LUDWIG INSTITUTE FOR CANCER RESEARCH

Imperial College London

Drug-induced Biliary Disease

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Drug-induced Biliary Disease

- Pathophysiology
- Clinical features
- Pathological features

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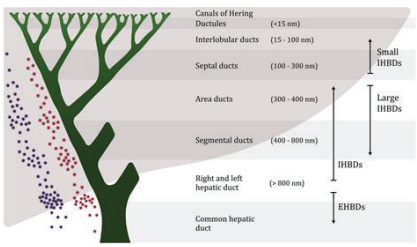


Repopulating the biliary tree from the peribiliary glands
BBA - Molecular Basis of Disease (in press)

Xenobiotic capacity of cholangiocytes

Drug metabolizing enzymes
- Cytochrome P450 1A, 2E1, 3A
- Glutathione S-transferase

Drug efflux transporters
- P-glycoprotein MRP-1,
- MRP-3

Sterol metabolism enzymes
- HMG-CoA reductase
- Cholesterol 7-α hydroxylase

Gut and Liver, 2016;10:687

Animal Models of DILI

Animal models have been useful in predicting intrinsic DILI.

Attempts to develop animal models of idiosyncratic DILI that involve the adaptive immune system have been largely unsuccessful.

Clin. Pharmacol. Ther. 101 (2017) 469–480.

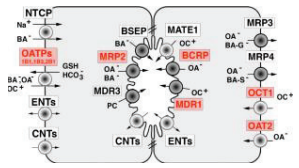
Pathophysiology I

Drug induced cholestasis may occur particularly under conditions of:
- increased drug concentration
- genetic alterations in expression of enzymes or transporters
- reduced hepatic concentrations of anti-oxidants

Drug induced cholestasis can be caused by:
- direct toxic effects of drugs / metabolites
- immune mediated process

Hepatology Communications 2017;1:726-735

Pathophysiology II



Hepatocyte couplet illustrating location of major transporters that determine bile production and hepatic drug transport.

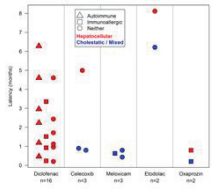
Pathophysiology III
BSEP

- The bile salt export pump (BSEP) is the major transporter for the secretion of bile acids from hepatocytes into bile in humans.
- **Mutations are associated with:**
  progressive familial intrahepatic cholestasis type 2 (PFIC-2),
  benign recurrent intrahepatic cholestasis type 2 (BRIC-2) and
- **Genetic polymorphisms are linked to:**
  intrahepatic cholestasis of pregnancy (ICP)
  drug-induced liver injury (DILI).

Clin Res Hepatol Gastroenterol. 2012;36: 536

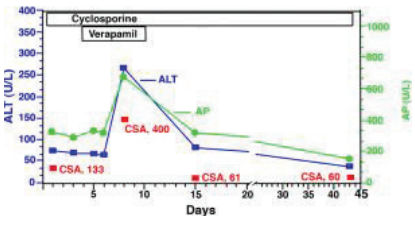
Chemical Properties

- The quinolones temafloxacin and trovafloxacin have a difluorinated side chain, making them highly lipophilic and subsequently associated with cholestatic liver disease.
- NSAIDs, despite only small differences in structure, have different patterns of liver disease:



Liver Int. 2016 April ; 36(4): 603–609

Simultaneous administration of 2 MDR1 substrates



Dosage

- In an American study, daily doses greater than 50 mg were significantly associated with severe DILI, of which 1/3 had a cholestatic injury pattern.
- In a Spanish study, 77% of patients with DILI received medications with daily doses greater than 50 mg
- This risk may be further enhanced with medications that are excreted by the biliary system compared to drugs with minimal biliary excretion (74% versus 40%).

