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Drug induced liver injury (DILI): update 2018

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Utrecht digestive Center

Universitair Medisch Centrum Utrecht

Disclosures

- No disclosures relevant to this presentation

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DILI and HILI

-Important cause of increased liver biochemistry

-16% persistently abnormal liver values 6 months after withdrawal, 12% after one yr (especially cholestatic pattern, associated with vanishing bile duct).

-

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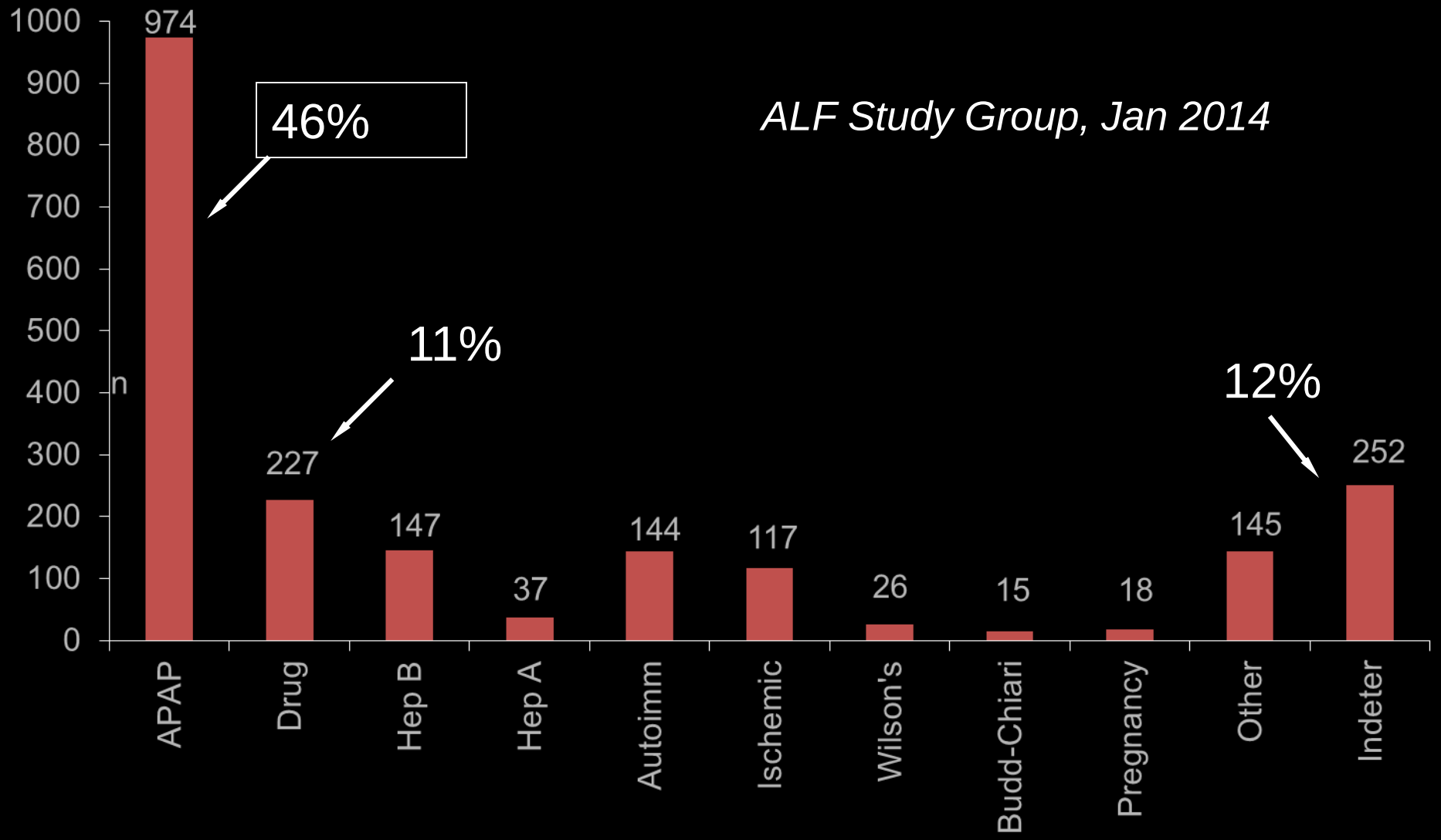
Sarges: drug saf. 2016 in press.

Etiology of Acute Liver Failure in the US

Adult Registry (n = 2,102)



DrugHurt - Claims for T | The National Invokana Settl

Niet beveiligd https://drughurt.com/

DrugHurt.com

As Seen on TV

1-800-378-4487

Invokana Claim?

Suffered a leg, foot, toe amputation or Ketoacidosis?

LEARN MORE »

Defective Hip Implant?

Defective hip implants requiring additional surgery

LEARN MORE »

Hernia Mesh Claim?

Manufacturers failed to warn of hernia mesh implant risks

LEARN MORE »

DrugHurt - Claims for T | The National Invokana Settl

Niet beveiligd https://drughurt.com/

IVC Filter Claim?

These filters often fail resulting injury or death

LEARN MORE »

Xarelto Claim?

Uncontrollable bleeding associated with use of Xarelto

LEARN MORE »

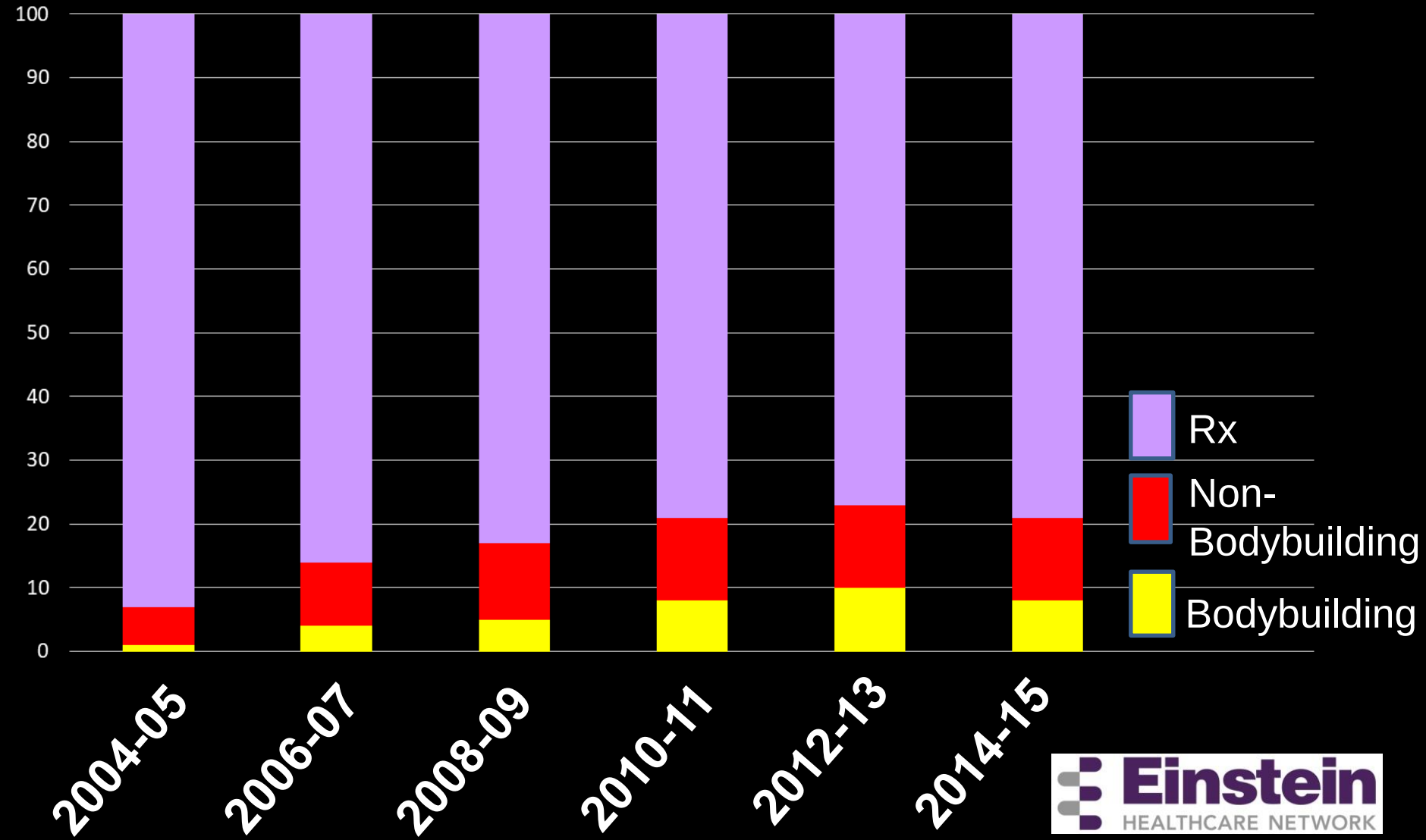
Taxotere Claim?

Chemotherapy resulted in permanent hair loss

LEARN MORE »

HDS as Causes of DILI

Temporal Trends in DILIN



Einstein HEALTHCARE NETWORK

Risk from individual compounds

Drug	Patients treated	Prescriptions (n)	Cases (n)	Risk of DILI among exposed	Per 100,000 (95% CI)
Amox-Clavu	35,252	83,379	15	1 in 2350	43 (24-70)
Diclofenac	54,889	112,801	6	1 in 9148	11 (4-24)
Azathioprine	532	3054	4	1 in 133	752 (205-1914)
Infliximab	593	n/a	4	1 in 148	675 (184-1718)
Nitrofurantoin	5476	12,034	4	1 in 1369	73 (20-187)
Isotretinoin	2169	7978	3	1 in 732	138 (29-404)
Atorvastatin	7385	34,171	2	1 in 3693	27 (4-98)
Doxycycline	32,677	54,232	2	1 in 16,339	6 (1-22)

Bjornsson E, et al. Gastroenterology 2013

DILI: idiosyncratic reaction versus direct hepatoxicity Ends of a spectrum?

-**Idiosyncratic**: most cases of DILI, unpredictable.

relatively rare, multiple hits required (immunologic, genetic, drug metabolism and other factors)

Direct hepatotoxicity: limited nr of drugs, more or less predictable

-**paracetamol**

-alcohol

-tuberculosis drugs (e.g. isoniazid, pyrazinamide, rifampicine)

-HAART therapy (e.g. nevirapine).

-**Methotrexate**

-Valproate

-Vitamin A

-Methimazole

-Nefazodone

-Propoxyphene

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Lewis JH et al. Aliment Pharmacol Ther 2013; 37: 1132-1156

Factors associated with DILI risk

-Dose >50-100 mg/day associated with 5-fold increased risk of idiosyncratic dili.

-Drugs which are hepatically metabolized are more hepatotoxic

-lipophilic drugs at increased risk?

-worse prognosis in hepatocellular injury than cholestatic injury

-acute liver failure and poor prognosis associated with:

Higher MELD score, hepatic encephalopathy, higher age, increase bili, low platelets

- Rechallenge should be avoided (more severe, shorter latency)

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Sarges: drug saf. 2016 in press.

Histochemical Patterns of DILI

Hepatocellular	Cholestatic
ALT AST	AlkPhos

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Hepatocellular vs cholestatic DILI: Calculating R-values

-AST or ALT value divided by ULN (fold elevation) : fold elevation of alkaline phosphatase above ULN.

