¿Como mejorar el diagnóstico de hepatotoxicidad?

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¿Qué es la hepatotoxicidad?

- **Alteración del perfil hepático** causado por fármacos (de prescripción o libre dispensación), productos de herboristería o suplementos dietéticos.
- **Elevación de los valores** de alanino aminotransferasa (ALT), fosfatasas alcalinas

Criterios bioquímicos para considerar DILI (conferencia de consenso)
ALT ≥ 5 xLimite superior de la normalidad (LSN)
FA ≥ 2 xLSN
ALT ≥ 3 xLSN + BT > 2 xLN

- La elevación aislada de bilirrubina o de gammaglutamil transferasa (GGT) no son suficientes para cualificar como DILI

Estos criterios pueden ser inaplicables en pacientes con enfermedad hepatica basal

Aithal GP,.., Andrade RJ,.., et al *Clin Pharmacol Ther* 2011; 89:806-15.

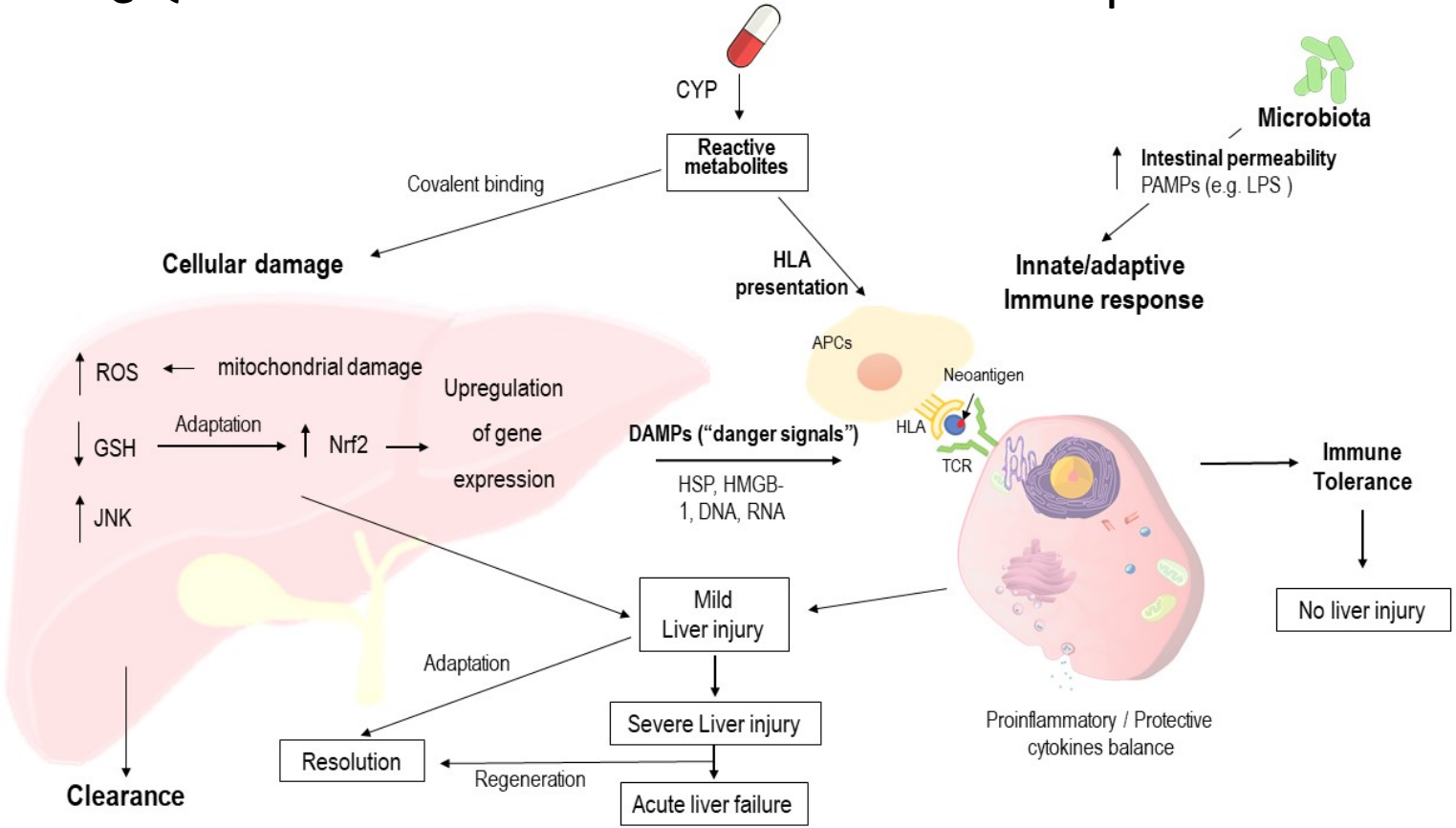
Drug induced liver injury (DILI) Types

Table 1. General categories of DILI

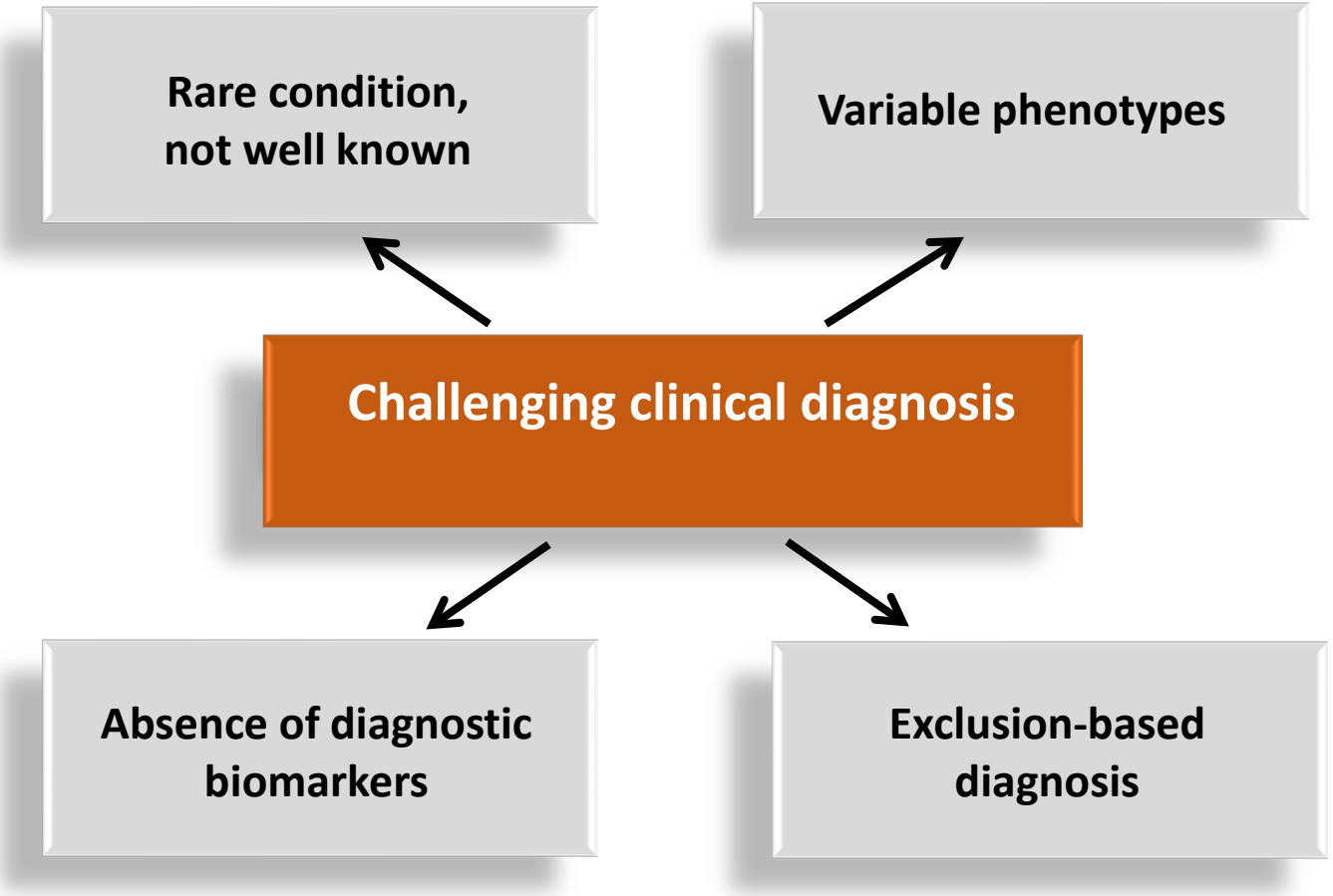
(Modified from: [Hoofnagle & Björnsson. N Engl J Med 2019;381:264-273])

