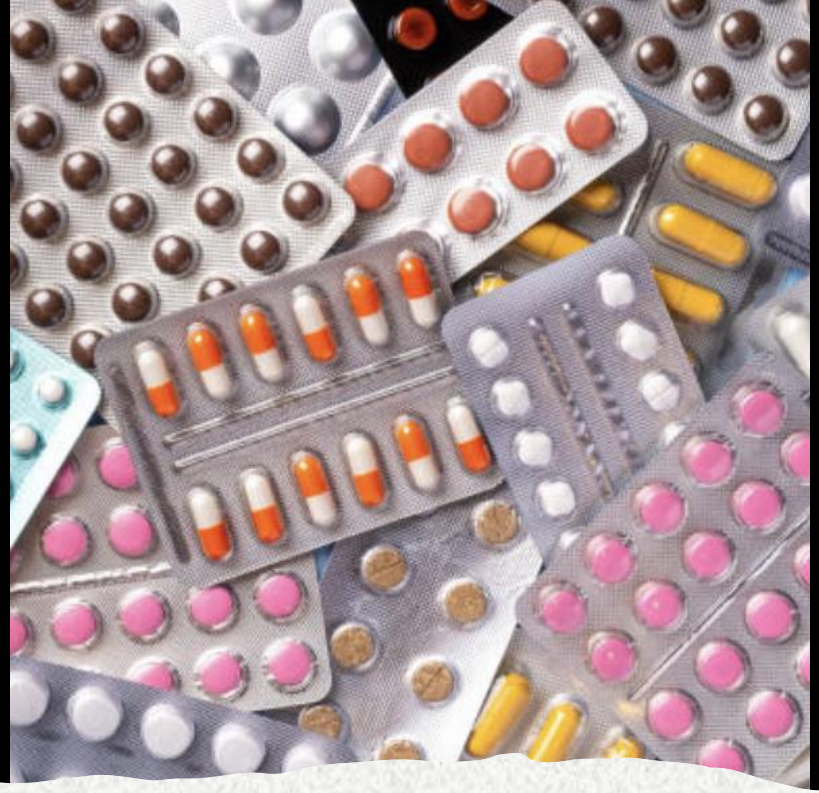
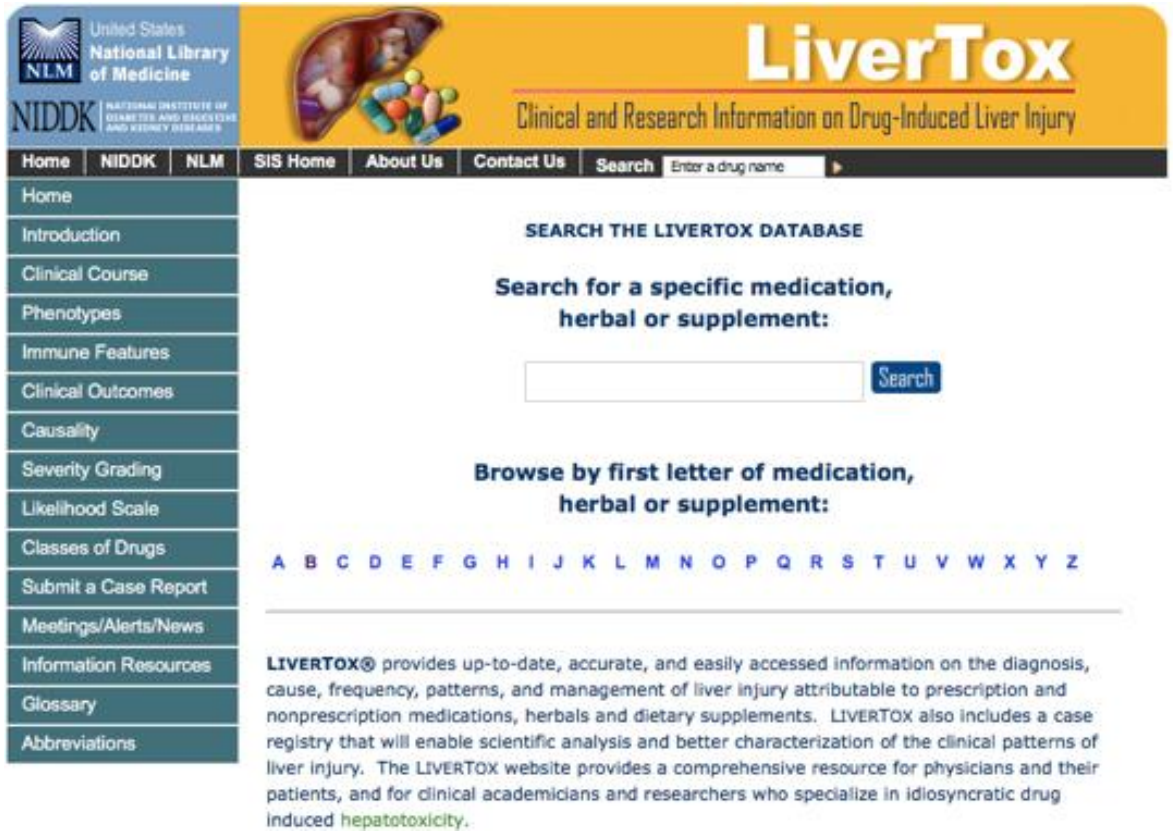



The pathology of drug-induced liver injury (including OTC dietary supplements and herbal medicines)

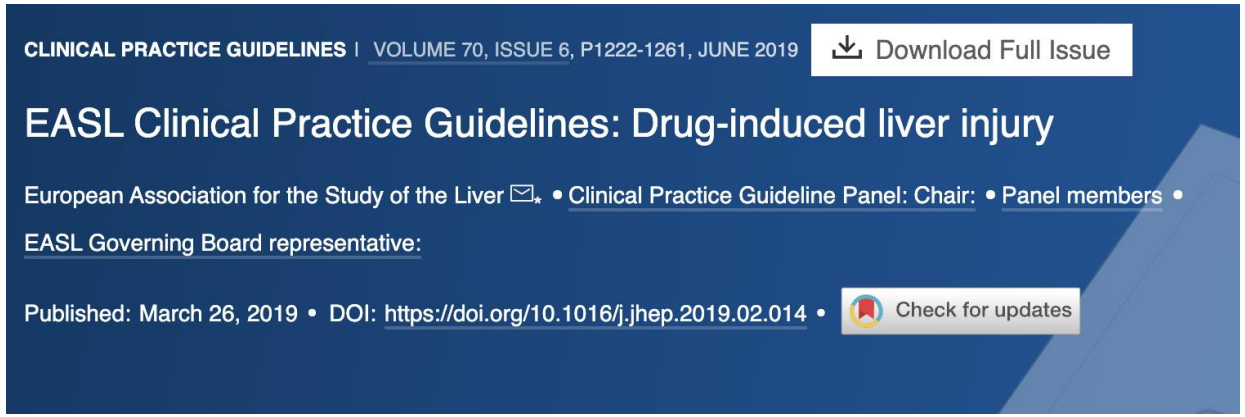
Professor Alastair Burt, Newcastle University, UK

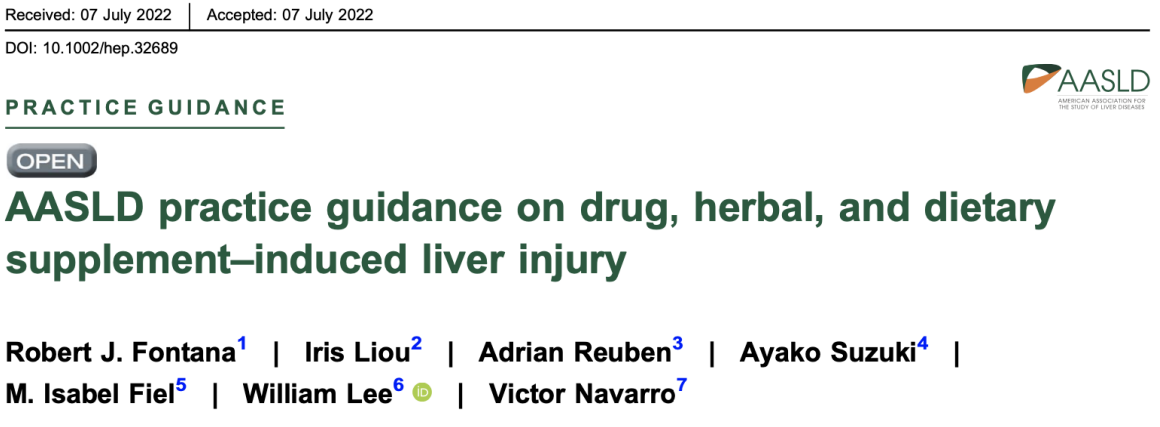
DILI

- > 1000 medicinal compounds and herbal agents cause liver injury
- Diagnosis of exclusion: there are no magic pointers to DILI!
- Commonest cause of acute liver failure in UK
- Incidence 3-20 per 100,000 persons per annum
- LiverTox: font of *much* knowledge
- Important to remember alternative/herbals as part of spectrum



Clinical guidelines in management of suspected DILI





DILI culprits (DILIN study US 2003-2013)

- Anti-infectives (almost 50%)
  - Amoxicillin-clavulanate
  - Nitrofurantoin
  - Trimethoprim
  - Minocycline
  - Cefazolin
- CNS agents
  - Phenytoin
  - Lamotrigine
  - Valproate
- Musculoskeletal
  - Diclofenac
  - Allopurinol

Note changing patterns, in particular with the introduction of ICIs etc

Country	United States/DILIN, n = 899	Spain, n = 843	Iceland, n = 96	Latin America, n = 311	China, n = 25, 927	India, n = 313/1288
Study design	Prospective registry[30]	Prospective registry[29]	Prospective, population-based[9]	Prospective registry[18]	Retrospective case series[22]	Prospective case series[21,31]
Publication year	2015	2021	2013	2019	2019	2010/2021
Age distribution, years	49 ± 17	54 (11–91)	55¥ (16–91)	50 (11–91)	43% (40–59 years)	39 (12–84)/43 (1–86)
% Female	59	48	56	61	49	42/48.6
% Liver- and non-liver-related fatality	Liver-related: 3.0; non-liver-related: 3.2	Liver-related: 2.1; non-liver-related: 1.7	Overall fatality: 1	Overall fatality: 4.9	Liver-related: 0.28[a]; non-liver-related: 0.11[a]	Overall fatality: 17.3/12.3
% Liver transplant	3.7	1.5	0	0	0.01	0
Top 3 implicated drug classes	Antimicrobials, HDS, cardiovascular agents	Anti-infectives, CNS drugs, musculoskeletal drugs (including NSAID)	Antibiotics, immuno-suppressants, psychotropic drugs	Antibiotics,[b] NSAIDs,[b] antitubercular[b]	TCM or HDS, antitubercular, antineoplastic or immune modulators	Antitubercular, HDS, antiepileptics
Top 10 implicated agents	HDS, amoxicillin/clavulanate, isoniazid, nitrofurantoin, trimethoprim-sulfamethoxazole, minocycline, cefazolin, azithromycin, ciprofloxacin, levofloxacin	Amoxicillin/clavulanate, antitubercular, HDS, ibuprofen, anabolic androgenic steroids, flutamide, isoniazid, atorvastatin, diclofenac, ticlopidine	Amoxicillin/clavulanate, diclofenac, infliximab, nitrofurantoin, isotretinoin, atorvastatin, doxycycline, azathioprine	Amoxicillin/clavulanate, nitrofurantoin, diclofenac, RIP + INH + PIZ, nimesulide, ibuprofen, cyproterone, carbamazepine, methyldopa, atorvastatin	Natural medicine, rifampicin, TCM, isoniazid, pyrazinamide, He Shou Wu, methimazole, propylthiouracil, atorvastatin, methotrexate	Antitubercular, phenytoin, dapsone, olanzapine, carbamazepine, cotrimoxazole, NSAIDs, atorvastatin, leflunomide, ayurvedic