-R> 5: hepatocellular

-R<2: cholestatic

2<R<5: mixed

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Outline of presentation

-DILI

- Pathogenesis
- diagnosis
- Special cases

-hepatotoxicity in setting of chronic liver disease

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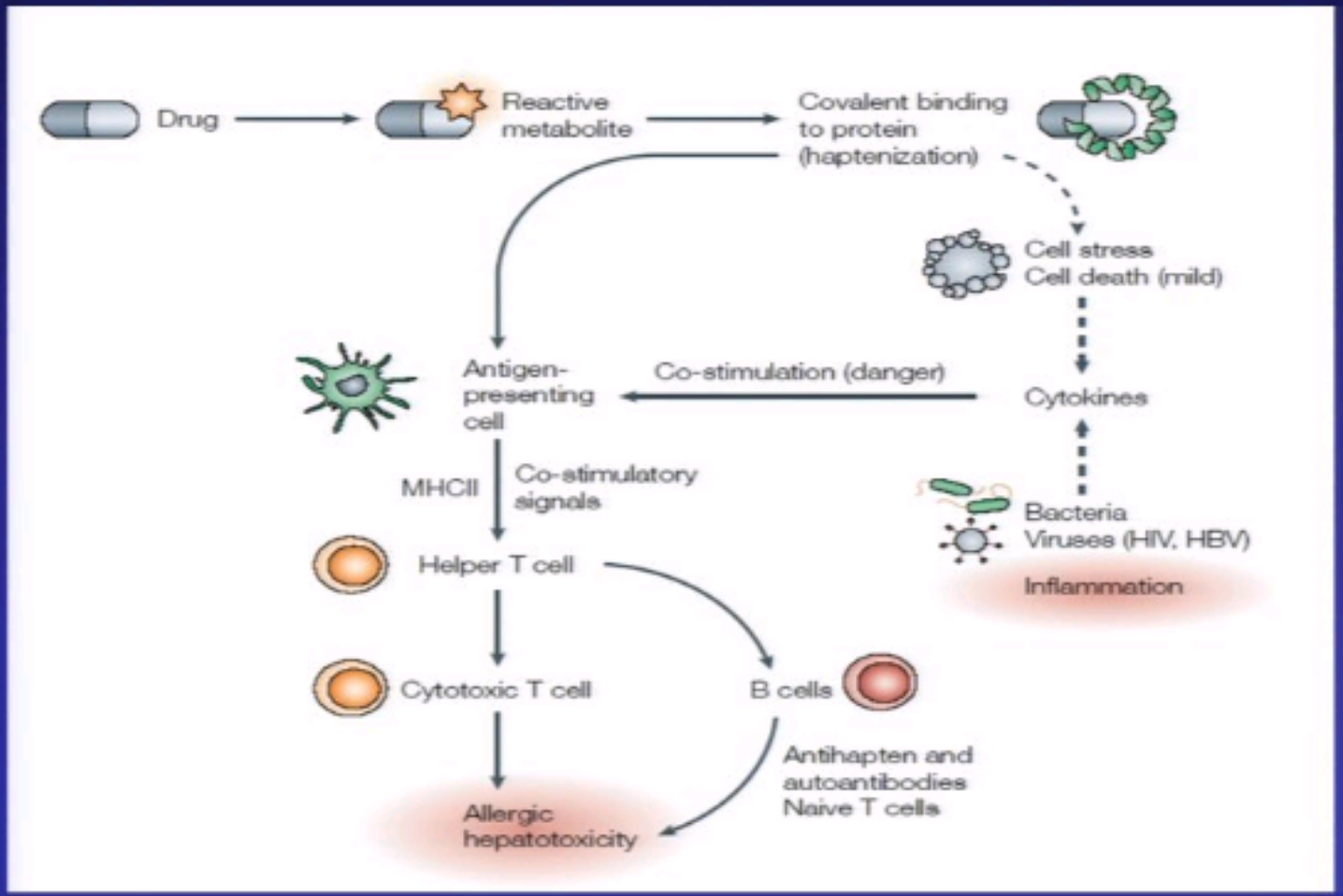
Pathogenesis

DILI: Pathogenesis

- **Applying the Danger Hypothesis* to immune-mediated idiosyncratic hepatotoxicity**

- Figure from Kaplowitz, Nat Rev Drug Disc 2005



** Danger Hypothesis - see:*

•Matzinger. Ann Rev Immunol 1994

GWAS & DILI

- Some success in identifying variants associated with liver injury due to specific compounds – mostly in the HLA region
  - **Abacavir:** only drug not prescribed based on HLA B*5701 testing, high likelihood of hypersensitive skin reaction and DILI.
  - **Flucloxacillin:** HLA B*5701 (OR ~ 80) [DILI risk 1:500 carriers & 1:100 carriers >65 years age)
  - **Amoxy-clavulanate:** HLA DRB1*15:01 & others (OR 2.6-9.3)XX
  - **Minocycline** (HLA B*35:02);
  - **Terbinafine & fenofibrate** (HLA A*33:01)

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Daly AK, et al. Nature Genet 2009; Lucena MI, et al. Gastroenterology 2011; Urban TJ, et al. J Hepatol 2017; Nicolette P, et al. Gastroenterology 2017

Diagnosis

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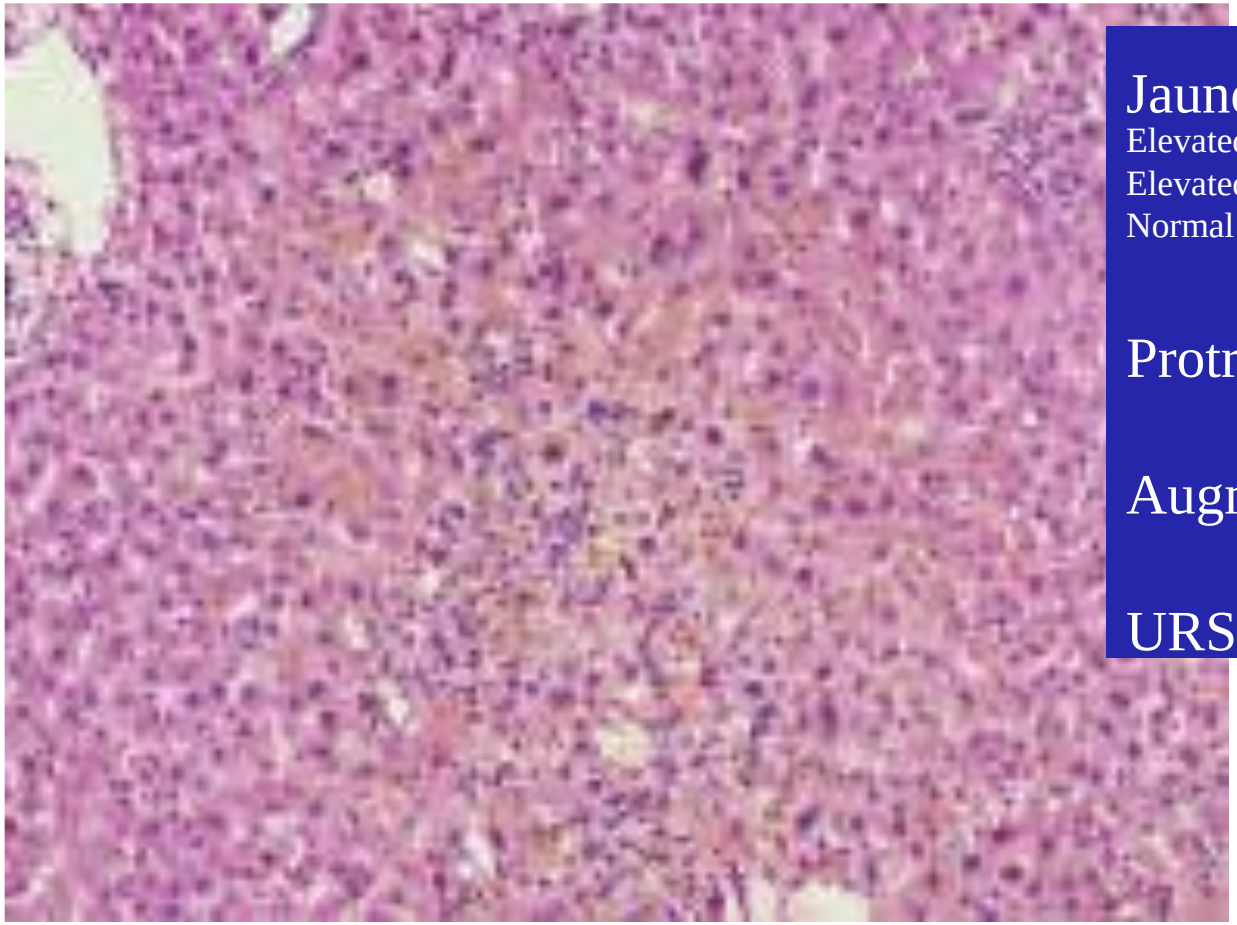
Cholestatic Hepatitis



Jaundice & Itching
Elevated Alk Phos
Elevated ALT/AST
Normal PT/INR

Protracted Course

Augmentin, Macrolides

URSO responsive?

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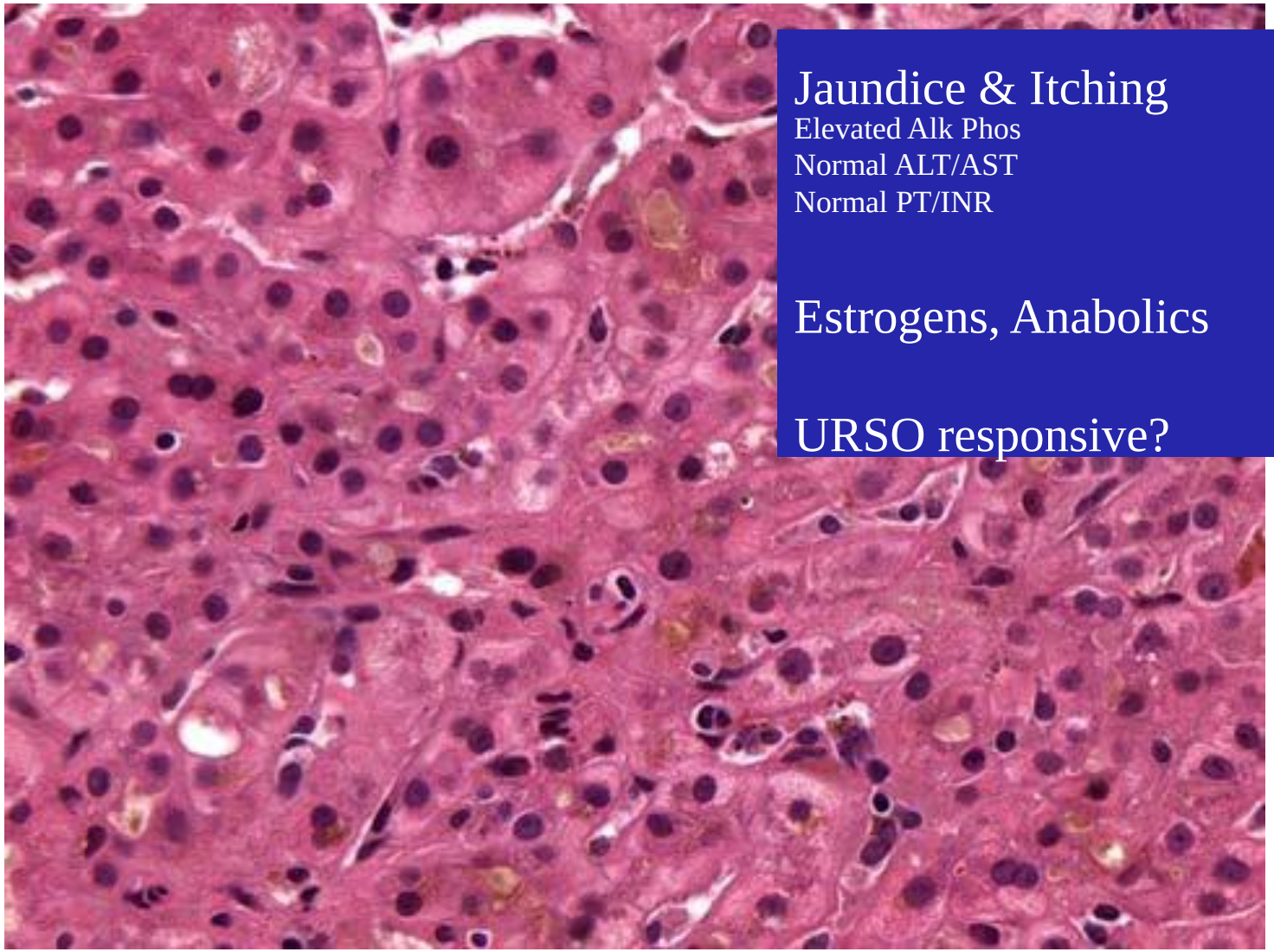
Bland Cholestasis



