PRO-EURO DILI NETWORK

Prospective European Drug-induced Liver Injury Network

Drug-induced liver injury: general concepts, interpretation of liver tests and common mistakes

RAUL J ANDRADE

1st TRAINING COURSE, ACTION COST 17-112 PRO EURO DILI NET

Málaga, 15st March, 2019

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ibima Instituto de Investigación Biomédica de Málaga

SPANISH DILI REGISTRY

Drug-induced liver injury

"Adverse drug reaction manifesting in liver damage following intake of presecription drugs, over-the-counter treatments, herbals or dietary supplements"

Intrinsic: dose-dependent, predictable reacion, e.g. acetaminophen (APAP) overdose

Idiosyncratic: unpredictable based on drug dose and pharmacological properties

Drug-induced liver injury (DILI)

Major threat to patients, substantial burden for drug development

Withdrawals

1959 Iproniazid

1962 Thalidomide

1967 Oxyphenisatin

1970 Ibufenac

1982 Benoxaprofen, Ticrynafen

1984 Methaqualon

1985 Perhexiline

1991 Triazolam

1996 Alpidem

1997 Tolcapone, Tolrestat

Fenfluramine

1998 Bromfenac, Terfenadine

2000 Troglitazone, Amineptine

Alosetron, Cisapride

2001 Trovafloxacin, Cerivastatin

2003 Nefazodone

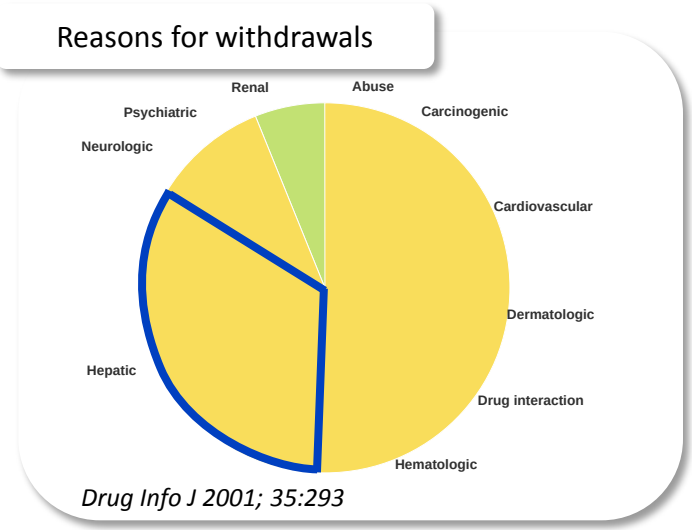
2004 Rofecoxib

2005 Pemoline

2006 Ximelagatran

2007 Lumiracoxib

Reasons for withdrawals



Drug Info J 2001; 35:293

Blackbox warnings

Docetaxel, Nefazodone, Nevirapine, Amiodarone, Adefovir, Idarubicin, Felbamate, Isoniazid, Ambrisentan, Epirubicin, Dantrolene

- Leading cause of acute liver failure in the US
- 3% fatal outcome, 5% need for transplantation
- Most frequent reason for drug withdrawals
- Substantially reduces treatment options for patients
- Significantly contributes to attrition in development
- Major challenge: lack of suitable biomarkers

Courtesy of Michael Merz

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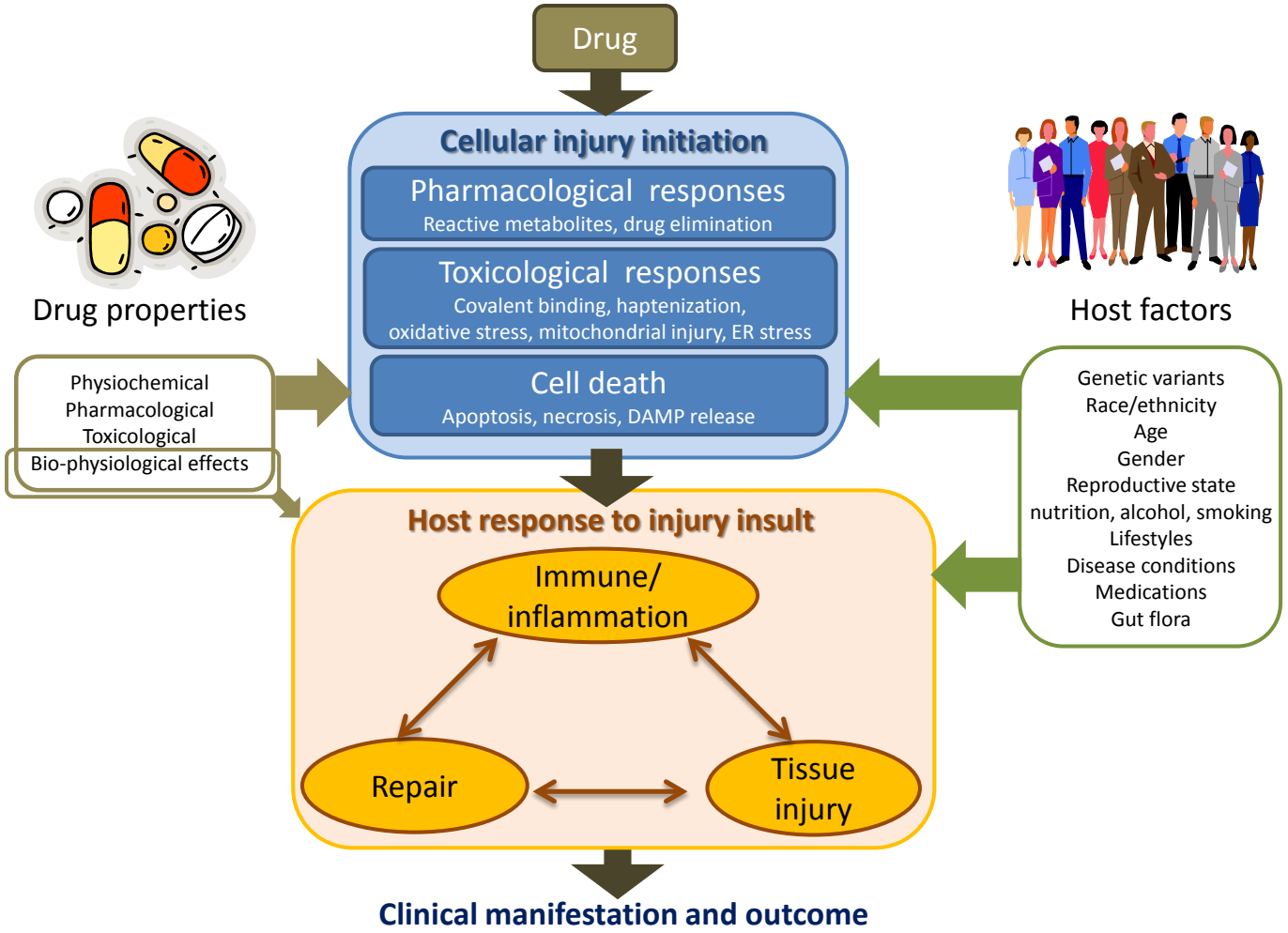
SPANISH DILI REGISTRY

