DILI på VIVU

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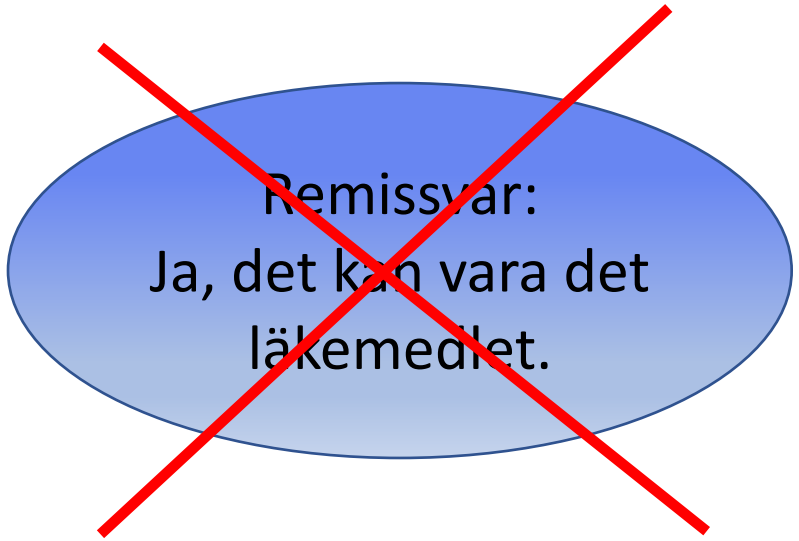
Litteratur

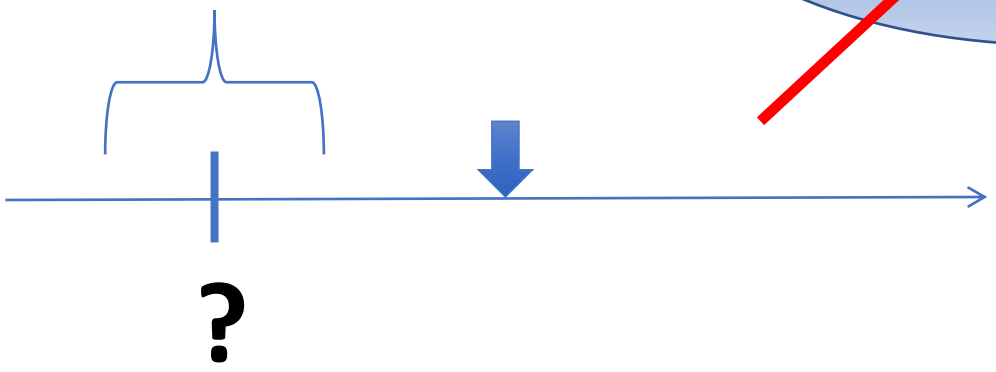
- *EASL practical guidelines, DILI,* J of Hepatology 2019
- Review: *Prescribing medications in patients with cirrhosis, a practical guide* J.H. Lewis, J.G Stine Alimentary Pharmacology and Therapeutics 2013; 37: 1132-1156
- *Drug induced liver injury: an update* Garcia-Cortez, Andrade, et al Archives of toxicology 2020
- LiverTox http://livertox.ncbi.nlm.gov

Hur hittar man sin DILI?

- Misstänk- nyupptäckt leverskada
- När rutinpaketet inte visar något
- Ifrågasätt dina kollegor…!