Jaundice & Itching
Elevated Alk Phos
Normal ALT/AST
Normal PT/INR

Estrogens, Anabolics

URSO responsive?

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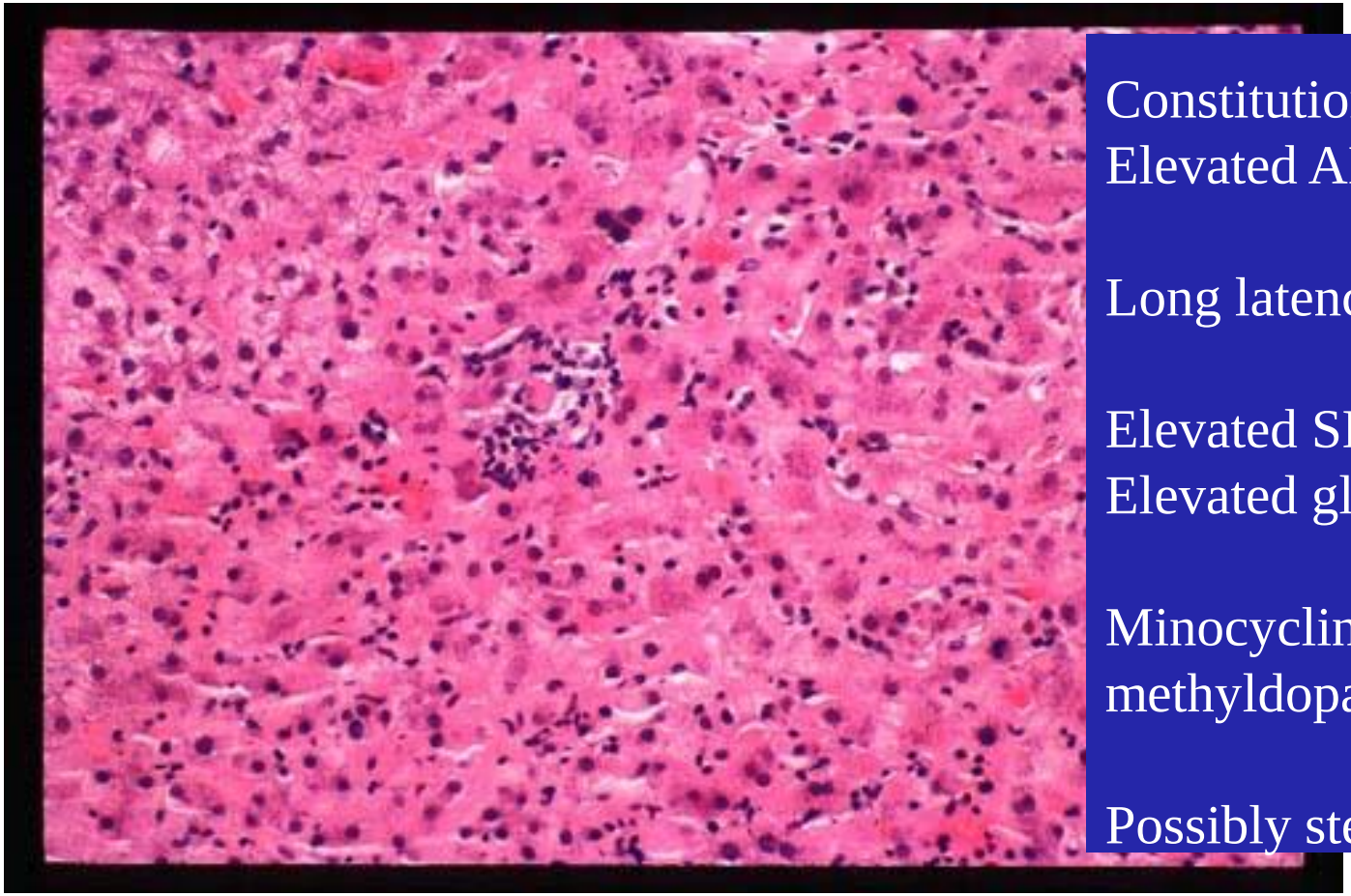
Autoimmune Hepatitis



Constitutional Sx
Elevated ALT/AST

Long latency, 1-12 months

Elevated SMA, ANA
Elevated globulins

Minocyclin, nitrofurantoin, methyldopa, statins

Possibly steroid responsive

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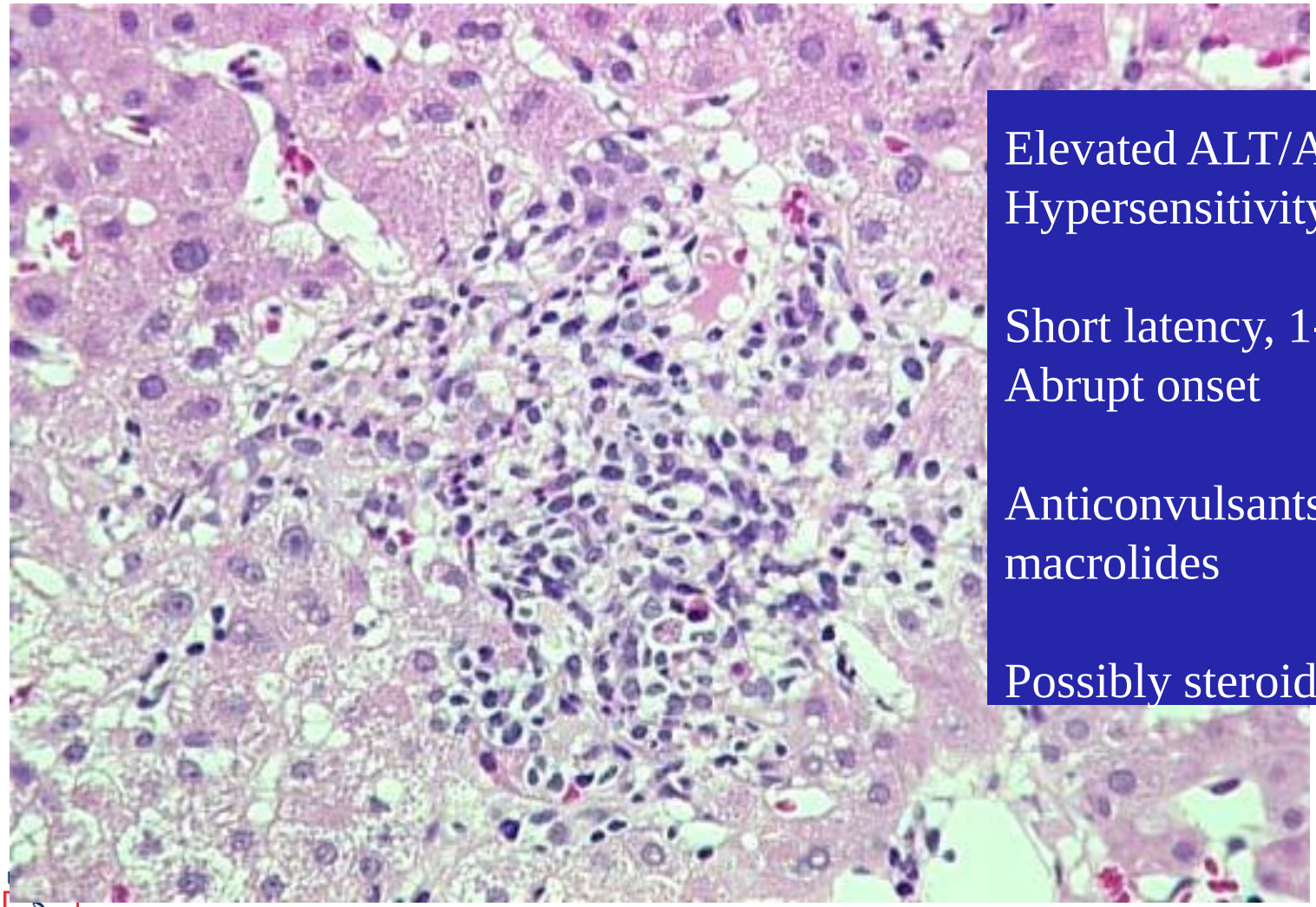
Immunoallergic Hepatitis



