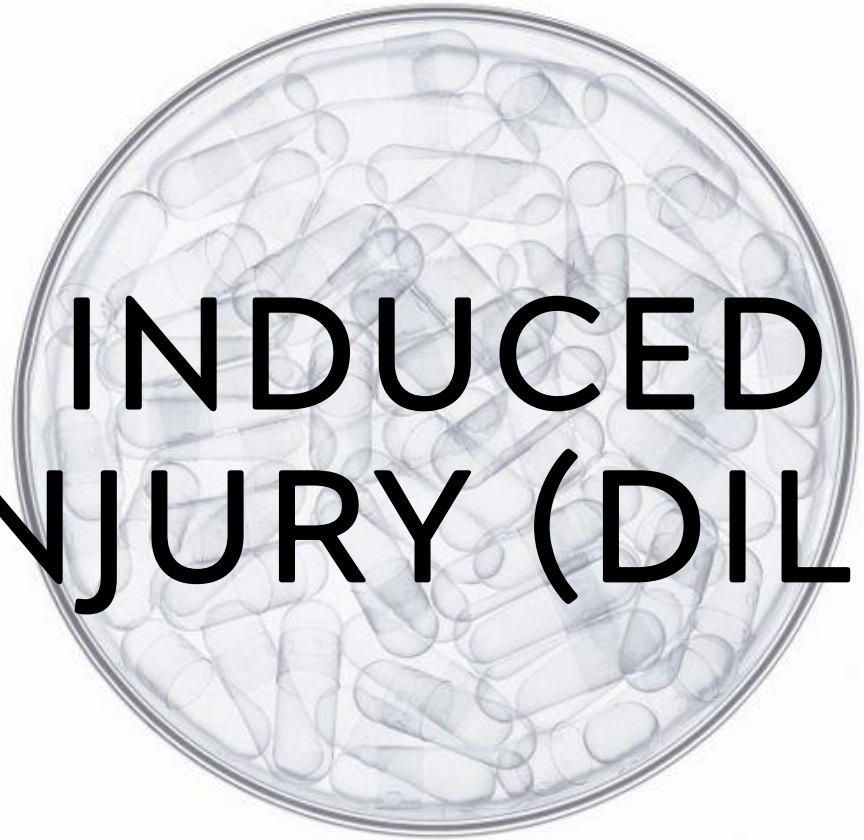


DRUG INDUCED LIVER INJURY (DILI)

PRESENTER: DR. ISNEEN HILMY

MODERATOR: DR. NELISWA GOGELA

MAY 29TH, 2023 (MONDAY)

