lomtadze 2013	5	54	7	234	6.5%	3.31 [1.01, 10.86]	2013
Liu 2014	5	37	70	355	7.8%	0.64 [0.24, 1.69]	2014
Shen 2014	19	35	56	150	9.3%	1.99 [0.95, 4.19]	2014
Total (95% CI)		**575**		**4128**	**100.0%**	**2.18 [1.41, 3.37]**	
Total events	120		561				

Heterogeneity: $Tau^2 = 0.39$; $Chi^2 = 33.72$, df = 14 (P = 0.002); $I^2 = 58\%$

Test for overall effect: Z = 3.52 (P = 0.0004)



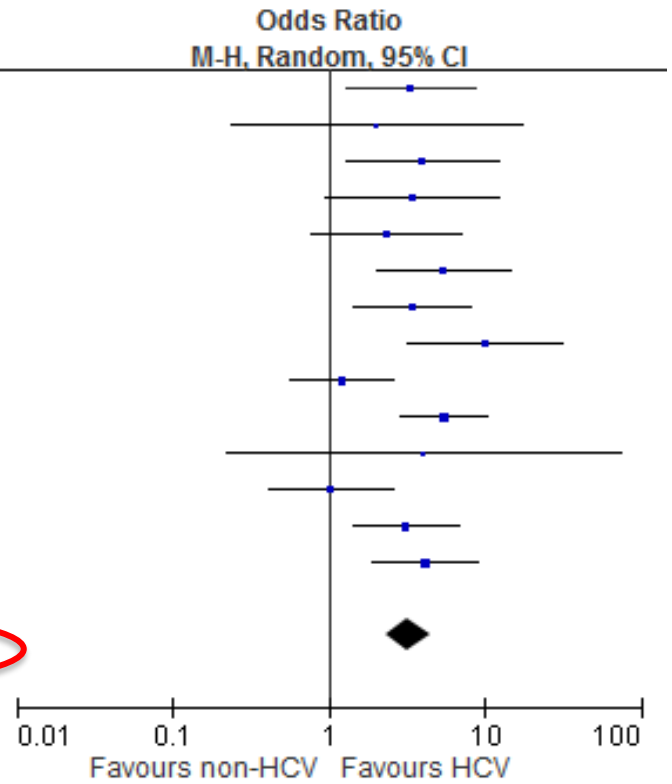
Wang NT, Huang YS, et al. 2016; JCMA; 79:368-374

Chronic hepatitis C infection increases the risk of anti-TB DILI: a meta-analysis

Study or Subgroup	DILI Events	DILI Total	Non-DILI Events	Non-DILI Total	Weight	Odds Ratio M-H, Random, 95% CI	Year
Ungo 1998	12	22	28	106	7.8%	3.34 [1.30, 8.59]	1998
Sadaphal 2001	31	32	107	114	2.2%	2.03 [0.24, 17.12]	2001
Fernandez-Villar 2003	16	20	198	395	6.3%	3.98 [1.31, 12.12]	2003
Kwon 2007	7	11	47	140	5.1%	3.46 [0.97, 12.42]	2007
Sun 2009	5	42	12	219	6.4%	2.33 [0.78, 7.01]	2009
Chien 2010	7	25	18	270	7.3%	5.44 [2.01, 14.73]	2010
Wang 2011	10	68	14	292	8.7%	3.42 [1.45, 8.09]	2011
Chan 2012	10	15	28	168	6.0%	10.00 [3.17, 31.51]	2012
Shu 2013	9	96	39	501	9.9%	1.23 [0.57, 2.62]	2013
Lomtadze 2013	25	54	32	234	11.5%	5.44 [2.84, 10.45]	2013
Mo 2014	0	6	17	940	1.2%	4.06 [0.22, 74.89]	2014
Liu 2014	6	38	65	425	8.1%	1.04 [0.42, 2.58]	2014
Bliven-Sizemore 2015	12	49	23	243	9.7%	3.10 [1.42, 6.77]	2015
Kim 2016	13	38	28	254	9.7%	4.20 [1.93, 9.13]	2016
Total (95% CI)		**516**		**4301**	**100.0%**	**3.21 [2.30, 4.49]**	
Total events	163		656				

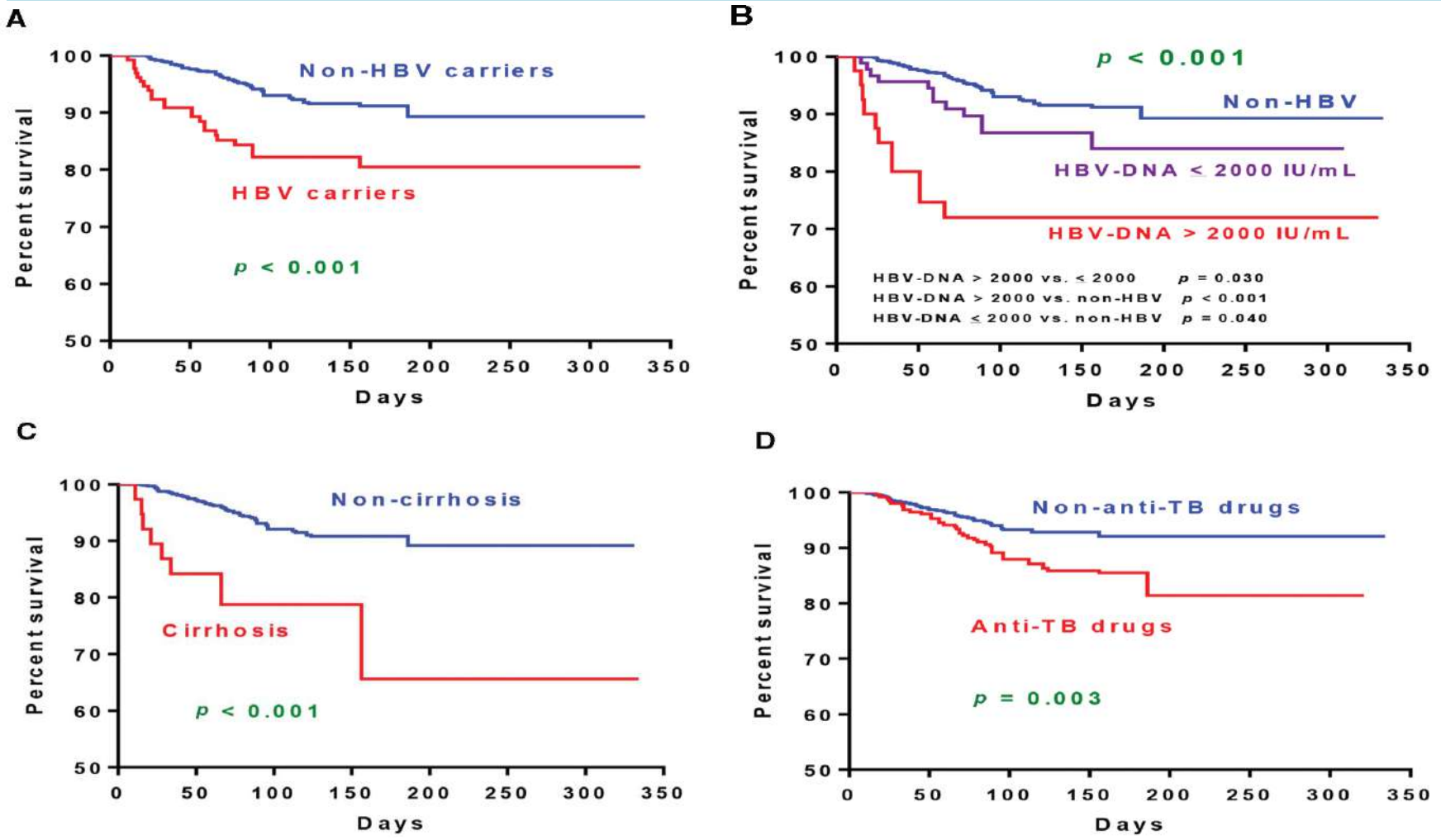
Heterogeneity: $Tau^2 = 0.14$; $Chi^2 = 20.70$, $df = 13$ ($P = 0.08$); $I^2 = 37\%$

Test for overall effect: $Z = 6.83$ ($P < 0.00001$)



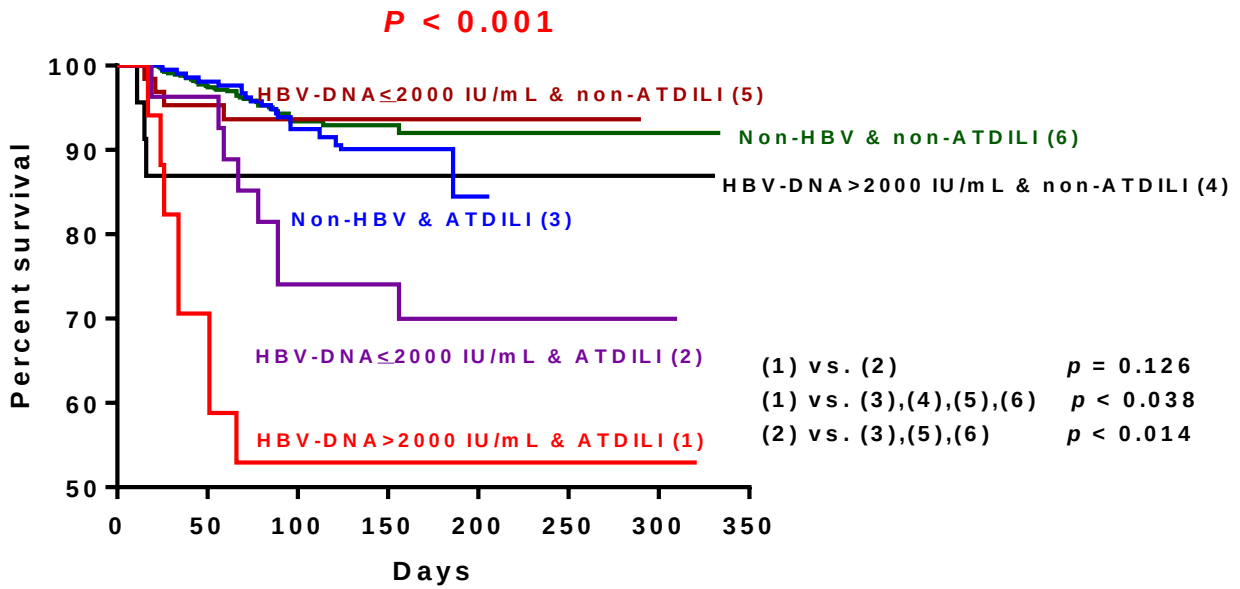
Chang TE, Huang YS, et al. JCMA 2018; 81: 111-118

Factors associated with survival of DILI in Taiwan



Huang YS, et al. JCMA 2022; 85: 286-294

Impact of HBV and anti-TB drugs on the survival of DILI in Taiwan



Number at risk								
(1)	17	14	10	10	4	4	4	0
(2)	27	27	22	19	2	2	2	0
(3)	213	210	199	174	2	1	1	0
(4)	23	19	10	8	5	2	2	0
(5)	64	60	28	16	3	2	1	0
(6)	670	638	234	104	8	3	2	0

Huang YS, et al. JCMA 2022; 85: 286-294

Different categories of HDS to induce liver injury in Taiwan

Category	Contents	
1. Processed herbs	Processed herbal extracts in the form of refined granules, powder, tablets or pills	
2. Crude herbs	Crude raw herbs for decoction	
3. Nutritional supplements	Vitamins, trace elements, amino acids, bodybuilding or weight-reducing agents	
4. Combinations	Combinations of at least 2 of above categories: herbs with nutrients	

Huang YS, et al. Hepatol Int 2021; 15: 1456-1465

Comparison of Different categories of HILI in Taiwan

	Processed herbs (n = 117)	Crude herbs (n = 128)	Nutritional supplements (n = 27)	Combination (n = 13)	*p*
Sex, male	58 (49.6)	78 (60.9)	17 (63.0)	6 (46.2)	0.235
Age (y/o)	56.0 ± 16.5	58.4 ± 14.6	59.4 ± 11.7	55.0 ± 15.2	0.500
Liver tests - peak					
ALT (U/L)	856.1 ± 615.9	912.1 ± 783.4	1029.5 ± 737.3	668.2 ± 565.7	0.436
ALP (U/L)	263.3 ± 180.7	284.7 ± 217.6	224.9 ± 129.5	255.8 ± 175.4	0.497
Bilirubin, total (mg/dL)	7.3 ± 7.4	10.7 ± 9.5	9.2 ± 7.9	6.3 ± 7.6	0.013
MELD score	12.3 ± 4.3	14.1 ± 4.5	13.9 ± 4.1	11.4 ± 4.4	0.005
Jaundice	72 (61.5%)	97 (75.8%)	22 (81.5%)	7 (53.8%)	0.027
Mortality	9 (7.7%)	24 (18.8%)	2 (7.4%)	1 (7.7%)	0.048

Huang YS, et al. Hepatol Int 2021; 15: 1456-1465

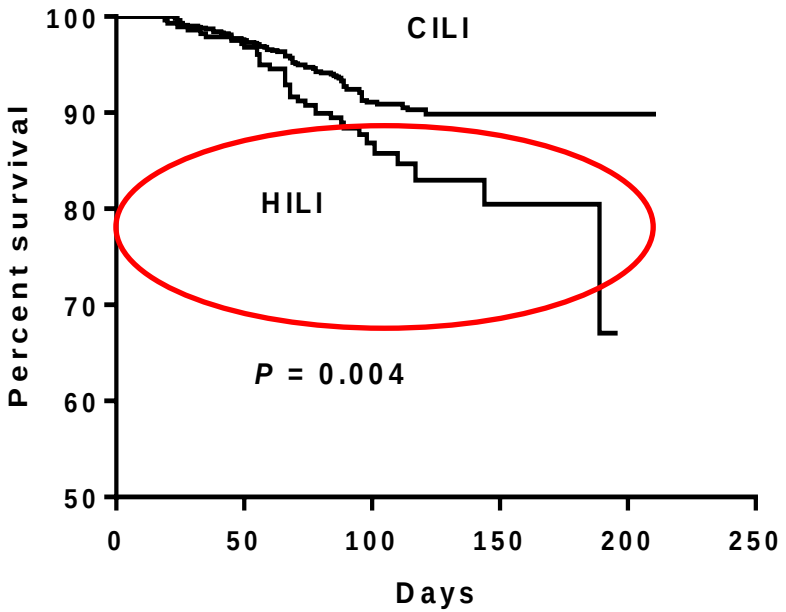
Risk factors associated with mortality of DILI in Taiwan

	Crude HR (95% CI)	p	Adjusted HR (95% CI)	p
All DILI				
hepatitis B infection	2.71 (1.83-4.03)	<0.001	2.64 (1.78-3.93)	<0.001
preexisting cirrhosis	3.21 (1.80-5.72)	<0.001	NS	NS
elevated baseline liver tests	1.78 (1.10-2.88)	0.019	NS	NS
HDS	1.76 (1.19-2.61)	0.005	1.68 (1.13-2.49)	0.010
CILI				
hepatitis B infection	2.38 (1.45-3.90)	0.001	2.38 (1.45-3.90)	0.001
preexisting cirrhosis	2.86 (1.32-6.21)	0.008	NS	NS
HILI				
hepatitis B infection	3.08 (1.56-6.09)	0.001	2.90 (1.43-5.88)	0.003
preexisting cirrhosis	2.98 (1.23-7.21)	0.016	NS	NS
elevated baseline liver tests	2.73 (1.19-6.25)	0.018	2.40 (1.01-5.68)	0.046
crude herbs	2.58 (1.29-5.17)	0.007	2.94 (1.45-5.97)	0.003

Huang YS, et al. Hepatol Int 2021; 15: 1456-1465

HILI had severer liver injury and poorer outcome than CILI in Taiwan

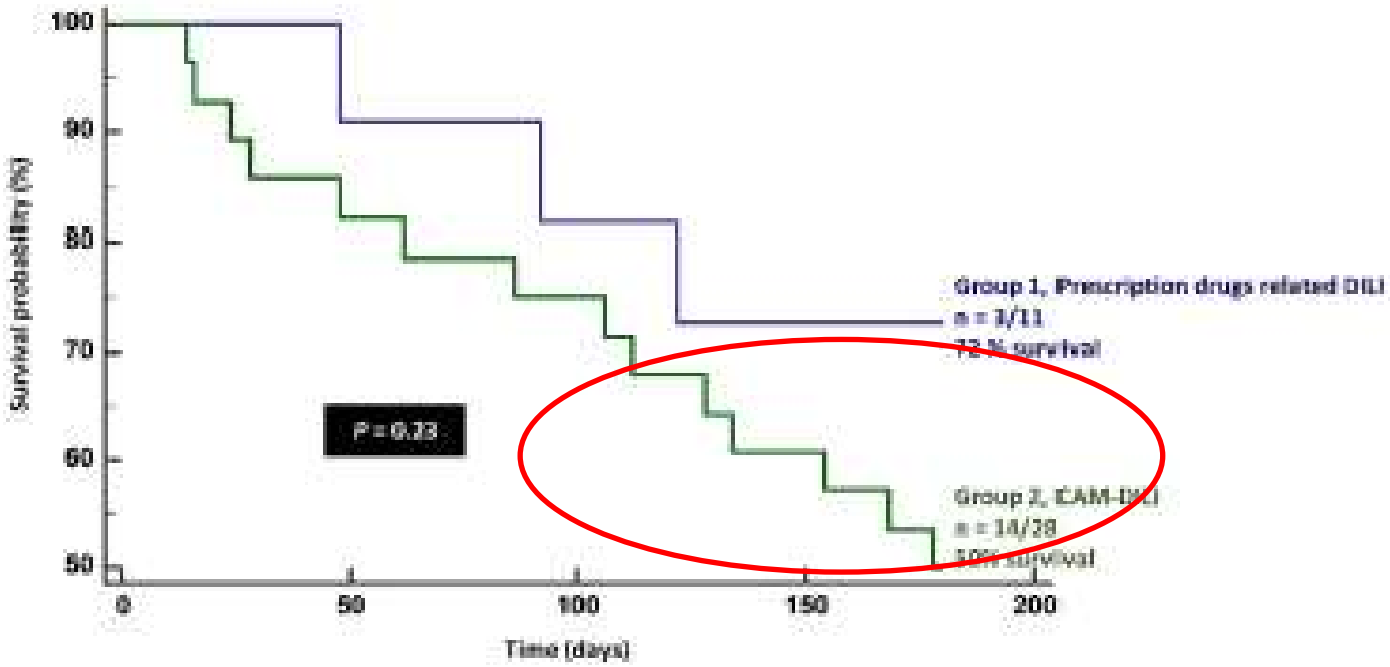
	HILI (n = 285)	CILI (n = 1012)	*P*
Sex, male	159 (55.8%)	541 (53.5%)	0.486
Age (years old)	57.3 ± 15.2	55.7 ± 19.7	0.140
Liver tests-recognition			
ALT (U/L)	734.9 ± 581.7	609.4 ± 639.8	0.003
ALP (U/L	223.3 ± 123.7	203.5 ± 155.2	0.047
Bilirubin, total (mg/dL)	3.7 ± 3.1	3.2 ± 3.7	0.061
Liver tests-peak			
ALT (U/L)	889.1 ± 705.3	821.6 ± 844.8	0.217
ALP (U/L)	268.9 ± 194.1	235.0 ± 203.3	0.012
Bilirubin, total (mg/dL)	9.0 ± 8.7	6.2 ± 8.2	<0.001
Jaundice	198 (69.5%)	498 (49.2%)	<0.001
MELD score	13.2 ± 4.4	11.2 ± 4.5	<0.001
Acute liver failure	40 (14.0%)	92 (9.1%)	0.015
Mortality	36 (12.6%)	81 (8.0%)	0.016



Number at risk					
CILI	1012	970	478	308	5
HILI	285	266	82	25	0

Huang YS, et al. Hepatol Int 2021; 15: 1456-1465

HILI had lower survival rate than CILI among cirrhotic patients in India



Philips CA, et al. Hepatol Commun 2019; 3: 1001-1012

中藥草導致肝損傷之複雜性

- 服用者個體因素:飲酒、既有疾病、基因等
- 藥品交互反應: 與西藥
- 中草藥本身問題:
  - 摻雜：不純物、西藥
  - 污染：殺蟲劑、除草劑、重金屬、微生物、化學物質、不當儲存
  - 錯置：植物誤認、採用部位錯誤
  - 劑量：未依體質加減方

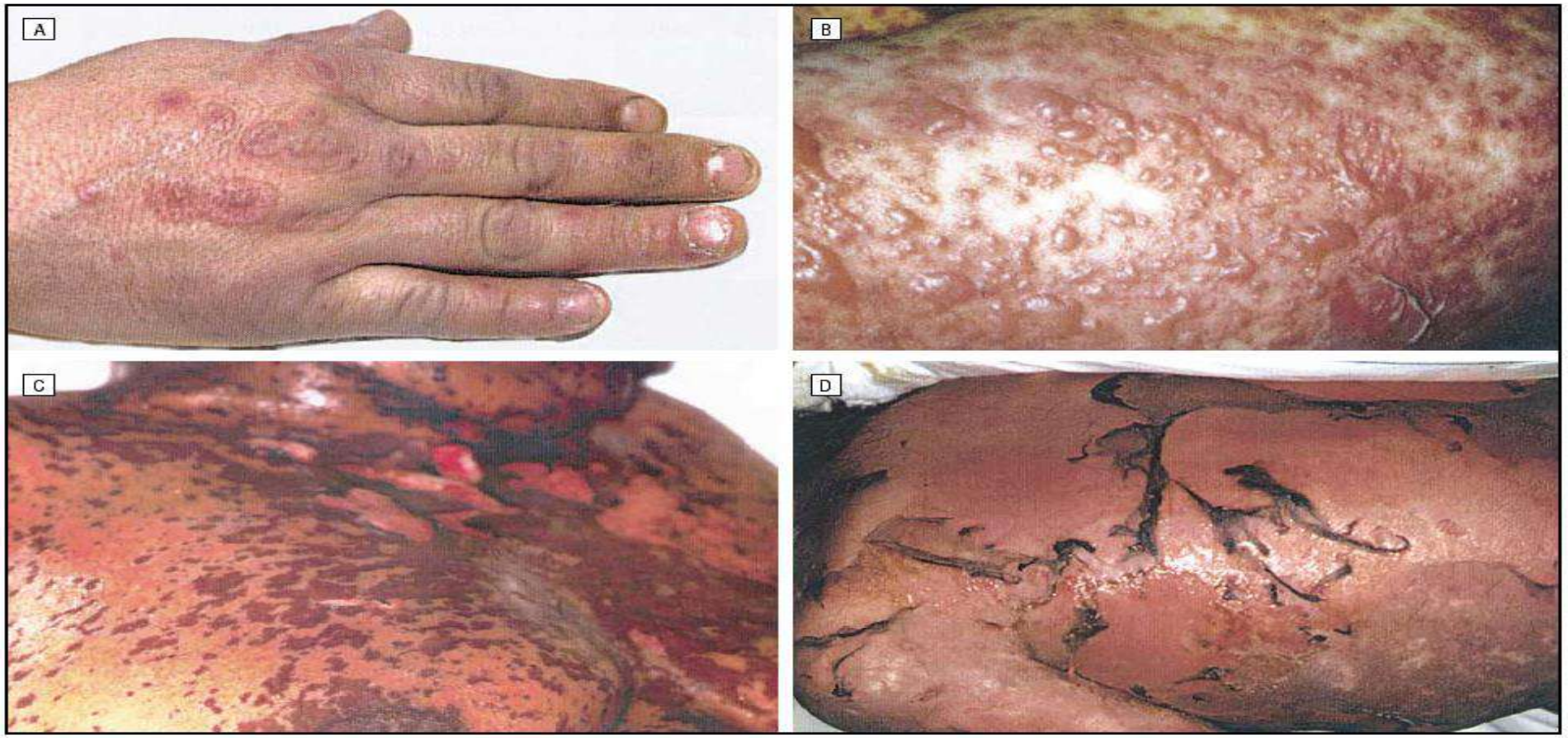
Severe cutaneous adverse reaction (SCAR)

Stevens-Johnson syndrome (SJS):<10% BSA

Toxic epidermal necrolysis (TEN): >30% BSA

SJS—TEN overlap: 10-30% BSA

Drug reaction with eosinophilia and systemic symptoms (DRESS)



DILI combined with SCAR in Taiwan
a multicenter study

	DILI with SJS/TEN (n = 81)	DILI with DRESS (n = 74)	DILI with AGEP (n =3)	DILI no SCAR (n = 1257)	*P*
Acute kidney injury	20 (24.7%)	15 (20.3%)	0 (0.0)	138 (11.0%)	<.001
Mortality, all-cause	28 (34.6%)	10 (13.5%)	0 (0.0)	132 (10.5%)	<.001
Culprit drugs					
-allopurinol (n = 51)	28	11	0	12	
-sulfamethoxazole-trimethoprim (n = 56)	16	19	1	20	
-carbamazepine (n = 39)	10	20	0	9	
-phenytoin (n = 45)	11	15	0	19	
-diclofenac (n = 77)	13	8	0	56	
-anti-tuberculosis drug (n = 303)	3	1	0	299	

Huang YS, et al. Liver Int 2021;41:2671–2680

Risk factors of mortality in patients with DILI combined with SCAR in Taiwan

	OR	95% CI	P
Jaundice	29.54	6.8 – 128.0	<.001*
Acute kidney injury	4.43	1.59 – 12.39	.004*
SJS/TEN	4.86	1.74 – 13.63	.003*
Chronic hepatitis B infection	6.72	1.07 – 42.23	.042*
Sex	0.70	0.24 – 2.04	.511
Age	0.99	0.97 – 1.02	.618
Habitual alcohol use	1.12	0.37 – 3.38	.838
Elevated baseline liver tests	2.52	0.44 – 14.52	.300
Non-hepatitis B liver diseases	1.34	0.30 – 6.12	.702

Huang YS, et al. Liver Int 2021;41:2671–2680

DILI combined with SCAR in India

- **SJS/TEN** occurred in **4.8%** of DILI, associated with a **high mortality (36%)**, which rose to 45.5% in the presence of **Jaundice**

-Devarbhavi H, et al. Heptology 2016; 63: 993-999

- **DRESS:** occurred in **19%** of DILI, with lesser degree injury, **lower mortality (7.8%)** than DILI without DRESS (**16%**)

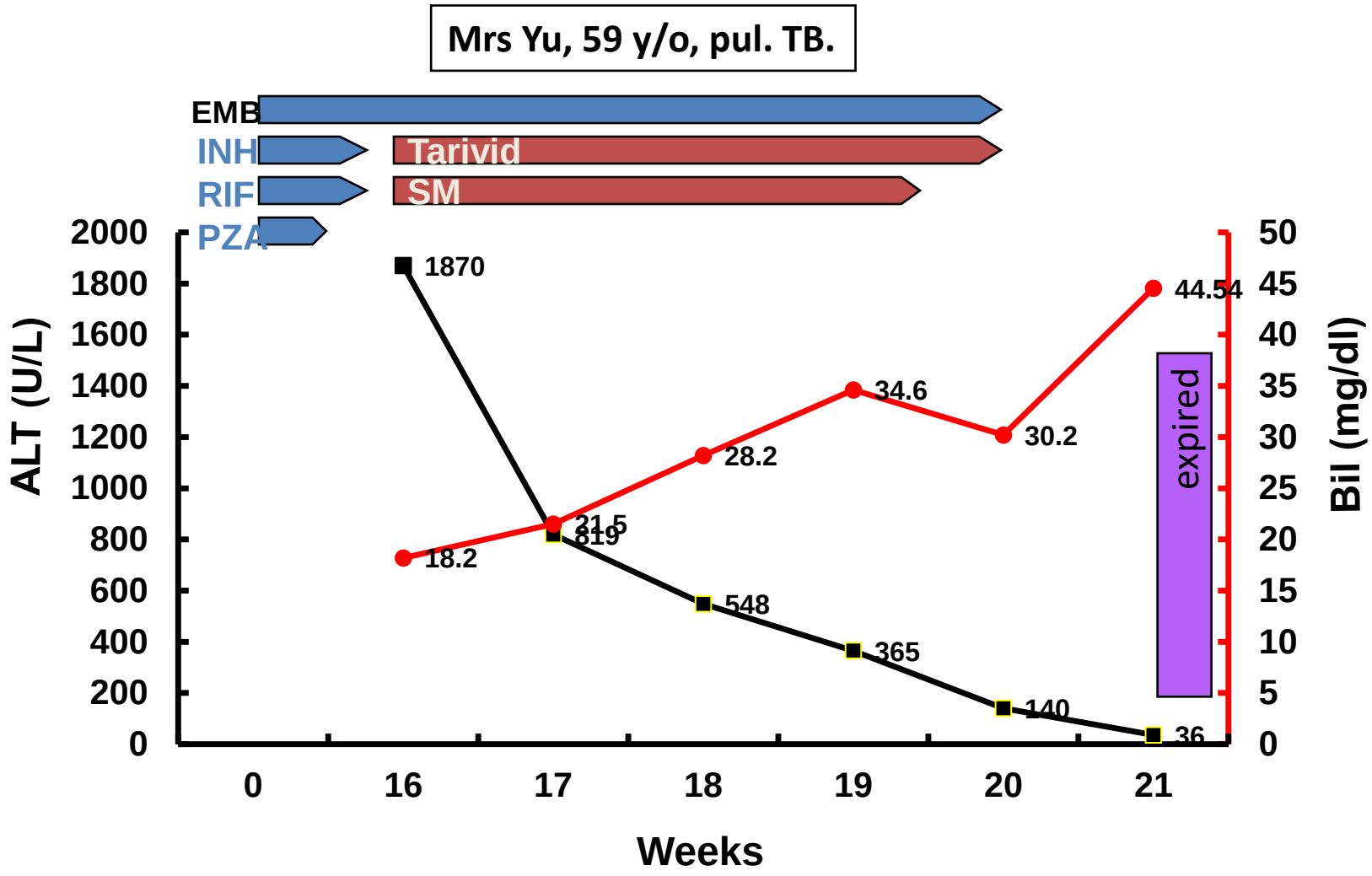
-Devarbhavi H, et al. Am J Gastroenterol 2022; 117: 1709-1713

Outline

- Global trend of drug-induced liver injury (DILI)
- Pathogenesis and diagnosis of DILI
- High-risk drugs to induce liver injury
- High-risk factors of incidence and severity in DILI
- **Anti-tuberculosis drug-induced liver injury (ATDILI)**
- Pharmacogenetics/pharmacogenomics and DILI
- Prevention and treatment of DILI
- Wrap up

Anti-TB drug-induced liver injury (ATDILI)

Mortality Case



Anti-tuberculosis drug-induced liver injury (ATDILI)

- Three first-line anti-TB drugs: isoniazid (INH), rifampicin (RIF) and pyrazinamide (PZA) may induce liver injury; especially INH
- The top drug category to induce liver injury all over the world
- Incidence:10-20%，severe: 1%
- Risk factors: chronic hepatitis B, C, alcohol, AIDS, old age, pregnancy, genetic variation of drug metabolizing enzyme and HLA

台灣疾病管制局結核病診治指引
2022年3月第7版

- 病毒學檢查：治療前，如果不確定是否有B、C型肝炎，應該為病人檢查HBsAg、Anti-HCV
- 血液及生化檢查：治療前以及開始治療後的第2、4、8週，應安排ALT、 AST、 bilirubin等檢查。若病人有B、C型肝炎，或生化指數異常，則返診的頻率以及生化檢查應更為密集

Non-monitoring liver biochemical tests increases the mortality of severe anti-TB DILI in Taiwan

A 12-year-experience of severe anti-TB DILI

Table 3 – Comparison between monitoring group and nonmonitoring group in patients with severe ATLI.

	Monitoring ($n = 10$)	Nonmonitoring ($n = 47$)	p
Male/female	7/3	38/9	0.445
Age (y)[a]	71.4 ± 11.1	58.6 ± 16.8	0.020
Hepatitis B carrier	6 (60.0%)	18 (38.3%)	0.441
Baseline serum ALT(U/L)[a]	34.3 ± 22.1	28.3 ± 22.8	0.230
After treatment			
Latency (wk)[a]	9.6 ± 7.4	7.9 ± 5.9	0.705
Peak serum ALT (U/L)[a]	702.4 ± 614.9	1432.6 ± 985.8	0.012
Peak serum bilirubin (mg/dL)[a]	15.1 ± 9.4	24.5 ± 12.4	0.019
Mortality	5 (50%)	36 (76.6%)	0.124

Table 4 – Multivariate analysis of risk factors for mortality in severe ATLI.

Risk factors	Odds ratio	95% CI	p
Nonmonitoring	8.87	1.32–59.41	0.024
Hepatitis B carrier	4.13	0.89–19.10	0.070
Gender	3.71	0.77–17.84	0.102
Age	1.04	0.99–1.09	0.117

ATLI = antituberculosis drug-related liver injury; CI = confidence interval.

Chih LH, Huang YS, et al. J Food Drug Anal 2014; 22: 356-362

Liver function monitoring status of 1062 patients receiving anti-TB tx in Taipei VGH 2009-2017

Characteristics	Good monitoring (N=469)	Poor monitoring (N=593)	P value
DILI, n (%)	69 (14.7)	31 (5.2)	0.01
Onset			
Latency (days)	21.4 ± 25.6	61.6 ± 36.2	0.01
ALT (U/L)	188.7 ± 345.1	352.0 ± 533.1	0.13
AST (U/L)	215.8 ± 347.7	318.4 ± 470.9	0.24
Total bilirubin (mg/dL)	1.89 ± 2.12	2.92 ± 4.82	0.28
Peak			
ALT (U/L)	276.1 ± 346.5	507.1 ± 604.8	0.05
AST (U/L)	296.1 ± 436.5	475.9 ± 627.9	0.16
Total bilirubin (mg/dL)	4.05 ± 4.44	7.20 ± 14.36	0.26

Chang TE, Huang YS, et al. JCMA 2019; 82: 535-40.