Elevated ALT/AST
Hypersensitivity

Short latency, 1-4 weeks
Abrupt onset

Anticonvulsants, sulfonamides, macrolides

Possibly steroid responsive

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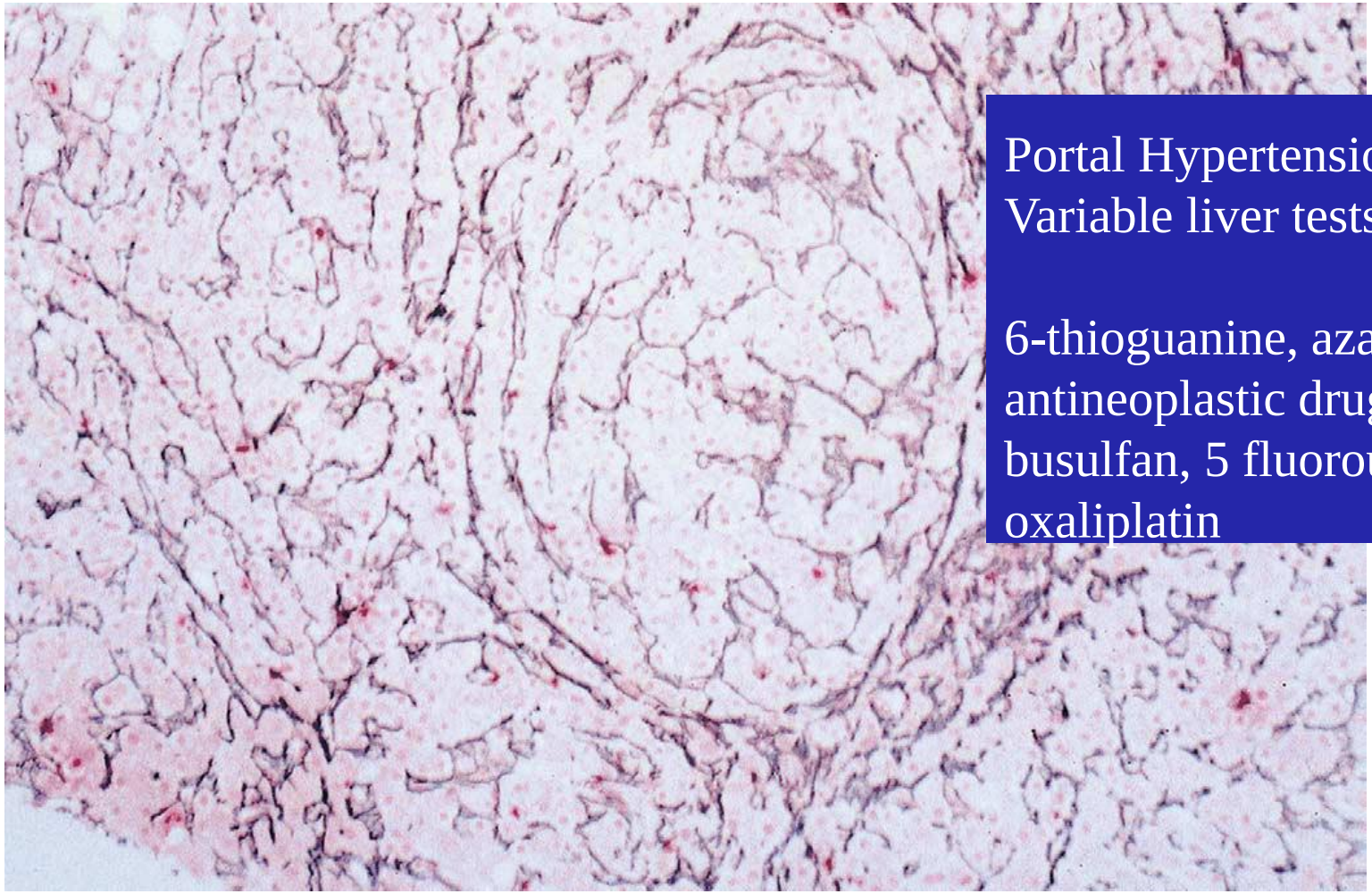
Nodular Regenerative Hyperplasia



Portal Hypertension
Variable liver tests

6-thioguanine, azathioprine and antineoplastic drugs including busulfan, 5 fluorouracil, and oxaliplatin

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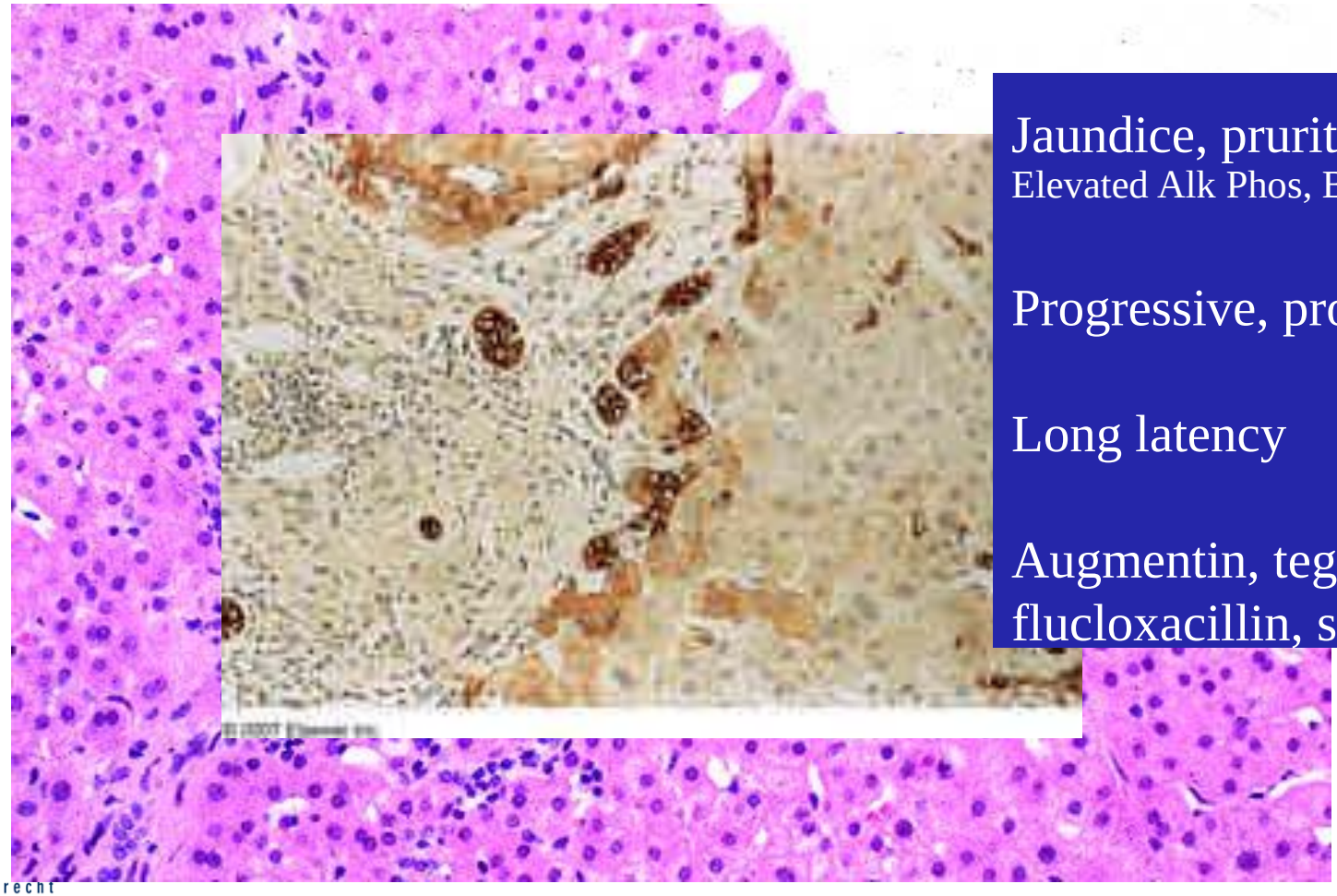
Vanishing Bile Duct Syndrome



Jaundice, pruritus
Elevated Alk Phos, Bilirubin

Progressive, protracted

Long latency

Augmentin, tegretol, cipro, flucloxacillin, sulfonamides

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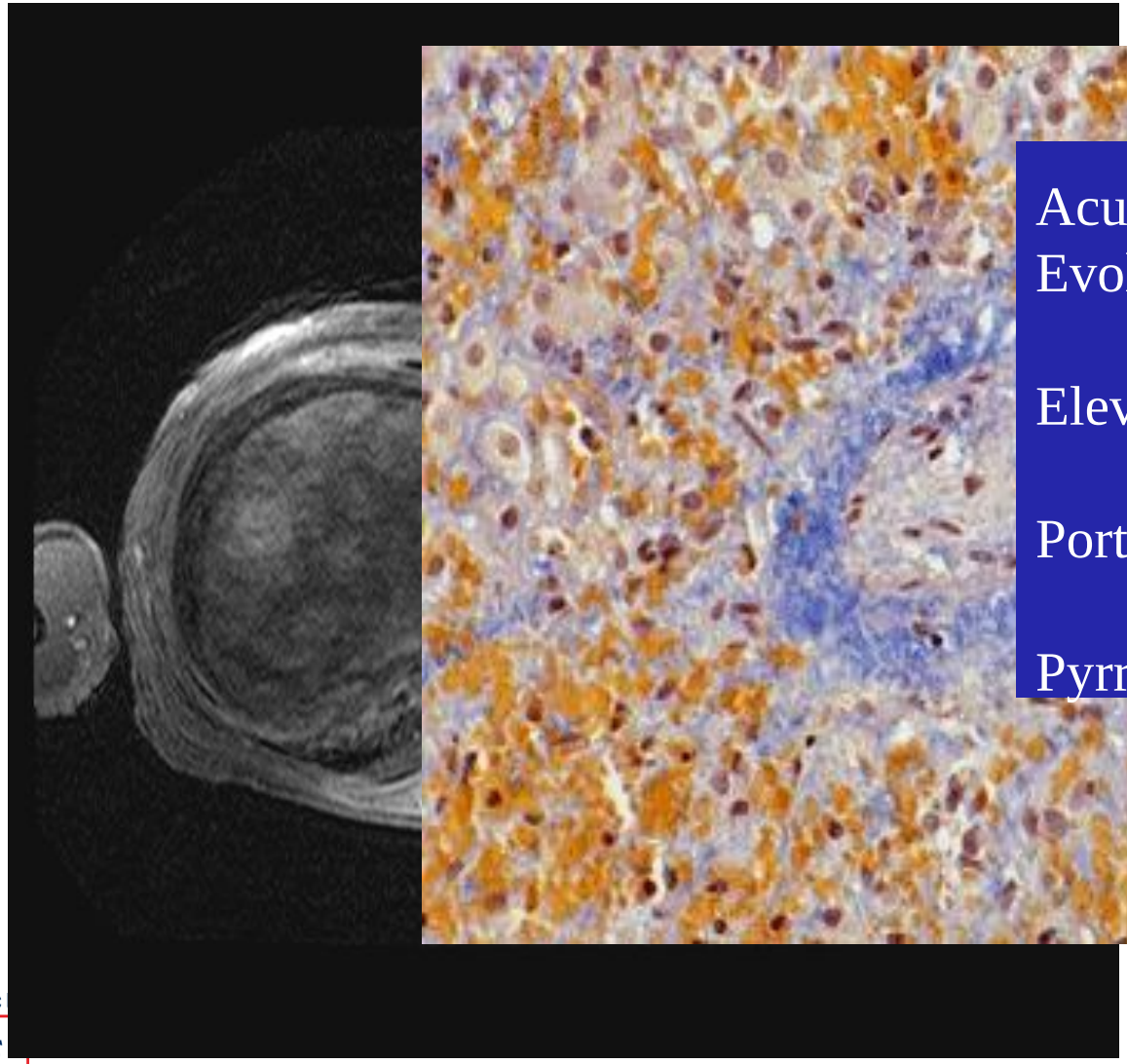
Sinusoidal Obstruction Syndrome



Acute presentation
Evolution to chronic disease

Elevated Alk Phos predominate

Portal hypertension

Pyrrizolidine alkaloids, terpenes

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Further clues

-Presentation < 7 days after first ingestion: antibiotics:

-Presentation >1 yr after first ingestion: nitrofurantoin, minocyclin

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Sarges: drug saf. 2016 in press.