OUTLINE

EPIDEMIOLOGY

MECHANISM OF DILI

TYPES

RISK FACTORS

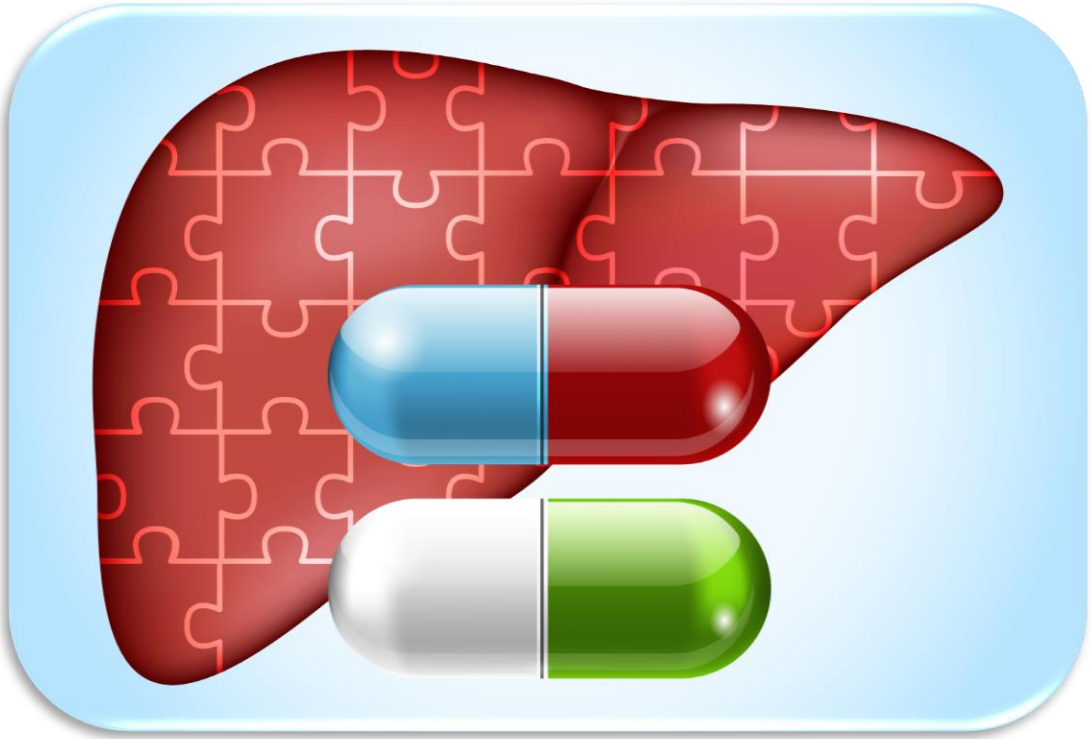
CLINICAL PRESENTATION

DIAGNOSIS

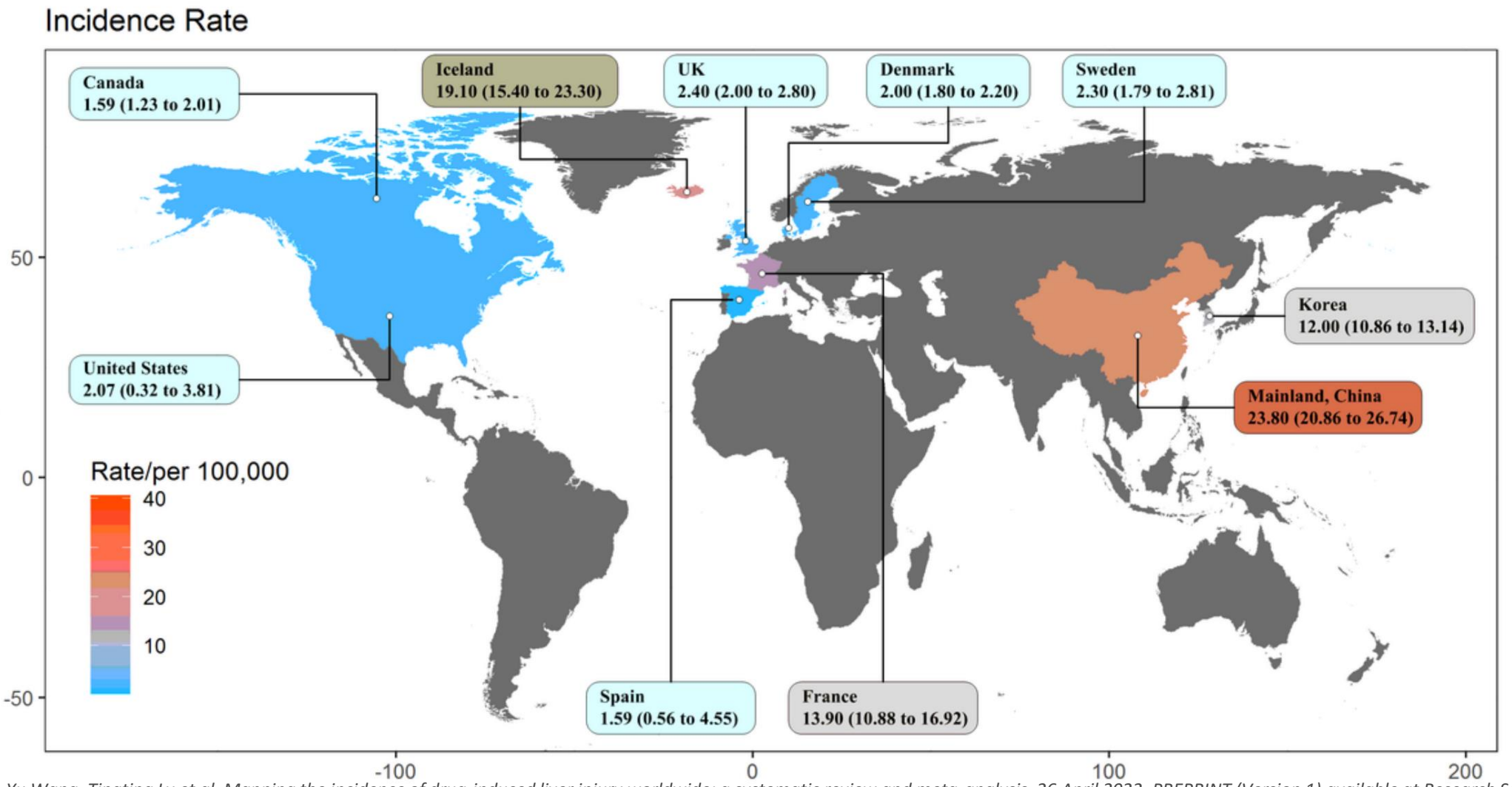
APPROACH

MANAGEMENT

SPECIAL CIRCUMSTANCES IN DILI



EPIDEMIOLOGY



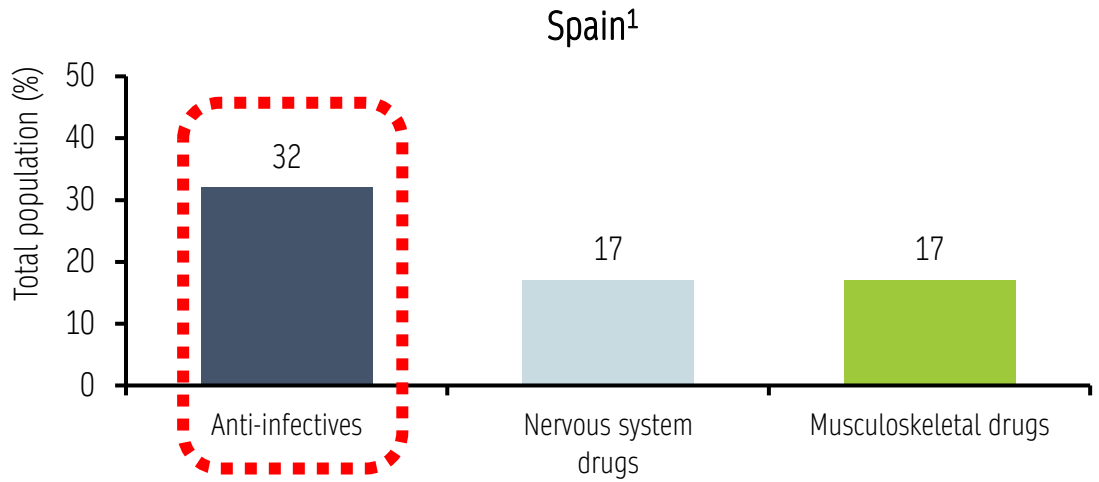
Min Li, Yu Wang, Tingting Lv et al. Mapping the incidence of drug-induced liver injury worldwide: a systematic review and meta-analysis, 26 April 2022, PREPRINT (Version 1) available at Research Square [https://doi.org/10.21203/rs.3.rs-1557481/v1]

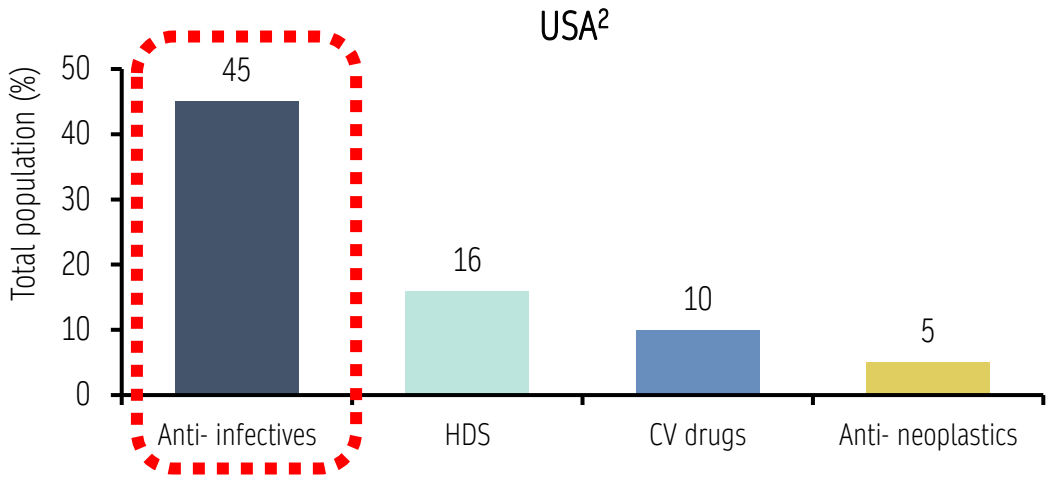
EPIDEMIOLOGY

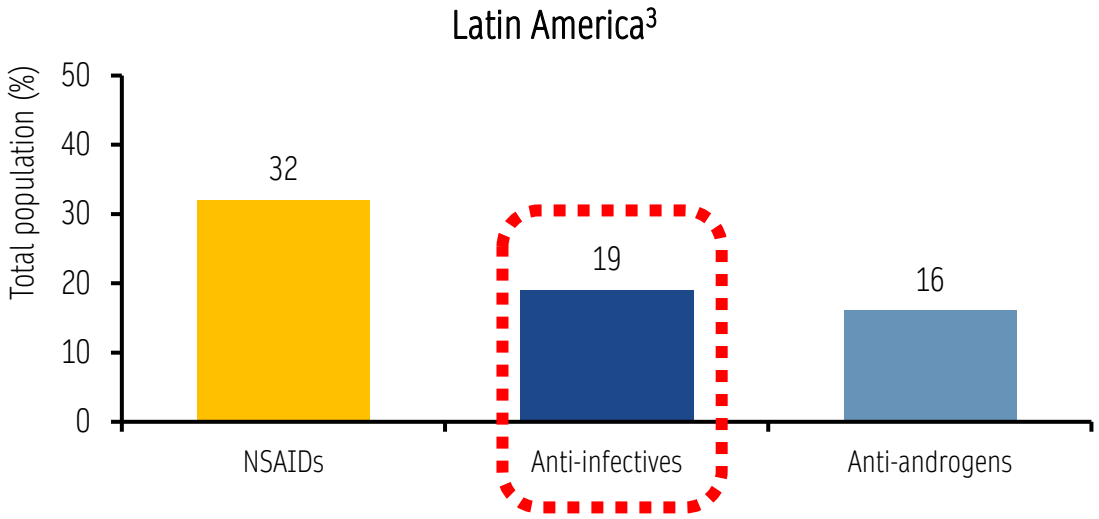
- In the US, annual incidence of DILI is 2.7 per 100,000
- Drug induced ALF is 1.6 per 1,000,000
  - Herbal or dietary supplements (HDS) account for 43% of DILI and 19% of ALF
  - HDS not subject to pre-market safety evaluations (Dietary supplement health and Education Act 1994 in the United States)
- DILI is the leading cause for drug withdrawal and use restriction

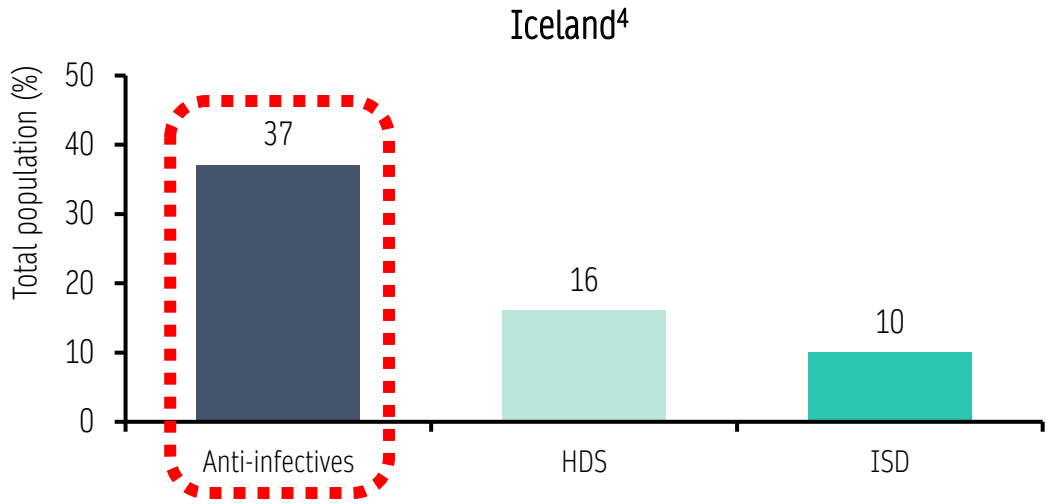
Vega M et al. Drug Saf 2017; 40:783
Goldberg DS et al. Gastroenterology 2015: 148:1353
Aithal GP. Et al. Liver Transpl. 2002. Feb:28(2):159
Ghabril M. et al. Liver Trasnpl. 2002. Feb:28(2):169

MOST COMMON CAUSATIVE DRUG CLASSES IN LARGE DILI POPULATIONS









1. Andrade RJ, et al. Gastroenterology 2005;129:512–21; 2. Chalasani N, et al. Gastroenterology 2015;148:1340–52.e7;
3. Bessone F, et al. Int J Mol Sci 2016;17:313; 4. Björnsson ES, et al. Gastroenterology 2013;144:1419–25.e3.
EASL CPG DILI. J Hepatol 2019;70:1222–61.