Prevention of ATDIL

- 藥害救濟給付案之抗結核藥肝損傷有75%死亡，大多未定期追蹤肝生化值
- 建議治療後的第2、4、(6)、8週病人應返診行生化檢查，因肝傷害最常發生於1-2個月， 2個月後則每月檢查一次
- 每次返診應詢問病人有無食慾不振、噁心、嘔吐、疲倦、上腹部不適、皮膚癢、茶色尿、皮膚發黃等可能之肝炎症狀
- 輕度肝生化值上昇，可繼續用藥，每週返診檢查肝生化值。但若無症狀ALT、AST > 5倍，有症狀ALT、AST > 3倍，或合併黃疸(total bilirubin > 3)，則宜停藥

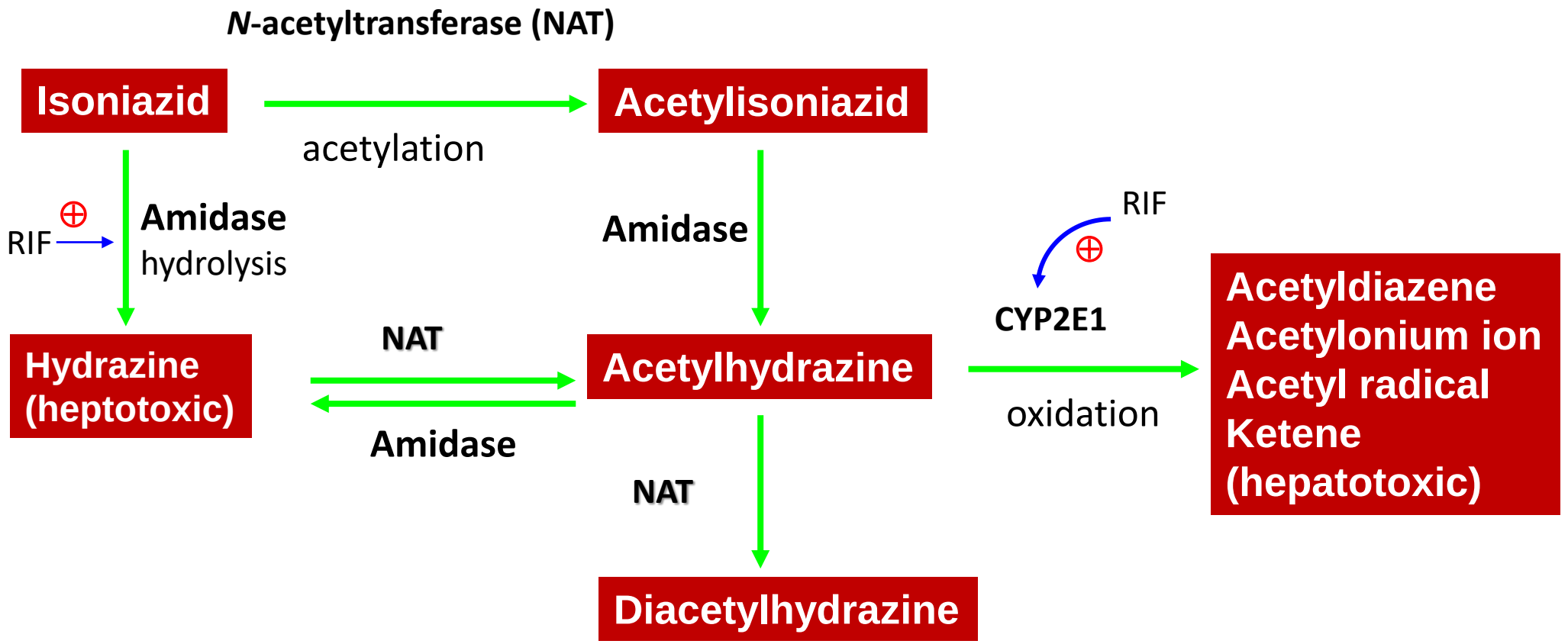
Outline

- Global trend of drug-induced liver injury (DILI)
- Pathogenesis and diagnosis of DILI
- High-risk drugs to induce liver injury
- High-risk factors of incidence and severity in DILI
- Anti-tuberculosis drug-induced liver injury (ATDILI)
- **Pharmacogenetics/pharmacogenomics and DILI**
- Prevention and treatment of DILI
- Wrap up

N-acetyltransferase (NAT)
乙醯轉化酶

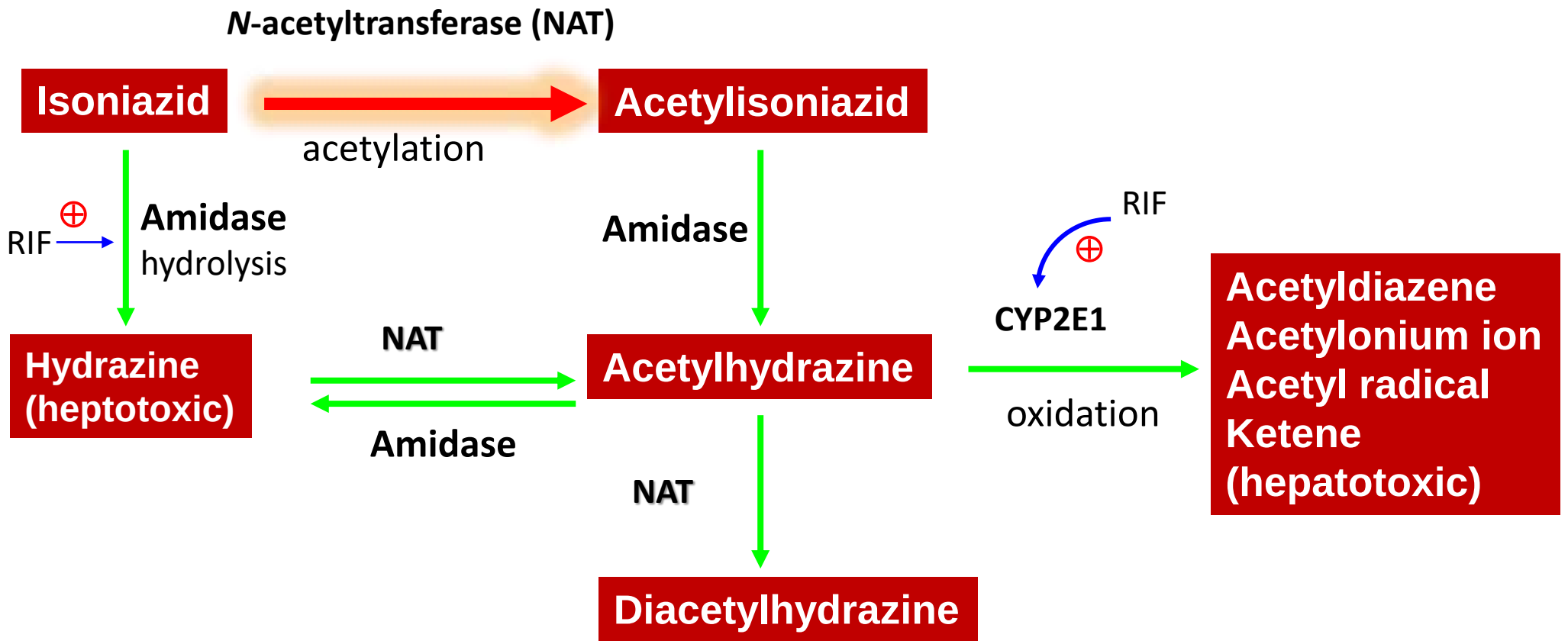
- **Important phase 1 enzyme, major drug-metabolizing enzyme (DME) for INH, gene*: NAT2***
- **Genetic variation (genetic polymorphism, single nucleotide polymorphism, SNP):**
  - **Wild type: *NAT2*4***
  - **Variant type: *NAT2*5, NAT2*6, NAT2*7*, etc.**
- **Rapid acetylators: 2 wild type alleles**
- **Intermediate acetylators: 1 wild type allele**
- **Slow acetylators: 0 wild type allele**

Metabolism of INH in the liver



Huang YS. Expert Opinion on Drug Metabolism and Toxicology 2007; 3: 1-8.

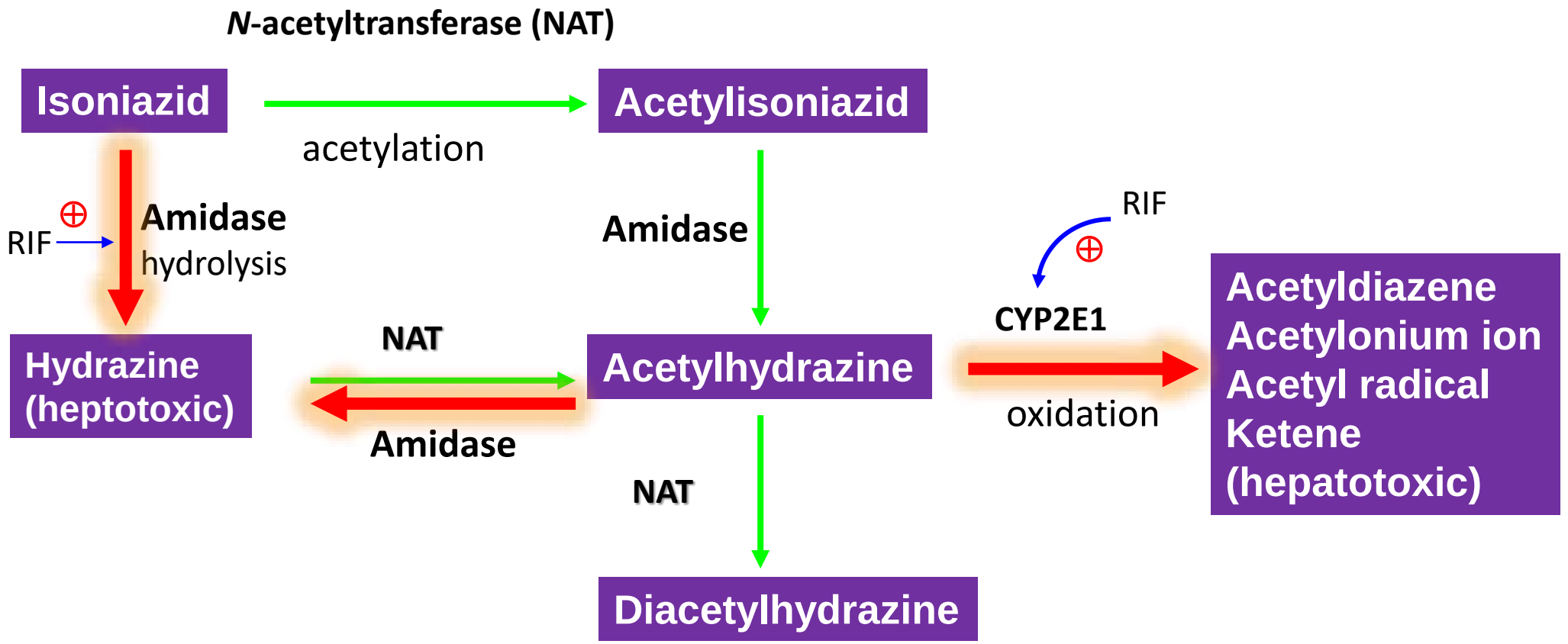
Metabolism of INH in the liver
Rapid acetylators



Huang YS. Expert Opinion on Drug Metabolism and Toxicology 2007; 3: 1-8.

Metabolism of INH in the liver

Slow acetylators



Huang YS. Expert Opinion on Drug Metabolism and Toxicology 2007; 3: 1-8.

NAT2 Slow acetylators higher risk of anti-TB DILI

	With Hepatitis (n = 33)	Without Hepatitis (n = 191)	OR*	95% CI
Rapid acetylator	19 (11.1%)	152 (88.9%)	0.35†	0.16-0.76
*NAT2*4/*4*	6	66	0.42	0.17-1.07
*NAT2*4/*5*	1	6	0.96	0.11-8.28
*NAT2*4/*6*	10	55	1.08	0.48-2.41
*NAT2*4/*7*	2	25	0.43	0.10-1.90
Slow acetylator	14 (26.4%)	39 (73.6%)	2.87†	1.32-6.23
*NAT2*5/*5*	0	1	1.90	0.08-47.56
*NAT2*5/*6*	0	6	0.43	0.02-7.75
*NAT2*5/*7*	0	2	1.13	0.05-24.11
*NAT2*6/*6*	6	10	4.02†	1.35-11.97
*NAT2*6/*7*	7	12	4.02†	1.45-11.13
*NAT2*7/*7*	1	8	0.72	0.09-5.91

*Using other genotypes as reference for OR.
†$P < .05$.

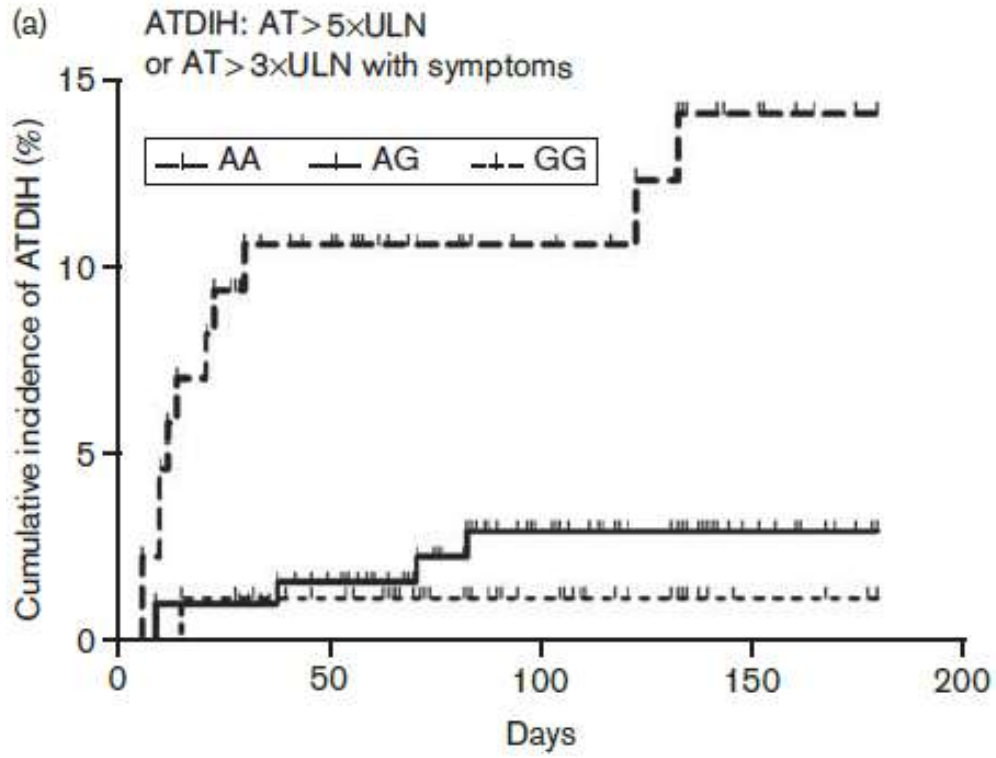
Huang YS, et al. Hepatology 2002;35:883-889.高引用論文: 618次

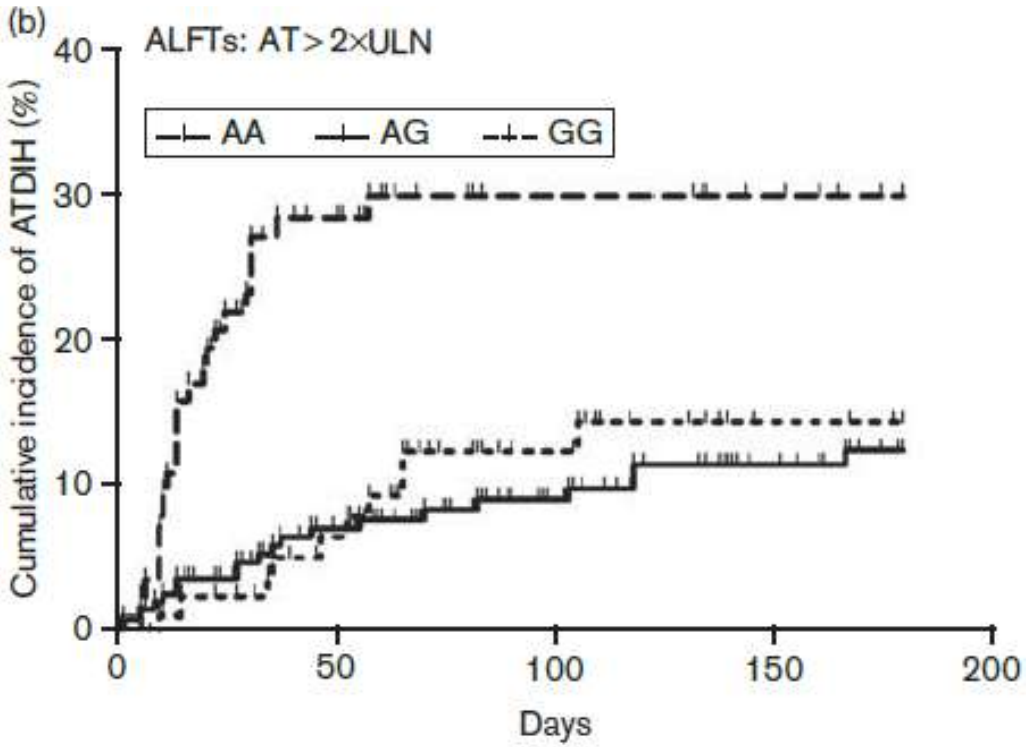
NAT2 slow acetylators severer anti-TB DILI

	Slow Acetylators (N=14)	Rapid Acetylators (N=19)	*P*
Peak ALT (U/L)	587.3 ± 462.5	250.8 ± 132.5	.008
Peak AST (U/L)	631.9 ± 462.6	260.2 ± 166.9	.038
Peak bilirubin (mg/dl)	3.89 ± 4.97	2.77 ± 2.05	.815
ALT > 3 X ULN in rechallenge	9 (64.3%)	5 (26.3%)	.040
Age (yr)	71.5 ± 3.9	74.7 ± 6.4	.024
BMI (kg/m^2)	21.3 ± 2.3	20.1 ± 2.1	.152

Huang YS, et al. Hepatology 2002;35:883-889.高引用論文: 618次

The *NAT2* tag SNP rs1495741 correlates with the susceptibility of ATDILI





Ho HT, Hu OY, et al. Pharmacogenetics and Genomics 2013, 23:200–207

The *NAT2* tag SNP rs1495741 correlates with the susceptibility of ATDILI

	ATDIH[a] (AT>5 × ULN or AT>3 × ULN with symptoms) [*N* (%)]			ALFTs[b] (AT>2 × ULN) [*N* (%)]		
Genotype	Absent	Present	Odds ratio	Absent	Present	Odds ratio
rs1495741						
GG	79 (98.8)	1 (1.2)	Reference	71 (88.8)	9 (11.3)	Reference
GA	176 (96.7)	6 (3.3)	2.693	160 (87.9)	22 (12.1)	1.085
AA	73 (86.0)	13 (14.0)	14.068*	58 (67.4)	28 (32.6)	3.808**
NAT2 alleles-inferred phenotype						
Rapid	86 (98.9)	1 (1.1)	Reference	77 (88.5)	10 (11.5)	Reference
Intermediate	176 (96.7)	6 (3.3)	2.932	161 (88.5)	21 (11.5)	1.004
Slow	67 (84.8)	12 (15.2)	15.403**	51 (64.6)	28 (35.4)	4.227***

ALFTs, abnormal liver-function tests; ALT, alanine transaminase; AST, aspartate transaminase; ATDIH, antituberculosis drug-induced hepatotoxicity; *NAT2*, *N*-acetyltransferase 2; TBil, total bilirubin; ULN, upper limit of normal.

[a]AT (AST and/or ALT) of more than five-fold of the ULN; or AT of more than three-fold the ULN in the presence of symptoms and/or in the presence of TBil of more than two-fold of the ULN.

[b]AT of more than two-fold the ULN.

*$P<0.05$.

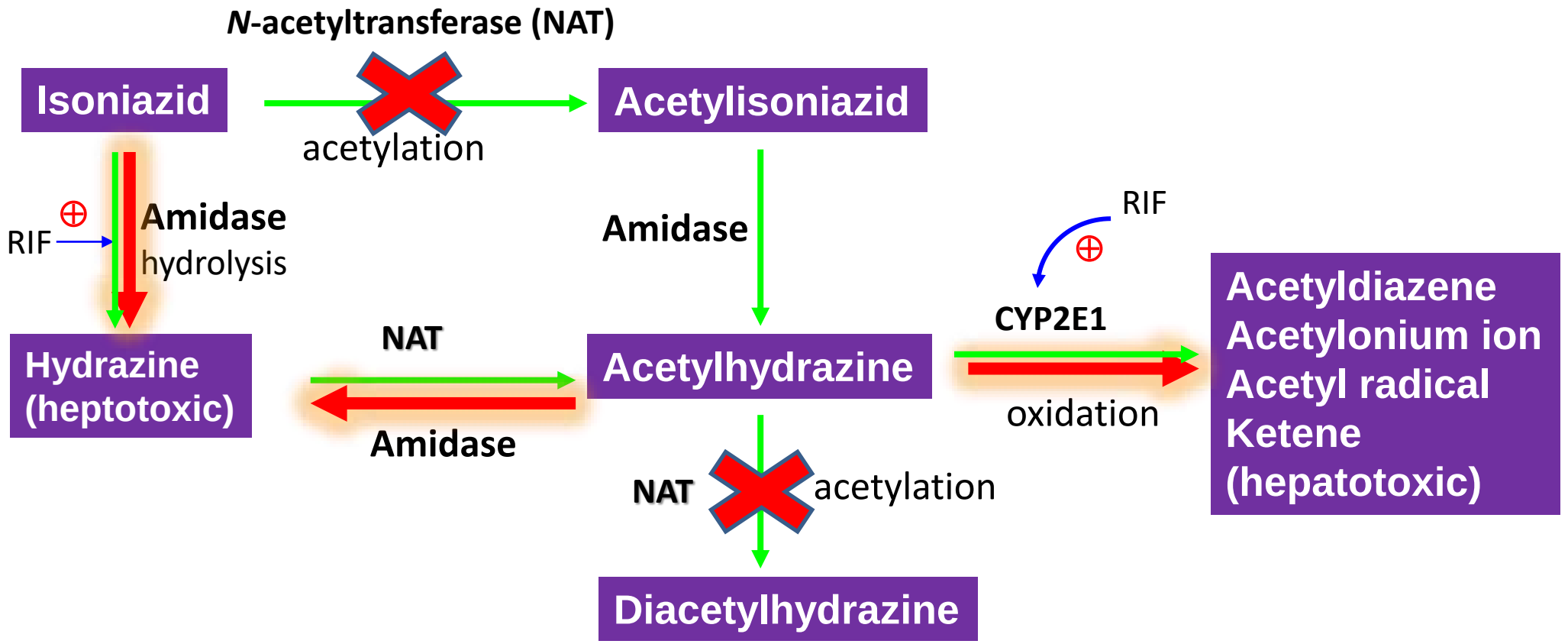
**$P<0.01$.

***$P<0.005$.

Ho HT, Hu OY, et al. Pharmacogenetics and Genomics 2013, 23:200–207

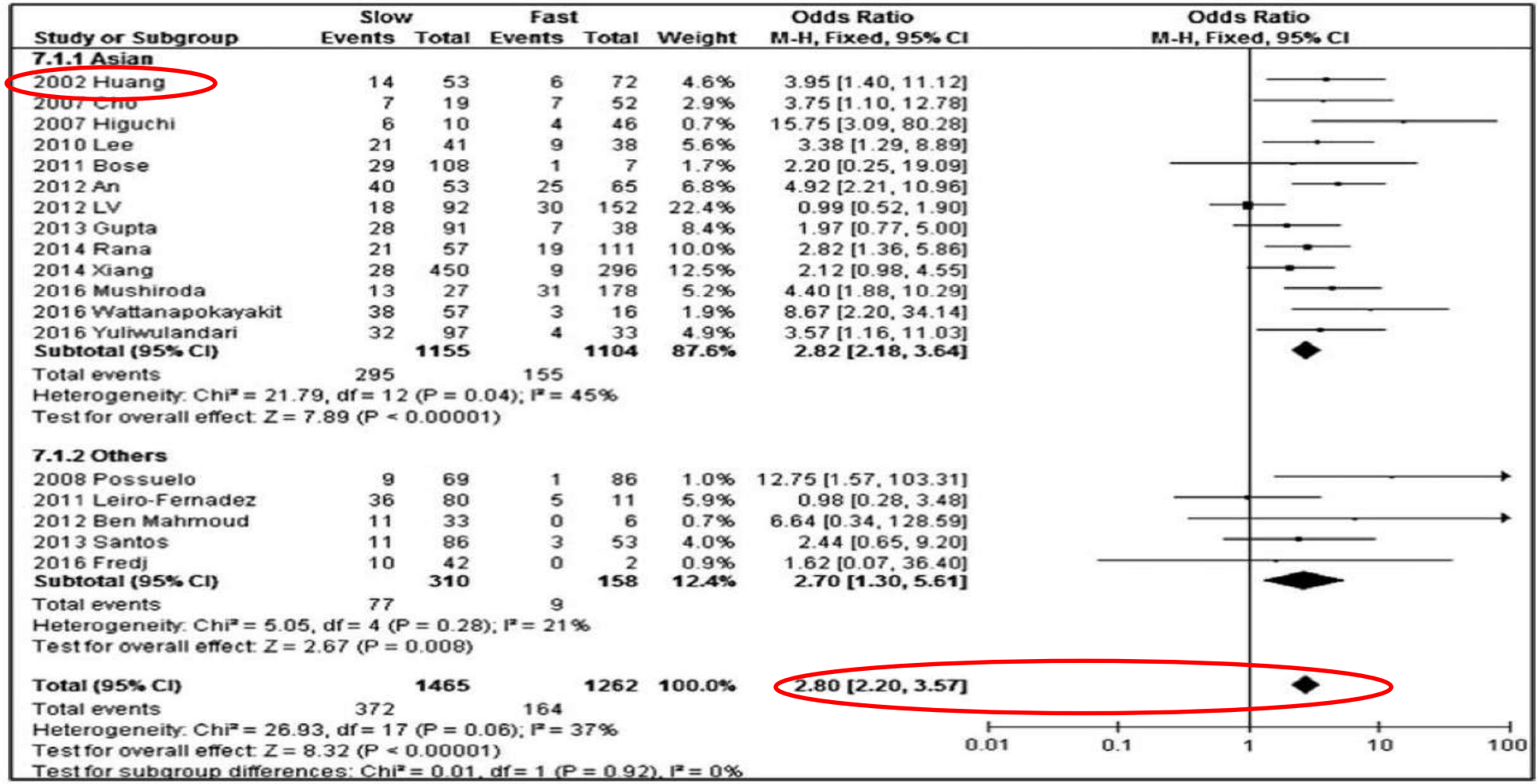
Metabolism of isoniazid in the liver

Slow acetylators



Huang YS. Expert Opinion on Drug Metabolism and Toxicology 2007; 3: 1-8

NAT2 slow acetylators: higher risk of ATDILI a meta-analysis



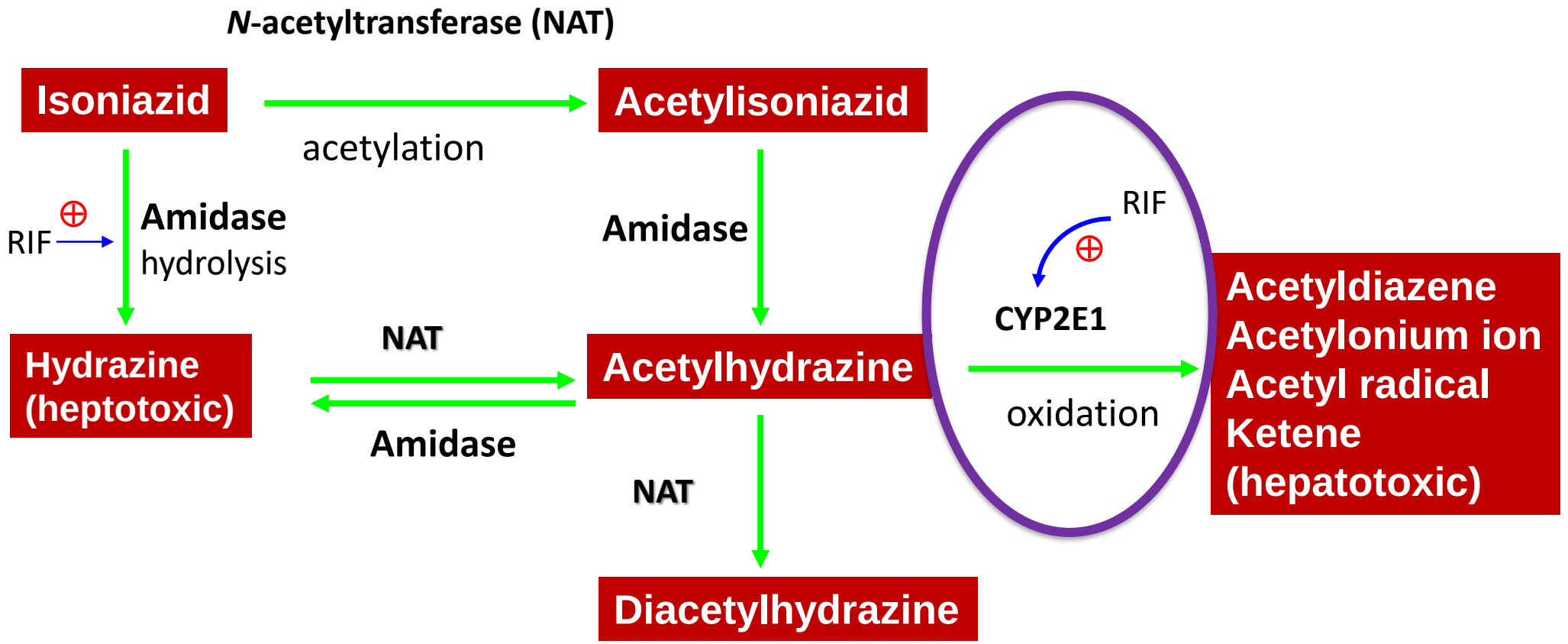
Study or Subgroup	Slow Events	Slow Total	Fast Events	Fast Total	Weight	Odds Ratio M-H, Fixed, 95% CI
7.1.1 Asian						
2002 Huang	14	53	6	72	4.6%	3.95 [1.40, 11.12]
2007 Cho	7	19	7	52	2.9%	3.75 [1.10, 12.78]
2007 Higuchi	6	10	4	46	0.7%	15.75 [3.09, 80.28]
2010 Lee	21	41	9	38	5.6%	3.38 [1.29, 8.89]
2011 Bose	29	108	1	7	1.7%	2.20 [0.25, 19.09]
2012 An	40	53	25	65	6.8%	4.92 [2.21, 10.96]
2012 LV	18	92	30	152	22.4%	0.99 [0.52, 1.90]
2013 Gupta	28	91	7	38	8.4%	1.97 [0.77, 5.00]
2014 Rana	21	57	19	111	10.0%	2.82 [1.36, 5.86]
2014 Xiang	28	450	9	296	12.5%	2.12 [0.98, 4.55]
2016 Mushiroda	13	27	31	178	5.2%	4.40 [1.88, 10.29]
2016 Wattanapokayakit	38	57	3	16	1.9%	8.67 [2.20, 34.14]
2016 Yuliwulandari	32	97	4	33	4.9%	3.57 [1.16, 11.03]
Subtotal (95% CI)		**1155**		**1104**	**87.6%**	**2.82 [2.18, 3.64]**
Total events	295		155			
Heterogeneity: Chi² = 21.79, df = 12 (P = 0.04); I² = 45%						
Test for overall effect: Z = 7.89 (P < 0.00001)						
7.1.2 Others						
2008 Possuelo	9	69	1	86	1.0%	12.75 [1.57, 103.31]
2011 Leiro-Fernadez	36	80	5	11	5.9%	0.98 [0.28, 3.48]
2012 Ben Mahmoud	11	33	0	6	0.7%	6.64 [0.34, 128.59]
2013 Santos	11	86	3	53	4.0%	2.44 [0.65, 9.20]
2016 Fredj	10	42	0	2	0.9%	1.62 [0.07, 36.40]
Subtotal (95% CI)		**310**		**158**	**12.4%**	**2.70 [1.30, 5.61]**
Total events	77		9			
Heterogeneity: Chi² = 5.05, df = 4 (P = 0.28); I² = 21%						
Test for overall effect: Z = 2.67 (P = 0.008)						
Total (95% CI)		**1465**		**1262**	**100.0%**	**2.80 [2.20, 3.57]**
Total events	372		164			
Heterogeneity: Chi² = 26.93, df = 17 (P = 0.06); I² = 37%						
Test for overall effect: Z = 8.32 (P < 0.00001)						
Test for subgroup differences: Chi² = 0.01, df = 1 (P = 0.92), I² = 0%						

Odds Ratio M-H, Fixed, 95% CI

0.01 0.1 1 10 100

Suvichapanich S, et al. Pharmacogenet Genomics 2018; 28: 167–176

Metabolism of INH in the liver



Huang YS. Expert Opinion on Drug Metabolism and Toxicology 2007; 3: 1-8.