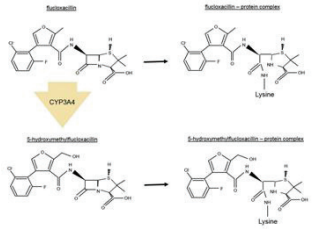
Hepatology Communications 2017;1:726-735

Age

- Cholestatic pattern of DILI is more common among the elderly, whereas hepatocellular DILI seems to be more common in younger individuals:
  - 61% of DILI cases in patients older than 60 years were cholestatic
  - 39% of DILI cases in patients younger than 60 were cholestatic
  - A mixed pattern was also more common in older patients.
- This age-related susceptibility to cholestatic liver injury may be related to reduced expression of hepatocellular transporters.

Hepatology Communications 2017;1:726-735

Flucloxacillin



BBA - Molecular Basis of Disease 1864 (2018) 1498–1506

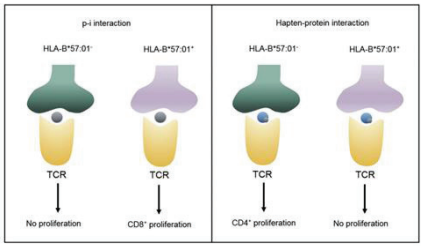
Genetic determinants

Drug	Cohort	Association
Amox/Clav[a]	35 (European)	DRB1*1501 #
Flucloxacillin[a]	51 (European)	HLA-B*5701 #
Terbinafine[b]	14 (mixed)	HLA-A*3301 #

- Increased susceptibility of cholestatic injury due to oral contraceptives has a reported association with the T to C polymorphism in BSEP 1331.

BBA - Molecular Basis of Disease 1864 (2018) 1498–1506

Flucloxacillin



Flucloxacillin

Lymphocytes of flucloxacillin-sensitized mice were stimulated to proliferate, secrete IFN-γ and granzyme B, and induce hepatocyte apoptosis in a concentration-dependent manner following *ex vivo* stimulation.

The T-cell response was antigen-specific; T-cells were not activated with other β-lactam antibiotics.

Flucloxacillin-specific T-cells were injected into CD4 deficient, flucloxacillin naive mice using

Oral exposure to flucloxacillin resulted in mild elevations in ALT , liver, and gall bladder leukocyte infiltration and a marked swelling of the gall bladder.

Toxicol. Sci. 2015: 146: 146

Drug-induced Biliary Disease

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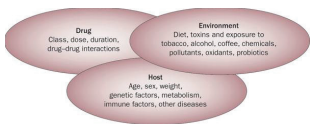
Figure 1 Potential risk factors involved in the pathogenesis of DILI



Tujios, S. & Fontana, R. J. (2011) Mechanisms of drug-induced liver injury: from bedside to bench *Nat. Rev. Gastroenterol. Hepatol.* doi:10.1038/nrgastro.2011.22

nature REVIEWS GASTROENTEROLOGY & HEPATOLOGY

Clinical Background

- Caused by many common drugs
  - Medically prescribed drugs: Antibiotics
  - Self prescribed drugs: Over the counter medications
  - Self prescribed "non-drugs": Herbal preparations/ Supplements
- 0.1 to 3% of hospital admissions
- 10% fatality seen in cases with severe ALT elevation and jaundice (Hy's Law)

Dig Dis Sci 2007;52:2463-71

Kaplowitz N. Nat Rev Drug Discov 2005;4:489-499

TABLE 1. Epidemiology of Drug-Induced Liver Injury

Group	N	F (%)	Age (y) (mean)	Drug (or class) no. 1	Drug (or class) no. 2	Drug (or class) no. 3	Herbal	Death	LTx	Chronicity
China (2013)	24,112	46	-	Tuberculosis medications 31%	CAMs (19%)	Antibiotics (10%)	19%	3%	-	-
France (2002)	34	65	M: 51 F: 58	Amoxicillin/clavulanate (12%)	NSAIDs (12%)	Nevirapine (9%)	-	6%	0	0
Iceland (2013)	96	56	55	Amoxicillin/clavulanate (22%)	Diclofenac (6%)	Azathioprine (4%)	16%	1%	0	(7) 7%
Korea (2012)	371	63	49	Antifungal (% not available)	-	-	63%[b]	-	(2) 1%	(3) 1%
Spain (2005)	461	49	53	Amoxicillin/clavulanate (13%)	T-2: Ebrotidine (5%) T-2: INH/rifampin/pyrazinamide (5%)	Ibuprofen (4%)	2%	5%	(8) 2%	(46) 10%
United States (2008)	300	60	48	Amoxicillin/clavulanate (8%)	Nitrofurantoin (4%)	T-3: Isoniazid (4%) T-3: Trimethoprim-sulfamethoxazole (4%)	9%	8%	(9) 2%	14%