Table 3. Most Frequent Causes of Idiosyncratic Prescription Drug–Induced Liver Injury.*

Rank	Agent	Year of FDA Approval	No. (%)†	Major Phenotypes
1	Amoxicillin–clavulanate	1984	91 (10.1)	Cholestatic or mixed hepatitis
2	Isoniazid	1952	48 (5.3)	Acute hepatocellular hepatitis
3	Nitrofurantoin	1953	42 (4.7)	Acute or chronic hepatocellular hepatitis
4	TMP-SMZ	1973	31 (3.4)	Mixed hepatitis
5	Minocycline	1971	28 (3.1)	Acute or chronic hepatocellular hepatitis
6	Cefazolin	1973	20 (2.2)	Cholestatic hepatitis
7	Azithromycin	1991	18 (2.0)	Hepatocellular, mixed, or cholestatic hepatitis
8	Ciprofloxacin	1987	16 (1.8)	Hepatocellular, mixed, or cholestatic hepatitis
9	Levofloxacin	1996	13 (1.4)	Hepatocellular, mixed, or cholestatic hepatitis
10	Diclofenac	1988	12 (1.3)	Acute or chronic hepatocellular hepatitis
11	Phenytoin	1946	12 (1.3)	Hepatocellular or mixed hepatitis
12	Methyldopa	1962	11 (1.2)	Hepatocellular or mixed hepatitis
13	Azathioprine	1968	10 (1.1)	Cholestatic hepatitis

* Data are from Chalasani et al.[13] The listed agents are those most frequently implicated in a total of 1257 cases of drug-induced liver injury reported between 2004 and 2013; agents were classified as definite, highly likely, or probable causes (in 899 cases). Agents that ranked from 14th to 25th in frequency were hydralazine, lamotrigine, and mercaptopurine (9 cases each); atorvastatin and moxifloxacin (8 cases each); and allopurinol, amoxicillin, duloxetine, rosuvastatin, telithromycin, terbinafine, and valproic acid (7 cases each). FDA denotes Food and Drug Administration.

† The percentages have been calculated on the basis of a total of 899 cases of drug-induced liver injury.

N Engl J Med 2019;381:264-73

MECHANISM

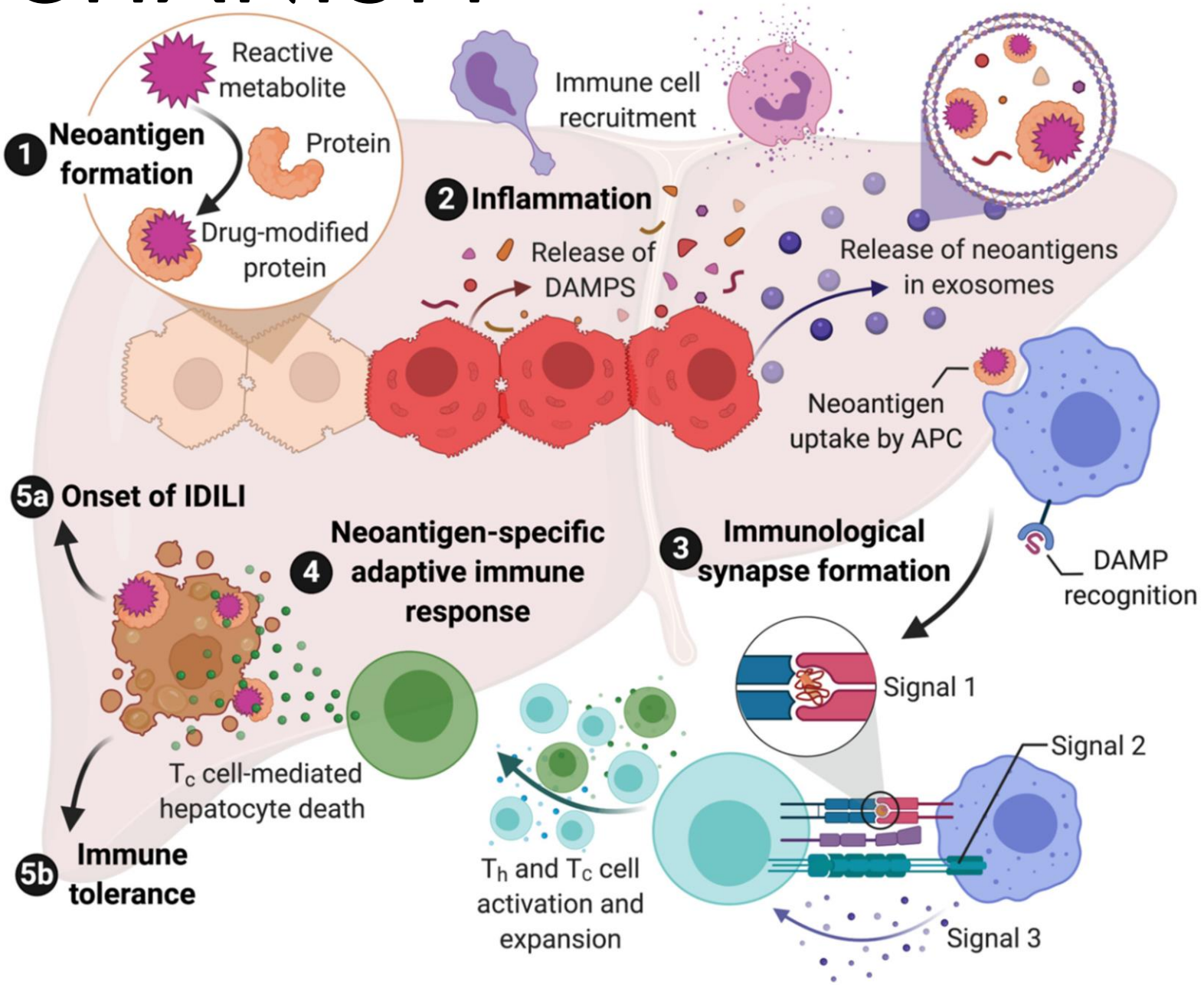


Image by Lectuiro.

TYPES OF DILI

Table 1. Drug-Induced Liver Injury According to Type.*

Variable	Direct Hepatotoxicity	Idiosyncratic Hepatotoxicity	Indirect Hepatotoxicity
Frequency	Common	Rare	Intermediate
Dose-related	Yes	No	No
Predictable	Yes	No	Partially
Reproducible in animal models	Yes	No	Not usually
Latency (time to onset)	Typically rapid (days)	Variable (days to years)	Delayed (months)
Phenotypes	Acute hepatic necrosis, serum enzyme elevations, sinusoidal obstruction, acute fatty liver, nodular regeneration	Acute hepatocellular hepatitis, mixed or cholestatic hepatitis, bland cholestasis, chronic hepatitis	Acute hepatitis, immune-mediated hepatitis, fatty liver, chronic hepatitis
Most commonly implicated agents	High doses of acetaminophen, niacin, aspirin, cocaine, IV amiodarone, IV methotrexate, cancer chemotherapy	Amoxicillin–clavulanate, cephalosporins, isoniazid, nitrofurantoin, minocycline, fluoroquinolones, macrolide antibiotics	Antineoplastic agents, glucocorticoids, monoclonal antibodies (against tumor necrosis factor, CD20, checkpoint proteins), protein kinase inhibitors
Cause	Intrinsic hepatotoxicity when agent given in high doses	Idiosyncratic metabolic or immunologic reaction	Indirect action of agent on liver or immune system

