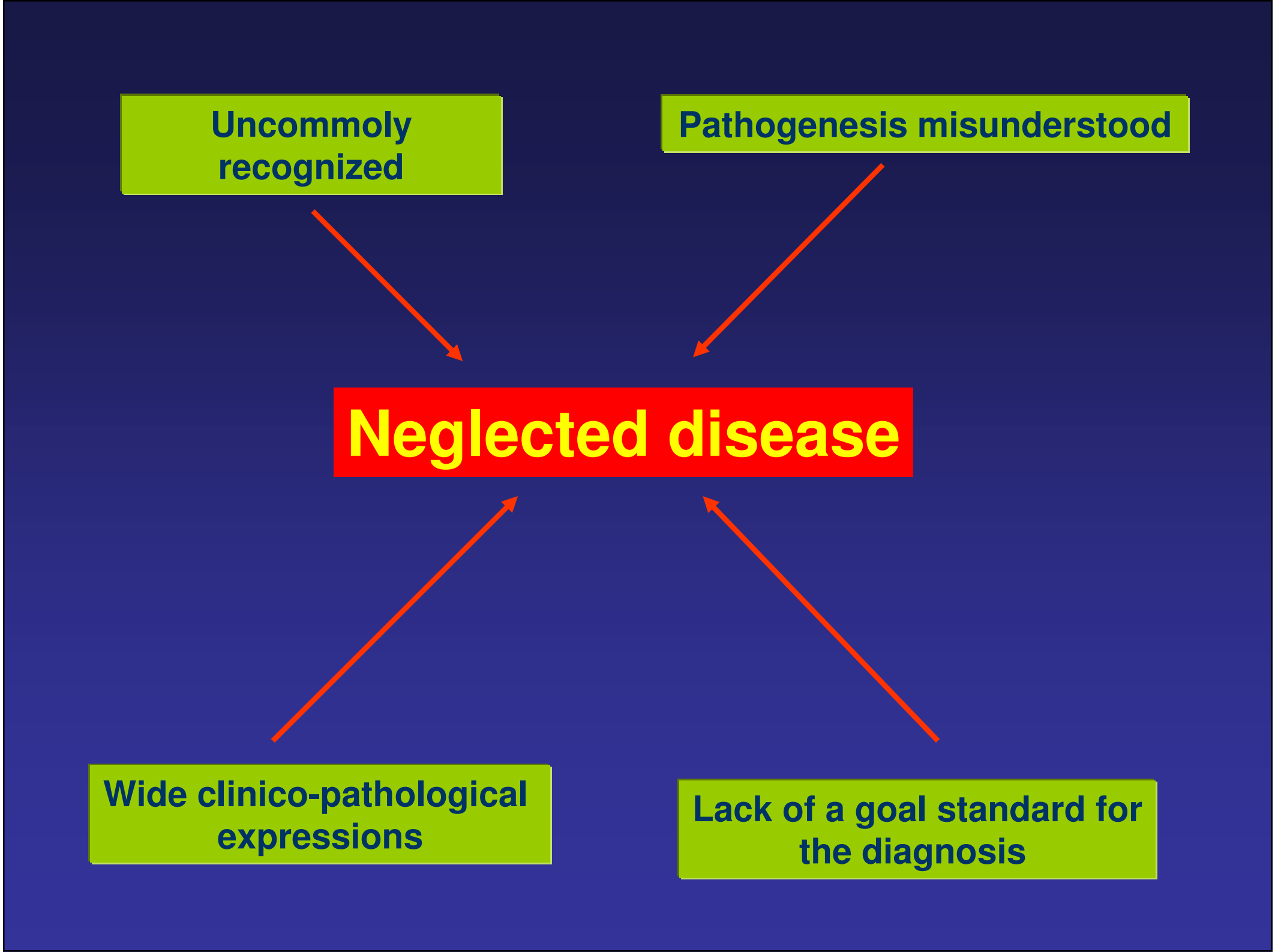
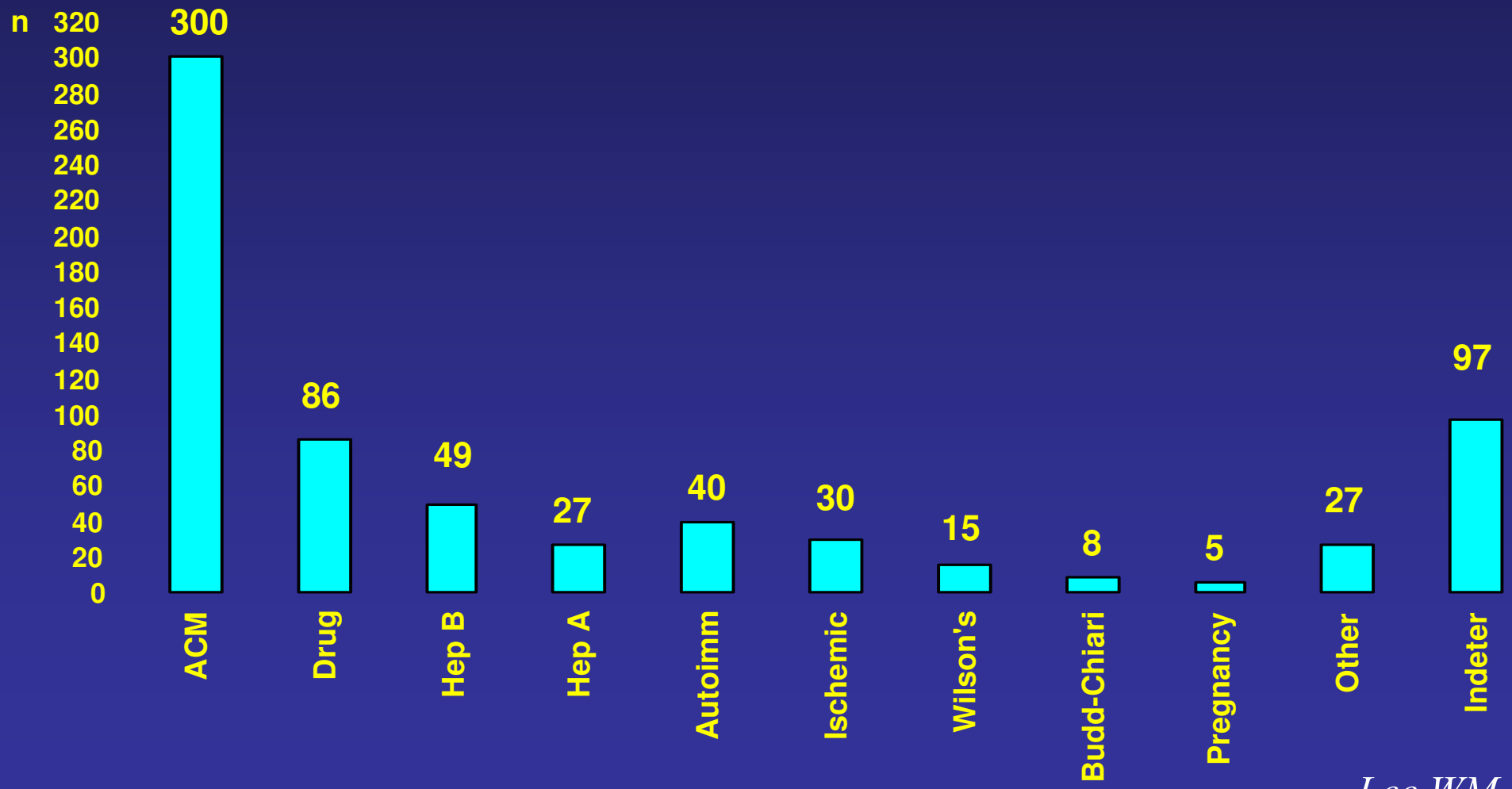
DAÑO HEPÁTICO INDUCIDO POR MEDICAMENTOS

Raúl J. Andrade
Unidad Hepatología. Hospital Universitario "V. de la Victoria"
Facultad Medicina. Málaga


Uncommoly recognized
Pathogenesis misunderstood
Neglected disease
Wide clinico-pathological expressions
Lack of a goal standard for the diagnosis

Etiology of ALF in the USA:

Adult Registry (n = 684)



Lee WM 2004

DRUG-INDUCED LIVER DISEASE

- **Leading single cause for drug withdrawal**

- **Difficult predictivity for hepatotoxicity in clinical drug development**
  - **-needs several thousands of treated patients (rule of threes)**
  - **-extensive exclusion criteria that low chances of unfavourable events**
  - **-drugs may be stopped lacking an appropriate profile of toxicity**

Senior and Lee, Toxicol Pathol 2005

Fármacos hepatotóxicos: medidas reguladoras recientes

- Agente
  - Ebrotidina*
  - Trovafloxacino*
  - Nefazodona*
  - Nimesulida*
  - Zafirlukast
  - Leflunomida
  - Telitromicina
  - Ximelagatrán#
- Indicación
  - AntiH2
  - Antibiótico
  - Antipsicótico
  - AINE
  - Antiasmático
  - Inmunomodulador
  - Antibiótico
  - Antitrombótico

*Retirado del mercado

#Interrupción del desarrollo (fase III)

Avances en DILI

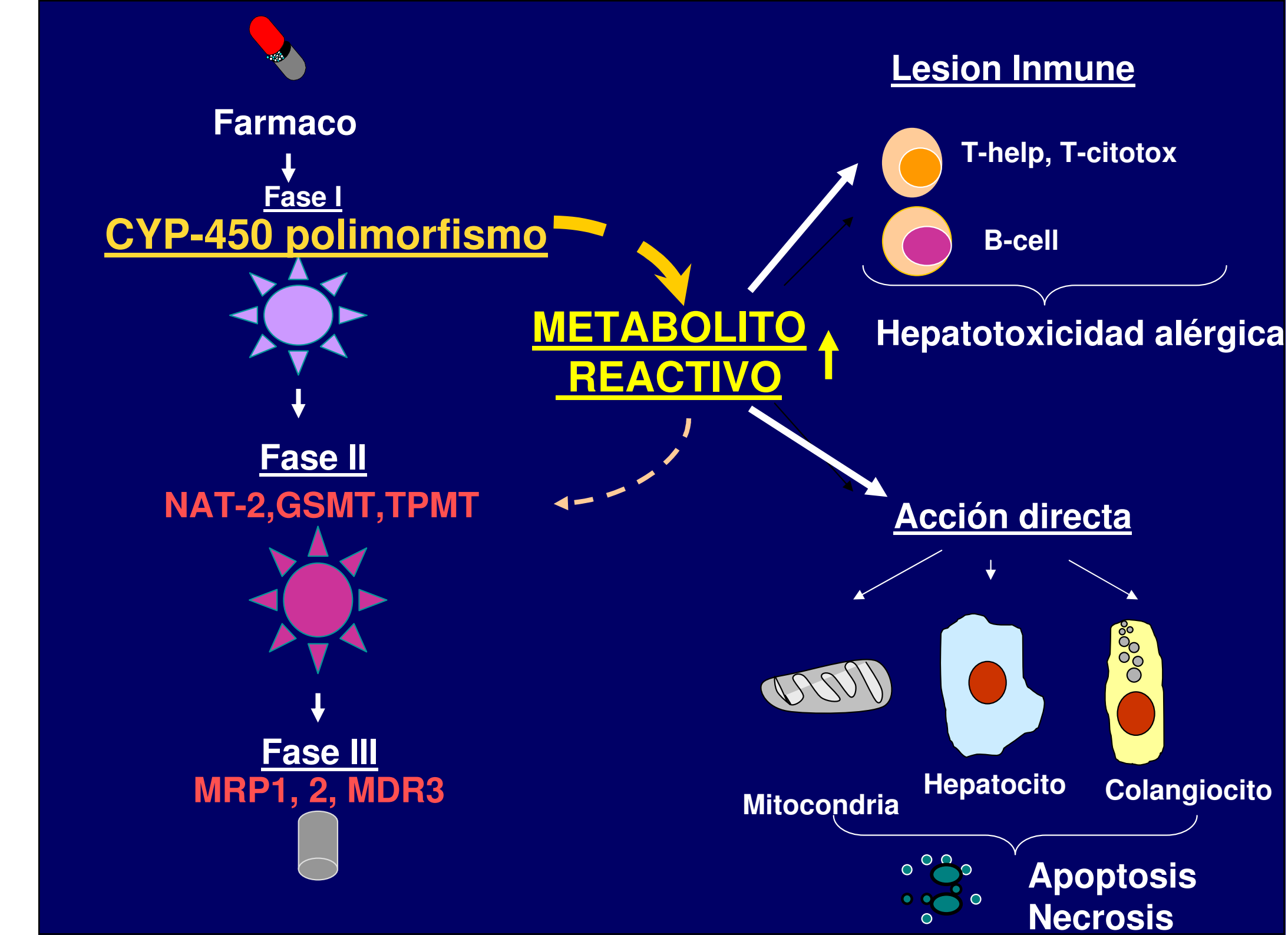
- Estudios fenotípicos
  - Incremento detección de casos
  - Evaluación de causalidad precisa
  - Estudios de expresión clínica y evolutiva
- Estudios genotípicos
  - -Vías del metabolismo hepático
  - -Identificación de SNPs funcionales en genes candidatos
  - -Wide genome analysis