Idiosyncratic DILI: the interplay between drug and host factors



Chen, Suzuki, Borlak, Andrade , Lucena. J Hepatol 2015 ;63:503–514

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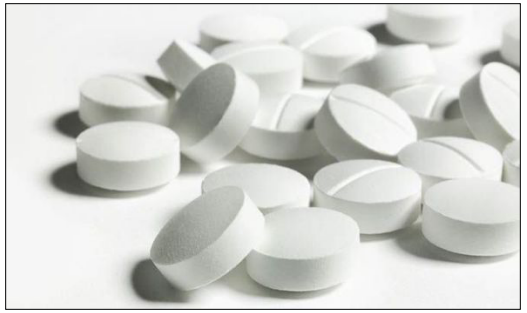
SPANISH DILI REGISTRY

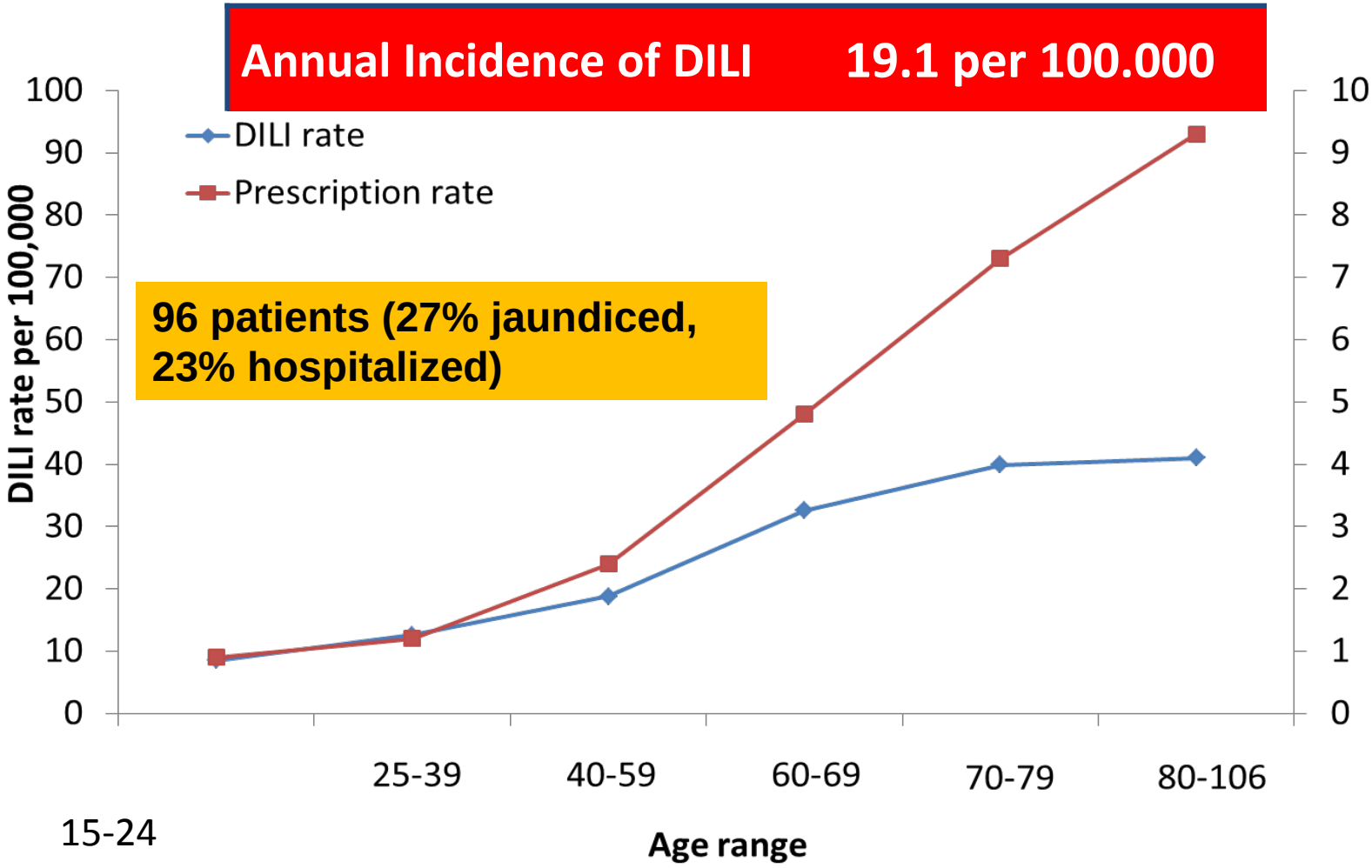
Idiosyncratic drug-induced liver injury



- Population-based studies

  - France: 13.9 cases/100,000 inhabitants/year *(Sgro et al., 2002)*
  - Iceland: 19.1 cases/100,000 inhabitants/year *(Björnsson et al 2013)*
  -Delaware:2.7 cases/100.000 inhabitants/year *(Vega et al Drug Saf 2017)*