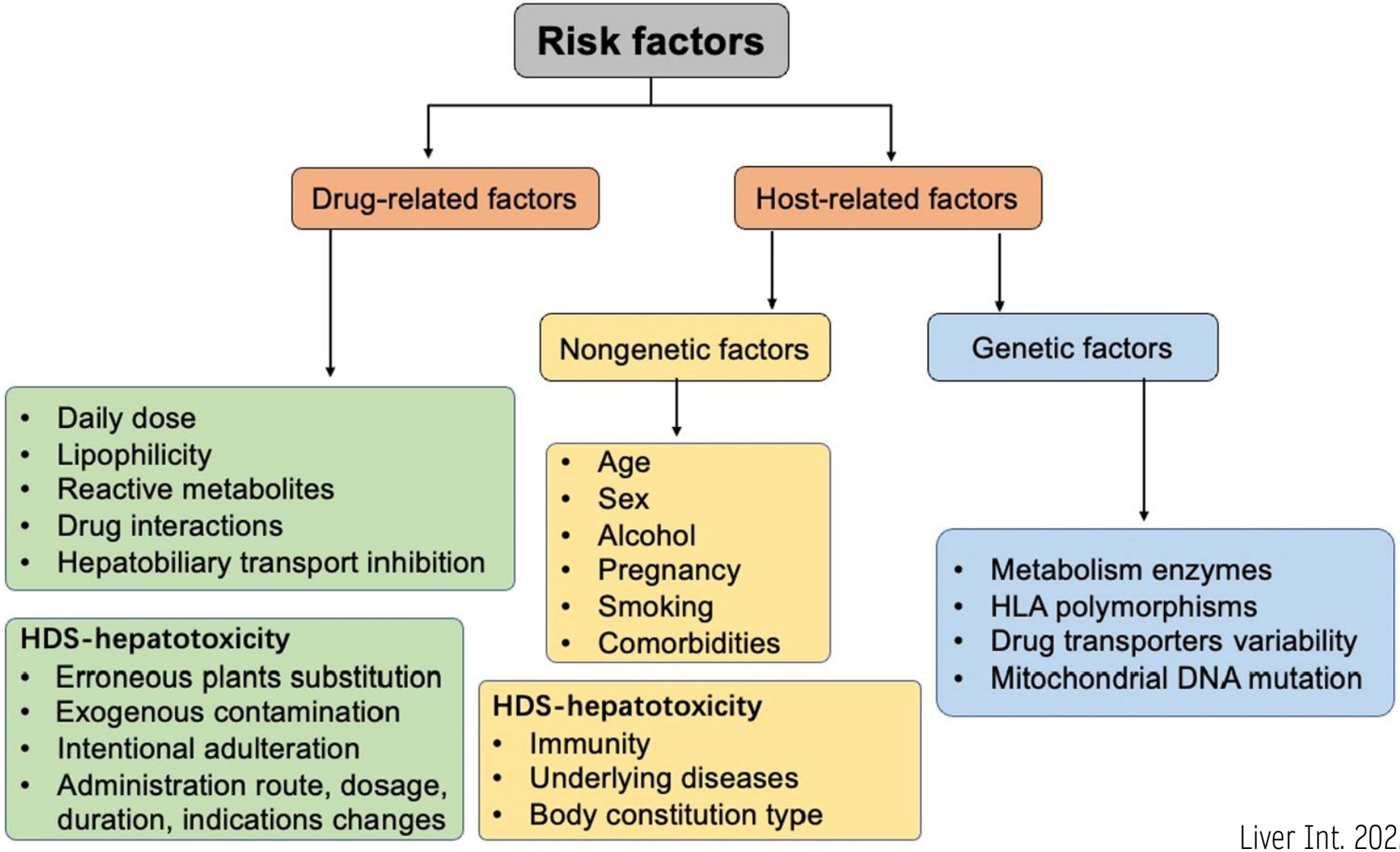
N Engl J Med 2019;381:264-73

Table 2. Phenotypes of Drug-Induced Liver Injury.*

Phenotype	Type of Liver Injury	Latency	Enzyme Pattern	Typical Agents	Comments
Acute hepatic necrosis	Direct	Days	Marked, abrupt ALT elevations; mild Alk P and bilirubin elevations	Acetaminophen, aspirin, niacin, "Ecstasy"	Often due to overdose
Enzyme elevations	Direct	Days to months	Mild-to-moderate ALT or Alk P elevations	Many agents	Usually transient and asymptomatic
Acute hepatitis	Idiosyncratic, indirect	Days to months	High ALT elevations, modest Alk P elevations	Isoniazid, diclofenac	High death rate
Cholestatic hepatitis	Idiosyncratic	Weeks to months	High Alk P elevations, modest ALT elevations	Amoxicillin–clavulanate, cefazolin	Pruritus, early and prominent
Mixed hepatitis	Idiosyncratic	Days to months	Moderate ALT and Alk P elevations	TMP-SMZ, phenytoin	Usually benign, self-limited
Chronic hepatitis	Idiosyncratic, indirect	Months to years	Moderate ALT elevations with bilirubin elevations	Diclofenac, nitrofurantoin, minocycline	Insidious onset; may require glucocorticoids
Bland cholestasis	Unknown, possibly idiosyncratic	Months	Moderate ALT elevations, mild Alk P elevations	Anabolic steroids, estrogens	Pruritus, prominent and prolonged
Acute fatty liver, lactic acidosis, and hepatic failure	Direct	Days to months	Lactic acidosis, modest ALT elevations, hepatic failure	Stavudine, linezolid, aspirin (Reye's syndrome)	Mitochondrial failure, pancreatitis
Nonalcoholic fatty liver	Indirect, direct	Months	Mild ALT and Alk P elevations	Glucocorticoids, tamoxifen, haloperidol	Asymptomatic; fatty liver seen on ultrasound
Sinusoidal obstruction syndrome	Direct	Weeks	Variable enzyme elevations	Cancer agents, busulfan, gemtuzumab	Hepatomegaly, weight gain, edema, ascites
Nodular regenerative hyperplasia	Direct	Years	Minimal ALT and Alk P elevations	Thioguanine, azathioprine, oxaliplatin	Noncirrhotic portal hypertension

* The phenotypes are listed very generally in order of frequency; there is some overlap between idiosyncratic and indirect forms of injury. Alk P denotes alkaline phosphatase, ALT alanine aminotransferase, and TMP-SMZ trimethoprim–sulfamethoxazole.

RISK FACTORS



Liver Int. 2022; 42: 1999– 2014

CLINICAL PRESENTATION

- Asymptomatic elevations of liver enzymes
- Symptomatic (highly variable):
  - Fatigue
  - Anorexia, N/V & RUQ pain
  - Jaundice / Pruritis
  - Hypersensitivity reactions
    - Fever, rash, lymphadenopathy & eosinophilia (Phenytoin, sulfonamides and allopurinol)
    - DRESS or SJS (HIV pts started on ARVs/ATT/Co-trimoxazole)
- Acute hepatitis / Chronic (>2months) hepatitis
- Sub-fulminant / fulminant liver failure
- Chronic cholestatic liver disease
  - Vanishing bile duct syndrome

DIAGNOSIS

- Challenging
- Based largely on exclusion of other causes
- Determine causality by RUCAM Model

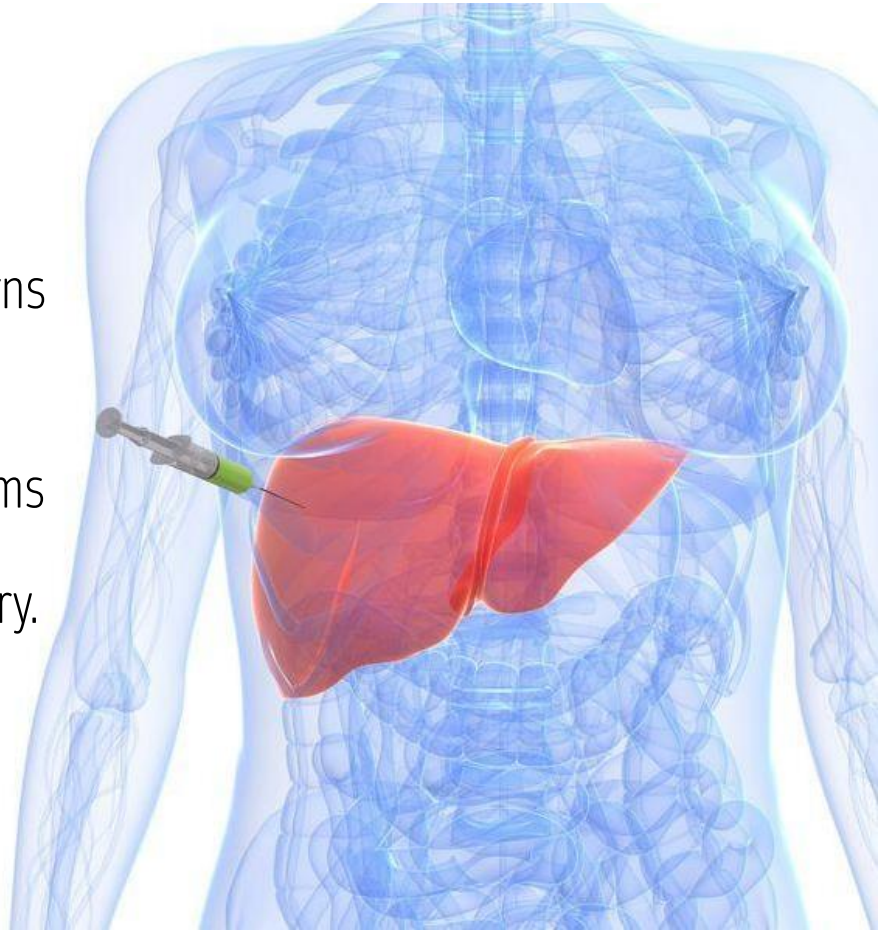
DIAGNOSTIC ELEMENTS

- Timing of the onset of injury after the implicating agent has been started: Latency
- Resolution after the agent is stopped – De-challenge
- Recurrence on re-exposure: Re-challenge

- Knowledge of the agent's potential for hepatotoxicity (likelihood), and clinical features of liver injury (phenotype)
- ALT, AST, ALT, T.Bil are the standard analytes to define the type of liver damage
- Persistently elevated LFTs in the second month from DILI onset should be used as marker for Chronic DILI

DIAGNOSIS

- Liver Biopsy
  - Not mandatory
  - Helpful in excluding other causes of liver disease
  - Certain medications are associated with specific histological patterns of liver injury that can be confirmed on biopsy.
  - Biopsy can also be useful when the liver biochemistries or symptoms do not improve with drug de-challenge or the patient remains jaundiced, and can be used to help assess the severity of liver injury.