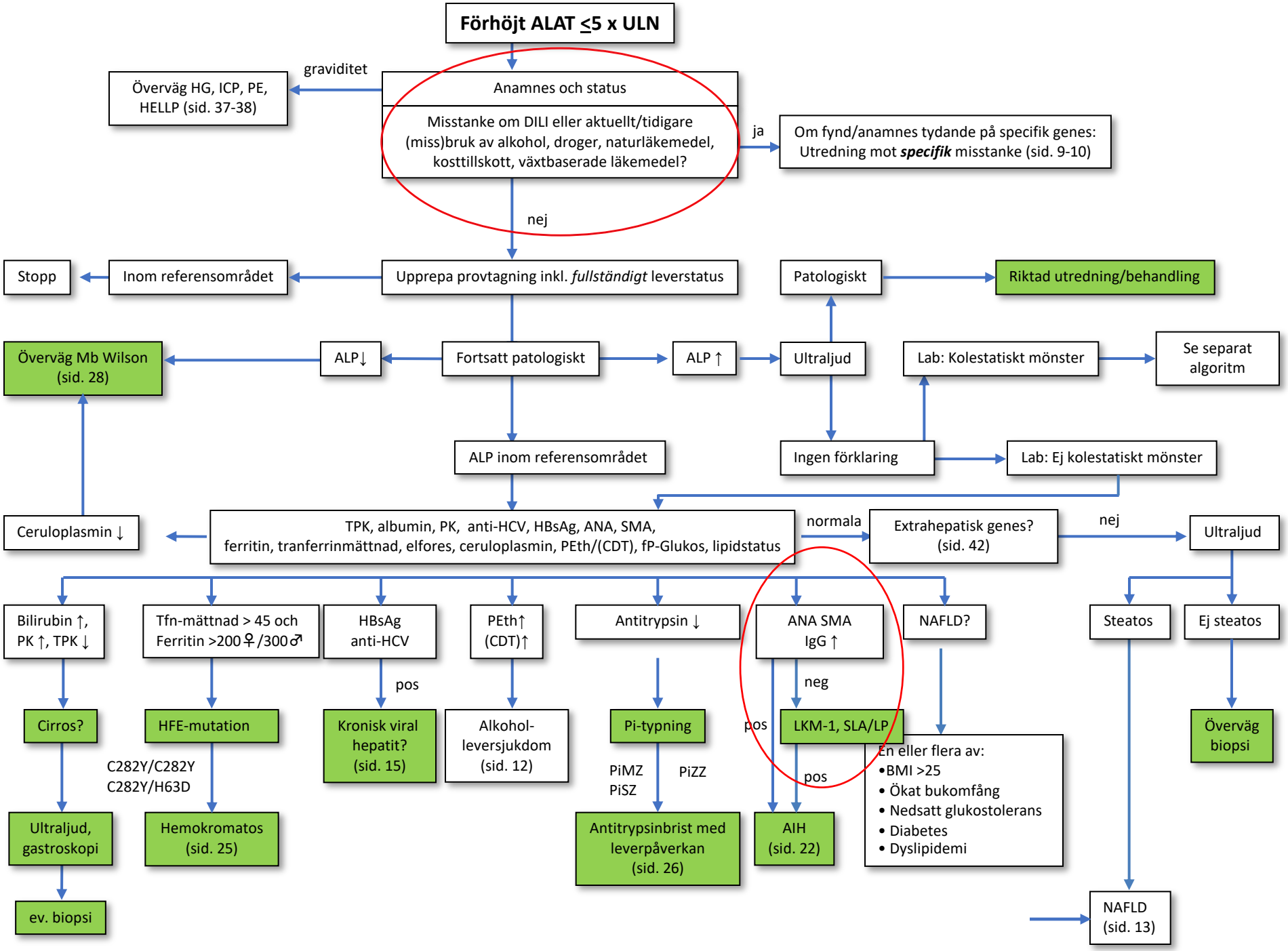
- Se på tidssambandet





Vill man vara petig- gå igenom ALLT, räka ut kvoter, R-värden, plotta tabell/kurva…Livsviktigt läkemedel för patienten??

…för vi har ett ess i rockfickan…


Förhöjt ALAT ≤5 x ULN
graviditet
Överväg HG, ICP, PE, HELLP (sid. 37-38)
Anamnes och status
Misstanke om DILI eller aktuellt/tidigare (miss)bruk av alkohol, droger, naturläkemedel, kosttillskott, växtbaserade läkemedel?
ja
Om fynd/anamnes tydande på specifik genes: Utredning mot ***specifik*** misstanke (sid. 9-10)
nej
Stopp
Inom referensområdet
Upprepa provtagning inkl. *fullständigt* leverstatus
Patologiskt
Riktad utredning/behandling
Överväg Mb Wilson (sid. 28)
ALP↓
Fortsatt patologiskt
ALP ↑
Ultraljud
Lab: Kolestatiskt mönster
Se separat algoritm
ALP inom referensområdet
Ingen förklaring
Lab: Ej kolestatiskt mönster
Ceruloplasmin ↓
TPK, albumin, PK, anti-HCV, HBsAg, ANA, SMA, ferritin, tranferrinmättnad, elfores, ceruloplasmin, PEth/(CDT), fP-Glukos, lipidstatus
normala
Extrahepatisk genes? (sid. 42)
nej
Ultraljud
Bilirubin ↑, PK ↑, TPK ↓
Tfn-mättnad > 45 och Ferritin >200♀/300♂
HBsAg anti-HCV
PEth↑ (CDT)↑
Antitrypsin ↓
ANA SMA IgG ↑
NAFLD?
Steatos
Ej steatos
pos
neg
Cirros?
HFE-mutation
Kronisk viral hepatit? (sid. 15)
Alkohol-leversjukdom (sid. 12)
Pi-typning
pos
LKM-1, SLA/LP
Överväg biopsi
C282Y/C282Y
C282Y/H63D
PiMZ
PiSZ
PiZZ
pos
En eller flera av:
•BMI >25
• Ökat bukomfång
• Nedsatt glukostolerans
• Diabetes
• Dyslipidemi
Ultraljud, gastroskopi
Hemokromatos (sid. 25)
Antitrypsinbrist med leverpåverkan (sid. 26)
AIH (sid. 22)
ev. biopsi
NAFLD (sid. 13)

Typer av DILI

	Direkt	idiosynkratisk	Indirekt
mekanism	toxisk	Mitokondrieskada, immunkrig	Effekt av läkemedlet
dosberoende	Ja	Nej (tröskelvärde?)	Generellt inte
fördröjning	Kort-dagar	Dagar –månader (2-3 v?)	Veckor till månader
förekomst	hög	låg	medium
förutsägbar	ja	nej? Ej reexponering	Ibland
Läkemedel	Paracetamol, aspirin, nikotinsyra, kokain Amiodaron, MTX -iv	Amoxicillin-clavulanat, isoniazid, makrolider, fluorokinoloner, statiner….	Immune checkpoint inhibitors, proteinkinas inhibitors, iv-boluskortison, monoklonala ak

Efter*: Drug induced liver injury: an update* Garcia-Cortez, Andrade, et al Archives of toxicology 2020

Idiosyncratic DILI: a complex drug–host interaction[1]

Drug properties
Physicochemical
Pharmacological
Toxicological

Biophysical effects

Drug

Cellular injury initiation

Pharmacological responses
Reactive metabolites, drug elimination

Toxicological responses
Covalent binding, haptenization, oxidative stress, mitochondrial injury, ER stress

Cell death
Apoptosis, necrosis, DAMP release

Host response to injury insult

Immune/inflammation

Repair ↔ **Tissue injury**

Clinical manifestation and outcome

Possible host factors
Genetic variants
Race/ethnicity
Age
Gender
Reproductive state
Nutrition/alcohol/smoking
Lifestyles
Disease conditions
Medications
Gut flora

1. Chen, et al. J Hepatol 2015;63:503–14. EASL CPG DILI. J Hepatol 2019;70:1222–61.

Diagnosis: a stepwise approach - EASL

Abnormal biochemistry/acute hepatitis

↓

DILI suspicion

Features supporting toxic aetiology
Skin involvement, kidney injury, previous DILI episodes

