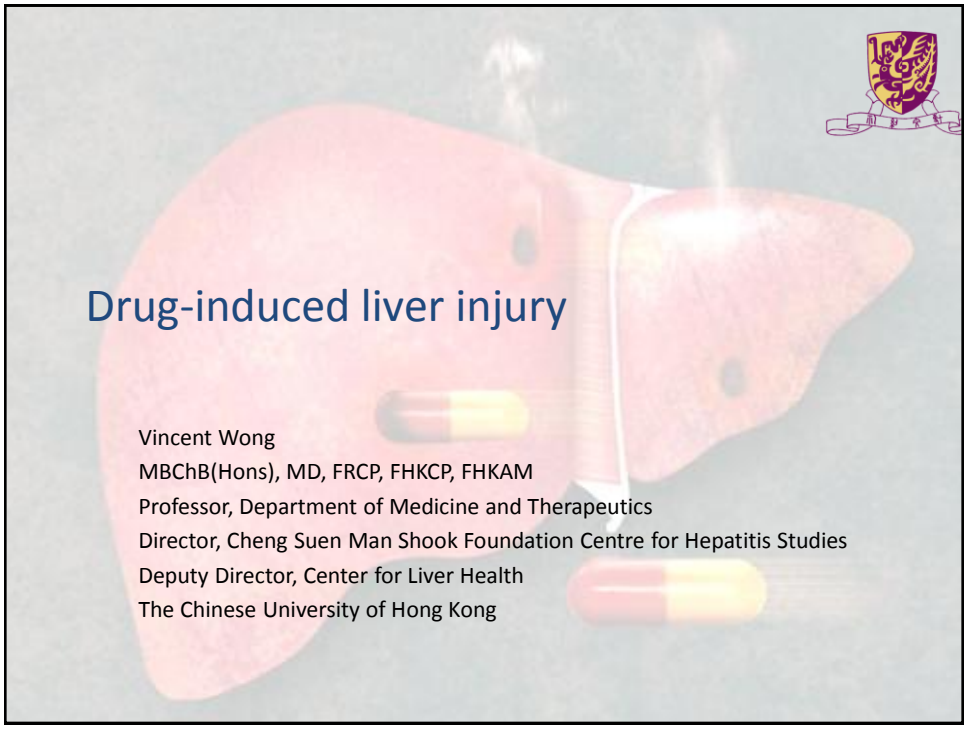


Drug-induced liver injury

Vincent Wong
MBChB(Hons), MD, FRCP, FHKCP, FHKAM
Professor, Department of Medicine and Therapeutics
Director, Cheng Suen Man Shook Foundation Centre for Hepatitis Studies
Deputy Director, Center for Liver Health
The Chinese University of Hong Kong

Drug-induced liver injury (DILI)

- Injury induced by drugs or herbal medicines leading to liver test abnormalities or liver dysfunction
- Reasonable exclusion of other etiologies
- Most are idiosyncratic or unexpected reactions

Impact of DILI

- Leading cause of acute liver failure in USA
- The survival of acute liver failure due to DILI is 20%
- The most common cause of post-marketing withdrawal of new drugs

Troglitazone-Induced Hepatic Failure Leading to Liver Transplantation

A Case Report

Brent A. Neuschwander-Tetri, MD; William L. Isley, MD; Julie C. Oki, PharmD; Sanjay Ramrakhiani, MD; Stella G. Quiason, MD; Nancy J. Phillips, MD; and Elizabeth M. Brunt, MD

Background: Troglitazone is a new drug for the treatment of type 2 diabetes. Although mild liver injury occurred in 1.9% of participants in controlled trials, the U.S. Food and Drug Administration has received reports of five postmarketing cases of severe liver disease that resulted in death or liver transplantation.

Objective: To report the clinical and histopathologic characteristics of a patient with troglitazone-associated severe liver injury leading to transplantation.