Epidemiology of Drug-induced Liver injury in Iceland n=251,860



Björnsson et al Gastroenterology 2013; 144(7):1419-1425

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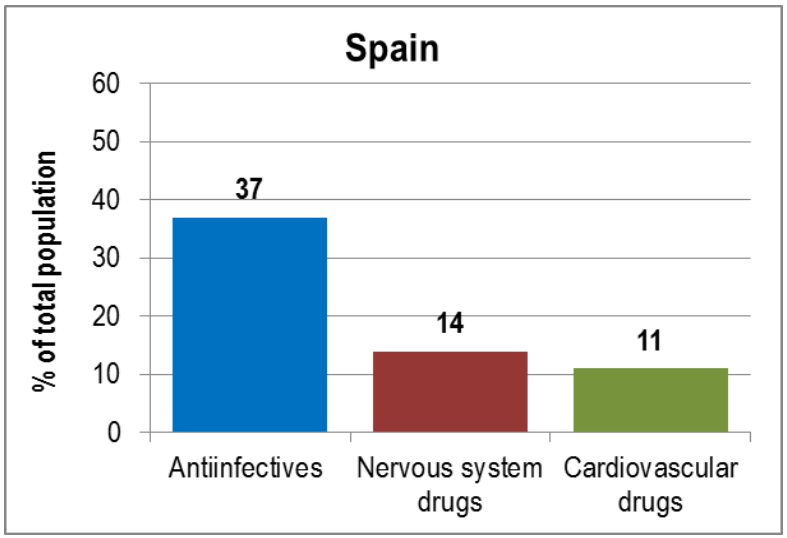
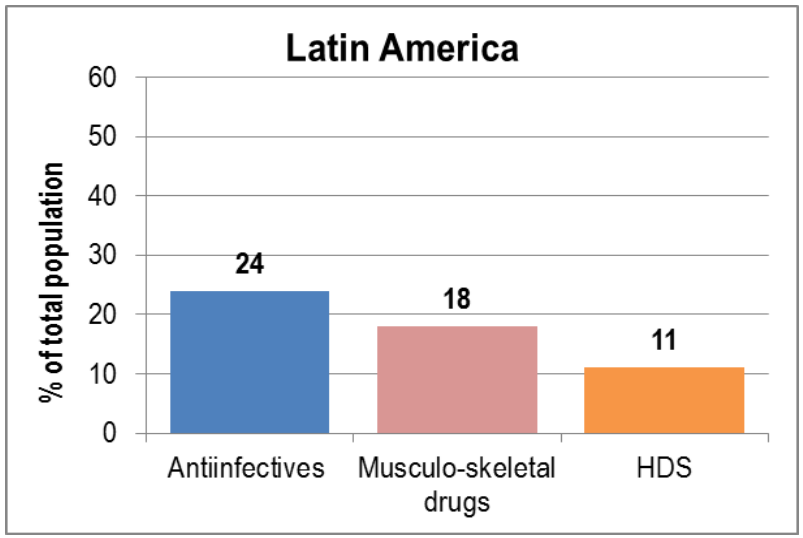
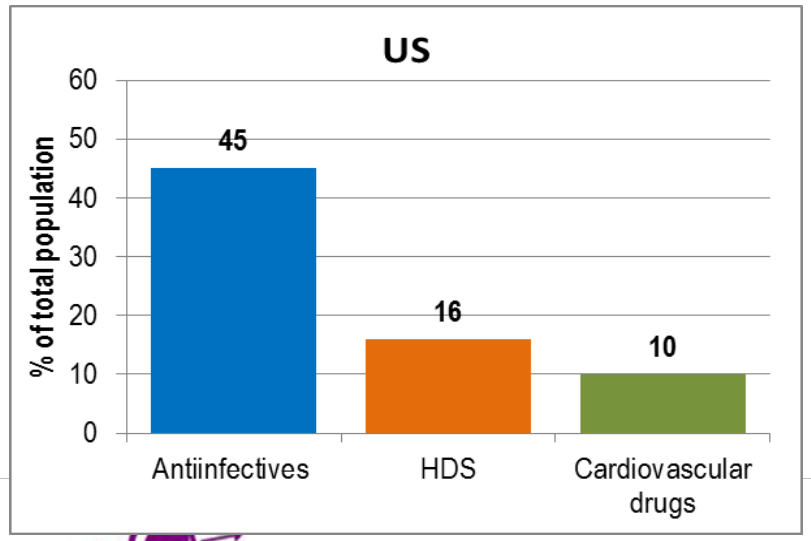
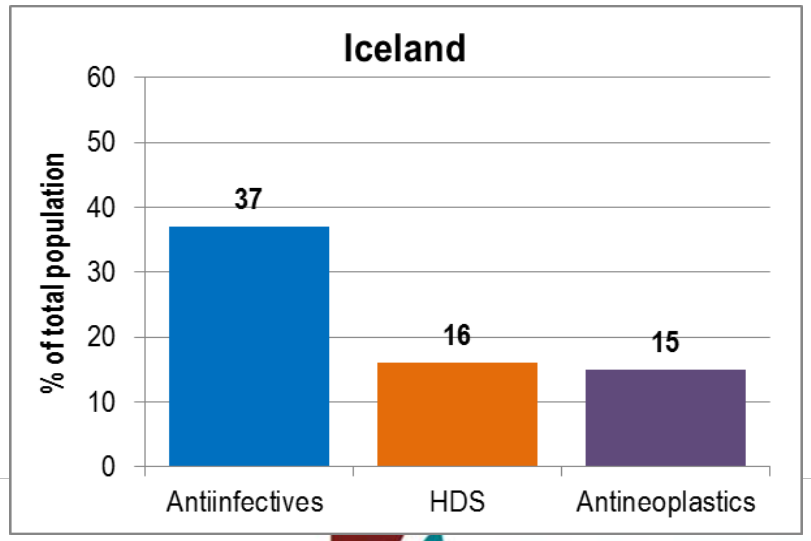
PANISH DILI REGISTRY

Most common causative drug classes in large DILI populations





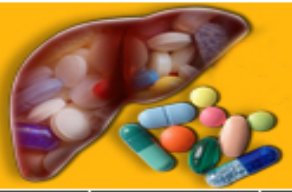




Andrade et al, Gastroenterology, 2005; Björnsson, Gastroenterology, 2013; Chalasani et al astroenterology, 2013

United States National Library of Medicine

NIDDK National Institute of Diabetes and Digestive and Kidney Diseases



LiverTox

Clinical and Research Information on Drug-Induced Liver Injury

- Home
- Introduction
- Clinical Course
- Phenotypes
- Immune Features
- Clinical Outcomes
- Causality
- Severity Grading
- Likelihood Scale
- Classes of Drugs
- Submit a Case Report
- Clinical Alerts/News
- Conference Proceedings
- Information Resources
- Glossary
- Abbreviations

SEARCH THE LIVERTOX DATABASE

Search for a specific medication, herbal or supplement:

Search

Browse by first letter of medication, herbal or supplement:

A B C D E F G H I J K L M N O P Q R S T U V W X Y Z

LIVERTOX provides up-to-date, accurate, and easily accessed information on the diagnosis, cause, frequency, patterns, and management of liver injury attributable to prescription and nonprescription medications, herbals and dietary supplements. LIVERTOX also includes a case registry that will enable scientific analysis and better characterization of the clinical patterns of liver injury. The LIVERTOX website provides a comprehensive resource for physicians and their patients, and for clinical academicians and researchers who specialize in idiosyncratic drug induced hepatotoxicity.

URL: http://livertox.nih.gov

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SPANISH DILI REGISTRY

United States National Library of Medicine
NIDDK National Institute of Diabetes and Digestive and Kidney Diseases
LiverTox
Clinical and Research Information on Drug-Induced Liver Injury
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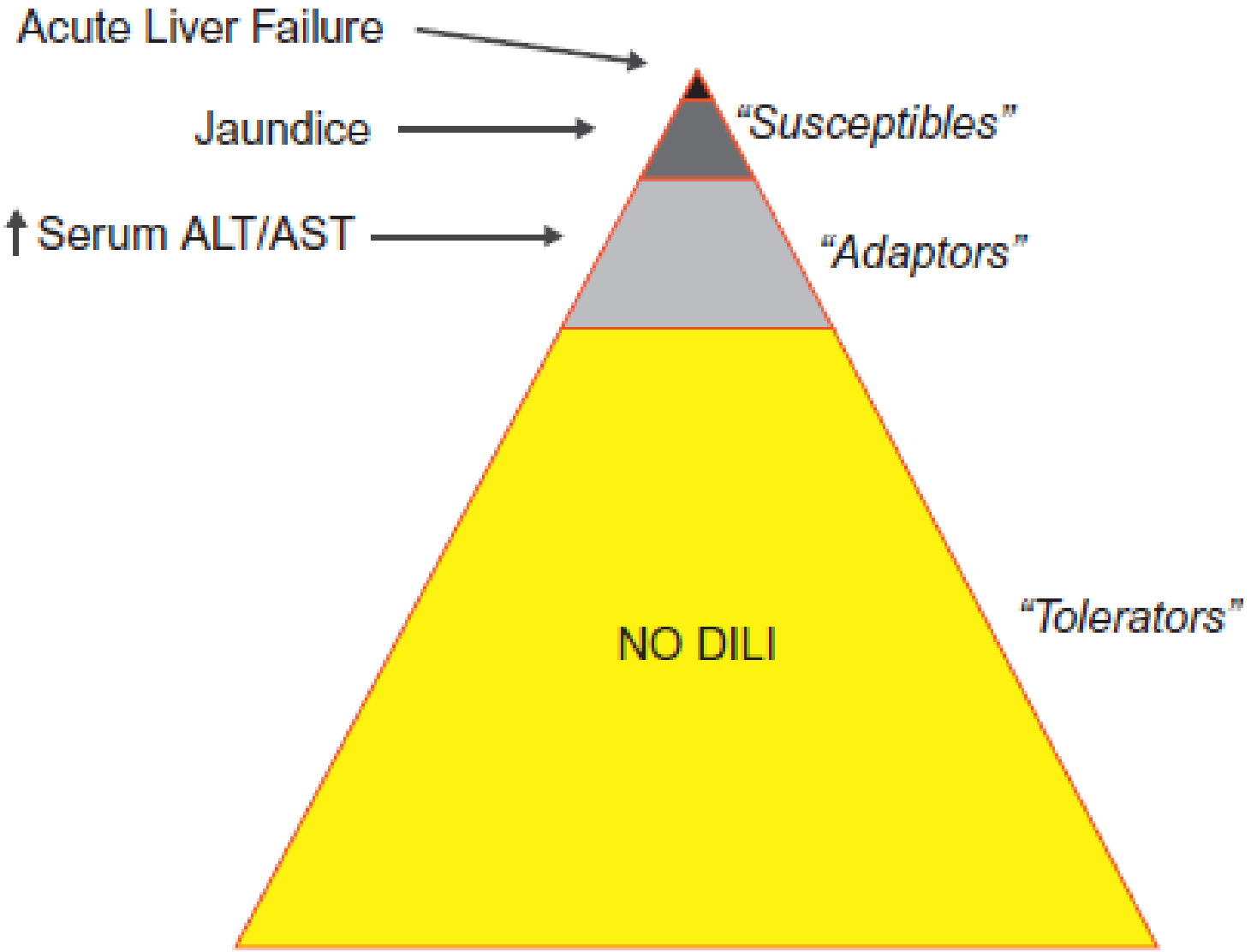
HEPATOLOGY
Official Journal of the American Association for the Study of Liver Diseases
AASLD
LIVER INJURY/REGENERATION

