

ANTIMICROBIAL-INDUCED LIVER TOXICITY



Arun J Sanyal M.D.

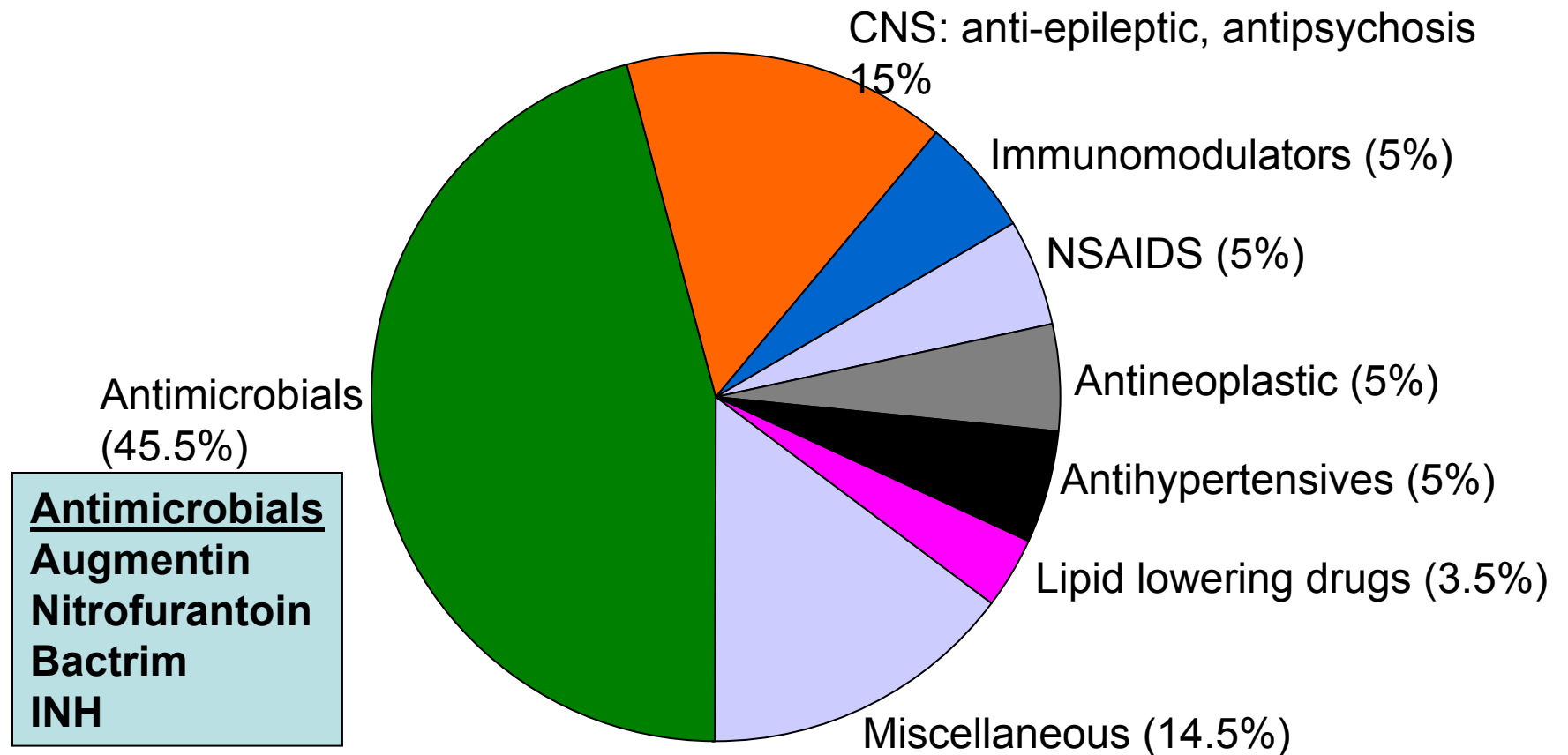
Chairman, Div. of Gastroenterology, Hepatology and
Nutrition