↓

Careful enquiry of exposure to HDS, drugs, OTC drugs*

Kalender!
NPÖ

Potential pitfalls
Lack of information (eg. dose, duration), several medications, hidden HDS and OTC drug intake

Discontinue non-essential drugs/HDS treatment

Search in hepatotoxicity resources (Liver tox)

www.livertox.nih.gov

↓

Calculate biochemical pattern of liver injury

$$\frac{\mathbf{ALT/ULN}}{\mathbf{ALP/ULN}}\ (\mathbf{R})$$

Hepatocellular	Mixed	Cholestatic
R ≥ 5	2 > R < 5	≤ 2

Search for alternative causes

- Viral infections (HAV, HBV, HCV, HEV, EBV, CMV)
- Alcohol-related liver disease, hepatic ischaemia
- Autoantibody titres, ↑ IgG

- Benign/malignant biliary obstruction
- Primary biliary cholangitis
- Primary sclerosing cholangitis

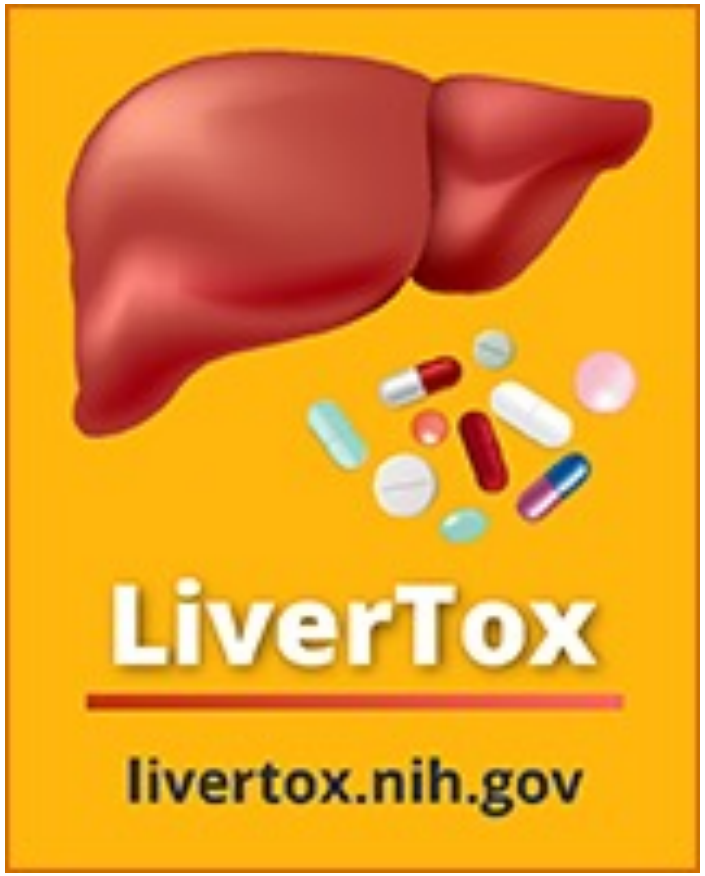
↓

Consider liver biopsy if
- Negative or incomplete rechallenge
- Acute or chronic atypical presentation†
- Autoimmune hepatitis

Rechallenge-???

*record start and stop dates;
†hepatic vascular disease, chronic hepatitis, fibrosis, microvesicular steatosis
EASL CPG DILI. J Hepatol 2019;70:1222–61.

Esset i rockfickan??



LiverTox: Clinical and Research Information on Drug-Induced Liver Injury [Internet].

< Prev Next >

Show details

Drug Records

Search this book

Nitrofurantoin

Last Update: May 1, 2020.

OVERVIEW

Introduction

Nitrofurantoin is an oral antibiotic widely used either short term to treat acute urinary tract infections or long term as chronic prophylaxis against recurrent infections. **Nitrofurantoin** is one of the most common causes of drug induced liver disease and can cause either an acute or a chronic hepatitis-like syndrome that can be severe and lead to liver failure or cirrhosis.

Background

Structurally, **nitrofurantoin** (nye" troe fure an' toyn) is a nitrated 5-member furan ring with a side chain of hydantoin. **Nitrofurantoin** inhibits several bacterial enzyme systems and has broad antibacterial activity. Its precise mechanism of action is not known. Importantly, antibacterial resistance to **nitrofurantoin** is rare, which makes it an attractive choice for long term treatment. In addition, **nitrofurantoin** is well absorbed orally and is rapidly excreted in the urine

Hepatocellulär skada - 2/3

- ASAT och ALAT > 2 x övre normalgränsen

Eller:

- Kvot ≥ 5 ALT / ALP- multipler av normalt*

*Ex	ALAT 9,3	ALP 3,6	9,3/0,7 = 13,3	3,6/1,8 =2	13,3/2=6,65

Hepatocellulär skada med bilirubinökning indikerar allvarlig leverskada med ökad mortalitet/ transplantation

Kolestatisk skada 1/3

- ALP > 2 x normalvärdet

eller kvoten ALT / ALP-

(multipler av normalt) >2

Blandbild

- ALAT > 2 x normalvärdet

och

- Kvoten > 2 och < 5

Vid kolestatisk eller blandbild större risk för utveckling av kronisk skada, än vid hepatocellulär

Andrade Hepatology 2006

R- värdet

- 83% faller inom ett av 5 mönster:
  - akut hepatit (54-58%) - vanligaste orsaken i världen till ALF
  - kronisk hepatit
  - akut kolestas (20-23%)
  - kronisk kolestas
  - kolestatisk hepatit- blandmönster (20-23%)
- Korrelation mellan histologi och klinisk bild hyfsad, men också overlap i lab mht R-värdet.
  - Kleiner Hepatology 2014 – Chalasani DILIN Gastroenterol 2015

- *R* = (ALAT patient/ULN)/(ALP patient/ULN).
- hepatocellulärt ($R \geq 5$), cholestatic ($R \leq 2$) och blandmönster($R > 2$ and <5).