DILI QUALIFICATION

- DILI can present with a very heterogeneous phenotype
- Liver biopsy is not available in most instances
- Qualification of liver injury for practical and scientific purposes is made by liver biochemistry[1]
  - ALT ≥5x ULN
  - ALP ≥2x ULN
  - ALT ≥3x ULN + TBL >2x ULN
- Pattern of liver injury is classified according to R ($\frac{\text{ALT / UNL}}{\text{ALP / UNL}}$)[1]
  - Hepatocellular = R≥5
  - Cholestatic = R≤2
  - Mixed = 2>R<5

1. Aithal GP, et al. Clin Pharmacol Ther 2011;89:806–15.
EASL CPG DILI. J Hepatol 2019;70:1222–61.

HY'S LAW: A SENSITIVE AND SPECIFIC PREDICTOR OF A DRUG'S POTENTIAL TO CAUSE SEVERE LIVER INJURY

- In the late 1960s, **Hyman Zimmerman** discovered a combination of jaundice and drug-induced hepatocellular injury was a/w a 10–50% fatality rate from liver failure
  - Temple's definition of 'Hy's Law cases' used by the **FDA** in drug development:
    - ALT >3x ULN and TBL >2x ULN without significant ALP increase
  - **'New Hy's Law' proposed by the Spanish DILI Registry**:
    - nR [(ALT or AST*/ULN)/(ALP/ULN)] >5 and TBL >2 ULN[1]

	ALT >3x ULN; TBL >2x ULN	R ≥5; TBL >2x ULN	nR ≥5; TBL >2x ULN
Sensitivity, %	90	83	90
Specificity, %	44	67	63
AUROC	0.67	0.74	0.77

*whichever higher

1. Robles-Diaz M, et al, Gastroenterology 2014;147:109-18; 2. Hayashi PH, et al. Hepatology, 2017; 66:1275-85.
EASL CPG DILI. J Hepatol 2019;70:1222–61.

APPROACH

Biochemical evidence of liver injury meeting one of the these criteria

1. AST or ALT > 5x UNL or ALP > 2x UNL (or pretreatment baseline if abnormal) on 2 separate occasions	2. T.Bil > 2.5 with elevated AST, ALT or ALP	3. INR > 1.5 with elevated AST, ALT or ALP

DILI suspected based on clinical history, symptoms and/or physical exam

1. Assess exposure to all prescription and OTC, HDS products and toxins, including start and stop dates, especially with the preceding 6months	2. Discontinue any non-essential medication and suppliments

Determine the R-Ratio

R >= 5 - Hepatocellular	R 2-5 - Mixed	R <= 2 - Cholestatic

APPROACH

R >= 5 – Hepatocellular & R 2-5 – Mixed	R <= 2 - Cholestatic
• Viral hepatitis (HAV IgM, HBsAg, HCV RNA, HEV IgM, CMV PCR, EBV PCR, HSV PCR) • Ischemic (H/o hypotension, sepsis or heart failure, ECHO) • Autoimmune Hepatitis (ANA, ASMA, IgG, Liver Biopsy) • Alcoholic hepatitis (History, AST >2x ALT, Serum Peth, Urine ethylglucuronide) • Drug/Toxin (eg. Mushroom, APAP) – (History, urine tox, serum APAP) • Budd-Chiari (Doppler uss or CT or MRI) • Wilsons (Ceruloplasmin, ALP:TB <4, AST:ALT > 2.2) • Alpha-1-antitrypsin deficiency (A1AT level) • Hereditary hemochromatosis (Ferritin, transferrin saturation) • Fatty liver disease (History and imaging features) • Celiac disease (Anti-tTG IgA) • Rhabdomyolysis (CPK) • Hypothyroidism/ Thyrotoxicosis (TSH, Free T4, T3)	• Choledocholithiasis (Doppler USS) • PSC (AMA, Liver Bx) • Biliary strictures (eg. PSC) – (Cholangiography) • Pancreaticobiliary tumors (CT or MRI) • Malignancy/ infiltrating (eg. Lymphoma) – LDH, imaging • TPN Cholestatsis (History) • Bone disease (ALP isoenzymes)

APPROACH

DRUG INDUCED LIVER INJURY

MANAGEMENT: DIRECT DILI

- Stop the suspect drug
- N-Acetylcysteine (NAC) for acetaminophen liver injury
- Transfer or refer for liver Tx:
  - Hight INR, Mental status changes
- Options with limited data
  - Corticosteroids for autoimmune and hypersensitivity cases
  - Ursodeoxycholic acid for cholestatsis

ACETAMINOPHEN LIVER INJURY

Recommendation	Intentional overdose	Unintentional overdose
Diagnostic approach		
Time of ingestion	Single time point	Several days of repeated use
Dose	Supratherapeutic (typically > 4 g over 24 h)	Repeated therapeutic (up to 4 g per day) or supratherapeutic dosing
Presence of coingestants	Diphenhydramine and other sedatives can lead to central nervous system depression	Opioids often used in combination
Liver injury parameters	From time of ingestion: 24–72 h: rapid rise in ALT to > 1000 IU/L associated with variable rise in INR; total bilirubin is typically < 10 mg/dl. 72–96 h: Biochemical elevations peak, and can progress to acute liver failure or rapid and full recovery	Presentation is often delayed, but still see rapid rise in ALT to > 1000 IU/L, associated with rise in INR. Comorbid conditions, such as alcohol use, can affect total bilirubin levels. Eventually, liver injury can progress to acute liver failure or recovery
Serum APAP level	Use modified Rumack-Matthew nomogram to estimate risk of hepatotoxicity	Often undetectable at initial presentation. APAP-protein adducts useful but assay not commercially available
Excluding other causes of acute liver injury	Review clinical history to exclude risk factors for hepatic ischemia and perform tests for acute viral hepatitis	
Management		
GI decontamination	Activated charcoal (1 g/kg, max dose 50 g) if within 4 h of ingestion. Gastric lavage also used in some cases[175]	Usually not helpful nor recommended
N-acetylcysteine	Oral dosing: 140 mg/kg load followed by 70 mg/kg every 4 h; antiemetics as needed. Intravenous dosing[176]: preferred if intolerant of oral intake/ileus or pregnant; telemetry monitoring recommended 150 mg/kg load over 15–60 min, followed by 50 mg/kg (12.5 mg/kg/h) over the next 4 h then 100 mg/kg (6.25 mg/kg/h) over 16 h thereafter (total 300 mg/kg over 24 h). For those with evidence of liver injury, treatment is extended at 6.25 mg/kg/h until ALT is decreasing and INR is < 2	
Evidence of acute liver failure (coagulopathy and encephalopathy)	Close monitoring in intensive care unit and consider prompt referral to a liver transplant center	

MANAGEMENT: I-DILI

- Rule out other etiologies
- Discontinue culprit medication
- Transfer or refer for liver transplantation
  - High INR, mental status changes
- Supportive care

STEROIDS IN I-DILI

- No RCTs to evaluate efficacy and safety
- In limited retrospective studies:
  - Steroid Rx may be a/w improvements in:
    - Women
    - Hepatocellular injury
    - Autoimmune like hepatitis
    - Hypersensitivity features
  - Steroid Rx not a/w improvement &/or a/w increase adverse events

Ma J, Gu J, Lammert C, et al. Gastroenterology 2020:158(6): S-1304
Hu PF, Wang PQ, Chen H. et al. J Dig Dis 2016; 17(9):618

IV NAC IN NON-ACETAMINOPHEN ALF

Prospective, double blind trial

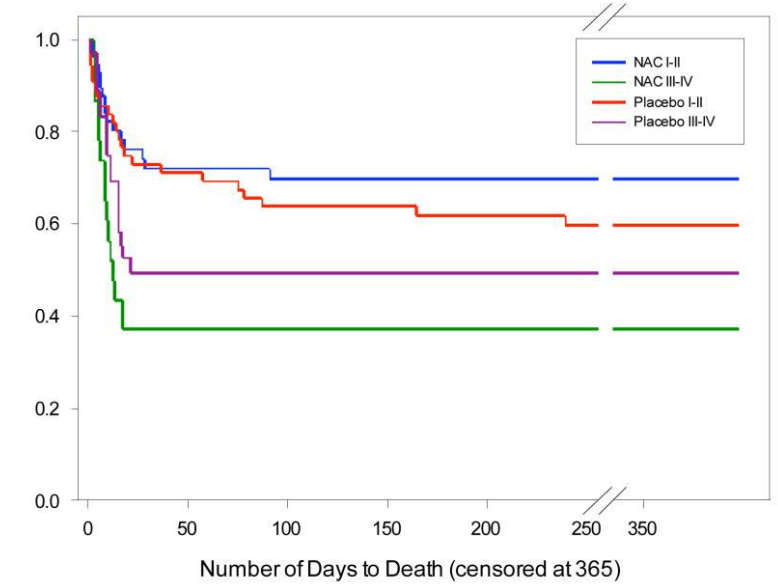
- 1^0 – Survival at 3 weeks
- 2^0 – Tx free survival, rate of Tx