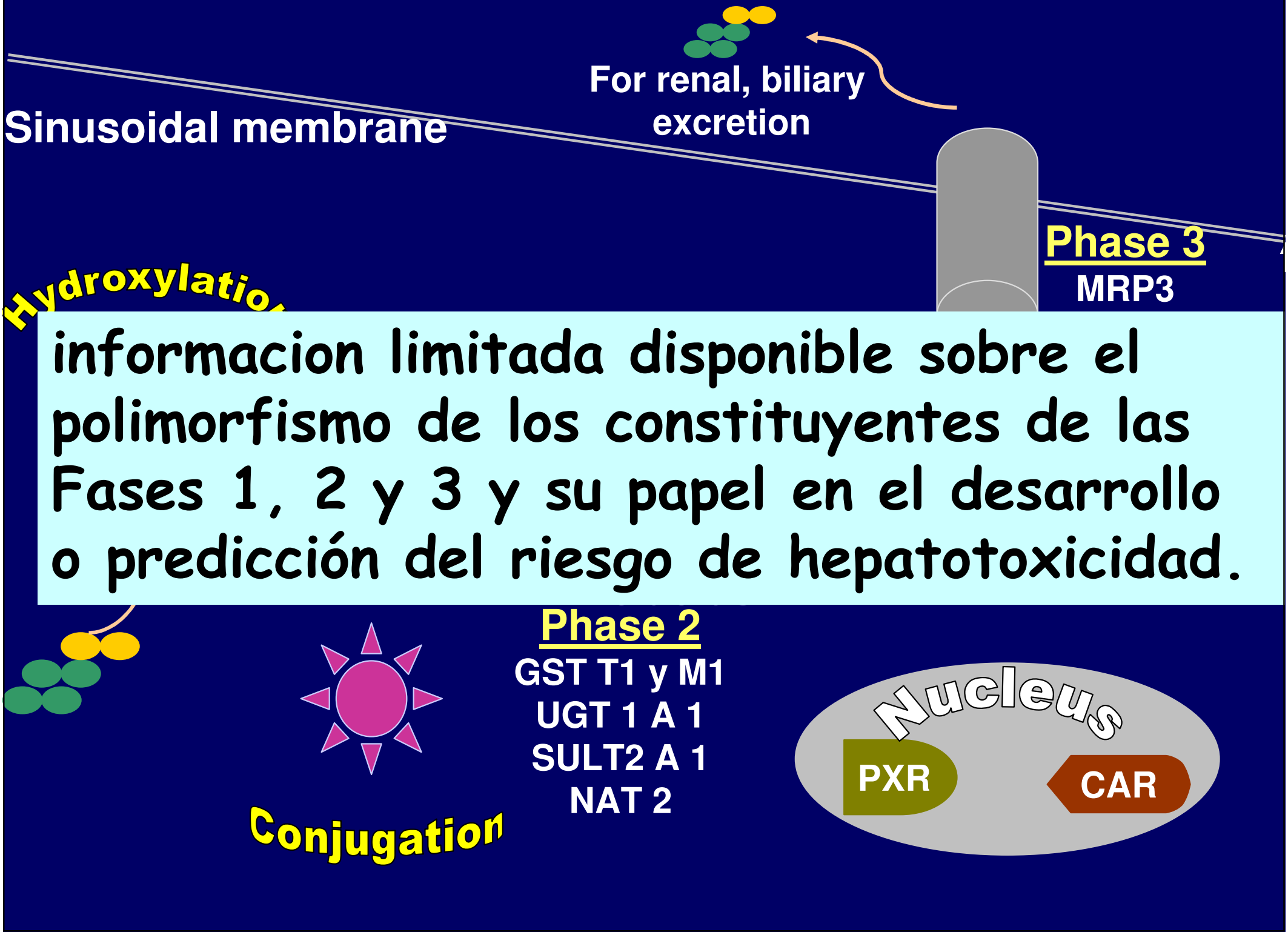
MAIN THERAPEUTIC GROUPS SUSPECTED IN HEPATOTOXICITY

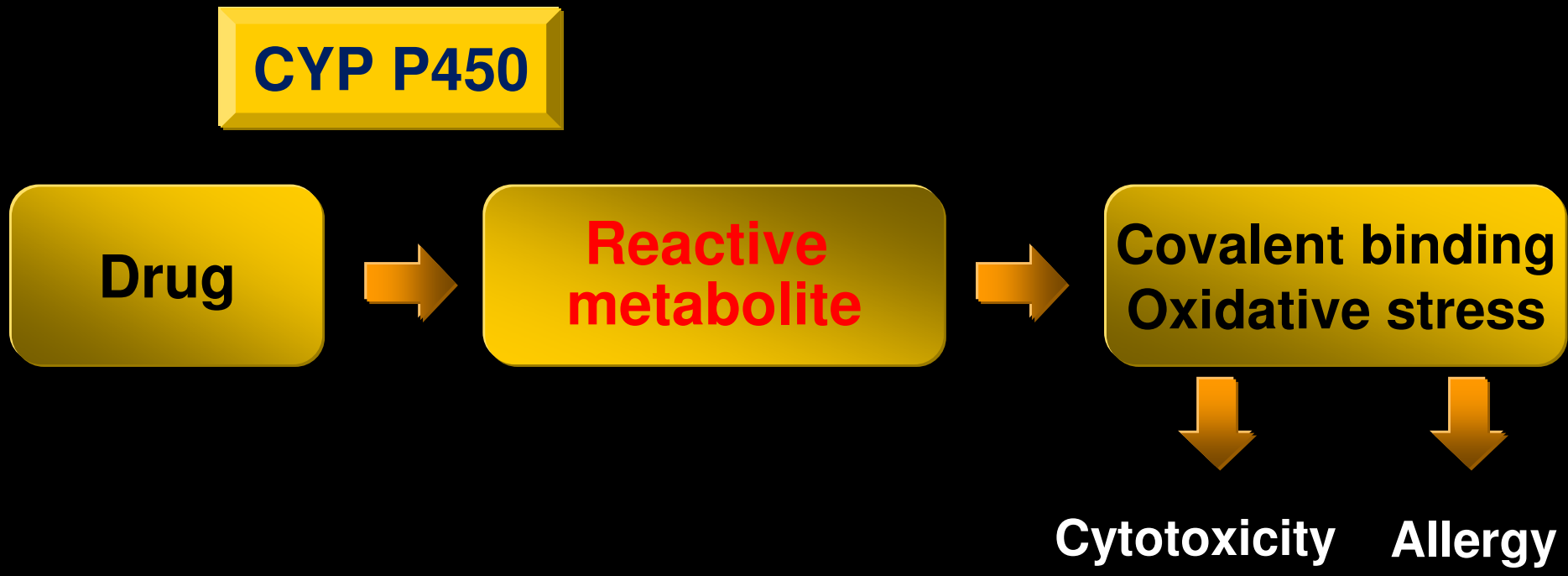
ANTIBIOTICS	140	24%
NSAIDs	63	11%
ANTITUBERCULOUS DRUGS	39	7%
LIPID REDUCING AGENTS	32	6%
H2- RECEPTOR ANTAGONISTS	30	5%
ENDOCRINE THERAPY	24	4%
ANTI-DEPRESSANTS	21	4%
ANTITHROMBOTIC AGENTS	18	3%
ANTIEPILEPTICS	18	3%
MEDICINAL HERBS	15	3%
ANALGESICS	11	2%
ANXYOLITICS	12	2%
ANTI-PSYCHOTICS	8	1%

MAIN ACTIVE INGRADIENTS INVOLVED IN HEPATOTOXICITY

AMOXICILLIN-CLAVULANATE	88	15,3%
IZN+RIF+PIZ	27	4,7%
FLUTAMIDE	22	3,8%
EBROTIDINE	21	3,7%
IBUPROFEN	20	3,7%
DICLOFENAC	15	2,6%
TICLOPIDINE	13	2,3%
ISONIAZID	11	1,9%
NIMESULIDE	9	1,6%
FLUVASTATIN	9	1,6%
BENTAZEPAM	8	1,4%
ATORVASTATIN	8	1,4%
VALPROIC ACID	8	1,4%
PAROXETINE	7	1,2%

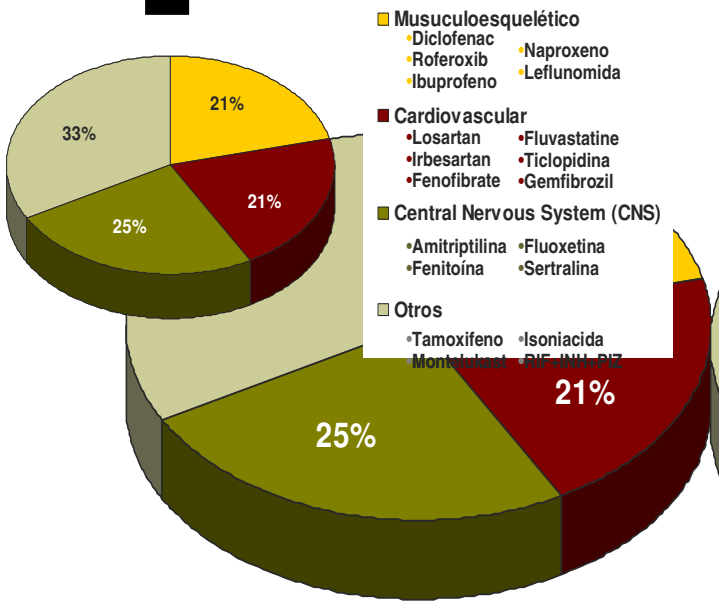

Farmaco
Fase I
CYP-450 polimorfismo
Fase II
NAT-2,GSMT,TPMT
Fase III
MRP1, 2, MDR3
METABOLITO REACTIVO
Lesion Inmune
T-help, T-citotox
B-cell
Hepatotoxicidad alérgica
Acción directa
Mitocondria
Hepatocito
Colangiocito
Apoptosis
Necrosis


For renal, biliary excretion
Sinusoidal membrane
Phase 3
MRP3
Hydroxylatio
informacion limitada disponible sobre el polimorfismo de los constituyentes de las Fases 1, 2 y 3 y su papel en el desarrollo o predicción del riesgo de hepatotoxicidad.
Phase 2
GST T1 y M1
UGT 1 A 1
SULT2 A 1
NAT 2
Conjugation
Nucleus
PXR
CAR

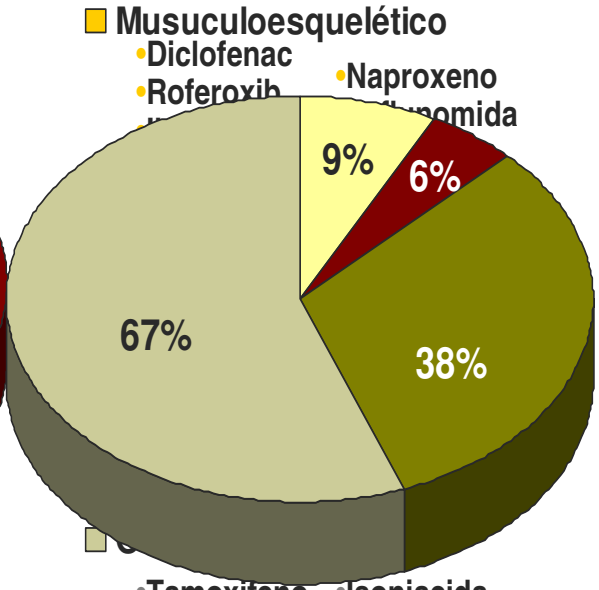

CYP P450
Drug
Reactive metabolite
Covalent binding
Oxidative stress
Cytotoxicity
Allergy

SUBSTRATOS

CYP2C9



CYP2C19



- Inhibidores de la bomba de protones
  - •Omeprazol
- Cardiovascular
  - •Propafenona
  - •Atenolol
- Central Nervous System (CNS)
  - •Sertralina
  - •Bentazepam
  - •Tetrabamato
  - •Clotiazepam
  - •Carbamazepina
  - •Paroxetine
  - •Fenitoína
  - •Amitriptiline
  - •Alprazolam
  - •Fluoxetine
  - •Clorazepam
  - •Ctalopram
- Otros
  - •RIF+INH+PIZ
  - •Indometacina

Edad, media	53	48
rango	17-82	14-70
Sexo, M/H	17/28	18/32
Daño HC	18 (64%)	21 (66%)

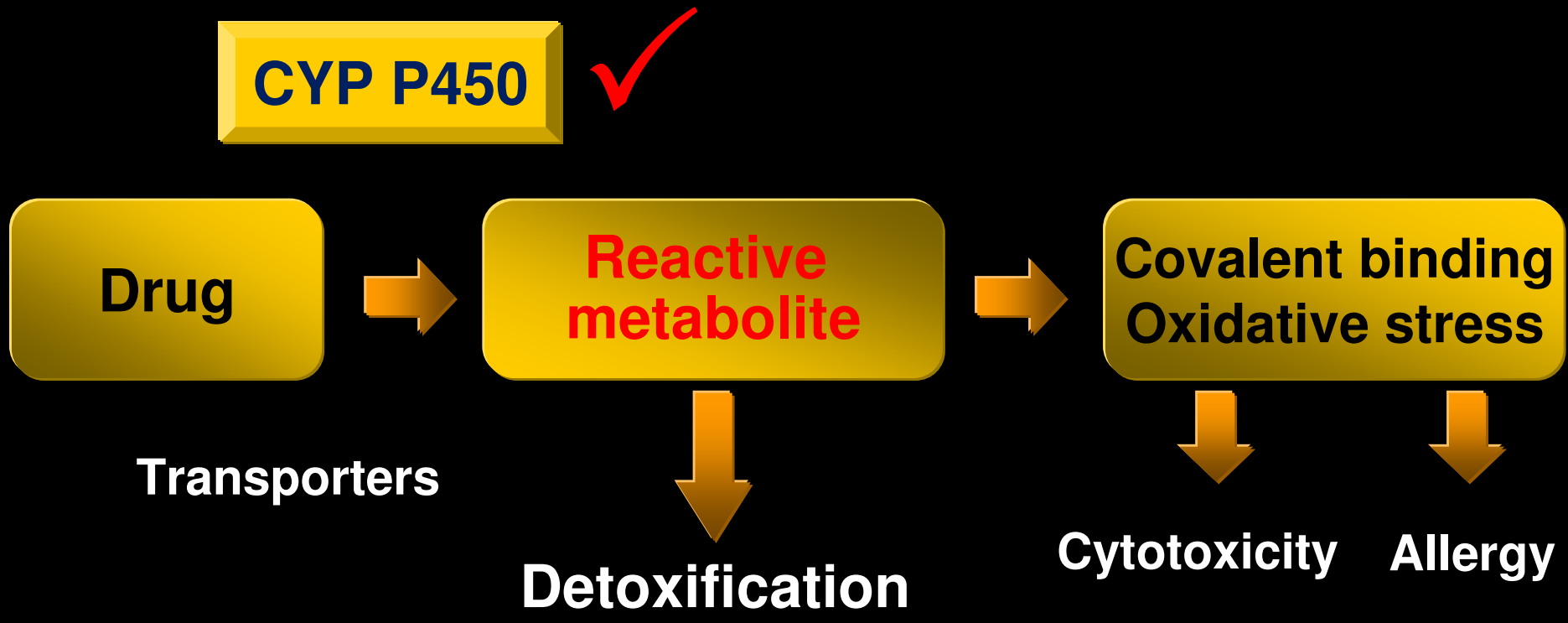
Daño hepático por fármacos sustrato CYP2C9/2C19