Cytochrome P450 2E1
CYP 2E1

- Important phase 1 enzyme, for INH
- Genetic variation (SNP by *Rsa*I RFLP)
  - Wild type：c1
  - Variant type：c2
- 3 genotypes： c1/c1, c1/c2, c2/c2
- SNP associated with HCC and many cancers
- No association study with ATDILI till 2003

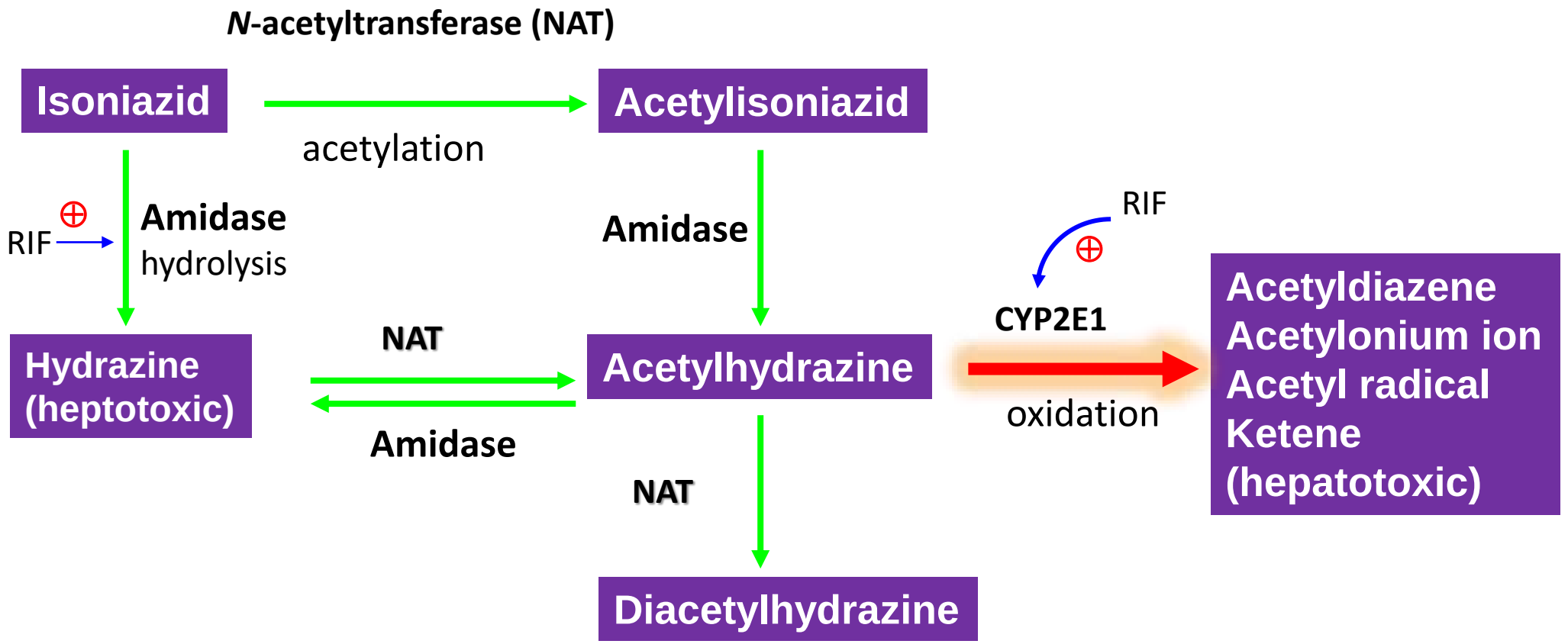
CYP2E1 wild genotype c1/c1 higher risk of ATDILI

	Hepatotoxicity			
	Present (n = 49)	Absent (n = 269)	Odds Ratio (95% CI)	*P*
CYP2E1 genotype				
c2/c2	2 (13.3%)	13 (86.7%)	1.00 (reference)	
c1/c2	10 (8.5%)	108 (91.5%)	0.60 (0.12-3.05)	.540
c1/c1	37 (20.0%)	148 (80.0%)	1.63 (0.35-7.52)	.534
CYP2E1 genotype				
c2/c2 or c1/c2	12 (9.0%)	121 (91.0%)	1.00 (reference)	
c1/c1	37 (20.0%)	148 (80.0%)	2.52 (1.26-5.05)	.009
Acetylator status				
Rapid	30 (12.4%)	211 (87.6%)	1.00 (reference)	
Slow	19 (24.7%)	58 (75.3%)	2.30 (1.21-4.39)	.011

Huang YS, et al. Hepatology 2003;37:924-930.高引用論文: 578次

Metabolism of isoniazid in the liver

CYP 2E1 wild genotype c1/c1



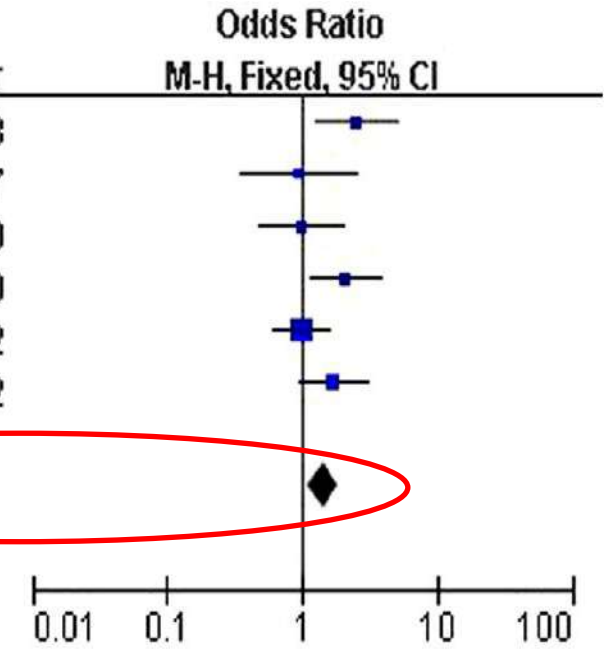
Huang YS. Expert Opinion on Drug Metabolism and Toxicology 2007; 3: 1-8

CYP2E1 wild genotype c1/c1
higher risk of anti-TB DILI: a meta-analysis

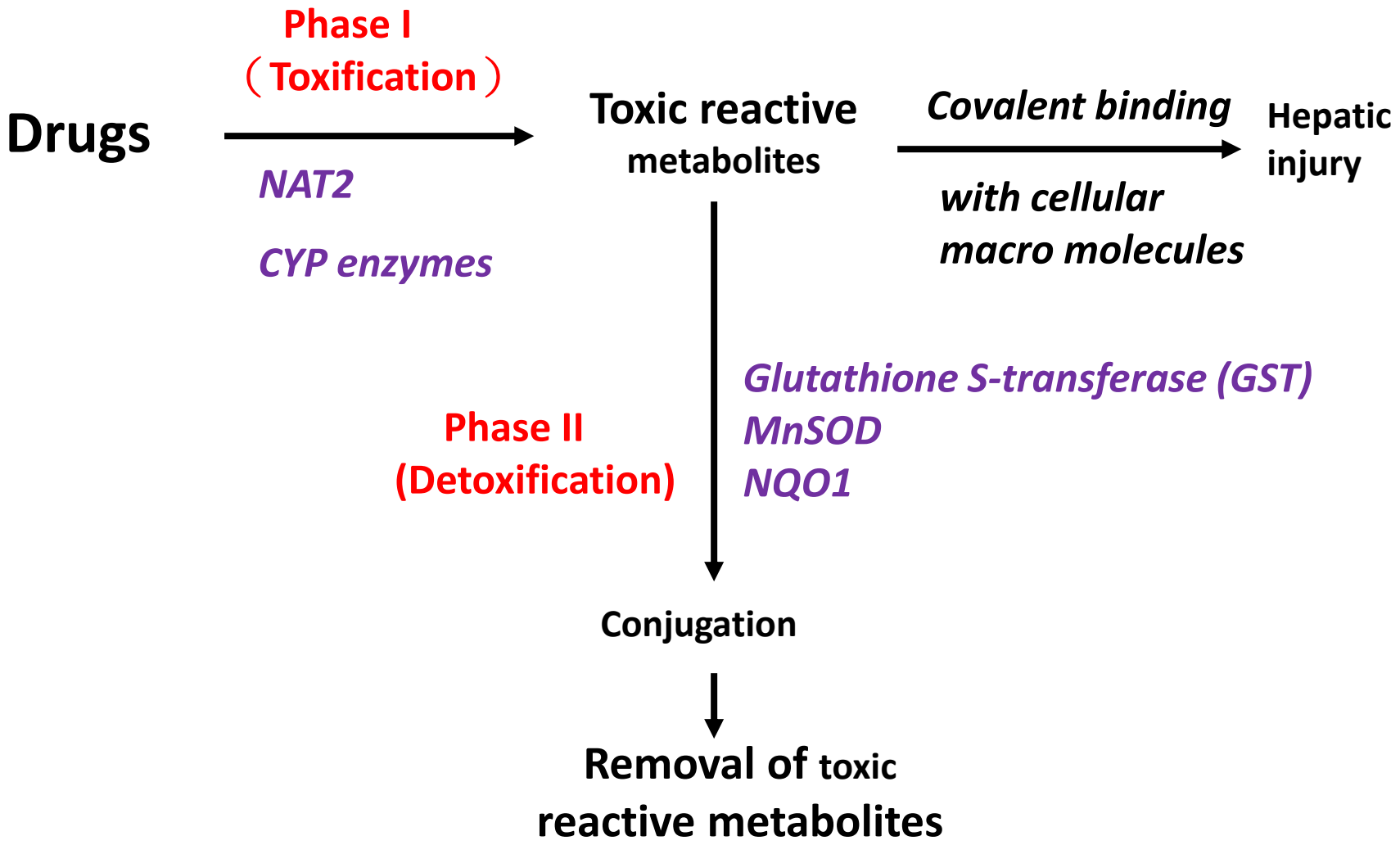
Study or Subgroup	c1/c1 Events	c1/c1 Total	c1/c2+c2/c2 Events	c1/c2+c2/c2 Total	Weight	Odds Ratio M-H, Fixed, 95% CI	Year
Huang 2003	37	185	12	133	11.2%	2.52 [1.26, 5.05]	2003
Cho 2007	10	75	8	57	7.9%	0.94 [0.35, 2.56]	2007
Lee 2010	26	81	19	59	15.0%	1.00 [0.49, 2.04]	2010
Wang 2010	82	153	22	62	14.6%	2.10 [1.14, 3.86]	2010
Tang 2012	56	281	33	164	33.5%	0.99 [0.61, 1.60]	2012
An 2012	72	136	29	72	17.9%	1.67 [0.93, 2.98]	2012
Total (95% CI)		**911**		**547**	**100.0%**	**1.44 [1.12, 1.86]**	
Total events	283		123				

Heterogeneity: Chi² = 8.28, df = 5 (P = 0.14); I² = 40%

Test for overall effect: Z = 2.80 (P = 0.005)



Sheng YJ, et al. Inf Genet Evol 2014; 24: 34-40



Metabolism of drugs in the liver

Genetic variation of phase 2 anti-oxidant enzyme MnSOD (SOD2) associated with DILI

	Patients (%)			Controls (%)		
	Anti-TB (n = 63)	Other drugs (n = 52)	Total (n = 115)	Anti-TB (n = 63)	Other drugs (n = 52)	Total (n = 115)
MnSOD						
T/T	36 (57.1)	28 (53.8)	64 (55.7)	48 (76.2)	39 (75.0)	87 (75.7)
T/C	23 (36.5)	20 (38.5)	43 (37.4)	12 (19.0)	13 (25.0)	25 (21.7)
C/C	4 (6.3)	4 (7.7)	8 (7.0)	3 (4.8)	0 (0.0)	3 (2.6)
T/C or C/C	27 (42.9)[a]	24 (46.2)[b]	51 (44.3)[c]	15 (23.8)[a]	13 (25.0)[b]	28 (24.3)[c]
NQO1						
C/C	17 (27.0)	12 (23.1)	29 (25.2)	15 (23.8)	17 (32.7)	32 (27.8)
C/T	36 (57.1)	29 (55.8)	65 (56.5)	34 (48.6)	25 (48.1)	59 (51.3)
T/T	10 (15.9)	11 (21.2)	21 (18.3)	14 (22.2)	10 (19.2)	24 (20.9)
C/T or T/T	46 (73.0)	40 (76.9)	86 (74.8)	48 (76.2)	35 (67.3)	83 (72.2)

[a]$P = 0.001$, [b]$P = 0.039$, [c]$P = 0.002$.

Huang YS, et al. J Hepatol 2007;47: 128–134

Genetic variation of phase 2 detoxification enzyme GSTM1 increases risk of ATDILI

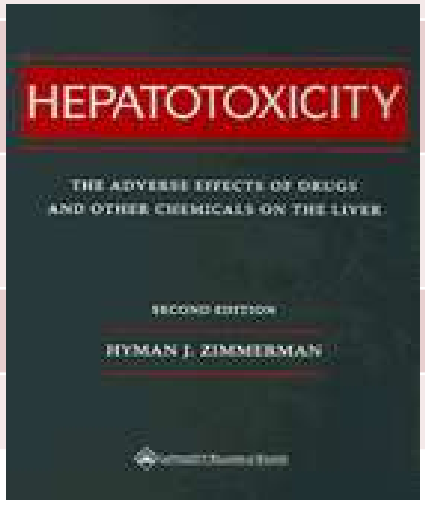
	Patients (%)			Controls (%)		
	Anti-TB (n = 63)	**Other drugs (n = 52)**	**Total (n = 115)**	**Anti-TB (n = 63)**	Other drugs (n = 52)	**Total (n = 115)**
GSTM1						
null	**42 (66.7)[d]**	**23 (44.2)**	**65 (56.5)**	**29 (46.0)[d]**	27 (51.9)	**56 (48.7)**
non-null	**21 (33.3)**	**29 (55.8)**	**50 (43.5)**	**34 (54.0)**	25 (48.1)	**59 (51.3)**
GSTT1						
null	**24 (38.1)**	**20 (38.5)**	**44 (38.3)**	**25 (39.7)**	20 (38.5)	**45 (39.1)**
non-null	**39 (61.9)**	**32 (61.5)**	**71 (61.7)**	**38 (60.3)**	32 (61.5)	**70 (60.9)**

[d]*P* = 0.020.

Huang YS, et al. J Hepatol 2007;47: 128–134

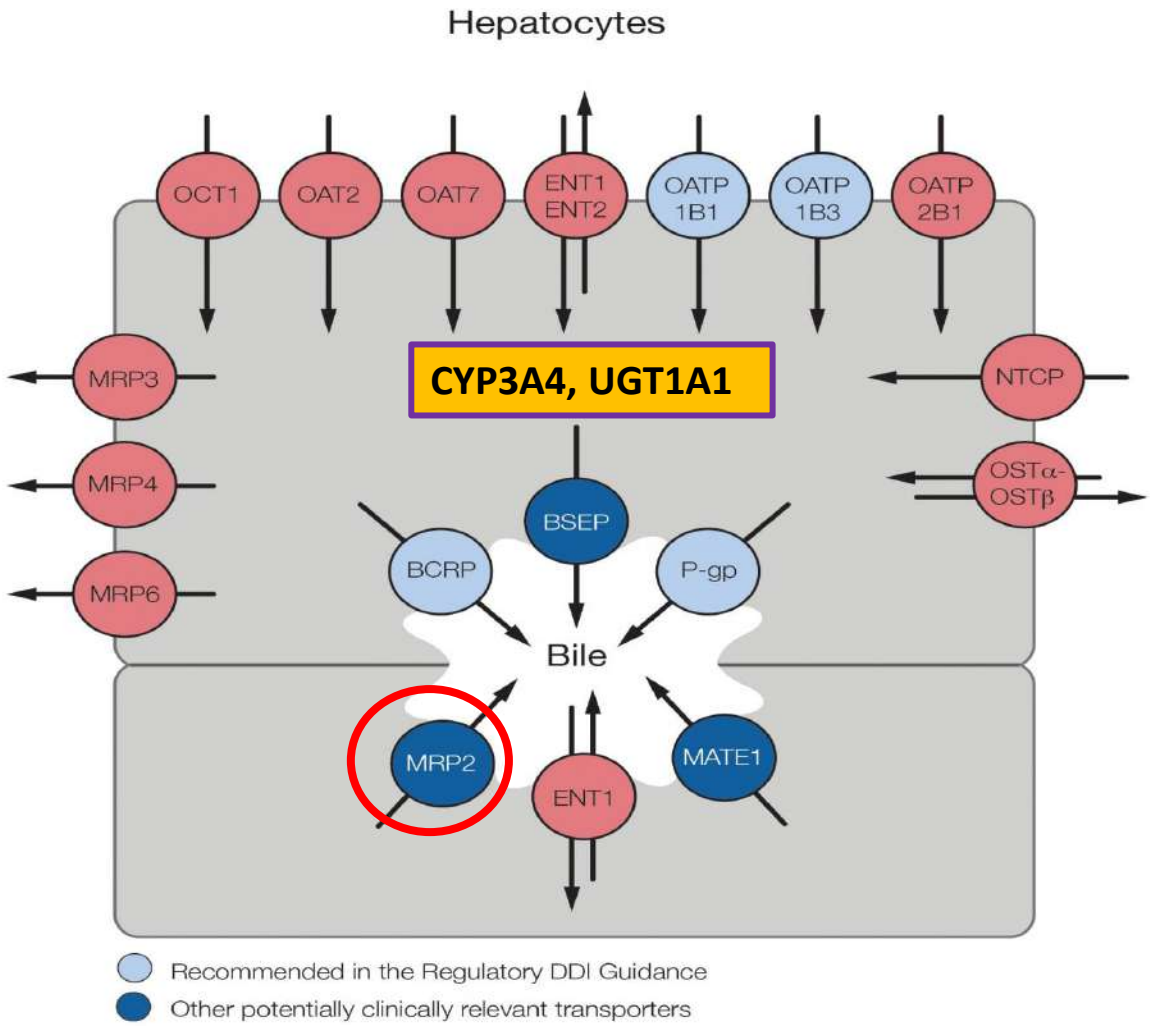
Hy's law: Hyperbilirubinemia in DILI

Term or concept	Definition
Hy's law	Observation made by late Hyman Zimmerman: suggesting 1/10 mortality of DILI
	1. Serum ALT or AST > 3 × ULN 2. Serum total bilirubin elevated to > 2 × ULN, without initial findings of cholestasis (elevated serum alkaline phosphatase)



Phase 3 transporters

Excretion of bilirubin and drugs



OATP: Organic Anion Transporting Polypeptide
BCRP: Breast Cancer Resistance Protein = ABCG2
ABC: ATP-binding cassette
P-gp: P-glycoprotein = MDR1
OAT: Organic Anion Transporter
OCT: Organic Cation Transporter
MRP: Multidrug Resistance-associated Protein
BSEP: Bile Salt Export Pump = ABCB11
ENT: Equilibrative nucleoside transporter
OST: Organic Solute Transporter
NTCP: Na^+-Taurocholate Cotransporting Polypeptide
SLC: Solute Carrier

Transporter *ABCC2 (MRP2)* low activity T allele higher risk of drug-induced hyperbilirubinemia

	Hyperbilirubinemia	Non-hyberbilirubinemia	*p*
	(n = 86)	(n = 114)	
ABCB11			
rs2287622	47/30/9	56/50/8	0.375
CC/CT/TT	(54.7/34.9/10.4)	(49.1/43.9/7.0)	
ABCB1			
rs1128503	7/38/41	20/49/45	0.136
CC/TC/TT	(8.1/44.2/47.7)	(17.5/43.0/39.5)	
rs1045642	34/39/13	40/53/21	0.744
CC/TC/TT	(39.5/45.3/15.2)	(35.1/46.5/18.4)	
ABCB4			
rs2230028	77/9/0	108/6/0	0.167
AA/GA/GG	(89.5/10.5/0)	(94.7/5.3/0)	
ABCC2			
rs1885301	7/25/54	2/30/82	0.075
AA/AG/GG	(8.1/29.1/62.8)	(1.8/26.3/71.9)	
rs717620	48/34/4	91/21/2	0.001*
CC/CT/TT	(55.8/39.5/4.7)	(79.8/18.4/1.8)	
rs2273697	2/18/66	1/20/93	0.570
AA/AG/GG	(2.3/20.9/76.8)	(0.9/17.5/81.6)	
rs3740066	50/30/6	83/28/3	0.066
CC/CT/TT	(58.1/34.9/7.0)	(72.8/24.6/2.6)	
rs8187710	86/0/0	113/1/0	0.384
GG/GA/AA	(100/0/0)	(99.1/0.9/0)	

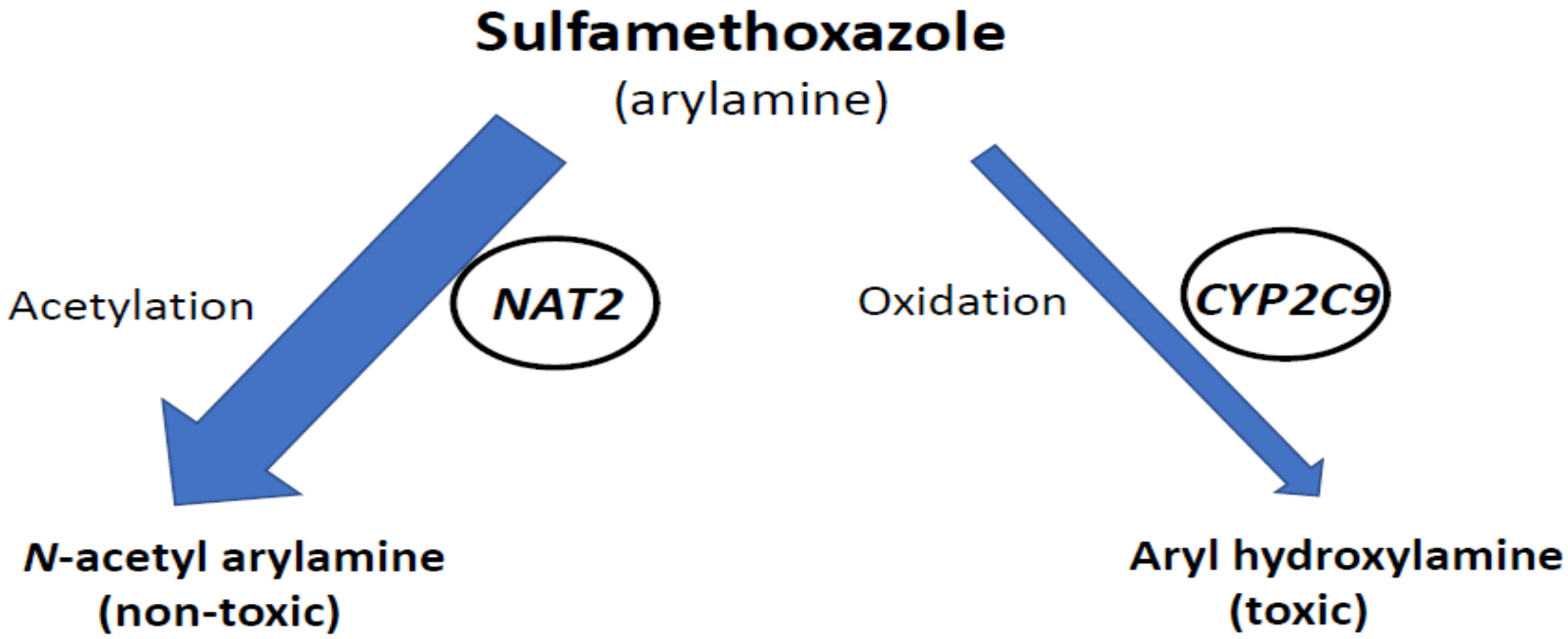
Huang YS, et al. JCMA 2021;84:129-135

Transporter *ABCC2 (MRP2)* low activity T allele higher drug-induced mortality

	Expired	Survival	*p*
	(n = 24)	(n = 176)	
ABCB11			
rs2287622	12/8/4	91/72/13	0.293
CC/CT/TT	(50.0/33.3/16.7)	(51.7/40.9/7.4)	
ABCB1			
rs1128503	2/13/9	25/74/77	0.486
CC/TC/TT	(8.3/54.2/37.5)	(14.2/42.0/43.8)	
rs1045642	7/15/2	67/77/32	0.195
CC/TC/TT	(29.2/62.5/8.3)	(38.1/43.8/18.2)	
ABCB4			
rs2230028	22/2/0	163/13/0	0.697
AA/GA/GG	(91.7/8.3/0.0)	(92.6/7.4/0.0)	
ABCC2			
rs1885301	1/5/18	8/50/118	0.725
AA/AG/GG	(4.2/20.8/75.0)	(4.5/28.4/67.0)	
rs717620	12/10/2	127/45/4	0.048*
CC/CT/TT	(50.0/41.7/8.3)	(72.2/25.6/2.3)	
rs2273697	0/4/20	3/34/139	0.764
AA/AG/GG	(0.0/16.7/83.3)	(1.7/19.3/79.0)	
rs3740066	17/6/1	116/52/8	0.889
CC/CT/TT	(70.8/25.0/4.2)	(66.0/29.5/4.5)	
rs8187710	24/0/0	175/1/0	1.000
GG/GA/AA	(100/0.0/0.0)	(99.4/0.6/0.0)	

Huang YS, et al. JCMA 2021;84:129-35

The Major and minor metabolism pathway of sulfamethoxazole



Huang YS, et al. Pharmacogenetics and Genomics 2021,31:200–6

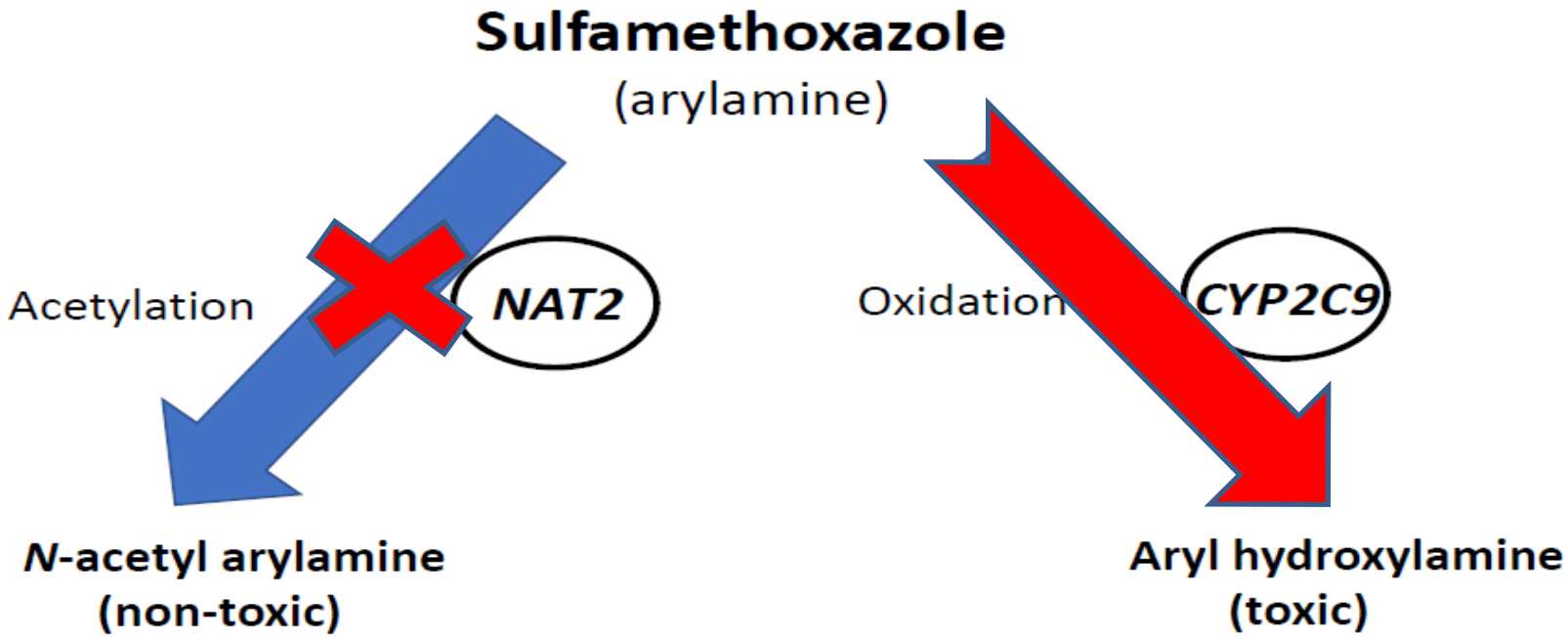
NAT2 slow acetylators

higher risk of sulfamethoxazole-trimethoprim-induced liver injury in Taiwan

Genetic variations	SILI (n=158)	Controls (n=145)	P
NAT2 Acetylators			
Slow (rs1495741 AA or rs1041983TT)	69 (43.7%)	37 (25.5%)	0.001
Intermediate/Normal	89 (56.3%)	108 (74.5%)	
CYP2C9 metabolizer			
Normal (rs4918758 TT or rs1799853 TT or rs1057910 CC)	157(99.4%)	144 (99.3%)	0.516
Intermediate/Poor	1 (0.6%)	1 (0.7%)	

Huang YS, et al. Pharmacogenetics and Genomics 2021,31:200–206

The Major and minor metabolism pathway of sulfamethoxazole



Huang YS, et al. Pharmacogenetics and Genomics 2021,31:200–6

Polymorphisms of DILI-related *HLA* genes in GWAS & candidate gene study

Genes	Drug	Method	Cohort	OR	P	95%CI
A*02:01 rs2523822 TRNAI25	Amoxicillin-clavulanate	GWAS	201 cases; 531 controls (European) Lucena et al. (2011)	2.3	1.8×10^{-10}	1.8–2.9
A*30:02	Amoxicillin-clavulanate	CGS	75 cases; 885 controls (Spanish) Stephens et al. (2013)	6.7	2.6×10^{-6}	2.8–15.9
A*33:01	Terbinafine	GWAS	21 cases; 10,588 controls (European) Nicoletti et al. (2017)	40.5	$6.7*10^{-10}$	12.5–131.4
A*33:01	Fenofibrate	GWAS	7 cases; 10,588 controls (European) Nicoletti et al. (2017)	58.7	3.2×10^{-7}	12.3–279.8
A*33:01	Ticlopidine	GWAS	5 cases; 10,588 controls (European) Nicoletti et al. (2017)	163.1	0.00002	16.2–1642
A*33:03	Ticlopidine	CGS	22 cases; 85 controls (Japanese) Hirata et al. (2008)	13.0	1.24×10^{-5}	4.40–38.59
B*14:01	Compound sulfamethoxazole	GWAS	51 cases; 12,156 controls (European and American) Li et al. (2021)	9.2	0.0003	3.16–22.35
B*18:01	Amoxicillin-clavulanate	CGS	75 cases; 885 controls (Spanish) Stephens et al. (2013)	2.9	0.0082	1.3 ± 6.2
B*35:01	Polygonum multiflorum	CGS	26 cases; 99 controls (Chinese) Li et al. (2019)	143.9	4.8×10^{-10}	30.1–687.5
B*35:02	Minocycline	GWAS	25 cases; 10,588 controls (European) Urban et al. (2017)	29.6	2.5×10^{-8}	7.8–89.8
B*39:01	Infliximab	GWAS	18 cases; 60 controls (white person) Bruno et al. (2020)	43.6	0.001	2.8-+∞
B*57:01	Flucloxacillin	GWAS	197 cases; 6835 controls (European) Nicoletti et al. (2019)	36.6	2.67×10^{-97}	26.14–51.29
B*57:01	Pazopanib	GWAS	429 cases; 1761 controls (Global) Xu et al. (2016)	2.0	0.0014	1.3–3.1
B*57:03	Flucloxacillin	GWAS	197 cases; 6835 controls (White person) Nicoletti et al. (2017)	79.2	1.2×10^{-6}	3.37–116.1
B*58:01	Nevirapine	CGS	57 cases; 111 controls (African) Hirata et al. (2008)	U	U	U
DRB1*01:02	Nevirapine	CGS	57 cases; 111 controls (African) Phillips et al. (2013)	U	U	U
DRB1*07	Ximelagatran	GWAS	74 cases; 130 controls (European) Kindmark et al. (2008)	4.4	U	U
DRB1*07:01	Lapatinib	GWAS	37 cases; 1071 controls (European) Schaid et al. (2014)	14	2.4×10^{-13}	6.36–31.32
DRB1*16:01-DQB1*05:02	Flupirtine	GWAS	614 cases; 10,588 controls (European) Nicoletti et al. (2016)	18.7	0.002	2.5–140.5
DRB1*15:01-DQB1*06:02	Amoxicillin-clavulanate	CGS	75 cases; 885 controls (Spanish) Stephens et al. (2013)	3.0	5.1×10^{-4}	1.6 ± 5.5

Qihui Shao Q, et al. Frontier Pharmacol 2021; 12: 735260

Polymorphisms of DILI-related drug metabolizing enzymes genes in GWAS & CGS

Genes	Drug	Method	Cohort	OR	P	95%CI
CYP1A1	Nevirapine	CGS	U (European) Singh et al. (2017)	3.68–4.91	0.13–0.21	U
CYP2A6*4	Valproic acid	CGS	807 cases (Global) Yoon et al. (2020)	0.48	0.01	0.10–0.86
CYP2A6*1/*4	Valproic acid	CGS	79 cases, 200 T (Chinese) Zhao et al. (2017)	2.5	0.035	1.06–5.69
CYP2A6*4/*4				20.27	0.006	2.38–172.62
CYP2B6 rs7254579	Ticlopidine	CGS	22 cases92 T (Japanese) Ariyoshi et al. (2010)	2.1	U	U
CYP2B6*6	Efavirenz	CGS	41 cases, 160 P (African) Yimer et al. (2012)	3.3	U	U
CYP2C9 rs1057910 and	Nevirapine	CGS	U (European) Singh et al. (2017)	1.78	0.35	U
rs1799853	Valproic acid	CGS	807 cases (Global) Yoon et al. (2020)	0.70	0.002	0.25–1.15
CYP2D6	Anti-TB drugs	GWAS	114 cases, 114 controls (Chinese) Wei et al. (2020)	9.193	<0.001	3.624–25.888
CYP2E1				4.390	<0.001	1.982–9.724
CYP2E1 rs203192	Anti-TB drugs	CGS	49 cases, 21 cases (Chinese) Huang et al. (2003)	2.52	U	U
		GWAS	2225 cases, 4906 controls (Global) Cai et al. (2012)	1.36	0.12	0.92–2.00
UGT2B7 rs7439366	Anti-TB drugs	CGS	182 cases, 13 controls (Chinese) Shi et al. (2014)	2.01	U	U
UGT2B7 rs7439366	Diclofenac	CGS	24 cases, 48 T, 122 P (European) Daly et al. (2007)	C *vs.* T: 7.7 C *vs.* P: 8.5	0.026	1.1–69.9
GSTM1/GSTT1(null)	Tacrine	CGS	18 cases, 123 controls (European) Simon et al. (2000)	2.3	U	U
	Troglitazone	CGS	25 cases, 85 controls (Japanese) Watanabe et al. (2003)	3.692	0.008	1.354–10.066
	Antimicrobial agents	CGS	44 cases, control data U (Spanish) Okada et al. (2011)	3.52	0.002	1.56–8.22
	Anti-infective Drugs	CGS	49 cases, control data U (Spanish) Lucena et al. (2008)	3.12	0.006	1.37–7.11
	NSAIDs	CGS	19 cases, control data U (Spanish) Lucena et al. (2008)	5.61	0.001	1.99–16.0
	Anti-TB drugs	CGS	50 cases, 246 controls (Indian) Gupta et al. (2013)	7.18	0.007	1.7–32.6
NAT2 slow acetylation type	Anti-TB drugs	GWAS	100 cases, 210 controls (Indonesian) Yuliwulandari et al. (2019)	3.64	0.000	2.21–6.00
		CGS	1527 cases, 7184 controls (Global) Zhang et al. (2018b)	3.15	0.000	2.58–3.84
		CGS	1527 cases, 7184 controls (Western Asian) Davidson et al. (2008)	6.42	U	2.41–17.10
		CGS	1527 cases, 7184 controls (European) Zhang et al. (2018b)	2.32	U	0.58–9.24