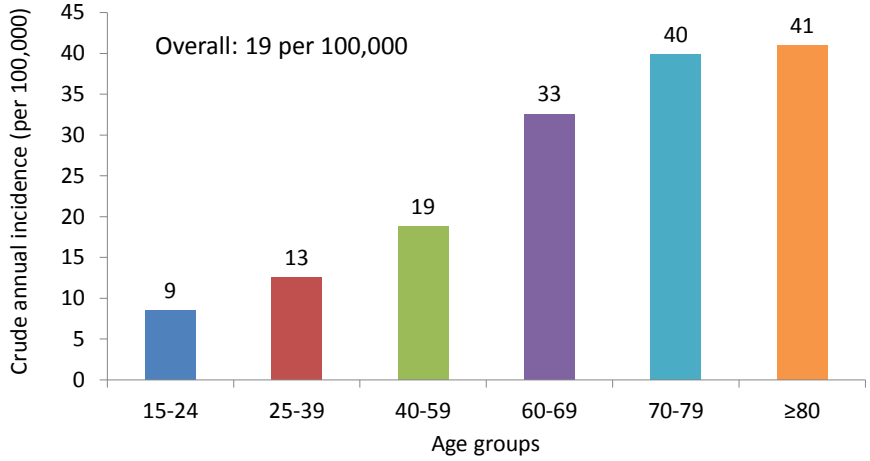
Design: Case report.

Setting: Two university hospitals.

Patient: A 55-year-old woman taking troglitazone, 400 mg/d, and insulin, 120 U/d.

Neuschwander-Tetri et al. Ann Intern Med 1998;129:38-41

Crude annual incidence of DILI: Icelandic experience



Björnsson et al. Gastroenterology 2013;144:1419

Common drugs implicated in liver injury

- N=784
- Swedish Adverse Drug Reactions Advisory Committee (1970-2004)

	Total Study Group	Death/LT
Antibiotics	212	16
Flucloxacillin	129	7
Erythromycin	42	0
Trimethoprim/sulfametoxazol	21	2
Isoniazide	7	3
Ciprofloxacin	7	2
Dicloxacillin	3	1
Pivmecillinam	3	1
Anesthetics	15	6
Halothane	15	6
NSAIDs	38	10
Diclofenac	20	4
Naproxen	11	4
Ibuprufen	4	1
Rofecoxib	3	1
Other drugs	106	19
Disulfiram	27	3
Carbamazepine	17	3
Ranitidin	10	1
Enalapril	8	2
Chlorpromazine	8	2
Sulfasalazine	7	1
Omeprazol	6	1
Cyclophosphamid	5	2
Ticlopidine	5	1
Atorvastatin	4	1
Simvastatin	4	1
Nefazodon	4	1
≥1 drug suspected	151	11

Björnsson et al. Hepatology 2005;42:481-9

Common drugs causing DILI

Drug	Patients treated, n	DILI, n	Per 100,000	Jaundice
Amoxicillin/clavulanate	35,252	15	43	40%
Diclofenac	54,889	6	11	33%
Azathioprine	532	4	752	0%
Infliximab	593	4	675	25%
Nitrofurantoin	5476	4	73	50%
Isotretinoin	2169	3	138	0%
Atorvastatin	7385	2	27	50%
Doxycycline	32,677	2	6	0%

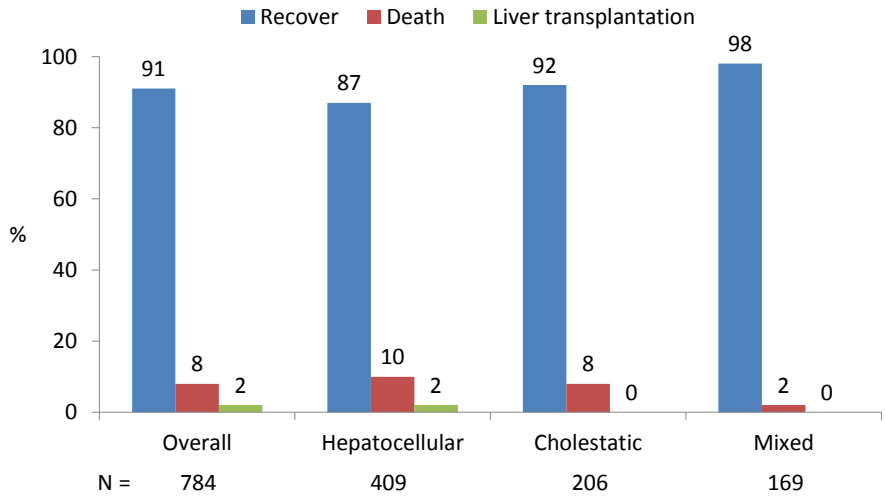
Björnsson et al. Gastroenterology 2013;144:1419