- **Leflunomida**
  - **-genotipo CYP2C9*3/*3.** ***Sevilla-Mantilla, 2004***
- **Tetrabamato**
  - **-genotipo CYP2C19*1/*2.** ***Larrey, 1997***
- **Troglitazona**
  - **-genotipo CYP2C19*3/*3.** ***Larrey, 2002***

Estudios aislados, escaso número de pacientes. Necesitan confirmación

Genotype	Activity	DILI patients	Observed Frequency	Predicted Frequency by Hardy-Weinberg Law
CYP2C9		N = 28		
1/1	Normal	13	46%	51
1/2	Minor Reduction	6	21%	18
1/3	Moderately reduced	8	29%	23
2/2	Moderately reduced	0	0%	1,5
2/3	Moderately reduced	1	4%	4
3/3	Very low	0	0%	2,5
CYP2C19		N = 32		
1/1	Normal	24	75%	74
1/2	Minor Reduction	7	22%	24
1/3	Moderately reduced	0	0%	0
2/2	Moderately reduced	1	3%	2
2/3	Moderately reduced	0	0%	0
3/3	Very low	0	0%	0

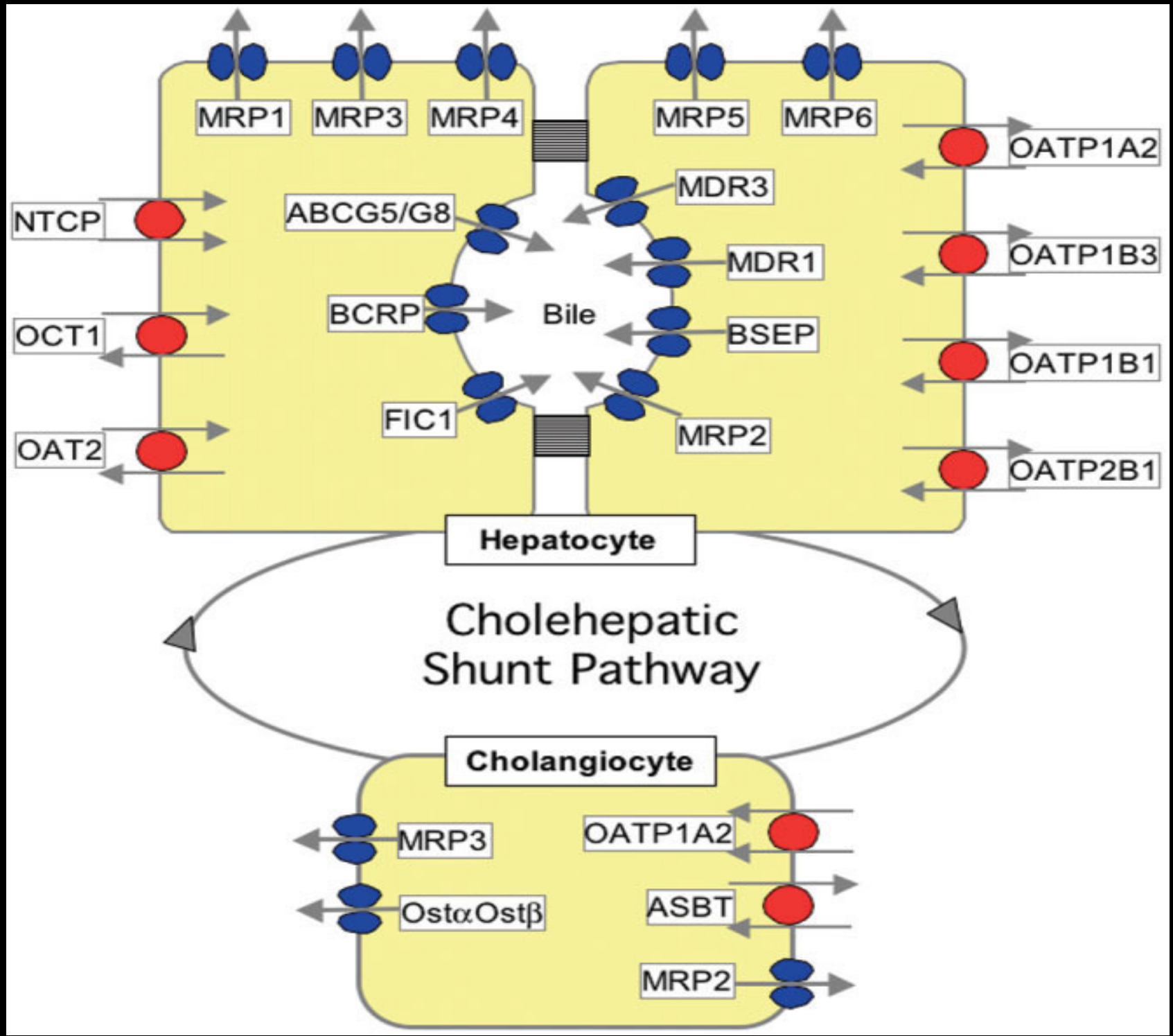
Pachkoria et al . B J Pharmacol 2007

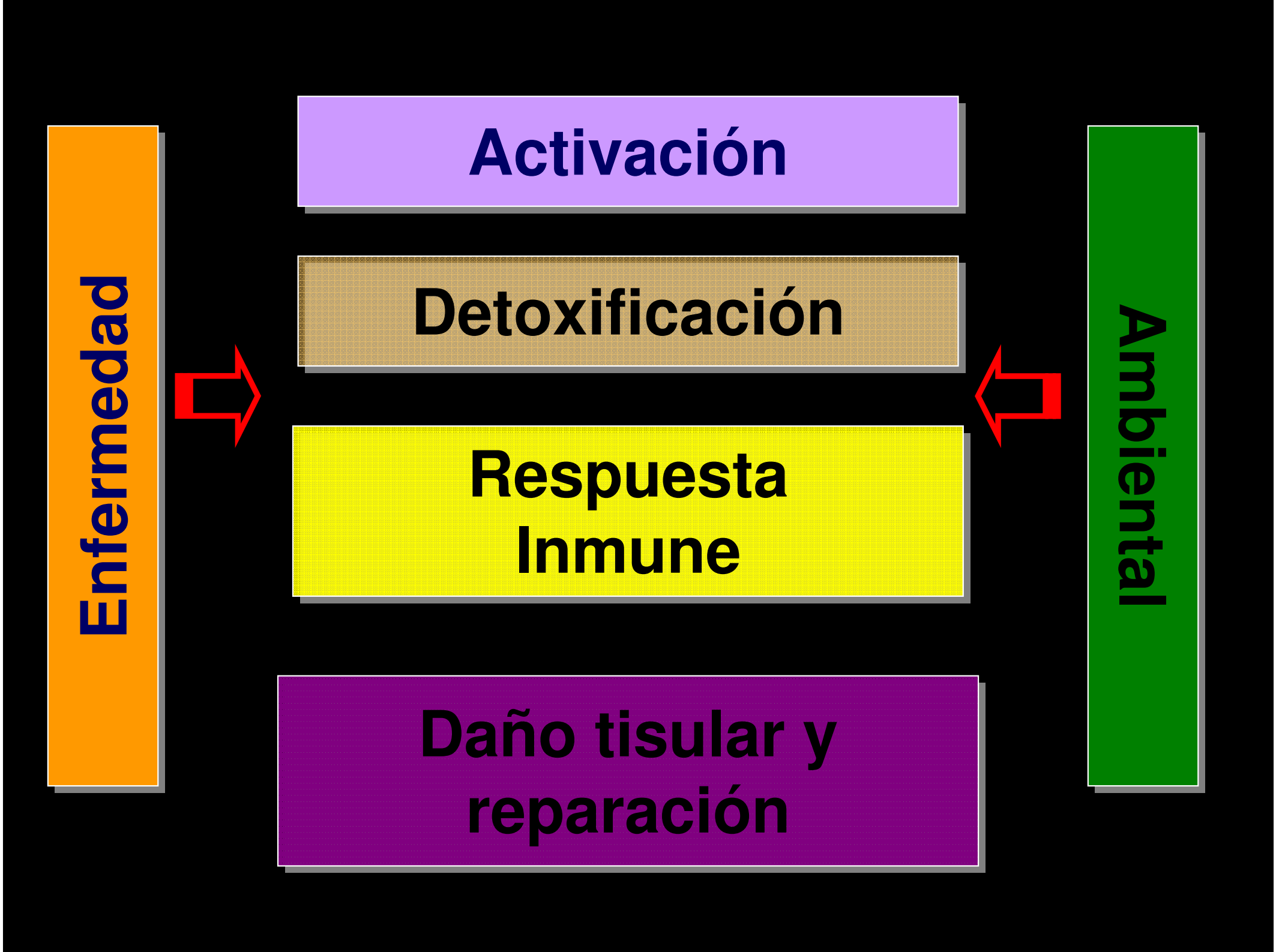

CYP P450
Drug
Reactive metabolite
Covalent binding
Oxidative stress
Transporters
Detoxification
Cytotoxicity
Allergy

Double null GST M1-T1 genotype

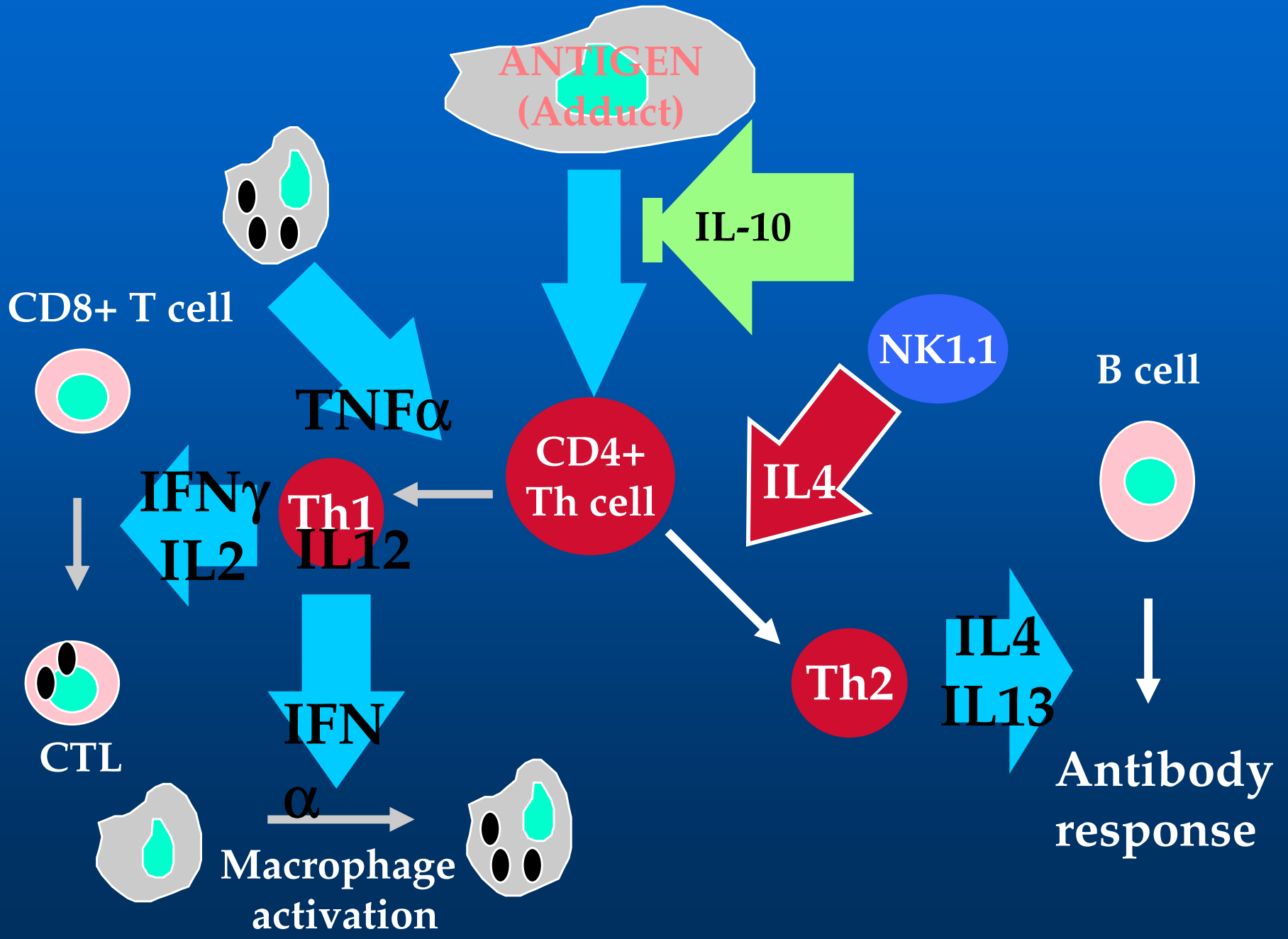
	N/N (n)	OR	95% CI	p
Antibacterianos n=44				
Amoxicilina-Clavulanate,n=32	8	3.52	1.56-8.22	0.002
	6	2.81	1.067-7.46	0.037
AINES, n=19	6	5.61	1.99-16.0	0.001
Cardiovascular n=17	4	3.74	1.18-12.08	0.024
SNC, n=24	3	1.74	0.51-5.99	0.400