Qihui Shao Q, et al. Frontier Pharmacol 2021; 12: 735260

Prevention of DILI
using pharmacogenetics/ pharmacogenomics

- *NAT2* slow acetylator, *CYP 2E1* c1/c1, *MnSOD* mutant C allele, null *GST M1, and ABC transports ABCC2 (MRP2) gene* variants may increase the risk of some DILI
- Pre-medication assay of high-risk genes may help to mitigate severe DILI by
  - avoiding some high-risk drugs
  - decrease dose of some drugs
  - close monitoring liver tests
  - early discontinuing drugs when abnormal liver tests, esp. hyperbilirubinemia, occur

Japanese *NAT2* genotype guided-TB treatment RCT

Genetic assay can help to prevent DILI

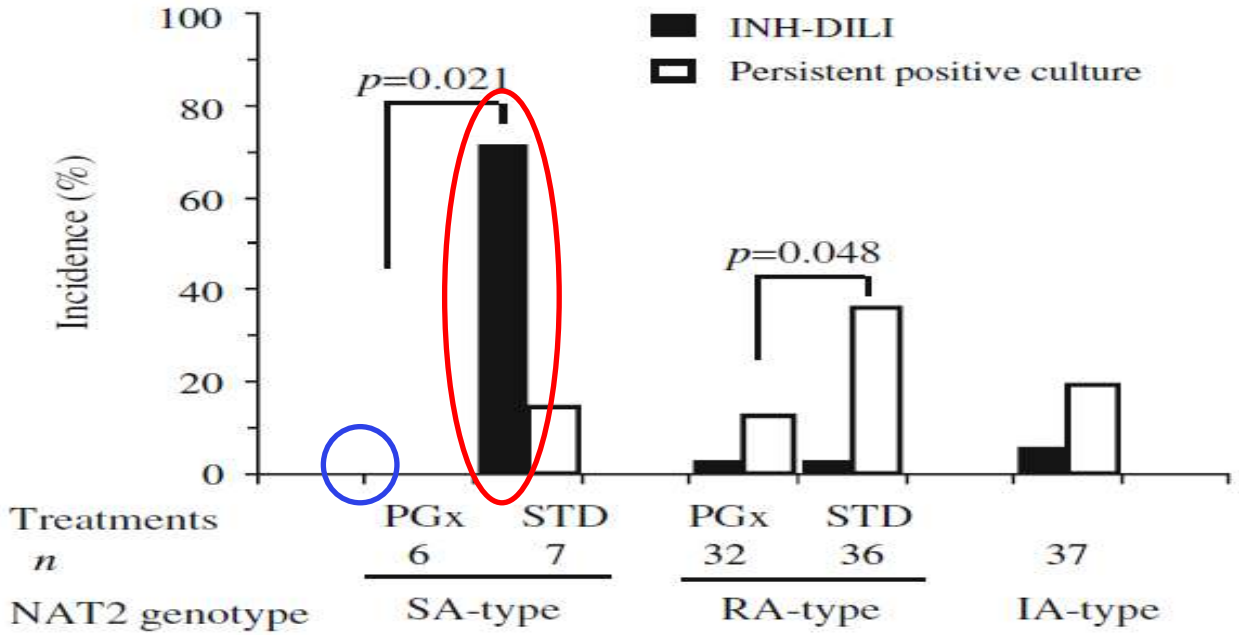


Fig. 4 Incidence of isoniazid induced liver injury (INH-DILI) and persistent positive culture among the patients with drug sensitive tuberculosis on sputum culture at screening. Closed columns, INH-DILI; open columns, persistent positive culture; RA-type, rapid acetylator genotype; IA-type, intermediate acetylator genotypes; SA-type, slow acetylator genotypes; PGx, PGx-guided treatment; STD, conventional standard-treatment

Azuma J, et al. Eur J Clin Pharmacol 2013; 69:1091–1101

Outline

- Global trend of drug-induced liver injury (DILI)
- Pathogenesis and diagnosis of DILI
- High-risk drugs to induce liver injury
- High-risk factors of incidence and severity in DILI
- Anti-tuberculosis drug-induced liver injury (ATDILI)
- Pharmacogenetics/pharmacogenomics and DILI
- **Prevention and treatment of DILI**
- Wrap up

New biomarkers for DILI

- Glutamate dehydrogenase (GLDH)
- Micro-RNA-122 (miR-122)
- Cytokeratin 18 (K18)
- Macrophage colony-stimulating receptor (MCSFR)
- Osteopontin

- They need further validation to allow early detection and assessment of DILI
  - -Devarbhavi H, et al. DILI: APASL guidelines. Hepatol Int 2021; 15: 258-282
  - -Fontana RJ, et al. AASLD guidance in DILI. Hepatology 2022 doi: 10.1002

State-of-the-art management of DILI

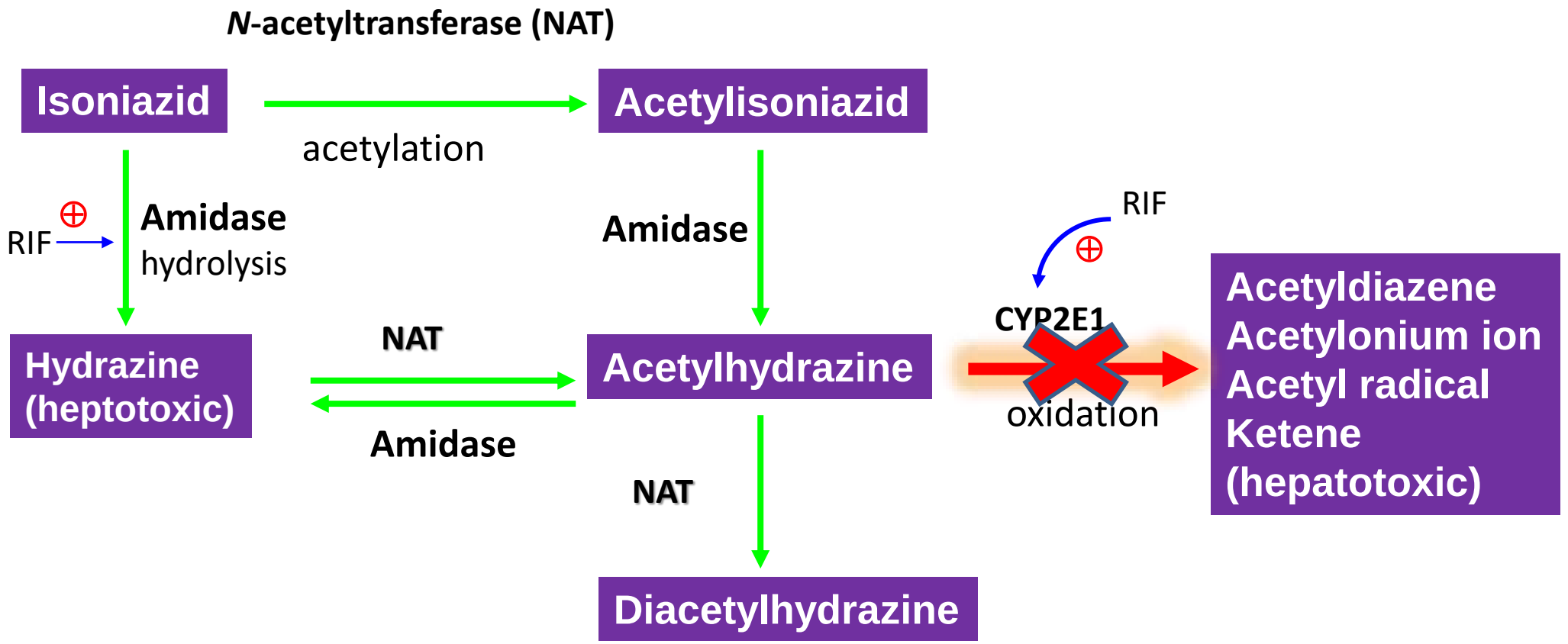
- Timely diagnosis by a high index of suspicion
- Identifying the offending agents, prompt withdrawal
- L-Carnitine: antidote for valproate-induced liver injury
- *N*-acetylcysteine: antidote for acetaminophen-induced liver injury; maybe helpful in early stage ALF of other DILIs
- Liver transplantation in ALF

-Devarbhavi H, et al. DILI: APASL guidelines. Hepatol Int 2021; 15: 258-282

- Steroid: DILI combined with SCAR, or autoimmune DILI
- Glycyrrhizin -Wang JB, et al. Alimet Pharmacol Ther 2022; 55-1297-1310
- Bicyclol -Tang J, et al. Liver Int 2022; 42: 1803-1813

Metabolism of isoniazid in the liver

CYP 2E1 wild genotype c1/c1



Huang YS. Expert Opinion on Drug Metabolism and Toxicology 2007; 3: 1-8

Mannitol: a CYP2E1 inhibitor
Prevents ATDILI in mice

Table 1. GSP levels, hepatic AST and ALT activities and Total HAI score in the Normal control (NC), INH/RIF alone (INH/RIF-control), high dose of mannitol alone (HM-control) and INH/RIF co-treatment with High-dose (HM-study), Medium-dose (MM-study) and Low-dose (LM-study) of mannitol groups following 3 weeks of treatment

Groups	GSP (mg/L)	AST (IU/L)	ALT (IU/L)	Total HAI score
Normal control (NC, n=8)	194 ± 18	80 ± 13	46 ± 10	0.0 ± 0.0
INH/RIF-control (n=8)	751 ± 75	420 ± 66	298 ± 43	5.3 ± 2.2
HM-control (n=8)	183 ± 21	76 ± 11	44 ± 13	0.0 ± 0.0
HM-study (n=8)	252 ± 24***	93 ± 12***	54 ± 18***	0.8 ± 0.5***
MM-study (n=6)	237 ± 30***	85 ± 16***	52 ± 16***	0.7 ± 0.8***
LM-study (n=6)	300 ± 40**	154 ± 62*	119 ± 55**	2.0 ± 0.6*

Data are shown as mean ± SD. Each groups contained eight or six mice.
Statistical analysis: Anova and LSD test.
*$p < 0.05$, **$p < 0.01$, ***$p < 0.005$: Study compare to INH/RIF-control group.

Shih TY, Hu OY, et at. Current Drug Metabolism 2013; 14, 720-728

Kaempferol: a CYP2E1 inhibitor
Prevents ATDILI in mice

Table III. GSP Levels, Hepatic AST and ALT Activities, and Total HAI Score in NC, INH/RIF-Control, LK-Study, and HK-Study Groups after 3 Weeks of Treatment

Groups	GSP (mg/L)	AST (IU/L)	ALT (IU/L)	Total HAI score
Normal control (n=9)	177±22	80±11	41±13	0.0±0.0
INH/RIF-control (n=8)	866±339***	571±295***	364±192***	5.3±2.1***
Study-LK (n=9)	401±178***	164±78***	117±62***	1.9±1.1*
Study-HK (n=9)	245±98***	89±19***	48±21***	1.6±1.0**

Data are shown as the mean±SD. Each group contained at least eight mice. Statistical analysis: ANOVA and LSD test
GSP: ***p<0.005 *vs.* NC group and *vs.* control group
AST and ALT: ***p<0.005 *vs.* NC group and *vs.* control group
Total HAI score: ***p<0.005 *vs.* NC group; *p<0.05, **p<0.01 *vs.* control group
GSP galactose single point, *AST* aspartate aminotransferase, *ALT* alanine aminotransferase, *HAI* histological activity index, *NC* normal control, *INH* isoniazid, *RIF* rifampicin

Shih TY, Hu OY, et al. AAPS J 2013; 15: 753-762

Outline

- Global trend of drug-induced liver injury (DILI)
- Pathogenesis and diagnosis of DILI
- High-risk drugs to induce liver injury
- High-risk factors of incidence and severity in DILI
- Anti-tuberculosis drug-induced liver injury (ATDILI)
- Pharmacogenetics/pharmacogenomics and DILI
- Prevention and treatment of DILI
- **Wrap up**

Wrap up - 1

1. **Anti-TB drugs and HDS:** the major agents to induce liver injury globally
2. Diagnosis of DILI by exclusion and causality assessment: RUCAM/RECUM; LiverTox
3. DILI due to HDS, anti-TB drugs, combined with SCAR, active hepatitis B infection or chronic liver diseases: poor prognosis
4. Genetic assays in some drug-metabolizing enzymes and HLA may aid in the prediction of some DILI; such as *NAT2* slow acetylators in anti-TB DILI

Wrap up - 2

5. High suspicion & early diagnosis of DILI by clinical S/S, and withdrawal of offending drugs: the mainstay of management
6. Regular monitoring liver tests in the high-risk patients with high-risk drugs, such as HBV carriers with anti-TB drugs
7. *N*-acetylcysteine, mannitol and kaempferol: treatment of DILI
8. Public education and professional alert to drug safety: urgently needed to prevent DILI and other ADRs

從臨床常見毒藥物中毒事件談藥品肝傷害之診斷

楊振昌特聘教授兼部主任

國立陽明交通大學醫學院環境與職業衛生研究所 、公共衛生研究所、急重症醫學研究所、臺北榮總職業醫學及臨床毒物部

大綱

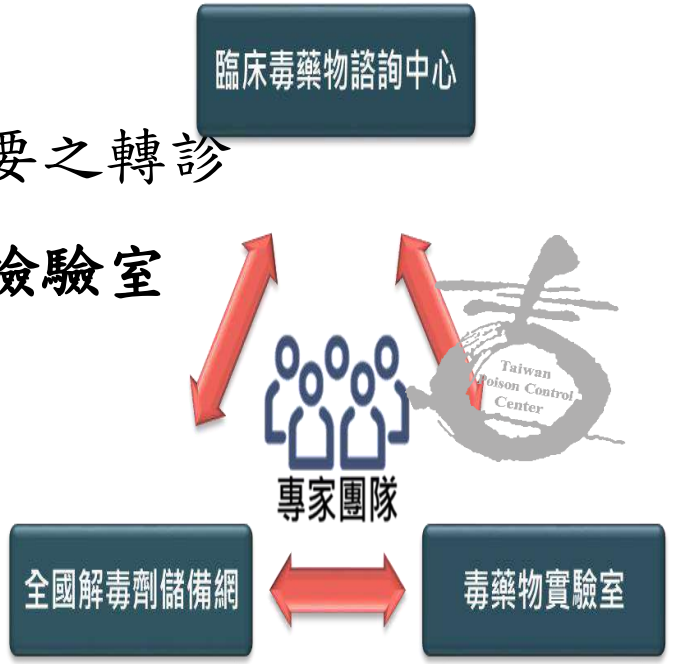
- **毒藥物防治諮詢中心之簡介**
- 國內常見毒藥物中毒之簡介
- 急性藥物中毒導致肝傷害之簡介
- 急性非藥物中毒導致肝傷害之簡介
  - 職業性毒物暴露導致肝傷害
  - 中草藥導致肝傷害(HILI)
  - 其他原因導致肝傷害
- 毒藥物中毒導致肝傷害之鑑別診斷與治療

毒藥物防治諮詢中心源起

- 二次世界大戰以後，農藥中毒、環境污染、職業性化學物質中毒、物質濫用及兒童意外中毒等各式各樣的中毒，日益增多。
- 中毒物質種類繁多，如何適當處理相當困難。
- 為因應日益增多的有毒物質及其危害，歐美自1940年代末期，開始逐步成立毒藥物防治諮詢中心 (Poison Control/Information Center、PCC)，輔以受過特殊訓練的醫師、藥師、護理師及諮詢師，經由24小時之線上電話服務，處理漸增的中毒個案。

北榮毒藥物防治諮詢中心

- 1985年7月成立
- **亞洲最早成立及全台唯一**國家級毒藥物諮詢中心
- 24小時免費線上專業諮詢服務
- 協助臨床醫師進行診斷、治療及必要之轉診
- **經驗最豐富、設備最完善的毒藥物檢驗室**
- **2000年建制全國解毒劑供應網**
- 提供完善的診治建議及評估服務
- 積極培養毒藥物防治專業人才

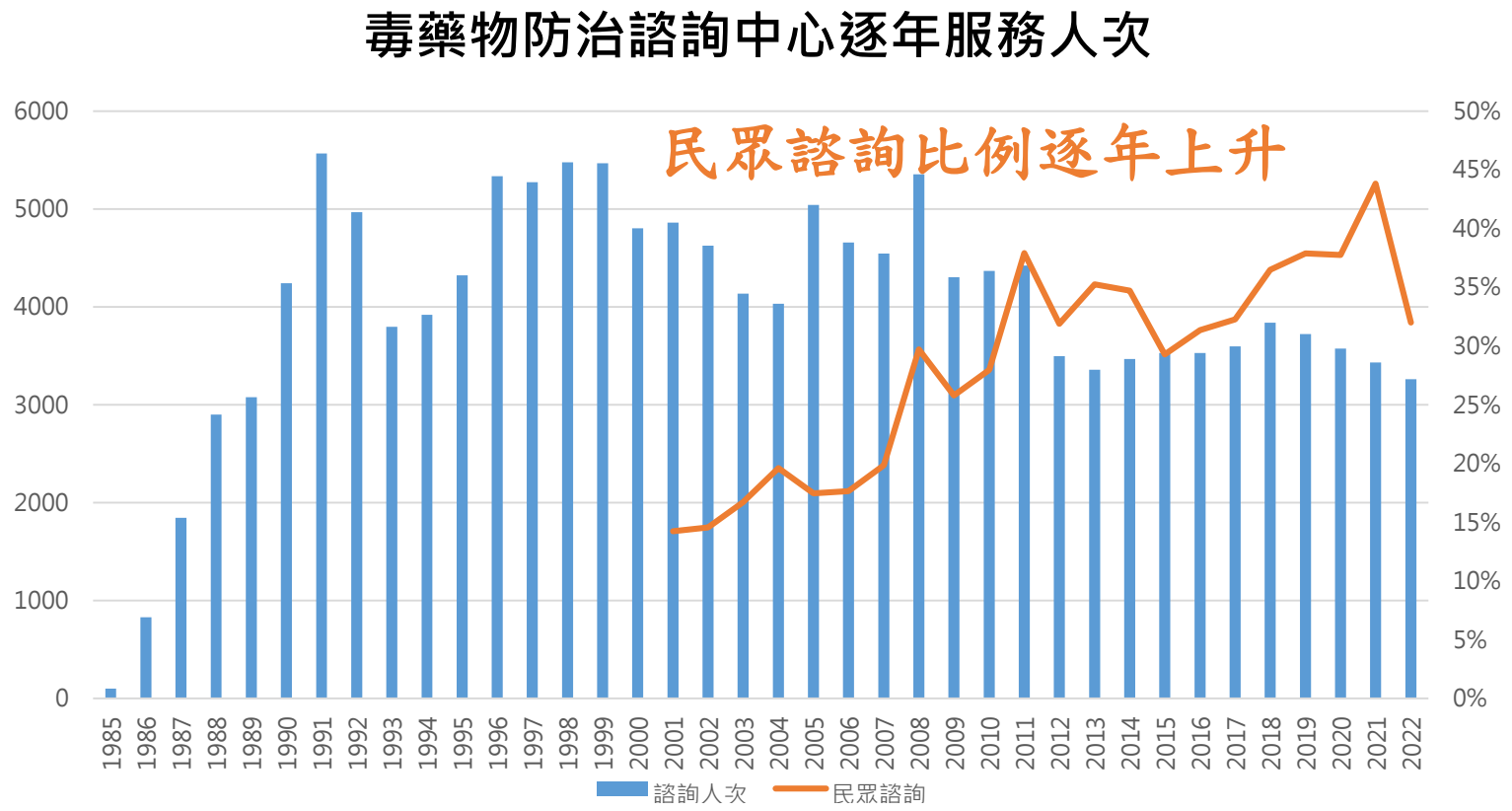


毒藥物防治諮詢中心特殊中毒事件服務軌跡

- 魚類農藥中毒1985
- 蔭花生中毒事件 1986
- **四氯化碳中毒1986**
- 陽明山溫泉硫化氫中毒1987
- 安非他命中毒1990
- 鋇鹽中毒1991
- 八角蓮中毒1992
- 減肥菜中毒1995
- 屏東織紋螺河魨中毒1995
- 全國解毒劑供應網建立2000
- 福國化工爆炸事件2001
- 馬兜鈴酸中毒2003
- 蠻牛飲料中毒2005
- PMMA轟趴中毒2006
- 三聚氰胺汙染奶粉2008
- 氨基甲酸鹽農藥下毒2009
- 氯化鋇中毒2009
- 瘦肉精中毒2010
- 塑化劑食品污染應變2011
- 亞硝酸鹽下毒2011
- 葡萄催芽劑下毒2011
- 瘦肉精爭議2012
- 順丁烯二酸化製澱粉2013
- 正溴丙烷中毒2013
- 鉈中毒2014
- W-Hotel濫用藥物中毒2016
- 農藥最大容許量修訂2017
- 醫療端新興濫用藥物監測機制計畫 2019
- 盛唐中醫鉛中毒2020
- 澳洲交換留學生滅鼠藥中毒2023
- 幼兒園巴比妥酸鹽事件2023

毒藥物防治諮詢中心服務量

- 至111年底累計服務量達15萬1,088人次



大綱

- 毒藥物防治諮詢中心之簡介
- **國內常見毒藥物中毒之簡介**
- 急性藥物中毒導致肝傷害之簡介
- 急性非藥物中毒導致肝傷害之簡介
  - 職業性毒物暴露導致肝傷害
  - 中草藥導致肝傷害(HILI)
  - 其他原因導致肝傷害
- 毒藥物中毒導致肝傷害之鑑別診斷與治療

國內常見中毒物質

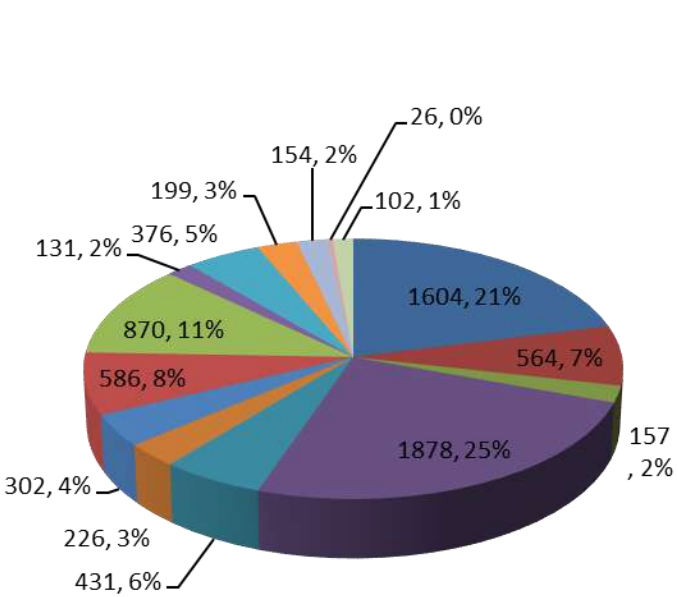
- **Pesticides (農藥)**: e.g., organophosphates, carbamate insecticides, pyrethroids, paraquat, glyphosate-surfactant herbicides, newer pesticides (e.g., imidacloprid, glufosinate)
- **Prescription drugs**: e.g., sedatives-hypnotics, analgesics, antipsychotics, antidepressants, panadol (acetaminophen)
- **Over-the-counter (OTC) drugs**
- **Illicit drugs**: e.g., heroin, cocaine, MDMA, marijuana, methamphetamine, mephedrone, bath salts (MDPV)
- **Toxic gases & industrial chemicals**: e.g., CO, H2S, solvents
- **Alcohols**: e.g., ethanol/methanol, ethylene glycol
- **Plant & animal toxins**: e.g., snakebites, wasp stings
- **Household chemicals**

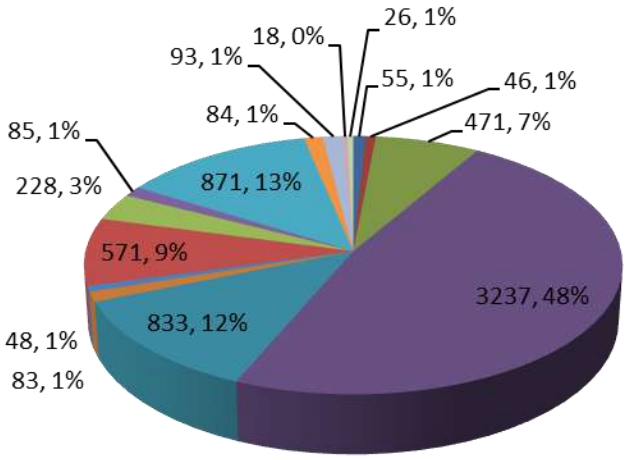
Toxic Category, PCC-Taiwan, 1985-1993

Category	≤ 18 y N	≤ 18 y %	≥ 19 y N	≥ 19 y %	Total N	Total %
Pesticides	633	10.9	6,239	35.4	6,872	29.3
Drugs	1,886	32.4	4,874	27.7	6,760	28.8
Cleaning substances	410	7.1	1,196	6.7	1,606	6.9
Solvents	285	4.9	736	4.2	1,021	4.4
Animal bites; stings	172	3.0	781	4.4	953	4.1
Rodenticides	148	2.5	658	3.7	806	3.4
Cosmetics	246	4.2	383	2.2	629	2.7
Insect repellents	251	4.3	257	1.5	508	2.2
Chinese herbs	ill	1.9	319	1.8	430	1.8
CO & toxic gases	93	1.6	331	1.9	424	1.8
Food-borne toxins	89	1.5	190	1.1	279	1.2
Hydrocarbons	49	0.8	168	1.0	217	0.9
Plants	63	1.1	126	0.7	189	0.8
Miscellaneous	1,376	23.7	1,366	7.8	2,742	11.7
Total	**5,812**	**100.0**	**17,624**	**100.0**	**23,436**	**100.0**

Yang CC, et al. *Clinical Toxicology* 1996;34:651-663.

2016-2020年成人及兒童中毒物質種類分布



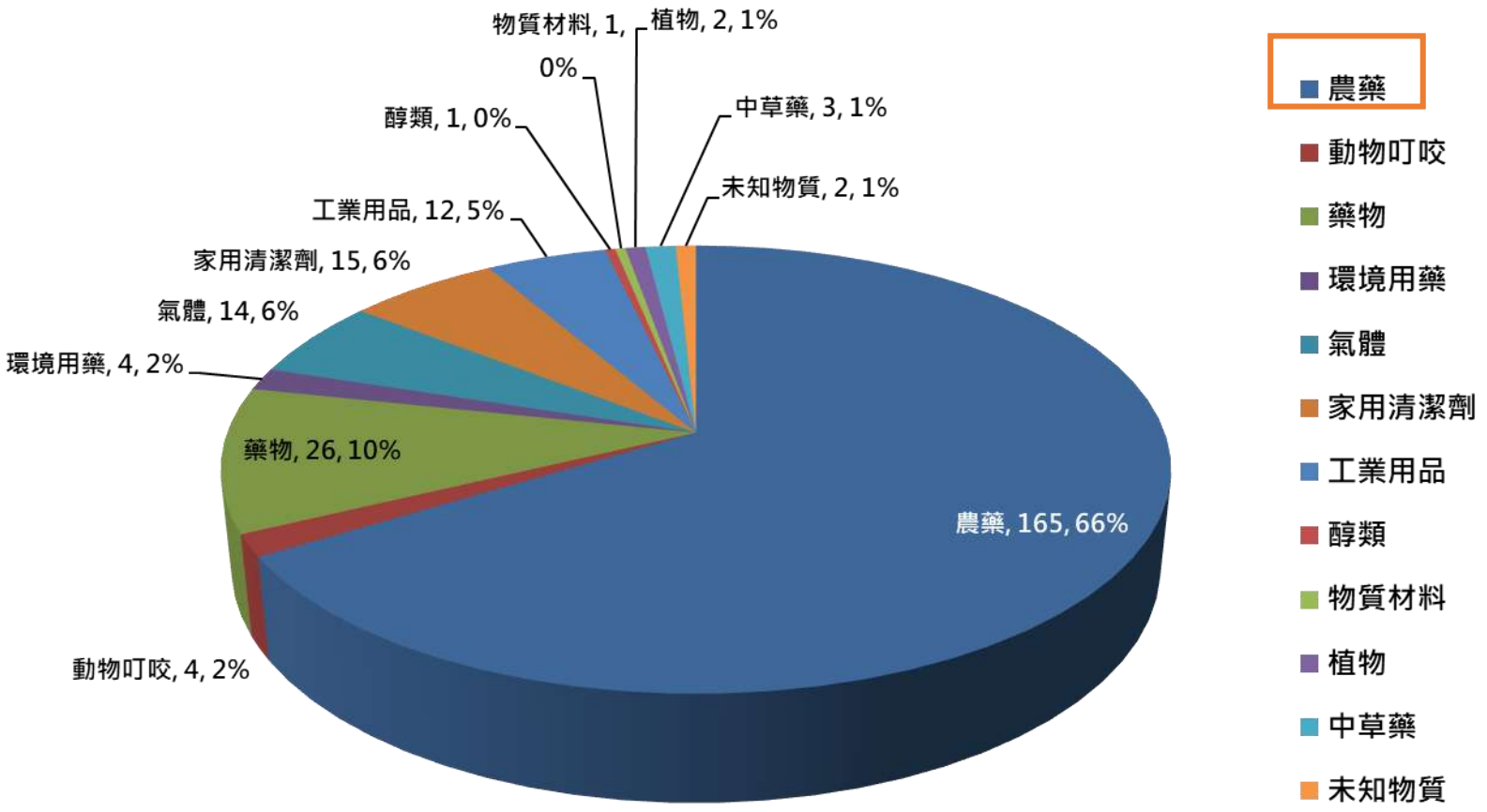


成人中毒物質分類

個案數(%)

兒童中毒物質分類

2016-2020年死亡個案中毒物質種類分布



大綱

- 毒藥物防治諮詢中心之簡介
- 國內常見毒藥物中毒之簡介
- **急性藥物中毒導致肝傷害之簡介**
- 急性非藥物中毒導致肝傷害之簡介
  - ➢職業性毒物暴露導致肝傷害
  - ➢中草藥導致肝傷害(HILI)
  - ➢其他原因導致肝傷害
- 毒藥物中毒導致肝傷害之鑑別診斷與治療

肝臟病生理(pathophysiology)

- The response of liver to chemical exposure **depends on the intensity of the insults, the cell population affected, and the duration of the exposure** (acute vs chronic)
- Exposure to estrogens → temporary cholestasis followed by adaptive response (conditioning)
- **Acetaminophen** or CCl4→ parenchymal cell necrosis
- **Ethanol**: steatosis, subsequent inflammation
- Table 13-2 (Casarett and Doull's Toxicology: The Basic Science of Poisons) includes pharmaceuticals, recreational drugs, vitamin, metals, hormones, industrial chemicals, compounds found in teas (germander), foods, and toxins produced by fungi and algae

Table 13-2

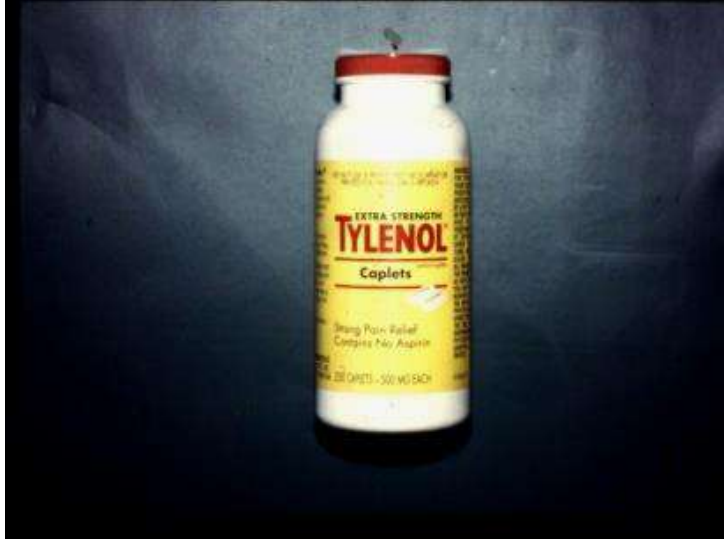
Types of Hepatobiliary Injury

TYPE OF INJURY OR DAMAGE	REPRESENTATIVE TOXINS
Fatty liver	Amiodarone, CCl_4, ethanol, fialuridine, tamoxifen, valproic acid
Hepatocyte death	Acetaminophen, allyl alcohol, Cu, dimethylformamide, ethanol
Immune-mediated response	Diclofenac, ethanol, halothane, tienilic acid
Canalicular cholestasis	Chlorpromazine, cyclosporin A, 1,1-dichloroethylene, estrogens, Mn, phalloidin
Bile duct damage	Alpha-naphthylisothiocyanate, amoxicillin, methylenedianiline, sporidesmin
Sinusoidal disorders	Anabolic steroids, cyclophosphamide, microcystin, pyrrolizidine alkaloids
Fibrosis and cirrhosis	CCl_4, ethanol, thioacetamide, vitamin A, vinyl chloride
Tumors	Aflatoxin, androgens, arsenic, thorium dioxide, vinyl chloride

Casarett and Doull's Toxicology: The Basic Science of Poisons, 7th ed.