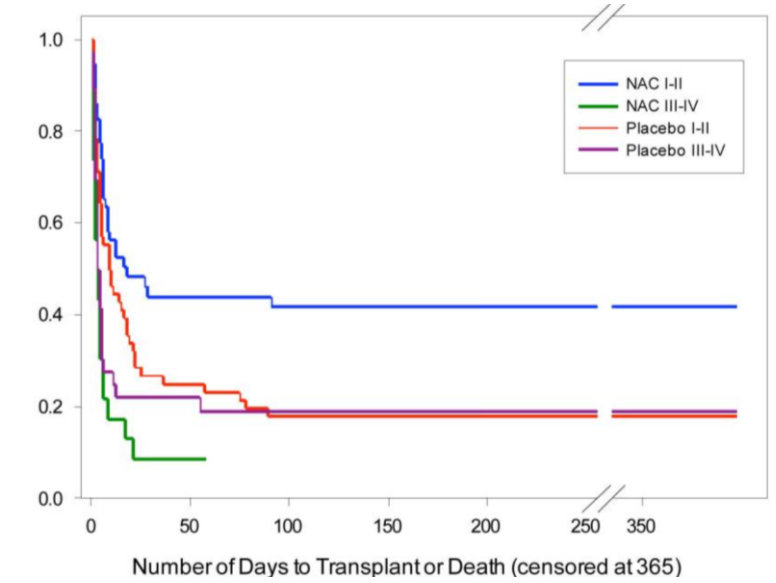
Results

- Placebo n = 92, NAC n = 81

Etiology of ALF

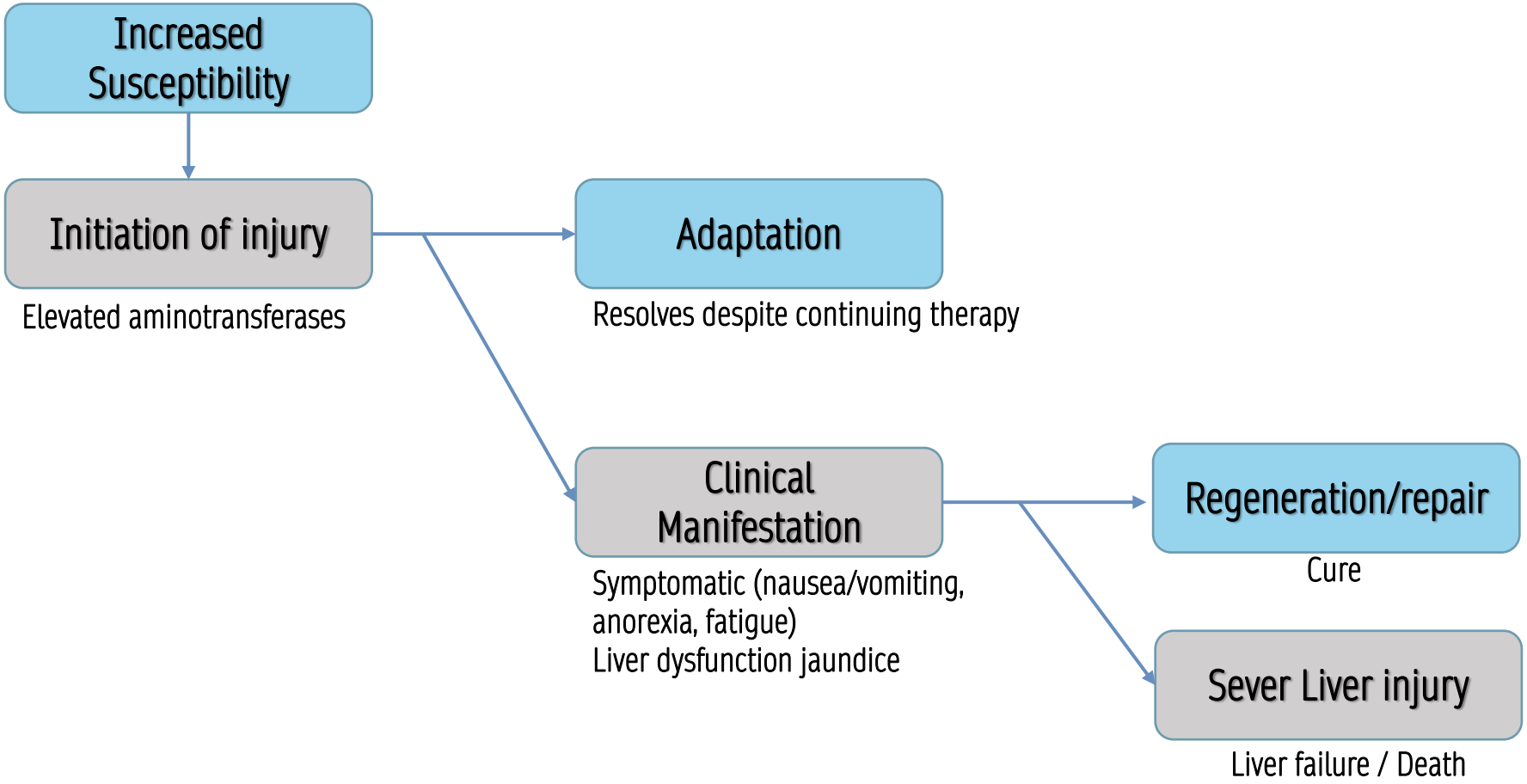
- DILI = 45
- AIH = 26
- HBV = 37
- Indeterminant = 41



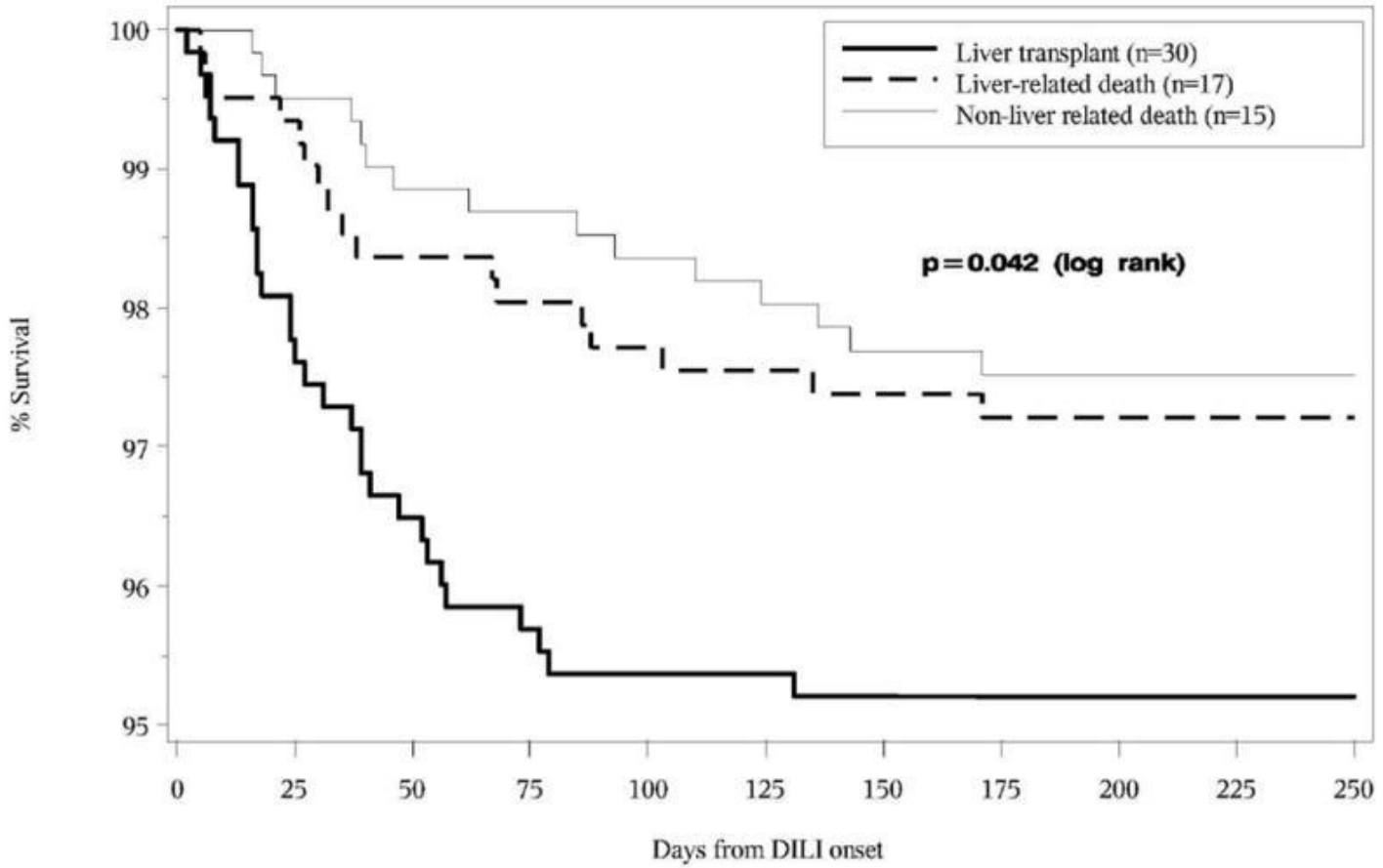


Lee WM, et al, Gastroenterology. 2009 Sep;137(3):856-64, 864.e1

DEVELOPMENT & PROGRESSION OF I-DILI



CLINICAL COURSE OF DILI CAN BE SEVERE



- 1 in 10 patients die or undergo liver transplantation within 6months of onset
- 1 in 5 of the remaining patient have persistent liver injury at 6months

Fontana RJ, et al. Gastroenterology 2014 Jul; 147(1):96

TB DILI

Asymptomatic

ALT 40 – 100 IU/L

(Continue TB treatment)