Patterns of DILI

Tempo	Pattern	Examples
Acute	Hepatocellular (ALT >3×ULN)	Paracetamol, isoniazid, pyrazinamide, statins, valproic acid
	Cholestatic pattern (ALP >2×ULN, ALT/ALP <2)	Augmentin, azathioprine, clopidogrel, estrogen, tricyclics
	Mixed	Azathioprine, amitryptilline, captopril, carbamazepine, phenytoin, carbamazepine
Chronic	Steatohepatitis	Amiodarone, tamoxifen
	Microvesicular steatosis	NRTIs, valproic acid, tetracycline
	Granulomatous hepatitis	Diltiazem, sulfur drugs
	Sinusoidal obstruction	Busulfan, cyclophosphamide
	Fibrosis	Methotrexate
	Hepatic adenoma	Oral contraceptives
	Autoimmune hepatitis	Nitrofurantoin, minocycline

Chang and Schiano. Aliment Pharmacol Ther 2007;25:1135-51

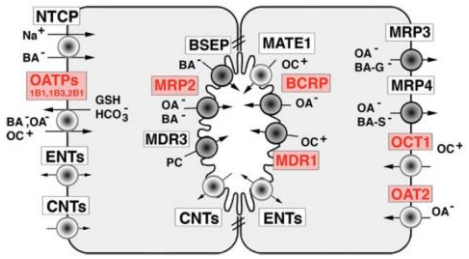
Outcomes of DILI



Bjornsson et al. Hepatology 2005;42:481-9

Pathophysiology of DILI

- Drugs >500 daltons are selectively removed by the liver
- Metabolism may generate toxic intermediates
- Increased risk:
  - High drug concentrations
  - Altered expression of enzymes or transporters
  - Reduced antioxidants (e.g. glutathione)
- Immune-mediated injury



Padda et al. Hepatology 2011;53:1377-87

Examples of hepatocyte membrane transporters and disease

Name	Abbreviation	Clinically relevant polymorphisms
Organic-anion-transporting polypeptides	OATPs	Statin-induced myopathy
Multidrug-resistance protein-3	MDR3	Risperidine hepatocellular cholestasis Oral-contraceptive-induced cholestasis
Canalicular bile salt export pump	BSEP	Fluvastatin-induced cholestasis

Clinical presentation

- Most idiosyncratic drug reactions occur between 1 week and 3 months
- More delayed presentation reported
- Asymptomatic elevated liver tests
- Acute hepatitis with and without jaundice
- Acute liver failure with severe encephalopathy
- Chronic hepatitis
- Drug cirrhosis

Drug history is the key to the diagnosis

- Exposure: Which drug? How long?
- Discontinuation: Improvement in liver tests?
- Is the pattern typical of the offending drug?
- Caution:
  - Recovery may be delayed, particularly for cholestatic type e.g. Augmentin
  - Were the drugs started after symptom onset?

Other diagnostic tests – Acute hepatitis

- Viral serology for hepatitis A, B, C and E; ±EBV and CMV
- Autoimmune markers: ANA, SMA
- Serum ceruloplasmin and urine copper may be misleading at the acute stage
- Other work up as clinically indicated

Other diagnostic tests – Chronic hepatitis

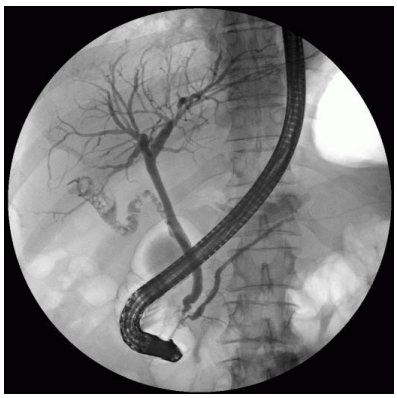
- Viral serology for hepatitis B and C
- Autoimmune markers: ANA, SMA
- Wilson's disease: Serum ceruloplasmin and 24-hour urine copper
- Hemochromatosis: Iron studies
- Other workup as clinically indicated

Other diagnostic tests – Cholestasis

- Rule out structural lesion before blaming drugs
- Simple imaging: USG, CT
- Formal cholangiogram in suspicious cases
- Anti-mitochondrial antibody (AMA) for primary biliary cirrhosis