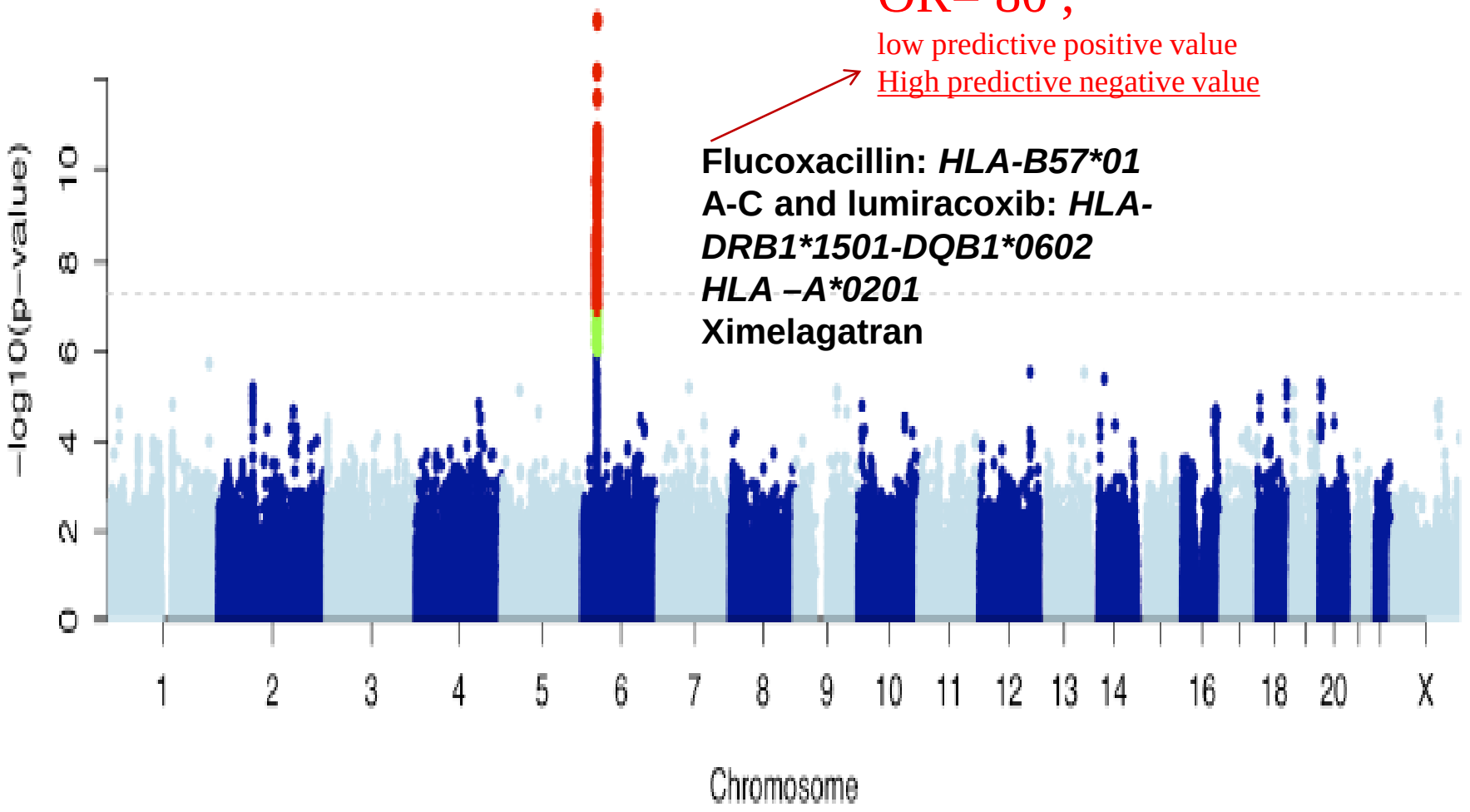
Categorization of Drugs Implicated in Causing Liver Injury: Critical Assessment Based on Published Case Reports

Einar S. Björnsson[1,2] and Jay H. Hoofnagle[3]