Wat staat oa in de DD bij AST en/of ALT > 1000 IU/mL

A) Alcohol, choledocholithiasis, paracetamol, ischemische hepatitis
B) choledocholithiasis, paracetamol, ischemische hepatitis
C) paracetamol, ischemische hepatitis

Alcohol hepatitis altijd relatief lage transaminasen: AST<500, ALT<250

10% van choledocholithiasis transen > 1000IU/mL in eerste 48 uur

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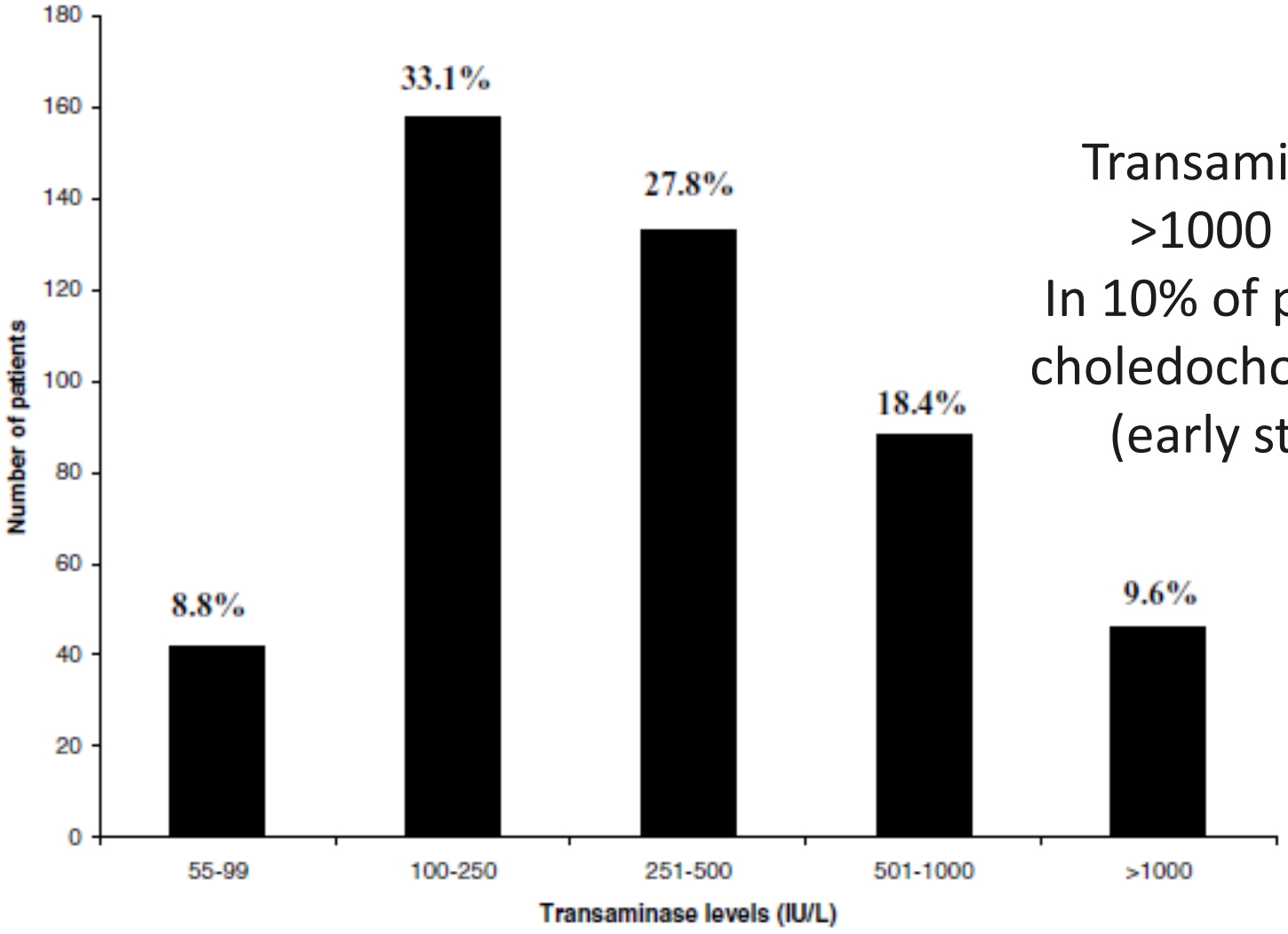
Transaminases and choledocholithiasis



Transaminases
>1000 IU/l
In 10% of pts with
choledocholithiasis
(early stage)

Nathwani RA, Kumar SR, Reynolds TB Marked Elevation in serum transaminases: an atypical presentation of choledocholothiasis. Am J Gastroenterol 2005;100:295–8.

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Differential diagnosis for suspected dili

-Hepatitis E: positive IgM anti HEV in 3% of 318 suspected DILI cases (especially older men and HIV patients: Gastroenterology 2011;141:1665-72)

-other viral hepatitis (HAV, HBV, HCV).

-Autoimmune hepatitis (some cases of DILI associated with autoimmune phenomena).

-Other (preexistent) liver disease.

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Cause of transaminases >1000 IU/mL (single center Irish study)

-ischemic hepatitis: 61%

-viral hepatitis 12%

-early choledocholithiasis 5%

-Unknown 5%.

(other DD: mushroom, chemical poisoning)

-DILI: 16%

paracetamol	*8%*
antituberculosis drugs	*3%*
other antibiotics	*2%*

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Galvin, Clin Med 2015;15(3):244–7

Special cases

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Vrouw 60 jaar

Voorgeschiedenis: Hemithyreoidectomie, hypertensie, hypercholesterolemie, recidiverend urineweginfecties.
Reden verwijzing: progressief gestoorde leverwaarden.

Anamnese: geen klachten. BMI 29.1
Medicatie atorvastatine (2 maanden), atenolol (3jr) nitrofurantoine (15 maanden), oxazepam (2 maanden), captopril (2 jr), furosemide (2 jr)

Lab: bili 17, AF piek 171, gGT piek 212, ASAT piek 414, ALAT piek 489. Negatieve immuunserologie.

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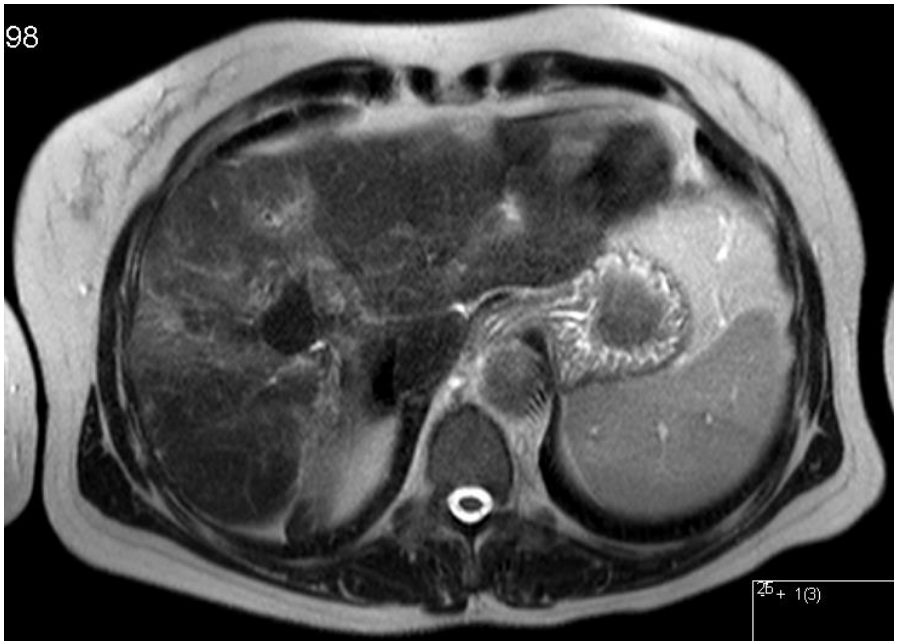
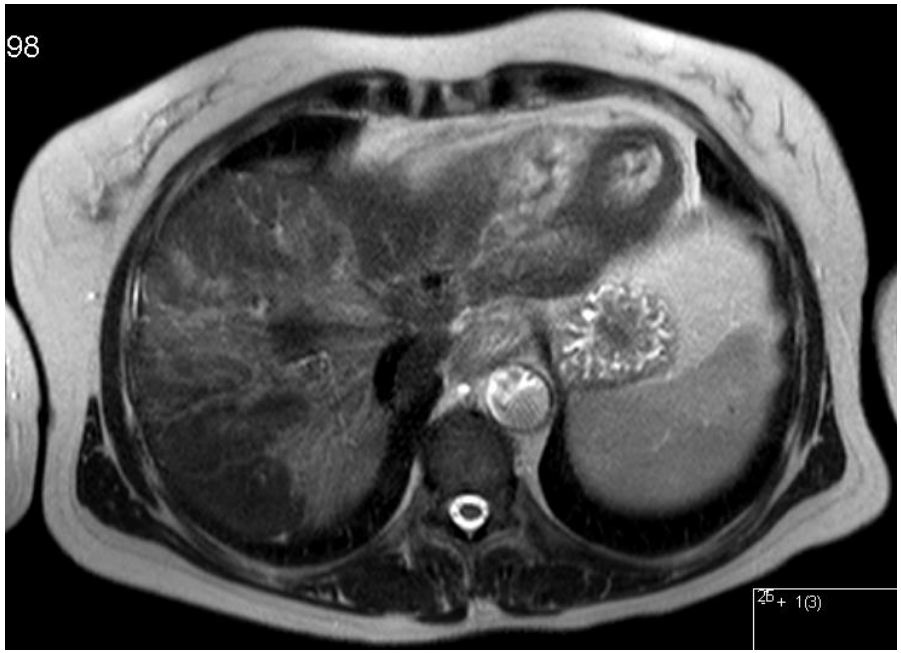
MRI / MRCP: Progressief beeld atrofie rechterleverkwab met verminderde flow door de rechter vena portatak





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Wat is de meest waarschijnlijke oorzaak van de gestoorde leverwaarden?

A) atorvastatine

B) nitrofurantoine

C) “Bona” fide autoimmuun hepatitis type 1.