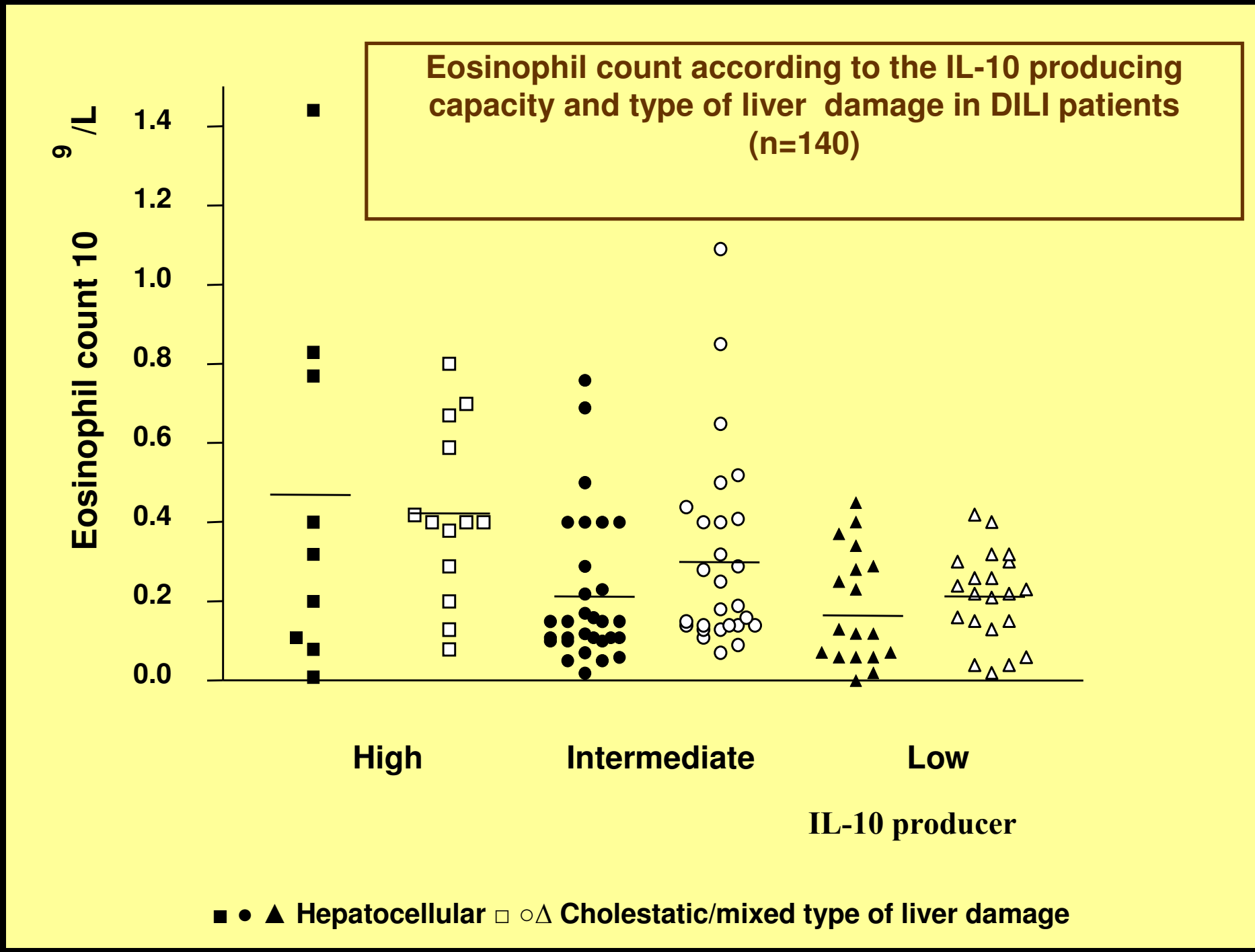
Lucena et al Hepatology 2008 in press


MRP1
MRP3
MRP4
MRP5
MRP6
OATP1A2
MDR3
NTCP
ABCG5/G8
MDR1
OATP1B3
BCRP
Bile
OCT1
BSEP
OATP1B1
FIC1
MRP2
OAT2
OATP2B1
Hepatocyte
Cholehepatic
Shunt Pathway
Cholangiocyte
MRP3
OATP1A2
OstαOstβ
ASBT
MRP2


Activación
Detoxificación
Respuesta Inmune
Daño tisular y reparación
Enfermedad
Ambiental

Th Cell Differentiation





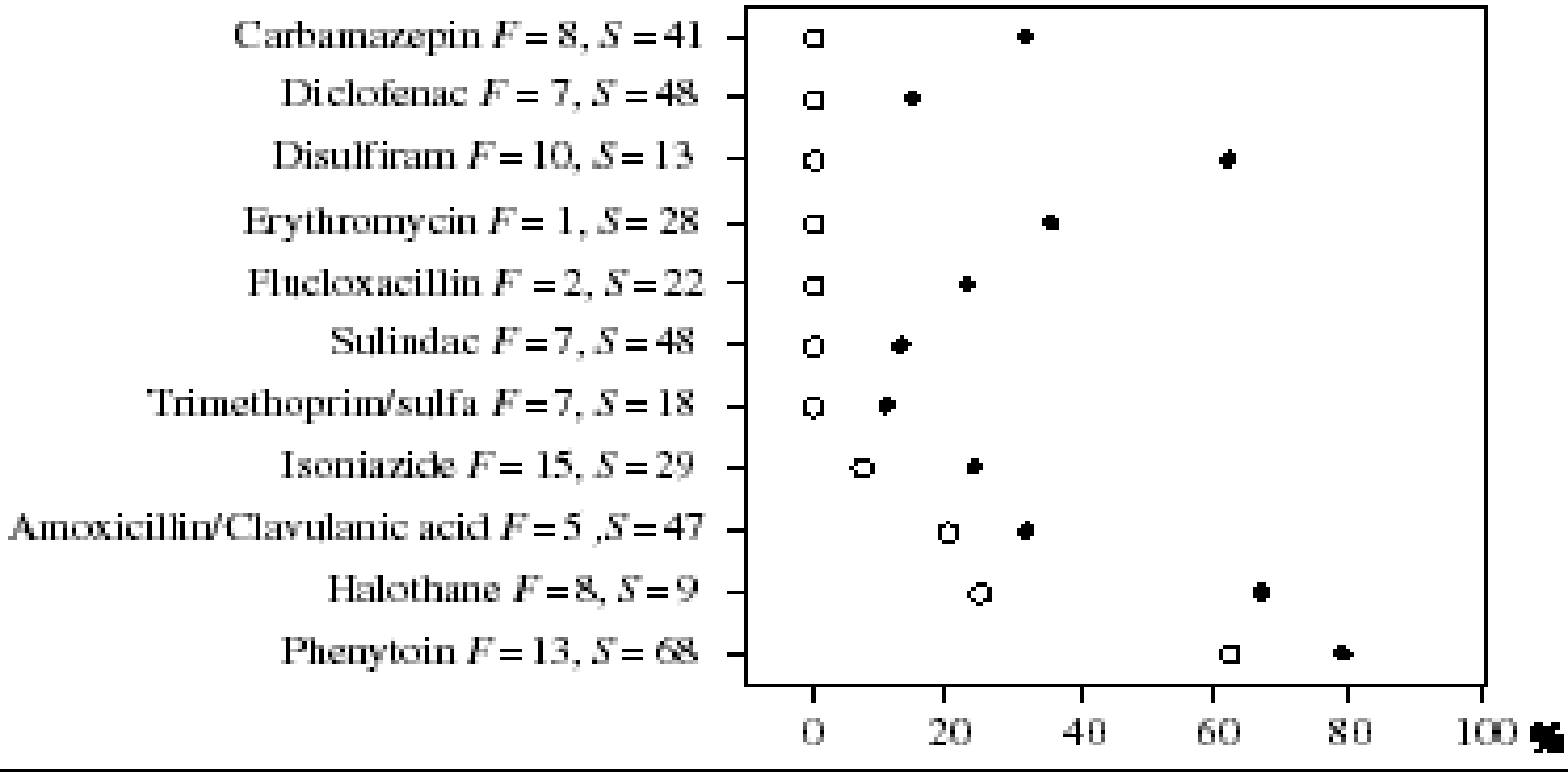
Pachkoria et al J Hepatol 2008 in press

Analysis of total patients with DILI (n=591) from Spanish RegHepat

Drugs,(n)	EOSINOFILIA %	
	Death/Tx/FHF	Other presentation
Total DILI , (591)	0/36	113/555 (20%)
Amoxicilin-clavulanate, (82)	0/2	23/80 (29%)
Nimesulide, (9)	0/2	2/7 (28.5%)
Flutamide, (22)	0/4	1/18 (6%)
Ebrotidine, (21)	0/1	2/20 (10%)
Anti-TBC, (24)	0/4	2/20 (10%)
Isoniazid, (11)	0/1	1/10 (10%)