[a]CAM = complementary and alternative medicine; F = female; M = male; NSAID = nonsteroidal anti-inflammatory drug; LTx = liver transplantation; T = tie.
[b]Includes herbal medicines, health foods and dietary supplements, medicinal herbs or plants, folk remedies, and herbal preparations.

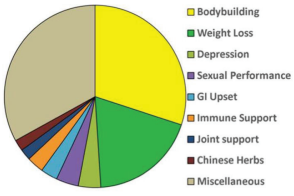
Mayo Clin Proc. 2014;89(1):95-106

TABLE 3. Selected Herbals and Dietary Supplements Causing Hepatoxicity

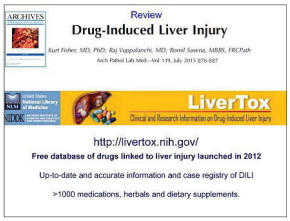
Aloe vera	Ma huang (*Ephedra sinica*)	Mistletoe (*Viscus album*)
Atractylis gummifera	Dai-saiko-to (Sho-saiko-to, TJ-19, D-chai-hu-tang, Xiao-chia-hu-tang)	Noni juice (*Morinda citrifolia*)
Black cohosh	Geniposide (*Gardenia jasminoides*)	Pennyroyal (squawmint oil)
Callilepsis laureola (Impila)	Germander (*Teucrium chamaedrys*) and other Teucrium varieties	Pyrrolizidine alkaloids (Crotalaria, Heliotropium, Senecio, Symphytium [Comfrey])
Cascara (*Cascara sagrada*)	Greater Celendine (*Chelidonium majus*)	Saw Palmetto (*Serrenoa repens*)
Camphor oil	Green tea (*Camellia sinensis*)	Senna (*Cassia angustifolia* and *C acutifolia*)
Centella asciatica (Gotu kola)	Herbalife	Skull cap (Scutellaria)
Chaparral (*Larrea tridentate*)	Hydroxycut (first-generation formulation; production halted 2009)	Valerian (*Valeriana officinalis*)
Jin Bu Huan (*Lypocodium serratum*)	Kava (*Piper methysticum*)	OxyElite Pro

Mayo Clin Proc. 2014;89:95-106

Herbal Induced Liver Injury (HILI)



HEPATOLOGY 2017;65:363-373



What is needed to make the diagnosis of DILI?

- An association between exposure and onset of liver disease has to be established
- Competing causes of liver disease have to be excluded

What is the role of the liver biopsy in DILI?

- Liver biopsy performed in less than half of suspected cases, including those enrolled in formal studies.
- Liver biopsy can provide useful information about:

nature and severity of liver injury
possible pathogenesis
expected clinical outcome.
guide therapy
exclude other causes of liver injury

Arch Pathol Lab Med. 2015;139:876–887
Annals of Hepatology 2014; 13 (1): 121-126

Drug-induced Biliary Disease

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Table 1 Clinicopathological presentations of DILI