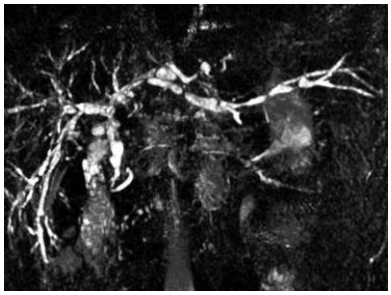
Endoscopic retrograde cholangiopancreatogram (ERCP)

- Inject contrast into the bile ducts and pancreatic duct
- Diagnostic and therapeutic
- Potential complications
  - Pancreatitis
  - Perforation
  - Bleeding



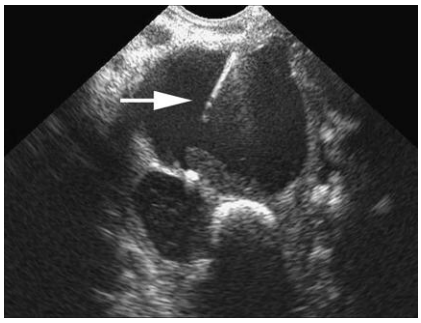
Magnetic resonance cholangiopancreatogram (MRCP)

- Non-invasive
- Overall accuracy comparable to ERCP
- Preferred diagnostic test



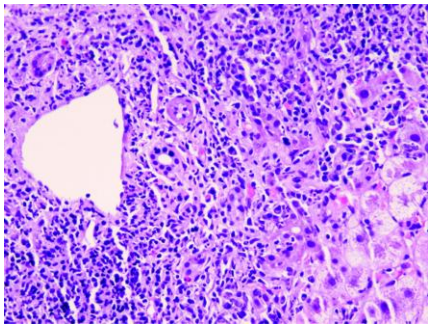
Endoscopic ultrasound (EUS)

- Combination of upper GI endoscopy and ultrasound
- High frequency ultrasound wave: High resolution
- Possible to obtain tissue



Histology

- Seldom pathognomonic
  - Prominent eosinophils
  - Granulomatous hepatitis
  - Central hepatocyte dropout
- Rule out other etiologies
- Complications



Ramachandran and Kakar. J Clin Pathol 2009;62:481-92

Roussel-Uclaf Causality Assessment Method

Type of liver injury	Hepatocellular		Cholestatic/Mixed		Points
Time of onset	1st exposure	2nd exposure	1st exposure	2nd exposure	-
Time from drug intake till reaction onset	5-90 days	1-15 days	5-90 days	1-90 days	+2
	<5 or >90 days	>15 days	<5 or >90 days	>90 days	+1
Time from drug withdrawal till reaction onset	≤15 days	≤15 days	≤30 days	≤30 days	+1
Risk factors	Alcohol		Alcohol or pregnancy		+1
	Age ≥55		Age ≥55		+1
Course of the reaction	>50% improvement in 8 days		-		+3
	>50% improvement in 30 days		>50% improvement in 180 days		+2
	-		<50% improvement in 180 days		+1
	Lack of information or no improvement		Lack of information or no improvement		0
	Worsening or <50% improvement in 30 days		-		-1

Prediction of outcome

Factors	Died or transplanted (N=85)	Recovered (N=712)	P
Age	65 (47-77)	58 (41-74)	0.04
Male gender	34%	43%	NS
Duration of treatment (days)	25 (10-94)	21 (10-49)	NS
Bilirubin (µmol/l)	19 (13-25)	6 (3-10)	<0.001
AST (× ULN)	34 (14-59)	7 (3-17)	<0.001
ALT (× ULN)	31 (16-56)	11 (6-24)	<0.001
ALP (× ULN)	2 (1-3)	2 (1-3)	NS
AST/ALT ratio	1.1 (0.8-1.4)	0.6 (0.4-0.9)	<0.001

Bjornsson et al. Hepatology 2005;42:481-9

General management

- Stop the offending drug
- Close monitoring of LFT, RFT and INR
- Consider liver transplantation