Current classification of DILI

Mechanistic classification	Direct hepatotoxicity	Idiosyncratic hepatotoxicity	Indirect hepatotoxicity
Incidence	Common	Rare	Intermediate
Dose relatedness	Yes	No	No
Predictable	Yes	No	Partially
Reproduced in animal models	Yes	No	Not usually
Latency	Rapid (days)	Variable (days to years)	Delayed (months)
Phenotypes of injury	Serum AST, ALT, or ALP elevations, hepatic necrosis, acute fatty liver, nodular regeneration	Mixed or cholestatic hepatitis, bland cholestasis, chronic hepatitis	Immune-mediated hepatitis, fatty liver, chronic hepatitis
Examples	Acetaminophen, niacin, intravenous methotrexate	Amoxicillin-clavulanate, cephalosporins, isoniazid, nitrofurantoin	Immune checkpoint inhibitors, anti-CD20 monoclonal Ab, protein kinase inhibitors
Touted mechanism of injury	Intrinsic hepatotoxicity that is dose-dependent	Idiosyncratic host metabolic or immune reaction	Indirect effect on liver or host immunity

Drug	HLA group	Genetic variants	OR	MAF in controls[a]
Multiple drugs[58,61]	Non-HLA	PTPN22 (rs2476601)	1.4	0.08
		rs72631567 (Chromosome 2)	2.0	0.03
Mixed/cholestatic	HLA-I	A*33:01/rs114577328[g]	5.0	0.01
		A*33:01/B*14:02/C*08:02.	5.6	0.009
Hepatocellular	Non-HLA	rs28521457 (chromosome 4/LRBA)	2.1	0.04
Amoxicillin-clavulanate[62,63]	HLA-I	A*02:01 (rs2523822)	2.3	0.28/0.28[b]
		A*30:02	6.7 (HC)	0.029
		B*18:01	2.9 (HC)	0.096
	HLA-II	DRB1*15:01/DQB1*06:02 (rs3135388)	2.8	0.14/0.05[b]
		rs9274407	3.1	0.15/0.081[b]
		rs9267992	3.1	0.14/0.063[b]
	Non-HLA	PTPN22 (rs2476601)	1.6	0.08
Flucloxacillin[64,65]	HLA-I	B*57:01	36.6	0.04
		B*57:03	79.2	0.0003
Minocycline[66]	HLA-I	HLA-B*35:02	29.6	0.006
Trimethoprim-sulfamethoxazole[67]	HLA-I	A*34:02 (EUR)	47.5	0.001
		B*14:01 (EUR)	9.2	0.009
		B*27:02 (EUR)	13.5	0.002
		HLA-B*35:01 (AA)	2.8[d]	0.087
Isoniazid-containing antitubercular treatments[61,68]	Non-HLA	rs72631567 (Chromosome 2)	5.8	0.03
		rs117491755 (ASTN2: EUR)	4.4	0.037
		NAT2*6/*6, *6/*7, or *7/*7 (ultraslow) (EUR/IND)	2.0/1.8	0.10/0.19
	HLA-I	C*12:02 (EUR)	6.4	0.006
		B*52:01 (EUR)	6.4	0.007
		B*52:01-C*12:02 (EUR/IND)	6.7/1.8	0.01/0.07
	HLA-II	DQA1*03:01(IND)	2.6	0.06
Terbinafine[69]	HLA-I	A*33:01/rs114577328[g]	40.5	0.01–0.03
		A*33:01/B*14:02/C*08:02	49.2	0.009
Valproate[70]	Non-HLA	Mitochondrial DNA polymerase γ (POLG)	23.6[e]	
		p.Q1236H		≤ 0.086
		p.E1143G		≤ 0.04
Allopurinol[71]	HLA-I	HLA-A*34:02 (AA)	8.0/4.5[f]	0.033/0.057[c]
		HLA-B*53:01 (AA)	4.1/2.5[f]	0.120/0.184[c]
		HLA-B*58:01 (AA)	5.6/13.3[f]	0.046/0.020[c]
Green tea[72]	HLA-I	B*35:01	6.8	0.06
		C*04:01	3.7	0.12
Polygonum multiflorum[73]	HLA-I	B*35:01	30.4	0.027

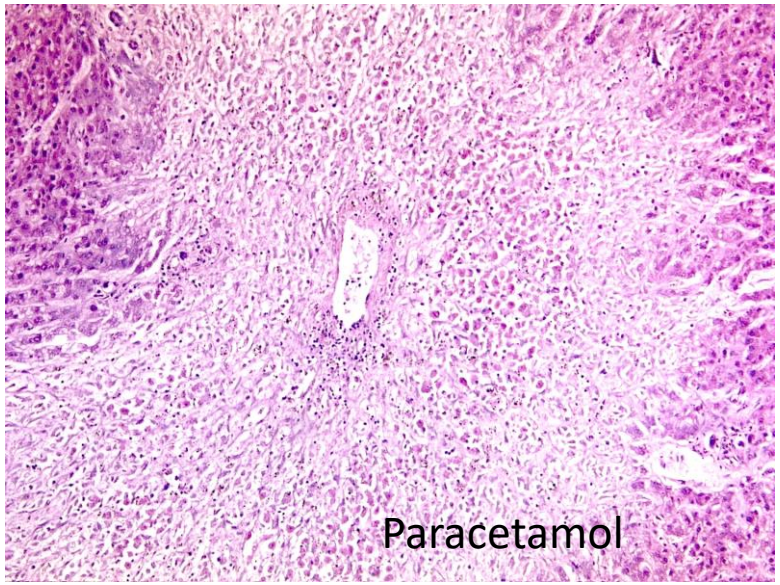
Genetic polymorphisms associated with DILI susceptibility

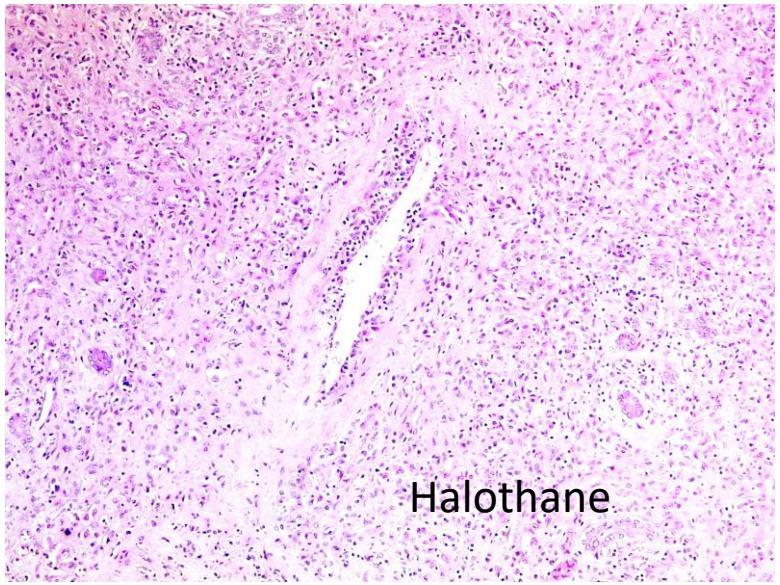
Phenotypes of DILI

- Classical forms: hepatocellular, cholestatic, mixed, chronic hepatitis
- Drug induced autoimmune-like hepatitis
- Ductopaenia
- Secondary sclerosing cholangitis
- Granulomatous hepatitis
- Steatotic liver disease
- Benign vascular changes
- Liver tumours

Acute zonal necrosis

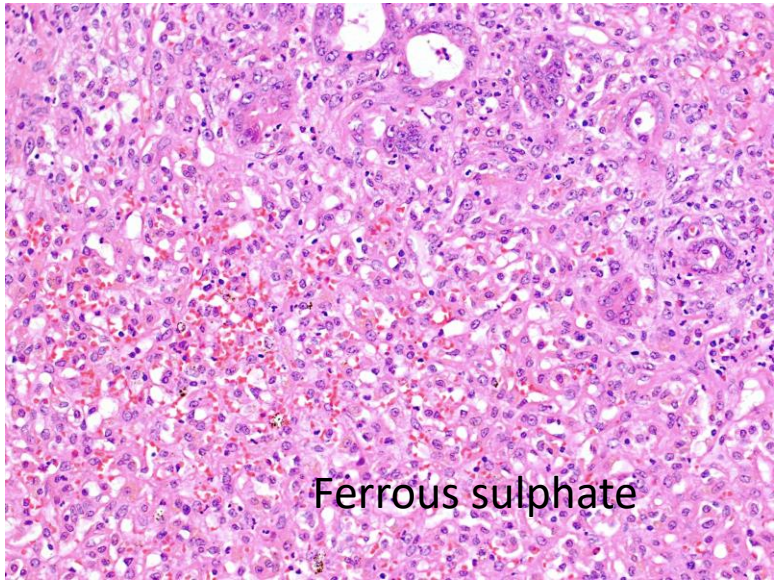
- Zonal: paracetamol, halothane, phosphorus, ferrous sulphate
- Can become panacinar/multiacinar
- Frequently ALF with very high transaminases
- Paracetamol: Indirect cytotoxic – metabolite is toxic: generated mainly in acinar zone 3
- Halothane: Idiosyncratic, immunological: antibodies to halothane altered hepatocyte membrane proteins

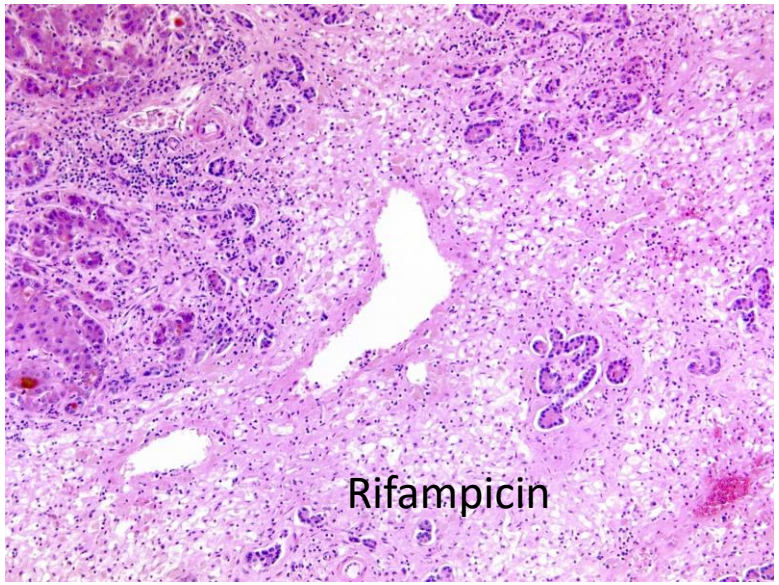




Acute zonal necrosis

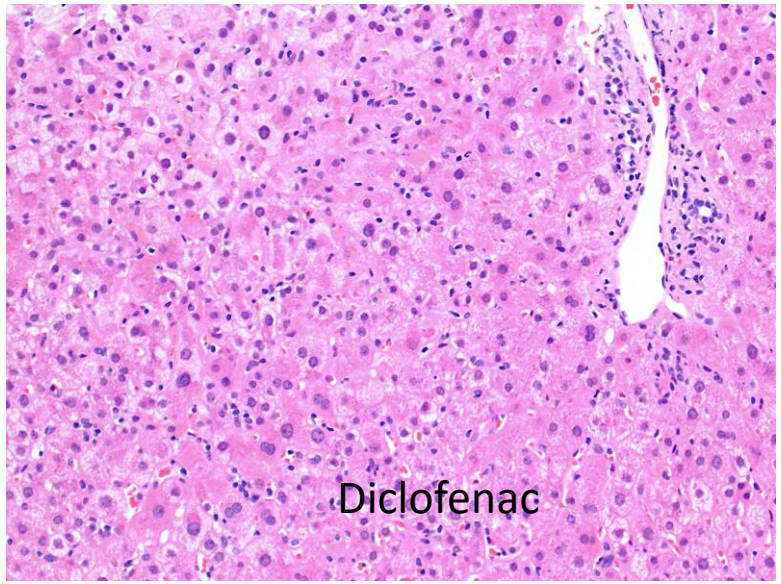
- Direct toxins may cause predominantly acinar zone 1 necrosis: area of highest concentration
- Areas of severe necrosis/panacinar necrosis may show marked ductular reaction: regenerative response rather than evidence of cholestatic injury