Acetaminophen (APAP)

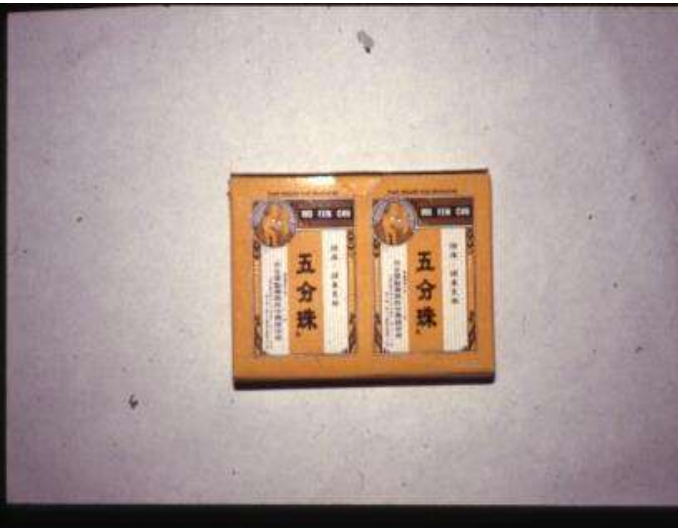
- 1890年代被發現，1960年代上市
- 名稱：普拿疼(panadol), Tylenol, Scanol
- 為phenacetin (一種已被禁用的具腎毒性及致癌性藥物)之代謝物
- **為全球最廣為使用之止痛解熱藥物之一**
- **對於prostaglandins基本上不具有抑制作用(與NSAIDs之主要不同)**
- 在很多非處方藥物及複方感冒藥中皆含有APAP
- 一般之劑型為500 mg/tablet

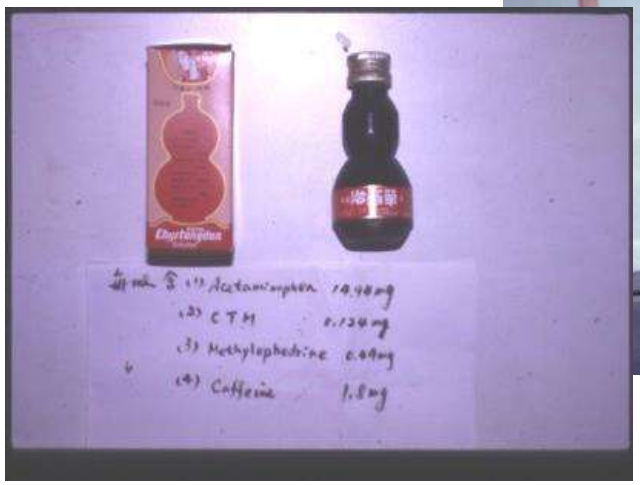

EXTRA STRENGTH
TYLENOL
Caplets


Panadol
Rapid
RELIEVES PAIN FAST
ABSORBED TWICE AS FAST AS REGULAR PANADOL TABLETS
20 CAPLETS


Panadol
Extra

普拿疼 (panadol)


五分珠
五分珠


(1) Acetaminophen 14.98mg
(2) CTM 0.124mg
(3) Methylephedrine 0.09mg
(4) Caffeine 1.8mg


EXTRA STRENGTH
TYLENOL
EXTRA STRENGTH
TYLENOL

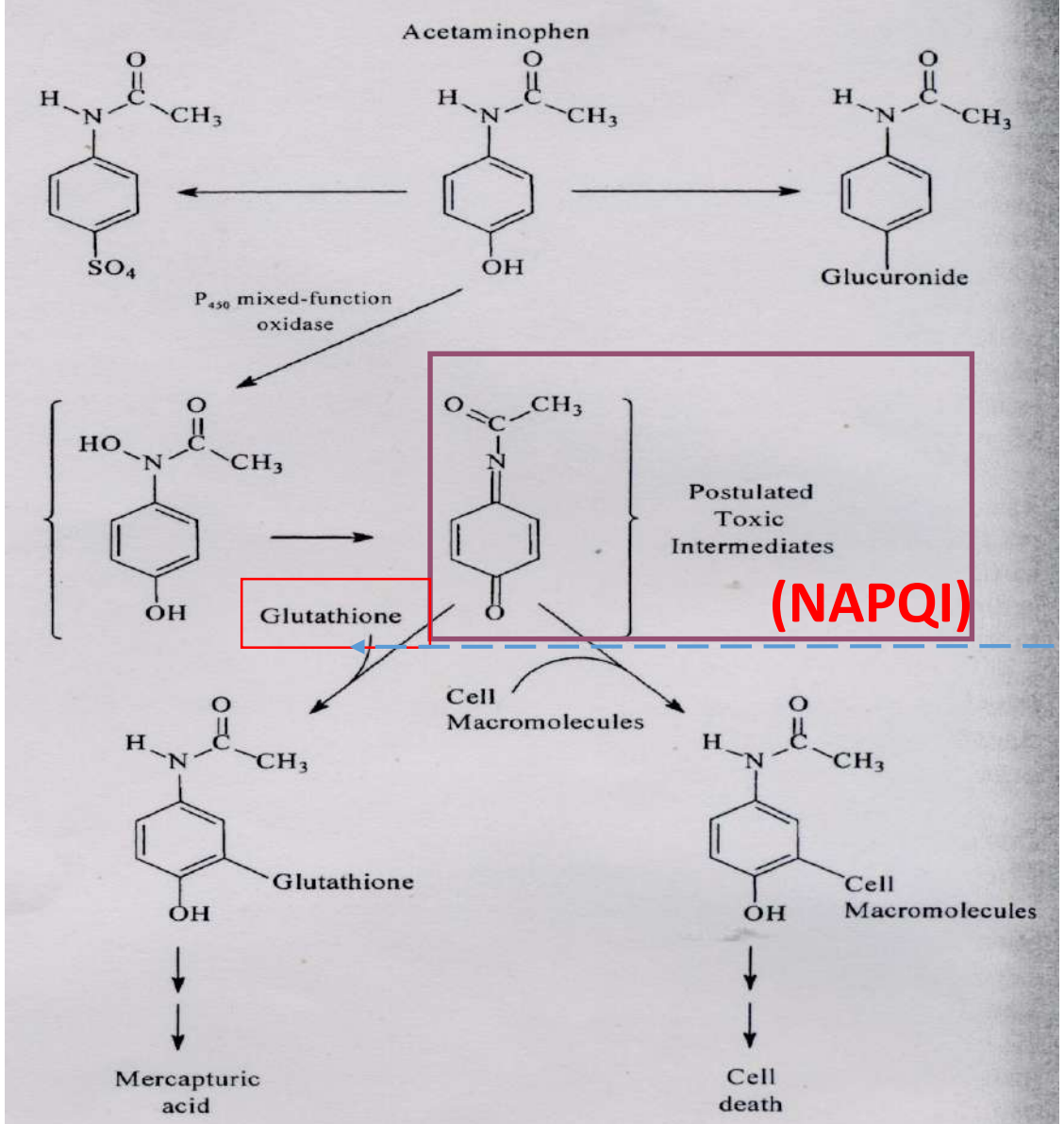


Figure 31-4 Pathways of acetaminophen metabolism. (From Mitchell JR, Thorgeirsson SS, Potter WZ, Jollow DJ, Keiser H. Acetaminophen-induced hepatic injury: protective role of glutathione in man and rationale for therapy. Clin Pharmacol Ther 1974;16:676.)

APAP中毒之典型表徵

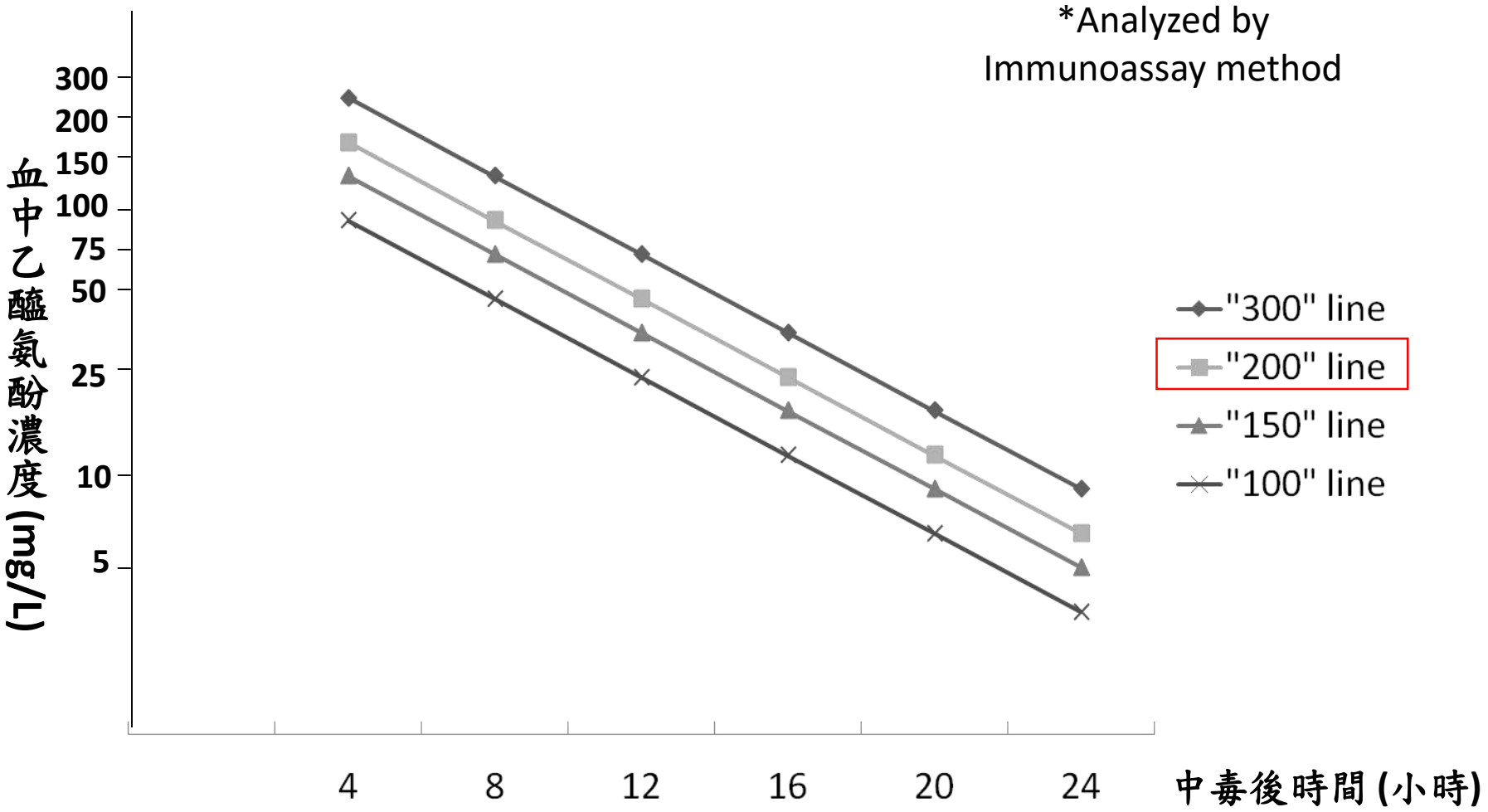
- 中毒初期(0-24 小時)

  無症狀或僅有噁心、嘔吐、冒汗、全身倦怠及臉色蒼白
- 中毒中期(24-48小時)

  初期症狀改善，但ALT/AST開始升高，凝血功能開始產生異常(prolongation of prothrombin time)
- **肝臟期(72-96小時)**

  肝臟壞死、黃疸、右上腹痛、肝腦病變(hepatic encephalopathy)、ALT/AST顯著升高
- 恢復期(5-14 天)

  多數中毒病人會完全恢復，但少數人會產生肝衰竭



圖二. 血中乙醯氨酚濃度之自然對數值與中毒後時間之關係圖 (濃度在 “300” line 以上: 90%會有嚴重肝毒性; “200” line: 60%會有嚴重肝毒性; “150” line: 可能會有肝毒性;“ 100” line: 酗酒者或併服促進 cytochrome P450 酵素之藥物者, 在此濃度以上, 可能會有肝毒性

A case of severe hyperammonemia and unconsciousness following sodium valproate intoxication

Lee WL, Yang CC, Deng JF, Chen YF, Lin HD, Wang PH
Vet Hum Toxicol 1998;40(6):346-8.

Abstract

Although valproic acid has gradually gained its popularity in the treatment of various seizure disorders, overdose of valproate is not common. An 18-y-old man with a history of epilepsy controlled by sodium valproate and clonazepam attempted suicide with an ingestion of 45 g sodium valproate. He presented to our service with drowsiness and irritability. Extremely high serum ammonia (623 ug/dL) and elevated serum valproate concentration (575 ug/mL) were found on admission. Several metabolic abnormalities, including hypernatremia, hypocalcemia and metabolic acidosis, as well as increased serum transaminase levels were also recorded. With supportive measures, he became clear 24 h later and was discharged 6 d after ingestion. Serial follow-up of his serum valproate and ammonia levels disclosed a close relationship between these 2 measurables. After acute overdose of valproic acid, patients usually present with mild and generally reversible depression of the central nervous system. However, impairment of liver function, hyperammonemia, fluid-electrolyte disturbances, coma, seizures, hypotension and even death may occur following valproate overdose. Symptomatic and supportive measures are the mainstay in the treatment of valproic acid overdose. With prompt diagnosis and early institution of treatment, a complete recovery should be anticipated.

Valproic acid poisoning in Taiwan: a poison center-based study

Pei-Yuan Ma[1], Chen-Chang Yang[2,3], Yueh-Ching Chou[1,4], Hsiang-Ling Chen[3], Jou-Fang Deng[3] and Yuh-Lih Chang[1,4]

[1] Institute of Pharmacology, National Yang-Ming University School of Medicine, Taipei, Taiwan
[2] Institute of Environmental & Occupational Health Sciences, National Yang-Ming University School of Medicine, Taipei, Taiwan
[3] National Poison Control Center, Taipei, Taiwan
[4] Pharmacy Department, Taipei Veterans General Hospital, Taipei, Taiwan

Background

Valproic acid (VPA) is a broad spectrum antiepileptic drug, and it has other indications including bipolar disorder, panic disorder, migraine prophylaxis, and peripheral neuropathy[1]. Because of the increased use of VPA, the numbers of VPA calls in American Association of Poison Control Centers were 7-folds between 1990 and 2000[2,3]. However, number of VPA poisoning slightly declines in recent years[7].

While VPA is generally considered a safe medication, in overdose, it may cause central nervous system (CNS) depression, cerebral edema, hyperammonemia, hypotension, and hepatitis.[4] Renal replacement therapy (RRT) and L-carnitine are the choice of management for severe symptoms of acute VPA overdose,[5,6] but their clinical evidence are limited.

Objective

This study was conducted to identify the demographic and clinical characteristics of VPA poisoning cases reported to the Taiwan Poison Control Center (PCC-Taiwan). The effectiveness of RRT as well as L-carnitine in the treatment of VPA poisoning was also evaluated.

Methods

A retrospective review of all VPA poisoning cases reported to PCC-Taiwan between 1985 and 2018 was conducted. Data for patients with relevant poisoning were collected. We then analyzed the patients' baseline characteristics as well as the prognosis of poisoning among patients who received RRT and/or L-carnitine treatment.

Results

There were 221 VPA poisoning cases reported to PCC-Taiwan during the study period, and the number decline in the last decade (Figure 1). Males and females were involved in 104 (47%) and 117 cases (53%), respectively. The median age was 27 years (range from 1 month to 83 years) (Figure 2A). Intentional exposure accounted for 74% of the poisoning cases. In terms of severity, 1% of the 221 patients died, 5% had severe effects, 24% had moderate effects, 46% had mild toxicity, 14% were asymptomatic, and 10% had unknown severity (Figure 2B). Older age and intentional exposure were positively associated with moderate-to-fatal poisoning (Table 1). Table 2 shows the outcome of different therapy for VPA poisoning cases. One of two patients who used L-carnitine was dead.

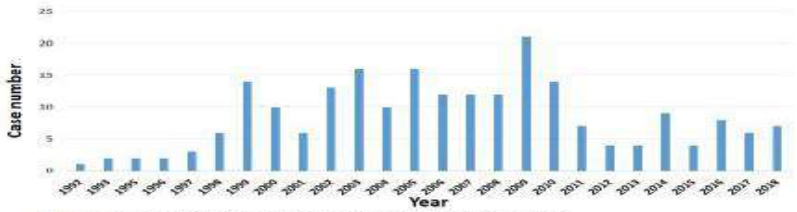


Figure 1. The number of VPA poisoning cases reported to PCC-Taiwan

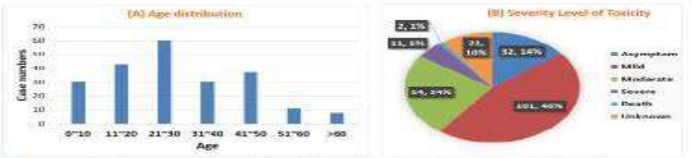


Figure 2. The demographic and clinical characteristics of VPA poisoning cases.

Table 1. Differences in baseline characteristics between patients with asymptomatic-to-mild and moderate-to-fatal VPA related poisoning in Taiwan.

Characteristics	Asymptomatic/mild N= 133 (%)	Moderate/severe/fatal N= 67 (%)	P-value
Age, mean (SD), y	25.5 (15.7)	34.7 (15.9)	0.0001
Male	55 (41.35)	36 (53.73)	0.101
Toxicity Type			0.182
Acute	130 (98.48)	63 (94.03)	
Chronic	2 (1.52)	4 (5.97)	
Reason			0.013
Non-intentional	34 (25.95)	6 (10.17)	
Intentional	97 (74.05)	53 (89.83)	

Table 2. The outcome of different therapy for VPA poisoning cases

Therapy	Outcome of therapy
RRT* (n=6)	The manifestations of altered mental status, hyperammonemia, and/or hypotension greatly improved after treatment
L-carnitine¥ (n=2)	One patient showed an improvement in hyperammonemia, whereas the other died from shock
CVVH combine L-carnitine (n=1)	Although treatment by intubation, CVVH and L-carnitine, the patient still succumbed

RRT: renal replacement therapy, CVVH: continuous venovenous hemofiltration
*Only RRT not received L-carnitine
¥Only L-carnitine not received RRT

Conclusion

Most cases of VPA poisoning in this study involved mild symptoms only. Older age and intentional exposure predicted the severity of poisoning in this study. However, severe effects can still occur and prompt treatment with RRT may be effective in alleviating the toxic effects of valproic acid.

References

1. Fagundes SBR. Valproic acid: review. Revista Neurociencias 2008;16:230-6.
2. Lheureux, T.L.; Bailey, K.M.; Schmitz, B.T.; Hulten, K.G.; Klein-Schwartz, W. 1990 Annual Report of the American Association of Poison Control Centers National Data Collection System. Am. J. Emerg. Med. 1991, 9, 401–509.
3. Lheureux, T.L.; Klein-Schwartz, W.; White, S.; Calvaugh, D.J.; Yoanna, J.; Greisert, J.C.; Desh, A.; Benson, B.E. 2000 Annual Report of the American Association of Poison Control Centers Toxic Exposure Surveillance System. Am. J. Emerg. Med. 2001, 19, 337–395.
4. Sztajnkrycer MD. Valproic acid toxicity: overview and management. J Toxicol Clin Toxicol 2002;40:789-801.
5. Ghannoum M, Laliberté M, Nolin TD, et al. Extracorporeal treatment for valproic acid poisoning: systematic review and recommendations from the EXTRIP workgroup. Clin Toxicol (Phila). 2015;53(5):454–465.
6. Perrott J, Murphy NG, Zed PJ. L-carnitine for acute valproic acid overdose: a systematic review of published cases. Ann Pharmacother. 2010;44(7-8):1287–1293.
7. Gummin DD, Mowry JB, Spyker DA, Brooks DE, Osterthaler KM, Banner W. 2017 Annual Report of the American Association of Poison Control Centers' National Poison Data System (NPDS): 35th Annual Report. Clin Toxicol (Phila). 2018;56(12):1213–1415.

日期	TP	ALB	CA	CHOL	BUN	UA	CREA	BILIT	ALKP	LDH	ALT	AST	FIB-4	NA	K	CL	GLU	IP	CK
24-04-21 11:41	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
24-04-21 12:04	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
24-04-21 12:04	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
24-04-21 12:04	-	4.7	-	-	14	-	1.01	0.55	116	459	35	-	-	142	3.7	-	113	-	11200
24-04-21 12:04	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
24-04-21 17:20	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	17416
24-04-22 07:44	-	-	-	-	-	-	-	-	-	-	-	-	-	143	3.8	-	113	-	17781
24-04-23 06:43	-	-	8.3	-	9	3.3	0.58	-	-	441	62	202	9.78	144	4.0	-	80	3.0	10449
24-04-25 08:51	-	-	-	-	12	-	0.54	0.26	-	362	58	99	4.96	143	3.8	-	-	-	-
24-04-25 08:51	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	3410
24-04-27 06:43	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	1161
24-04-29 09:16	-	-	-	-	-	-	0.61	-	-	322	37	-	-	142	3.9	-	-	-	550
24-05-01 09:28	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	289

長效型殺鼠劑+精神科用藥中毒個案

ACCEPTED: CLINICAL VIGNETTES/CASE REPORTS—LIVER

Rhabdomyolysis Masquerading as Acute Liver Failure: A Case Report

2242

Hogan, Daniel E. Jr. DO; Kesar, Varun MD; Chun, Alexander MD

Author Information

American Journal of Gastroenterology 113():p S1272, October 2018.

FREE

Acute liver failure is a life-threatening condition characterized by acute liver injury, encephalopathy, and coagulopathy in a patient with preexisting liver disease. Etiologies are broad, but given the poor prognosis rapid recognition is key to treatment. Those diagnosed with acute liver failure should be treated in the ICU at a transplant facility. Acute liver injury itself can result from a wide array of causes, though elevation of AST and ALT rarely exceed the low 1,000s. We present a case of a patient with an acute change in mental status, found down with LFTs exceeding the upper limit of detection concerning for acute liver failure.

→ **AST >7,000 U/L, ALT 2,907 U/L, and CK of 9,333 U/L**

大綱

- 毒藥物防治諮詢中心之簡介
- 國內常見毒藥物中毒之簡介
- 急性藥物中毒導致肝傷害之簡介
- **急性非藥物中毒導致肝傷害之簡介**
  - **職業性毒物暴露導致肝傷害**
  - 中草藥導致肝傷害(HILI)
  - 其他原因導致肝傷害
- 毒藥物中毒導致肝傷害之鑑別診斷與治療

職業性肝臟疾病

- 急性肝實質病變：如**急性肝傷害**(acute liver injury)、脂肪變性、膽汁鬱積
- 血管性障礙：如肝靜脈竇擴張、門脈擴張
- 慢性肝實質病變：如慢性肝炎、肝肉芽腫、肝纖維化/肝硬化
- 肝腫瘤：如肝癌、惡性血管瘤(angiosarcoma)
- 以往國內曾有相關報告之毒性物質：如**四氯化碳、氯仿、氯乙烯、二甲基甲醯胺、二甲基乙醯胺**……

Table 22-1. Chemical agents associated with occupational liver disease

Compound	Type of injury	Occupation/use
Arsenic	Cirrhosis, HCC, angiosarcoma	Pesticides
Beryllium	Granulomatous disease	Ceramics workers
Carbon tetrachloride	Acute liver injury, cirrhosis	Chemical manufacturing
Dimethylformamide	Acute liver injury	Solvent, chemical manufacturing
Dimethylnitrosamine	HCC	Rocket manufacturing
Dioxin	Porphyria cutanea tarda	Pesticides
Halothane	Acute liver injury	Anesthesiology
Hydrazine	Steatosis	Rocket manufacturing
Methylene dianiline	Cholestasis	MDA production workers
2-Nitropane	Acute liver injury	Painters
Phosphorus	Acute liver injury	Munitions workers
Polychlorinated biphenyls	Subacute liver injury	Production, electrical utility
Tetrachloroethane	Acute or subacute liver injury	Aircraft manufacturing
Trichloroethylene	Acute liver injury	Cleaning solvent sniffing
Trinitrotoluene	Acute or subacute liver injury	Munitions workers
Vinyl chloride	Angiosarcoma	Rubber workers

化學性肝傷害

- 化學性肝傷害：臨床上主要可分為肝細胞傷害、膽汁鬱積、及混合型等三類
- 可能導致化學性肝傷害之物質：如**有機溶劑(四氯化碳、氯仿、苯、甲苯、二甲基甲醯胺、二甲基乙醯胺、二甲基硫、三氯乙烯、四氯乙烯)**；環境污染物(戴奧辛、黃麴毒素)；塑膠原料(苯乙烯、氯乙烯)；農藥(巴拉刈除草劑、葡萄催芽劑)；外用消毒液(煤餾油酚、酚)；金屬(砷、銅)；黃磷等

Int J Hyg Environ Health. 2002 Oct;205(6):479-91.

Industrial solvents and liver toxicity: risk assessment, risk factors and mechanisms.

Brautbar N, Williams J 2nd.

University of Southern California, School of Medicine, Department of Medicine, 6200 Wilshire Blvd., Ste. 1000, Los Angeles, CA 90048, USA. Brautbar@aol.com

Abstract

Organic solvents utilized in various industrial processes may be associated with hepatotoxicity. The hepatotoxicity of some of the solvents was recognized as early as 1887, 1889 and 1904. Factors contributing to the hepatotoxicity of solvents include 1) species differences, 2) **liver** blood flow, 3) protein binding, 4) point of binding intracellularly, 5) genetic factors, 6) different cellular enzymatic degradation, 7) age, 8) nutritional condition, 9) interaction with alcohol, and 10) interaction with medications of use and abuse. The hepatotoxicity of solvents in general and of carbon tetrachloride, trichloroethylene, tetrachloroethylene, toluene, and 1,1,1-trichloroethene are discussed. Experimental animal data, human data, and in vitro studies are explored. Suggested mechanisms of direct toxicity, indirect toxicity and autoimmune mechanisms are elaborated. The most important message from this review is that laboratory testing that is commonly used by clinicians to detect **liver** toxicity may not be sensitive enough to detect early **liver** hepatotoxicity from industrial solvents and new methodologies are being encouraged and utilized in the early recognition and diagnosis of hepatotoxicity for solvents. The final clinical assessment of hepatotoxicity and industrial solvents must take into account synergism with medications, drugs of use and abuse, alcohol, age, and nutrition. Early recognition and reporting will be helpful in further understanding the incidence, cofactors and possible mechanisms.

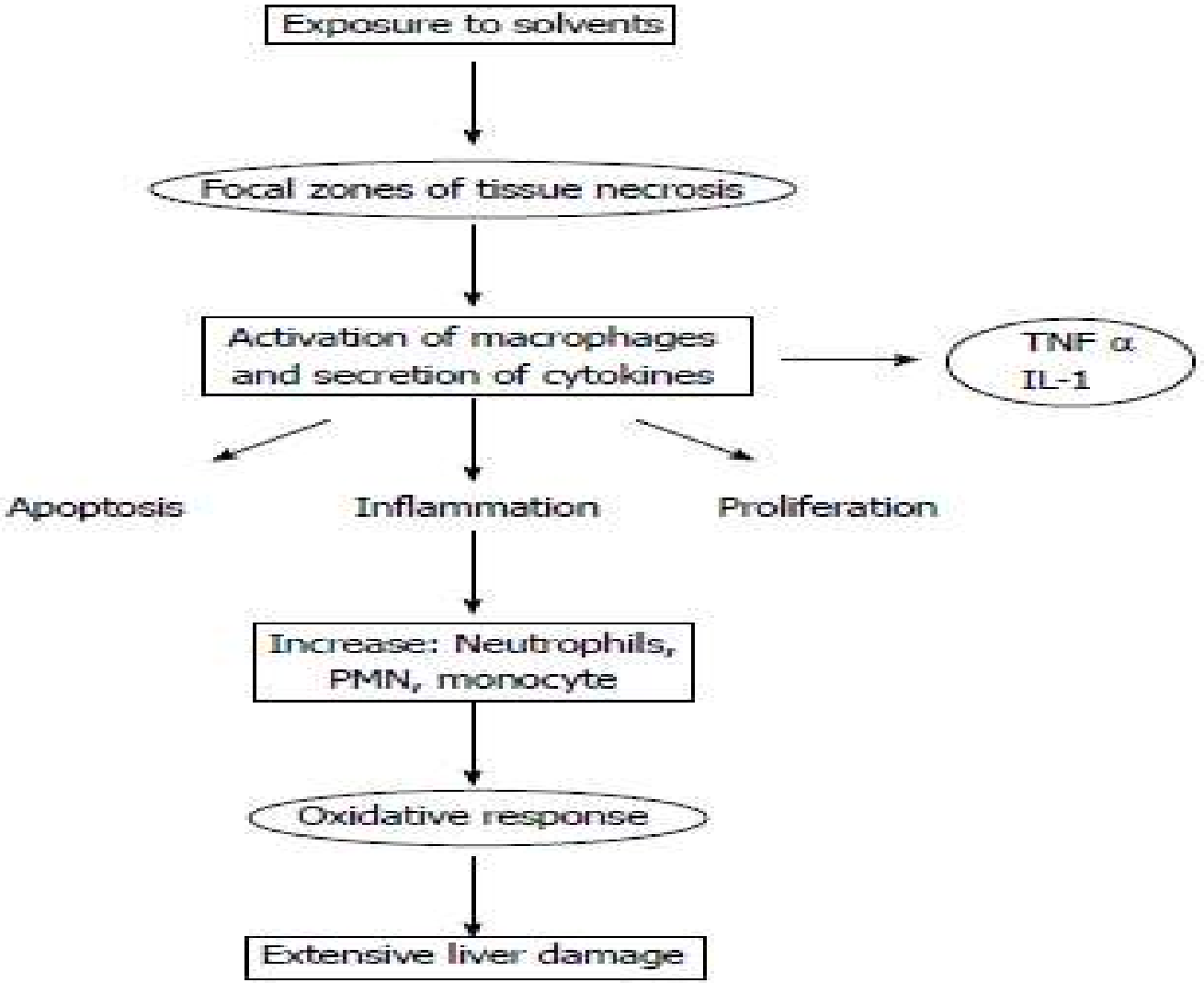


Figure 1 Hypothetical role of inflammation in chemical-induced hepatotoxicity. TNF: Tumor necrosis factor; IL: Interleukin; PMN: Prime neutrophils.

World J Gastroenterol 2012;18:2756-2766.

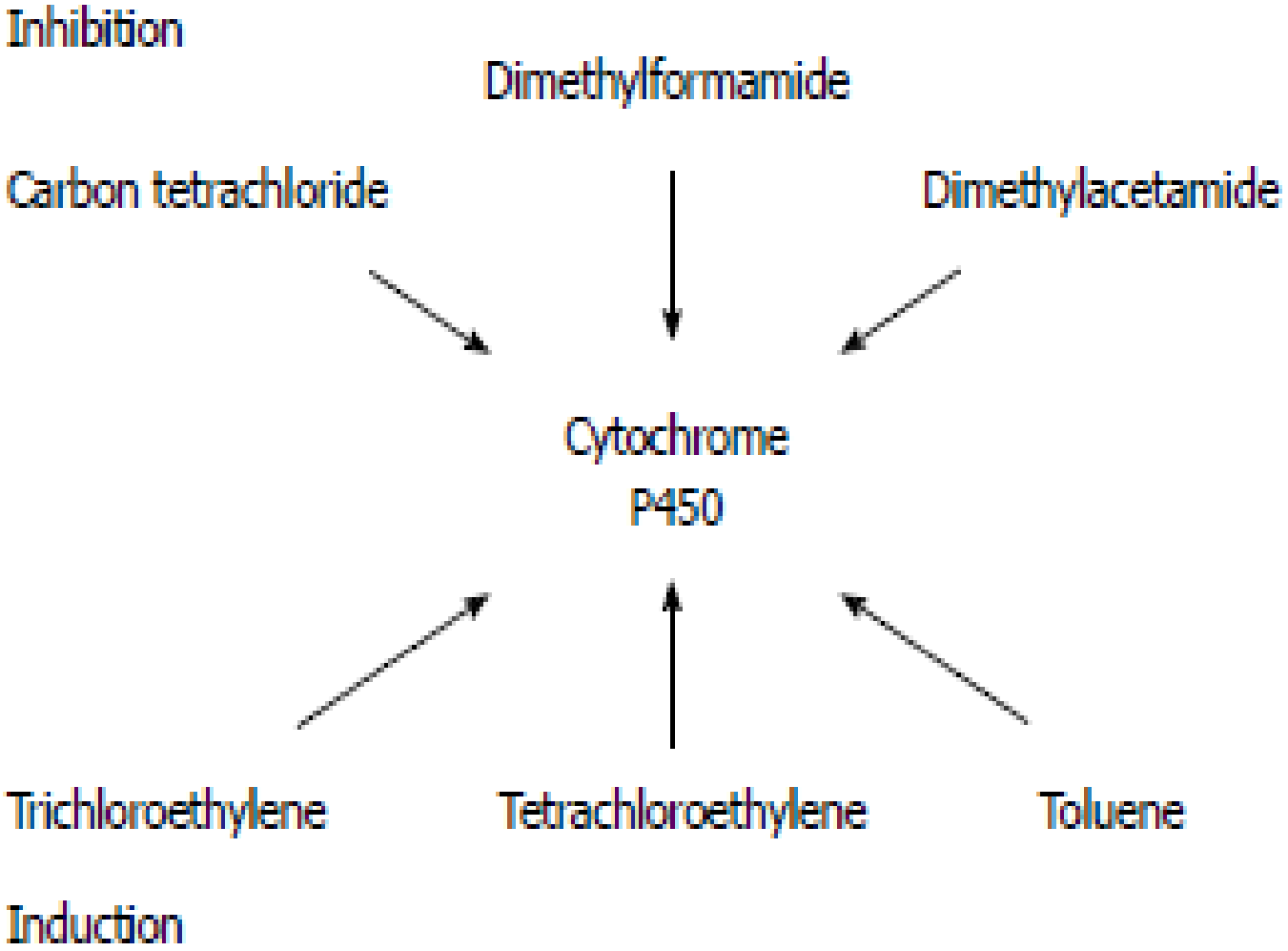


Figure 2 Effects of solvents on cytochrome P450.