Table 3 Classification of patterns of liver injury, special phenotypes and DILI syndromes

Hepatocellular DILI	Cholestatic/mixed DILI	Liver tumors	Vascular liver disease
Hepatocellular DILI: ALT ≥ 5 × ULN or R ≥ 5 Diclofenac Flutamide	*Cholestatic:* ALP ≥ 2 × ULN or R < 2 Pure cholestasis (bland or canalicular) Acute cholestasis or hepatocanalicular hepatitis *Mixed DILI:*	*Hepatocellular adenoma/carcinoma:* Estrogens Anabolic androgenic steroids	*Nodular regenerative hyperplasia* *Sinusoidal obstruction syndrome* Azathioprine Oxaliplatin Thioguanine Mercaptopurine Antiretroviral agents *Peliosis hepatis* Anabolic steroids Oral contraceptives tamoxifen Thiopurines
Special syndromes *Drug-Induced autoimmune hepatitis:* Methyldopa, minocycline, nitrofurantoin, diclofenac, biological agents, and statins *Immune mediated Liver injury:* Immune checkpoint inhibitors *Fatty liver disease*	*Vanishing bile duct syndrome:* Ductopenia Chlorpromazine, amoxicillin, carbamazepine, azathioprine, meropenem and flucloxacillin *Secondary sclerosing cholangitis:* Amiodarone, amoxicillin-clavulanate, atorvastatin, infliximab, 6-mercaptopurine a… …venlafaxi…		

Diklofenak
Isoniazid
Flutamide (Eulexin)
Nimezulid (NSAID)

hepato cellulär

Amoxycillin-clavunlanate
Östrogener
Flucloxacillin
azythromycine

Kolestatisk/ mixed

SOS
NRH

AZA
Oxaliplatin (cytostatika)
Thioguanin
Mercaptopurin
Antiretrovirala medel

DILI-AiH:

Metyldopa
Minocycline
NITROFURANTOIN
Diklofenak
Biologiska lm
statiner

Sek. scl kolangit

Amiodaron
Amoxycillin-clavunalate
Atorvastatin
Infliximab
6-mercaptopurine
venlafaxin

…te and

…oate,

Drug-induced liver injury: an update Garcia-Corte… …ology 2020

Steatos - sekundär fettlever till DILI

- Amiodaron
- Metotrexat
- Tamoxifen

- 5-fluorouracil
- irinotecan

Table 5: Most common or well-described DILI agents and the patterns of their liver injury

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

Antibiotics	Latency[a]	Typical pattern of injury/identifying features
Amoxicillin/clavulanate	Short to moderate	Cholestatic injury, but can be hepatocellular; DILI onset is frequently detected after drug cessation
Isoniazid	Moderate to long	Acute hepatocellular injury similar to acute viral hepatitis
Trimethoprim/sulfamethoxazole	Short to moderate	Cholestatic injury, but can be hepatocellular; often with immunoallergic features (e.g., fever, rash, eosinophilia)
Fluoroquinolones	Short	Variable: hepatocellular, cholestatic, or mixed in relatively similar proportions
Macrolides	Short	Hepatocellular, but can be cholestatic
Nitrofurantoin		
Acute form (rare)	Short	Hepatocellular
Chronic form	Moderate to long (months–years)	Typically hepatocellular; often resembles idiopathic autoimmune hepatitis
Minocycline	Moderate to long	Hepatocellular and often resembles autoimmune hepatitis
Anti-epileptics		
Phenytoin	Short to moderate	Hepatocellular, mixed, or cholestatic often with immune-allergic features (e.g., fever, rash, eosinophilia) (anti-convulsant hypersensitivity syndrome)
Carbamazepine	Moderate	Hepatocellular, mixed, or cholestatic often with immune-allergic features (anti-convulsant hypersensitivity syndrome)
Lamotrigine	Moderate	Hepatocellular often with immune-allergic features (anti-convulsant hypersensitivity syndrome)
Valproate		
Hyperammonemia	Moderate to long	Elevated blood ammonia, encephalopathy
Hepatocellular	Moderate to long	Hepatocellular
Reye-like syndrome	Moderate	Hepatocellular, acidosis; microvesicular steatosis on biopsy
Analgesics		
Non-steroidal anti-inflammatory agents	Moderate to long	Hepatocellular injury

Chalasani et al

Immune modulators		
Interferon-β	Moderate to long	Hepatocellular
Interferon-α	Moderate	Hepatocellular, autoimmune hepatitis-like
Anti-TNF agents	Moderate to long	Hepatocellular. Can have autoimmune hepatitis features
Azathioprine	Moderate to long	Cholestatic or hepatocellular, but can present with portal hypertension (veno-occlusive disease, nodular regenerative hyperplasia)
Herbals and dietary supplements		
Green tea extract (catechin)	Short to moderate	Hepatocellular
Anabolic steroids	Moderate to long	Cholestatic; likely contained as adulterants in performance-enhancing products
Pyrrolizidne alkaloids	Moderate to long	Sinusoidal obstruction syndrome/veno-occlusive disease; contained in some teas
Flavocoxib	Short to moderate	Mixed hepatocellular and cholestatic
Miscellaneous		
Methotrexate (oral)	Long	Fatty liver, fibrosis
Allopurinol	Short to moderate	Hepatocellular or mixed. Often with immune-allergic features. Granulomas often present on biopsy
Amiodarone (oral)	Moderate to long	Hepatocellular, mixed, or cholestatic. Macrovesicular steatosis and steatohepatitis on biopsy
Androgen-containing steroids	Moderate to long	Cholestatic. Can present with peliosis hepatis, nodular regenerative hyperplasia, or hepatocellular carcinoma
Inhaled anesthetics	Short	Hepatocellular. May have immune-allergic features±fever
Sulfasalazine	Short to moderate	Mixed, hepatocellular, or cholestatic. Often with immunoallergic features
Proton pump inhibitors	Short	Hepatocellular; very rare

DILI, drug-induced liver injury; TNF, tumor necrosis factor.