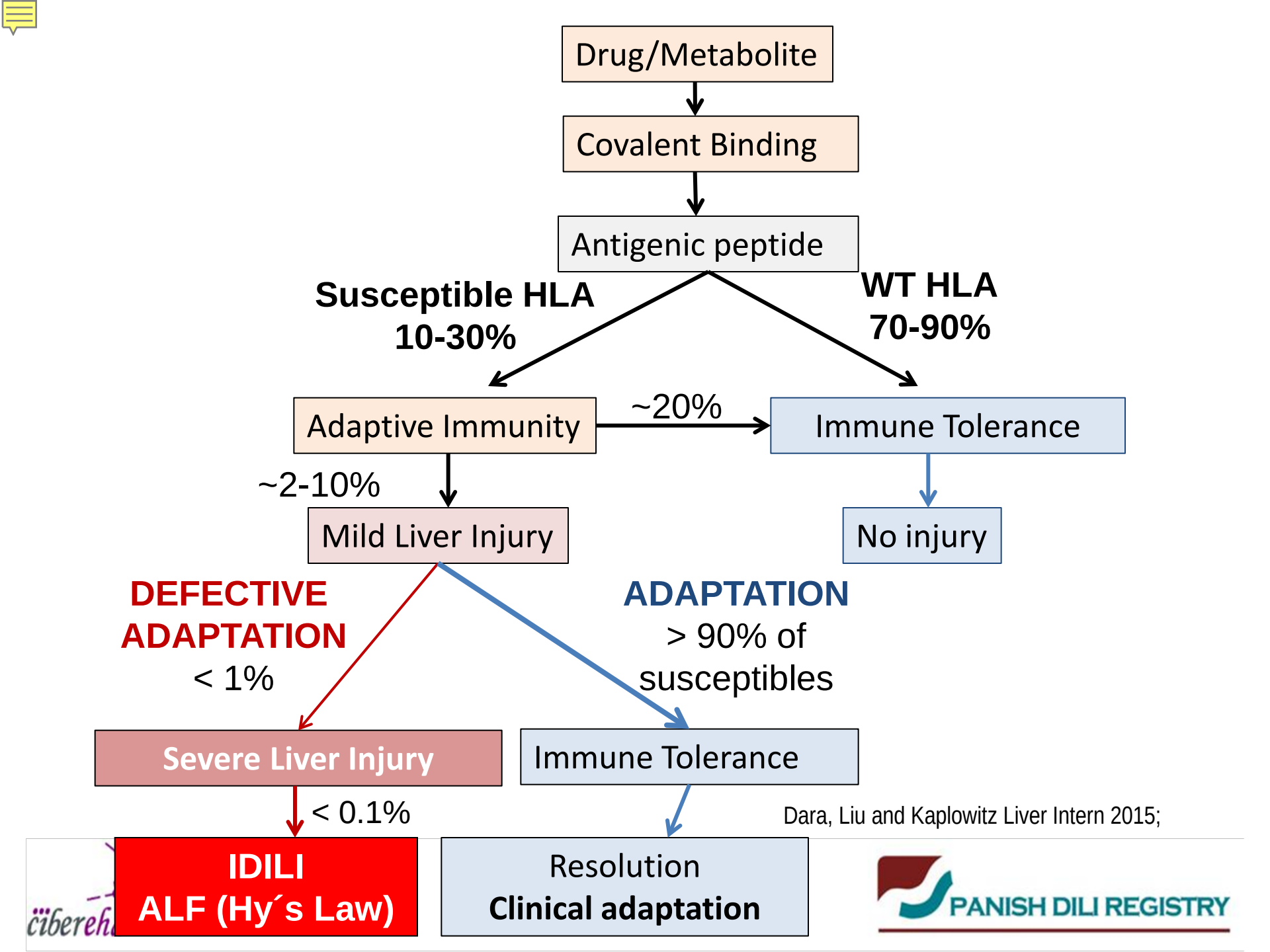
Category A	The drug is well known, well described and well reported to cause either direct or idiosyncratic liver injury, and has a characteristic signature; more than 50 cases including case series have been described
Category B	The drug is reported and known or highly likely to cause idiosyncratic liver injury and has a characteristic signature; between 12 and 50 cases including small case series have been described
Category C	The drug is probably linked to idiosyncratic liver injury, but has been reported uncommonly and no characteristic signature has been identified; the number of identified cases is less than 12 without significant case series
Category D	Single case reports have appeared implicating the drug, but fewer than 3 cases have been reported in the literature, no characteristic signature has been identified, and the case reports may not have been very convincing. Thus, the agent can only be said to be a possible hepatotoxin and only a rare cause of liver injury
Category E	Despite extensive use, no evidence that the drug has caused liver injury. Single case reports may have been published, but they were largely unconvincing. The agent is not believed or is unlikely to cause liver injury
Category E*	The drug is suspected to be capable of causing liver injury or idiosyncratic acute liver injury but there have been no convincing cases in the medical literature. In some situations cases of acute liver injury have been reported to regulatory agencies or mentioned in large clinical studies of the drug, but the specifics and details supportive of causality assessment are not available. The agent is unproven, but suspected to cause liver injury
Category X	Finally, for medications recently introduced into or rarely used in clinical medicine, there may be inadequate information on the risks of developing liver injury to place it in any of the five categories, and the category is characterized as “unknown”


Acute Liver Failure
Jaundice
Serum ALT/AST
"Susceptibles"
"Adaptors"
"Tolerators"
NO DILI

GWAS: chromosome 6 (HLA genes)

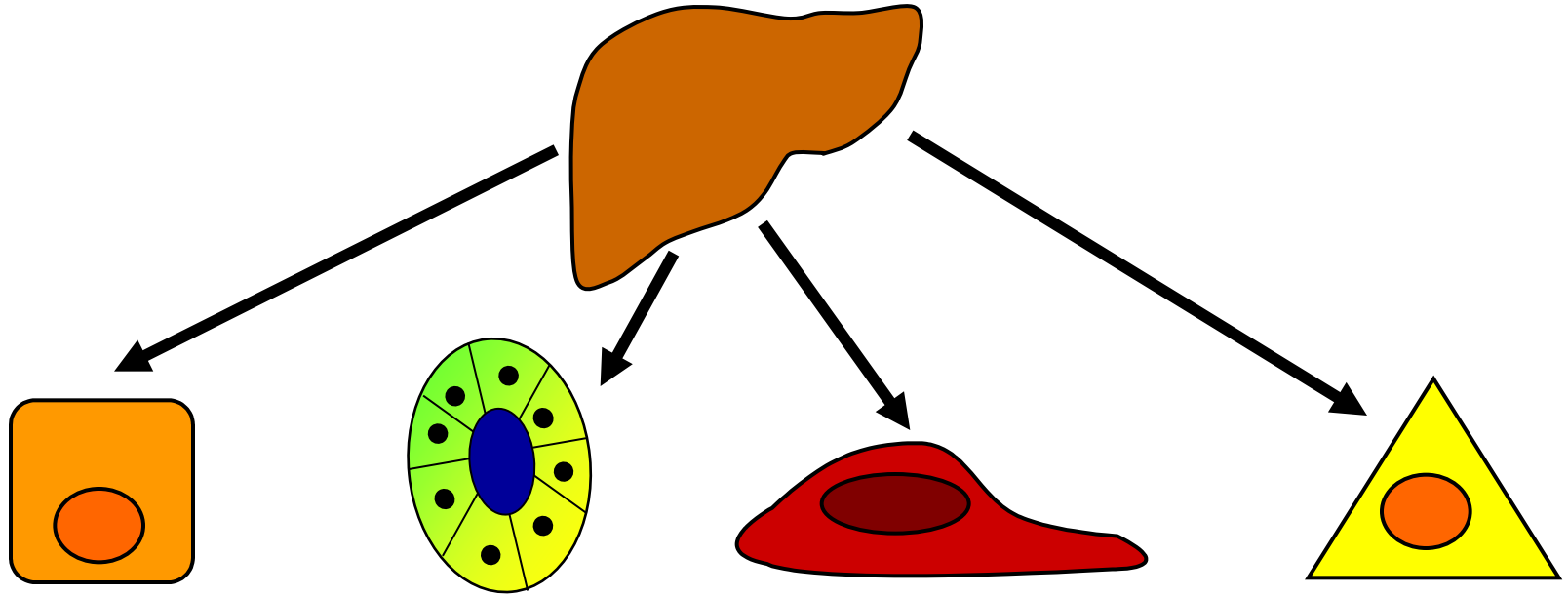


Daly et al Nat Genet 2009
Lucena et al Gastroenterology 2011



Dara, Liu and Kaplowitz Liver Intern 2015;

Clinico-pathological patterns



Hepatocyte	Colangiocyte	Endothelial cell	Stellate cell
Cholestatic hepatitis Chronic hepatitis Esteatosis NASH Neoplasia	Acute and chronic Cholangitis Sclerosing cholangitis	Veno-occlusive disease peliosis angiosarcoma	fibrosis