	Direct (intrinsic)	Indirect	Idiosyncratic
Dose-related	Yes	No (generally)	No (with some exceptions)
Latency	Short (few days)	Typically delayed (weeks to months)	Variable (days to months), may occur after treatment discontinuation
Rate of occurrence	High	Intermediate	Low
Predictable	Yes	Occasionally	No
Implicated drugs (examples)	Acetaminophen, nicotinic acid, aspirin, cocaine, many cancer chemotherapies, fialuridine, amiodarone, methotrexate (intravenous), plants containing pyrrolizidine alkaloids	High-dose corticosteroids; some antineoplastic agents: immune checkpoint inhibitors, protein kinase inhibitors, monoclonal antibodies (*e.g.*anti-TNF, anti-CD20), daclizumab	Isoniazid, amoxicillin-clavulanate, macrolide antibiotics, fluoroquinolones, statins, flucloxacillin, diclofenac; certain herbal and dietary supplements (HDS), *e.g.* green tea extract, *Polygonum multiflorum*
Pathologic mechanisms	Liver damage occurs if parent drug or metabolite concentrations in liver cells exceed a toxic threshold	Unintended effects of drug actions on the liver (*e.g.* increased drug-induced immune autoreactivity or reduced insulin sensitivity may cause immune-mediated hepatitis and fatty liver, respectively)	Adaptive immune response to a parent drug or drug metabolite may contribute. Mitochondrial damage and hepatic steatosis may also be observed

¿Qué sabemos de los mecanismos de hepatotoxicidad?



Lucena,.. Andrade RJ. *Lancet Gastroenterol Hepatol* 2020; 5: 862-74


Rare condition, not well known
Variable phenotypes
Challenging clinical diagnosis
Absence of diagnostic biomarkers
Exclusion-based diagnosis

Manifestaciones clínicas y presentación

- Enormemente **variable** desde **asintomático** a **necrosis hepática masiva**
- Período de latencia muy variable usualmente < 3 meses
- Manifestaciones **de alergia asociadas,** clínicas o de laboratorio (eosinofilia, linfopenia) implican a farmacos como responsables. Presentes en 20-25% de casos.
- Multitud de fenotipos, **DILI puede simular cualquier enfermedad hepática** aguda o crónica

EASL Clinical Practice Guidelines: DILI. J Hepatol 2019; 70:1222-61
Stephens C,.. Andrade RJ. *J Hepatol* 2021; S0168-8278(21)00043-X. doi: 10.1016/j.jhep.2021.01.029.

Fenotipos de DILI

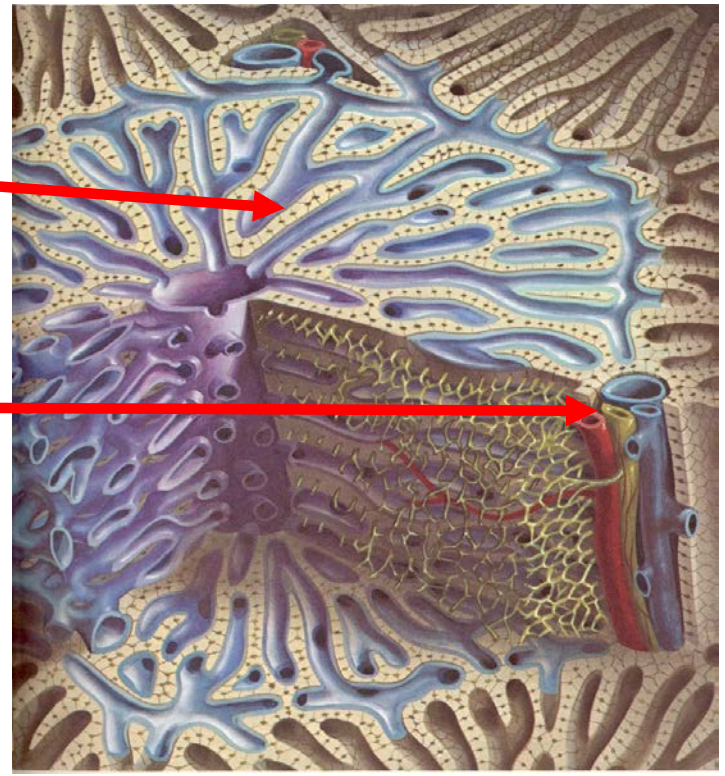
Hepatitis aguda (simulando hepatitis viral)	isoniazida, ketoconazol, ximelagatran
Hepatitis colestásica o mixta	amoxicilina-clavulánico, macrolidos
Necrosis hepatica aguda	Paracetamol, amiodarona IV
Síndrome de hipersensibilidad (DRESS)	Difenilhidantoína, carbamazepina
Esteatosis/ esteatohepatitis	metrotexato, tamoxifeno, irinotecan
Hígado graso agudo y acidosis metabólica	stavudina, tetraciclina, valproate sódico
Hepatitis autoimmune inducida por fármacos	minociclina, nitrofurantoina
Síndrome obstruction sinusoidal	ciclofosfamida, azatioprina
Hiperplasia nodular regenerativa	azatioprina, HAART, bleomicina
Daño hepático inmuno-mediado	ipilimumab, pembrolizumab, nivolumab

- Diferentes manifestaciones clínicas
- Diferentes alteraciones bioquímicas
- Diferente pronóstico

Drug-induced liver injury (DILI): Current status and future directions for drug development and the post-market setting.
https://cioms.ch/wp-content/uploads/2020/06/CIOMS_DILI_Web_16Jun2020.pdf