[a]Short=3–30 days; moderate=30–90 days; long >90 days.

Chalasani et al: ACG Clinical Guideline: The Diagnosis and Management of Idiosyncratic Drug-Induced Liver Injury

Am J Gastroenterology 2014

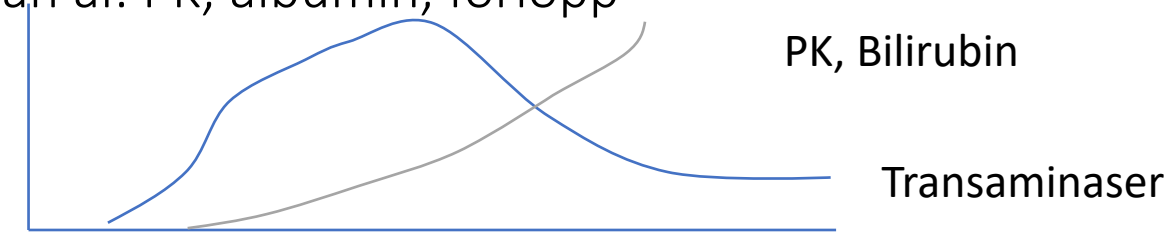
Tänk inte på läkemedel

- Om levervärdena börjar sjunka innan läkemedlet hunnit elimineras
- Vid T1/2 ASAT ≤ 24-36 timmar (undantag = paracetamol - enbart?)
- Vid fluktuerande värden trots konstant behandling
- Vid lätta stegringar som inte progredierar trots fortsatt terapi (undantag = vitamin A, könshormoner, azatioprin)
- Vid isolerad ALP-stegring (undantag = fenemal, fenytoin, karbamazepin)
- Vid isolerad bilirubinstegring (undantag = fucidinsyra, ciklosporin och kanske något ytterligare udda undantag)

Professor Rolf Olsson

Vad bör man göra..? Behandling?

- Hepatocellulär skada- farligast? Hy's law
  - Överväg hur svår skadan är. PK, albumin, förlopp



  - Uteslut väsentliga diffdiagnoser
    - Viral akut hepatit A,B,D, E, ev CMV,HS, VZV
    - Autoimmun hepatit
  - Leta x flera efter orsakande lm
    - Pat får ta fram sin mobil…almanacka…
  - Om ALI+ hotande ALF överväg biopsi, utred som ALF- ta kontakt med LTX center
  - Behandla med acetylcystein (ev kortison)
  - Rapportera!

Specifik terapi:

- **Acetylcystein paracetamol JA**
- **Acetylcystein annan ALF ? Ja..**

- **Cholestyramine:** a short administration may be used to decrease the course of hepatotoxicity induced by very selected drugs, such as leflunomide (Arava, DMARD) and terbinafine (Lamisil)
- **Carnitine** may be used to decrease the course of valproate (Ergenyl) hepatotoxicity
- Kortison? Inte rekommenderat som rutin.

Vad bör man göra..?

- Kolestatisk skada: - långvarig…….
  - Uteslut väsentliga diffdiagnoser
    - Malign obstruktiv gallvägssjukdom – mer än en undersökning
    - sten
    - MRCP, AMA, IgM, IgG4
  - Leta x flera efter orsakande läkemedel/substans
    - Pat får ta fram sin mobil…almanacka…
  - Sätt ut läkemedel som metaboliseras via lever/galla
  - Följ förloppet…….biopsi..?
  - Behandla ev symtom, klåda – rifampicin 150 mg x 1-2 x 1-2
  - Ursofalk? Questran?
  - Rapportera!

Paracetamol- toxisk effekt

Väl kartlagt.

Största delen metaboliseras atoxiskt till glucoronat och sulfatkonjugat och utsöndras i urin.

Liten del metaboliseras dock av P450 till N-acetyl-p-benzoquinoneimin, **NAPQI**. Denna intermediär konjugeras snabbt till reducerat glutation, varvid den detoxikeras men **glutation förbrukas**.