表一、肝毒性物質之致病機轉[7]

分類	發生率	動物實驗再現性	劑量反應	潛伏期	機轉	病理變化	例子
內因性							
● 直接	高	是	是	十分短(數分至小時)	細胞膜破壞，細胞整體受損	壞死或脂化	CCl_4 Chloroform Dimethylformamide
● 間接							
－肝細胞毒性	高	是	是	短(數小時至數日)	代謝路徑阻礙	壞死或脂化	Ethanol, Urethane, Mycotoxin, Ethionine, Bromobenzene
－膽汁鬱積性	高	是	是	短(數天)	膽汁排泄路徑阻礙	膽汁圓柱	Methylene dianiline, Rapeseed oil
特異體質							
● 過敏性	低	低	否	長(1~4 週)	過敏	壞死或膽汁鬱積	Halothane
● 代謝異常	低	低	否	不一定，長(數週至數月)	肝毒性代謝產物堆積	壞死或膽汁鬱積	Iproniozid Cincophen Isoniazid

職業暴露有機溶劑引起之急性肝傷害認定參考指引(107年3月)

表三、肝傷害的型態。[24]

傷害型態		舉例
急性	肝細胞毒性	
	– 帶狀壞死	– 四氯化碳、氯仿
	– 大片壞死	– 三硝基甲苯、黃磷
	– 脂化	– 四氯化碳、氯仿、黃磷、二甲基甲醯胺、聯胺(hydrazine)
	膽汁鬱積性	– 4,4-二氨基二苯甲烷
亞急性		– 三硝基甲苯
慢性	–肝硬化(cirrhosis)	– 三硝基甲苯、多氯聯苯、四氯乙烷、乙醇
	–硬化(sclerosis)	– 砷、氯乙烯
	–脂化(steatosis)	– 二甲基甲醯胺、四氯化碳
	–紫質(porphyria)	– 戴奧辛
	–肉芽腫	– 鈹、銅
	–腫瘤	– 砷、氯乙烯、黃麴毒素、二氧化釷

職業暴露有機溶劑引起之急性肝傷害認定參考指引(107年3月)

職業性毒物暴露致肝傷害案例

- 一名於印刷廠工作的員工因全身倦怠及黃疸而就醫，被診斷有化學性肝炎，經現場訪視後，確認肝炎係因過量之**四氯化碳**導致

題名: CLINICAL MANIFESTATIONS AND LABORATORY FINDINGS OF CASES IN AN OUTBREAK OF CARBON TETRACHLORIDE - INDUCED HEPATIC INJURY AT A PRINTING FACTORY
突發於某印刷廠之四氯化碳肝傷害病例之臨床表徵與實驗檢查所見

作者: HUANG, YI-SHIN;DENG, JOU-FANG;WANG, JUNG-DER;LEE, SHOU-DONG;WU, JAW-CHING;WANG, JIIN-YU;TSAI, YANG-TE;TSAY, SHYH-HAW
黃以信;鄧昭芳;王榮德;李壽東;吳肇卿;王襄瑜;蔡養德;蔡世豪

貢獻者: 職業醫學與工業衛生研究所;Institute of Occupational Medicine and Industrial Hygiene

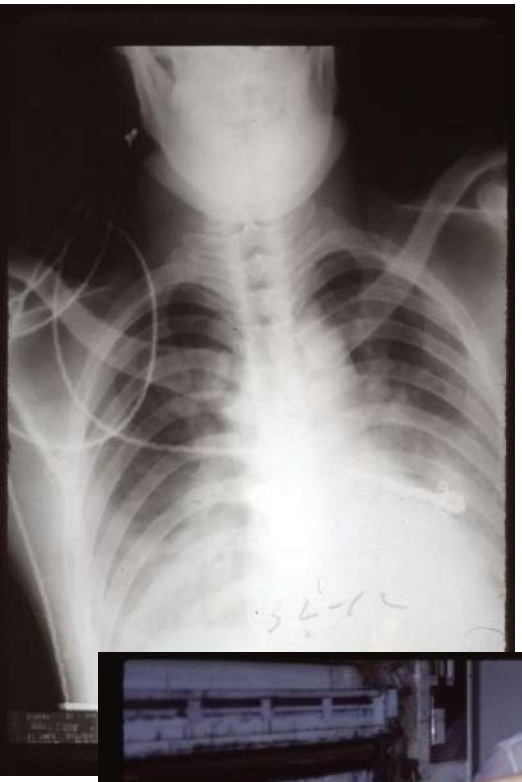
關鍵詞: carbon tetrachloride;hepatic injury;hepatitis;isopropyl alcohol

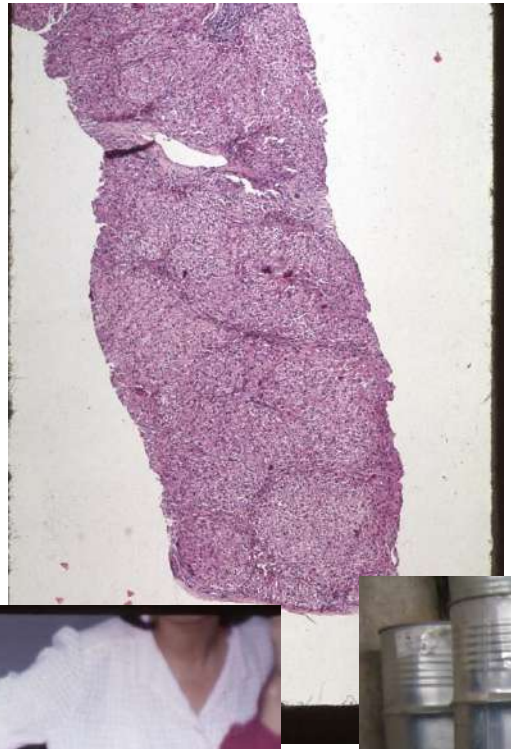
日期: 1987

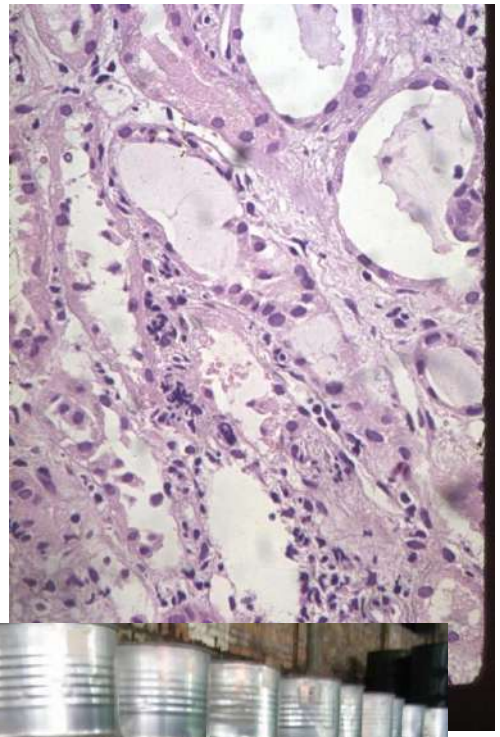
上傳時間: 2008-07-10T01:33:54Z

關聯: 臺灣醫學會雜誌 v.86 pp.743-749

職業性毒物暴露致肝傷害案例





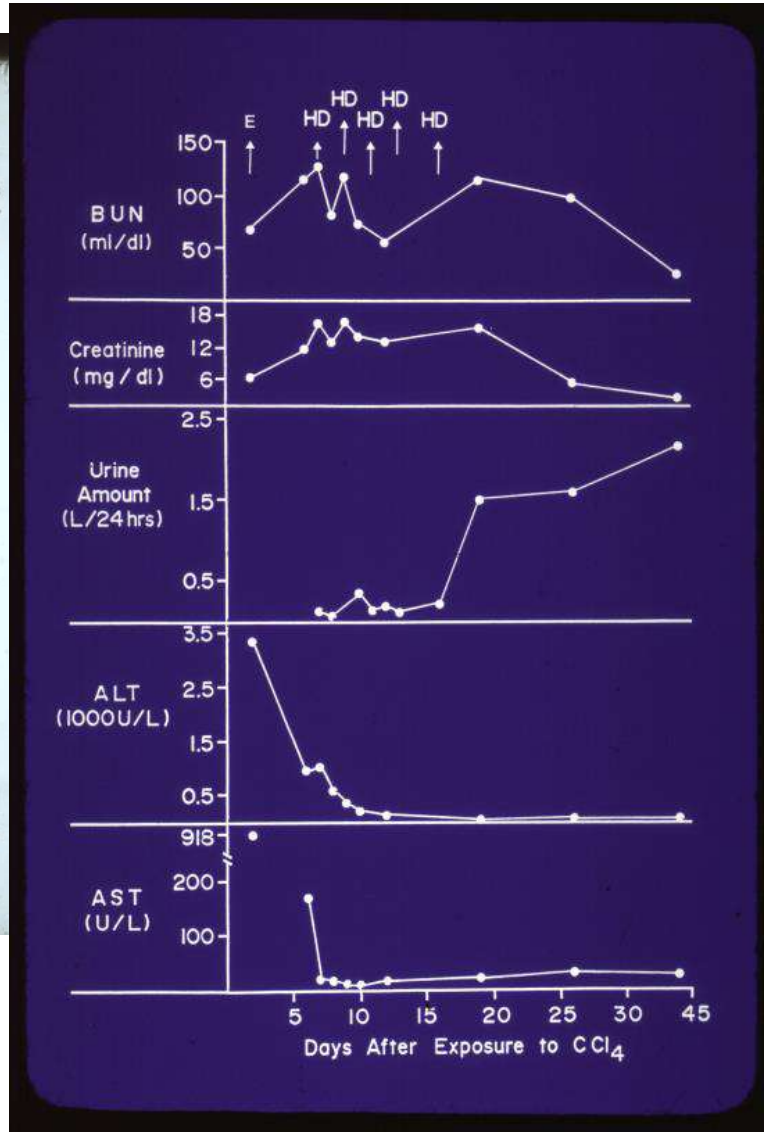


CCl4 Poisoning (1986)

The results of liver function tests of all personnel

Case	Age	Sex	Job category	ALT	AST	r-GT	HBsAg	HAVIgM	Alc
1	22	M	Printing	203	6	?	–	–	+*
2	31	M	"	840	90	226	–	–	–
3	19	M	"	690	107	66	+	–	–
4	18	M	"	63	27	109	–	–	–
5	31	M	"	46	23	96	–	–	+
6	16	M	"	24	16	11	–	–	–
7	26	M	"	620	57	67	+	–	–
8	32	M	"	610	28	45	–	–	–
9	17	M	"	263	46	80	+	–	–
10	17	M	"	88	21	28	–	–	–
11	18	M	"	101	24	12	+	–	–
12	19	M	"	169	29	99	–	–	–
13	24	M	"	368	64	101	+	–	–
14	26	M	"	33	21	13	–	–	–
15	59	M	manager	193	29	105	–	–	+
16	62	M	guard	121	28	46	–	–	–
17	28	M	P-P*	83	20	23	–	–	–
18	19	M	P-P	143	61	30	+	–	–
19	62	M	P-P	620	52	154	–	–	–
20	37	F	accountant	36	21	18	+	–	–
21	30	F	secretary	7	5	7	+	–	–
22	31	M	salesman	29	17	24	–	–	–
23	29	M	"	17	8	11	–	–	–
24	55	M	"	12	6	20	–	–	–
25	55	M	employer	17	9	13	–	–	–

P-P*: Printing process. +*: Drank 3.5% beer 1.2L in the next afternoon after the episode.



J Formos Med Assoc 1987; 86:743-749.

Outbreak of carbon tetrachloride poisoning in a color printing factory related to the use of isopropyl alcohol and an air conditioning system in Taiwan

Dr. Jou-Fang Deng MD[1,*], Jung-Der Wang MD[2], Tung-Sheng Shih[3], Fwu-Liang Lan[3]

Article first published online: 11 JAN 2007

DOI: 10.1002/ajim.4700120103

Issue

American Journal of Industrial Medicine

Volume 12, Issue 1, pages 11–19, 1987

*PEL-TWA of CCl4= 2ppm

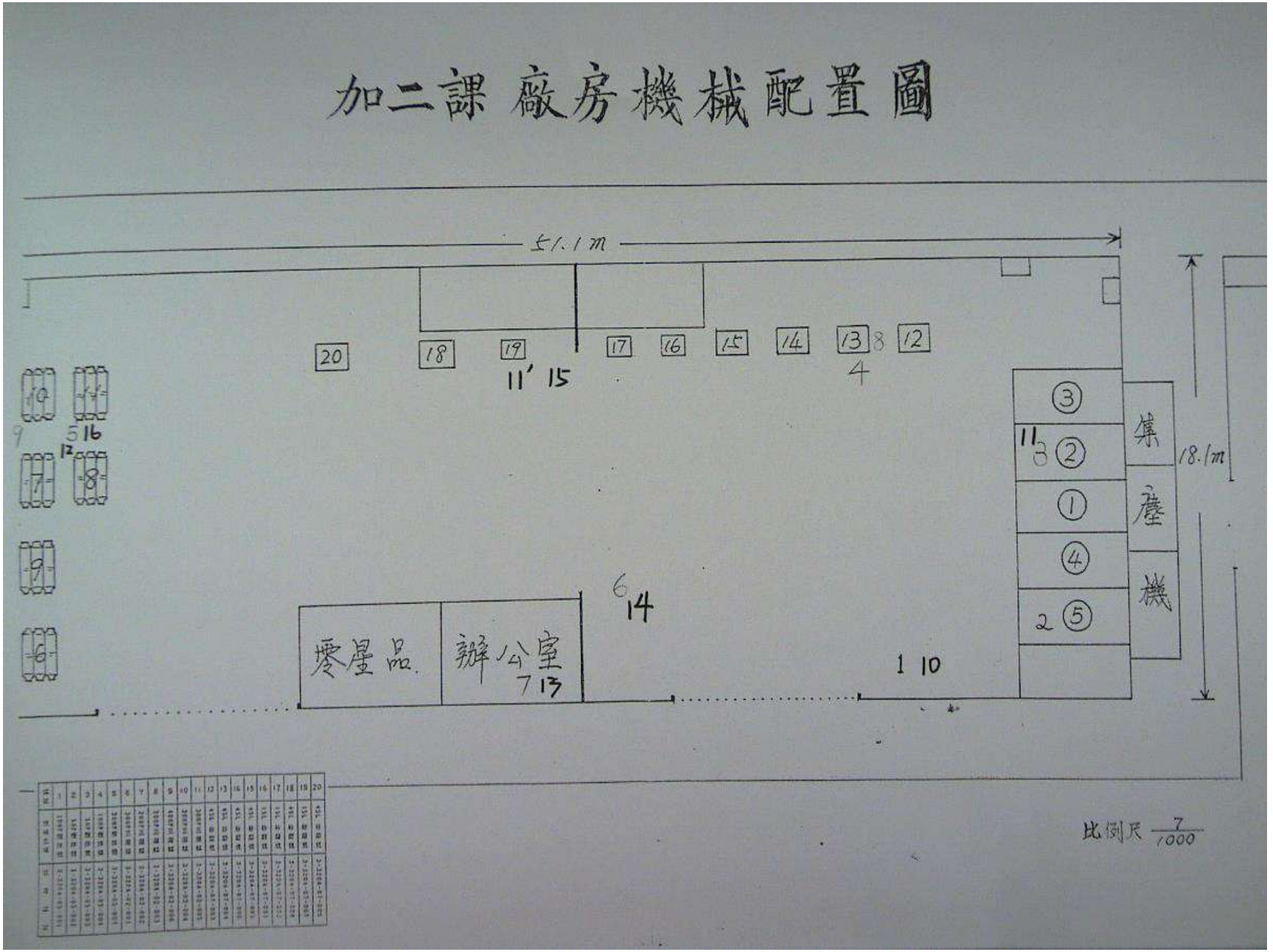
Three workers from a color printing factory were admitted to community hospitals in 1985 with manifestations of acute hepatitis. One of the three had superimposed acute renal failure and pulmonary edema. An investigation was subsequently conducted at the plant to determine the etiology of the outbreak and the prevalence of liver disease among the remaining workers. Comprehensive medical evaluations were conducted, which included physical examinations, liver function tests, and serological screening for hepatitis. Seventeen of 25 workers from the plant had abnormal liver function tests 10 days after the outbreak, and a significant association was found between the presence of abnormal liver function tests and a history of recently having worked inside any of three rooms in which an interconnecting air conditioning system had been installed to cool the printing machines. After further investigation, it was determined that the incident occurred following inadvertent use of carbon tetrachloride to clean a pump in the printing machine. A simulation of the pump cleaning operation revealed ambient air levels of carbon tetrachloride of 300–500 ppm. Ultimately, it was concluded that the outbreak was in all likelihood due to the combined use of carbon tetrachloride and isopropyl alcohol in the cleaning operation. This outbreak underscores the importance of adopting appropriate industrial hygiene measures in a rapidly industrializing nation such as Taiwan.

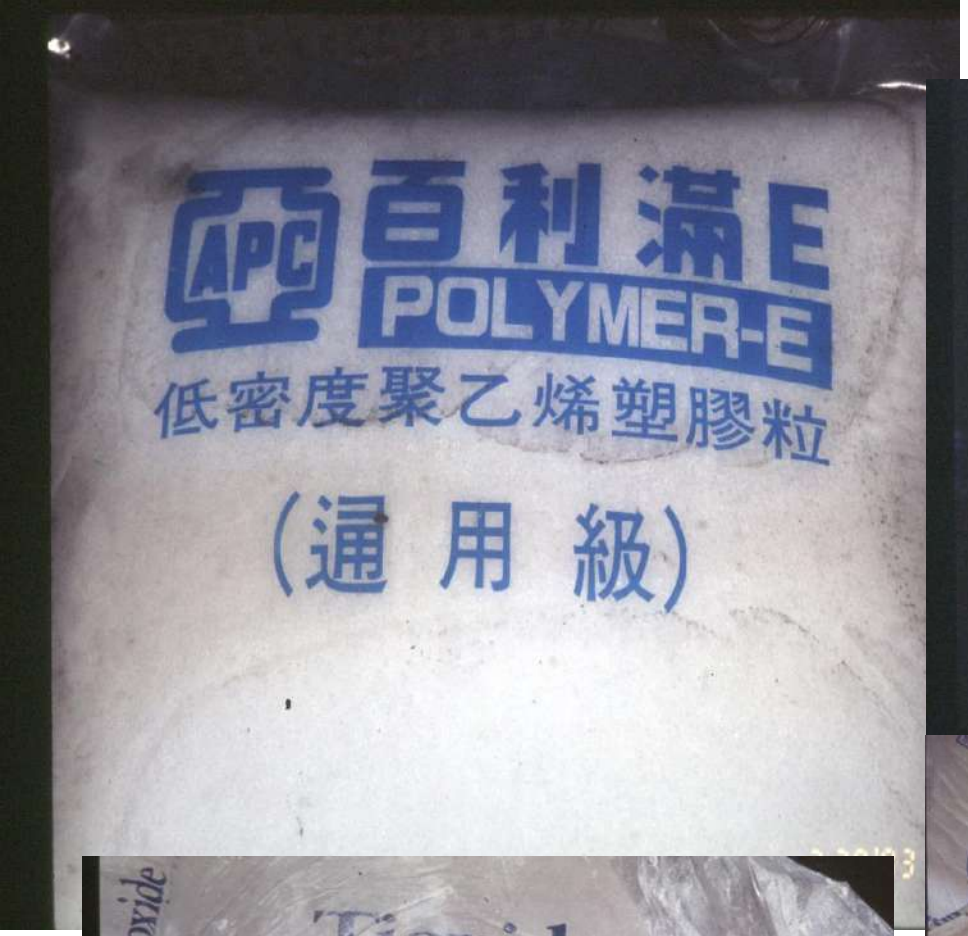
職業性毒物暴露致肝傷害案例

- 10餘名於染料廠工作的勞工因腹部絞痛而就醫，經檢查後並未發現胃部或腸部的病兆，但多數人的ALT及AST皆明顯偏高，大於正常值的2-3倍以上
- 經現場訪視後，確認肝傷害係因過量之**二甲基甲醯胺**(N,N-dimethylformamide, DMF，(CH3)2NC(O)H)導致

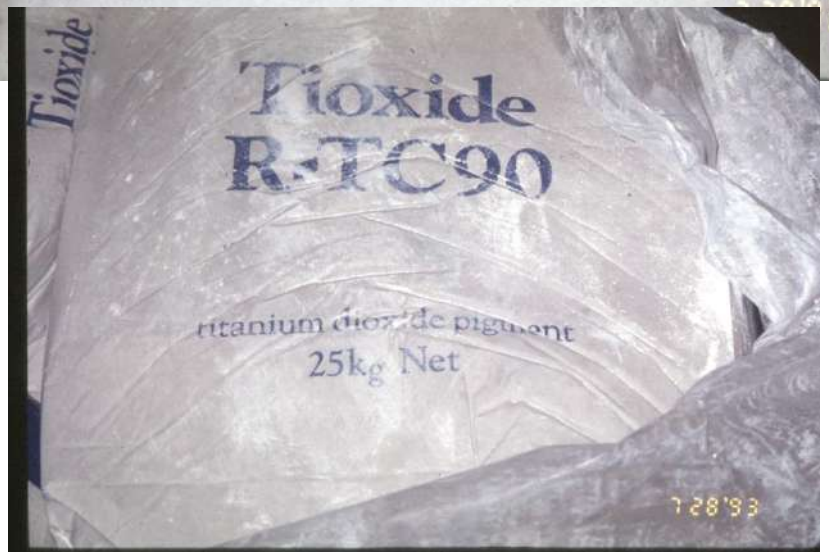
二甲基甲醯胺(DMF)

- Dimethylformamide常溫下為無色液體，有淡魚腥味
- **PEL-TWA：10 ppm**；STEL：15 ppm
- 主要用於製造合成皮、PU及壓克力等樹脂(纖維)的製造、PVC製造、尿素-甲醛聚合物回收萃取；亦可用於藥品業、農藥製造、黏膠製造、底片製造及表面塗佈(surface coatings)
- 勞研所2003年之資料顯示，國內仍有15家乾、濕式製程之生產單位，雇用勞工約7,500人
- 可能致癌物(IARC Group 2B carcinogen)
- 可以dimethyl sulfoxide(**二甲基亞碸**)取代


加二課 廠房機械配置圖
51.1m
20
18
19
11' 15
17
16
15
14
13
8
12
4
10
11
5
16
12
9
17
8
9
6
6
14
麥屋品
辦公室
7
13
1 10
③
11
3
②
①
④
2
⑤
集塵機
18.1m
比例尺 7/1000


APC
百利滿E
POLYMER-E
低密度聚乙烯塑膠粒
(通用級)

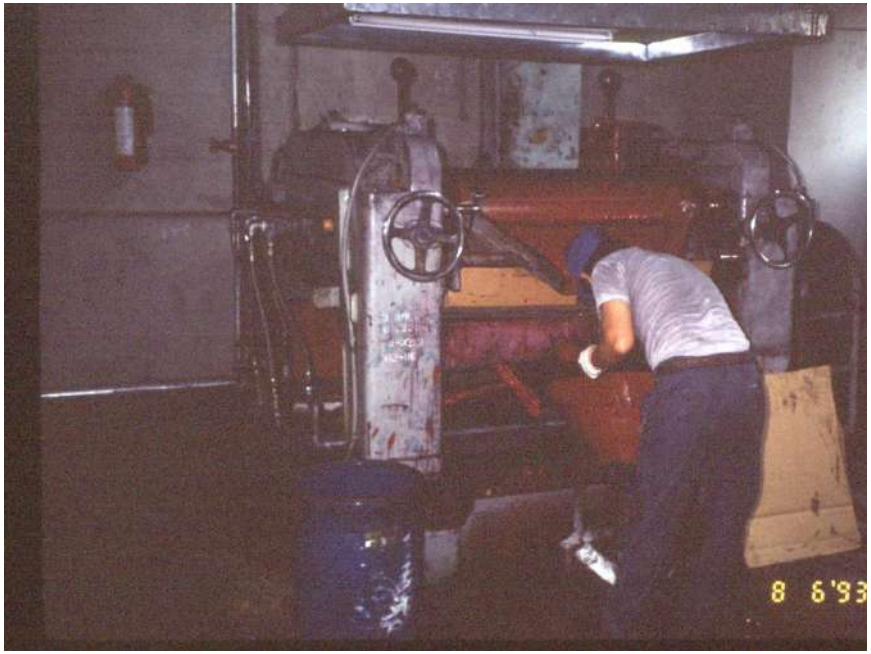

LOT NO. MA00413
CARBON MA-100 BLACK
7'28'93


Tioxide
Tioxide
R-TC90
titanium dioxide pigment
25kg Net
7'28'93


CHROME YELLOW
鉻黃
8. 6'93


MASTER
D M F KEELUNG
DIMETHYLFORMAMIDE
190KG NET
7 28'93


8 6'93


8 6'93


8 6'93

Ann Intern Med. 1988 May;108(5):680-6.

Liver disease associated with occupational exposure to the solvent dimethylformamide.

Redlich CA, Beckett WS, Sparer J, Barwick KW, Riely CA, Miller H, Sigal SL, Shalat SL, Cullen MR.

Department of Internal Medicine, Yale University School of Medicine, New Haven, Connecticut.

Abstract

STUDY OBJ
and to determ
and preventio

DESIGN: clini

SETTING: ac

PATIENTS: fi
least once. Fo
recognized liv

RESULTS: a
and symptom
industrial solv
appropriate sl
workers teste
levels. Enzym
whereas only
Serologic test
of toxic liver i
of AST to ALT
workers most
most patients

CONCLUSIO
dimethylforma
histories, neg
epidemiologic
enzyme abno
than is genera

Arch Environ Health. 1991 May-Jun;46(3):161-6.

Dimethylformamide-induced liver damage among synthetic leather workers.

Wang JD, Lai MY, Chen JS, Lin JM, Chiang JR, Shiau SJ, Chang WS.

Center for the Research of Environmental and Occupational Disease, Graduate Institute of Public Health and Department of Internal Medicine, National Taiwan University, College of Medicine, Republic of China.

Abstract

Prevalence of liver injury associated with dimethylformamide (DMF) exposure was determined. Medical examinations, liver function tests, and creatine phosphokinase (CPK) determinations were performed on 183 of 204 (76%) employees of a synthetic leather factory. Air concentrations of solvents were measured with personal samplers and gas chromatography. The concentration of DMF in air to which each worker was exposed was categorized. High exposure concentrations of DMF (i.e., 25-60 ppm) were significantly associated with elevated alanine aminotransferase (ALT) levels (ALT greater than or equal to 35 IU/l), a result that did not change even after stratification by hepatitis B carrier status. Modeling by logistic regression demonstrated that exposure to high concentrations of DMF was associated with an elevated ALT ($p = .01$), whereas hepatitis B surface antigen (HBsAg) was slightly but independently associated with an elevated ALT ($p = .07$). In those workers who had normal ALT values, there occurred still significantly higher mean ALT and aspartate aminotransferase (AST) activities, especially among those who were not HBsAg carriers. A significant association existed between elevated CPK levels and exposure to DMF. However, an analysis of the CPK isoenzyme among 143 workers did not reveal any specific damage to muscles. This outbreak of liver injury among synthetic leather workers is ascribed to DMF. It is recommended that the occupational standard for DMF and its toxicity among HBsAg carriers be evaluated further.

二甲基乙醯胺 (dimethylacetamide)

October 2014

Started to work at a chemistry factory for 2 months. 5 days/week, 8 hrs/day(XX合纖)

November 2014

Epigastralgia and poor appetite. Thus he first visited A hospital in 新竹 where some prokinetics were given Panendoscopy showed no specific finding.

November 2014

Then he went to B hospital in 新竹 where **total bilirubin level increased dramatically**. **HBV and HCV was ruled out by antigen and antibody screen. Abdominal sonography was unyielding.**

December 5, 2014

He was referred to Taipei VGH for further management due to R/I Chemical hepatitis.

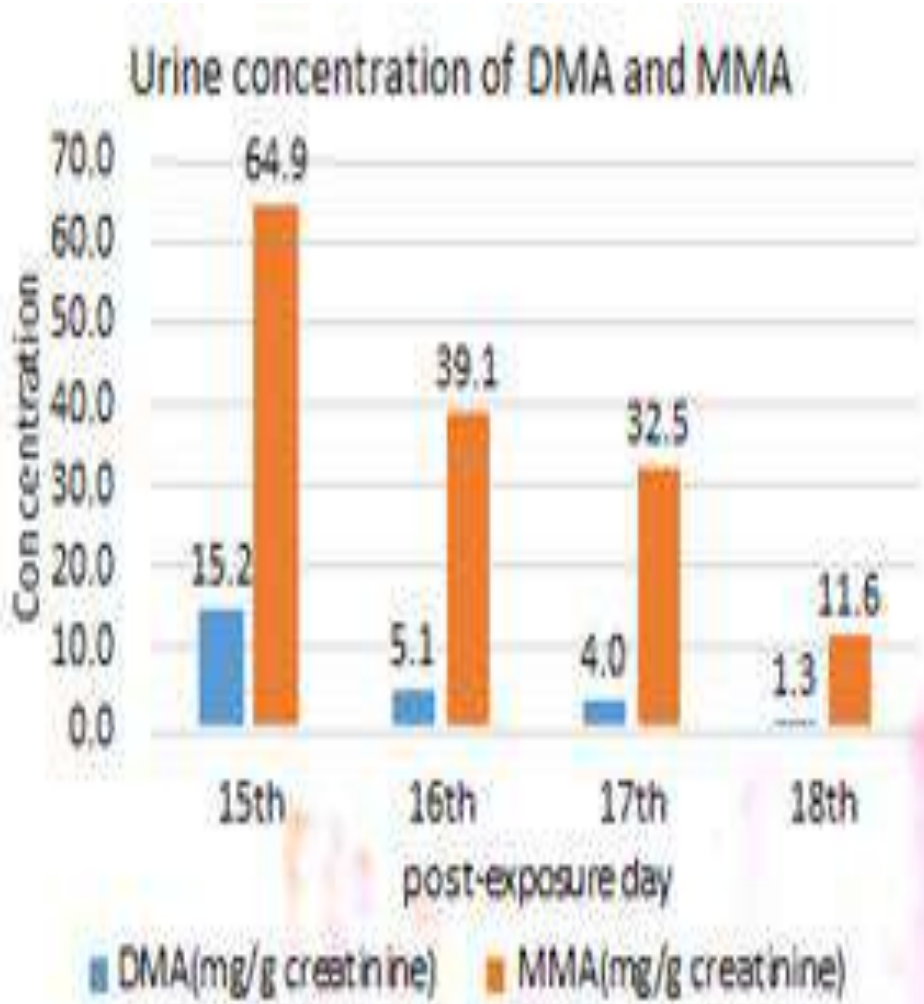
Hospital Course

December 5, 2014: Admission

December 5, 2014: Silymarin 150 mg po BID
N-acetylcysteine (*NAC*) 10.2 gm IV stat (150 mg/kg), followed by *NAC* 3600 mg IV for 4hrs
December 6th-8th, 2014 *NAC* 10.2 gm IV QD

December 11th, 2014: Abdominal sonography: no focal lesions can be identified.