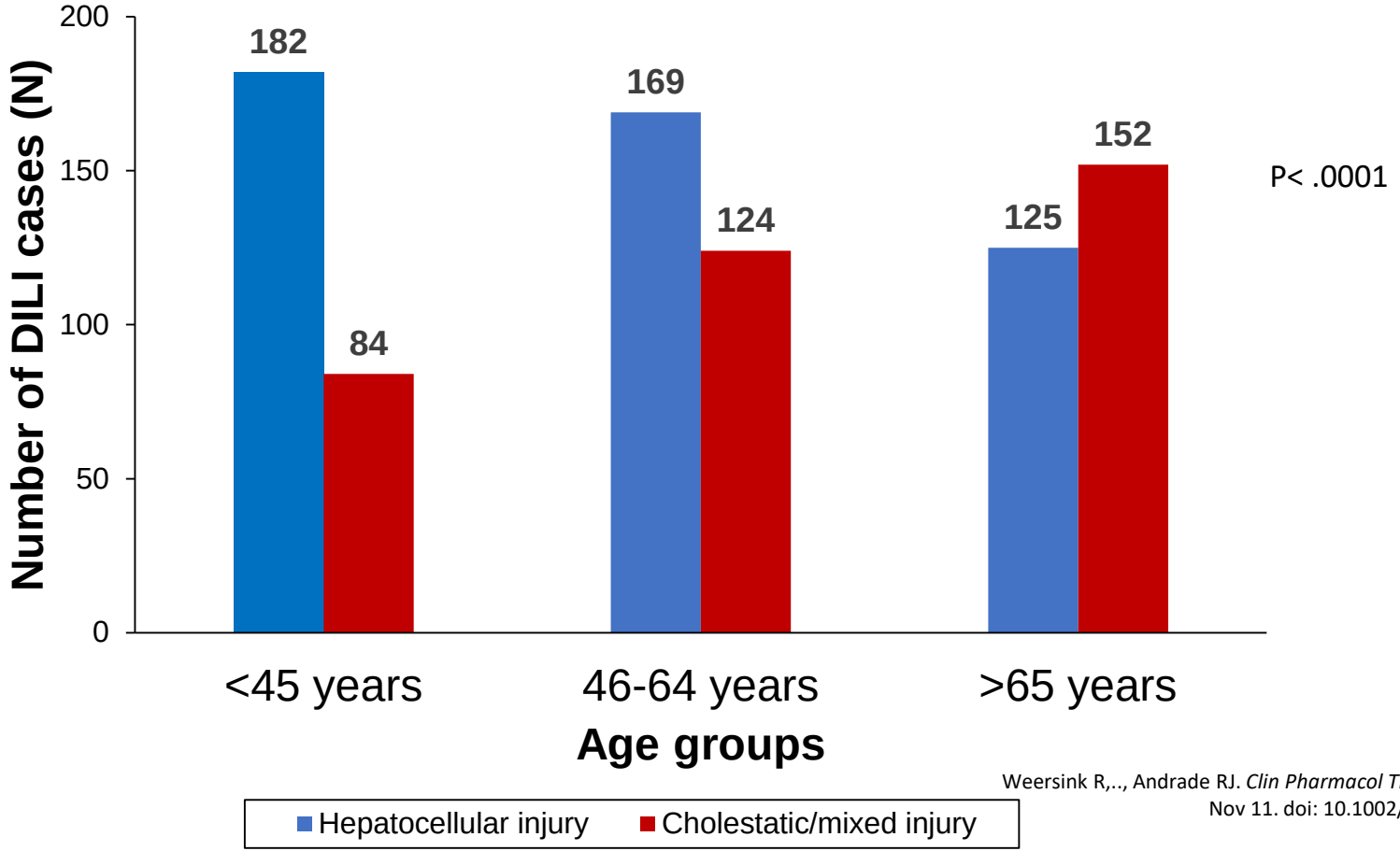
Clasificación DILI

- **HEPATOCELULAR**: elevación predominante de ALT (ALT xLSN/FA xLSN) ≥5
- **COLESTASICO**: elevación predominante de FA (ALT xLSN/FA xLSN) ≤2
- **MIXTO** ALT & FA se incrementan, and 2<ALT xLSN/FA xLSN<5



Bénichou C. *J Hepatol.* 1990; 11: 272-6.
Fontana RJ,…, Andrade RJ,.., et al. *Hepatology* 2010;52:730-42.
Aithal GP,.., Andrade RJ,.., et al *Clin Pharmacol Ther* 2011; 89:806-15.

Fenotipos de presentación de acuerdo a la edad en el Spanish DILI Registry



Weersink R,.., Andrade RJ. *Clin Pharmacol Ther* 2020; Nov 11. doi: 10.1002/cpt.2108

ARTICLE IN PRESS

Clinical Practice Guidelines

JOURNAL OF HEPATOLOGY

EASL Clinical Practice Guidelines: Drug-induced liver injury☆

European Association for the Study of the Liver*

April 2019 | **Topic:** Metabolism, alcohol and toxicity

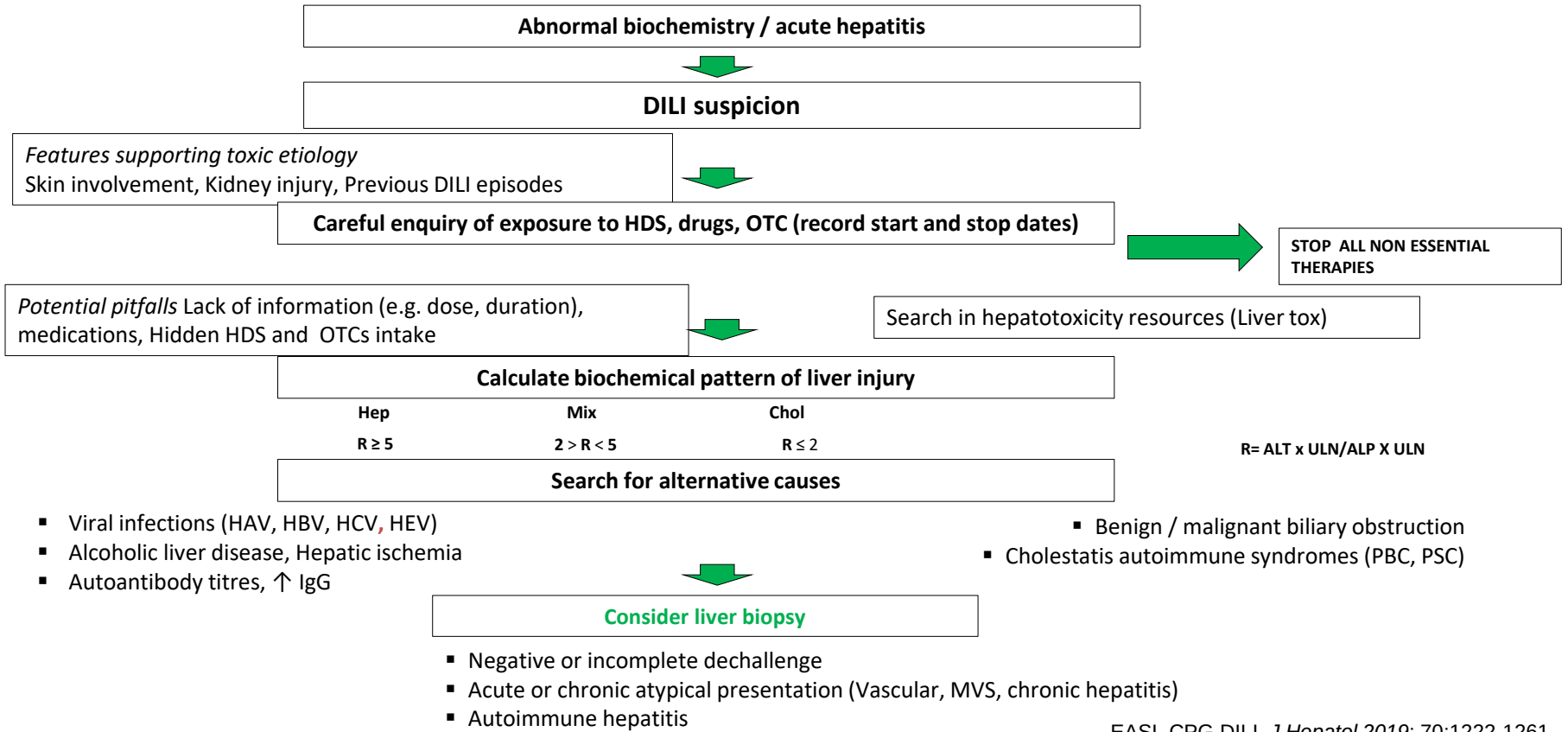
Drug-induced liver injury

Idiosyncratic (unpredictable) drug-induced liver injury is one of the most challenging liver disorders faced by hepatologists, because of the myriad of drugs used in clinical practice, available herbs and dietary supplements with hepatotoxic potential, the ability of the condition to present with a variety of clinical and pathological phenotypes and the current absence of specific biomarkers.

Read More >

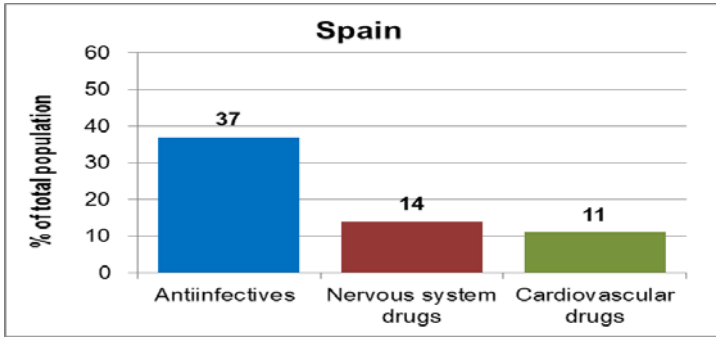
☆ **Clinical practice guidelines panel:** Chair: Raul J. Andrade; Panel members: Guruprasad P. Aithal, Einar S. Bjornsson, Neil Kaplowitz, Gerd A. Kullak-Ublick, Dominique Larrey; EASL Governing Board representative: Tom H. Karlsen.