Virginia Commonwealth University School of Medicine
Richmond, VA

Drug induced liver injury (DILI)

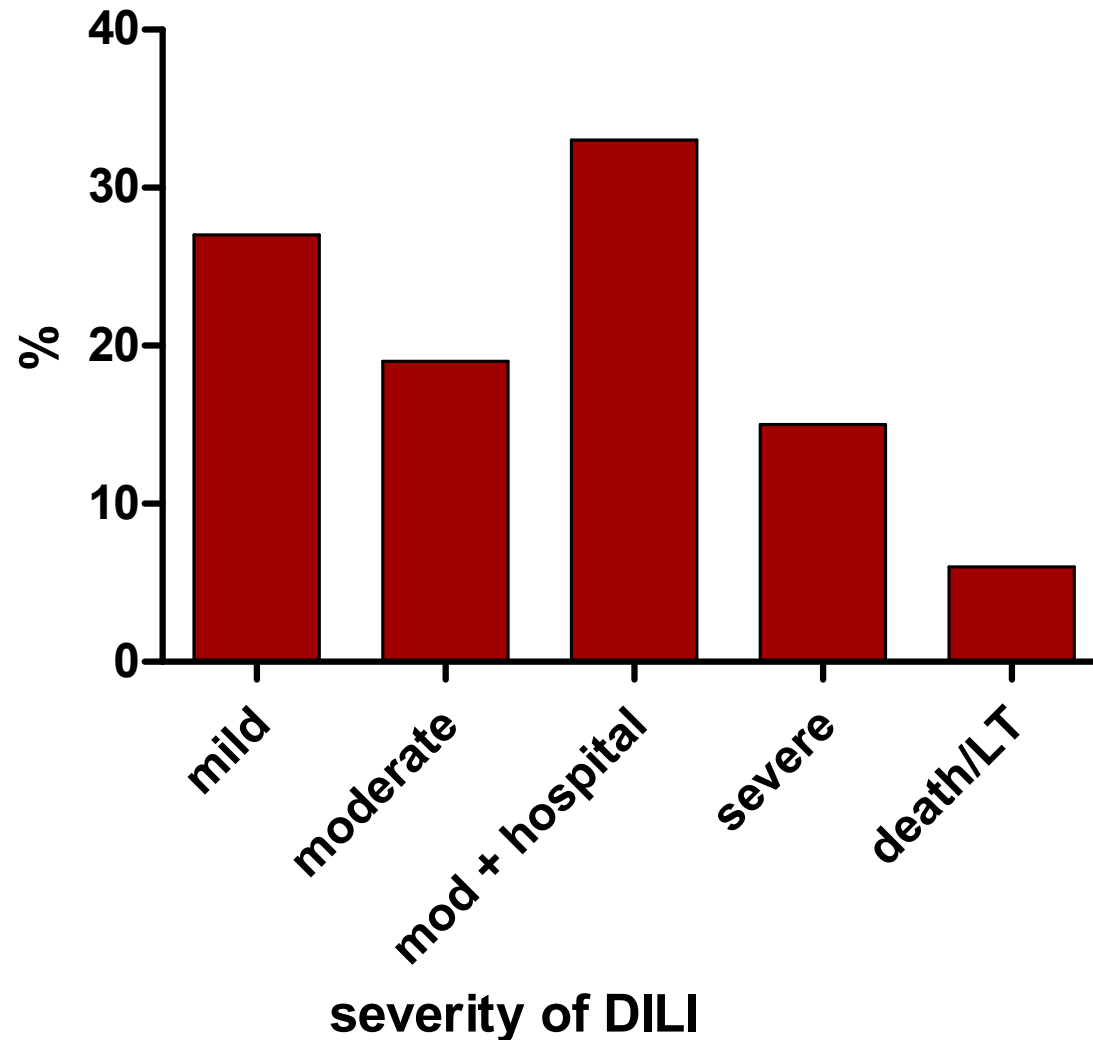
- An injurious and unintended effect of a drug on the liver.
- Defined by any of the following:
 - AST and/or ALT $> 3 \times$ upper limit of normal (ULN) if previously normal
 - AST/ALT $> 5 \times$ ULN if abnormal when drugs started
 - Alk phos $> 2 \times$ ULN
 - Rise in conjugated bilirubin or INR