DILI presentation

- Hepatitis/cholestasis «like» syndrome or abnormalities in liver enzymes
- Atypical phenotypes
  - -AIH
  - -NAFLD
  - -NRH, SOS, peliosis hepatis
- Hypersensitity syndromes (point to drug allergy and makes DILI more probable)
  - -Non-specific Rash
  - -Erythema multiforme
  - -Drug reaction with eosinophilia and systemic symptoms (DRESS)
  - -Steven-Johnson/toxic epidermal necrolysis

- Rechallenge unintentional (6%)
- Previous DILI episodes (1.2%)

Andrade et al, Gastroenterology, 2005; Lucena et al , J Hepatol 2011

Interpretation of toxic liver damage by liver biochemistry alterations

- What are liver enzymes?
- Biochemical tests that reflect the health or pathologic , mainly inflammation and alteration in liver function.
- Useful
  - Screening of diseases or check in health population
  - Study of persistent and unspecific symptoms
  - Evaluation previous to surgery or diagnostic or therapeutic procedure
  - Study of liver disease suspicion

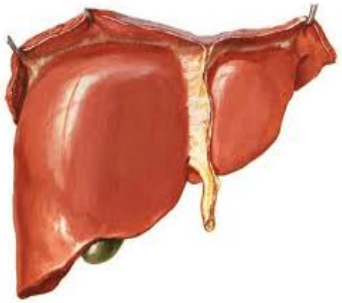
Liver tests panel

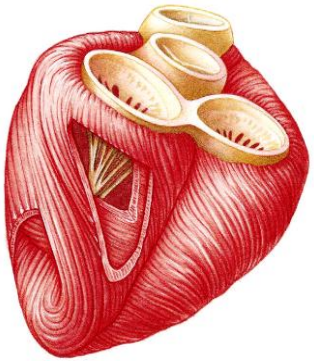
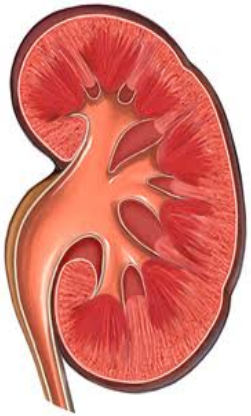
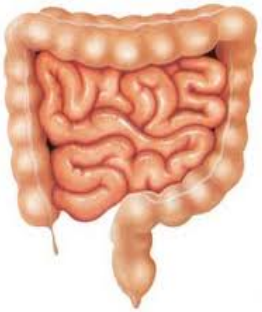
- AST
- ALT
- Alkaline phosphatase
- GGT
- Bilirubin (total and direct)
- INR
- Others: albumin globulins,

Source of AST and ALT

The transamination reaction ocurrs in several organs exchanging an amino group for a ketogroup

- ALT is also in the hearth and muscle but it is more concentrated in the liver
- Increases in both transaminases show liver injury
- Levels do not correlated with severity of the lesion
- Normal range vary among laboratories (31-72 U/L)



What does an elevated ALT value mean?

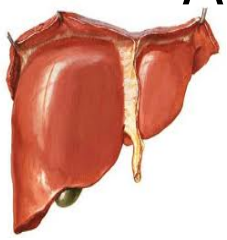
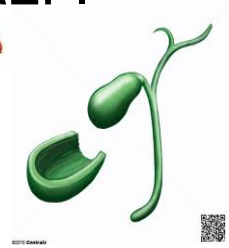
- It is not a test of liver function
- It does not necessarily predict worse effects to come (in a given person)
- It is not a valid measure of severity of liver injury or dysfunction.
- It is too unspecific to be reliable in screening for relatively rare effects on the liver.
- ALT remain the hallmark for detecting and classifying liver damage in DILI

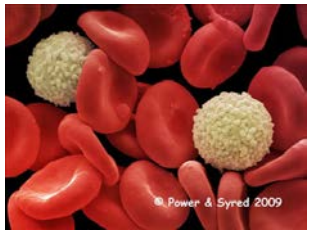
Source of Alkaline Phosphatase

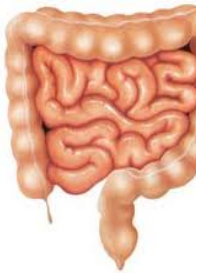
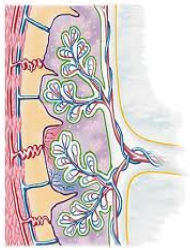
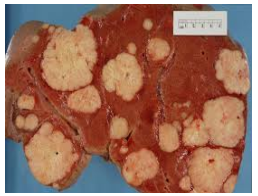
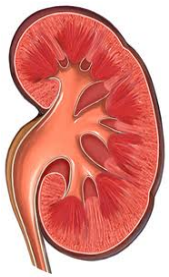
- Physiologic increase in the 3 first months of life, puberty (2-5 times higher than in adults) with a gradual increase between 40–65 years old mainly in women.

- In smokers ALP can be a 10% higher.

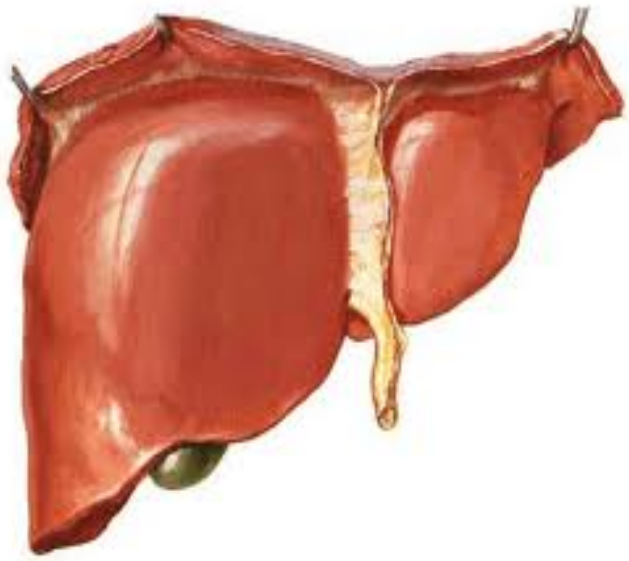
- People with blood type B and 0 could have an increase in ALP after a fatty meal due to liberation of intestinal ALP.