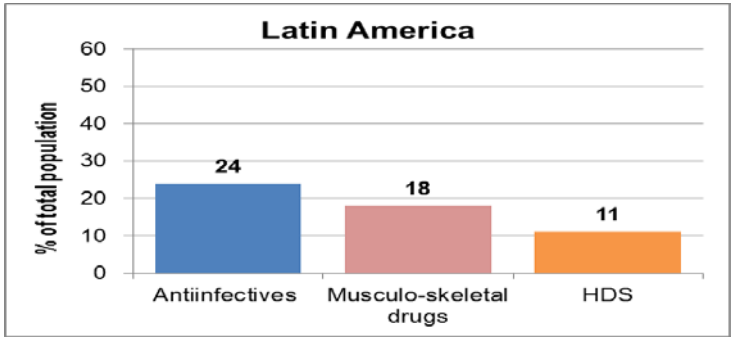
Algoritmo para un diagnostico ordenado del DILI

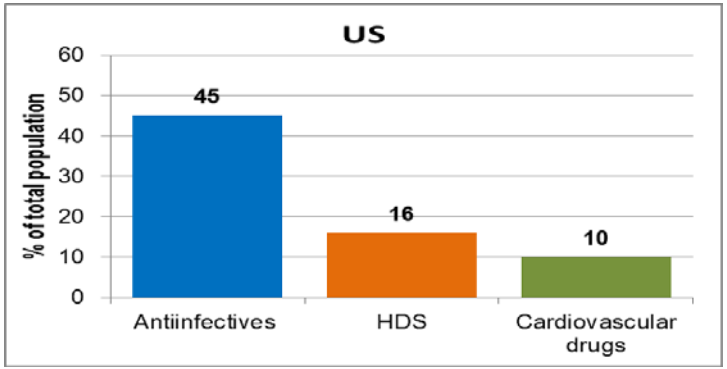


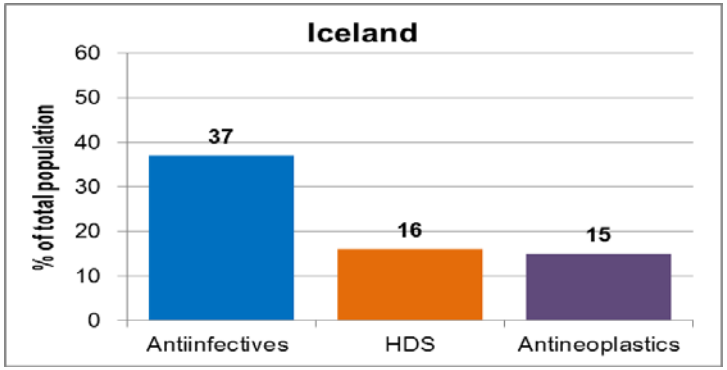
EASL CPG DILI. *J Hepatol 2019*; 70:1222-1261

Most common causative drugs in large DILI populations









Andrade RJ, et al. *Gastroenterology* 2005;129:512–21; Chalasani N, et al. *Gastroenterology* 2015;148:1340–52.e7; Bessone F, et al. *Int J Mol Sci* 2016;17:313; 4. Björnsson ES, et al. *Gastroenterology* 2013;144:1419–25.e3.

DRUG RECORD

TERBINAFINE

OVERVIEW
Terbinafine

Introduction
Terbinafine is an orally and topically active allylamine fungicidal agent which is used to treat superficial fungal infections of the skin and nails. Terbinafine has been clearly linked to rare instances of acute liver injury that can be severe and sometimes fatal.

Background
Terbinafine (ter' bin a feen) is a synthetic allylamine derivative that has potent activity against many dermatophytes that affect skin and nails, including Epidermophyton floccosum, Trichophyton mentagrophytes and Trichophyton rubrum. The antifungal activity of terbinafine is believed to be due to the selective inhibition of fungal squalene epoxidase, which increases squalene to toxic levels, thus killing the fungal cell. Terbinafine was approved for use in the United States in a topical form in 1992 and as an oral antifungal agent in 1998. Topical terbinafine is available over-the-counter as a 1% cream or spray for treatment of dermatophyte infections of the skin (tinea pedis, cruris or corporis). Oral terbinafine is available by prescription only in tablets of 250 mg generically and under the brand name of Lamisal. Oral terbinafine is used in the therapy of onychomycosis or fungal infections of the fingernails or toenails (tinea unguium) typically in a dose of 250 mg once daily for 6 weeks (fingernails) or 12 weeks (toenails). The most common side effects of terbinafine include gastrointestinal disturbances, headache, change in taste and rash.

Hepatotoxicity
Drug induced liver injury due to terbinafine was identified shortly after its introduction into

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Hepatotoxicity

Drug induced liver injury due to terbinafine was identified shortly after its introduction into medical use. Oral therapy with terbinafine is associated with elevations in serum aminotransferases in less than 1% of patients and the elevations are generally asymptomatic and resolve without stopping therapy. The estimated probability of developing elevated serum aminotransferase levels requiring stopping treatment is about 0.31% for 2 to 6 weeks' treatment and 0.44% for treatment longer than 8 weeks.

Clinically apparent liver injury from terbinafine occurs rarely (1 in 50,000 to 120,000 prescriptions), but many case reports and even case series have been described in the literature. Liver injury usually arises within the first 6 weeks of therapy. The pattern of injury can be either hepatocellular or cholestatic initially, but typically evolves into a cholestatic pattern which can be prolonged (Cases 1 and 2). Some cases may progress to vanishing bile duct syndrome. Signs of hypersensitivity (rash, fever, eosinophilia) are not common and, when present, are generally mild-to-moderate in severity. Autoantibody formation is rare. In addition, cases with severe hepatocellular injury with acute liver failure have been described. These instances are marked by precipitous onset with marked elevations in serum aminotransferase levels and progressive jaundice and hepatic failure. Terbinafine has also been implicated in cases of Stevens-Johnson syndrome, in which case the hepatic injury may be overshadowed by rash and allergic symptoms.

Likelihood score: B (highly likely cause of clinically apparent liver injury).

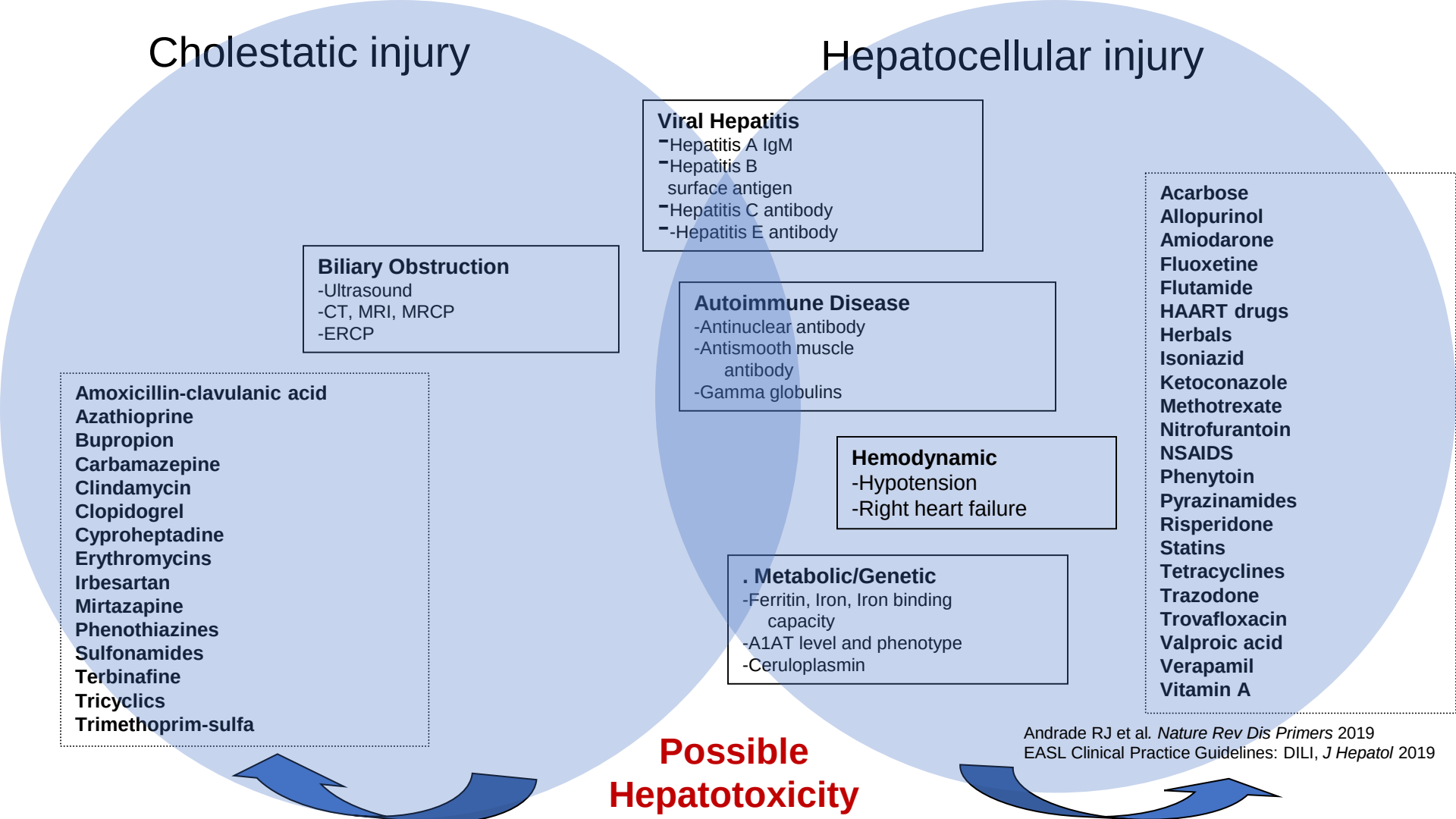
HEPATOLOGY
Official Journal of the American Association for the Study of Liver Diseases
AASLD
LIVER INJURY/REGENERATION