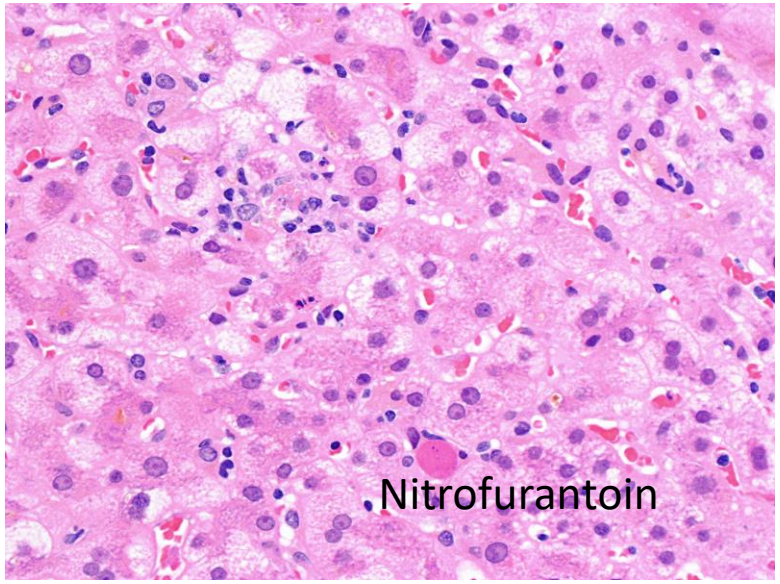




Acute hepatitis

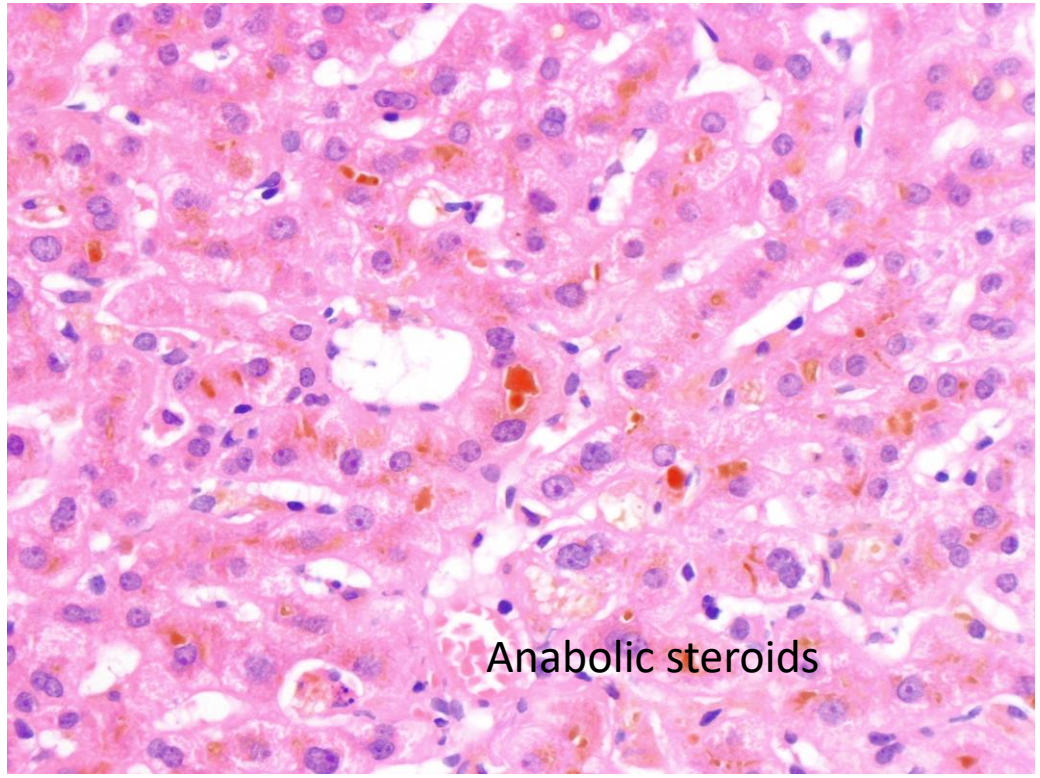
- May have insidious onset but often presents with jaundice
- Lobular disarray with apoptotic bodies and spotty necrosis
- May be acinar 3 predominant
- Sinusoidal infiltrate: mainly T cells
- Occasionally EBV like changes (diclofenac)
- Differential diagnosis includes viral hepatitides, AIH or even Wilson disease
- Most recover on withdrawal





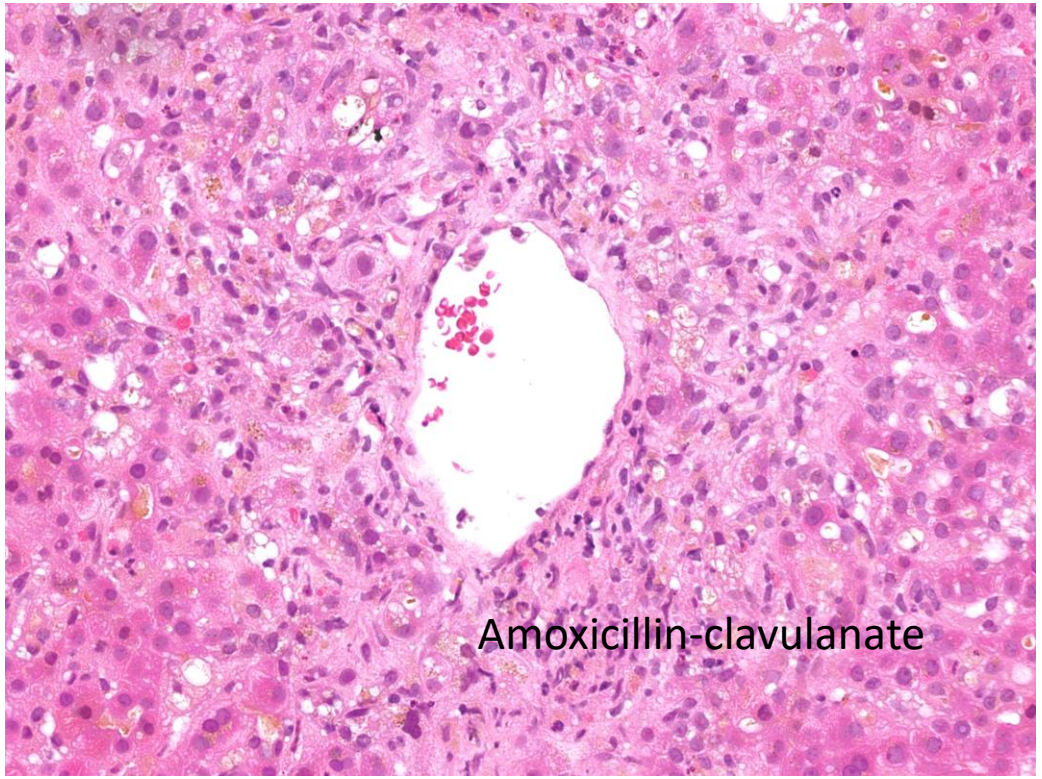
Cholestatic injury: bland (acute) cholestasis

- Main feature: bilirubin in hepatocytic cytoplasm, canaliculi and Kupffer cells
- ++ acinar zone 3
- Cell swelling
- May be accumulation of ceroid and bile laden macrophages
- Distribution of bile varies with drug; classically cholangiolar seen with benoxaprofen (now discontinued)
- Often associated with antibiotics (especially flucloxacin) and steroids



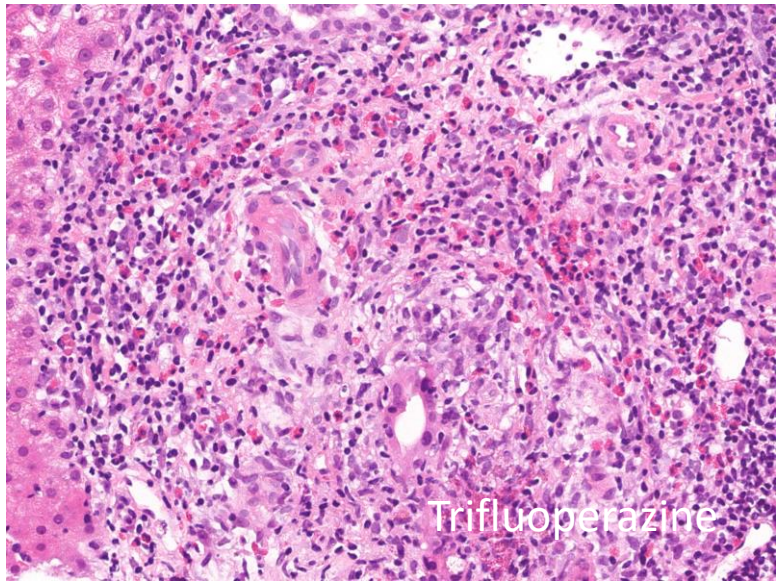
Cholestatic hepatitis

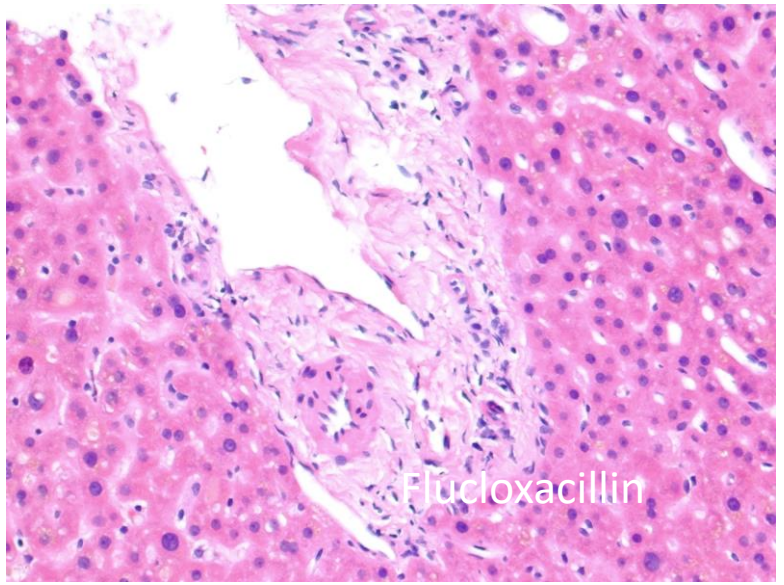
- Combination of marked bilirubinostasis and necroinflammation
- 30% of all DILI
- May be significant latent phase: important to have lengthy drug history
- Classical example: Amoxicillin-clavulanate
- DD: includes viruses in particular HEV
- Rarely may lead to chronic cholestasis