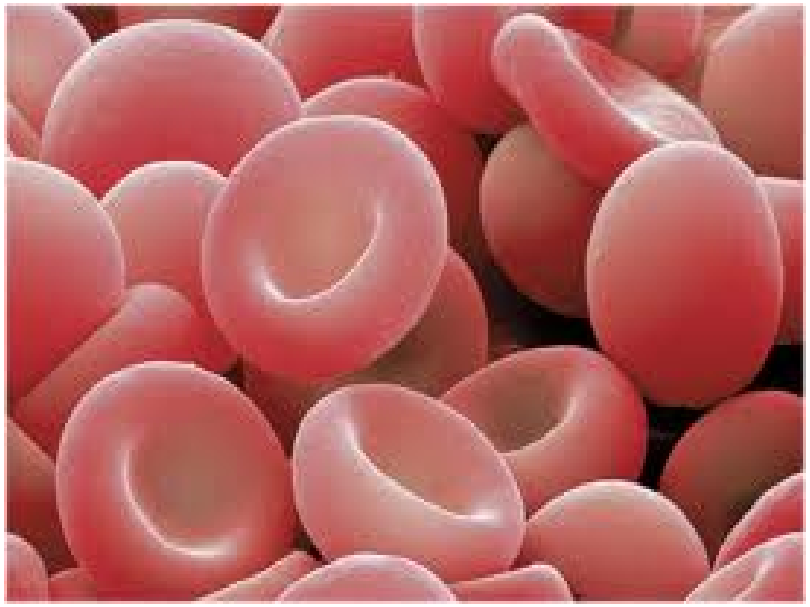





Source of GGT



The foremost value of GGT is to confirm the hepatic origin of ALP

Source of bilirubin



Serum total biliruin is an indicator of liver function
(the ability of the liver to clear plasma of bilirubin)

Alteration of liver profile

Sodio		135	mEq/L	135 - 145
Potasio		3.7	mEq/L	3.5 - 5.0
Cloro		102	mEq/L	85 - 110
Calcio		9.2	mg/dL	8.5 - 10.5
L.D.H	*	**1715**	U/L	84 - 246
GOT -ASAT-	*	**1922**	U/L	10 - 37
GPT -ALAT -	*	**633**	U/L	10 - 65
Gamma -GT	*	**506**	U/L	5 - 85
Fosfatasa Alcalina (ALP)	*	**434**	U/L	50 - 136
Bilirrubina Total		1.33	mg/dL	0.25 - 1.50
Bilirrubina Directa	*	**0.93**	mg/dL	0.10 - 0.50
Proteínas Totales		7.3	g/dL	6.4 - 8.2
Albúmina Sérica		3.9	g/dL	3.3 - 5.2
Cociente Albúmina / Globulina :		1.2	-	

Alteration of liver biochemistry

Aspartato transaminasa	*	**116**	U/L	13 - 40
Alanina transaminasa	*	**235**	U/L	7 - 40
Gamma glutamiltransferasa	*	**622**	U/L	15 - 85
Fosfatasa Alcalina	*	**246**	U/L	45 - 117
Bilirrubina Total	*	**7.49**	mg/dL	0.20 - 1.00
Bilirrubina Directa	*	**5.88**	mg/dL	< 0.30

What to do?

- A careful interrogatory:
  - Drugs or alcohol intake
  - Risk behaviour
  - Underlying disease
- A complete diagnostic work-up including blood analytes and a imaging tests

Coagulation parameters

Tiempo de protrombina			
Tiempo de protrombina (segundos)	13.4	seg	10.0 - 15.0
Tiempo de protrombina (porcentaje)	80	%	70 - 130
Tiempo de protrombina (ratio)	1.2	ratio	0.8 - 1.2
Tiempo de protrombina normalizado (INR)	1.1	INR	0.8 - 1.2
Tiempo de tromboplastina parcial activada			
Tiempo de tromboplastina parcial activada (segundos)	25.8	seg	25.0 - 38.0
Tiempo de tromboplastina parcial activada (ratio)	1.0	ratio	0.8 - 1.2

Virus serology

HBsAg	Negativo
Anti-HBs	Negativo
Anti-HBc	Negativo
Anti-HAV-IgM	Negativo
Antc-Virus Hepatitis C	Negativo
Citomegalovirus IgG	Positivo
Citomegalovirus IgM	Negativo
Herpesvirus IgG	Pendiente
Herpesvirus IgM	Pendiente
Epstein Barr IgG	Negativo
Epstein Barr IgM	Negativo

Serum proteins

Proteínas Totales		6.5	g/dL	6.4 - 8.2
PROTEINOGRAMA				
Albúmina	*	**3.4**	g/dL	3.8 - 4.2
Alfa 1 Globulina	*	**0.4**	g/dL	0.4 - 0.7
Alfa 2 Globulina		0.7	g/dL	0.6 - 1.0
Beta Globulina	*	**0.5**	g/dL	0.5 - 0.8
Gamma Globulina	*	**1.7**	g/dL	0.7 - 1.3
Cociente A/G	*	**1.1**		1.2 - 2.2
Albúmina %		51.60	%	50.30 - 63.60
Alfa 1 %		5.40	%	4.80 - 10.00
Alfa 2 %		10.20	%	8.40 - 15.00
Beta %		7.20	%	7.20 - 11.90
Gamma %	*	**25.60**	%	9.50 - 19.90
Comentario (proteinograma)		Componente monoclonal en fracción gamma		
Inmunoglobulina A	*	**41**	mg/dl	70 - 400
Inmunoglobulina G	*	**2000**	mg/dl	700 - 1600
Inmunoglobulina M	*	**15**	mg/dl	40 - 230
Alfa1 -Antitripsina		156	mg/dL	90 - 200
Ceruloplasmina	*	**18**	mg/dl	20 - 60
Cobre en Suero		120.0	mcg/dl	70.0 - 152.0

Screening for Autoimmune disorders

- Antinuclear autoantibody (ANA)
- Anti-smooth muscle autoantibody (ASMA)
- Anti liver kidney microsomal type 1 autoantibody (AntiLKM-1)
- Antimitochondrial autoantibody (AMA)
- IgG levels

Imaging techniques

- Abdominal Ultrasound
- CT
- MRI (ERCP)

Common patterns of liver biochemistry abnormalities

- Pattern with predominance of marked cytolysis with high levels of aminotransferases
- Chronic and recurrent moderate increase in transaminases
- Pattern with predominance of cholestasis (mixed cytolysis and alkaline phosphatase)
- Isolated increase in bilirubin
- Isolated increase in alkaline phosphatase and/or GGT

Pattern with markedly raised aminotransferases

- Acute viral hepatitis (A, B, C, E)
- Autoimmune hepatitis.
- Ischemic hepatitis.
- Unknown etiology hepatitis

Chronic and recurrent moderate increase in transaminases

- Chronic hepatitis B
- Chronic hepatitis C
- Chronic hepatitis E (infrequent)
- Non alcoholic fatty liver disease
- Alcoholic fatty liver disease
- Hemocromatosis
- Wilson disease

Pattern with predominance of cholestasis (mixed cytolisis /ALP + GGT)

- Obstructive biliary malignacies
- Liver metastasis
- Choledocolitiasis
- Primary biliary cirrhosis
- Primary sclerosing cholangitis.

Isolated increase in ALP

- Growth
- Bone metastasis
- Paget disease
- Others (physiologic: pregnancy)

Isolated increase in GGT

- Alcoholism
- Obesity
- Drugs (phenytoin)

Isolated increase in bilirubin

- Gilbert syndrome
- Hemolysis (increase in LDH)

Key concepts when assessing liver biochemistry in DILI suspicion

- Isolated increase in GGT does not reflect liver injury (enzimatic drug induction)
- Isolated increase in ALP is associated with physiological and pathological conditions other than liver injury (i.e.puberty, pregnancy, bone metastasis)
- ALT, ALP and total bilirubin should be screened in every DILI suspicion

Key concepts when using liver biochemistry in DILI suspicion (cont.)