Causes of DILI in the United States



Chalasani et al, Gastroenterology, 2008, 35:1924-34

Distribution of severity of DILI



Chalasani et al, Gastroenterology, 2008, 35:1924-34

Types of DILI

- **Type A (Dose-dependent)**

- *Most common, reactions are expected exaggerations of a drug's known pharmacologic effects, therefore they are usually dose-dependent, predictable and preventable.*
- *Occur with overdosing, altered drug metabolism or increased sensitivity to normal pharmacologic effects.*

- **Type B (Idiosyncratic)**

- *unrelated to the known pharmacologic action of a drug, usually unpredictable, uncommon and potentially more serious than type A reactions*

Patterns of liver injury

$$R = \frac{\text{ALT (fold change from ULN)}}{\text{AP (fold change from ULN)}}$$

- **Hepatocellular:**
 - AST, ALT are mainly elevated
 - $R > 5$
- **Cholestatic:**
 - Alk phos (AP) mainly elevated
 - $R < 2$ and Alk phos $> \text{ULN}$
- **Mixed:**
 - $2 < R < 5$

(J Hepatol 1990; 11: 272)

Clinical patterns of DILI

- **Asymptomatic** elevation of liver enzymes
- **Acute hepatocellular necrosis**
 - mild, moderate and severe
 - severity determined by ALT > 10x ULN, Bili and INR change
 - fulminant hepatic failure (severe hepatocellular necrosis + encephalopathy)
- **Cholestatic liver disease**
 - pruritus, jaundice, alk phos elevation
- **Cholestatic hepatitis**
 - features of both hepatocellular necrosis and cholestasis
 - mixed pattern of liver enzyme abnormality

How to diagnose DILI

- Temporal relationship to starting or discontinuing drug
- Signature pattern of injury
- Improvement with discontinuation
- Recurrence with rechallenge (usually not recommended)
- R/O alternate causes of injury

A case report

A 60 yr w male executive develops urgency, frequency and dysuria while on a business trip to San Francisco. He was seen at a local ER and noted to have prostate tenderness. UA showed many WBC. He was started on Augmentin. He takes a 10 day course and is back in his hometown. A month later, he develops dark urine, pruritus and jaundice.

- **LABS:** AST: 250 IU/L, ALT: 350 IU/L, Alk Phos: 325 IU/L, Bili: 6 mg/dl, INR: 1.1

What to do next?