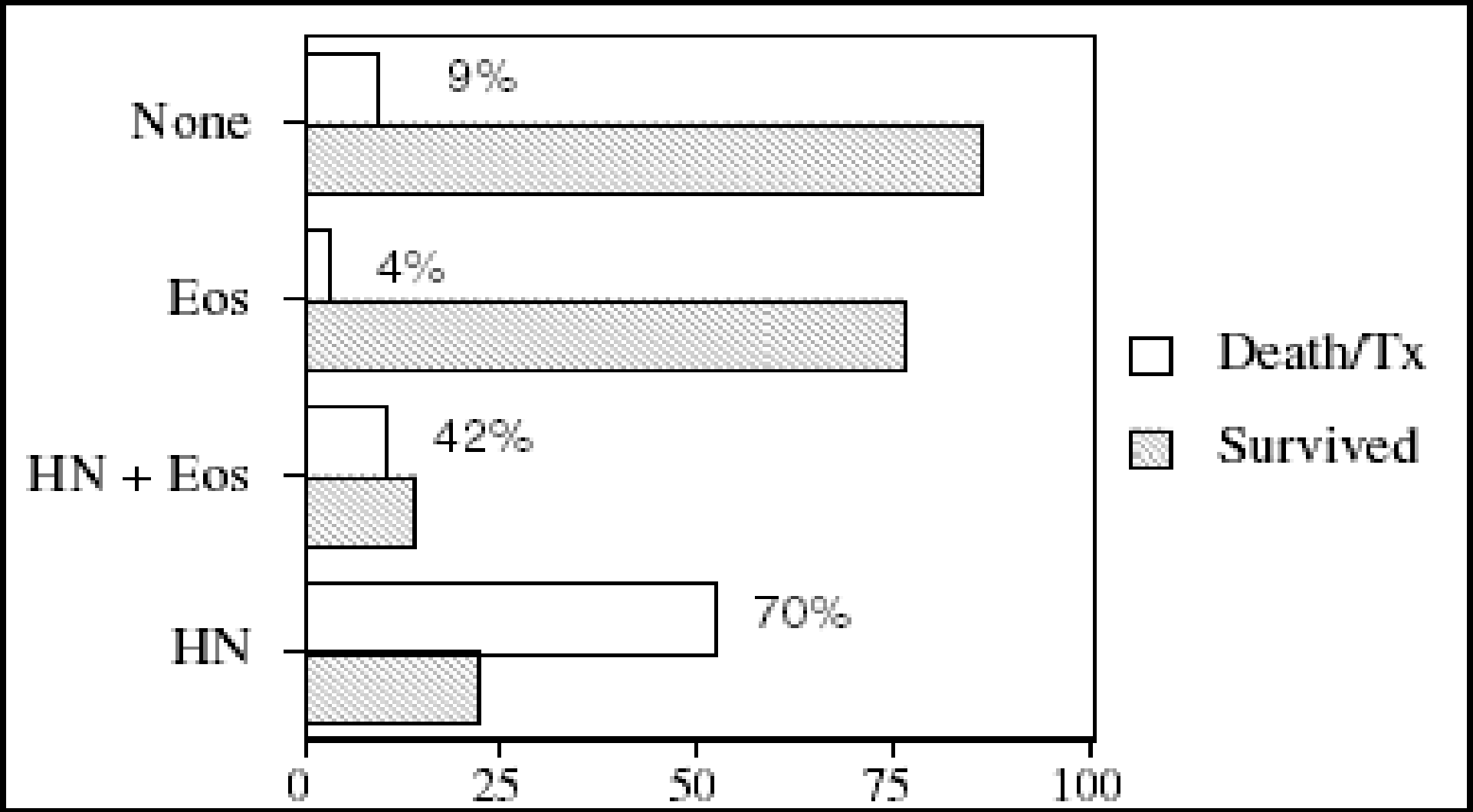
Pachkoria et al J Hepatol 2008 in press

Peripheral eosinophilia and mortality/LvTx

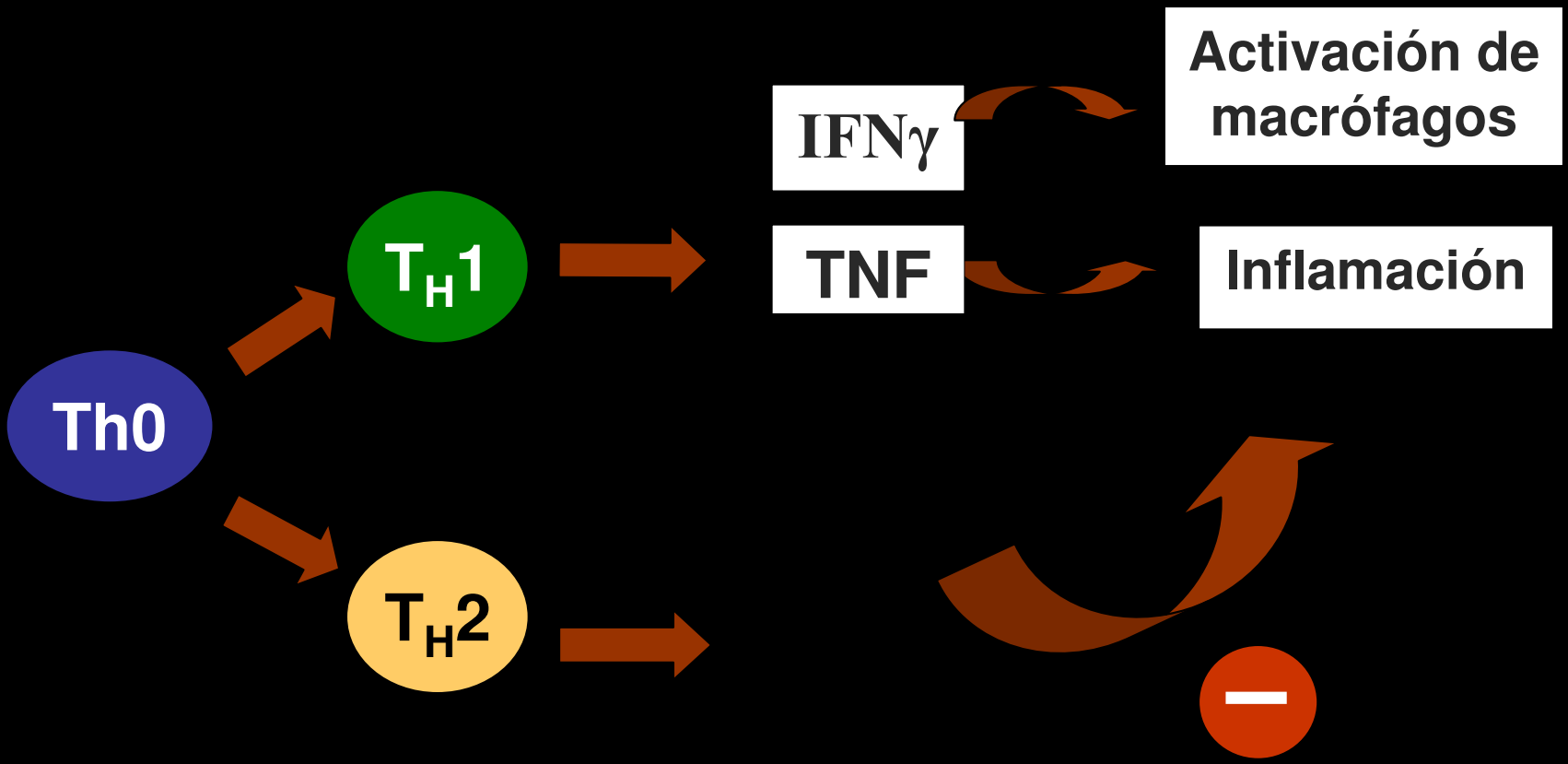


Björnrsson Aliment Pharmacol Ther 2007

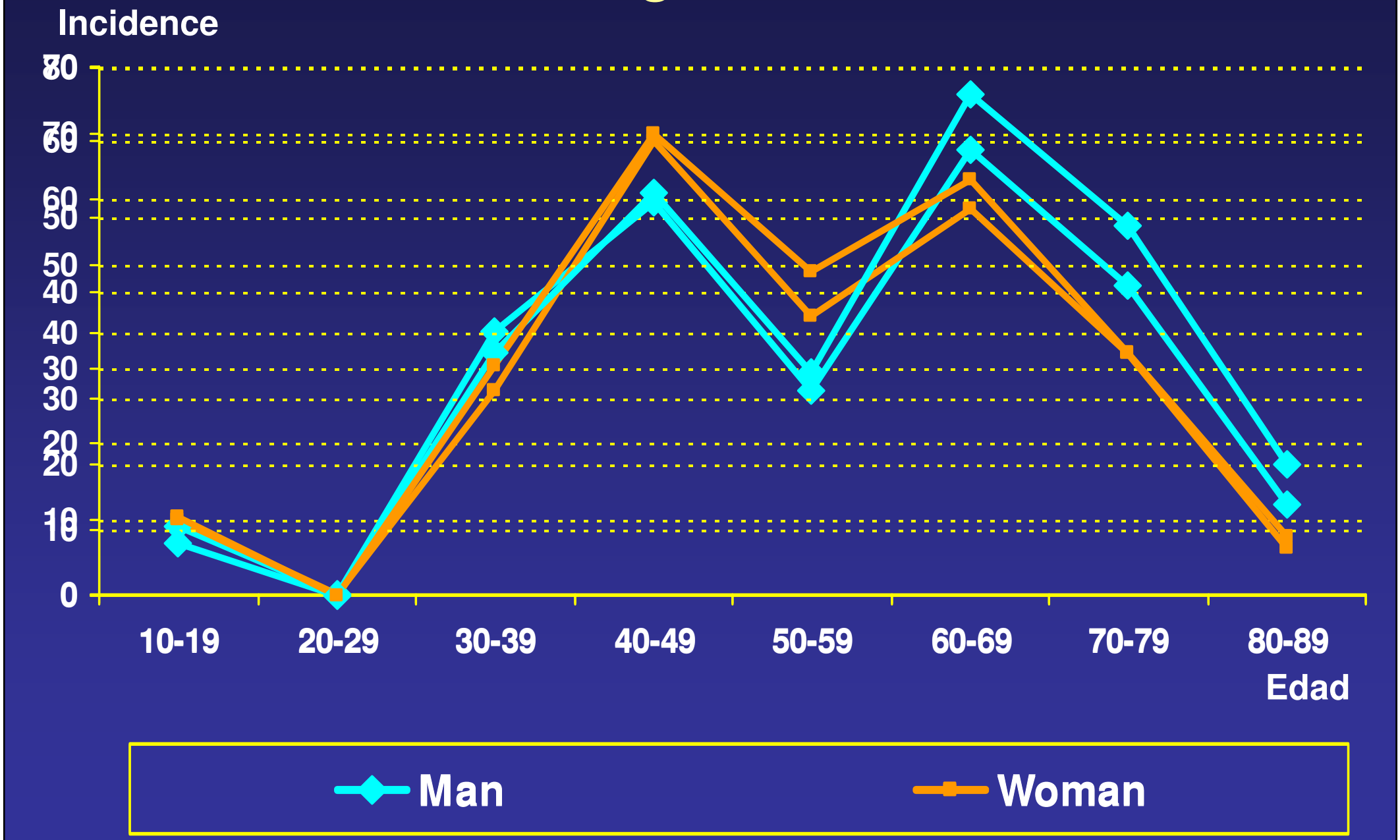
Liver eosinophilic infiltrate and mortality/LvTx



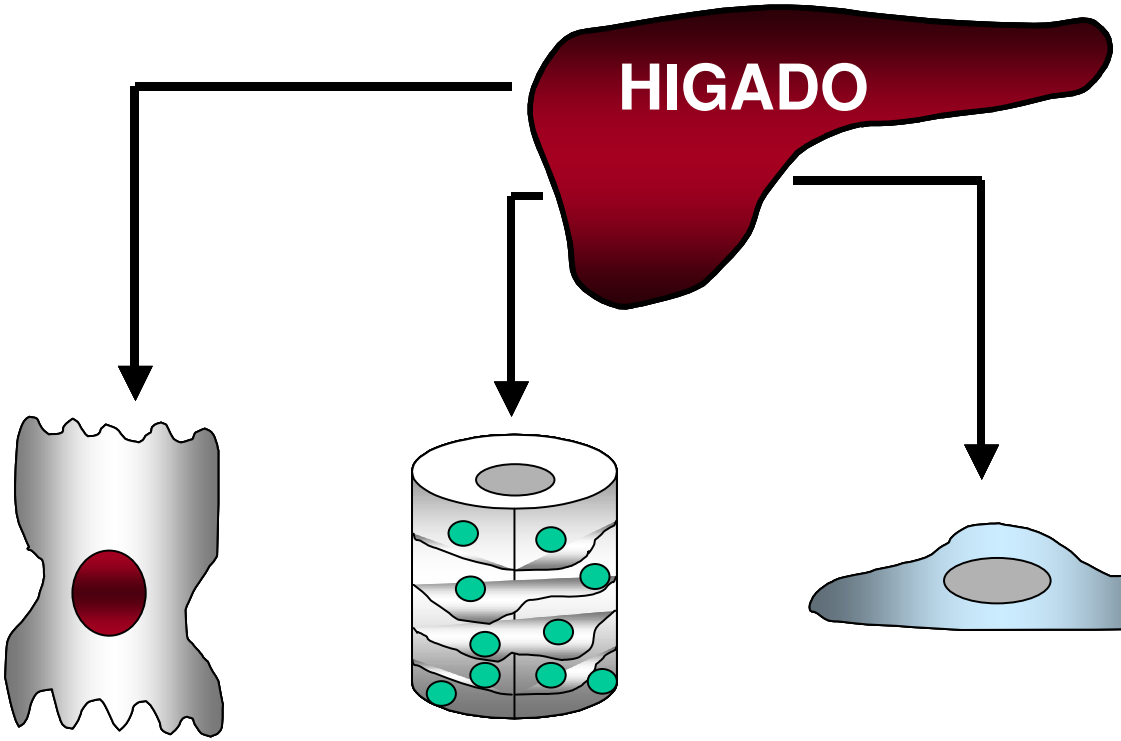
Björnrsson Aliment Pharmacol Ther 2007


Th0
T_H1
T_H2
IFNγ
TNF
Activación de macrófagos
Inflamación
–

Incidence of drug-induced liver disease according to Age and Sex



TIPOS DE LESIÓN



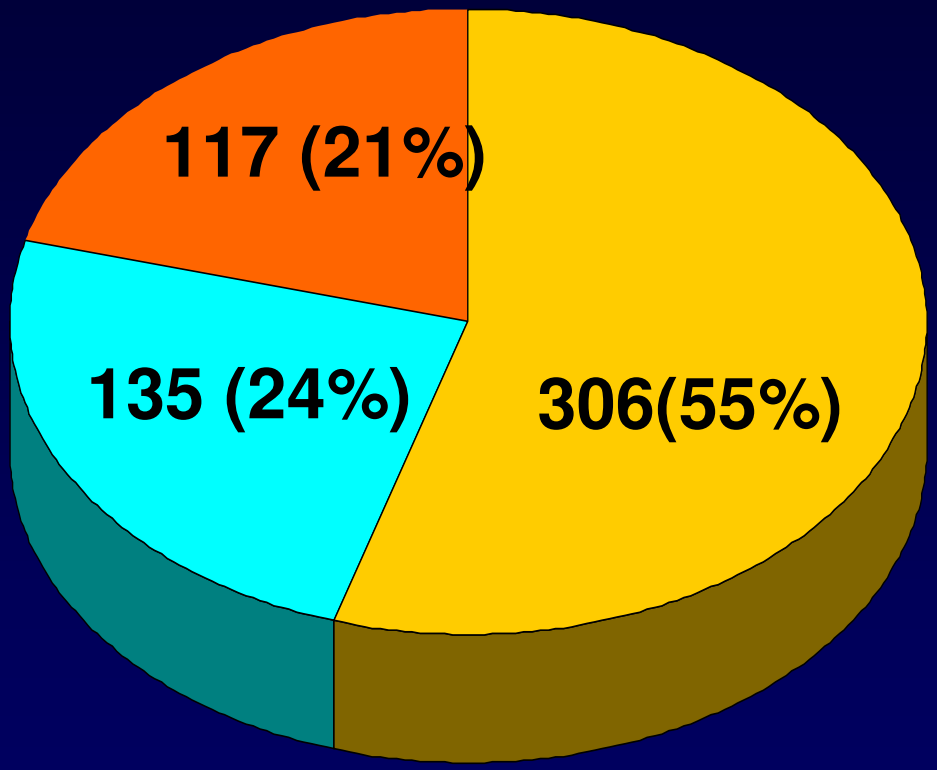
Hepatocito
- Hepatitis aguda
- Colestasis
- Hepatitis crónica
- Cirrosis
- Esteatosis
- Hepatitis granulomatosa

Colangiocito
- Colangitis aguda y crónica
- Colangitis esclerosante

Célula endotelial
- Enfermedad veno-oclusiva
- Dilatación sinusoidal
- Peliosis hepatitis
- Síndrome de Budd-Chiari