- Elevated ALT itself is useful for detecting liver damage but not severity of whole liver impairment
- Liver biochemistry may not represent the true onset time of liver cell injury, which may already be advanced, subsiding or past when first found
- To determine how severe the injury is and whether it is *progressing* or *regressing*
  - Immediate testing and serial measurements of ALT, total bilirubin and INR is required
  - Diagnostic work-up for alternative causes should start inmediatly

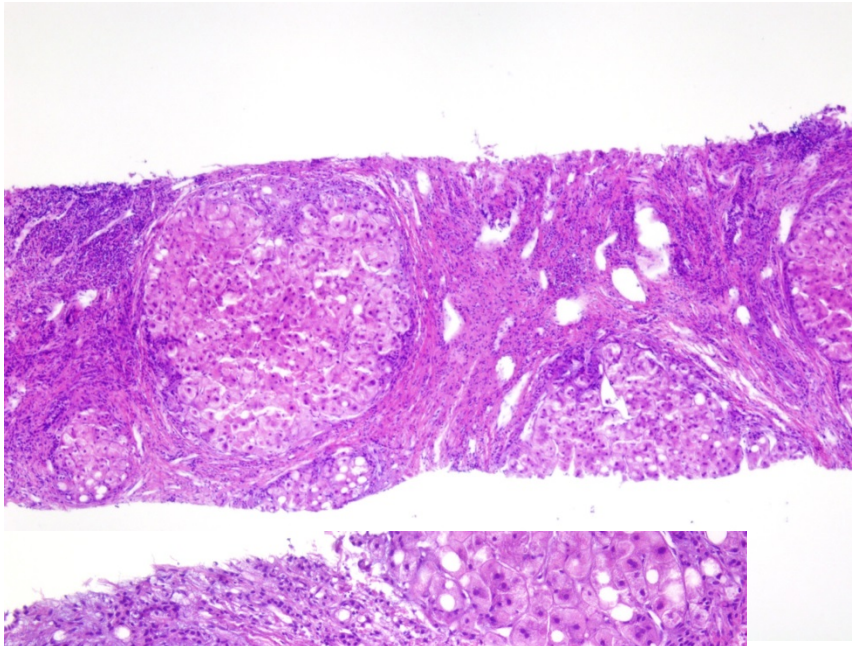
Clinical case 1

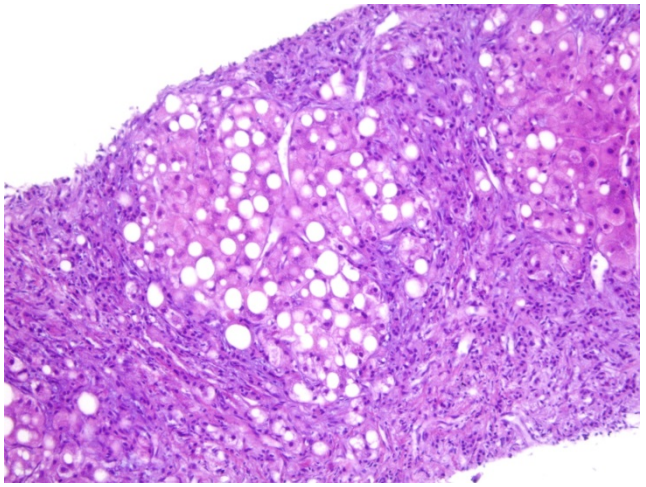
- A 37 yr female (BMI 24.6) started **azithromycin** (500 mg/d) during 3 days in Nov 2013, followed by **amoxicillin-clavulanic acid** (immediately before suspending azithromycin for 7 days) because of respiratory tract infection. No other drugs.
  - Previously diagnosed of cholestasis of pregnancy and diabetes during pregnancy in 2011
- While on amoxicillin-clavulanate she experienced dark urine, pale stools and itching. At examination she was slightly jaundiced
  - Liver tests at admission TB: 3,24 (Normal < 1,1mg/dL), AST 427 (Normal < 40UI/L), ALT 602 (Normal < 42 UI/L), ALP 216 (Normal < 130UI/L). Colagulation was normal. Blood cell count 2.7 x 10^9/L eosinophils 2.2%)
  - Diagnostic workup ruled out viral hepatitis A, B, C, E. Serum autoantibodies were negative.

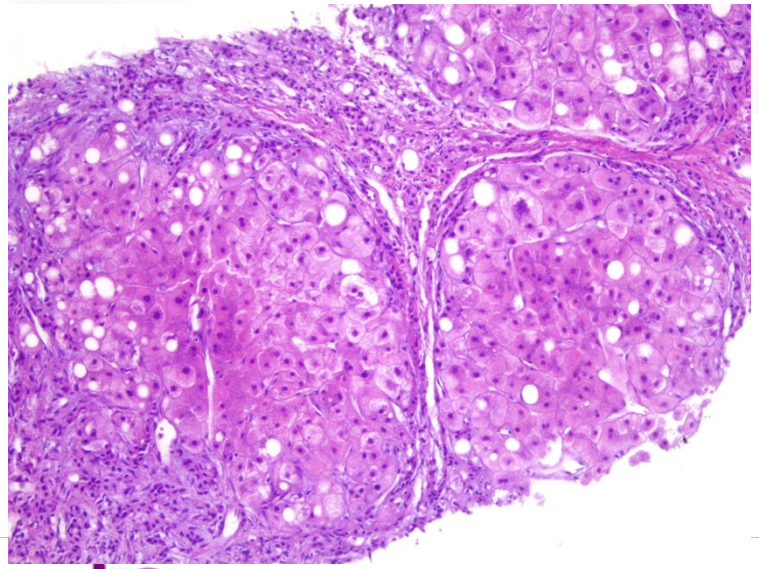
Clinical case 2

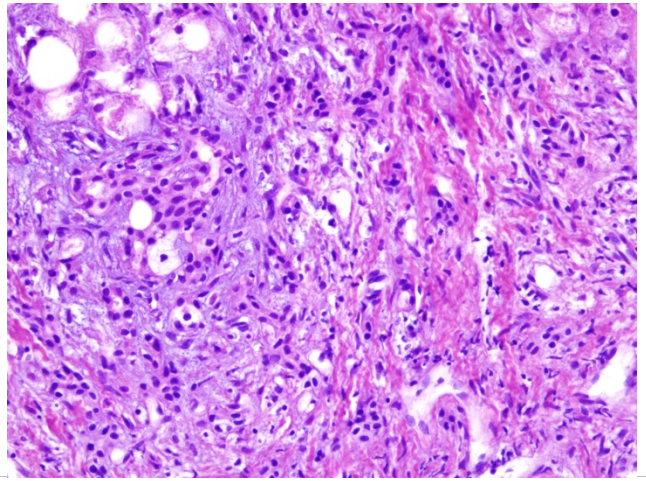
- 44 yr female, (BMI 28.9)started **tamoxifen** on Jan 2003 after breast cancer surgery.
  - Baseline liver tests: AST 68 U/L (normal < 35), ALT 86 U/L (normal<43), and GGT 280 U/L (normal < 35), with normal TB and ALP.
- In June 2003 jaundice
  - TB 1.85 mg/dL, AST 186 U/L, ALT 112 U/L, and GGT 446 U/L.
- TB reached 3.68 mg/dL and **tamoxifen** was discontinued on December 2003
- She voluntary decided to reintroduce **tamoxifen** on March 2004
  - TB 10.83 mg/dL, AST 154 U/L, ALT 47 U/L, ALP 132 U/L (normal < 100) and GGT 351 U/L.
  - Serology ruled out viral causes and screening for autoantibodies was negative

Liver biopsy









Liver biopsy