Chronic cholestasis

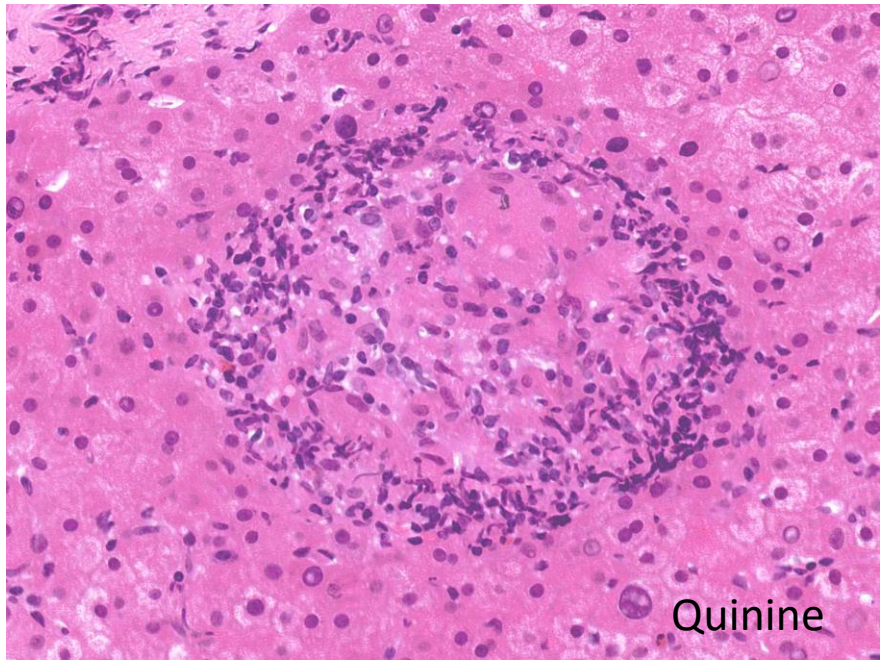
- Some forms of cholestatic DILI progress to chronic cholangiopathy
- Can have PBC-like or PSC-like lesions
- Seen with some antibiotics and anti-psychotics and phenytoin
- Early changes may be ++ inflammatory with eosinophils
- Can progress to ductopaenia and progressive biliary fibrosis

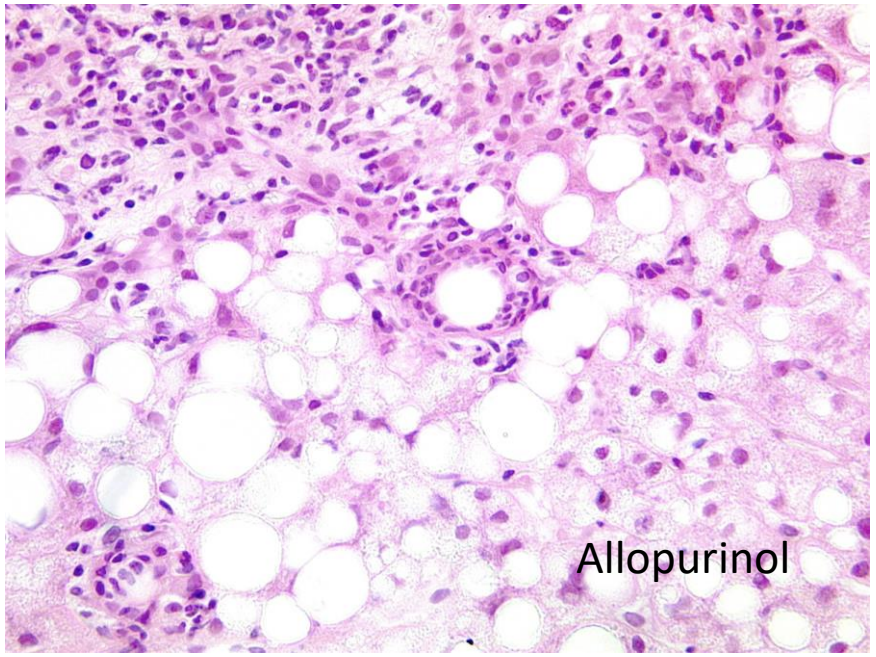




Granulomas

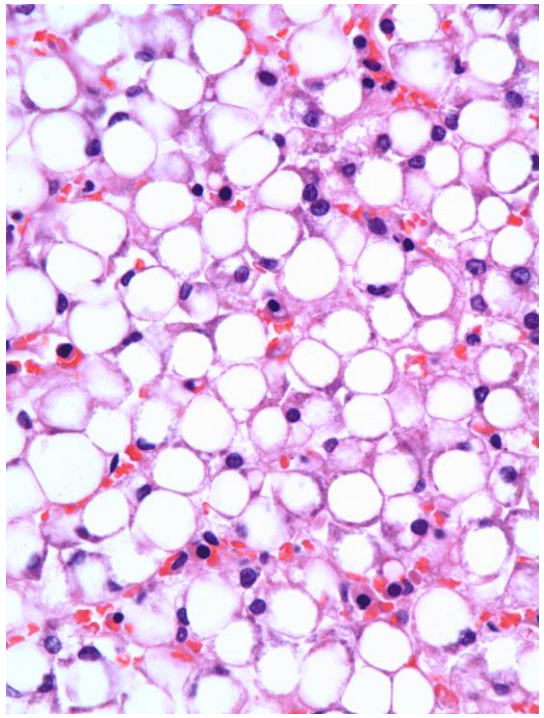
- Observed in a large number of DILI
- DILI responsible for 29% of all cases of hepatic granulomas
- Some are in the form of microgranulomas (common)
- Others isolated but in some true granulomatous hepatitis
- May be seen alone or in association with other changes
- > 60 drugs implicated: some appear to be hypersensitivity syndrome (eg. phenylbutazone)
- Fibrin ring granulomas seen with allopurinol (as in Q fever)

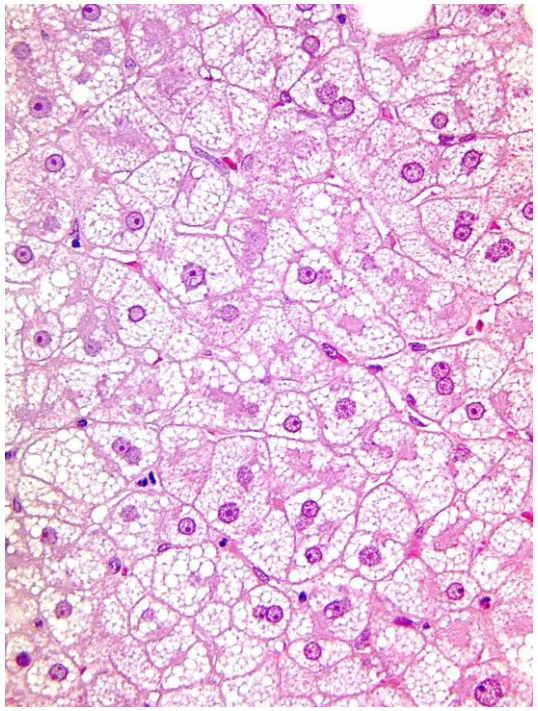


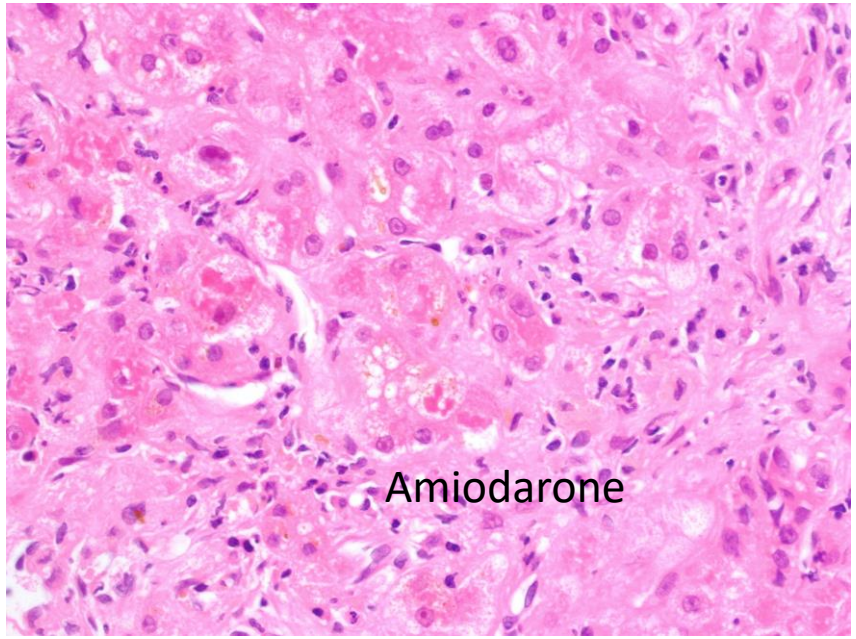


Steatotic liver disease

- Macrovesicular steatosis seen with several agents including methotrexate, corticosteroids, cisplatin, cocaine
- Microvesicular form seen with oxytetracycline and anti-retroviral agents
- Similar pattern seen in a small number of alcohol abusers (alcoholic foamy degeneration)
- Steatohepatitis also seen: best examples in cardiological therapies (amiodarone)
- Some (methotrexate, tamoxifen) may require co-factor such as metabolic syndrome

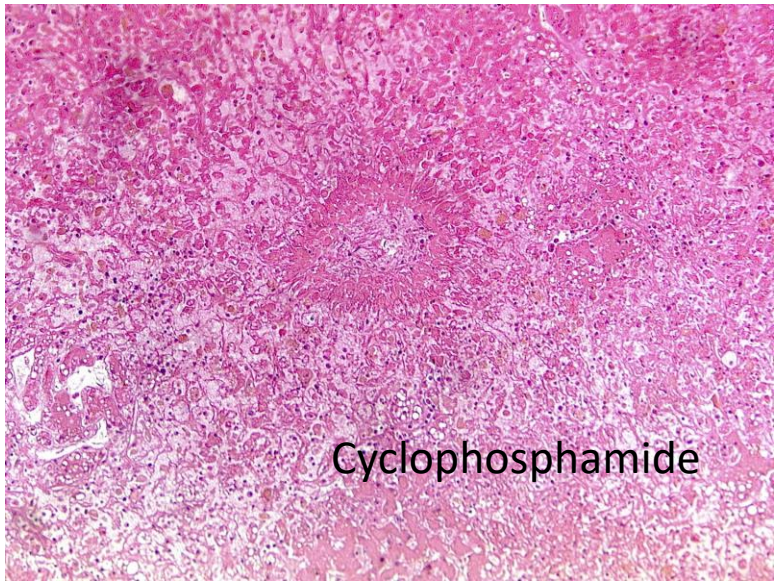


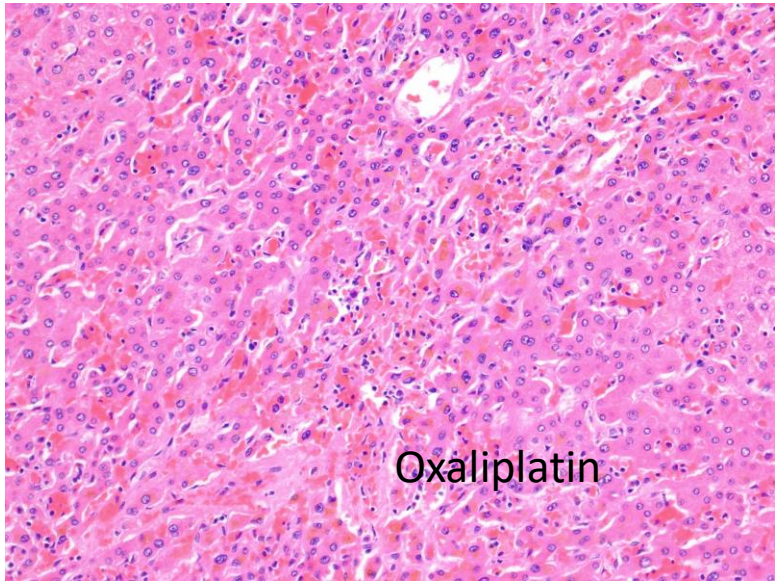




Vascular disorders

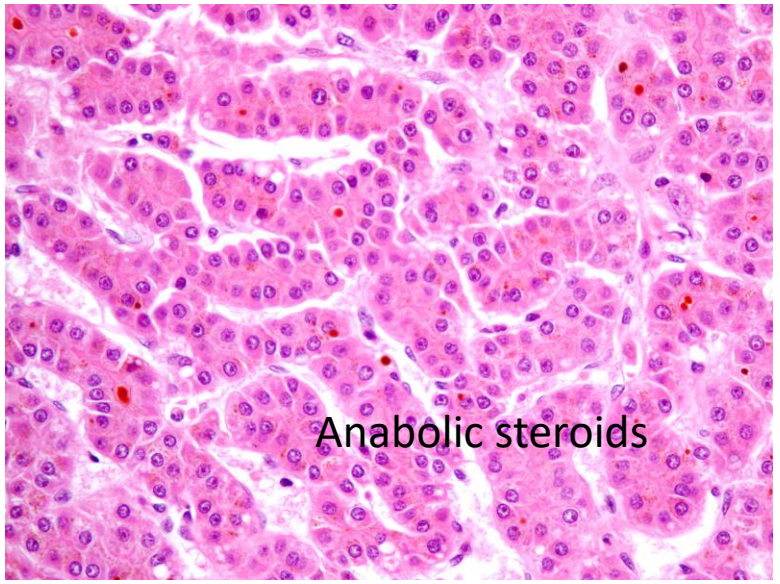
- ‘Veno-occlusive disease’ seen with chemotherapeutic agents: may be acute or sub-acute.
- Former leads to Budd Chiari syndrome
- Sinusoidal obstruction syndrome favoured term: ++ with oxaliplatin
- Other vasculopathies also involve portal veins: may lead to NRH and portal hypertension
- Sinusoidal dilatation and peliosis can also occur