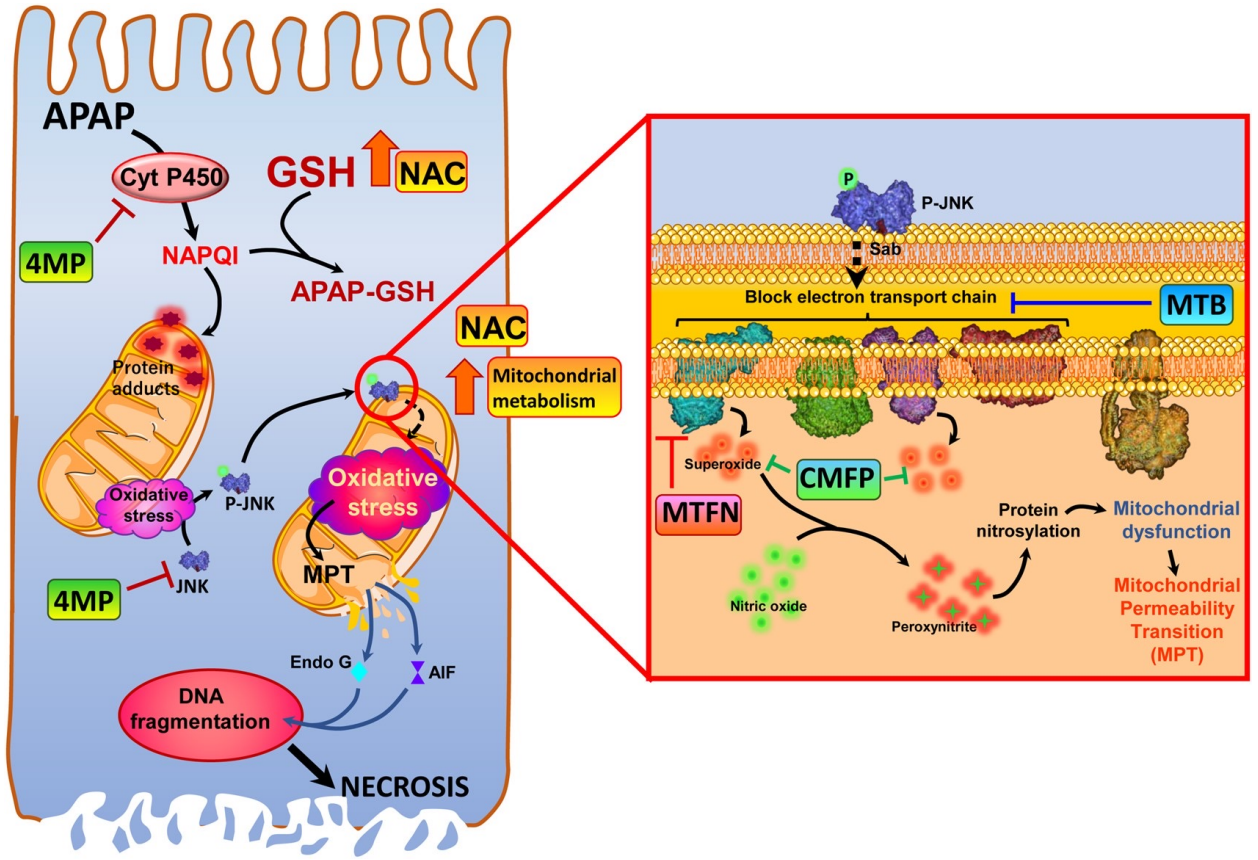
Glutation saknas även vid svält, anorexi, lågt BMI, *kronisk alkoholkonsumtion*. Då kommer större del att metaboliseras till toxisk metabolit, NAPQI.

Sen bildas proteiner som är toxiska och fäster i mitokondriemembranet, ger oxidative stress, JNK- aktivering, blockad av elektrontransportkedjan.

Frisättning av superoxid ger aktivering av peroxynitrit, som är en svårt reaktiv nitrit, som i ett par steg sen leder till "**mitochondrial permeability transition**".

Följden nu blir att apoptosinducerande faktorer bildas och läcker ut i cytoplasman, ledande till **hepatocytdöd**.

Figure 1. Pharmacological targets for acetaminophen hepatotoxicity. Acetaminophen (APAP, N-acetyl-p-aminophenol, ...



Toxicol Sci, Volume 174, Issue 2, April 2020, Pages 159–167

- Pharmacological targets for acetaminophen hepatotoxicity.
- Acetaminophen (APAP, N-acetyl-*p*-aminophenol, paracetamol)-induced liver injury is initiated by its metabolism by cytochrome P450 enzymes to the reactive metabolite N-acetyl-*p*-benzoquinone imine (NAPQI), which depletes cellular glutathione and forms protein adducts, especially on the mitochondria.
- This results in mitochondrial oxidative stress, which results in activation of the mitogen-activated protein c-Jun N-terminal kinase (JNK), and its translocation to the mitochondria. On the mitochondria (inset) phosphorylated JNK binds to the outer membrane protein Sab, and initiates a blockade of the electron transport chain, which subsequently induces release of superoxide from respiratory complexes I and III. Superoxide reacts with nitric oxide within mitochondria to form the highly reactive nitrogen species peroxynitrite, which results in protein modification by nitration of tyrosine residues. This amplifies the mitochondrial dysfunction, ultimately causing induction of the mitochondrial permeability transition and release of mitochondrial proteins such as endonuclease G and apoptosis inducing factor into the cytosol.
- Nuclear translocation of these proteins then induces DNA fragmentation, and finally hepatocyte necrosis.
- The standard of care antidote N-acetylcysteine protects against APAP hepatotoxicity by increasing GSH resynthesis, thus replenishing GSH stores, and also facilitating mitochondrial energy metabolism to surmount detrimental effects of protein adduct formation.
- Newer therapeutic interventions have alternate mechanisms of action, with the majority targeting mitochondrial dysfunction, while 4-methylpyrazole acts upstream, inhibiting cytochrome P450-mediated NAPQI formation as well as inhibiting JNK activation.
- Calmangafodipir functions as a superoxide dismutase mimetic, scavenging superoxide to prevent formation of peroxynitrite, whereas metformin inhibits mitochondrial oxidant stress by inhibition of respiratory complex I.
- Methylene blue, however, improves mitochondrial function by bypassing electron transport chain blockade and preventing formation of free radicals.

Toxicol Sci, Volume 174, Issue 2, April 2020, Pages 159–167

DILI med autoimmun bild

- Ökar?
- Kvinnligt kön, ålder, HLA klass associerat
- Kan ha positiv ANA, SMA, LKM1, IgG stegring, interfashepatit i biopsi…
- Nitrofurantoin, örtpreparat, minocyklin, metyldopa, diklofenac, TNF blockad, statiner
- Svårt skilja mot ”vanlig” AIH
- båda kan recidivera
- Ingen cirros i biopsi, långtidsremission efter steroidutsättning- kan tala för DILI-AIH

Delemos, Semin Liver Dis 2014, Castiella, World J Hepatol 2014, Bjornsson Hepatol 2010, Foureau, Clin exp Immunol 2015

Immune Checkpoint inhibitors - behandling av solida tumörer
(mal. melanom, njur, kolorektal, esofaguscancer…)