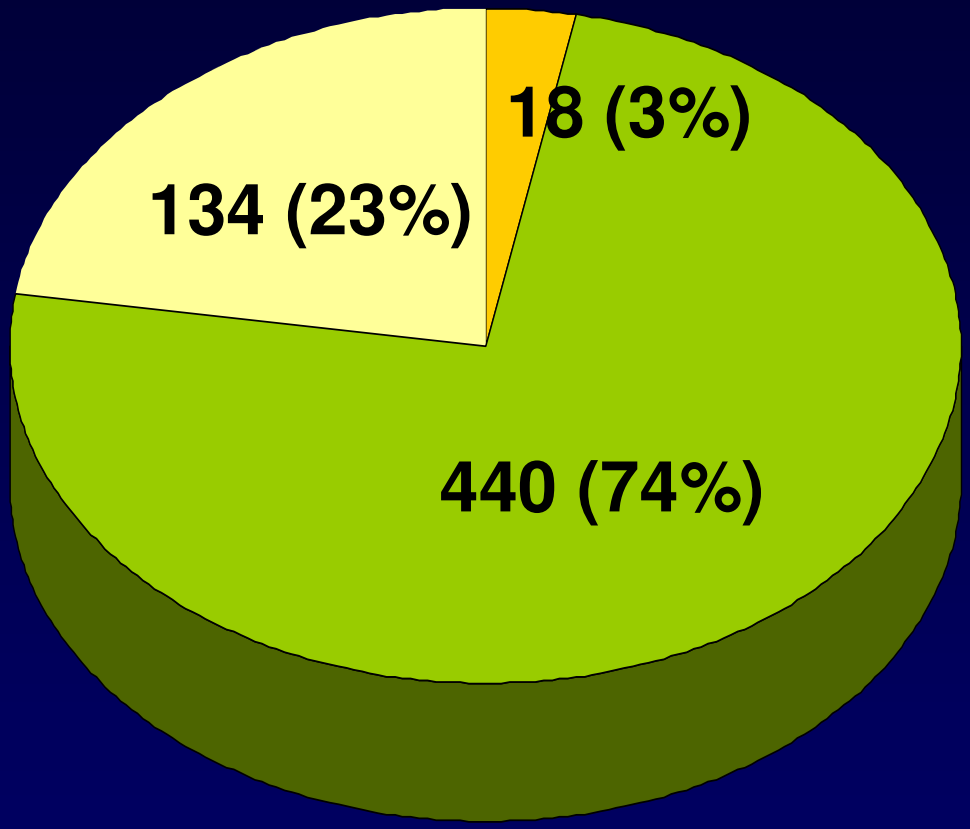
Célula de Ito
- Fibrosis perisinusoidal

Type of liver damage



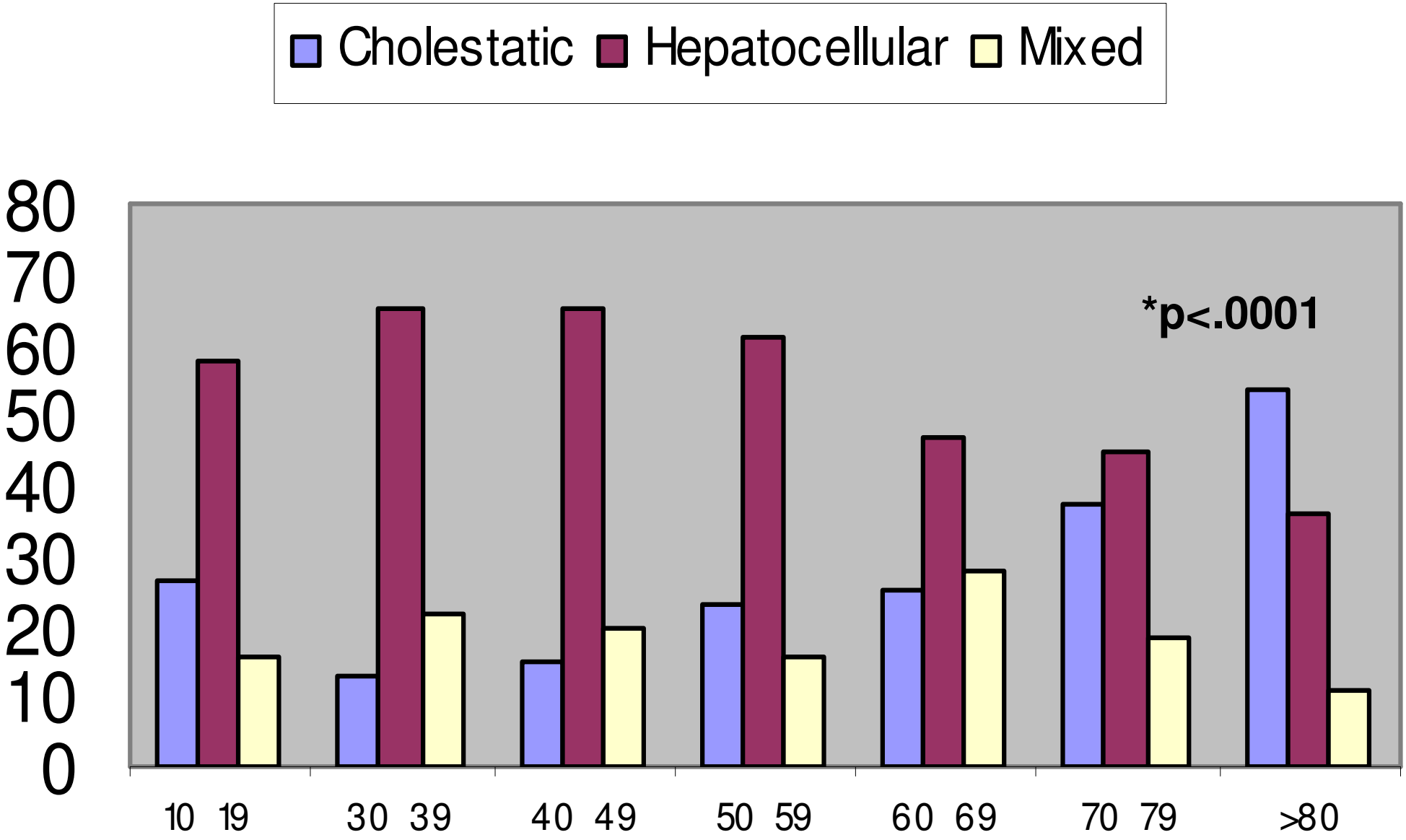
- Hepatocellular — ALT > 2(3)N o ALT/AP > 5
- Cholestatic — AP > 2N o ALT/AP < 2
- Mixed — ALT/AP > 2 y < 5

Mechanism



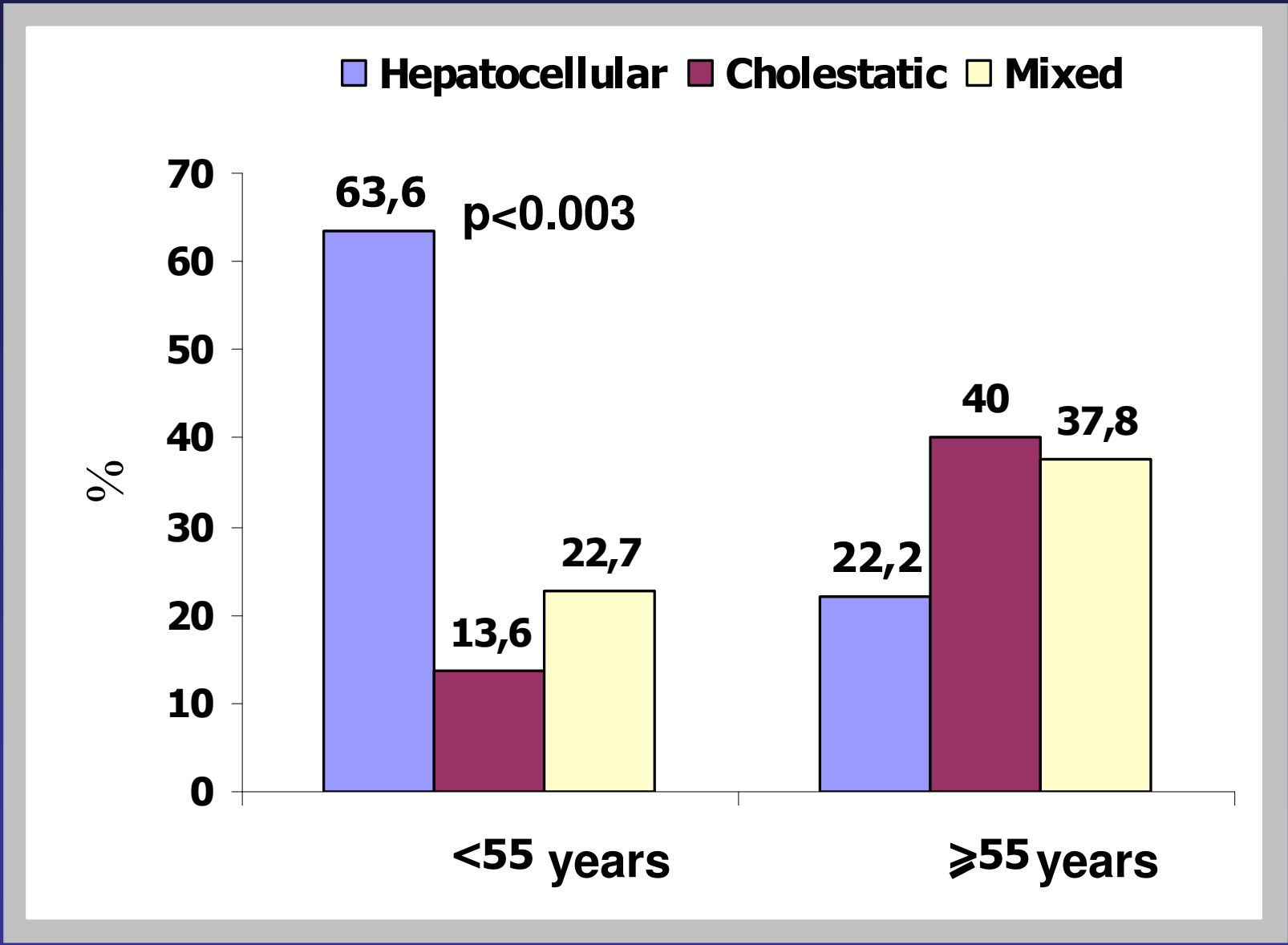
- Intrinsic
- Idiosyncratic - metabolic
- Idiosyncratic - immunologic

Age and Sex-related Liver Damage



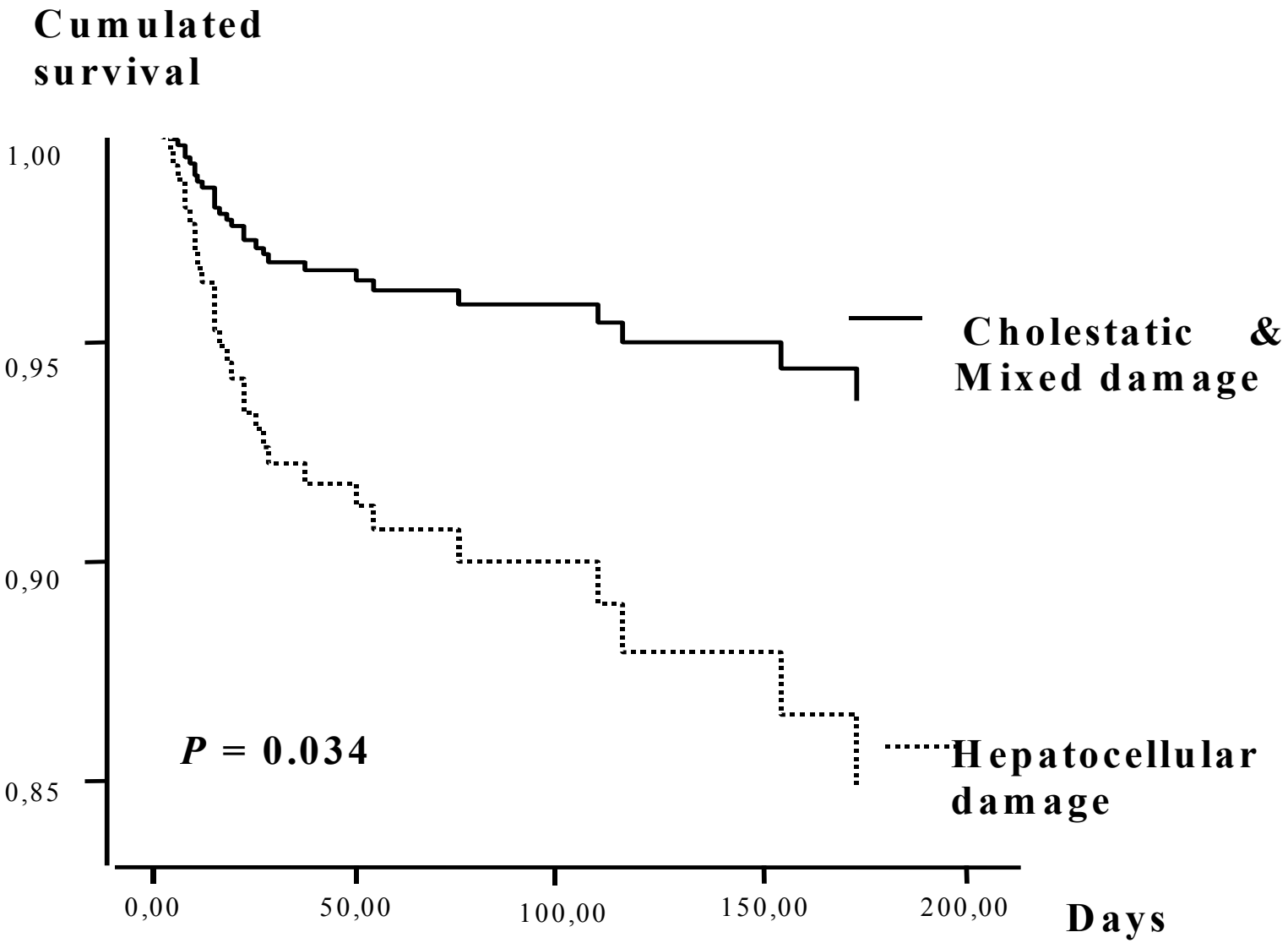
Andrade et al. 2007

Amox-Clav induced Liver damage according to age



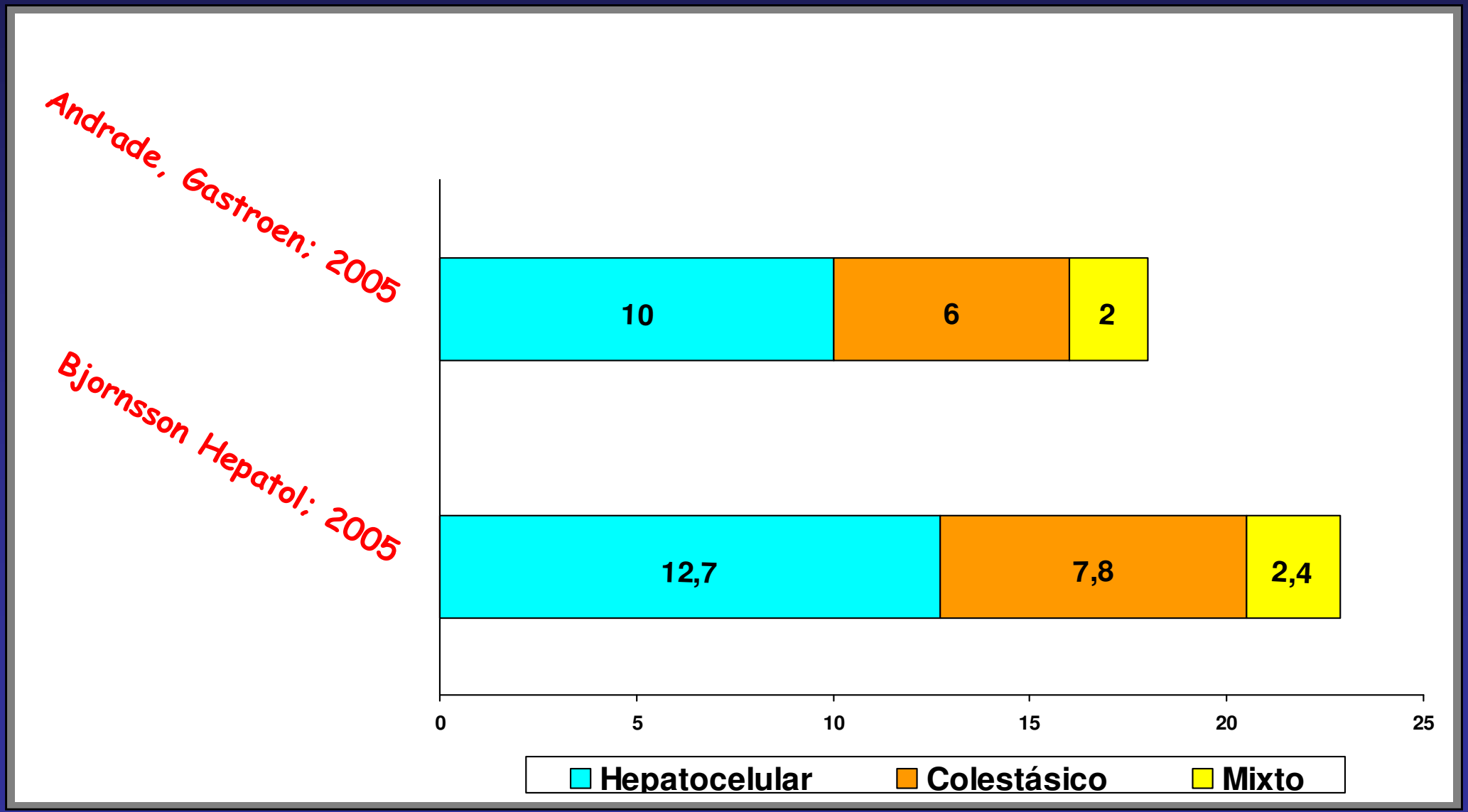
Lucena, et al Hepatology 2006

Cumulated survival curves of hepatocellular and cholestatic/mixed cases of drug-induced liver injury