Phenotype	Features	Causative drugs
Acute fatty liver with lactic acidosis	Microvesicular steatosis with systemic mitochondrial dysfunction	Valproate, fialuridine, nucleoside analogues
Acute hepatic necrosis	Collapse and necrosis of liver parenchyma	Many drugs, including isoniazid
Acute liver failure	Collapse and necrosis of liver parenchyma with INR >1.5 and encephalopathy	Many drugs, including isoniazid, bromfenac, nitrofurantoin
Acute viral hepatitis-like liver injury	Prodrome of malaise, fatigue and lassitude	Isoniazid, halothane
Autoimmune-like hepatitis	Detectable autoantibodies and/or autoimmune features on liver biopsy specimen	Minocycline, nitrofurantoin, methyldopa
Bland cholestasis[a]	Might have severe pruritis with hyperbilirubinemia	Anabolic steroids, estrogens
Cholestatic hepatitis	Predominance of elevated serum levels of alkaline phosphatase and bilirubin	Amoxicillin–clavulanate
Cirrhosis	Variable degrees of collagenization	Methotrexate
Immunoallergic hepatitis	Skin rash, eosinophilia and fever suggestive of drug allergy	Carbimazole, phenytoin, halothane
Nodular regeneration	Formation of micronodules or macronodules	Azathioprine
Nonalcoholic fatty liver	Microvesicular or macrovesicular steatosis with or without ballooning and chronic hepatitis	Amiodarone, tamoxifen
Sinusoidal obstruction syndrome	Obliteration of central veins	Cyclophosphamide, busulfan, pyrrolizidine alkaloids
Vanishing bile duct syndrome	Paucity of interlobular bile ducts with cholestasis	β-lactam antibiotics

[a]Diseases without inflammation. Abbreviations: DILI, drug-induced liver injury; INR, international normalized ratio.

Tujios, S. & Fontana, R. J. (2011) Mechanisms of drug-induced liver injury: from bedside to bench *Nat. Rev. Gastroenterol. Hepatol.* doi:10.1038/nrgastro.2011.22

nature REVIEWS GASTROENTEROLOGY & HEPATOLOGY

Drug Induced Liver Disease

"any kind of (biliary) liver disease can be caused by a drug"

Classification Of Drug Induced Cholestasis Syndromes

Hepatology 2011;53: 1377,
Histopathology 2017; 70: 81

Classification of DILI based on Serum Biochemistry

The R-value is defined as:
serum alanine aminotransferase/upper limit of normal (ULN) divided by serum alkaline phosphatase/ULN.

By convention:
R≥5 is labeled as hepatocellular DILI,
R<**2** is labeled as cholestatic DILI, and
2<R<5 is labeled as "mixed" DILI.

Am J Gastroenterol 2014; 109:950–966;

Classification Of Drug Induced Cholestasis Syndromes

INTRAHEPATIC

a) Acute

Cholestasis without hepatitis (pure, simple, canalicular, or bland cholestasis)
Cholestasis with hepatitis (hepatocanalicular hepatitis or mixed cholestatic hepatitis)
Cholestasis with bile duct injury (ductular, cholangiolar, or cholangiolytic cholestasis)

b) Chronic (Cholangiopathies)

(Mild non-specific bile duct injury)
Vanishing bile duct syndrome (VBDS)
Primary Sclerosing cholangitis-like

EXTRAHEPATIC

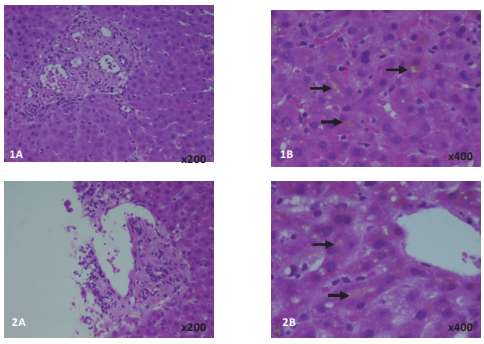
Cholelithiasis
Primary Sclerosing cholangitis-like

Acute Drug Induced Cholestasis without Hepatitis

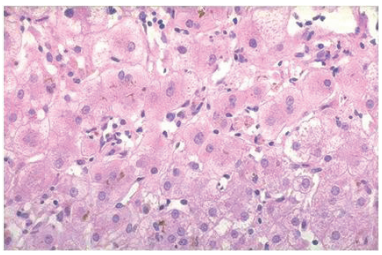
- Cause minimal hepatic parenchymal involvement with almost pure canalicular cholestasis.
- **DDx:** Sepsis, post-surgical, acute LDO, cholestasis of pregnancy, benign recurrent cholestasis
- Examples: Androgens/Estrogens, Chlorpromazine, Erythromycin Warfarin Thiabendazole Procholperazine