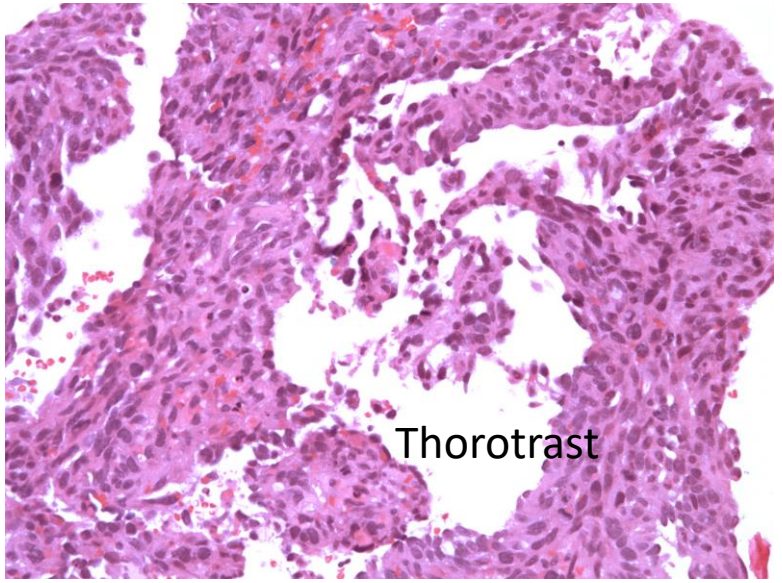




Neoplasms

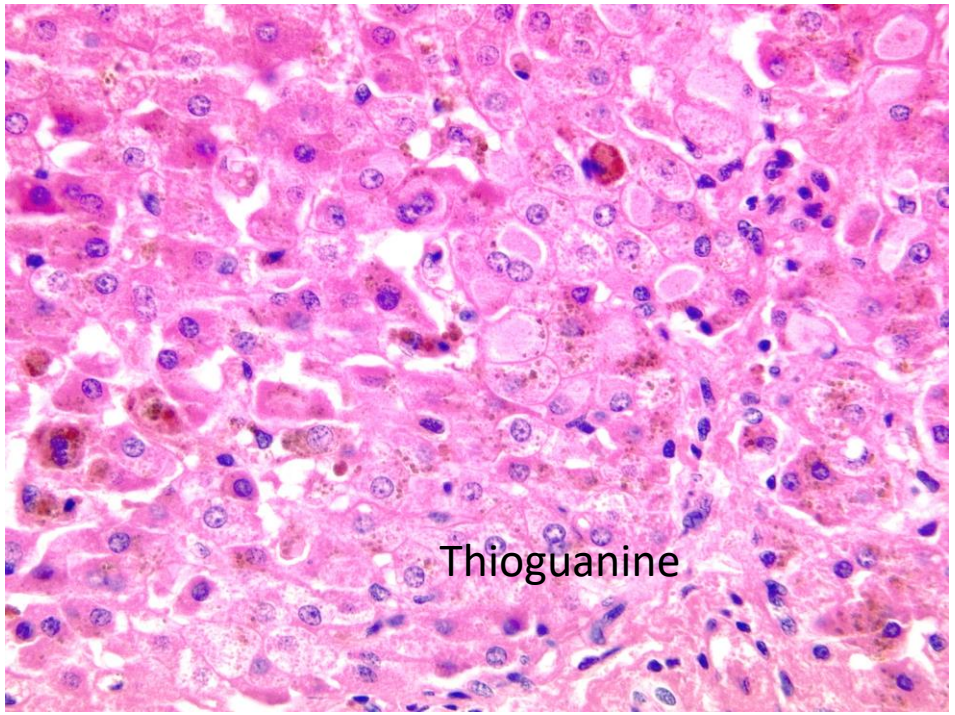
- Adenomas associated with anabolic steroids, danazol, oxymethalone etc.
- May transform to hepatocellular carcinoma
- Other agents implicated in HCC: arsenicals, thorotrast
- Angiosarcoma also associated with thorotrast

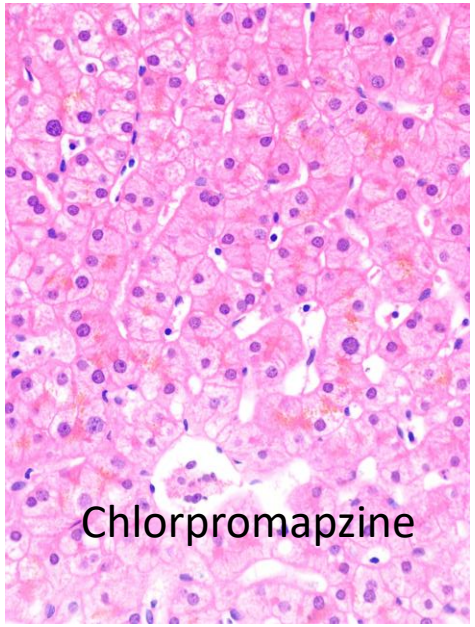


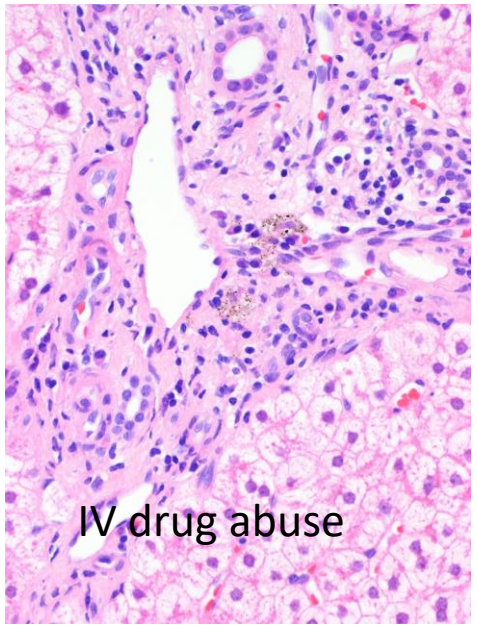


Other changes

- Enzyme induction
- Ground glass –like change (adult polyglucosan storage)
- Lipofuscin accumulation
- Gold pigment
- Iron overload
- Portal macrophage pigment

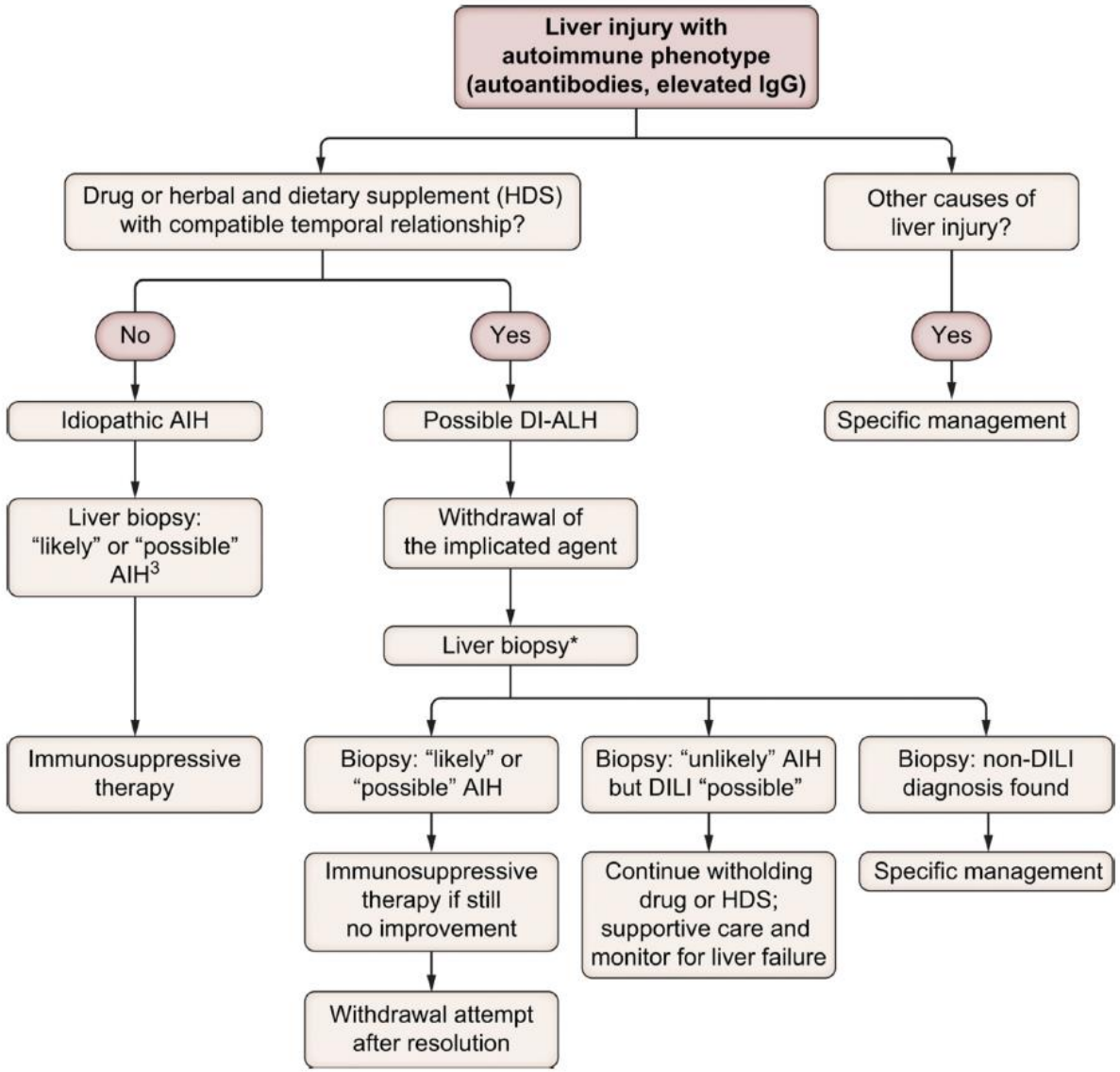






Drugs and AIH (DI-ALH)

Definite Association	Probable Association	Possible Association
Minocycline[187,192-198]	Propylthiouracil[579,580]	Ipilimumab (anti-CTLA-4)[581]
Nitrofurantoin[187,199-205]	Isoniazid[582]	Tremelimumab (anti-CTLA-4)[581]
Infliximab[206-221]	Diclofenac[583,584]	Nivolumab (anti-PD-1)[581]
Alpha-methyldopa[585-587]	Etanercept[216,432,433]	Pembroluzimab (anti-PD-1)[230,588]
Adalimumab[216,433,589-591]	Atorvastatin[592-595]	Atezolizumab (anti-PD-L1)[581]
Halothane[596,597]	Rosuvastatin[598]	Black cohosh (herbal medicine)[599,600]
Oxyphenisatin*[601]	Clometacine[602,603]	Dai-saiko-to (herbal medicine)[604]
Dihydralazine*[573,574,605]		Germander (herbal medicine)[606]
Tienilic acid*[607]		Hydroxycut (nutritional supplement)[608]
		Trichloroethylene (toxin)[609]
		Papaverine[610]
		Indomethacin[611]
		Imatinab[612]