Andrade et al, Gastroenterology 2005

Mortalidad en relación con la expresión clínica



	Fulminant outcome (n=18)	Other Presentations (n=428)	P value
Mean age (range), y	53 (14-83)	53 (13-88)	
Women, n(%)	16 (89%)	201 (47%)	<.0001
Clinical presentation			
Jaundice, (%)	100%	69%	<.003
Hepatocellular damage	15 (83%)	243 (57%)	<.028
Laboratory parameters			
Br (mg/dL)	16.3± 10.7	7.5±7.5	<.0001
ALT(XULN)	30.4± 21.6	19.9±23.9	
Liver transplantation	6 (37%)	2 (0.5%)	<.001
Drug <3y on the market	3 (17%)	56 (13%)	

Andrade et al,Gastroenterology 2005

Risk factors for development of acute liver failure

Variables	Coefficient	OR (95% CI)	*P* value
Female Sex	3.220	25.04 (4.14-151)	<.0001
Hepatocellular damage	2.064	7.87 (1.68-36.9)	<.009
Total Bilirubin	0.143	1.15 (1.09-1.22)	<.0001

Constant = -8.7 Abbreviations: CI, confidence interval; OR, odds ratio.

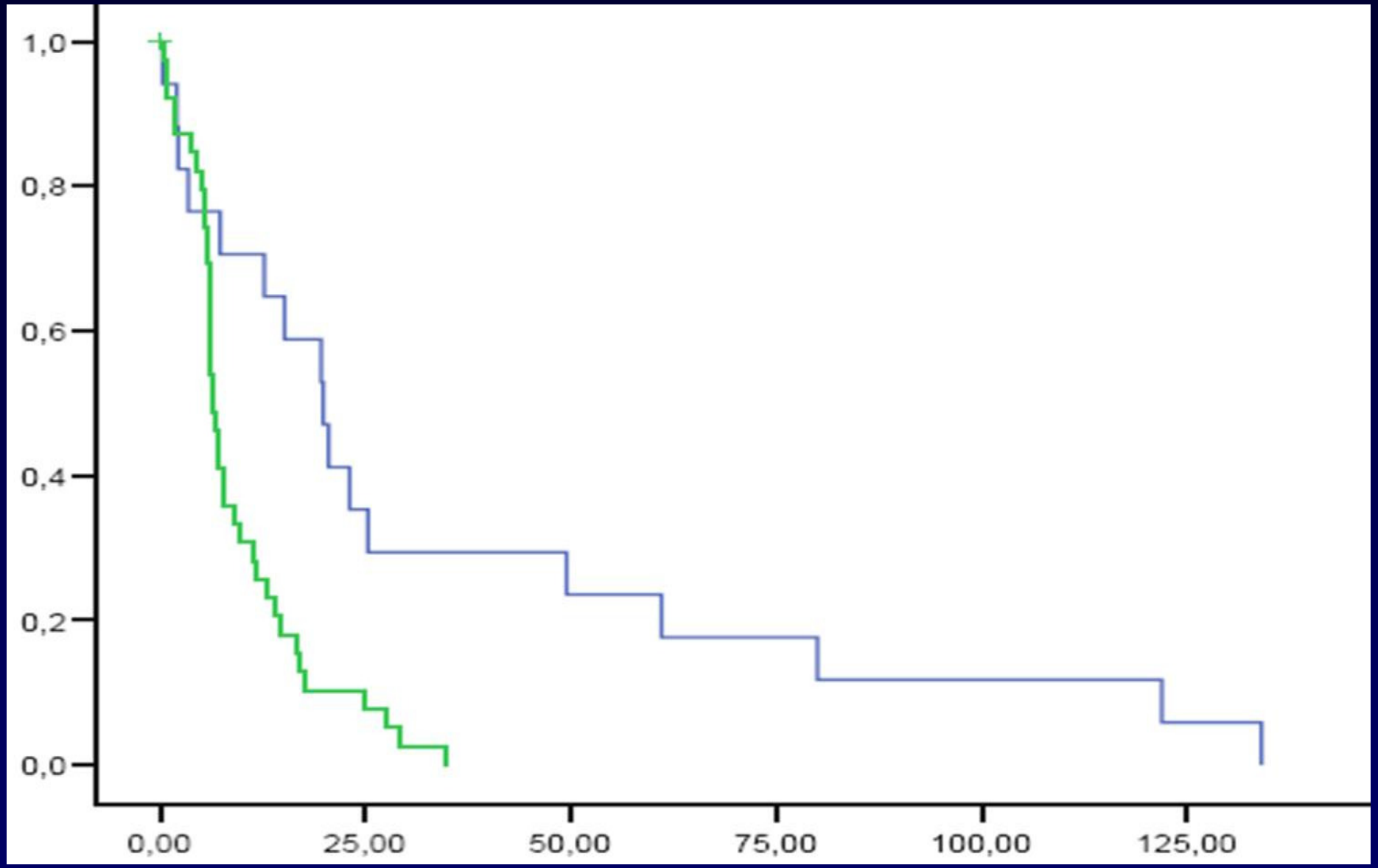
Andrade et al, Gastroenterology 2005

Presentations and outcome of ALF

	ACM n = 407	IDILI n = 111	Indeterminate n = 131	Hepatitis A/Hepatitis B n = 29/69	All others n = 159
Age (median)	36.0	42.0	38.0	48.0/41.0	42.0
Sex (% female)	74	67	57	48/48	78
Jaundice (days) (median)	0.0	8.0	8.0	3.0/6.0	6.0
Coma ¾ (%)	52	39	49	52/50	42
ALT (median)	4248	586	899	2622/1740	674
Bilirubin (median)	4.5	20.9	22.7	11.8/19.7	15.8
Transplantation (%)	9	42	41	31/49	35
Spontaneous survival (%)	63	25	26	55/26	30
Overall survival (%)	71	64	63	83/68	60

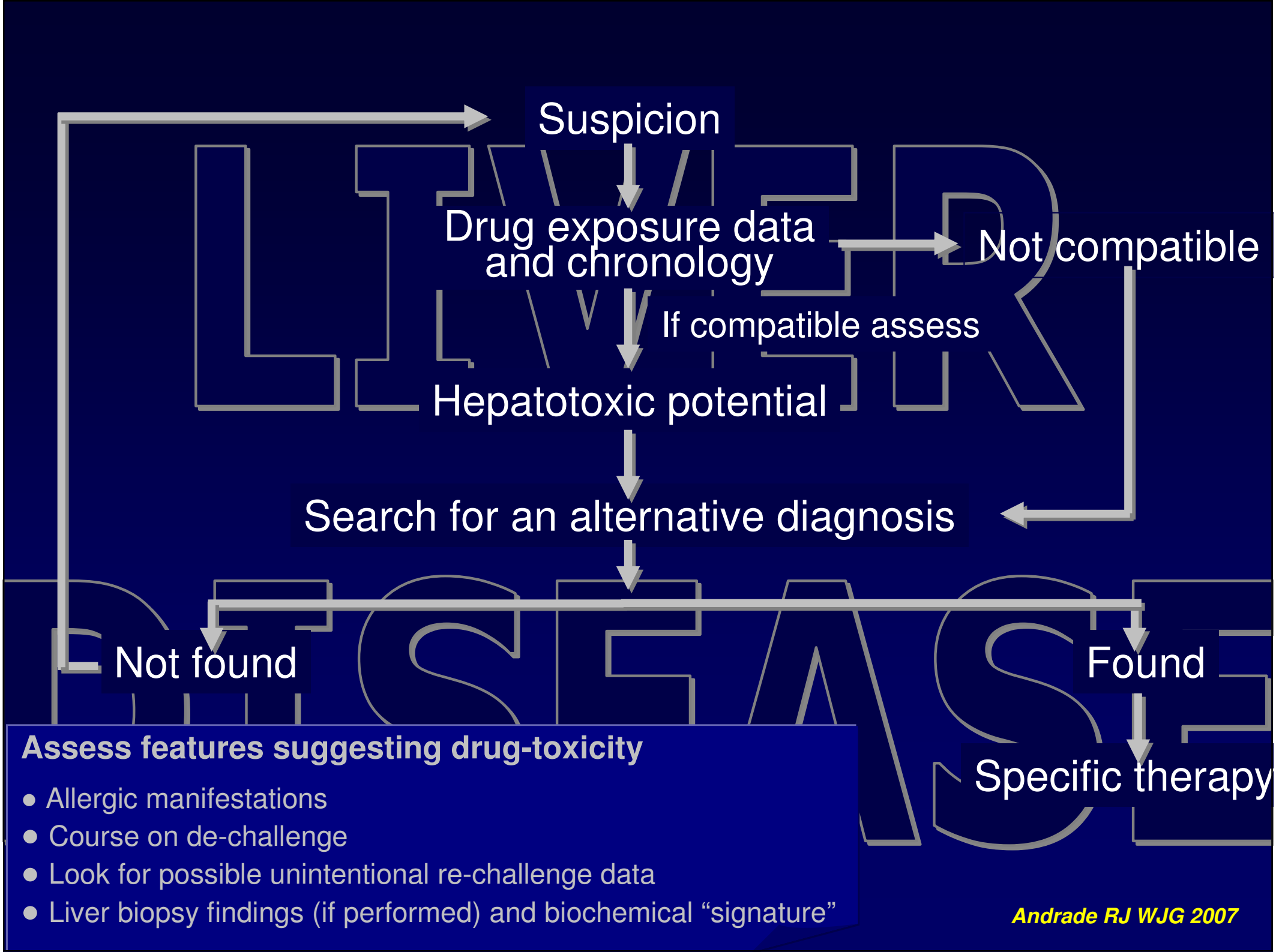
Lee WM, 2007

Evolución a largo plazo de DILI HC vs Col/Mix

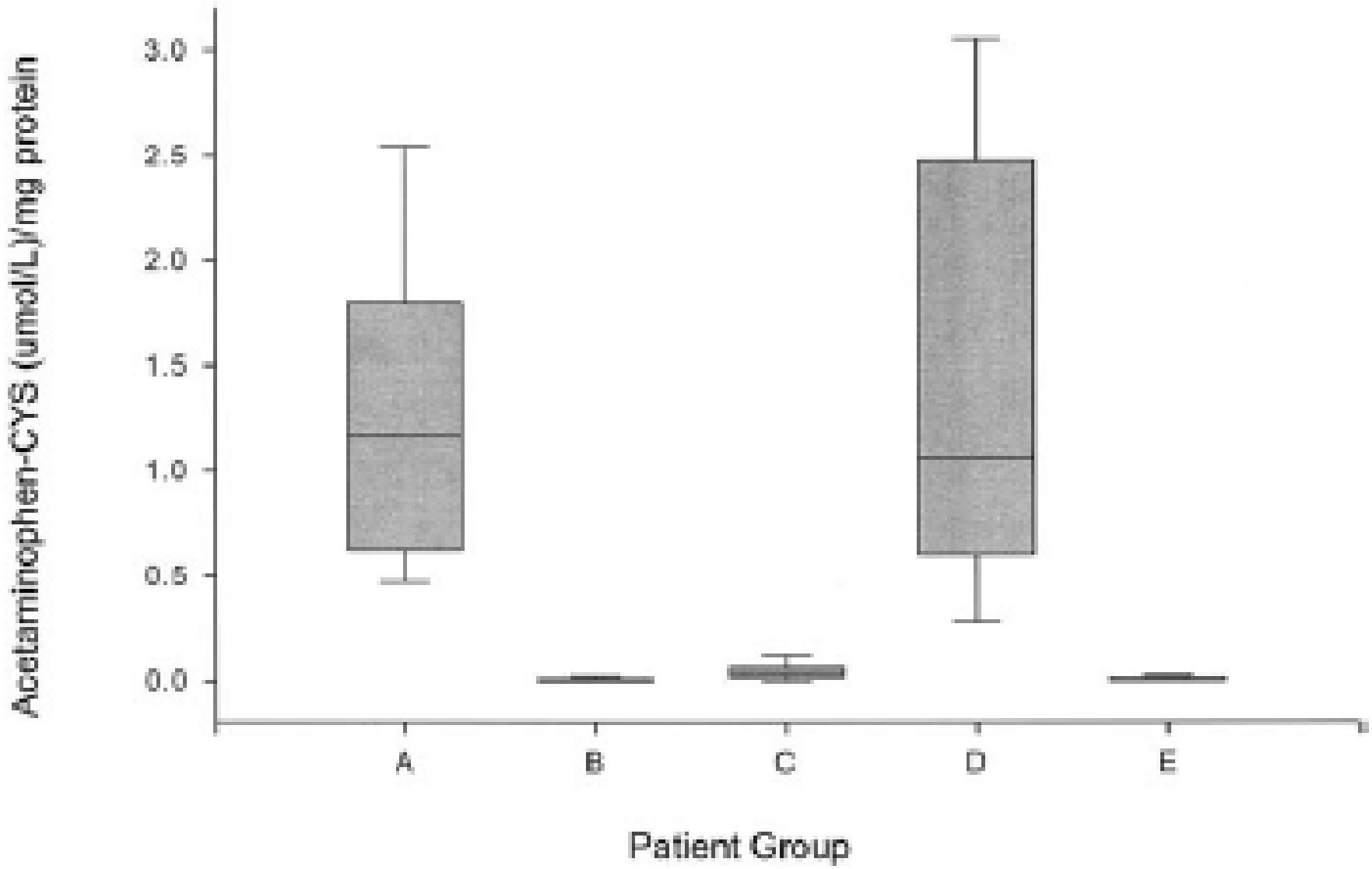


HC (n=32)	32	3	3	3	3	3
Col/Mx (n=46)	46	7	5	5	5	5

García-Muñoz et al EASL 2008


Suspicion
Drug exposure data and chronology
Not compatible
If compatible assess
Hepatotoxic potential
Search for an alternative diagnosis
Not found
Found
Specific therapy
Assess features suggesting drug-toxicity
Allergic manifestations
Course on de-challenge
Look for possible unintentional re-challenge data
Liver biopsy findings (if performed) and biochemical “signature”
Andrade RJ WJG 2007