Acute Drug Induced Cholestasis with Hepatitis

- Combination of hepatitis (usually lobular) with canalicular/ hepatocellular cholestasis, duct injury
- DDX: Acute cholestatic hepatitis e.g. virus (espec HEV), AI
- Examples: Penicillins, Sulfonamides, Fluoroquinolones, Tetracyclines, Antifungals (terbinafine, griseofulvin, ketoconazole, itraconazole) Antiretroviral therapy (stavudine, didanosine, nevirapine) Anti-inflammatory (diclofenac, sulindac, piroxicam, ibuprofen, phenylbutazone, gold, pencilamine, allopurinol, azathioprine) Psychotropes (chlorpromazine, prochlorperazine, fluphenazine, thiroridazine, tricyclic antidepressants, risperidone, duloxetine, benzodiazepines, diazepam)



Acute Drug Induced Cholestasis with Hepatitis



HEV and DILI

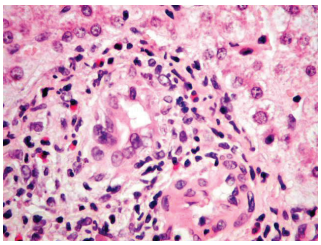
- Seroprevalence rate of 21%.
- In the US DILIN prospective study 16% patients with suspected DILI tested positive for HEV IgG and 9 tested positive for HEV IgM 3%.
- In the United Kingdom, 13% suspected cases of DILI had evidence of acute HEV infection.
- Travel to endemic areas, consumption of pork or liver meats, blood transfusions, and pet ownership may be risk factors for HEV infection and should be queried during the initial evaluation.

Mayo Clin Proc. 2014;89(1):95-106

Acute Drug Induced Cholestasis without Hepatitis

- Inflamed bile ducts and biliary ductules filled with bile casts, scattered steatosis and minimal /no hepatocellular damage
- Associated with eosinophilia and/ or the Stevens-Johnson syndrome
- May have prolonged jaundice (> 6 months) and progress to the vanishing bile duct syndrome.
- Possible causes include: Flucoxacillin, Pioglitazone and Amoxicillin-clavulanate

Acute Drug Induced Cholestasis without Hepatitis

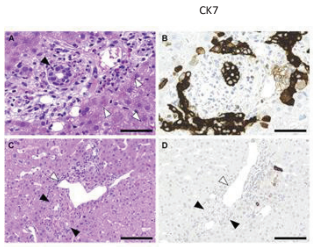


Vanishing Bile Duct Syndrome / PSC – Like

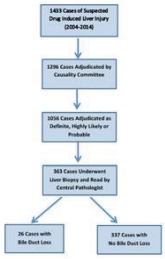
- Duct injury/loss with cholate stasis, periportal Cu /CK7 staining fibrosis, may have chronic hepatitic changes
- DDx: PBC, PSC, GVHD
- Bile duct loss was seen in 5–6% of the DILIN cohort, and was the most frequent finding in biopsies from cases of DILI with very protracted recovery times.

Am. J. Gastroenterol. 2015; 110; 1450–1459.

A and B: Augmentin
C and D: NSAID



Clinical Presentations and Outcomes of Bile Duct Loss caused by Drugs and Herbal and Dietary Supplements



Hepatology 2017; 65:1267

Vanishing Bile Duct Syndrome

- **Psychotropes** (*chlorpromazine*, imipramine, carbamazepine, amitriptyline, haloperidol, cyproheptadine, phenytoin)
- **Antibiotics** (amoxicillin/clavulanate, flucloxacillin, quinolones, clindamycin, macrolides, tetracyclines)
- **Nonsteroidal anti-inflammatory drugs** (diclofenac, ibuprofen)
- **Others** (amiodarone, cimetidine, thiabendazole, zonisamide, ajmaline)

Clinical Presentations and Outcomes of Bile Duct Loss caused by Drugs and Herbal and Dietary Supplements

26 (7%) of the 363 patients with drug, herbal or dietary supplement associated liver injury had bile duct loss on liver biopsy.