D) Atenolol

E) IgG4 related disease (ook gezien afwijkingen op MRI)

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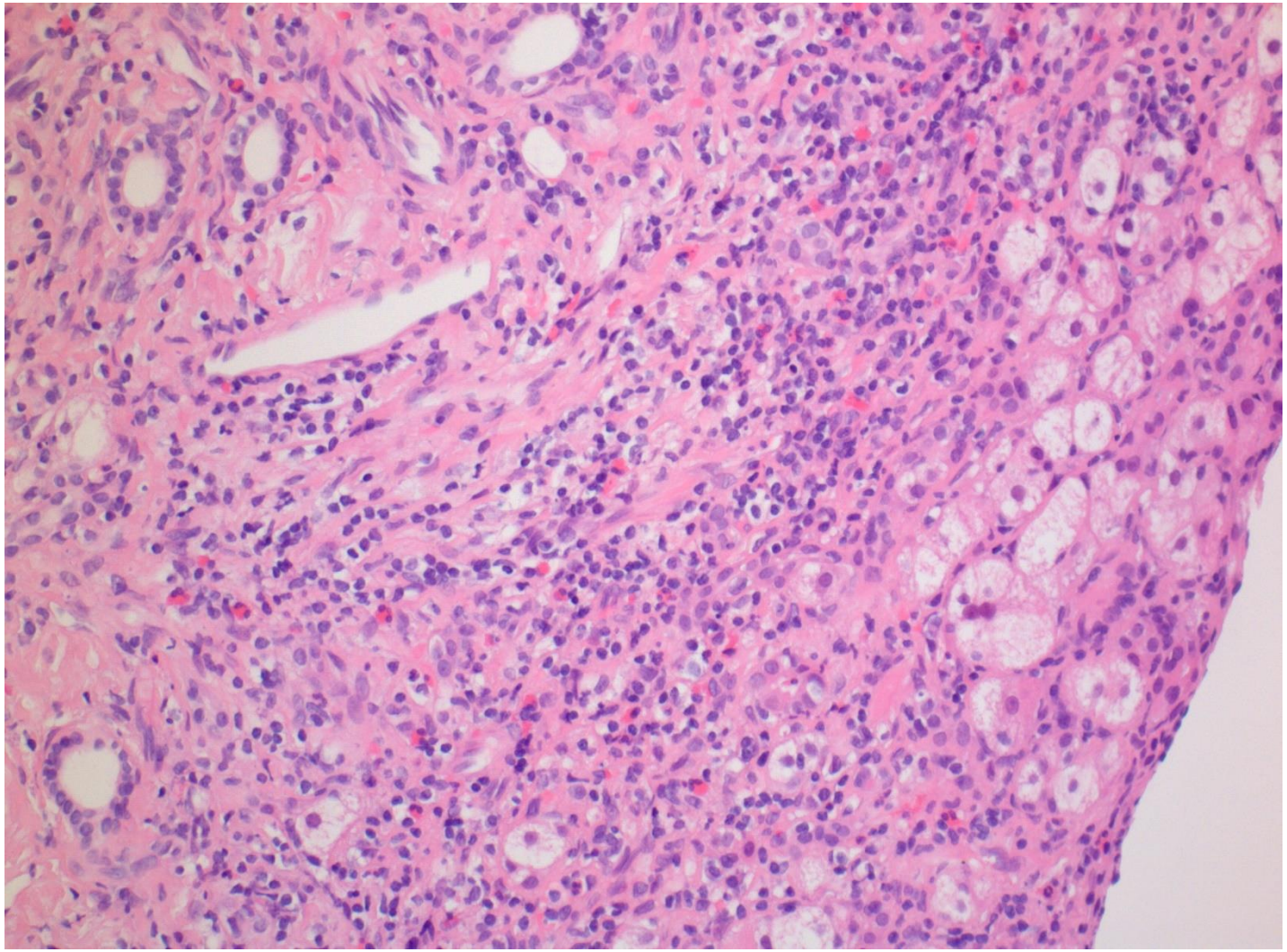
PA beeld; ernstige autoimmuun hepatitis



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Beloop leverproeven na stop nitrofurantoine en tijdelijk prednison + azathioprine

Bepaling	Eenheid	Ref. waarde	01-12-2011 11:11 KERPEC	05-01-2012 11:51 KERPEC	05-01-2012 15:14 KERPEC	07-02-2012 08:39 KERPEC	21-02-2012 08:52 KERPEC	21-02-2012 08:52 KERPEC	06-03-2012 08:29 MBUMDL	01-05-2012 11:59 KERPEC	05-06-2012 10:14 KERPEC
Bloedchemie											
Natrium	mmol/L	136 - 146									
Kalium	mmol/L	3.8 - 5.0									
Calcium geïoniseerd	mmol/L	1.15 - 1.32									
HbA1c (oud)	%										
Ureum	mmol/L	3.0 - 7.5									
Creatinine	µmol/L	58 - 103	59							85	82
GFR (MDRD)	ml/min/1.73m²	60 -	>60							>60	>60
Bilirubine Totaal	µmol/L	3 - 21	13	18		15		16	15	12	9
Bilirubine Direct	µmol/L	0 - 5		2							
Alkalische fosfatase	U/L	0 - 120	151 H	171 H		133 H		153 H	137 H	104	92
gamma-GT	U/L	0 - 40	180 H	212 H		151 H		133 H	120 H	92 H	43
ASAT	U/L	0 - 30	319 H	414 H		107 H		36 H	35 H	40 H	36
ALAT	U/L	0 - 35	358 H	489 H		122 H		59 H	56 H	54 H	30
LD	U/L	0 - 250	394 H	396 H		295 H		277 H			294

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Non Steroidal Anti-inflammatory Drugs (NSAIDS)

- Diclofenac
  - only NSAID clearly associated with increased risk of clinically relevant DILI. OR 4.1 (95% CI 1.9-8.8).
  - Idiosyncratic
  - 85% of cases within 6 months, 3% after one year
  - Hepatocellular pattern (AST, ALT), centrolobular necrosis.
  - Increased risk in rheumatoid arthritis and concomitant hepatotoxic medication

Nature Rev Rheumatol 2011;7:(2) and www.medscape.org/viewarticle/736129

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Immunosuppressive medication

- **Anti-TNF** (Gastroenterol. 2013;144:1419–1425 and Clin Gastro Hepatol 2013;11:558-64): DILI incidence 1:150
  median latency 13 weeks (up to >24 weeks)
  In majority positive auto-antibodies and AIH like histology
  general improvement after anti TNF withdrawal (± steroids)
  class effect, but other agent may be tried.

- **Azathioprine** (Gastroenterol. 2013;144:1419–1425 and Nat Rev Rheumatol 2011:7 (2). DILI incidence 1: 130
  Acute DILI 1:1000: weeks 2-33: cholestatic pattern with fever, arthralgia and rash. Resolves on withdrawal of drug. Delayed resolution and ductopenia may occur.
  Vascular syndromes: nodular regenerative hyperplasia (NRH), veno-occlusive disease (VOD) and peliosis hepatis.

- **Methotrexate**: direct hepatotoxic injury, hepatic fatty infiltration with fibrosis and cirrhosis
  Risk factors: Diabetes, obesity, dose >20 mg/week and high cumulative dose
  Growing evidence for Fibroscan® and serum procollagen-III in follow up

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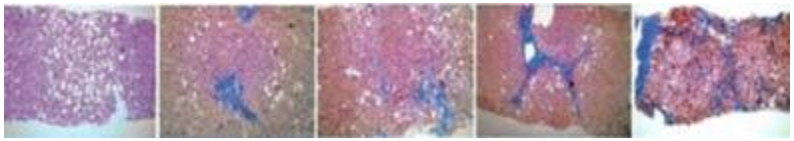
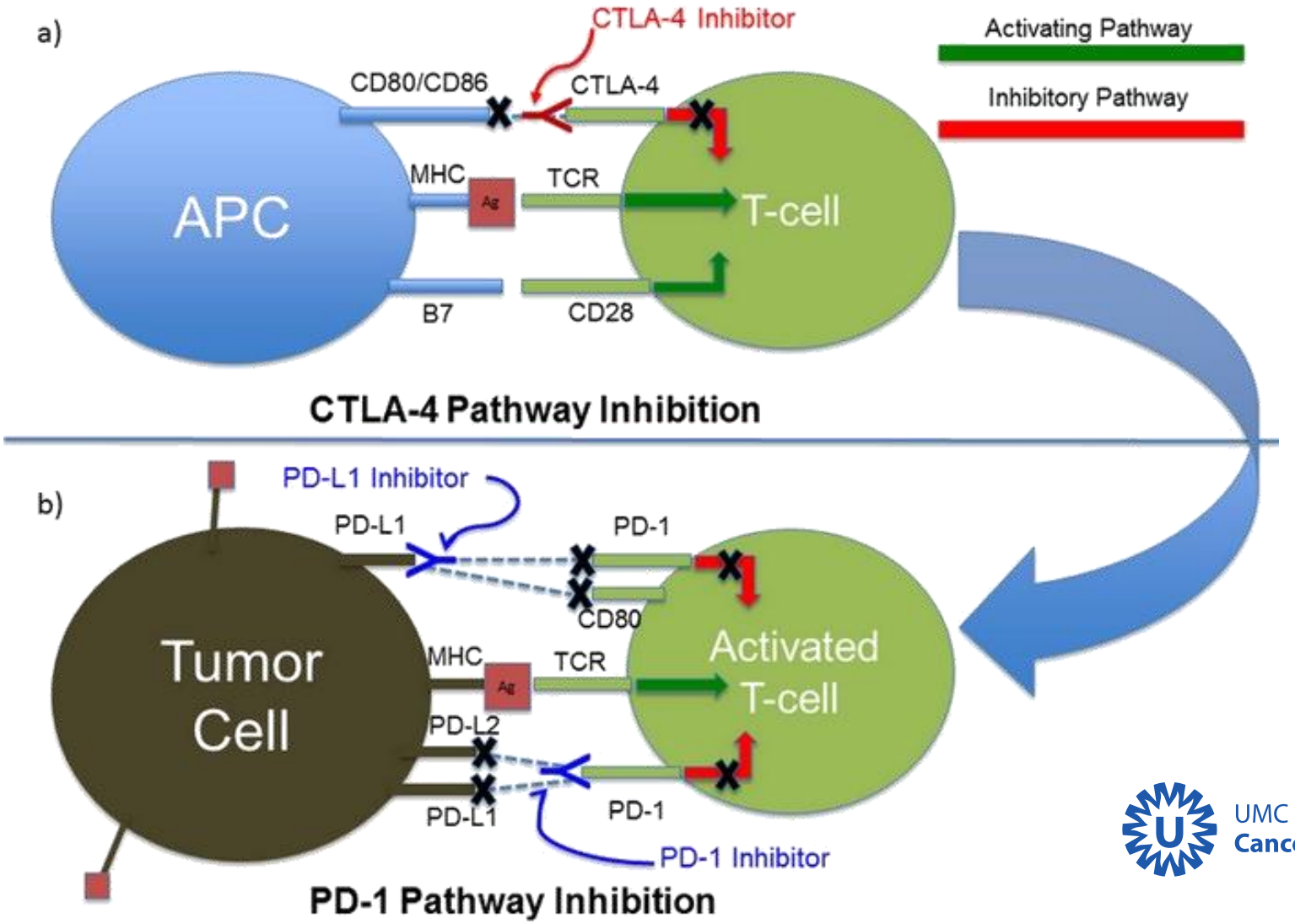


Checkpoint inhibitors



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Clinically available immune checkpoints inhibitors

FDA approved Indications:

- Melanoma
- Non-small cell lung
- Renal cell carcinoma
- Head and neck cancer
- Urothelial carcinoma
- Hodgkin lymphoma
- Merkel cell carcinoma
- MSI-H and dMMR
- Gastric or GEJ

Anti-PD1	Anti-PDL1	Anti-CTLA4
Pembrolizumab (Keytruda)	Atezolizumab (Tecentriq)	Ipilimumab (Yervoy)
Nivolumab (Opdivo)	Avelumab (Bavencio)	
	Durvalumab (Imfinzi)	

Many more in clinical trials in various combinations.