Discharged uneventfully on December 19th, 2014



Post-exposure day	T-bili (mg/dL)	D-bili (mg/dL)	ALT (U/L)	AST (U/L)
3rd	18.09	13.77	469	181
5th	14.67	-	390	219
8th	12.93	-	405	242
12th	9.06	-	418	250
16th	5.09	4.00	286	160
22th	6.47	1.58	196	105
42th	2.90	0.71	27	27

二甲基乙醯胺 (dimethylacetamide)

- Dimethylacetamide (DMA) is an excellent dipolar solvent, with a high dielectric constant, that readily dissolves gases and numerous organic and inorganic substances
- It is most commonly used in the **acrylic fiber, polyester films** and pharmaceutical industries, with occupational exposures via the **dermal and inhalation** routes being most common
- This chemical is primarily used as a **polar solvent in the acrylic fiber industry** in the manufacture of acrylic fibers. In the polyester film industry it is used as a solvent for the manufacture of polyester films

二甲基乙醯胺之毒性作用

- DMA appears to affect cell membrane and macromolecular synthesis through interaction with cell membranes, changing the entry of nucleotides into the cell and decreasing the synthesis of phospholipids (Kim, 1988)
- Human data on DMA toxicity is limited
- Clinical effects: conjunctivitis, chemical burn, GI and respiratory irritation, rhabdomyolysis, hypotension, CNS depression, liver injury
- **Liver toxicity** (elevated liver enzymes, jaundice, hepatomegaly) **is the primary clinical effect of DMA exposure**

勞工作業環境空氣中有害物容許濃度標準

修正規定									現行規定								
編號	中文名稱	英文名稱	化學式	符號	容許濃度		化學文摘社號碼(CAS No.)	備註	編號	中文名稱	英文名稱	化學式	符號	容許濃度		化學文摘社號碼(CAS No.)	備註
					ppm	mg/m³								ppm	mg/m³		
155	N，N—二甲基乙醯胺	N,N-Dimethylacetamide	$CH_3CON(CH_3)_2$	皮	10	36	127-19-5		155	N，N—二甲基乙醯胺	N,N-Dimethylacetamide	$CH_3CON(CH_3)_2$	皮	10	36	127-19-5	

ACGIH TLV Values for CAS127-19-5 (American Conference of Governmental Industrial Hygienists, 2010): threshold limit value TLV-TWA: **10 ppm**

如何診斷職業性毒物暴露致肝傷害

- **主要基準：**
- 職業上暴露可能導致化學性肝傷害之有毒物質，且時序性符合
- ALT昇高2-3倍，符合急性肝傷害之診斷；或肝病理切片檢查之發現與暴露之肝毒性物質(或職業)相符合
- **須排除其他非職業可能導致急性肝傷害的原因**，譬如病毒性肝炎、酒精性肝炎、藥物性肝傷害、及自體免疫性肝傷害等

Table 1 Clinical-diagnostic types of occupational toxic hepatitis

Type of disease	ALT	ALP	γ-GT	Bilirubin	Bile acids
Hepatocellular	> 2 ULN >5	N	> 2	Elevated levels	Elevated levels
Cholestatic	N	> 2 ULN	> 4	Normal or moderate level	Elevated levels
Mixed	> 2 ULN 2-5	⩾ ULN	> 2	Normal or moderate level	Elevated Levels

ALT: Alanine aminotransferase; ALP: Alkaline phosphatase; GT: Glutamyl transferase; ULN: Upper limit of normal; N: Normal value. Normal value, ALT 9-63 U/L; ALP 38-126 U/L; γ-GT 7-50 U/L; Bilirubin 0.20-1.5 mg/dL; Bile acids < 10 μmol/L.

如何診斷職業性毒物暴露致肝傷害

- **輔助基準：**
- 移除暴露源後，ALT在一個月內下降一半以上(且不再升高)
- 有其他足以證明(或支持)暴露化學物質過量，已達可能引起肝傷害濃度之數據；譬如作業環境中之化學物濃度過高，或體內化學物質及其代謝物濃度過高等
- 同一工作環境下之其他勞工亦有類似之傷害

大綱

- 毒藥物防治諮詢中心之簡介
- 國內常見毒藥物中毒之簡介
- 急性藥物中毒導致肝傷害之簡介
- **急性非藥物中毒導致肝傷害之簡介**
  - 職業性毒物暴露導致肝傷害
  - **中草藥導致肝傷害(HILI)**
  - 其他原因導致肝傷害
- 毒藥物中毒導致肝傷害之鑑別診斷與治療

案件 9 專家審查 (編號：ADR1240016)

人	65 歲 / 性別: 女 其他相關資料：過去病史：右側眼黃斑部皺褶、雙側眼前青光眼
事	★不良反應發生日（時序） **案件描述：** 因【腰部神經推管問盤狹窄等致之腰痛】於【2023/11/22】起服用中藥，於【2024/1/5 下午 03:00:00】就診時發現【胃腸系統疾病與症狀徵候,目黃、面黃、茶色尿，懷疑黃疸】。 案件發生後建議患者至消化內科進行進一步的檢查。 【2024/1/8】實驗室檢查發現肝指數 AST, ALT, Total bilirubin 升高，診斷：右上四分之一腹痛，消化內科給予 Cefixime 預防膽囊炎及感染。 處置【2024/1/10 起停用藥品】。 1/11 後續未再進行抽血檢驗。 病患於 1/12、1/15、1/17、1/19 有回診，其面黃現象已減退。 **檢驗數據：(服中藥後)**

檢驗日期	檢驗項目	檢驗結果	檢驗結果單位
2024/1/8	AST	1146	U/L
2024/1/8	ALT	1648	U/L
2024/1/8	Alkaline Phosphatase	263	U/L
2024/1/8	Total Bilirubin	5.47	mg/dL

	★停藥&再投藥敘述 有無他人使用相同藥品，是否發生不良反應？是 停藥後不良反應是否減輕？減輕 再投藥是否發生不良反應？無法得知
時	發生日期：2024/1/11
地	中國醫藥大學附設醫院 / 臺中市 通報來源: 民眾
不良反應	不良事件結果：1 非嚴重不良事件 非嚴重不良反應事件 不良反應症狀：#肝膽系統疾病與症狀徵候，目黃、面黃、茶色尿，懷疑黃疸#

物：

可疑藥品或處方								
藥名	劑型	給藥途徑	劑量	劑量/日	服(使)用方法	服(使)用頻率	服用起日期	服用迄日期
"港香蘭" 延胡索濃縮細粒	濃縮顆粒劑	口服	2	gm	飯後	一天二次	2023/11/22	2024/1/10
併用產品								
"港香蘭" 芍藥甘草湯濃縮顆粒	濃縮顆粒劑	口服	1.5	gm	飯後	一天二次	2023/11/22	2024/1/10
"港香蘭" 虎潛丸濃縮散（去虎骨）	濃縮散劑	口服	4.5	gm	飯後	一天二次	2023/11/22	2024/1/10
"港香蘭" 獨活寄生湯濃縮顆粒	濃縮顆粒劑	口服	4.5	gm	飯後	一天二次	2023/11/22	2024/1/10

疑似中藥延胡索(*Corydalis yanhusuo* W. T. Wang)致肝傷害個案

番瀉 (*Cassia angustifolia*)

- **番瀉葉**長久以來被人類拿來作為瀉藥使用，若是按照醫師指示服用且不過量，應不會有明顯的安全性疑慮；但長期或高劑量使用番瀉自我療癒，容易對健康造成危害(譬如肝傷害)
- **番瀉葉**造成的肝傷害主要與植物萃取物中的蒽醌衍生物有關，根據已發表案例的臨床特徵，蒽醌衍生物，包括cascarosides (cascara)及烴基蒽醌(hydroxyanthraquinone)，被認為可能與引起肝傷害有關

類別	草、木本植物類(1)
中文名稱	番瀉
外文名稱	Senna
學名	*Cassia angustifolia Vahl*
部位	葉、莢
備註	番瀉?(sennosides)之每日食用限量為12 mg以下。產品應標示番瀉?含量及每日建議食用量，且應標示相關之警語。
檔案下載	

阿勃勒 (*Cassia fistula*)

- 別名：婆羅門皂莢、波斯皂莢、豬腸豆、臘腸樹、牛角樹、塊花青
- 外觀：樹皮為灰白色，枝條細直；花呈黃色；莢果圓筒形長條狀，初為綠色後變為暗褐色；種子呈扁圓形
- 一般作為行道樹或庭園樹
- 果肉中含有游離蒽醌(anthraquinone)
- 坊間宣稱療效:緩瀉劑(果肉)；果實主治熱病、下痰、殺蟲、通經絡；樹皮和葉(含鞣酸)可治療皮膚病

阿勃勒 (*Cassia fistula*)

- 一名42歲婦女因盆腔炎、哮喘、間歇性腹痛及心律不正常之症狀而入院接受治療
- 入院一段時間後，病人抽血檢查意外發現其肝功能指數明顯升高(**ALT 394 U/L、AST 533 U/L**)
- 經詳細問診及腹部超音波等檢查後，排除其他可能導致肝傷害的原因(如病毒性或酒精性肝炎)，由於病人自述近期**有食用草藥的習慣**，因此會診臨床毒物科醫師
- 醫師問診後，病人自陳在**抽血前3日曾服用阿勃勒種子治療腸胃疾病，之後產生噁心及腹瀉10餘次**，但誤以為在排毒故不以為意。經綜整相關資料後，醫師診斷此病人應該係阿勃勒相關之肝傷害個案

中草藥之肝傷害 - 西醫觀點
Liver Injury From Herbs – The View From Modern Medicine

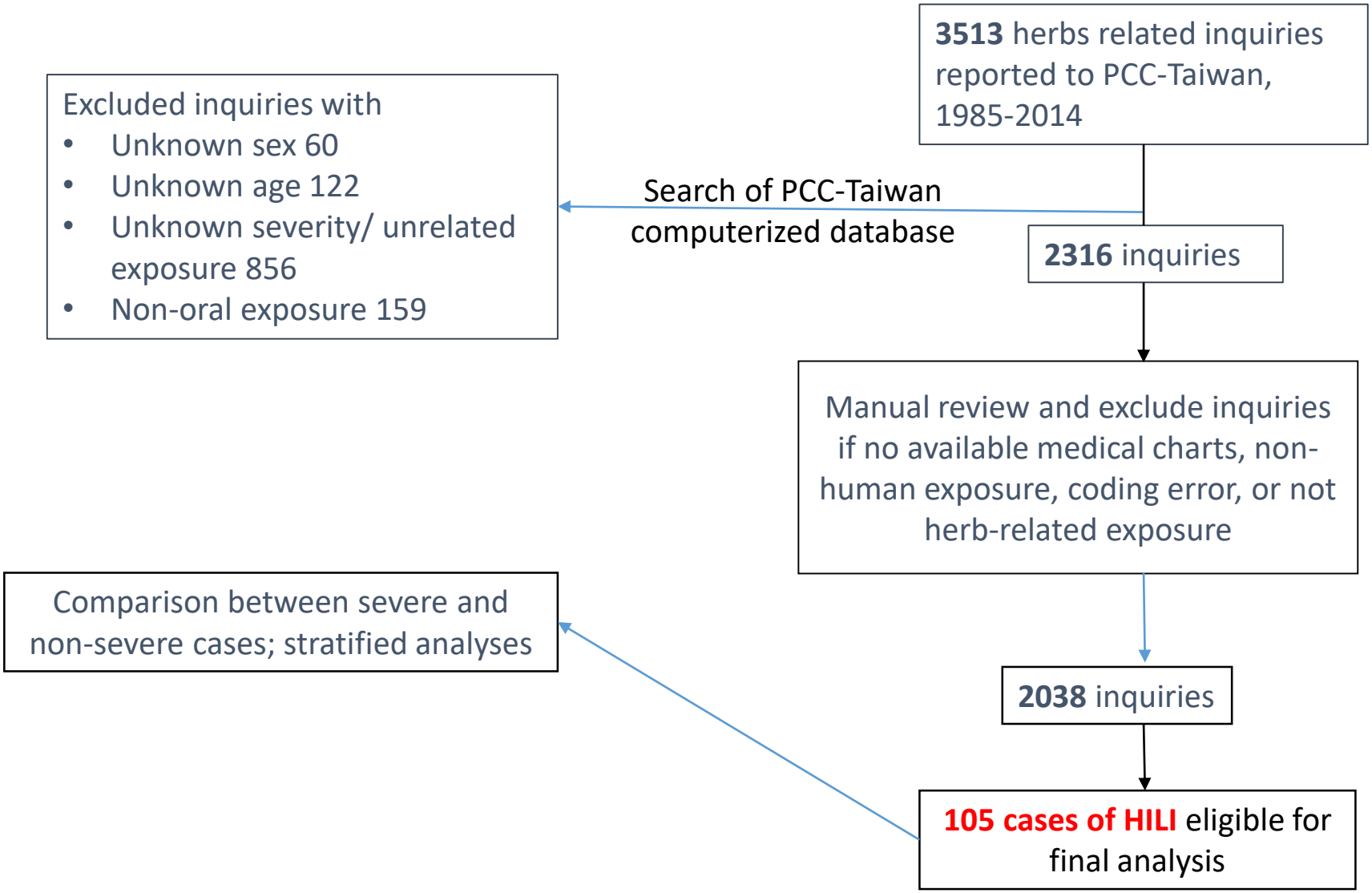
吳明玲 台北榮民總醫院內科部臨床毒物科

- 已知具肝毒性的植物類中藥種類繁多，至少有 100 種以上。依照其病理型態分類如下：(一)、肝細胞毒性反應 (cytotoxic reactions)：如蒼耳子、黃藥子、虎杖、何首烏、桑寄生、貫 眾、合歡皮、土荊芥、大風子、常山、苦揀皮、川楝子、土細辛、篦麻子、番瀉葉、天花粉、 山慈菇、石榴皮、艾葉、蘇鐵、七日暈、龍葵、相思子、半夏、松蘿、紫莖牛膝、款冬、蘇 鐵、麝香草、旱蓮、白消容、五色梅、油桐子、三十六蕩、臭草、杜衡、棉籽、及己、黑面 葉、金不換、藜蘆、防己、罌粟、鴉片、商陸、金果欖、鴉膽子、毛冬青、澤瀉、蒲黃、槐 花、纈草、雷公藤、八角蓮、薄荷及柴胡制劑等。
- (二)、膽汁鬱積性反應 (cholestatic reactions)： 如大黃、四季青、川楝子、黃連或澤瀉。
- (三)、脂肪變性或脂肪肝 (steatosis, fatty liver)：如肉 豆蔻。
- (四)、慢性肝炎 (chronic hepatitis) 及肝硬化 (cirrhosis)：長期暴露於肝毒性藥物或重度 急性肝炎恢復後，可能發展為慢性肝炎或肝硬化。
- (五)、肝臟靜脈阻塞性疾病 (hepatic veno-occlusive diseases)：含 pyrrolizidine 生物鹼類中草藥，包括 Heliotropium spp.、Senecio spp.、Crotolia spp.、Symphytum spp.、Ilex sp.、Cordolobo yerba、菊三七等。
- (六)、肝肉芽腫 性反應 (hepatic grouuloma)
- (七)、引發動物肝種瘤

中藥對肝臟的影響

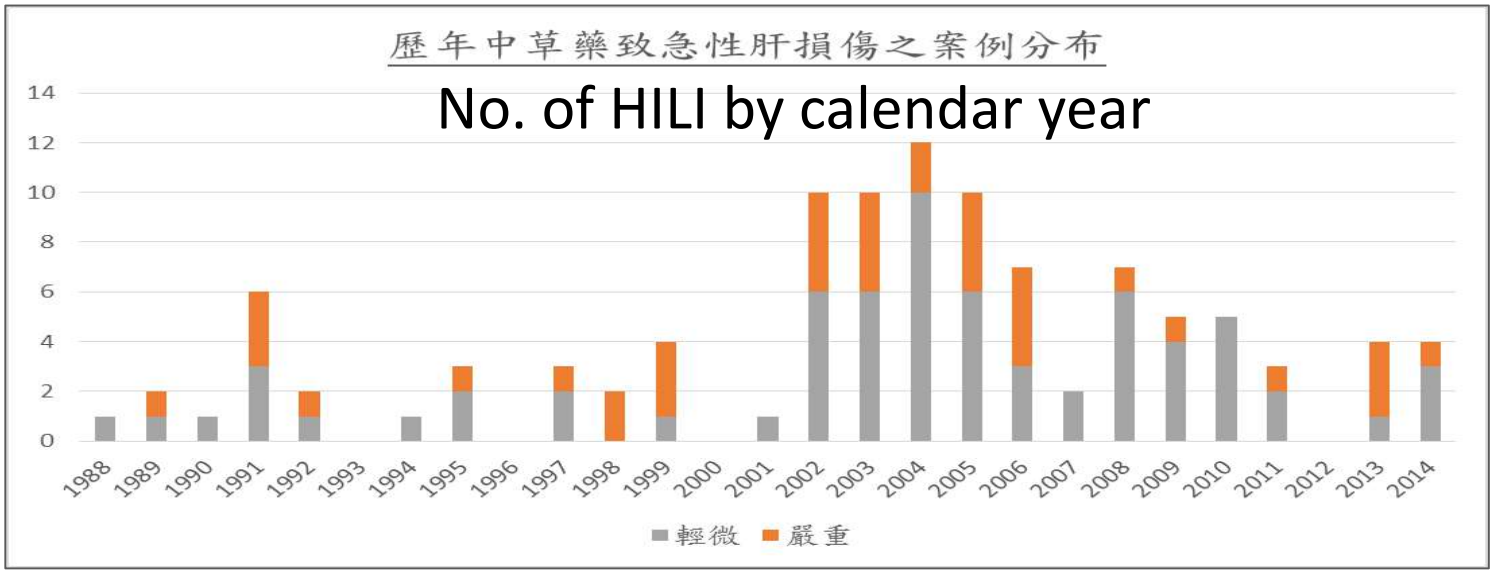
- **中藥本身因素**
  - 生物鹼類：如延胡索
  - 皂苷類：如黃藥子
  - 毒蛋白類：如蒼耳子
  - 萜類：如雷公藤
  - 動物及礦物類：如蜈蚣及雄黃
- **藥物品種混亂(同物異名、同名異物)**
- 人為因素
- 過敏或特異型反應(idiosyncratic reaction)
- 中西藥交互作用

HILI reported to PCC-Taiwan



HILI reported to PCC-Taiwan

- 105 eligible cases
- 15 (14.3%) had mild effects, 53 (50.5%) moderate effects, **20 (19.1%) severe effects and 17 (16.2%) patients died**
- Six (5.7%) cases presented with multi-organ injury on admission



Mild Severe

Herbs related hepatic failure

- Cases manifesting hepatic failure or multi-organ failure were exposed to the following herbs: *Taxus Chinensis, Cupressus duclouxian, Taraxacum,* TCM containing arsenic, **snake gallbladder (purchased from Vietnam)**, *Caulis Tinosporae Sinensis*, *Melastoma candidum D.*, *Caulis Polygoni Multiflori*, *Cassia occidentalis*, *Xanthium sibiricum* and Java tea




A case of fatal HILI

- A 57 years old lady drank tea made ***Caulis Tinosporae Sinensis*** *(Tinosporae sinensis Caulis*; Kuan Jin Teng、寬筋藤) for health promotion. She developed fulminant hepatic failure 1 month later and died despite receiving intensive therapy
- The diagnosis was most likely to be *Caulis Tinosporae Sinensis* related fatal HILI
- Five similar cases were reported to PCC-Taiwan

大綱

- 毒藥物防治諮詢中心之簡介
- 國內常見毒藥物中毒之簡介
- 急性藥物中毒導致肝傷害之簡介
- **急性非藥物中毒導致肝傷害之簡介**
  - ➢職業性毒物暴露導致肝傷害
  - ➢中草藥導致肝傷害(HILI)
  - **➢其他原因導致肝傷害**
- 毒藥物中毒導致肝傷害之鑑別診斷與治療

Table 13-3

Factors in the Site-Specific Injury of Representative Hepatotoxicants

SITE	REPRESENTATIVE TOXICANTS	POTENTIAL EXPLANATION FOR SITE-SPECIFICITY
Zone 1 hepatocytes (vs zone 3)	Fe (overload) Allyl alcohol	Preferential uptake and high oxygen levels Higher oxygen levels for oxygen-dependent bioactivation
Zone 3 hepatocytes (vs zone 1)	CCl_4 Acetaminophen Ethanol	More P450 isozyme for bioactivation More P450 isozyme for bioactivation and less GSH for detoxification More hypoxic and greater imbalance in bioactivation/detoxification reactions
Bile duct cells	Methylenedianiline, sporidesmin	Exposure to the high concentration of reactive metabolites in bile
Sinusoidal endothelium (vs hepatocytes)	Cyclophosphamide, monocrotaline	Greater vulnerability to toxic metabolites and less ability to maintain glutathione levels
Kupffer cells	Endotoxin, $GdCl_3$	Preferential uptake and then activation
Stellate cells	Vitamin A Ethanol (chronic)	Preferential site for storage and then engorgement Activation and transformation to collagen-synthesizing cell

Casarett and Doull's Toxicology: The Basic Science of Poisons, 7th ed.

Amanita phalloides poisoning: Mechanisms of toxicity and treatment

Juliana Garcia [1], Vera M Costa [2], Alexandra Carvalho [3], Paula Baptista [4], Paula Guedes Maria de Lourdes Bastos [2], Félix Carvalho [5]

Food Chem Toxicol 2015;86:41-55.

Abstract

Amanita phalloides, also known as 'death cap, is one of the most poisonous mushrooms, being involved in the majority of human fatal cases of mushroom poisoning worldwide. This species contains three main groups of toxins: **amatoxins**, phallotoxins, and virotoxins. From these, amatoxins, especially **α-amanitin**, are the main responsible for the toxic effects in humans. It is recognized **that α-amanitin inhibits RNA polymerase II, causing protein deficit and ultimately cell death**, although other mechanisms are thought to be involved. **The liver is the main target organ of toxicity**, but other organs are also affected, especially the kidneys. Intoxication symptoms usually appear after a latent period and may include gastrointestinal disorders followed by jaundice, seizures, and coma, culminating in death. Therapy consists in supportive measures, gastric decontamination, drug therapy and, ultimately, liver transplantation if clinical condition worsens.

實驗室檢查

		Lactate	AST	ALT	T-bil	D-bil	LDH	INR	Ammonia
3/21		138.9	4524	5302	1.8	0.9	5664	9.21	1009
3/22	HD+CPFA +CVVH	51.0	8883	>10000	2.6	0.8	11228	4.72	771
3/23	CVVH	49.8	-	-	-	-	7942	>10.0	783
3/24	CVVH	59.7	-	-	-	-	3084	6.77	541
3/25	CVVH	58.1	-	1019	6.4	2.5	1031	>10.0	477
3/26	HD	17.1	1280	182	8.8	-	565	3.54	157
3/28	HD	26	82		11.7	2.5	408	4.39	217
3/29	plasma exchange	17.1			9.5	2.8	463	6.31	200
3/30	plasma exchange	29.9	37	169	10.2	3.2	355	2.94	251
4/1	CVVHDF	18.3	54		11.5		520	3.87	200
4/2	CVVHDF	12.7			13.9		495	8.5	127

日期	TP	ALB	CA	CHOL	BUN	UA	CREA	BILIT	ALKP	LDH	ALT	AST	FIB-4	NA	K	CL	GLU	IP	CK
24-04-29 08:05	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
24-04-29 08:05	-	-	-	-	26	-	0.95	1.02	-	-	83	-	-	140	4.2	-	156	-	15011
24-04-29 09:07	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
24-04-29 09:23	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	15134
24-04-29 10:26	-	-	-	-	-	-	-	-	-	633	-	-	-	-	-	-	-	-	-
24-04-29 14:32	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	13642
24-04-29 21:23	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	12219
24-04-30 03:57	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
24-04-30 03:57	-	-	-	-	16	-	0.73	-	-	-	78	306	4.40	142	4.2	-	145	-	-
24-04-30 03:57	-	-	-	-	-	-	-	-	62	-	-	-	-	-	-	-	-	-	-
24-04-30 04:44	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	12265
24-04-30 15:22	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	8642
24-05-01 03:47	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
24-05-01 03:47	-	-	-	-	-	1.3	0.53	-	-	-	-	-	-	139	3.7	-	111	-	7026

一氧化碳(CO)中毒個案

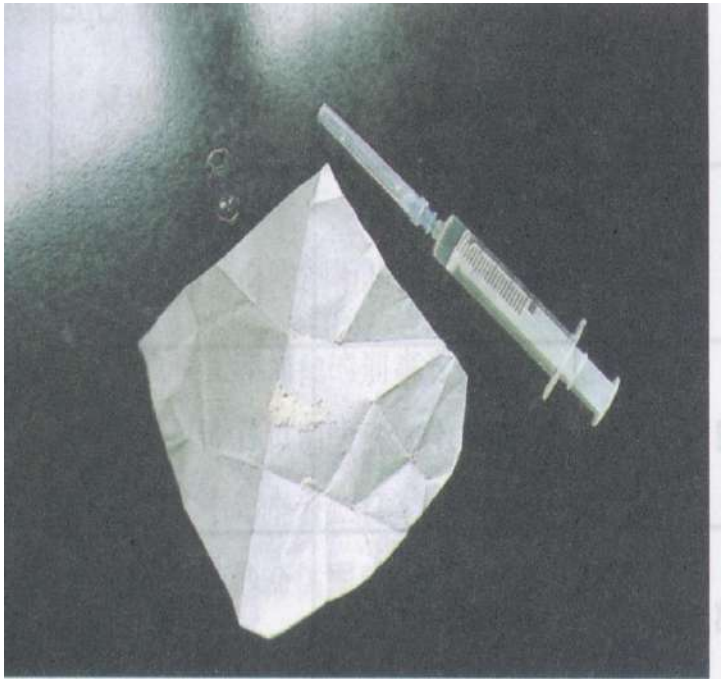
Severe Rhabdomyolysis Mimicking Transverse Myelitis in a Heroin Addict

Chen-Chang Yang, M.D.; Guang-Yang Yang, M.D.; Jiin Ger, M.D.; Wei-Jen Tsai, M.D.; Jou-Fang Deng, M.D.

Veterans General Hospital, Taipei, Taiwan, R.O.C.

Clinical Toxicology 1995;34(1):591-5.

- BUN 28 mg/dL (7-20 mg/dL)
- Creatinine 2.8 mg/dL (0.5-1.5 mg/dL)
- LDH 6402 U/L (95-213 U/L)
- **ALT 422 U/L (0-40 U/L)**
- **AST 1828 U/L (5-45 U/L)**
- Free calcium 0.55 mmol/L (1.13-1.31 mmol/L)



scientific reports

Check for updat

OPEN

Incidence of rhabdomyolysis occurrence in psychoactive substances intoxication: a systematic review and meta-analysis

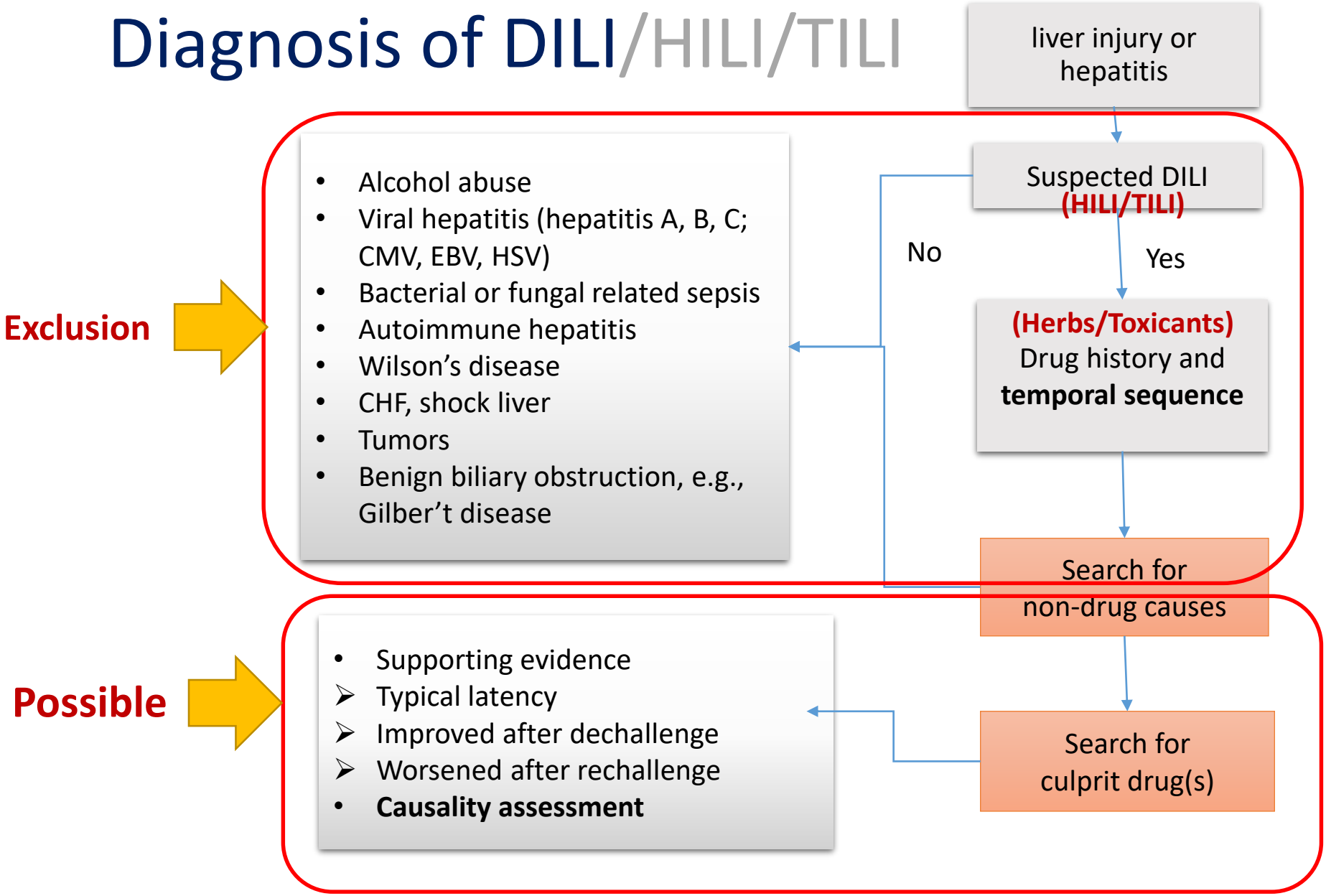
Alireza Amanollahi[1], Tannaz Babeveynezhad[2], Mohsen Sedighi[3], Shahin Shadnia[4], Sadaf Akbari[5], Mahbobeh Taheri[6], Mahboobeh Besharatpour[1], Goljamal Jorjani[1], Elham Salehian[7], Koorosh Etemad[1]✉ & Yadollah Mehrabi[1]✉

- The highest incidence of rhabdomyolysis was observed in **intoxication with heroin** (57.2 [95% CI 22.6–91.8]), **amphetamines** (30.5 [95% CI 22.6–38.5]), and **cocaine** (26.6 [95% CI 11.1–42.1]).
- The results showed a **high incidence of rhabdomyolysis induced by psychoactive substance intoxication in ICU patients** when compared to total wards.

大綱

- 毒藥物防治諮詢中心之簡介
- 國內常見毒藥物中毒之簡介
- 急性藥物中毒導致肝傷害之簡介
- 急性非藥物中毒導致肝傷害之簡介
  - ➢職業性毒物暴露導致肝傷害
  - ➢中草藥導致肝傷害(HILI)
  - ➢其他原因導致肝傷害
- **毒藥物中毒導致肝傷害之鑑別診斷與治療**

Diagnosis of DILI/HILI/TILI



García-Cortés M, et al. *J Hepatol* 2011;55:683-91.

Table 2: Biochemical features of common causes of moderate to marked increase in aminotransferase levels

Cause	Aminotransferase level increase (value × URL)	Bilirubin level increase (value × URL)	Comments
Ischemic injury	> 10 to > 50	< 5	AST > ALT; rapid decrease of aminotransferase levels after initial peak ALT/LDH ratio < 1 Presence of comorbid conditions
Toxic injury	> 10	< 5	Pattern of enzyme alteration similar to that of ischemic hepatitis History suggestive of toxic injury
Acute viral hepatitis	5–10 to > 10	5–10	Slow decrease of aminotransferase levels Presence of risk factors
Acute biliary obstruction	5–10	5–10 to > 10	Aminotransferase increase precedes cholestasis Presence of typical symptoms
Alcoholic hepatitis	5–10	5–10 to > 10	AST/ALT ratio > 2 May occur as both acute and acute-on-chronic injury

Note: URL = upper reference limit, AST = aspartate aminotransferase, ALT = alanine aminotransferase, LDH = lactate dehydrogenase.

治療

- 主要為移除暴露之毒性物質及支持性療法
- 特定毒藥物可能有解毒劑可以使用，譬如n-acetyl cysteine (for acetaminophen)、silibinin (for amatoxin)
- 嚴重時須肝臟移植

TABLE 1 | Basal principles of DILI management.

Principles	Describes	
I. Identify & Withdrawal	Identifying the offending drug(s) and prompt withdrawal before irreversible liver damage	
II. Monitor & Assessment	Monitoring liver biochemistries, assessing risk and benefit of dubious drug(s) for primary diseases	
III. Appropriate medication (according to the clinical pattern of DILI)	Hepatocellular type	Give priority to with hepatoprotective drugs (eg. NAC, MgIG, PPC, etc.)
	Cholestatic type	Give priority to with anticholestatic drugs (eg. UDCA, SAMe, etc.)
		Immunosuppressants (eg. GCs)
	Specific type	Specific treatment agents (eg. LC, Anticoagulants, etc.)
IV. Liver transplantation	Artificial liver supporting therapy and liver transplantation for ALF/SALF patients	

Note: NAC, N-acetylcysteine; MgIG, magnesium isoglycyrrhizinate; PPC, Polyene phosphatidylcholine; UDCA, Ursodeoxycholic acid; SAMe, S-adenosylmethionine; GCs, Glucocorticoids; LC, L-carnitine; ALF, acute liver failure; SALF, subacute liver failure.

Front Pharmacol 2022;12:806249.

TABLE 2 | Pharmacotherapy strategies of DILI.