- Human recombinant ak mot cytotoxiska T celler
- Biverkningar, och immunrelaterade biverkningar; kolit, dermatit, nefrit…

- Hepatit, eller kolestatisk skada
- Kan bli allvarliga, livshotande
- 2-30%
  - Blockerar cytotoxiska T lymfocyter – ipilimumab
  - programmerad celldöd, PD-1, pembrolizumab, nivolumab
  - Programmerad celldödsloigand 1, PD-L1: avelumab, atezolizumab och durvalumab
  - Ipilimumab och nivolimumab i kombination mest hepatotoxiskt
  - Steroider ges, ganska bra evidens

CF - Orkambi, Kalydeco mfl

Transaminasföröjning, kan bli stor ex ASAT 20 ALAT 40….
Än ingen rapporterad ALF

Elexacaftor, Ivacaftor KaftrioR
Tezacaftor
Okänd mekanism trol toxisk/immunogen metabolit
Cytokrom P450- mycket interaktioner

SAFE-T's new liver safety biomarkers

- Nine new liver safety biomarkers supported by the EMA and/or FDA for exploratory use in clinical drug development:

Marker	Application
Total HMGB1	Mechanism (necrosis), prognosis
Hyperacetylated HMGB1	Mechanism (immune activation), prognosis
Osteopontin	Prognosis
Total keratin 18	Mechanism (necrosis), prognosis
Caspase-cleaved keratin 18	Mechanism (apoptosis), prognosis
M-CSFR1	Mechanism (immune activation), prognosis
miR-122	Detection, mechanism (hepatocyte leakage)
GLDH	Detection, mechanism (mitochondrial injury)
SDH	Detection

Kullak-Ublick G. DILI Conference XVII, 2017; Session IV.
EASL CPG DILI. J Hepatol 2019;70:1222–61.

Läkemedel till leversjuka…

Generella hållpunkter:

Om cirrhos:

Sämre nedbrytning av lm

Välj helst kortverkande

Portal hypertension: Tänk på första passageeffekten- biotillgänglighet

Brukar gå bra:

SSRI, statiner, antibiotika, PPI

Värk: inte NSAID

Paracetamol ok om PK ≤ 1,5 ? eller kompenserad cirrhos

MO, sömntabl, bensodiazepiner; ok, men försiktighet om encefalopati!

Metronidazol- låg dos

AKTA njurarna

Leversjukdom kan spela in genom:

Patofysiologisk faktor	**Klinisk konsekvens**
• Minskat blodflöde i levern/ lägre förstapassageeffekt/ porto systemisk shunting	• Ökad biotillgänglighet/s-nivå
• Hypoalbuminemi	• Minskad proteinbindning = högre s-konc
• ascites/ ödem	• Ökad distr volym (vattenlösliga lm)
• Hypertensiv gastropati	• Ändrat (+/-) upptag
• Minskad CYP aktivitet (CYP450)	• Minskad förstapassageeffekt/metabolism
• Minskad biliär clearence	• Ökad S-konc
• Minskad renal clearence	• Ökad S-konc

J H Lewis, J G Stine, Aliment Pharmacol Ther, 2013

Läkemedlets levermetabolism

- läkemedel med hög levermetabolism (=låg biotillgänglighet hos friska):
  - Biotillgängligheten ökar och leverclearence minskar hos cirrhospatienter

    P o läkemedel till dessa: initiala dosen måste minskas

    och underhållsdos måste anpassas oavsett administrationssätt.

- Läkemedel med låg levermetabolism: biotillgängligheten minskas inte, men clearence kan påverkas, varför endast underhållsdos behöver minskas.

  kodein, amiodaron, ciprofloxacin, erytromycin, itraconazole, atorvastatin, pravastatin, simvastatin, tricykl antidepr, omeprazol

- Mittemellan: startdos väljs i nedre intervallet, och underhållsdoser reduceras.