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Nomenclature, diagnosis and management of drug-induced autoimmune-like hepatitis (DI-ALH): An expert opinion meeting report

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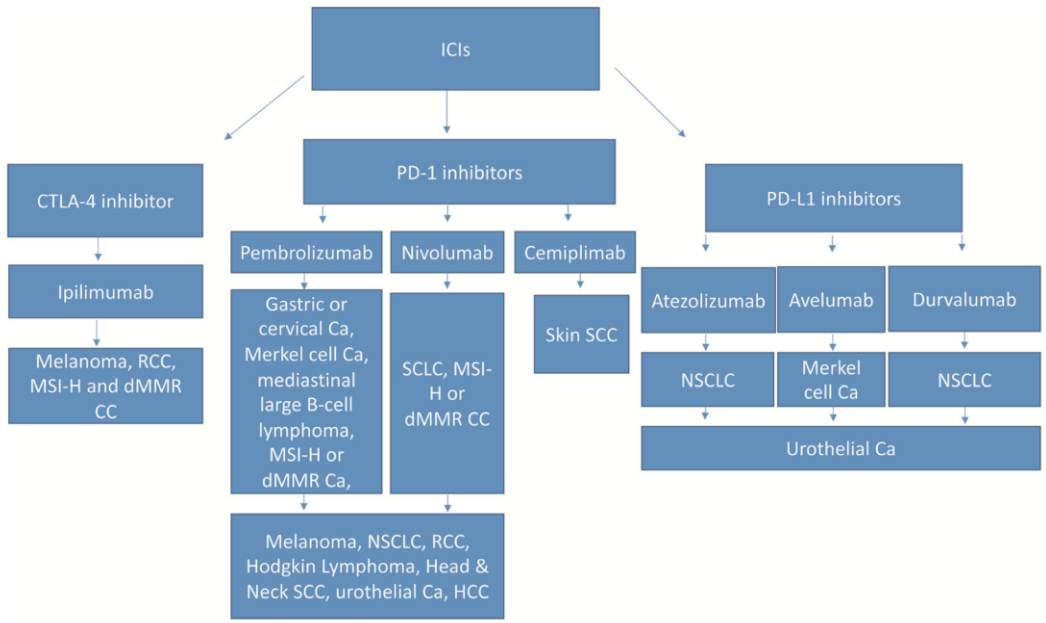
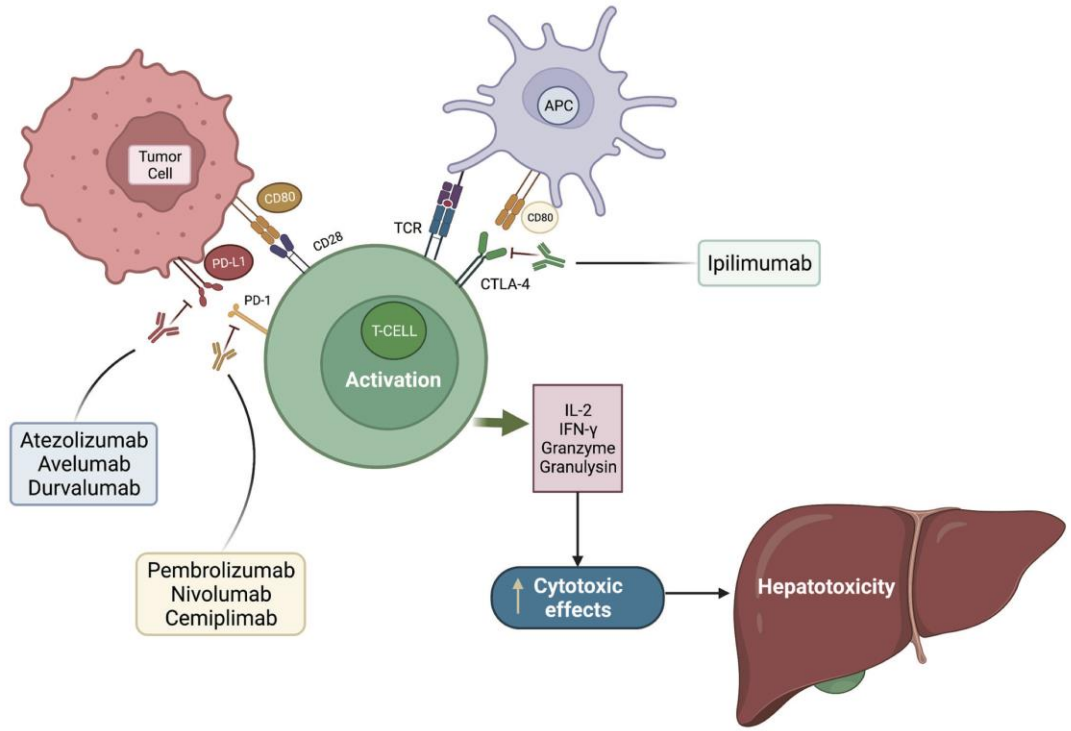
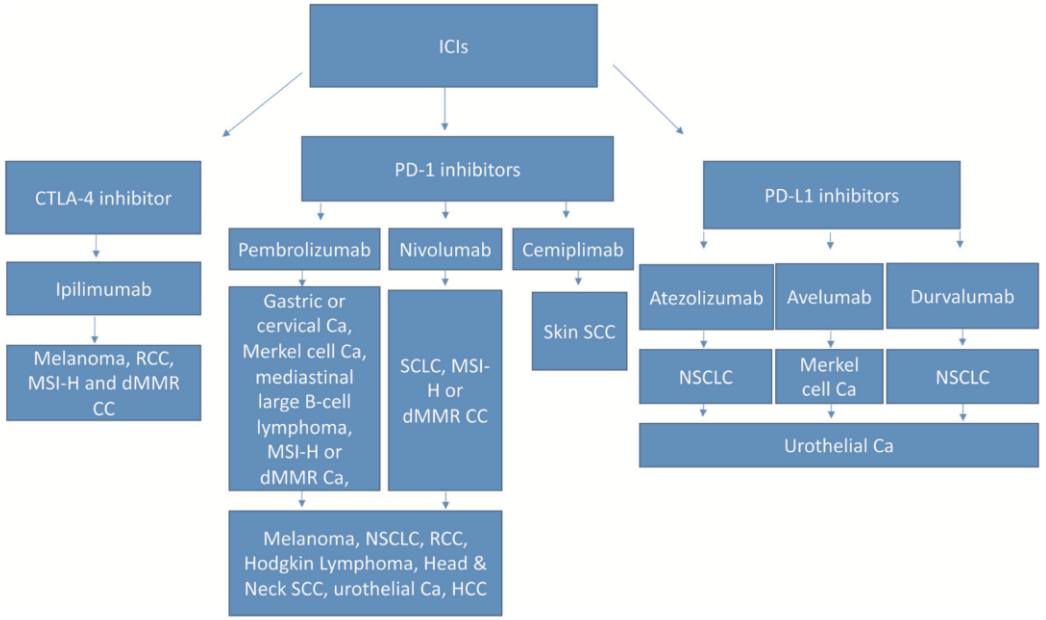
DILI with anti-neoplastic agents

- Anti-metabolites
  - Floxuridine – sclerosing cholangitis
  - 6-mercaptopurine - hepatocellular or cholestatic
- Alkylating agents
  - Cyclophosphamide, melphalan – SOS/VOD
  - Temozolomide – chronic cholestasis and VBDS
- Biologics and monoclonal antibodies
- Kinase inhibitors
  - Sorafenib – acute hepatitis
  - Imatinib – acute and chronic hepatitis; reactivation of HBV
- Oxaliplatin – SOS and NRH
- Taxanes
  - Docetaxal and paclitaxel – massive necrosis


ICIs
CTLA-4 inhibitor
Ipilimumab
Melanoma, RCC, MSI-H and dMMR CC
PD-1 inhibitors
Pembrolizumab
Nivolumab
Cemiplimab
Gastric or cervical Ca, Merkel cell Ca, mediastinal large B-cell lymphoma, MSI-H or dMMR Ca,
SCLC, MSI-H or dMMR CC
Skin SCC
Melanoma, NSCLC, RCC, Hodgkin Lymphoma, Head & Neck SCC, urothelial Ca, HCC
PD-L1 inhibitors
Atezolizumab
Avelumab
Durvalumab
NSCLC
Merkel cell Ca
NSCLC
Urothelial Ca


Tumor Cell
APC
CD80
CD80
CD28
TCR
PD-L1
PD-1
CTLA-4
Ipilimumab
T-CELL
Activation
Atezolizumab
Avelumab
Durvalumab
Pembrolizumab
Nivolumab
Cemiplimab
IL-2
IFN-γ
Granzyme
Granulysin
Cytotoxic effects
Hepatotoxicity



- Low level LFT abnormalities in high number of treated patients
- More severe injury occurs most frequently after several cycles
- Most are manifest by hepatocellular pattern of injury biochemically and acute hepatitis on biopsy
- In some: considered to be DI-ALH; may be accompanying autoimmune processes in GIT and skin
- In some there is an immune-mediated cholangiopathy; PBC and PSC-like picture reported with pembrolizimab
- Other abnormalities recorded: SOS and fibrin ring granulomas