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]

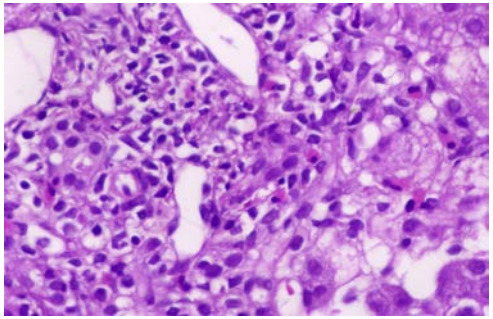
Category A	The drug is well known, well described and well reported to cause either direct or idiosyncratic liver injury, and has a characteristic signature; more than 50 cases including case series have been described
Category B	The drug is reported and known or highly likely to cause idiosyncratic 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”

Björnsson ES, Hoofnagle JH. *Hepatology.* 2016;63:590-603.

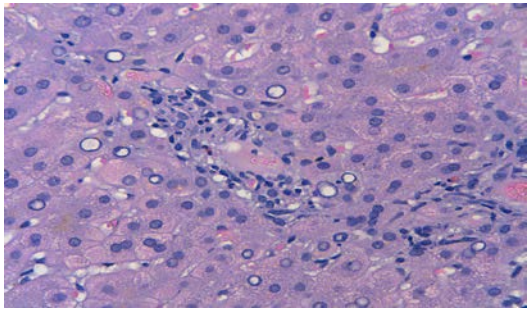


Andrade RJ et al. *Nature Rev Dis Primers* 2019
EASL Clinical Practice Guidelines: DILI, *J Hepatol* 2019