Before
After
In only 6 weeks of drinking
FitTea™ Robert lost $500

Table 3 Characteristics of the 14 main herbs that induced-liver injury

Generic or trade names	Latin name	*n*	Age (mean)	Sex (male) (%)	Country/territory (%)	Symptoms (%)	AST (mean)	ALT (mean)	ALP (mean)	GGT (mean)	BT (mean)	BD (mean)	Biopsy (%)	HILI patterns (%)	Maira and Victorino score (mean)	Treatment (%)	Clinical outcome (%)
He-Shou-Wu; Fo-ti; Shou Wu Pian	*Polygonum multiflorum*	91	46	47 (51.6)	China (54.9), South Korea (28.5)	Jaundice (80), choluria (17.7), fatigue (15.5), hepatomegaly (13.3)	1279	1511	222	264	10.8	6.3	20 (31.7)	Hepatocellular (72.5), cholestatic (18.6), mixed (8.7)	8	Adenosylmethionine (12.3), glutathione (12.3), glycyrrhizin (12.3), polyene phosphatidylcholine (12.3), supportive care (45.8)	Recovery (93.4), chronification (3.3), died (3.3)
Green tea extract	*Camellia sinensis*	90	44	22 (24.4)	Usa (32.5), Spain (19.1), Japan (14.6)	Jaundice (61.4), fatigue (30.4), nausea (27.5), abdominal pain (26)	1715	1870	330	271	12.8	9.2	36 (60)	Hepatocellular (78.8), cholestatic (8.8), mixed (11.1)	9	Liver transplantation (10.5), corticoid (9.4), acetylcysteine (3.1), supportive care (45.8), udca (3.1), supportive care (69.4)	Recovery (91.7), chronification (1.1), died (7)
Kava kava	*Piper methysticum*	62	43	15 (24.1)	Germany (65), United States (21.6), Spain (3.3)	Jaundice (86.8), nausea (47.8), fatigue (34.7)	1206	1605	310	284	19	10	36 (69.2)	Hepatocellular (77.4), cholestatic (9.6), mixed (8)	8	Liver transplantation (23.9), corticoid (4.2), suportive care (57.7)	Recovery (91.9), died (8)
Greater celandine	*Chelidonium majus*	48	49	8 (17)	Germany (81.2), Italy (8.3)	Jaundice (34.2), choluria (31.4), pruritus (28.5), nausea (27.7)	631	1109	321	236	11.5	6.9	34 (79)	Hepatocellular (72.9), cholestatic (6.2), mixed (20.8)	10	Udca (6.1), corticoid (4), glutathione (2), supportive care (87.7)	Recovery (97.9), died (2)
Germander	*Teucriumchamaedrys*	35	49	11 (31.4)	France (28.5), Greece (22.8), United States (14.2)	Jaundice (77.1), nausea (17.1), choluria (17.1), abdominal pain (17.1)	1091	1127	251	183	13.7	9.1	13 (40.6)	Hepatocellular (94.2), mixed (5.7)	12	Udca (15.7), vit K (13.1), liver transplantation (5.2), supportive care (65.7)	Recovery (97.1), died (2.8)
Skullcap	*Scutellaria spp.*	35	54	9 (25.7)	United States (45.7), Australia (14.2), Scotland (11.4)	Jaundice (68), nausea (15.3), choluria (20)	859	1234	227	359	14	NA	12 (67.7)	Hepatocellular (74.2), CHOLESTATIC (5.7), MIxed (14.2)	9	Liver transplantation (11.1), corticoid (2.7), udca (2.7), supportive care (77.7)	Recovery (85.7), died (14.2)
Kratom	*Mitragyna speciosa*	33	36	20 (62)	United States (75), Canada (6.2), Sweden (6.2)	Jaundice (70), choluria (53.3), abdominal pain (43.5), nausea (23.3), fatigue (23.3)	1125	957	304	258	11.7	11.3	11 (39.2)	Hepatocellular (45.4), cholestatic (27.2), mixed (21.2)	11	Acetylcysteine (12.7), udca (7.6), corticoid (5.1), liver transplantation (5.1), supportive care (48.7)	Recovery (90.6), died (9.3)

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Tusanqi or Jusanqi	*Gynura segetum*	29	54	14 (48.2)	China (75.8), Hong Kong (20.6), New Zeeland (3.4)	Ascites (100), hepatomegaly (86.9), jaundice (26)	469	460	NA	NA	1	0.5	1 (50)	Sinusoidal obstruction syndrome (100)	4	Glutathione (6.6), antibiotics (6.6), furosemide (6.6), supportative care (80)	Recovery (50), chronification (22.2), died (27.7)
Garcinia cambogia; Malabar tamarind	*Garcinia gummi-gutta*	29	45	3 (10.3)	United States (39.2), Italy (35.7)	Abdominal pain (56), jaundice (44), nausea (40), vomiting (24), fatigue (16)	1918	1927	243	249	10.9	7.5	12 (50)	Hepatocellular (86.2), cholestatic (10.3), mixed (3.4)	10	Liver transplantation (20.6), acetylcysteine (10.3), corticoid (3.5), supportive care (65.5)	Recovery (96.6), died (3.4)
Ma huang	*Ephedra sinica*	27	44	8 (32)	United States (68), South Korea (12), United Kingdom (8)	Abdominal Pain (72.7), nausea (63.6), jaundice (54.5), fatigue (45.4), hepatomegaly (36.3)	3173	2092	188	161	12.5	NA	10 (55.5)	Hepatocellular (96), mixed (4)	9	Liver transplantation (19.2), corticoid (3.8), urine alkalization (3.8), hemodialysis (3.8), diuretics (3.8), suportive care (65.3)	Recovery (92), died (8)
Chaparral	*Larrea tridentata*	26	44	9 (34.6)	United States (80.7), Australia (7.6), Canada (7.6)	Jaundice (84), abdominal pain (40), fatigue (36), nausea (28), pruritus (24)	1300	1081	189	317	17.7	9.6	10 (43.4)	Hepatocellular (84.6), steatosis (15.3)	11	Corticoid (7.6), liver transplantation (7.6), vit K (3.8), supportive care (80.7)	Recovery (92.3), died (7.6)
Senna; Sene	*Senna spp.*	25	33	5 (21.7)	India (24), Italy (16), Yemen (16)	Jaundice (43.4), abdominal pain (34.7), encephalopathy (20), asthenia (20), choluria (13)	1637	1688	477	128	7.4	5.1	7 (50))	Hepatocellular (84), cholestatic (4), mixed (12)	10	Antibiotics (9.6), vit K (12.9), lactulose (6.4), liver transplantation (3.2), acerylcysteine (3.2), supportive care (58)	Recovery (81.8), died (18.1)
Aloe Vera	*Aloe vera*	22	50	5 (22.7)	South Korea (18.1), Spain (9), Usa (9)	Abdominal pain (50), jaundice (40.9), fatigue (31.8), nausea (27.2)	1762	1300	414	167	10.1	8.7	11 (52.3)	Hepatocellular (86.3), cholestatic (4), mixed (9)	11	Antibiotics (4.1), liver transplantation (4.1), vit K (4.1), hemodialysis (4.1), supportive care (75)	Recovery (85.7), chronification (4.7), died (9.5)
Jin Bu Huan	*Lycopodium serratum*	19	46	2 (10.5)	United States (73.6), Canada (10.5), Italy (10.7)	Fatigue (52.6), hepatomegaly (42.1), pruritus (36.8), jaundice (31.)	596	1057	231	185	7.5	NA	6 (40)	Hepatocellular (84.2), cholestatic (5.2), mixed (10.5)	13	Cholestyramine (15.7), supportive care (84.2)	Recovery (100)

(31.)

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Tack!