Drugs Classification	Drugs name	Author & Year	Type of Study	Culprit drug	Outcomes/
Hepatoprotective Drugs	NAC and GSH	Prescott et al. (1979)	Comparative Study	Paracetamol	LFP, SVI
		Moosa et al. (2020)	Randomized, double-blind, placebo-controlled trial	Anti-tuberculosis drug	SHS
		Borlak et al. (2018)	Retrospective cohort study	Flupirtine	LFP
		Patel et al. (2019)	Case Reports	Tyrosine Kinase Inhibitor	LFP
		Elliott et al. (2016)	Case Reports	Norfloxacin	LFP
		Lee et al. (2009)	Randomized Controlled Trial	Non-APAP agents	LFP, SVI
		Reuben et al. (2010)	Prospective observational study	Multiple drugs	LFP, SVI
		Squires et al. (2013)	Randomized Controlled Trial	Non-APAP agents	NSD
	Glycyrrhizin acid preparation	Wang et al. (2019)	Randomized, double-blind, controlled trial	Multiple drugs	LFP
		Tang et al. (2012)	Phase III clinical trial	Anti-neoplastic drugs	LFP
	Bicyclol	Naiqiong et al. (2017)	Randomized Controlled Trial	Statin	LFP
		Chen et al. (2018)	Comparative Study	Anti-tuberculosis drug	LFP
		Li et al. (2018)	Retrospective cohort study	Anti-neuropathy drug	LFP
		Zhou et al. (2015)	Randomized controlled study	Anti-psoriasis drug	LFP
	Polyene phosphatidylcholine	Lei et al. (2021)	Literature analysis	Multiple drugs	LFP
		Liu et al. (2021)	Retrospective controlled study	Anti-tuberculosis drug	LFP
	Silymarin	Enjalbert et al. (2002)	Retrospective analysis	Toadstool	SVI
		Grabhorn et al. (2013)	Retrospective controlled study	Toadstool	SVI
		Masoumeh et al. (2015)	Open-label, randomized clinical trial	Anti-convulsive drugs	LFP
		Majid. et al. (2019)	Randomized, double-blind clinical trial	Anti-tuberculosis drug	NSD
		Zhao et al. (2021)	Retrospective cohort study	Multiple drugs	LFP

結論

- **很多毒藥物皆由肝臟代謝**，因此容易經由多種病生理機轉導致肝傷害，甚至肝衰竭
- **藥物中毒**導致的急性肝傷害以**acetaminophen最常見**
- **非藥物中毒**導致的急性肝傷害則以**鹵素族有機溶劑**(如四氯化碳及二甲基甲醯胺)**最常見**
- 毒藥物中毒導致的急性肝傷害嚴重時可能會進展至肝衰竭，因此有不適症狀時須及早接受診治，並須與**藥品肝傷害(DILI)**、病毒性肝炎、酒精性肝傷害、及肝臟本身疾病等因素進行**鑑別診斷**
- 治療部分除了少數毒藥物中毒有解毒劑或特定藥品可供使用，**主要採取支持性療法**，肝衰竭時則須評估是否接受**肝臟移植**

謝謝聆聽，敬請指教!

從藥品上市後安全監視資料看近年藥品肝損傷趨勢

執行長室
趙必暉 藥師

財團法人藥害救濟基金會
Taiwan Drug Relief Foundation

Disclaimer

- 任職藥害救濟基金會
  - 接受食品藥物管理署(TFDA)委託辦理「藥品安全監視體系精進」計劃、「優化完善醫療器材上市後風險評估及管理機制」計畫、藥害救濟相關業務
  - 協助食品藥物管理署(TFDA)辦理「全國藥物不良反應通報中心」
- 本次演講僅代表個人之觀點，不代表衛生主管機關之立場

財團法人藥害救濟基金會
Taiwan Drug Relief Foundation

財團法人藥害救濟基金會
Taiwan Drug Relief Foundation

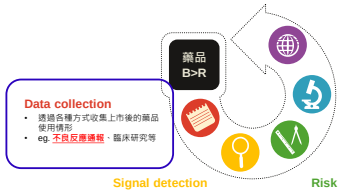
藥害救濟基金會

- **藥害救濟法立法**
  - 民國87年：藥害救濟法起草 -> 88年：藥害救濟要點實施
  - 民國89年：藥害救濟法公布實施
- **藥害救濟基金會成立**
  - 民國90年依法由衛生署(現衛生福利部)捐助成立

維護用藥權益
守護醫療安全

3

藥品安全監視策略



Risk communication
- 有效的雙向風險溝通，包含醫療人員、健康照顧者與病人都能即時且清楚獲得相關訊息或給予回饋

Risk minimization
- 藉由適當的風險管理措施降低危害的嚴重程度 eg. 仿單醫語加註、限制使用族群、特殊風險教育、執行風險管理計畫等
- 如果無法有效降低風險危害即可能被下市

Data collection
- 透過各種方式收集上市後的藥品使用情形
- eg. 不良反應通報、臨床研究等

Signal detection
- 藉由個案評估與流行病學方法偵測潛在的安全訊號

Risk identification/assessment
- 識別不良反應特徵、發生率、危險因子
- 分析受影響的範圍與嚴重度
- 評估整體風險效益平衡

財團法人藥害救濟基金會
Taiwan Drug Relief Foundation

藥害救濟(TDRS)

財團法人藥害救濟基金會
Taiwan Drug Relief Foundation

藥害救濟法

- **目的**
  - 使正當使用合法藥物而受害者，獲得及時救濟
  - 避免不必要訴訟浪費社會成本
  - 維護廠商及醫療機構名譽
  - 避免事件過度渲染，健全醫藥產業發展
- **原則**
  - 無過失責任之救濟制度，非過失賠償

財團法人藥害救濟基金會
Taiwan Drug Relief Foundation

適用對象

- 申請類別與資格：

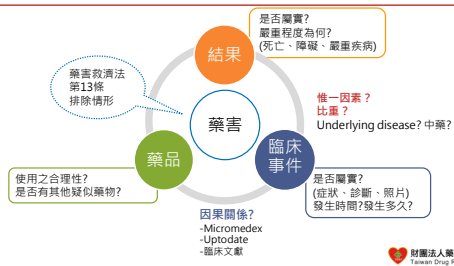
嚴重疾病(住院)
由受害人本人或
法定代理人申請

身心障礙(身心障礙證明)
由受害人本人或
法定代理人申請

死亡
法定繼承人申請

財團法人藥害救濟基金會 Taiwan Drug Relief Foundation

藥害救濟審議原則（通則）



財團法人藥害救濟基金會 Taiwan Drug Relief Foundation

排除情形

- **輕微的不良反應**
  未達死亡、障礙或嚴重疾病(住院)程度
- **臨床試驗用藥物**
  急救時超量藥物
- **適應症外使用**
  符合當時醫學原理及用藥適當性者，不在此限
- **常見且可預期**
  WHO定義發生率≧1%為common[常見]
- **其他經主管機關公告之情形**
- **打疫苗受害**
  依傳染病防治法申請預防接種受害救濟

*藥害救濟法第13條參照

財團法人藥害救濟基金會 Taiwan Drug Relief Foundation

歷年藥害救濟申請案件數統計

財團法人藥害救濟基金會 Taiwan Drug Relief Foundation

藥害救濟給付案之前五大藥品不良反應

不良反應類別	性別 女	性別 男	總計	症狀分類	小計
Skin and subcutaneous tissue disorders 皮膚及皮下組織疾患	839	762	1601 (67.21%)	Stevens Johnson Syndrome 史蒂文生氏-強生症候群	828
				Toxic Epidermal Necrolysis 毒性表皮壞死溶解症(包含SJS/TEN overlap)	309
				Drug reaction with Eosinophilia and Systemic Symptoms 藥物綜合併嗜伊紅血症及全身症狀	198
				Other 其他	266
Hepatobiliary disorders 肝膽疾患	86	120	206 (8.65%)	Hepatitis (急性)肝炎	80
				Hepatic failure (急性)肝衰竭	52
				Drug-induced liver injury 藥物性肝傷害	24
				Fulminant Hepatitis 猛爆性肝炎	23
				Other 其他	27
Immune system disorders 免疫系統疾患	88	101	189 (7.93%)	Anaphylactic shock 過敏性休克	146
				Drug hypersensitivity 藥物過敏	26
				Other 其他	17

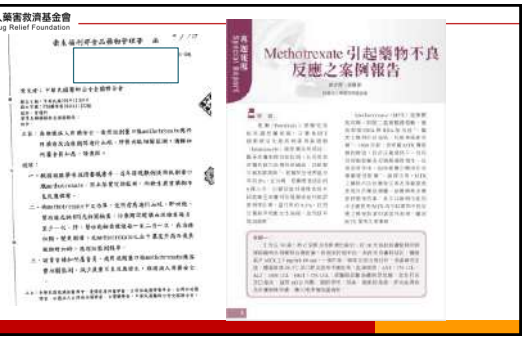
財團法人藥害救濟基金會 Taiwan Drug Relief Foundation

藥害救濟給付案之前五大藥品不良反應

不良反應類別	性別 女	性別 男	總計	藥品不良反應	小計
Blood and lymphatic system disorders 血液及淋巴系統疾患	71	29	100 (4.20%)	Agranulocytosis 顆粒性白血球減少症	32
				Pancytopenia 全血球減少症	24
				Thrombocytopenia 血小板減少症	12
				Neutropenia 嗜中性球減少症	10
				Leukopenia 白血球低下症	7
				Other 其他	15
Nervous system disorders 神經系統疾患	41	41	82 (3.44%)	Neuroleptic malignant syndrome 抗精神病藥物惡性症候群	17
				Hypoxic-ischaemic encephalopathy 缺氧性腦病變	6
				Encephalopathy 腦病變	5
				Cerebral infarction 腦梗塞	5
				Other 其他	49

財團法人藥害救濟基金會 Taiwan Drug Relief Foundation

財團法人藥害救濟基金會
Taiwan Drug Relief Foundation



不良反應通報資料(ADRS)

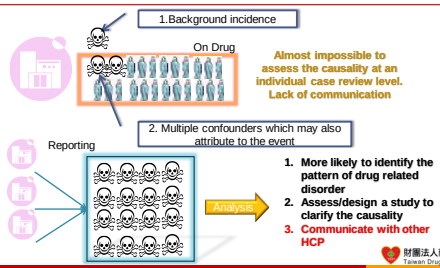
財團法人藥害救濟基金會
Taiwan Drug Relief Foundation

台灣全國藥品不良反應通報系統

- 87年起由臨床藥學會受託辦理
- 92年起委託藥害救濟基金會執行
- 94年起將通報業務中央化，統一由全國藥物不良反應通報中心為單一窗口受理各界通報
- 電子化的通報介面
  https://adr.fda.gov.tw/

財團法人藥害救濟基金會
Taiwan Drug Relief Foundation

Concept of reporting



財團法人藥害救濟基金會
Taiwan Drug Relief Foundation

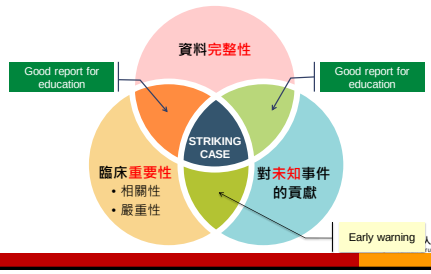
Pros and Cons

- Large population
- All medicines
- Hospital & out-patient care
- Long perspective
- Patient analyses possible
- Non-interventional
- Low cost
- High sensitivity in detecting rare AE
- Can be used for follow-up studies ("signal generation")

- Under-reporting
- Biased reporting
- Cannot calculate incidence (but other means of estimating rates)
- Not good at identifying
  - Delayed reactions
  - Late onset reactions
  - Reactions with high background rate
  - Deaths
- Report quality

財團法人藥害救濟基金會
Taiwan Drug Relief Foundation

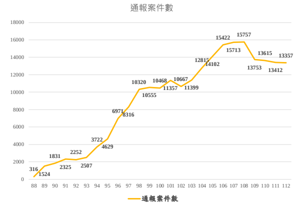
Report quality

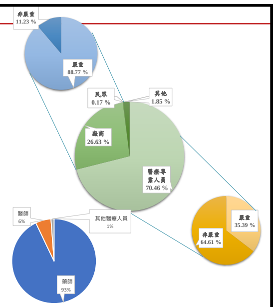


財團法人藥害救濟基金會
Taiwan Drug Relief Foundation

財團法人藥害救濟基金會
Taiwan Drug Relief Foundation

ADR通報現況

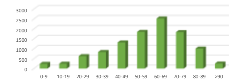




112年通報案例分析

財團法人藥害救濟基金會
Taiwan Drug Relief Foundation

年齡分布(歲)



類別	案件數	百分比(%)
通報之不良反應嚴重性		
死亡	663	4.96
危及生命	218	1.63
造成永久性殘疾	14	0.11
胎兒先天性畸形	1	0.01
導致病人住院或延長病人住院時間	1,803	13.50
其他嚴重不良反應(具重要臨床意義之事件)	3,898	29.18
非嚴重不良反應	6,760	50.61

類別	藥品症狀配對數	百分比(%)
評估相關性		
幾乎確定	11	0.07
極有可能	289	1.85
可能	6,606	42.34
存疑	1,047	6.71
不相關	400	2.57
資料不全	2,766	17.73
無法評估	4,483	28.73

112年通報案例分析

財團法人藥害救濟基金會
Taiwan Drug Relief Foundation

通報藥品 ATC 分類	通報數	百分比 (%)
Antineoplastic and immunomodulating agents	4,558	27.94
Antiinfectives for systemic use	3,543	21.72
Nervous system	1,697	10.40
Musculo-skeletal system	1,564	9.59
Various	1,065	6.53
Alimentary tract and metabolism	1,047	6.42
Cardiovascular system	944	5.79
Blood and blood forming organs	466	2.86
Systemic hormonal preparations	464	2.84
Sensory organs	361	2.21
Respiratory system	242	1.48
Genito urinary system and sex hormones	188	1.15
Dermatologicals	115	0.70
Antiparasitic products, insecticides and repellents	42	0.26
Drugs without ATC code	19	0.11

藥品	通報數	百分比
iohexol	306	1.88
piperacillin/tazobactam	296	1.82
bevacizumab	286	1.76
diclofenac	266	1.64
iopromide	266	1.64
ketorolac	249	1.53
teriparatide	248	1.53
levofloxacin	246	1.52
celecoxib	237	1.46
ranibizumab	220	1.36
vancomycin	185	1.14
amoxicillin/clavulanic acid	181	1.11
rituximab	180	1.11
docetaxel	174	1.07
cisplatin	168	1.03
ciprofloxacin	163	1.00
atezolizumab	162	1.00
metoclopramide	162	1.00
ceftriaxone	161	0.99
cefazolin	154	0.95
小計	4,310	26.42

112年通報案例分析

財團法人藥害救濟基金會
Taiwan Drug Relief Foundation

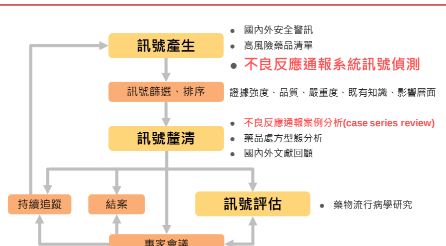
不良反應症狀器官系統分類	通報數	百分比(%)
Skin and subcutaneous tissue disorders	2,169	27.27
Blood and lymphatic system disorders	803	10.10
Nervous system disorders	633	7.96
Gastrointestinal disorders	618	7.77
Respiratory, thoracic and mediastinal disorders	474	5.96
General disorders and administration site conditions	458	5.76
Infections and infestations	404	5.08
Immune system disorders	345	4.34
Investigations	314	3.95
Metabolism and nutrition disorders	289	3.63
Eye disorders	253	3.18
Vascular disorders	202	2.54
Hepatobiliary disorders	199	2.50
Cardiac disorders	197	2.48
Renal and urinary disorders	188	2.36
Musculoskeletal and connective tissue disorders	146	1.84
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	72	0.91
Injury, poisoning and procedural complications	69	0.87
Psychiatric disorders	56	0.70
Ear and labyrinth disorders	23	0.29
Endocrine disorders	20	0.25
Reproductive system and breast disorders	8	0.10
Surgical and medical procedures	8	0.10
Pregnancy, puerperium and perinatal conditions	2	0.03
Social circumstances	2	0.03
Product issues	1	0.01

通報症狀	通報數	百分比(%)
Rash	896	11.27
Pruritus	258	3.24
Rash pruritic	201	2.53
Neutropenia	200	2.51
Anaphylactic shock	172	2.16
Thrombocytopenia	164	2.06
Leukopenia	161	2.02
Dyspnoea	155	1.95
Stevens-Johnson syndrome	155	1.95
Diarrhoea	109	1.37
Pyrexia	107	1.35
Vomiting	102	1.28
Nausea	97	1.22
Acute kidney injury	93	1.17
Eye swelling	89	1.12
Anaemia	88	1.11
Dizziness	86	1.08
Angioedema	85	1.07
Seizure	77	0.97
Urticaria	71	0.89
小計	3,366	42.32

*通報案件之不良反應症狀數目可能大於一項，因此總不良反應症狀數目可能大於通報案件數。

112年通報案例分析

安全訊號管理



財團法人藥害救濟基金會
Taiwan Drug Relief Foundation

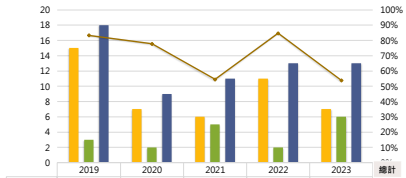
財團法人藥害救濟基金會
Taiwan Drug Relief Foundation

DILI在在TDRS近年的趨勢

財團法人藥害救濟基金會 Taiwan Drug Relief Foundation

近五年DILI藥害救濟案件數及審議結果統計

(2019-2023)



	2019	2020	2021	2022	2023	總計
給予救濟	15	7	6	11	7	46
不予救濟	3	2	5	2	6	18
案件總數	18	9	11	13	13	64
救濟比例	83%	78%	55%	85%	54%	72%

財團法人藥害救濟基金會 Taiwan Drug Relief Foundation

近五年DILI藥害救濟案件-不予救濟之理由統計

(2019-2023)

排名	不予給付之理由	案例數	百分比
1	常見且可預期之藥物不良反應	8	44.4%
2	申請類別(主張嚴重不良反應導致之結果)與藥品無相關	5	27.8%
3	非屬藥害救濟法第3條第1款所稱因藥物不良反應致死亡、障礙或嚴重疾病之藥害	4	22.2%
4	藥物不良反應未達死亡、障礙或嚴重疾病之程度	1	5.6%
	總計	18	100.0%

財團法人藥害救濟基金會 Taiwan Drug Relief Foundation

近五年DILI相關藥害救濟給付類別及金額

(2019-2023)

給予救濟	案例數（百分比%）	總金額 （百分比%）
死亡	17（37.0%）	$16,580,000 （92.7%）
障礙	0（0.0%）	$0 （0.0%）
嚴重疾病	29（63.0%）	$1,297,756 （7.3%）
總計	**46 （100.0%）**	**$17,877,756（100.0%）**

財團法人藥害救濟基金會 Taiwan Drug Relief Foundation

近五年DILI相關獲藥害救濟案件之不良反應型態統計

(2019-2023)

排名	藥品不良反應	筆數	百分比
1	(Acute) hepatitis	13	28.3%
	(Acute) hepatic failure	13	28.3%
2	Hepatitis fulminant	7	15.2%
	Liver injury	7	15.2%
3	Hepatic function abnormal	4	8.7%
4	Hepatitis cholestatic	1	2.2%
	Autoimmune hepatitis	1	2.2%
	總計	46	100.0%

財團法人藥害救濟基金會 Taiwan Drug Relief Foundation

近五年DILI相關獲藥害救濟案件之疑似藥品類別

(2019-2023)

排名	藥品類別	ATC類別編碼前三碼	筆數	百分比
1	Antimycobacterials	J04	39	50.0%
2	Antibacterials for systemic use	J01	7	9.0%
3	Lipid modifying agents	C10	4	5.1%
4	Antiinflammatory and antirheumatic products	M01	3	3.8%
5	Antidiarrheals, intestinal antiinflammatory/antiinfective agents	A07	2	2.6%
	Cardiac therapy	C01	2	2.6%
	Thyroid therapy	H03	2	2.6%
	Antivirals for systemic use	J05	2	2.6%
	Immunosuppressants	L04	2	2.6%
	Antigout preparations	M04	2	2.6%
	Analgesics	N02	2	2.6%
	Others		11	14.1%
	總計		78	100.0%

*列出累計超過1筆之項目

財團法人藥害救濟基金會 Taiwan Drug Relief Foundation

近五年DILI相關獲藥害救濟案件之疑似藥品

(2019-2023)

排名	藥物名稱	案例數	百分比
1	抗結核藥 Rifampin、Isoniazid、Pyrazinamide、Ethambutol、Rifabutin、Rifapentine、Protionamide (單方或複方)	17	30.4%
2	Cephalexin	2	3.6%
	Co-trimoxazole	2	3.6%
	Etoricoxib	2	3.6%
	Methimazole	2	3.6%
	Sulfasalazine	2	3.6%
	Others	29	51.8%
	總計	56	100.0%

*列出累計超過1筆之項目

Antimycobacterials

- DILI發生率約10%~20%、嚴重DILI發生率約1%
  - 依年齡層及藥品種類而異
  - 服藥後1週~12週、多出現在3個月內
- 治療中監測
  - 建議用藥前檢查B、C 型肝炎以及愛滋病毒感染
  - 治療前以及開始治療後的第2、4、8 週進行血液及生化檢查
- 結核病治療
  - INH+RMP+PZA+EMB (16案)
- 潛伏性結核病治療
  - 9H(5案)、3HP(3案)、3HR(2案)、4R

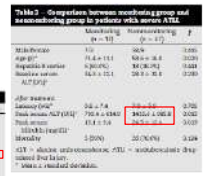
引用自結核病診治指引第7版

財團法人藥害救濟基金會 Taiwan Drug Relief Foundation

Antimycobacterials

Original Article

Correlation of antituberculosis drug-related liver injury and liver function monitoring: A 12-year experience of the Taiwan Drug Relief Foundation



Journal of foodanddruganalysis 22(2014)356 e3 62

財團法人藥害救濟基金會 Taiwan Drug Relief Foundation

財團法人藥害救濟基金會 Taiwan Drug Relief Foundation

https://www.tdrf.org.tw/2024/04/02/knowledge01-1-75/

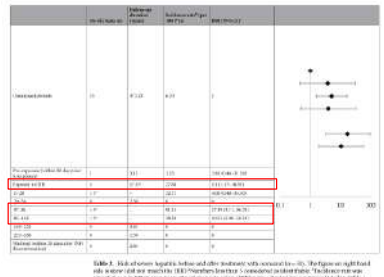
財團法人藥害救濟基金會 Taiwan Drug Relief Foundation

Association between 9-month isoniazid prophylaxis of latent tuberculosis and severe hepatitis in patients treated with TNF inhibitors

Figure 2. Flow diagram showing patient population of cohort selection.

Scientific Reports | (2021) 11:18013

財團法人藥害救濟基金會



- an association between risk of severe hepatitis and exposure to isoniazid
- a close monitoring of liver function is mandatory to minimize the risk

Scientific Reports | (2021) 11:18013

其他特殊案例

- 過敏反應(含DRESS)合併肝損傷(10案)
  - Gemifloxacin、Cephalexin、Co-trimoxazole、 Propafenone、 Etoricoxib、Azathioprine、Sulfasalazine、Allopurinol
- Etanercept induced autoimmune hepatitis(1案)
  - The latency to onset has ranged from 2 weeks to several years
  - Autoantibodies, including antinuclear antibody (ANA)
  - Stopping the TNFα antagonist and may require corticosteroid therapy

引用自：
LiverTox: Clinical and Research Information on Drug-Induced Liver Injury

財團法人藥害救濟基金會 Taiwan Drug Relief Foundation

Rituximab相關之B型肝炎病毒再活化(1)

▶ **病情概要**

- **背景**：61歲男性，有類風濕性關節炎、HBV帶原等病史。
- **用藥原因**：因類風濕性關節炎就醫，檢驗ALT：22 U/L、HBsAg(+)，處方rituximab 。
- **不良反應**：接受rituximab第一個療程後約3個月，個案因上腹痛至急診就醫，肝功能指數上升（ALT：525 U/L、T Bil：1.59mg/dL）、HBV病毒量大於6.9×10^8，同日轉住院治療，入院診斷為B型肝炎急性復發，給予抗病毒藥物治療，總膽紅素仍持續上升（最高至33 mg/dL ）且出現肝性腦病變，個案於2個月後死亡。

財團法人藥害救濟基金會 Taiwan Drug Relief Foundation

38

Rituximab相關之B型肝炎病毒再活化(2)

▶ **審議結果**

- 本案有關B型肝炎病毒再活化（HBV reactivation）之發生，雖無法排除與rituximab 無關聯，然...
  病人因接受rituximab治療造成免疫力下降，對於潛伏性感染之抵抗力相對較低，出現B型肝炎病毒再活化之情形，非屬藥物直接引起之不良反應，與藥害救濟法第3條第1款之規定不符，不符合藥害救濟之給付要件。

依據rituximab仿單警語記載，接受rituximab治療的病人可能發生B型肝炎病毒再活化，在某些案例會導致猛爆性肝炎、肝衰竭及死亡，開始治療『前』所有病人皆應接受HBV感染篩檢，並於治療『期間』及『之後』持續監測，對於有感染過HBV的病人，應在rituximab靜脈注射前治療前及治療期間，諮詢B型肝炎專業醫師有關HBV監測及抗病毒治療之考量，以保障病人用藥安全並避免可能的醫療爭議。

財團法人藥害救濟基金會 Taiwan Drug Relief Foundation

39

DILI在在ADRS近年的趨勢

財團法人藥害救濟基金會 Taiwan Drug Relief Foundation

近五年DILI相關ADR通報案件(1)

Aim of study	分析近五年藥物性肝傷害(DILI)通報案件
Source	全國不良反應通報系統資料庫
Time-frame	2019-2023
Inclusion criteria	通報症狀符合藥物性肝傷害之Standardised MedDRA Queries (SMQ)者： Drug related hepatic disorders - comprehensive search (SMQ)
Exclusion criteria	通報症狀為肝臟相關基血異常者： Liver-related coagulation and bleeding disturbances (SMQ)

年齡分布(歲)

	Age	median	range/IQR
Age, median (Range)	62.4	0.1-102.8	
Age, median (IQR)	62.4	50.4-72.35	

各年度通報案例數比較

不良反應嚴重性

Seriousness	n	(%)
死亡		7.27
危及生命		1.32
導致病人住院或延長病人住院時間		31.12
其他嚴重不良反應（其重要臨床意義之事件）		36.16
非嚴重不良事件（罕見案例者）		24.14
總計		100%

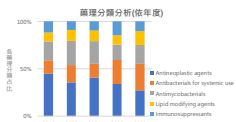
台灣醫學 Formosa J Med 2013;17:457-67

近五年DILI相關ADR通報案件(2)

藥理分類排名－不良反應嚴重性：嚴重

排序	藥理分類	n	%
1	Antineoplastic agents		28.30
2	Antimycobacterials		13.99
3	Antibacterials for systemic use		12.62
4	Immunosuppressants		9.26
5	Lipid modifying agents		6.10
6	Antiepileptics		3.05
7	Antivirals for systemic use		2.89
8	Antimycotics for systemic use		2.37
9	Cardiac therapy		2.05
10	Thyroid therapy		1.26

藥理分類分析(依年度)



嚴重不良反應(死亡+危及生命+導致病人住院或延長病人住院時間+其他嚴重不良反應(其重要臨床意義之事件))－藥品名

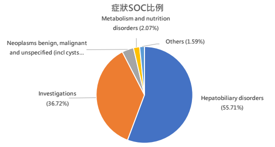
排序	藥品名稱	n	%
1	nivolumab		3.63
2	pyrazinamide		3.05
3	isoniazid		2.84
4	pembrolizumab		2.52
5	atorvastatin		2.05
6	rifampicin		1.95
7	rifampicin and isoniazid		1.79
8	amiodarone		1.74
9	ethambutol		1.68
10	regorafenib		1.68
11	valproic acid		1.63
12	bevacizumab		1.53
13	sorafenib		1.42
14	rosuvastatin		1.26
15	ipilimumab		1.26
16	tofacitinib		1.21
17	fluorouracil		1.21
18	rifampicin, pyrazinamide, ethambutol and isoniazid		1.21
19	fenofibrate		1.16
20	adalimumab		1.16

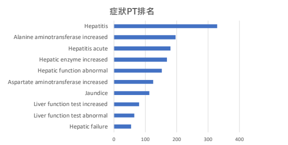
嚴重不良反應(死亡+危及生命+導致病人住院或延長病人住院時間+其他嚴重不良反應(其重要臨床意義之事件))－藥品名

排序	藥品名稱	n	%
1	pyrazinamide		4.62
2	isoniazid		4.29
3	atorvastatin		3.28
4	rifampicin and isoniazid		2.86
5	rifampicin		2.86
6	amiodarone		2.77
7	valproic acid		2.61
8	ethambutol		2.35
9	rosuvastatin		2.02
10	rifampicin, pyrazinamide, ethambutol and isoniazid		1.93
11	fenofibrate		1.76
12	fluorouracil		1.60
13	sulfamethoxazole and trimethoprim		1.51
14	fluconazole		1.43
15	ceftriaxone		1.43
16	oxacillin		1.43
17	piperacillin and beta-lactamase inhibitor		1.26
18	azathioprine		1.26
19	sulfasalazine		1.18
20	thiamazole		1.09
20	nivolumab		1.09
20	remdesivir		1.09

財團法人藥害救濟基金會
Taiwan Drug Relief Foundation

近五年DILI相關ADR通報案件(3)





不良反應嚴重性：嚴重：死亡

排序	PT	n	%
1	Hepatic failure		12.79
2	Jaundice		9.30
3	Hepatitis acute		8.72
4	Ascites		5.81
5	Hepatitis		5.81
6	Acute hepatic failure		5.23
7	Alanine aminotransferase increased		4.07
8	Blood bilirubin increased		4.07
9	Aspartate aminotransferase increased		3.49
10	Hepatic function abnormal		3.49
10	Hepatic encephalopathy		3.49

不良反應嚴重性：嚴重：死亡+危及生命

排序	PT	n	%
1	Hepatic failure		11.65
2	Jaundice		9.22
3	Hepatitis acute		8.25
4	Hepatitis		8.25
5	Ascites		6.31
6	Alanine aminotransferase increased		4.37
7	Acute hepatic failure		4.37
8	Aspartate aminotransferase increased		3.88
9	Hepatic encephalopathy		3.88
10	Hepatic function abnormal		3.88

不良反應嚴重性：嚴重

排序	PT	n	%
1	Hepatitis		13.86
2	Alanine aminotransferase increased		8.46
3	Hepatitis acute		7.66
4	Hepatic enzyme increased		7.36
5	Aspartate aminotransferase increase		6.74
6	Jaundice		6.62
7	Hepatic function abnormal		6.13
8	Liver function test increased		3.86
9	Liver function test abnormal		3.37
10	Hepatocellular carcinoma		3.25

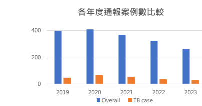
財團法人藥害救濟基金會
Taiwan Drug Relief Foundation

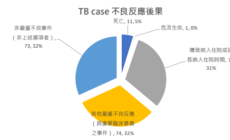
近五年DILI相關ADR通報案件(4)
Antimycobacterials

年齡 Age/Age group	TB case		Overall	
Age	median	range/IQR	median	range/IQR
Age, median (Range)	66.85	41-99	62.4	0.1-102.8
Age, median (IQR)	66.85	57-81.125	62.4	50.4-72.35
UKN	n=24		n=	
Age group	n	(%)	n	(%)
>=65		89.57		42.96
50-64		3.48		29.12
40-49		1.30		9.50
30-39		0.00		5.15
18-30		0.00		4.29
<18		0.00		3.09
UKN		5.65		5.89

可疑藥品分析 - 依Anti-TB藥品成分分析

藥品名稱	案件數
rifampicin	155
isoniazid	183
ethambutol	87
pyrazinamide	130
rifabutin	3
rifapentine	13
protionamide	1
rifamycin	1





財團法人藥害救濟基金會
Taiwan Drug Relief Foundation

Amiodarone引起的慢性肝損傷

76/M

- 病史：DM、HTN、CVA、CKD stage III、CHF
- 目前沒有肝臟相關病史
- 無酗酒習慣、吸菸史40年(已戒6年)

- 2014：肝功能檢驗正常
- 2015/2/27：Amiodarone (200mg QD) for CHF
- 2016：肝功能檢驗正常
- 2018年底~2019年初：肝指數略上升 AST/ALT: 91/79 U/L
- 2019/12/19：多天嚴重背痛，ER診斷肝硬化腹水。治療後出院，OPD追蹤 AST/ALT: 173/98 U/L T-Bil: 2.01 mg/dL
- 2019/12/24：昏迷、失語、無法走路而就醫，經CT和抽血檢測後懷疑為amiodarone hepatotoxicity AST/ALT: 198/115 U/L T-Bil: 2.52 mg/dL ALK-P: 303 U/L
- 2019/12/25：肝功能持續降低，導致漸進式多重器官衰竭而死亡

相關性評估：可能

Amiodarone引起的慢性肝損傷

回顧文獻資料

- 長期口服amiodarone潛在**慢性肝損傷**風險
- 組織學結果可能**類似酒精性肝炎或肝硬化**
- 肝損傷進程中**臨床徵兆和表現可能有限**，但最後卻可能造成肝衰竭而導致病人死亡

檢視中文仿單

- 於**「警語及注意事項」及「不良反應」處已刊載慢性肝損傷風險**
- 提醒口服amiodarone引起的慢性肝異常，其臨床及生化徵兆可能有限
- 開始amiodarone治療後建議**定期監測肝功能**

國內ADR資料庫

- 另接獲數件疑似長期口服amiodarone導致肝毒性之通報案例，其**相關性皆評估為可能**
- 部分個案的肝臟相關症狀並不明顯（如肝指數輕微上升），但也有急性發作導致嚴重肝炎的案例
- **有1件通報案件提及病人於使用amiodarone期間並未追蹤肝功能**

財團法人藥害救濟基金會
Taiwan Drug Relief Foundation

Amiodarone引起的慢性肝損傷

- 經TFDA藥品安全評估諮議會討論後，決議發布風險溝通表提醒醫療人員和民眾留意長期使用amiodarone可能潛在之肝損傷風險，並應注意相關臨床症狀及定期監測肝功能

財團法人藥害救濟基金會
Taiwan Drug Relief Foundation

"To know something harmful and not report is unethical."

Report of good quality leads to better understanding and more opportunities to prevent similar harm upon others.

每位通報者、每一件通報都是藥品安全監視的基石！

財團法人藥害救濟基金會
Taiwan Drug Relief Foundation

感謝聆聽

全國藥物不良反應通報中心
Taiwan National ADR Reporting Center
財團法人藥害救濟基金會
Taiwan Drug Relief Foundation

專線：(02)2396-0100
傳真：(02)2358-4100
網址：www.tdrf.org.tw
地址：10092台北市中正區愛國東路22號10樓