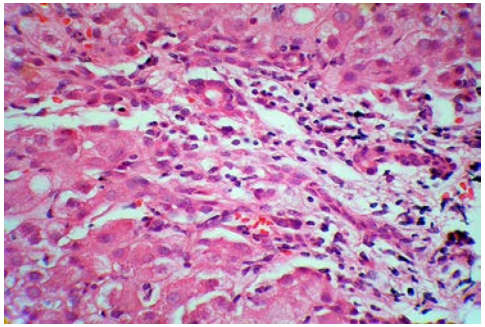
DILI: histología



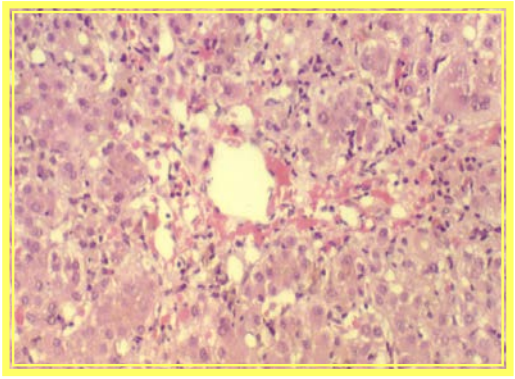
Inflamación portal y eosinófilos



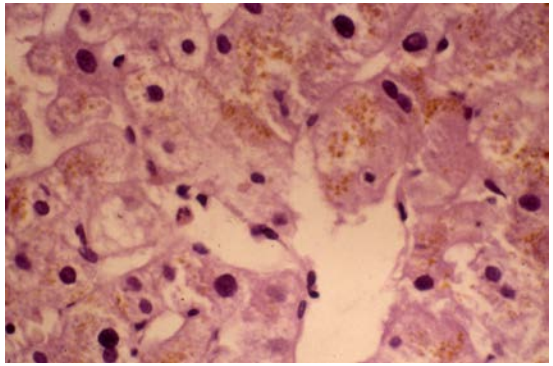
Inflamación lobular y eosinófilos



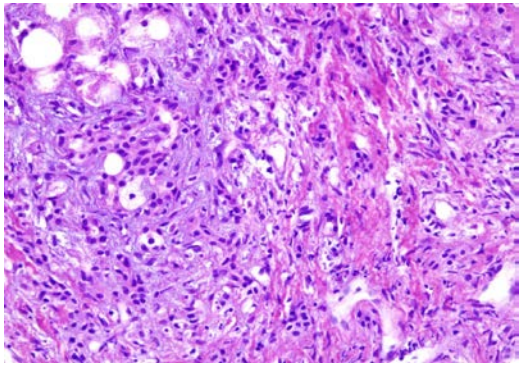
Hepatitis y colestasis



Necrosis centrolobulillar



Colestasis pura

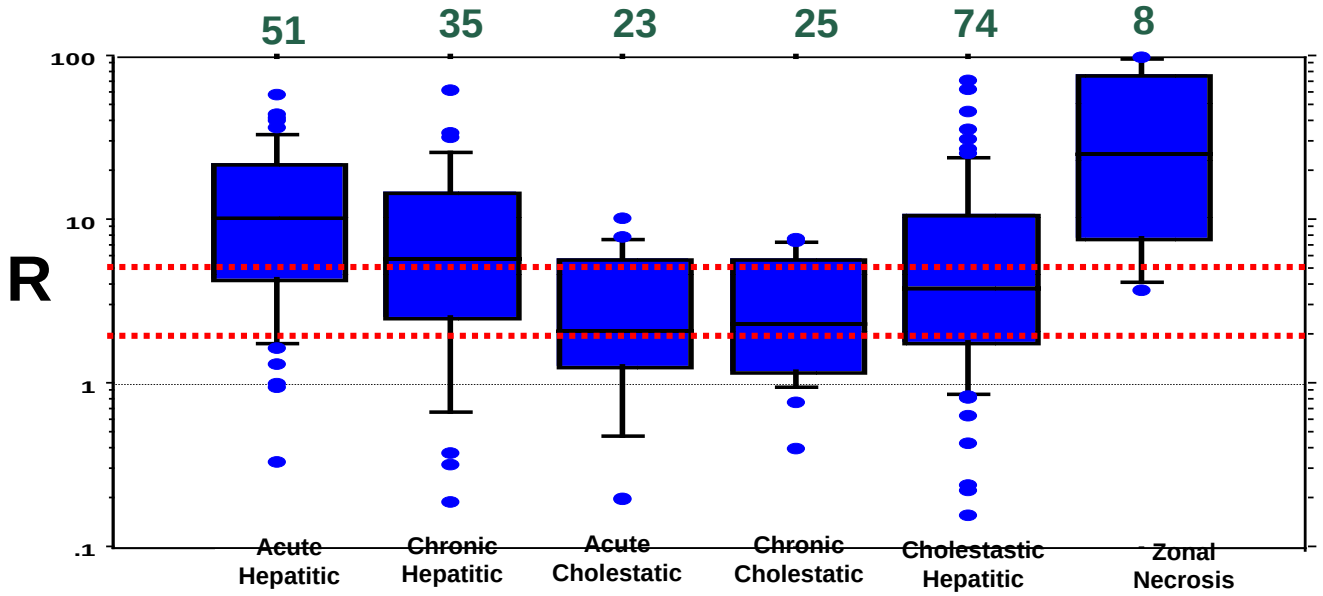


Esteatohepatitis con cirrosis

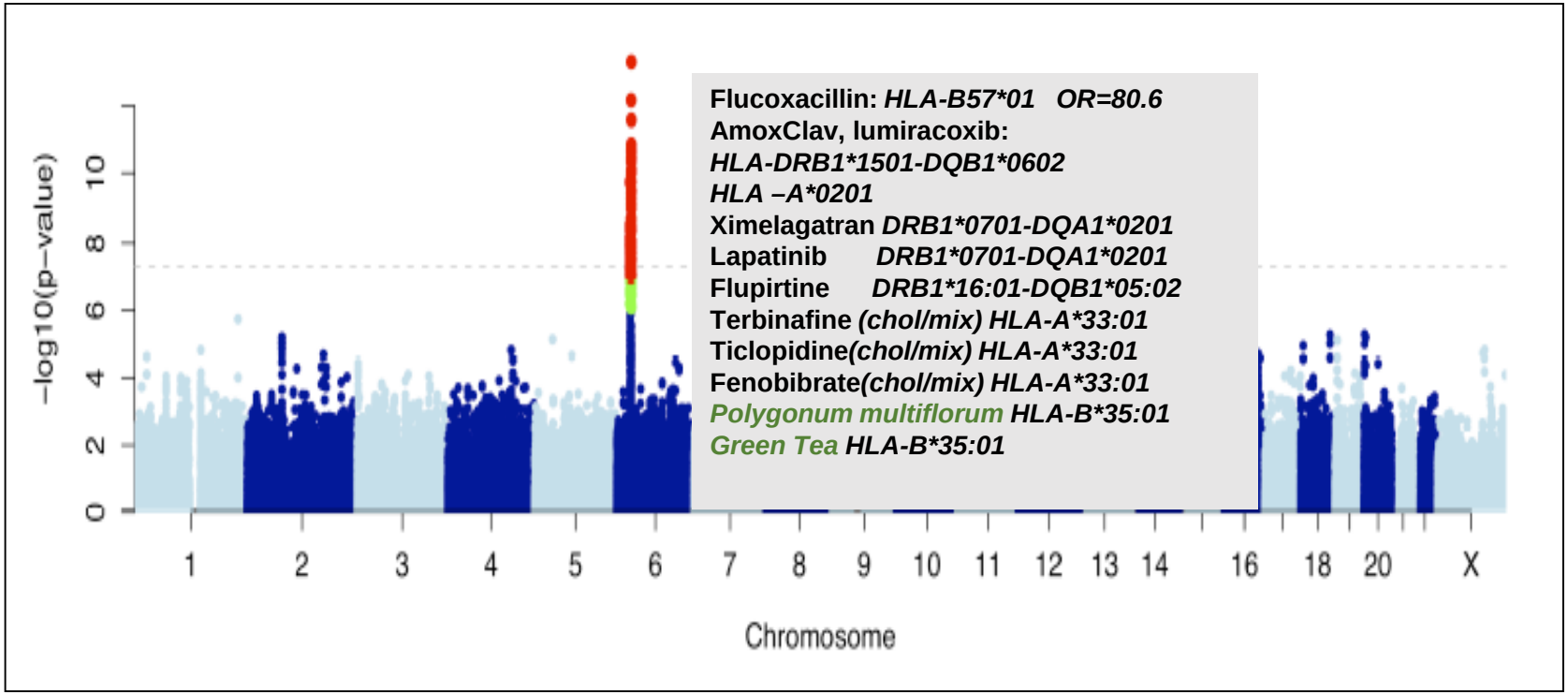
Hepatic Histological Findings in Suspected Drug-Induced Liver Injury: Systematic Evaluation and Clinical Associations

Kleiner et al., *Hepatology*, 2014 ;59:661-70

- **Liver biopsies from 249 cases of suspected DILI blindly reviewed – 18 DILI patterns identified**



GWAS DILI : cromosoma 6 (genes HLA)



Kindmark A e al. *Pharmacogenomics J* 2008;8:186-95; Daly AK et al. Nat Genet 2009; 41:816-9. Spraggs, CF, et al. J Clin Oncol 2011;29:667-73; Lucena MI et al, Gastroenterology 2011; 141:338-47; Nicoletti P et al. *Gastroenterology* 2017 152:1078-1089.; Li C, et al. *Hepatology* 2019; 70:346-357; Hoofnagle JH, et al. *Hepatology* 2020 ; doi: 10.1002/hep.31538

Utilidad de los test genéticos en DILI

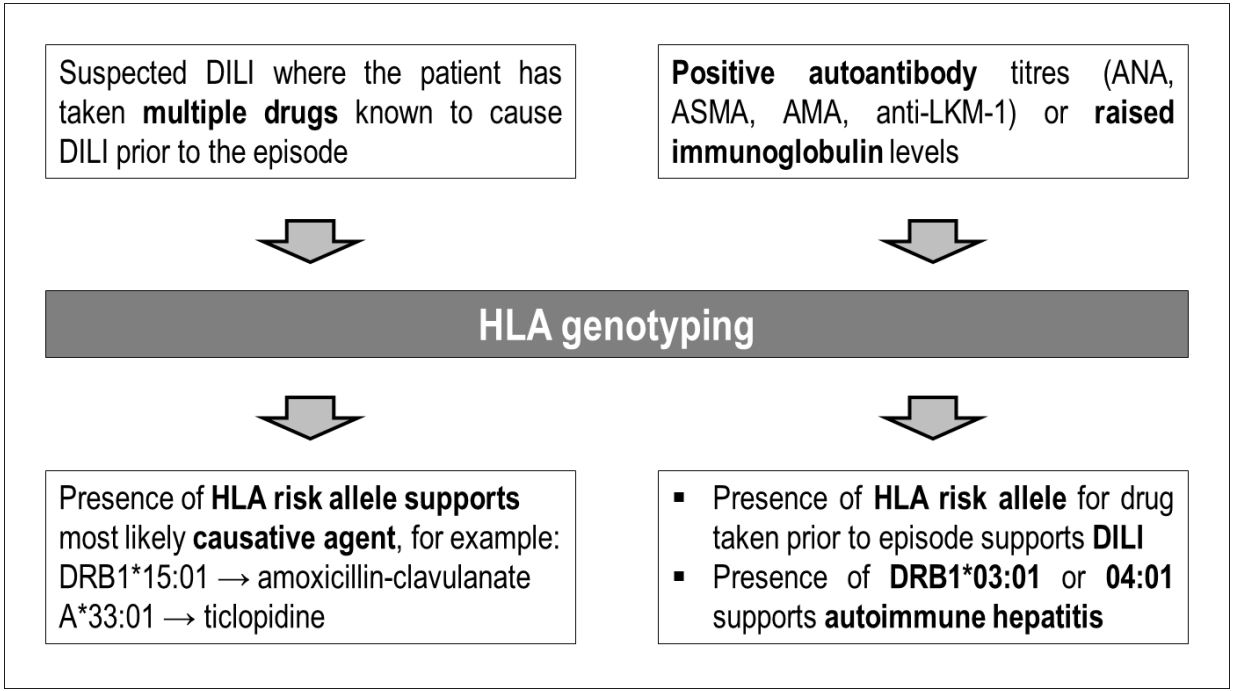
- Elevado valor predictive negativo (>95%) → para excluir DILI frente a otras alternativas

- Presencia/ausencia de alelos de riesgo apoyan o refutan el diagnostico de DILI

- Indican el agente causal mas probable en sospechas de DILI en tratamiento con varios fármacos simultáneamente

- Ayudan a distinguir entre el DILI con manisfestaciones autoinmunes y la hepatitis autoimmune idiopática