Symptomatic
(nausea, vomiting, abdominal pain, malaise, anorexia, right upper quadrant tenderness, jaundice)

ALT 100 – 200 IU/L

(Monitor weekly for Jaudice & other symptoms and signs of DILI)

ALT > 100 or T.Bil > 34

ALT > 5x
(>200IU/L)

Admit patient

STOP TB treatment and other hepatotoxic drugs
(e.g. co-trimoxazole, fluconazole, amoxicillin-clavulanic acid)

Calculate ratio

Follow up 1/52

ALT improving

- Stop Monitoring
- F/u in 1/12 or if symptoms re-appear

ALT unchanged or increased

- Continue weekly monitoring x 4 consecutive weeks
- If ALT > 200 or T.Bil >34 or symptoms develops → Admit & stop TB treatment

Adapted from National HIV & TB HCW Hotline, Medicines Information Centre, Division of Clinical Pharmacology, Faculty of Health Sciences, University of Cape Town, Second edition 2020

TB DILI

DRUG INDUCED LIVER INJURY

1. Hepatitis A IgM, hepatitis B surface antigen, hepatitis B core IgM antibody, hepatitis C antibody
2. Herpes simplex virus PCR
3. Immune reconstitution inflammatory syndrome (IRIS)

Hepatocellular

Cholestatic or Mixed

1.Perform an abdominal ultrasound to exclude obstructive causes of liver dysfunction e.g. lymphoma, disseminated TB with obstruction, extra-hepatic obstruction
2.Sepsis as a contributing factor
3.HIV cholangiopathy
4.IRIS
For mixed pattern also exclude alcohol abuse

Management after admission

- Check INR and blood glucose
- Start TB background regimen:
  - Levofloxacin (15-20mg/kg daily, max 1000mg) +
  - Ethambutol (800-1200mg daily) +
  - Linezolid (600mg daily).
- Avoid linezolid if Hb<8.
- Terizidone (10-15mg/kg daily, max 750mg) and amikacin (15mg/kg daily, IV/IM) are also options if any of the above are contra-indicated/unavailable.
- Avoid amikacin if eGFR < 60 mL/min or INR raised.
- If levofloxacin not available, moxifloxacin (400mg daily) can be used, but its concentrations are reduced by rifampicin and it has a higher risk of QT interval prolongation.

Adapted from National HIV & TB HCW Hotline, Medicines Information Centre, Division of Clinical Pharmacology, Faculty of Health Sciences, University of Cape Town, Second edition 2020

TB DILI

Once the ALT is < 100 IU/L, bilirubin is normal and patient is asymptomatic, consider rechallenge of TB drugs.

DO NOT rechallenge first-line TB treatment if the patient presented with acute liver failure (jaundice with encephalopathy and/or coagulopathy)

Continue background regimen

Day 1

- Then start Rifampicin 10mg/Kg (600mg Max)

Day 3

- Repeat ALT
- If normal, Add INH 5mg/kg (300mg Max) on day 4 or-6

Day 7

- Repeat ALT
- If normal, consider adding Pyrazinamide 25mg/kg/day on day 8
- Consider Pyrazinamide rechallenge in cases of severe forms of TB or resistance/intolerance to rifampicin and isoniazid

Day 10

- Repeat ALT
- If ALT < 100 and pyrazinamide re-challenge successful restart RHZE fixed dose combination. Otherwise continue RHE.
- Stop TB background regimen
- Then repeat ALT weekly for 1month

Adapted from National HIV & TB HCW Hotline, Medicines Information Centre, Division of Clinical Pharmacology, Faculty of Health Sciences, University of Cape Town, Second edition 2020

TB DILI

Unable to tolerate Rifampicin

STOP rifampicin

Start shorter regimen for rifampicin resistant TB treatment with normal dose INH (total duration 9 months).

Unable to tolerate INH

STOP isoniazid

Pyrazinamide rechallenged successfully (if required for severe forms of TB):

- Continue rifampicin, ethambutol, levofloxacin (preferred)/ moxifloxacin and pyrazinamide for 6 -9 months.

Pyrazinamide not rechallenged:

- Continue rifampicin, ethambutol and levofloxacin (preferred) / moxifloxacin for 9 - 12 months

Unable to tolerate Pyrazinamide

STOP pyrazinamide

Continue rifampicin, isoniazid and ethambutol for 9 months.

Pyrazinamide not challenged

Continue rifampicin, isoniazid and ethambutol for 9 months.

Monitor ALT weekly for 4 weeks after rechallenge.

Adapted from National HIV & TB HCW Hotline, Medicines Information Centre, Division of Clinical Pharmacology, Faculty of Health Sciences, University of Cape Town, Second edition 2020

ARV DILI

- All ARV classes have been a/w hepatotoxicity – most commonly NNRTIs.
- Mild ALT elevations occur commonly and in general are transient.
- DILI occurs more commonly with nevirapine than efavirenz.
- Lopinavir/ritonavir and dolutegravir can also rarely cause DILI.
- Abacavir, tenofovir, emtricitabine and lamivudine do not cause DILI.

ARV DILI

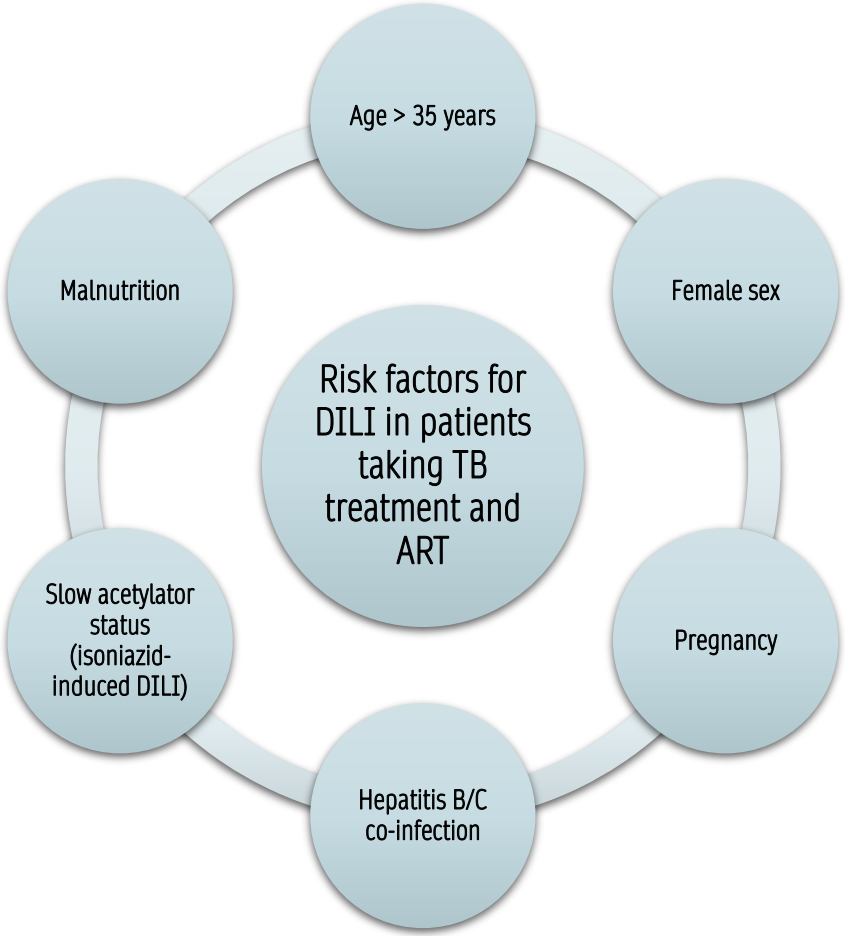
- EFV recognized as an infrequent cause of DILI.
  - Can present with severe jaundice and raised INR and Liver Bx showing 'sub-massive necrosis'
  - May not be a/w hypersensitivity (rash) rather often a/w jaundice and abdominal pain
  - Overall mortality was 11%.
  - Generally after a longer duration on EFV 3-6months.
  - Usually takes > 6months for LFTs to normalize after stopping EFV
  - EFV switched to an alternative drug (e.g. DTG).

ARV DILI

- Routine LFT monitoring in patients on ART → not advised
- Monitor for symptoms and signs of hepatitis (nausea, vomiting, right-sided abdominal pain, or jaundice). If + → do ALT / Bil

Elevation	< 2.5 x ULN	2.5-5 x UNL	> 5x UNL
ALT	Repeat at 1-2 weeks	Repeat at 1 week	Discontinue relevant drug(s)
Bilirubin	Repeat at 1 week	Discontinue relevant drug(s)	Discontinue relevant drug(s)
* Any elevations with symptoms of hepatitis (n/v, RUQ pain) should be regarded as an indication to discontinue the relevant drugs			

TB + ARV DILI



ALT > **100** + symptomatic OR
ALT > **200** OR
Total bilirubin > **34**

Stop TB treatment

Start TB background regimen:

- Levofloxacin (15-20mg/kg daily, max 1000mg) +
- Ethambutol (800-1200mg daily) +
- Linezolid (600mg daily).