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UMC Utrecht protocol

Uitsluiten virale hepatitis, hepatitis door andere oorzaken en progressie van levermetastasen. Identificeren en staken levertoxische medicatie

Graad 1 (ASAT-ALAT <3x ULN en/of bili <1,5x ULN)

· Continueer immuuntherapie; vervolg leverlab

Graad 2 (ASAT-ALAT 3-5x ULN en/of bili 1,5-3x ULN)

· Controleer leverlab minimaal iedere 3 dagen

· Onderbreek immuuntherapie tot verbetering ≤ graad 1

· Prednison 1 mg/kg/dag (oraal of iv). Continueren tot graad ≤ 1; afbouwen ≥4 weken

Graad 3-4: ASAT-ALAT >5x ULN en/of bili >3x ULN)

· Opname met dagelijks leverlab

· Prednison 2 mg/kg/dag iv

· Definitief staken huidige immuuntherapie

· Bij onvoldoende herstel na 3-5 dgn: voeg mycofenolaatmofetil 2dd 1000 mg oraal toe

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Hepatotoxicity in setting of chronic liver disease

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Hebben patienten met chronisch leverlijden een verhoogd risico op DILI?

-A) ja

-B) nee.

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Hy's observation

Most patients with pre-existing liver disease are not more likely than others to experience hepatic injury on exposure to drugs that can cause idiosyncratic liver damage.

However, should a DILI reaction occur, the consequences could be more dire in patients with impaired hepatic function (mortality 16 vs 5% in recent series).

Exceptions: direct hepatotoxic medications

Reuben A. Hy's law. Hepatology 2004;39:574–8; Lewis JH. Clin Gastroenterol Hepatol. 2015;13:2173–89

Paracetamol, statins and oral hypoglycaemics in cirrhosis

-**Paracetamol**: relatively safe (much better than NSAIDS).

may lead to increased liver values

simultaneous alcohol use may be protective, chonic alcohol use detrimental

reasonable limit: 2 gram/day

-**Oral hypoglycaemics:** generally safe. May reduce HCC risk

-Statins: generally safe. Decrease portal HT and HCC risk

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Vrouw 60 jaar

Voorgeschiedenis: hypertensie, hypercholesterolemie,.

Reden verwijzing: progressief gestoorde leverwaarden.

Anamnese: geen klachten. BMI 29.1
Medicatie atorvastatine (2 maanden), atenolol (3jr), oxazepam (2 maanden), captopril (2 jr), furosemide (2 jr)

Lab: bili 17, AF 171, gGT 212, ASAT piek 141, ALAT 138.
Negatieve immuunserologie en overige diagnotiek.

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Wat is uw beleid

A) vervolgen

B) Vervang atorvastatine door pravastatine

C) Stop cholesterolsynteseremmer, indien leverwaarden herstellen start pravastatine

D) Leverbiopt (toch AIH?)

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Paracetamol, statins and oral hypoglycaemics in cirrhosis

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may lead to increased liver values

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reasonable limit: 2 gram/day

--**Oral hypoglycaemics:** generally safe. May reduce HCC risk

-Statins: generally safe. Decrease portal HT and HCC risk

atorvastatin: metabolism via CYP3A4. clinical relevant hepatic injury 1:3000. Pravastatin: minimal hepatic metabolism. clinical relevant hepatic injury 1:100,000.

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Enhanced pharmacodynamics effect in decompensated cirrhosis

precipitation of encephalopathy: opioids, anxiolytics, sedatives

Precipitation of renal failure: NSAIDs (RAAS system).

Decreased therapeutic response: beta blockers (normally 90% first pass effect, but not in portal hypertension: low starting dose preferable), loop diuretics, codeine

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Lewis JH et al. Aliment Pharmacol Ther 2013; 37: 1132-1156

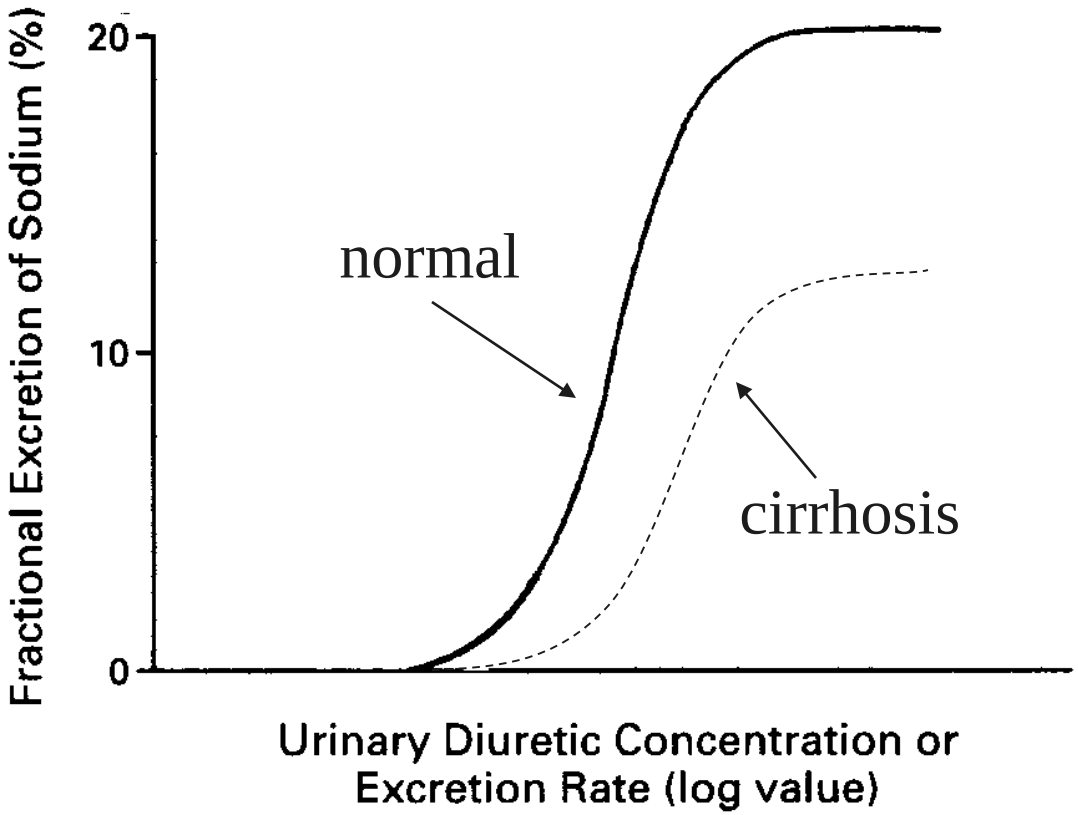

Figure 1. Pharmacodynamics of a Loop Diuretic.

The relation between the natriuretic response and the amount of diuretic reaching the site of action is represented by a sigmoid curve.

New Engl. J. Med. 1998;339:387-395


obrigado
Dank U
Merci
mahalo
Köszi
спасибо
Grazie
Thank you
mauruuru
Takk
Gracias
Dziękuję
Děkuju
danke
Kiitos

Nadere diagnostiek

- Leverbiopten:
  - Langer bestaande intrahepatische cholestase
  - Enige periportale fibrose
  - Geringe ductulaire proliferatie

  - Nadere anamnese: 1 maand voor klachten begonnen met OAC

- Genetisch onderzoek:
  - FIC type 1 (ATP8B1) Allel 1: normaal
    Allel 2: normaal

  - FIC type 2 galzouttransporter (ABCB11) Allel 1: c.2296 G>A (Gly766Arg)
    Allel 2: normaal

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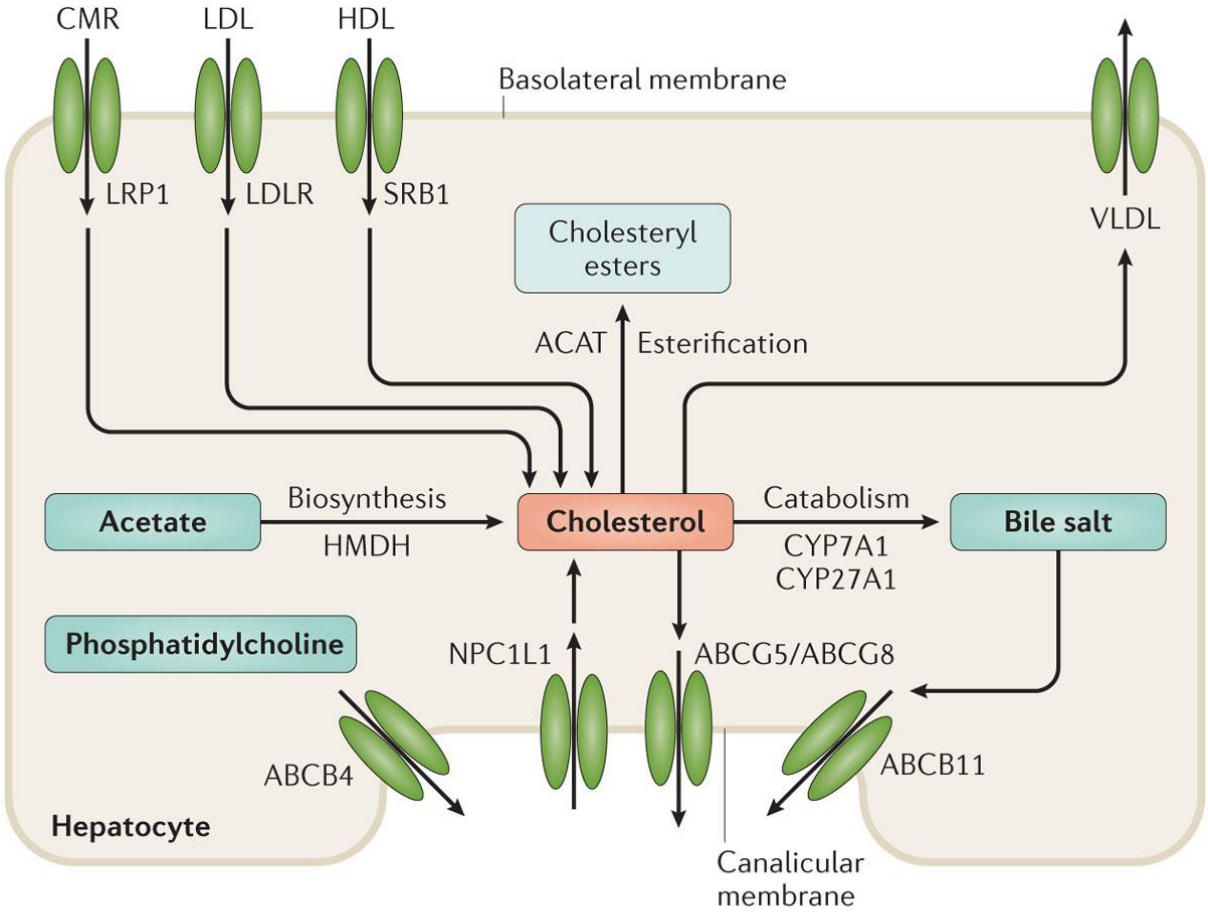
Transport proteins in the hepatocyte canalicular membrane



Nature Reviews | Disease Primers

Lammert, F. *et al.* (2016) Gallstones
Nat. Rev. Dis. Primers doi:10.1038/nrdp.2016.24

Altered pharmacokinetics in decompensated cirrhosis

Increased drug concentrations

-reduced hepatic blood flow and reduced first pass effect with portal HT (e.g. propranolol).