Note: " In a prospective study from Iceland over a 2-year period with approximately 100 DILI patients, no VBDS cases were identified and all patients with severe cholestatic reaction recovered with time. "Gastroenterology 2013;144:1419-1425.

The most common clinical pattern was a severe cholestatic hepatitis.

The commonest implicated agents were:
- amoxicillin/clavulanate,
- temozolomide,
- herbal products,
- azithromycin

Clinical Presentations and Outcomes of Bile Duct Loss caused by Drugs and Herbal and Dietary Supplements

Ten or more portal tracts are thought to be needed for an adequate liver biopsy in estimating bile ducts.

Degree of bile duct loss:

- moderate to severe bile duct loss (<50% of portal areas with bile ducts) just over half
- mild bile duct loss (50–75% with bile ducts) in just under half

Compared to those without, those with bile duct loss were more likely to develop chronic liver injury (94% vs 47%)

Bile ducts were present in 64% of portal areas in biopsies from patients with benign outcome, in contrast to only 17% of portal areas having bile ducts in the biopsies from patients with poor outcome.

Increased risk of Cholelithiasis (and Cholecystitis)

Gall Stones:

- Oral contraceptives
- Clofibrate
- Thiazide
- Ceftriaxone
- Octreotide

Cholecystitis:

- Erythromcyin
- Amoxycillin

Drug Safety 1992;7:32

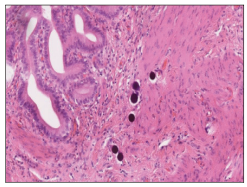
EXTRAHEPATIC

Cholelithiasis

Primary Sclerosing cholangitis-like

Sirtex

- Radioactive microspheres injected into hepatic artery to treat metastatic colorectal cancer
- Microspheres within the gall bladder in 5 out of 9 cases



Primary Sclerosing cholangitis-like

- Ketamine
- Docetaxel
- Methimazole
- Chemotherapeutic agents
- Atorvastatin
- Moxifloxacillin
- Various herbal supplements

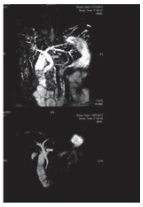
10% of all cases of DILI have PSC like changes on imaging
Dig Liv Dis 2015;47:502-507

Histological features suggesting possible hepatotoxicity

- Well-defined zone 3 necrosis
- Mixed hepatitis/cholestatic picture
- Predominantly lobular changes
- **Bile duct damage**
- Many neutrophils/ eosinophils/ plasma cells
- Granulomas

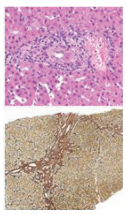
…..but always think of drugs as a possible cause!

Ketamine induced bile duct damage



- Bile duct injury was observed in all 7 patients assessed by liver biopsy.
- 3 of 6 patients who underwent MRCP were found to have prominent or dilated common bile ducts without obstructions or extrinsic compressions.

Clinical Gastroenterology and Hepatology 2014;12:1759–1762



The impact of eosinophilia and hepatic necrosis on prognosis in patients with drug-induced liver injury

Granulomas associated with better outcome
Eosinophils showed a non-significant trend to better outcome

The presence of multiacinar or bridging necrosis but not the degree of confluent necrosis was associated with poor outcome
Ductular reaction was associated with poor outcome

Aliment Pharmacol Ther 2007: 25; 1411–1421

Drug-induced Biliary Disease

- **Pathophysiology**
  Cholangiocytes are metabolically active cells
- **Clinical features**
  One of the commonest forms of DILI
- **Pathological features**
  A wide range (and anatomical distribution) of biliary disease