Utilidad de los test genéticos en DILI



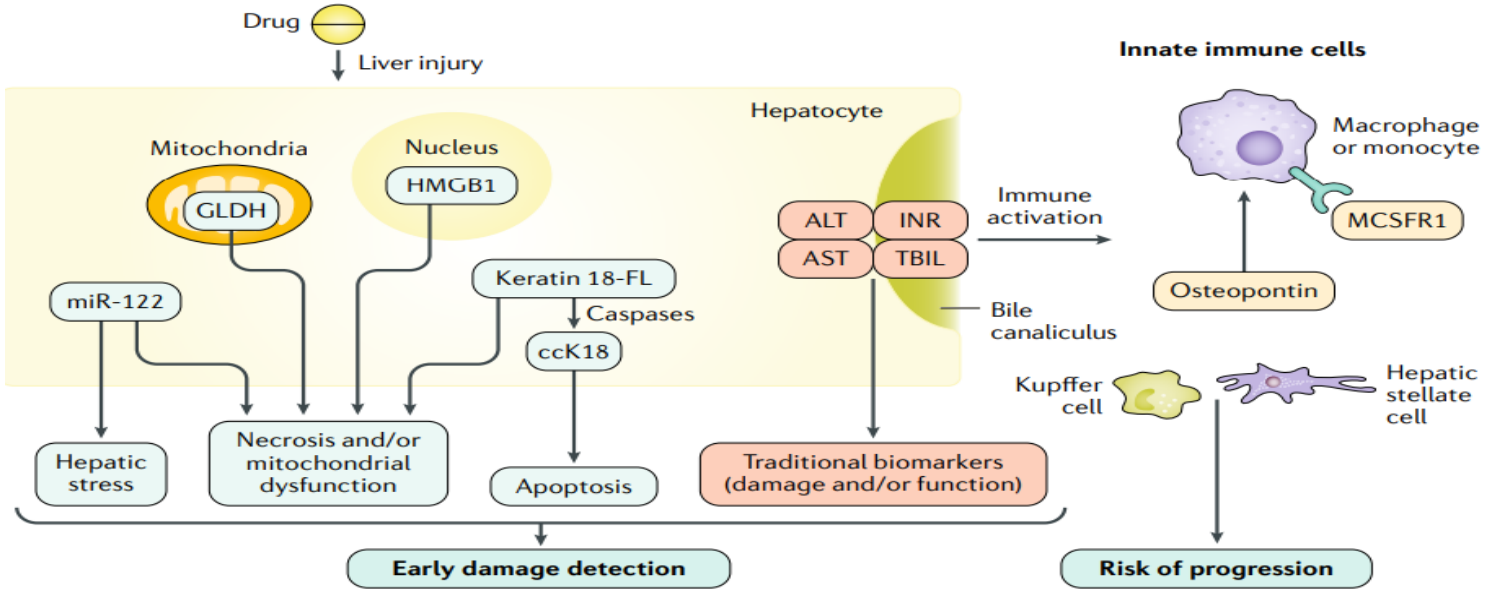
Stephens C & Andrade RJ, *Clin Liver Dis* 2020; 24:11-23

Similar performance characteristics between HLA risk alleles in DILI and important criteria in AIH?

Test: antibodies	% positive in AIH cases	% + in 'normal' population
ANA 1:60	68%-75%	15% (< 40 ♀) - 24% (> 40 ♀)
ASMA	52%-59%	Up to 43%
IgG >1600 mg/dL	86%	5%
Anti-LKM	4%-20%	1%
Test: HLA type	**% positive in DILI cases**	**% + in 'normal' population**
*DRB1*15:01*	57%-67% (Amoxicillin-clavulanate)	15%-20%
*B*57:01*	84%-87% (Flucloxacillin)	6%
*A*31:01*	17% (Carbamazepine)	2%
*DRB1*16:01-DQB1*05:02*	25% (Flupirtine)	1%
*A*33:01*	80% (Ticlopidine) 50% (Methyldopa) 50% (Enalapril) 43% (Fenofibrate) 43% (Terbinafine) 40% (Sertraline) 20% (Erythromycin)	1%
*B*35:02*	16% (Minocycline)	0.6%

Kaliyaperumal et al, *J Hepatol* 2018; 69:948-957.
EASL Clinical Practice Guidelines: DILI. *J Hepatol* 2019; 70:1222-61

Nuevos biomarcadores en DILI



Andrade, R.J. et al. Drug-induced liver injury. *Nat. Rev. Dis. Primers* doi.org/10.1038/s41572-019-0105-0

CIOMS/RUCAM REPORT FORM

RUCAM Causality Assessment of a Drug in a Case of Acute Liver Injury

	Hepatocellular Type		Cholestatic or Mixed Type		Assessment
1 Time to onset:					
Incompatible	Reaction occurred before starting the drug or more than 15 days after stopping the drug (except for slowly metabolized drugs)		Reaction occurred before starting the drug or more than 30 days after stopping the drug (except for slowly metabolized drugs)		**Unrelated**
Unknown	When information is not available to calculate time to onset, then case is:				**Insufficiently documented**
	Initial Treatment	**Subsequent Treatment**	**Initial Treatment**	**Subsequent Treatment**	**Score** *(check the results)*
1a From the beginning of the drug:					
Suggestive	5–90 days	1–15 days	5–90 days	1–90 days	☐ +2
Compatible	< 5 or > 90 days	> 15 days	< 5 or > 90 days	> 90 days	☐ +1
1b From the cessation of the drug:					
Compatible	≤ 15 days	≤ 15 days	≤ 30 days	≤ 30 days	☐ +1
2 Course:	**Difference between the Peak of ALT** *(SGPT)* **and Upper Limit of Normal Values**		**Difference between the Peak of A.P.** *(or TB)* **and Upper Limit of Normal Values**		
2a After cessation of the drug:					
Highly suggestive	Decrease ≥ 50% within 8 days		Not applicable		☐ +3
Suggestive	Decrease ≥ 50% within 30 days		Decrease ≥ 50% within 180 days		☐ +2
Compatible	Not applicable		Decrease < 50% within 180 days		☐ +1
Inconclusive	No information **OR** Decrease ≥ 50%, after the 30th day		Persistence or increase or no information No situation		☐ 0
Against the role of the drug **OR**	Decrease < 50%, after the 30th day **OR** Recurrent increase		Not applicable		☐ –2
2b If the drug is continued:					
Inconclusive	All situations		All situations		☐ 0
3 Risk factors:	**Ethanol**		**Ethanol or Pregnancy**		
Presence					☐ +1
Absence					☐ 0
Age of the patient ≥ 55 years					☐ +1
Age of the patient < 55 years					☐ 0

CIOMS/RUCAM REPORT FORM

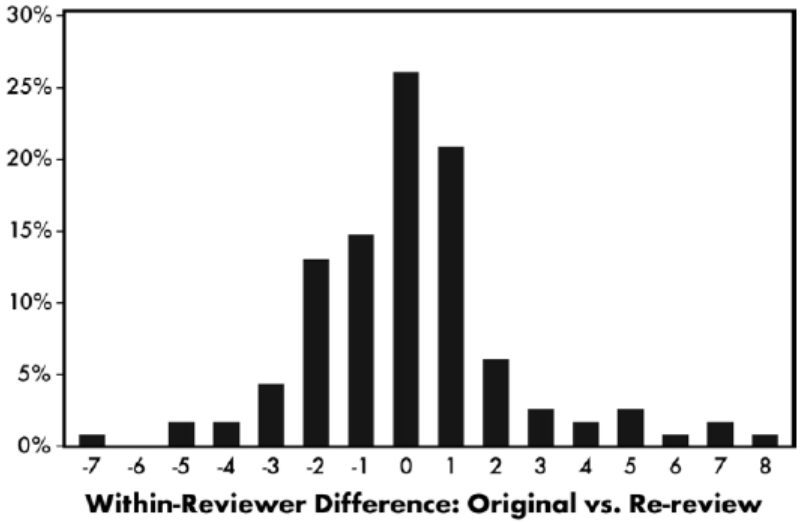
RUCAM Causality Assessment of a Drug in a Case of Acute Liver Injury (continued)

			Score
4	**Concomitant drug(s):**		
	None or no information or concomitant drug with incompatible time to onset		☐ 0
	Concomitant drug with compatible or suggestive time to onset		☐ –1
	Concomitant drug known as hepatotoxin and with compatible or suggestive time to onset		☐ –2
	Concomitant drug with evidence for its role in this case *(positive rechallenge or validated test)*		☐ –3
5	**Search for nondrug causes:**		
	Group I *(6 causes)*: **Recent viral infection with HAV** *(IgM anti-HAV antibody)* or **HBV** *(IgM anti-HBc antibody)* or **HCV** *(anti-HCV antibody and circumstantial arguments for non-A, non-B hepatitis)*; **Biliary obstruction** *(ultrasonography)*; **Alcoholism** *(AST/ALT ≥2)*; **Acute recent hypotension history** *(particularly if underlying heart disease)*. **Group II:** Complications of underlying disease(s); clinical and/or biological context suggesting CMV, EBV or herpes virus infection.	• All causes–groups I and II–reasonably ruled out	☐ +2
		• The 6 causes of group I ruled out	☐ +1
		• Five or 4 causes of group I ruled out	☐ 0
		• Less than 4 causes of group I ruled out	☐ –2
		• Non drug cause highly probable	☐ –3
6	**Previous information on hepatotoxicity of the drug:**		
	Reaction labeled in the product characteristics		☐ +2
	Reaction published but unlabeled		☐ +1
	Reaction unknown		☐ 0
7	**Response to readministration:**		
	Positive	Doubling of ALT with the drug alone	Doubling of AP *(or TB)* with the drug alone ☐ +3
	Compatible	Doubling of ALT with the drugs already given at at the time of the first reaction	Doubling of AP *(or TB)* with the drugs already given at the time of the first reaction ☐ +1
	Negative	Increase of ALT but less than N in the same conditions as for the first administration	Increase of AP *(or TB)* but less than N in the same conditions as for the first administration ☐ –2
	Not done or not interpretable	Other situations	Other situations ☐ 0