Complete TB drug rechallenge before restarting ART

Adapted from National HIV & TB HCW Hotline, Medicines Information Centre, Division of Clinical Pharmacology, Faculty of Health Sciences, University of Cape Town, Second edition 2020

TB + ARV DILI

DILI developed on a nevirapine-based regimen

- DO NOT rechallenge the patient with nevirapine.
- If previously on nevirapine and life-threatening DILI (transaminitis with bilirubin > 34 μmol/L with encephalopathy and/or coagulopathy) commence a protease inhibitor or integrase inhibitor.
- In less severe cases that were previously on nevirapine, commence efavirenz.
- Monitor ALT every 2 weeks for 2 months.

DILI developed on efavirenz-based regimen

- DO NOT rechallenge efavirenz, even with an asymptomatic DILI
- If previously on efavirenz, switch to a protease inhibitor or an integrase inhibitor.
- Monitor ALT every 2 weeks for 2 months.

Adapted from National HIV & TB HCW Hotline, Medicines Information Centre, Division of Clinical Pharmacology, Faculty of Health Sciences, University of Cape Town, Second edition 2020

STATINS IN DILI

- DILIN studied statin associated DILI
  - 22/1188 patients had DILI from statins
  - Median ALT 892, ALP 358 and Tbil 6.1
- Lack of distinctive phenotype
  - Mild and severe, short and long latency, Cholestatic and hepatocellular
- Clinically significant liver injury rare, dose dependent
- Individuals with underlying liver disease are not at increased risk for statin hepatotoxicity

Russo MW, et al. Hepatology; 2014 Aug:60(2):679

AUTOIMMUNE HEPATITIS DUE TO DILI

- AIH-DILI is a clinical syndrome resembling AIH
  - Presence of autoantibodies, IgG
  - Response to glucocorticoid steroid treatment
- Culprits: Nitrofurantoin, Minocycline, TNF alpha antagonists

Features	Drug-induced autoimmune-like hepatitis (%)	Classical autoimmune hepatitis (%)
Female propensity	80–90 [27, 97, 113, 118, 119]	>70 [54, 55, 105]
Age ≥ 60 years	18 [33, 51]	20 [236–238]
Acute onset	≤66 [113, 116]	16 [239]
Asymptomatic	≤39 [116]	25–34 [19, 20]
Jaundice	27–73 [27]	46–69 [239, 240]
Hypersensitivity (fever, rash, eosinophila)	12–28 [31–34, 106, 113]	≤18 [105]
Autoantibodies	96 [27]	≤12 [27]
Hypergammaglobulinemia	90 [27, 31]	97 [3, 28]
Cirrhosis at presentation	0 [27]	16–28 [5, 241, 242]
Progression to cirrhosis	0 [27]	7–40 [241, 243, 244]
Response to corticosteroids	96 [27]	90 [27, 214, 245]
Relapse after drug withdrawal	0 [27]	60–87 [6, 7, 246]

Czaja, A.J. Drug-Induced Autoimmune-Like Hepatitis. Dig Dis Sci 56, 958–976 (2011)

IMMUNE-MEDIATED DILI

- Type of Indirect DILI
- Immune-mediated hepatitis, pancreatitis, and cholangitis are found in patients receiving or who have previously received immune checkpoint inhibitors.
- Nivolumab is an antibody directed at programmed cell death protein 1 (PD-1), for the second-line treatment of advanced HCC.

Hsu C, et al. The Oncologist 2020;25:105–111

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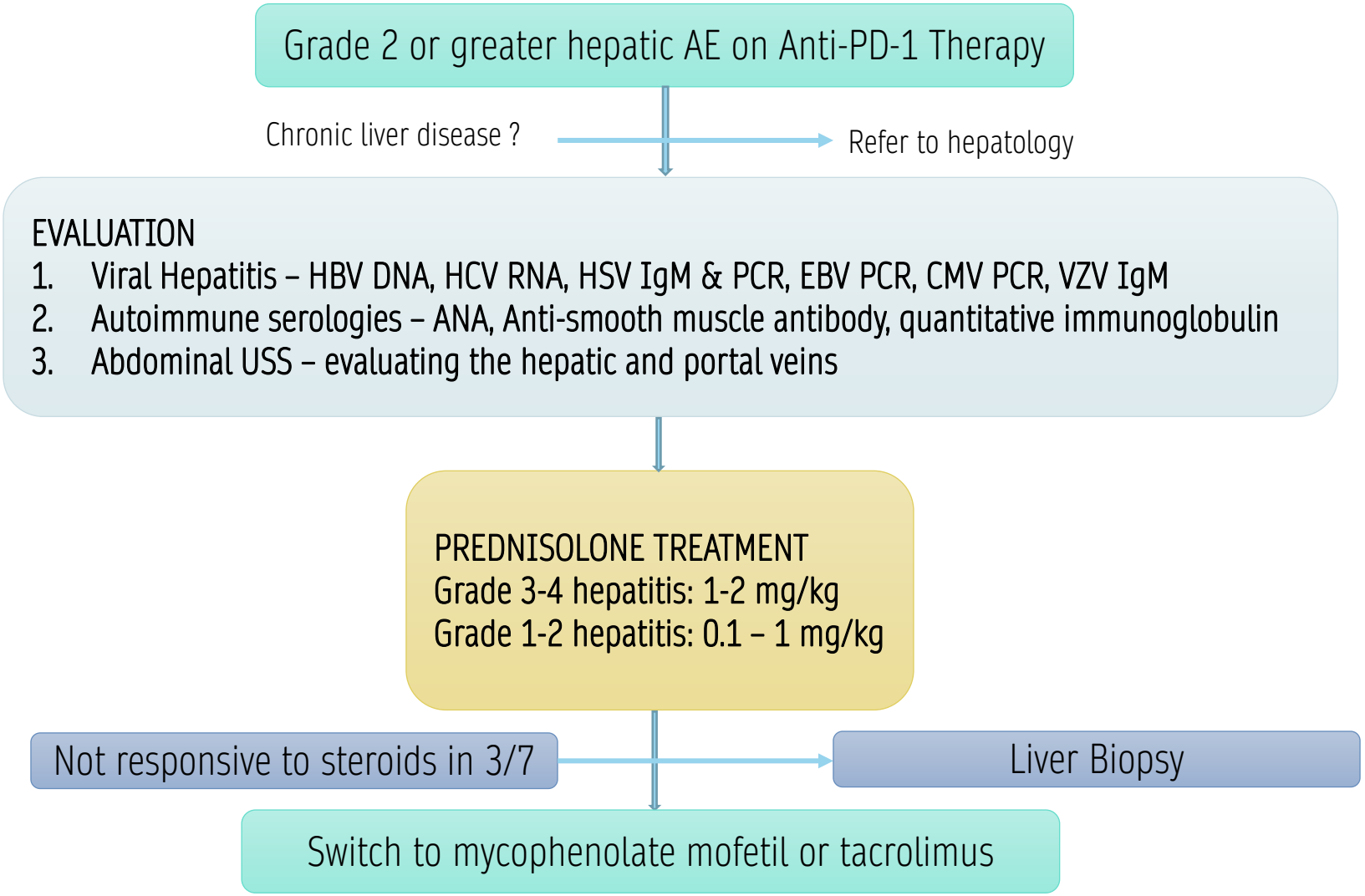

Workup and treatment of immune mediated hepatitis

Hsu C, et al. The Oncologist 2020;25:105–111

IMMUNE-MEDIATED DILI

	Withhold nivolumab for any of the following:	Permanently discontinue
Hepatitis in patients without hepatocellular carcinoma	AST/ALT 3–5 × ULN Total bilirubin 1.5–3 × ULN	AST/ALT > 5 × ULN Total bilirubin > 3 × ULN
Hepatitis in patients with hepatocellular carcinoma	Baseline AST/ALT is normal and increases to 3–5 × ULN Baseline AST/ALT 1–3 × ULN and increases to 5–10 × ULN Baseline AST/ALT 3–5 × ULN and increases to 8–10 × ULN	AST/ALT > 10 × ULN or Total bilirubin > 3 × ULN

Guideline to withhold or discontinue immune checkpoint inhibitor treatment

Hsu C, et al. The Oncologist 2020;25:105–111

IMMUNE-MEDIATED DILI

	Autoimmune hepatitis	Immune-mediated hepatitis
Liver enzyme abnormality	AST and ALT elevated	AST and ALT elevated
Autoimmune serologies •ANA •ASMA •Serum IgG	Mostly positive ANA > 1:80 ASMA > 1:40 Serum IgG elevated	Mostly negative Described Isolated ANA positive
Pathology	•Interface hepatitis •Lymphocytic or lymphoplasmacytic portal inflammatory infiltrate •Hepatocyte rosette formation •Advanced fibrosis	•Panlobular hepatitis •Zone 3 hepatitis •Mixed inflammatory infiltrates include T lymphocytes, histiocytes, scattered plasma cells, and eosinophils. •Central vein endotheliitis •Vanishing bile duct syndrome
Treatment	Steroids and azathioprine	Steroids, mycophenolate mofetil, tacrolimus, antithymocyte immunoglobuin

Difference between the diagnosis and treatment of autoimmune hepatitis and immune-mediated hepatitis

Hsu C, et al. The Oncologist 2020;25:105–111

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Gastroenterology Foundation of sub Saharan Africa

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