Biomarcadores



Davern et al Gastroenterology 2006

Escalas diagnósticas

- **Aproximación uniforme a la evaluación de sospecha de hepatotoxicidad**
- **Cualidades exigibles: validez y reproducibilidad**
- **Diversas escalas generales para la evaluación de RA** ***(Karch y Lasagna 1977; Naranjo 1981)***
- **Escalas específicas para RAH** ***(CIOMS/RUCAM 1990 y M & V/CDS 1997)***

Scores for individual axes of the diagnostic scales CIOMS/RUCAM and Maria & Victorino

CIOMS/RUCAM (1990)		Maria & Victorino/CDS (1997)	
AXIS	**SCORE**	**AXIS**	**SCORE**
CHRONOLOGICAL CRITERIA		**CHRONOLOGICAL CRITERIA**	
From drug intake until onset event	+2 to +1	From drug intake until onset event	+1 to +3
From drug withdrawal until onset event	+1 to 0	From drug withdrawal until onset event	-3 to +3
Course of the reaction	-2 to +3	Course of the reaction	0 to +3
RISK FACTORS		Exclusion alternative causes	-3 to +3
Age	+1 to 0		
Alcohol	+1 to 0	Extrahepatic manifestations	0 to +3
Concomitant therapy	-3 to 0	Bibliographical data	-3 to +2
Exclusion non-drug related causes	-3 to +2	Rechallenge	0 to +3
Bibliographical data	0 to +2		
Rechallenge	-2 to +3		

CIOMS/ RUCAM	María & Victorino/CDS					
	Excluded	Unlikely	Possible	Probable	Definite	Total
Excluded	21	2				23
Unlikely	4	3				7
Possible		8	1			9
Probable	1	30	43	16		90
Definite		5	40	53	1	99
Total	26	48	84	69	1	228

Kappa weighted: 0.28

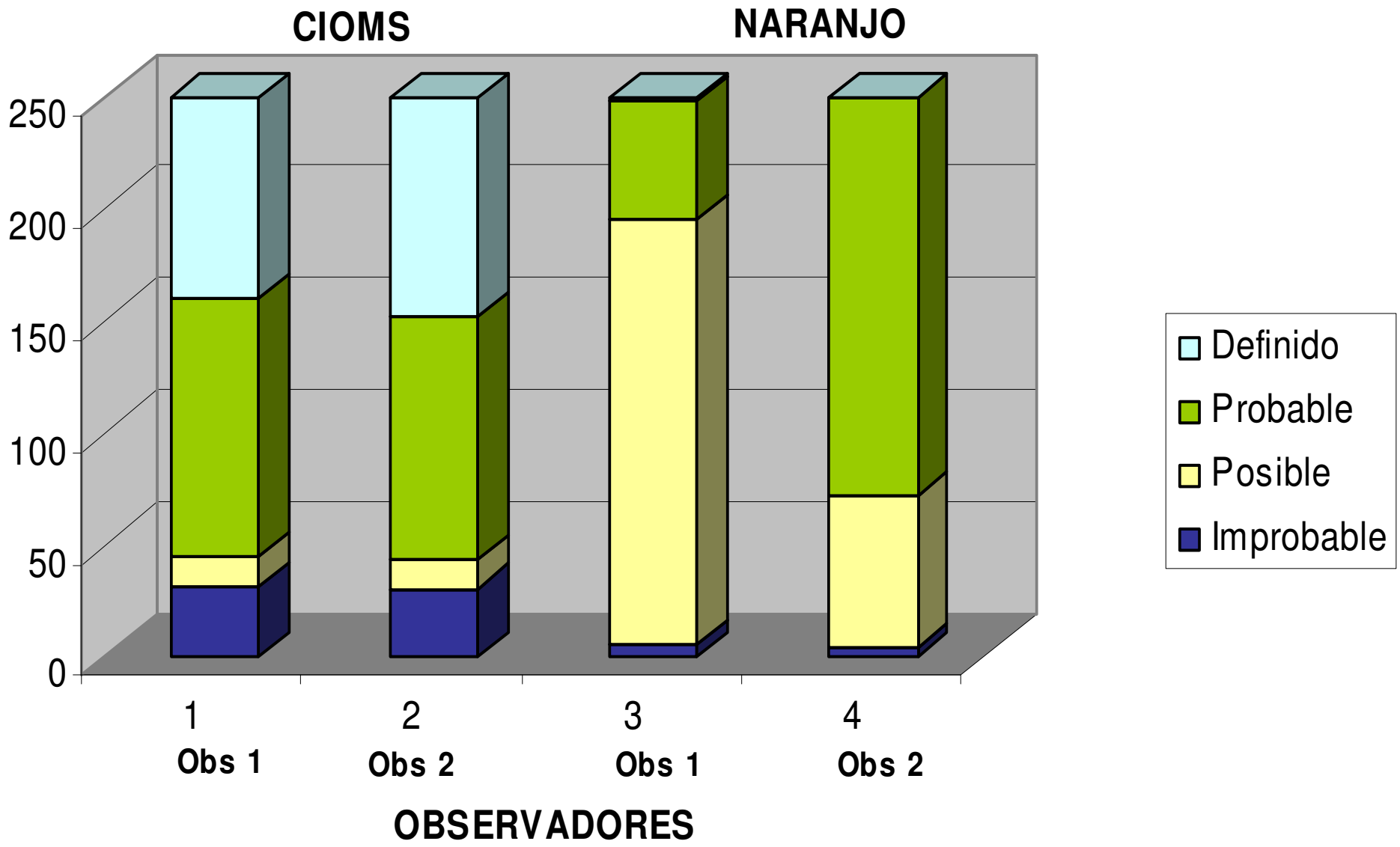
Lucena et al, Hepatology 2001.

Is the Naranjo scale useful in assessing DILI ?

NARANJO SCALE	Yes	No	??
1. It is reported in the literature?	+1	0	0
2. Temporal relationship	+2	-1	0
3. Improvement after dechallenge or antidote therapy?	+1	0	0
4. Positive rechallenge	+2	-1	0
5. Exclusion of alternative causes	-1	+2	0
6. Placebo response	-1	+1	0
7. Toxic levels in blood or fluids	+1	0	0
8. Dose-response effect	+1	0	0
9. Similar event in previous exposure	+1	0	0
10. Confirmation using an objective test	+1	0	0

Probability : Doubful: ≤ 0; Possible: 1-4; Probable: 5-8; Definite ≥ 9.

CORRELACIÓN ENTRE LOS RESULTADOS DE 2 OBSERVADORES APLICANDO LAS ESCALAS DE CIOMS Y NARANJO

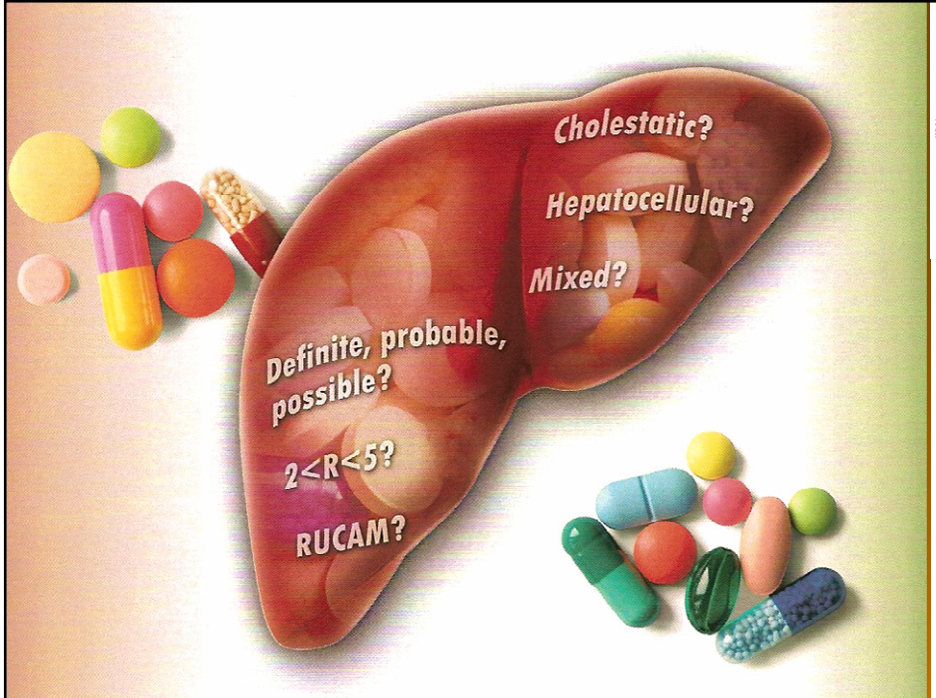


García-Cortés et al Alim Pharmacol Ther 2008

¿Es reproducible la escala de CIOMS/RUCAM?

- Estudio en 40 casos, por 3 evaluadores utilizando la escala de CIOMS/RUCAM en 2 ocasiones distintas
  - -Causalidad por consenso definida (26%), muy probable (49%), probable (21%) y posible (5%)
  - -Score 1ª revisión 6.2 (0.2) y 2ª revisión 6.4 (0.2); p=0.99. Diferencias 3.1
  - -Acuerdo completo en 2ª revisión en 26% de casos, diferencia > 2 puntos en 19%. Diferencias 2.7

Rochon et al AASLD 2007



Drug-Induced Liver Injury

Standardization of Nomenclature and Causality Assessment

NIH Workshop

December 1 - 2, 2008
Lister Hill Auditorium
NIH Campus, Bethesda, MD

Sponsored by NIDDK and NLM

NIDDK | NATIONAL INSTITUTE OF DIABETES AND DIGESTIVE AND KIDNEY DISEASES

DEPARTMENT OF HEALTH & HUMAN SERVICES
Public Health Service
National Institutes of Health

National Institute of Diabetes and
Digestive and Kidney Diseases
Bethesda, Maryland 20892

Drug-Induced Liver Disease: Standardization of Nomenclature and Causality Assessment

National Institutes of Health Workshop

December 2008
(Monday-Tuesday)

Lister Hill Auditorium

Organizers:
Robert Fontana, M.D.
Christopher Day, M.D.
Raul Andrade, M.D.
Jose Serrano, M.D. and
Leonard B. Seeff, M.D.

El futuro inmediato

Grupo de Estudio Hepatopatías Asociadas a Medicamentos *(GEHAM)*

Hospital Torrecárdenas, Almería: MC Fernández, G Peláez, M. Casado, JL Vega,
Hospital Virgen Macarena, Sevilla: JA Durán, M. Villar .
Hospital Universitario Virgen de Valme, Sevilla: M Romero,
Hospital Central de Asturias, Oviedo: L Rodrigo-Saez, V. Cadahía, R. De Francisco.
Hospital de Puerto Real, Cádiz: JM Pérez-Moreno, M Puertas.
Hospital Universitario San Cecilio, Granada: J Salmerón, A Gila.
Hospital Germans Trias i Puyol, Barcelona: R Planas,I Barriocanal, Eva Montané,J Costa
Hospital Universitario Virgen de las Nieves, Granada: R Martín-Vivaldi, F Nogueras.
Hospital Costa del Sol, Málaga: JM Navarro, JF Rodríguez.
Hospital La Inmaculada. Huércal-Overa, Almería: H Sánchez-Martinez.
Hospital Puerta del Mar, Cádiz: F Díaz, MJ Soria, L Martín-Herrera
Hospital Reina Sofía, Córdoba: JL Montero, M De la Mata.
Hospital 12 de Octubre, Madrid: T. Muñoz-Yagüe, J.A. Solis-Herruzo
Hospital Marqués de Valdecilla, Santander: F. Pons, R. Tab
H. Sant Pau, Barcelona: C Guarner, D Monfort
Hospital Carlos Haya, Málaga: M Jiménez.
Hospital Xeral-Calde, Lugo: S. Avila-Nasi.
Hospital Nuestra Sra. de Aranzazu, San Sebastián: M. Castiella.
Hospital de Mendaro, Guipuzcuoa: S. Blanco
Hospital Clínico Provincial: M Bruguera
Hospital Morales Messeguer: H Hallaf