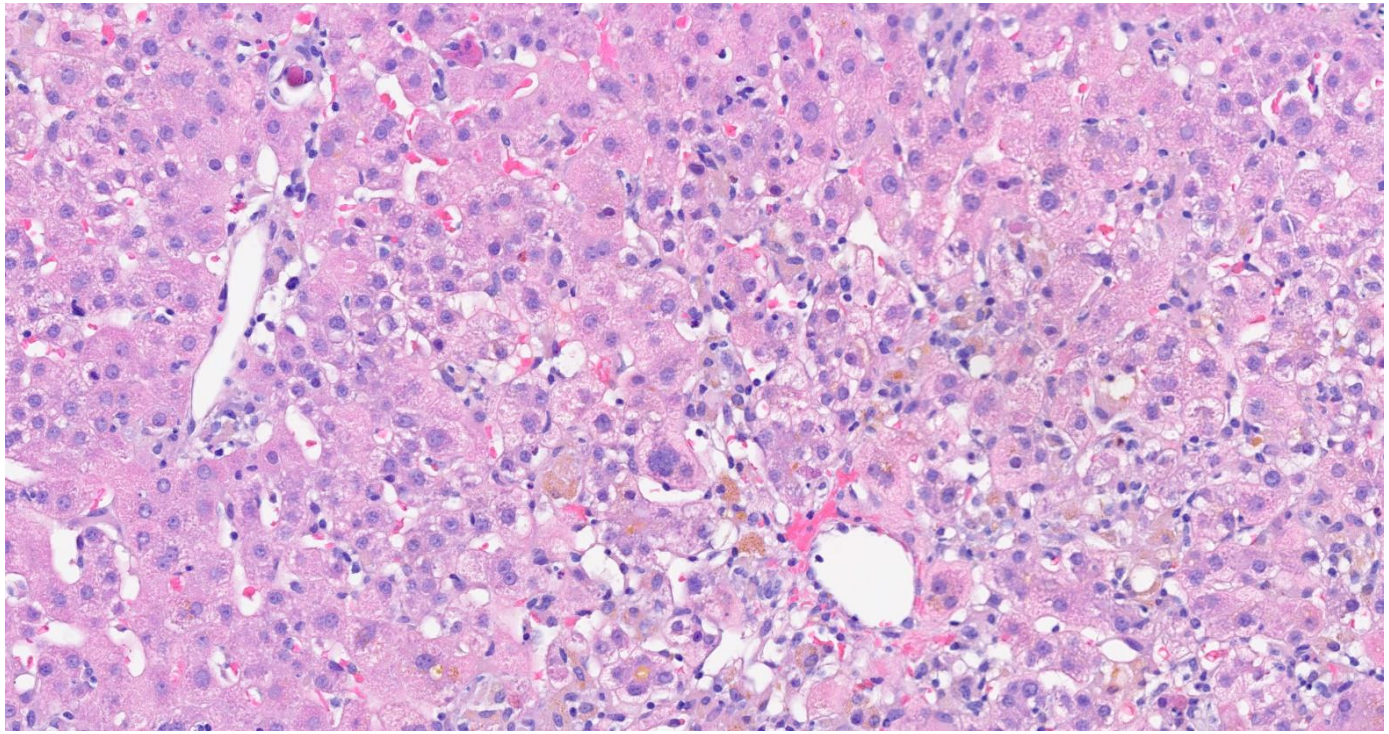
Dietary supplements and herbal products

Herbal preparations	
Pyrrolizidine alkaloids, *e.g.* Crotalaria,senecio, heliotrpium, Symphytum officinale (comfrey)	Acute and chronic SOS
Teucrium chamaedrys (germander)	AHH, ACH, ALF, chronic hepatitis, cirrhosis, cholangitis
Teucrium polium	AHH, ACH, A LF
Atractylis gummifera L.	AHH, ACH, ALF
Callilepis laureola L.	AHH, ALF
Mentha pulegium	AHH, ACH, ALF
Hedeoma pulegioides	AHH, ACH, ALF
Chelidonium majus (greater celandine)	AHH, ACH, chronic hepatitis, cholangitis
Piper methysticum (kava-kava)	AHH, ACH, ALF, chronic hepatitis
Camellia sinensis (green tea extracts)	AHH, ACH, ALF
Actaea racemosa (black cohosh)	AHH, ACH
Cimicifuga racemosa	AHH, ACH
Morinda citrifolia (Noni juice)	AHH, ACH, ALF
Serenoa	ACH
Azadirachta indica	Microvesicular steatosis
Catha edulis (khat)	AHH, ACH, ALF
Borago officinalis (borage)	AHH, ACH
Cassia angustifolia (senna)	AHH, ACH
Larrea tridentata (chaparral)	AHH, ACH, cholangitis, chronic hepatitis/cirrhosis

J R Coll Physicians Edinb 2021; 51: 363–5 | doi: 10.4997/JRCPE.2021.409 CASE REPORT

Drug-induced hepatocellular injury due to herbal supplement ashwagandha

Peter J Ireland[1], Timothy Hardy[2], Alastair D Burt[3], Mhairi C Donnelly[4]



- 39 year old female
- Basil powder, biotin and ashwaganda (*Withania somnifera* or Indian Ginseng)
- Self medication for anxiety
- ANA 1:40
- Normal Ig and viral serology incl. HEV negative
- Moderate response to discontinuation with empiric UDCA

Blood test	Date of blood test (day/month)									
	16/7	14/8	17/8	18/8	19/8	20/8	21/8	24/8	28/8	03/9
Albumin	49	44	42	42	43	42	44	47	42	44
Bilirubin	8	154	220	252	279	293	327	292	182	115
Alkaline phosphatase	69	184	167	162	152	140	144	142	112	125
Alanine aminotransferase	14	1,514	1,494	1,503	1,443	1,316	1,301	995	520	495
Prothrombin time	n/a	14	13	n/a	14	13	14	12	12	12

Dietary supplements and herbal products

Asian herbal medicine (Chinese, Japanese, ayurvedic medicines)	
Lycopodium serratum (Jin Bu Huan)	AHH, ACH, ALF
Ephedra (Ma Huang)	AHH with autoimmunity
Sho-Saiko-To (Xiao-Chai-Hu-Tang; complex preparation)	AHH/chronic hepatitis
Dai-Saiko-To (complex preparation)	AHH with autoimmunity
Chaso and Onshido	AHH, ACH, ALF
Boh-Gol-Zhee/Bu Ku Zi	ACH
Polygonum multiflorum (Shou-Wu-Pian)	AHH, ACH
Ganoderma lucidum (Linghzi)	AHH
Brena officinalis (Chi R Yun)	AHH
Dysosma pleiantha (Boh-Gol-Zhee)	AHH

Herb-induced injury in Asia

frontiers | Frontiers in Pharmacology

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A review of herb-induced liver injury in mainland china

Yan Yang[1†], Fei-Lin Ge[2†], Jin-Fa Tang[3†], Shuang-Lin Qin[4], Rui Zeng[5], Meng-Lin Yao[5], Xiao-He Xiao[6*], Zhao-Fang Bai[6*] and Cheng-Lin Tang[1*]

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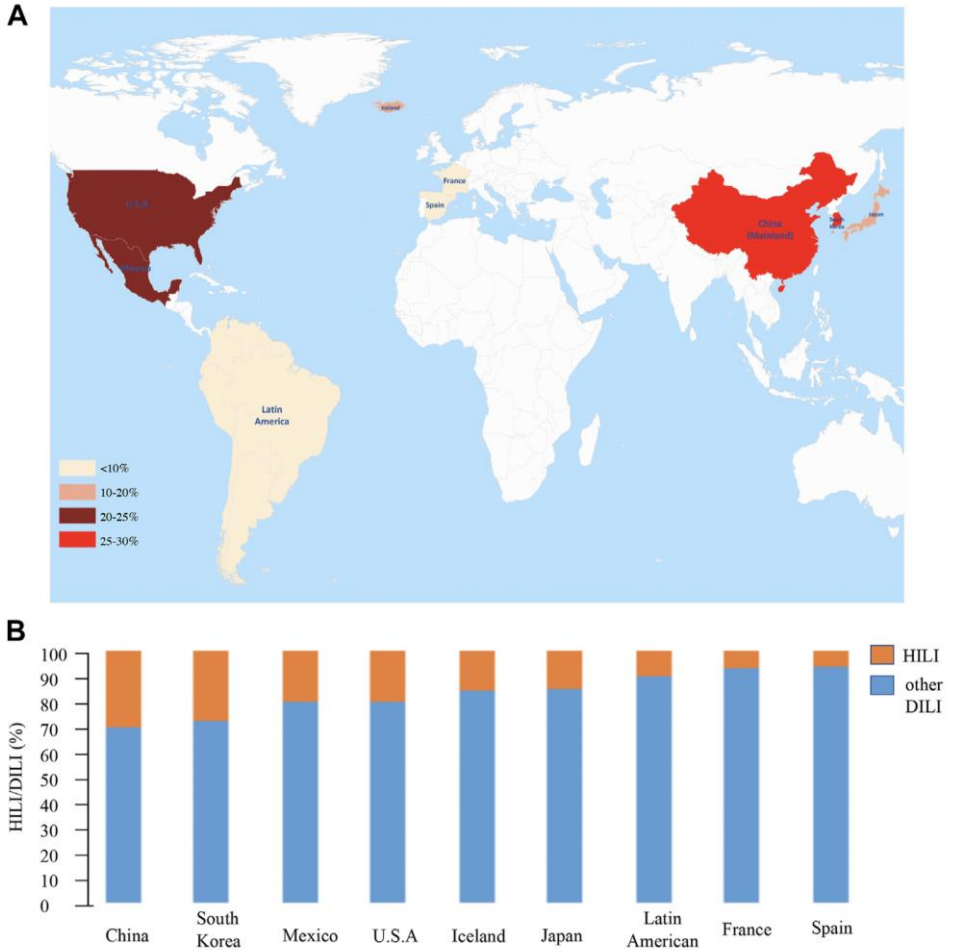

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ISSN 2307-8960 (online)

SYSTEMATIC REVIEWS

Herb-induced liver injury: Systematic review and meta-analysis

Vinícius Remus Ballotin, Lucas Goldmann Bigarella, Ajacio Bandeira de Mello Brandão, Raul Angelo Balbinot, Silvana Sartori Balbinot, Jonathan Soldera

Herbs	1084 (100)
He-Shou-Wu	91 (8.3)
Green tea extract	90 (8.3)
Herbalife	64 (5.9)
Kava kava	62 (5.7)
Greater celandine	48 (4.4)
Multiple herbs	38 (3.5)
Germander	35 (3.2)
Hydroxycut	35 (3.2)
Skullcap	35 (3.2)
Kratom	33 (3.0)
Gynura segetum	29 (2.6)
Garcinia cambogia	29 (2.6)
Ma huang	27 (2.4)
Chaparral	26 (2.4)
Senna	25 (2.3)
Aloe vera	22 (2.0)
Jin Bu Huan	19 (1.7)

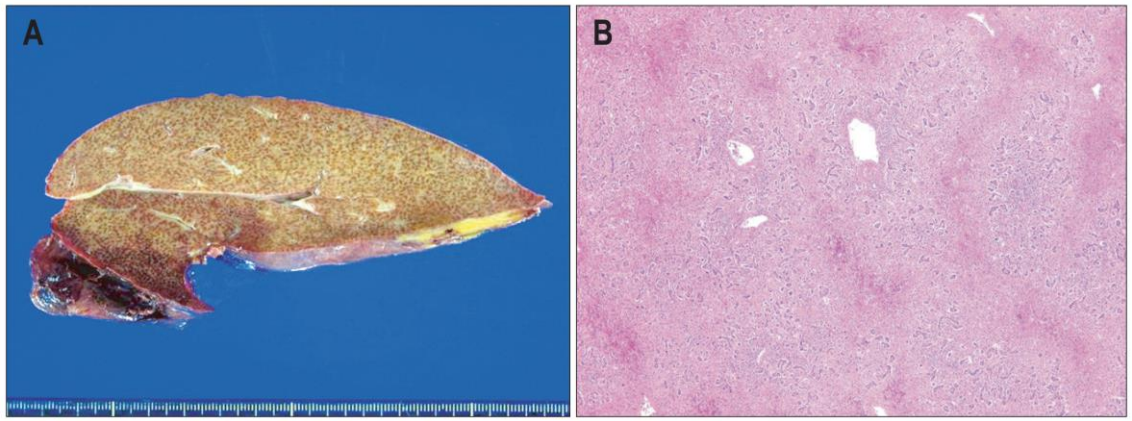
Polygonum liver injury: acute hepatitis

ORIGINAL ARTICLE

Gut and Liver, Vol. 5, No. 4, December 2011, pp. 493-499

Drug-Induced Liver Injury: Twenty Five Cases of Acute Hepatitis Following Ingestion of *Polygonum multiflorum* Thunb

Kyoung Ah Jung*, Hyun Ju Min*, Seung Suk Yoo*, Hong Jun Kim*, Su Nyoung Choi*, Chang Yoon Ha*, Hyun Jin Kim*, Tae Hyo Kim*, Woon Tae Jung*, Ok Jae Lee*, Jong Sil Lee†, and Sang Goon Shim‡



- *Ho-Shou-Wu*: consumed raw or as extract
- Anti-ageing or as tonic for dizziness, constipation
- Case series
- Median age: 48
- 76% presented with jaundice
- 10 cases biopsied: hepatitic process with no signs of chronicity
- 23 patients recovered
- One death due to ALF and one underwent transplantation

Liver injury with strength enhancing supplements

- Anabolic steroids
- Selective androgen receptor modulators SARMs

Received: 20 November 2023 | First decision: 11 December 2023 | Accepted: 5 February 2024
DOI: 10.1111/apt.17906
APT Alimentary Pharmacology & Therapeutics WILEY

Drug-induced liver injury from selective androgen receptor modulators, anabolic-androgenic steroids and bodybuilding supplements in Australia

Emily Nash[1,2] | Amanda Nicoll[3] | Nicholas Batt[3] | Jacob George[4,5] | Varan Perananthan[6] | David Prince[7,8] | Michael Wallace[9,10] | Paul Gow[11] | Karl Vaz[11] | Shivakumar Chitturi[12] | Joan Ericka Flores[12] | Alicia Braund[13] | Mark Bonnichsen[7] | Stephen Riordan[14] | Jeremy Humphris[15] | Tuan Duong[15] | Catriona McKenzie[16] | Ken Liu[1,2] | Simone I. Strasser[1,2]