King's College criteria for liver transplantation in fulminant hepatic failure

- Paracetamol
  - Arterial pH <7.3

    or
  1. Grade III-IV encephalopathy **and**
  2. PT >100 s **and**
  3. Cr >301 µmol/l
- Non-paracetamol
  - PT >100 s

    or

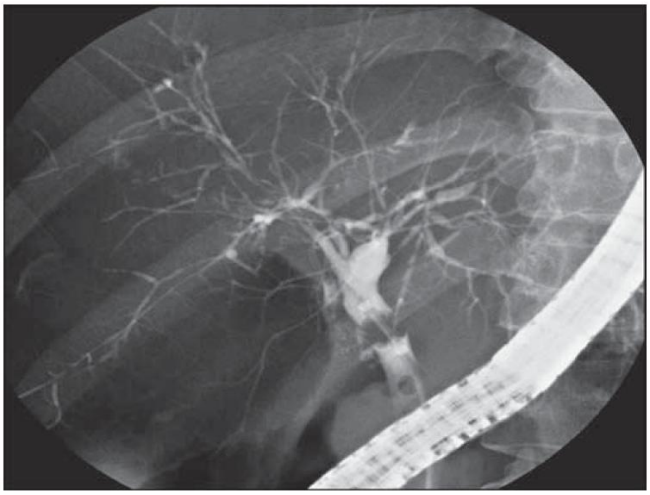
  3 of the followings:
  - Age <10 or >40
  - Non-A, non-B hepatitis, halothane, idiosyncratic DILI
  - Duration of jaundice before onset of encephalopathy >7 days
  - PT >50 s
  - Bilirubin >308 µmol/l

Ketamine-induced cholangiopathy

Ketamine-induced cholangiopathy: Clinical features

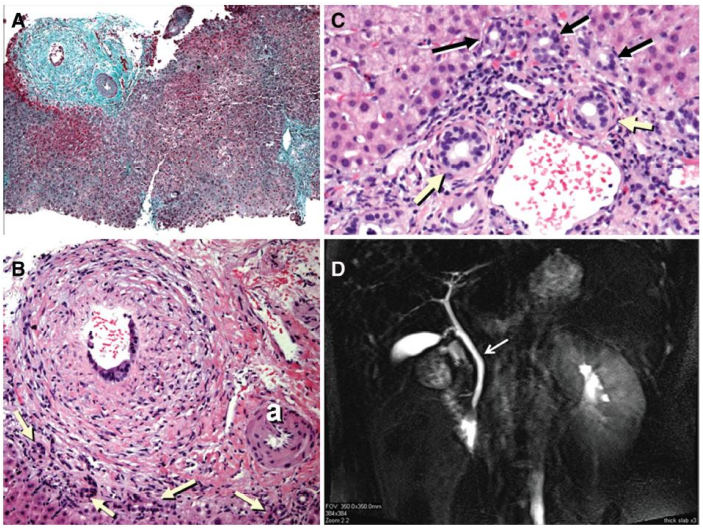
- Mainly cholestatic picture
- Incidental finding
- May have jaundice and intense pruritus

Ketamine-induced cholangiopathy: ERCP findings



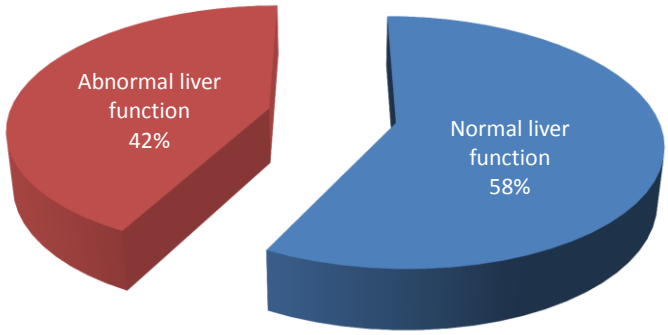
Seto et al. Am J Gastroenterol 2011;106:1004

Ketamine-induced liver injury: Histology



Turkish et al. Hepatology 2013;58:825

CUHK experience in 297 ketamine abusers



Factors associated with ketamine-induced cholangiopathy

Factors	OR	95% CI	P
Female	2.2	1.3-3.8	0.004
Abstinence	0.5	0.3-0.9	0.02
CRP (per 5 mg/l)	2.6	1.8-3.8	<0.001

Conclusions

- DILI is common in the hospital setting and can present in a variety of ways. High index of suspicion and good history taking are the key to diagnosis.
- Other liver diseases should be excluded by blood tests, imaging studies and histology as clinically indicated.
- Cessation of the offending drug is the most important management. Liver transplantation should be considered in severe cases.