-less albumin binding (increased free drug conc).

-lower CYP metabolic activity

-less biliary and renal drug excretion.

Increased drug toxicity

-reduced glutathione stores

Lower drug concentrations

-increased distribution volume with ascites (lower conc. hydrophilic drugs)

End organ resistance (e.g. propranolol, furosemide)

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Recently detected causes of DILI

-Sorafenib

-Tolvaptan

-NOACS (especially rivaroxaban)

-Anti-hepatitis C Direct Acting Antivirals

NS3 protease inhibitors simeprevir, asunaprevir, paritaprevir

only 3 RCT with DAA: 2 with 3D+ribavirin, 1 with sofosbuvir + valpatasvir: more SAE with active treatment (2.3%, 2.6%, 2.4% vs 0%, 0.5% and 0%. NEJM 2014;370:1594: NEJM 2014;370:1604. NEJM 2015;373:2599)

-methylprednisolone (especially in multiple sclerosis).

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Decreased natriuresis with furosemide in cirrosis: end organ resistance

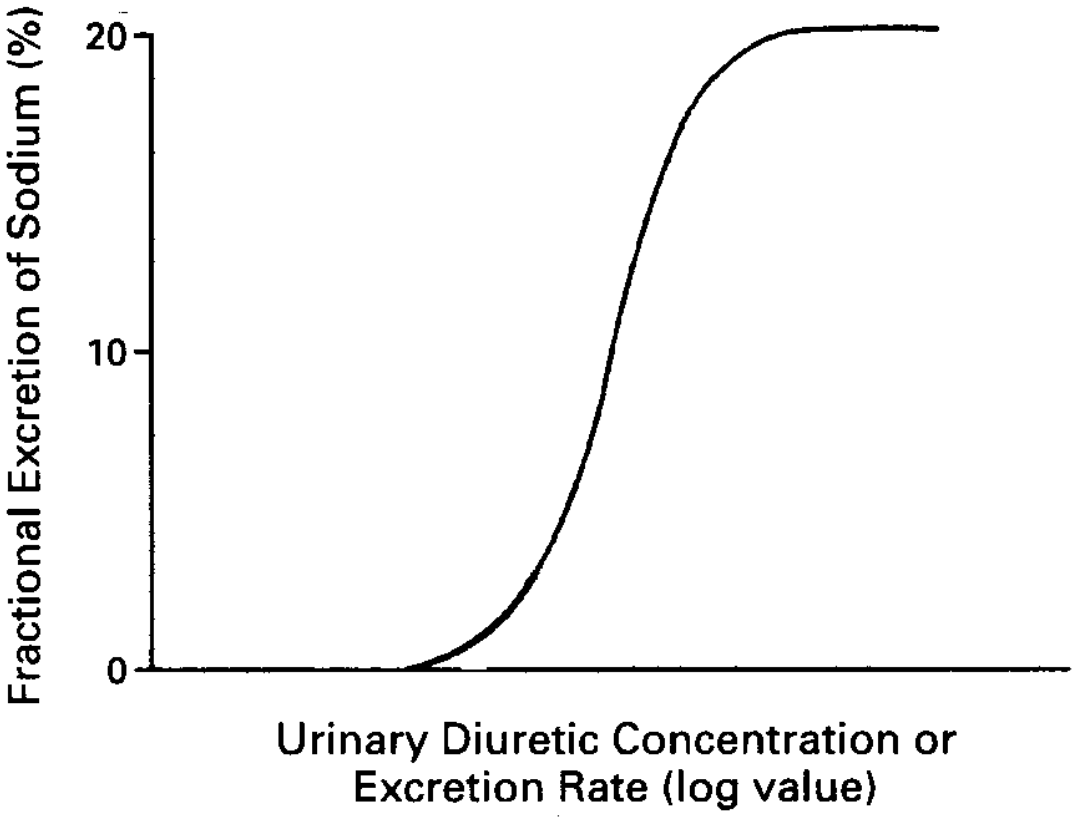

Figure 1. Pharmacodynamics of a Loop Diuretic.

The relation between the natriuretic response and the amount of diuretic reaching the site of action is represented by a sigmoid curve.

New Engl. J. Med. 1998;339:387-395

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Casus

- Vrouw, 20 jaar
- Blanco VG
- Medicatie: OAC, propanolol 2dd 40 mg, acetylcysteine

- Sinds 2 maanden plotseling ontstane geelzucht en jeuk, snel progressief. Wisselend ontkleurde ontlasting en donkere urine.

- Familiair: geen leverziekten/auto-immuunziekten

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laboratorium

- Lab 25-01-2013

Bili totaal 479	Albumine 33.4
Bili direct >170	PT 13.1
AF 551	APTT 36
gamma-GT 32	Ferritine 202
ASAT 64	Transferrine 3.08
ALAT 72	ijzer verzadiging 0.17
	IJzer 14

- Virologie, immuun serologie negatief, ceruloplasmine gb
- Echografie: gb

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Wat is de meest waarschijnlijke diagnose?

- A): benigne recurrente intrahepatische cholestase (BRIC)
- B): cholestase door orale anticonceptie (ze gebruikt vast de pil, ben ik vergeten te vragen in de anamnese)
- C): primair biliaire cirrose
- D): HILI (herb-induced liver injury: ze gebruikt vast afrodisiacum: of ander alternatief middel: ben ik vergeten te vragen in de anamnese)

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Nadere diagnostiek

-

–Nadere anamnese: 1 maand voor klachten begonnen met OAC

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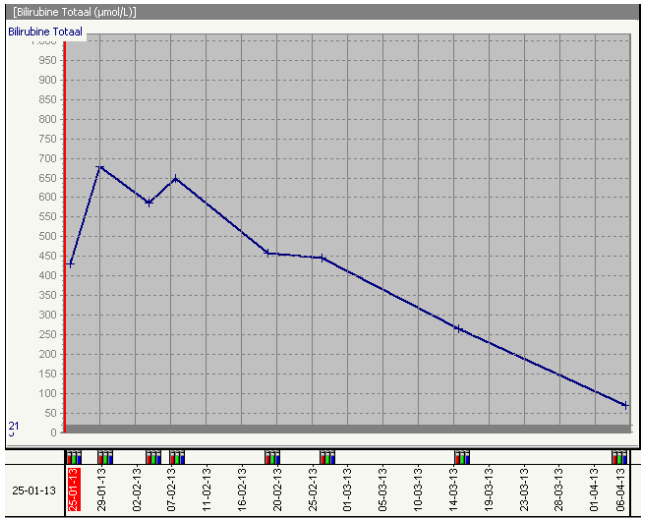
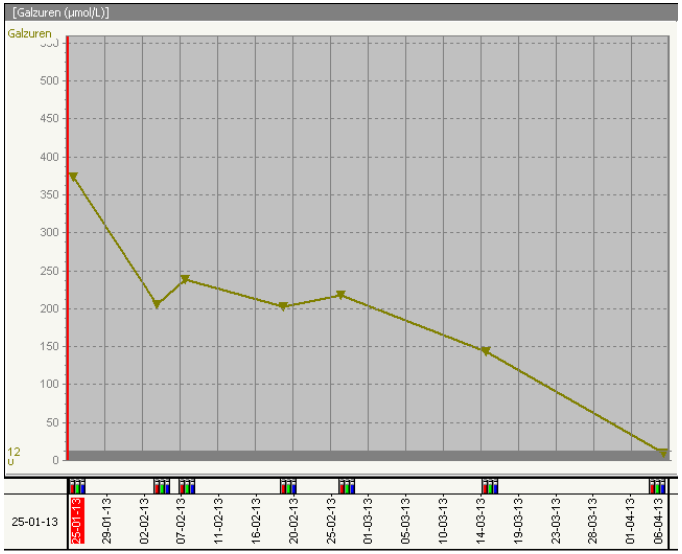
Beloop na staken pil, met symptomatische therapie

bilirubine



galzuren



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DILI and skin.

-**Dress** syndrome: **Dr**ug Reaction with **E**osinophilia and **S**ystemic **S**ymptoms.

-Stevens Johnson syndrome (<10% skin involved)

-Toxic epidermal necrolysis (>30% of skin involved).

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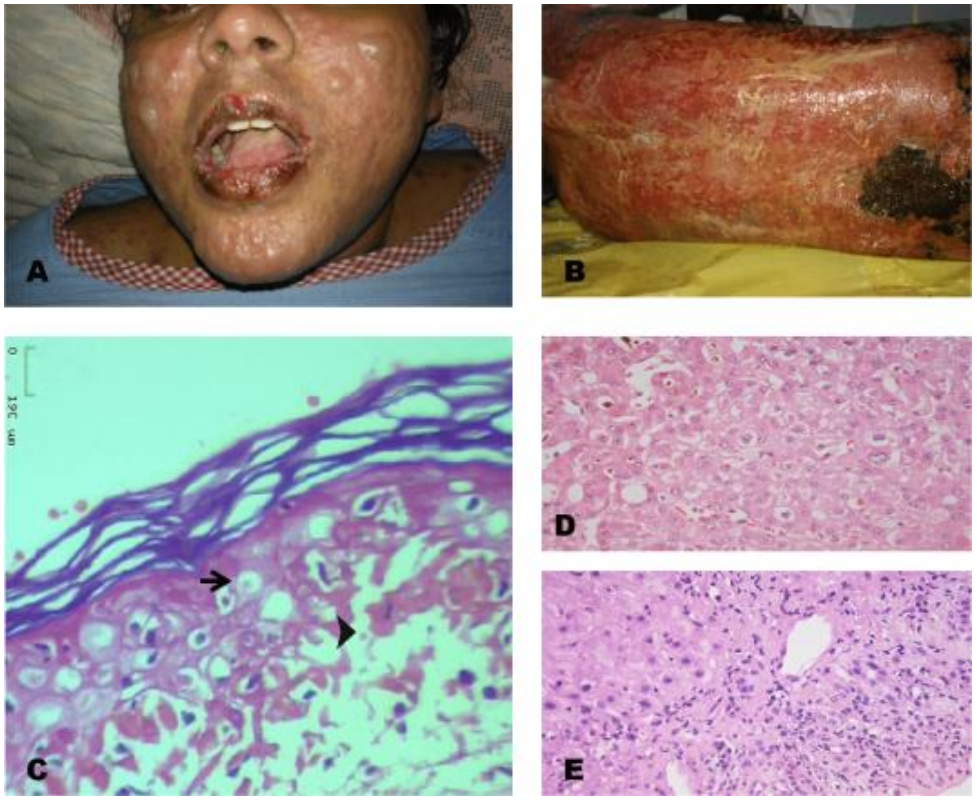
Drug-induced liver injury associated with stevens-Johnson syndrome/toxic epidermal necrolysis



Hepatology
Volume 63, Issue 3, pages 993-999, 26 NOV 2015 DOI: 10.1002/hep.28270
http://onlinelibrary.wiley.com/doi/10.1002/hep.28270/full#hep28270-fig-0001

DILI incidence: Iceland

- Crude annual incidence 19.1 cases per 100,000 Icelandic inhabitants
  - 5 jaundice cases per 100,000 people/year
  - Steady increase in the incidence rate according to age, but no relationship with gender, alcohol and other generally quoted risk factors

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Bjornsson E, et al. Gastroenterology 2013