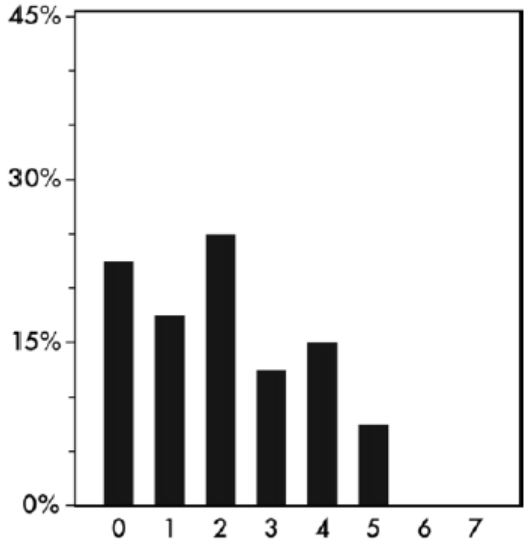
Investigator Signature

Investigator's signature: _____ Date signed: __ __ / __ __ / __ __ __ __
(day / month / year)

CIOMS/RUCAM Reproducibility



Within reviewer differences



Between reviewer differences

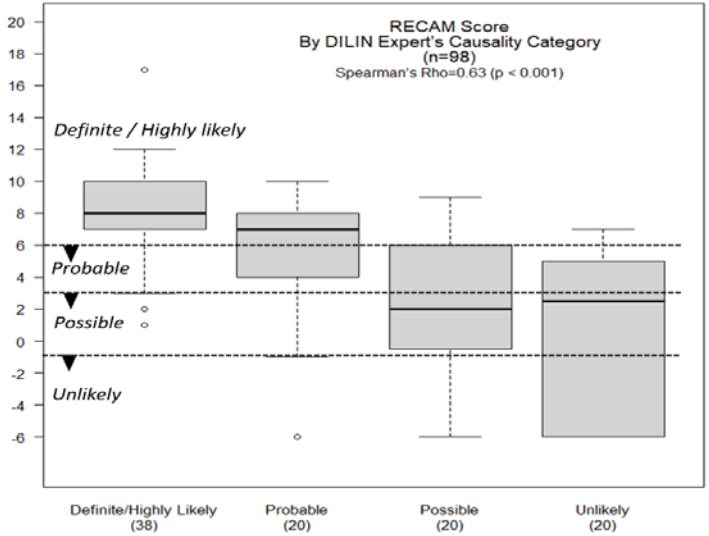
*Rochon et al Hepatology, 2008; 48(4): 1175-11836

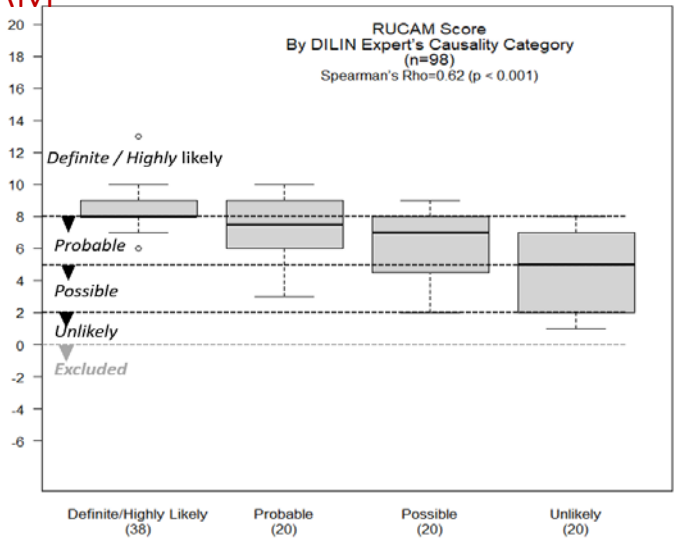
ReCAM

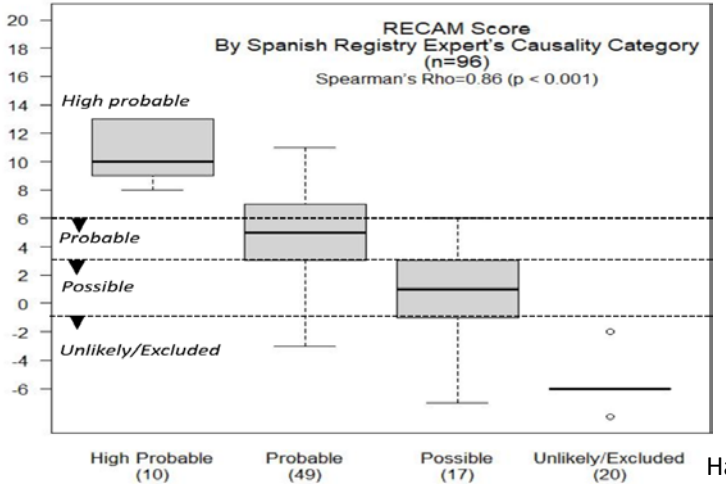
- Criterios RUCAM revisados por consenso de expertos (DILIN, Spanish DILI, NIH, FDA, Nottingham, Iceland)
  - Latencia: desde inicio y desde interrupción
  - Dechallenge: no diferencia entre hepatocelular y colestásico mixto
  - Factores de riesgo: no se puntúan la edad, el alcohol o el embarazo
  - Fármacos concomitantes: no sustraen puntos, se evalúan aparte
  - Causas alternativas: criterios específicos para disminuir la subjetividad en hepatitis C, hepatitis E y hepatopatía alcohólica.
  - Potencial hepatótoxico: vinculado a la categoría de LiverTox
  - Rechallenge: se puntua mas si el rechallenge es prospectivo y documentado
  - *Datos adicionales*: histología hepática, serología viral atípica, lesiones cutáneas
  - Stop: si causa alternativa claramente identificada (-6 puntos) o secuencia temporal incompatible.

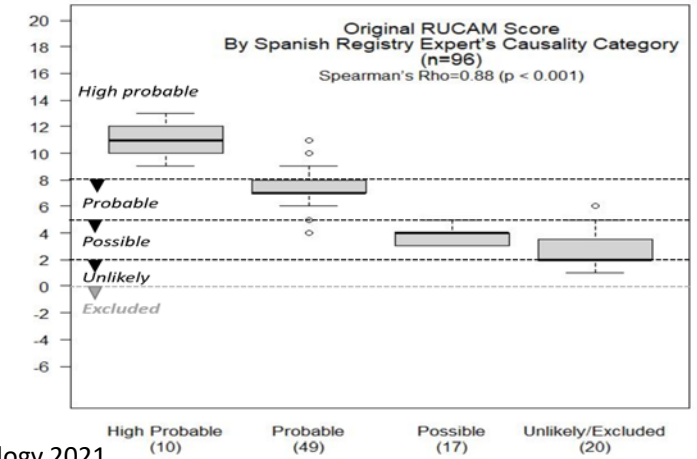
Hayashi P, Lucena MI, et al. *Hepatology.* 2020; submitted

RUCAM vs "ReCAM"









Hayashi et al Hepatology 2021

Conclusiones

- El diagnostico de DILI continua siendo incierto debido a la no disponibilidad de biomarcadores específicos
- Test genéticos pueden clarificar casos dudosos para algunos fármacos específicos.
- Uso de escalas computarizadas disminuye la variabilidad en la adjudicación de un evento hepático a un fármaco determinado