Liver injury with strength enhancing supplements

- Anabolic steroids
- Selective androgen receptor modulators SARMs

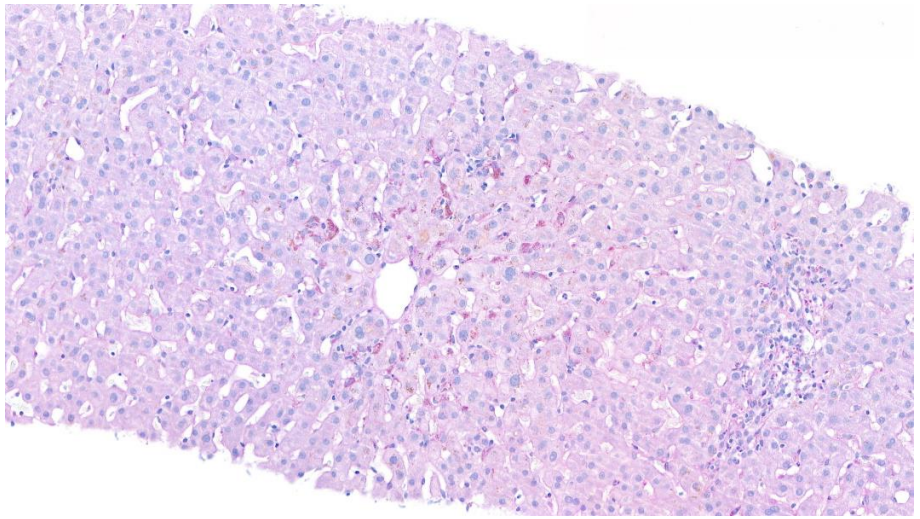
TABLE 4 Histopathological patterns of drug-induced liver injury, by drugs taken per patient.

AAS ($n=4$)	SARMs ($n=5$)	BBS ($n=1$)	Combinations ($n=3$)
• Cholestatic hepatitis ($n=1$) • Acute cholestasis ($n=1$) • Hepatocellular carcinoma (well-differentiated) and focal nodular hyperplasia ($n=1$) • Hepatocellular adenoma with atypical features and focal nodular hyperplasia ($n=1$)	• Chronic cholestasis ($n=2$) • Cholestatic hepatitis ($n=2$) • Mixed acute hepatitis and chronic cholestasis ($n=1$)	Acute hepatitis ($n=1$)	• Acute cholestasis (AAS & SARM & BBS) ($n=1$) • Cholestatic hepatitis (AAS & BBS) ($n=1$) • Cholestatic hepatitis and focal nodular hyperplasia (SARM & BBS) ($n=1$)

Abbreviations: AAS, anabolic-androgenic steroids; BBS, bodybuilding supplements; SARMs, selective androgen receptor modulators.

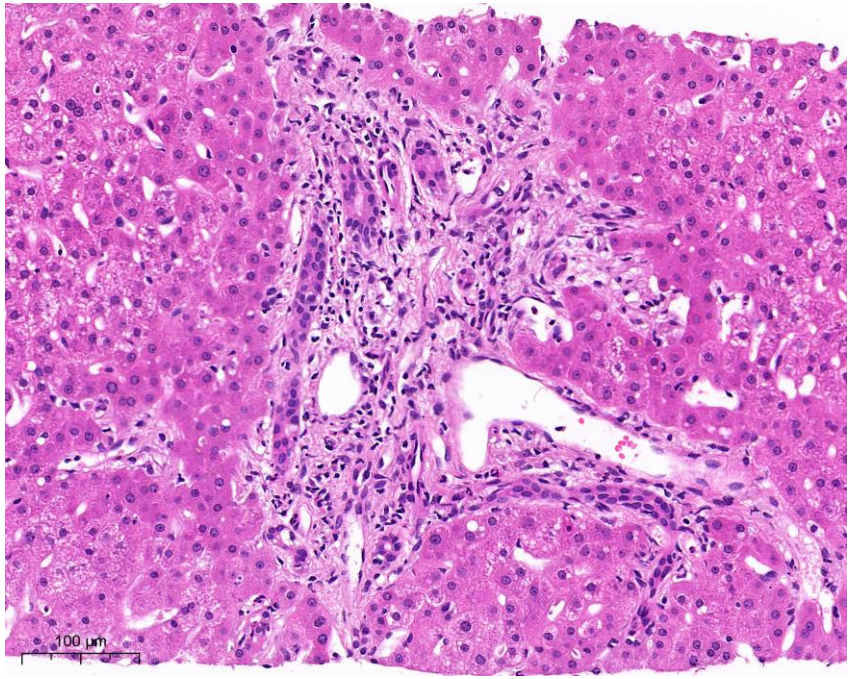
Liver injury with strength enhancing supplements

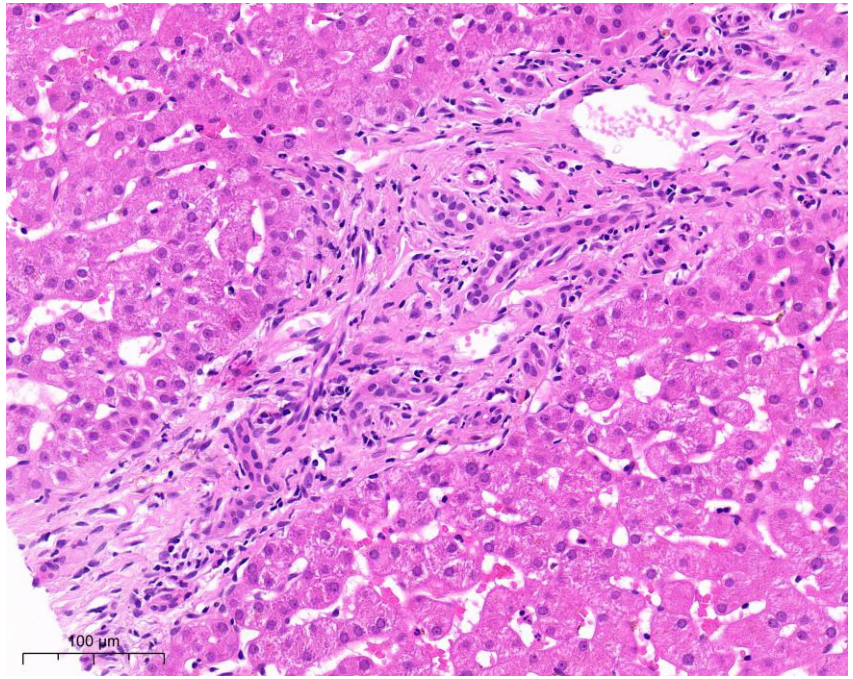
- Anabolic steroids
- Selective androgen receptor modulators SARMs
- Ghrelin receptor agonists eg MK-677
- (No reports on LiverTox)

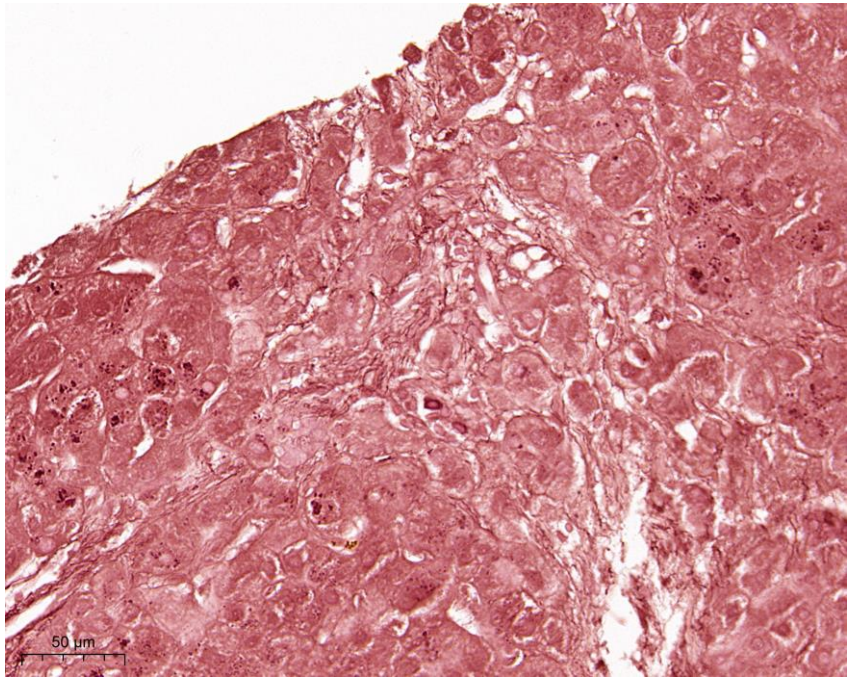


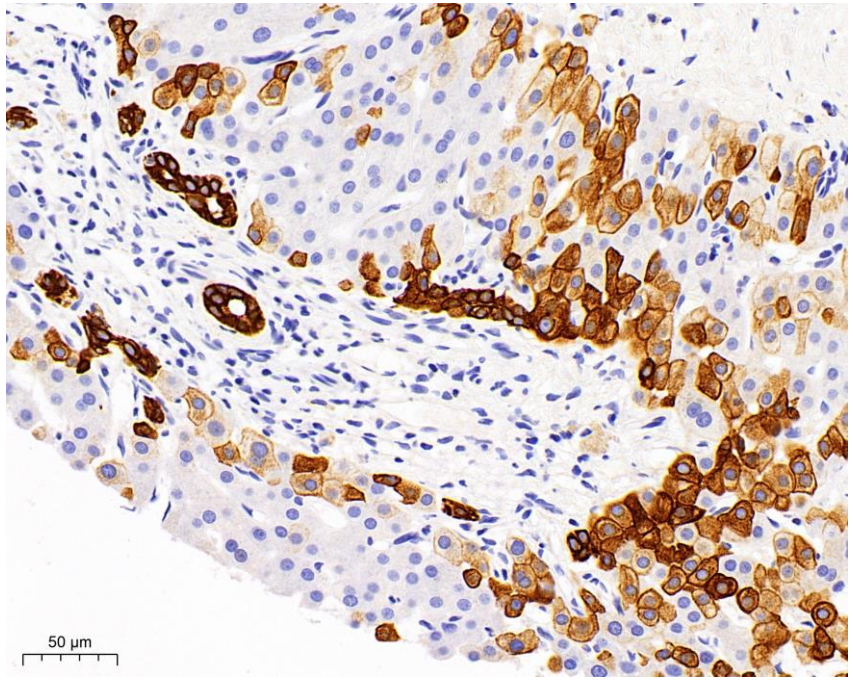
Ketamine and the liver

- Medical use: anaesthetics, sedation, pain control
- Therapy for psychiatric disorders: epileptic seizures, alcohol dependence, treatment-resistant major depressive disorder
- Non-medical recreational use started in 1970s (US) and 1990s (Europe), and it has been widespread across the world.
- Side effects in the urinary tract: Fibrosing cystitis (ketamine bladder), ureteral stenosis and hydronephrosis.









Yoh Zen

Ketamine cholangiopathy

- A great mimicker of PSC.
- Histological findings are almost indistinguishable from those of PSC.
- The association with cystitis, the lack of inflammatory bowel disease and mild extrahepatic duct dilatation without irregularity are potential diagnostic clues.
- May be less progressive than PSC.
- Obtaining sufficient information from patients is essential.

DILI: general considerations

- Recognising DILI can be challenging
- Essential to rule out all other possible causes of liver injury
- Note there may be more than one process: DILI + another form of disease
- Biopsy appears to be helpful in 50% cases: either confirming DILI or demonstrating an alternative explanation
- A detailed history essential including OTC dietary supplements and herbals
- Duration and type of exposure important to consider
- Temporal issues: latent period?
- Ultimate proof of causality: rechallenge but rarely justified
- Role for HLA typing?