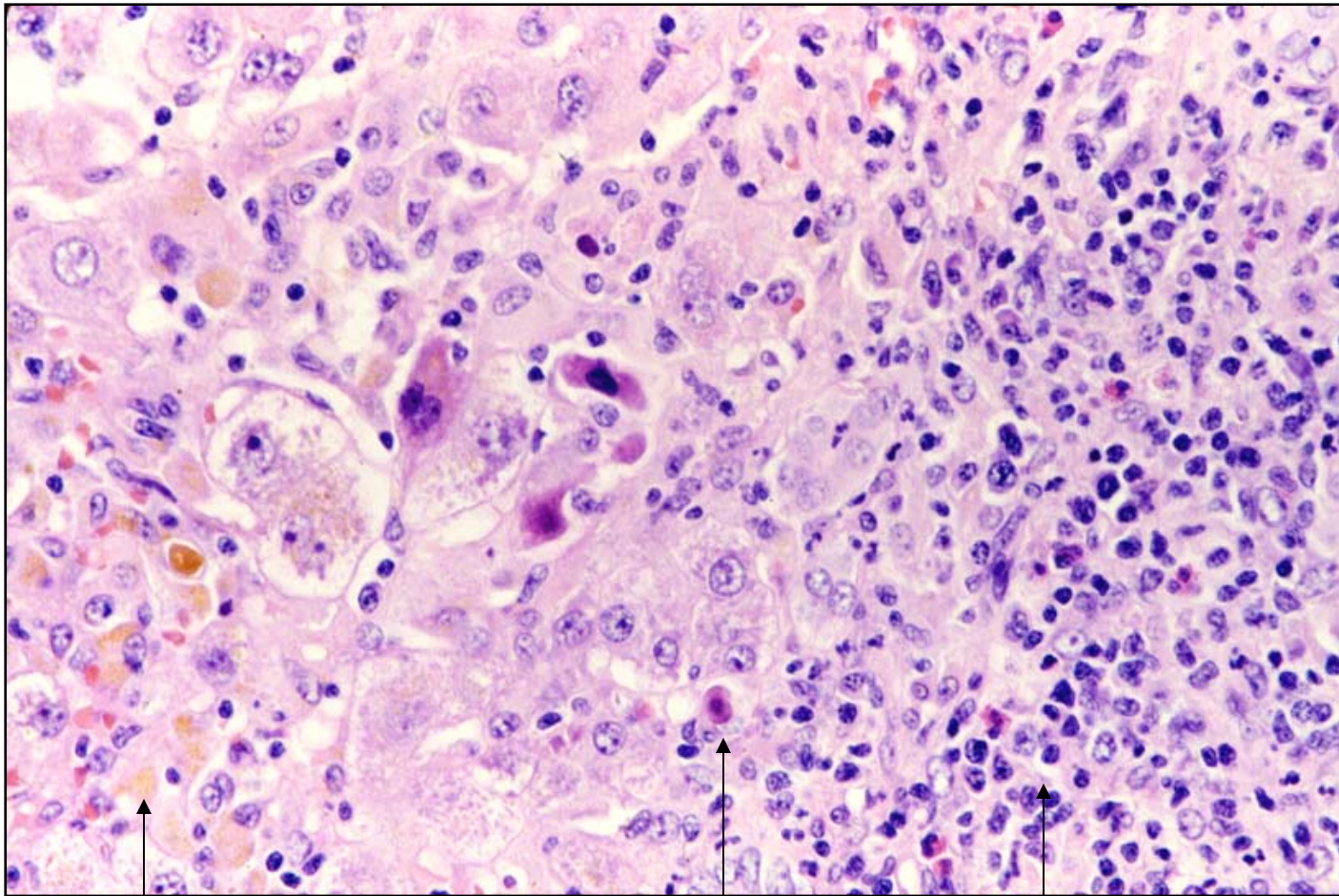
- Check for viral serologies (HAV, HBV, HCV)
- Perform liver biopsy
- Obtain liver ultrasound
- Perform an ERCP

Labs:

- IgM HAV –ve
- HBsAg –ve
- IgM anti-HBcAg –ve
- HCV negative
- ANA (1:80)

Liver biopsy

40 x



bilirubinostasis

apoptosis

Portal inflammation

Augmentin hepatotoxicity

- How dx of DILI made:

- Signature pattern
- Temporal relation
- Exclusion of other causes

Patient is advised to not take any meds and return for periodic checks. When is his cholestasis expected to completely reverse:

- Days
- Weeks
- Months
- Never

Augmentin hepatotoxicity

- **Prevalence:** (1.7/10K prescriptions)
- **Time course:** 1-9 wks after starting and up to 6 wks after discontinuation
- **LFT pattern:** typically cholestatic, but mixed or hepatocellular may also occur
- **Biopsy:** cholestatic hepatitis, may sometimes progress to vanishing bile duct syndrome
- **Recovery:** may take up to 3-4 mnths, consider progression to vanishing duct syndrome if jaundice persists after 8-10 wks

Garcia-Rodriguez et al, Arch Int Med, 1996, 156:1327-1332

Signature patterns of common anti-microbial DILI

Drug	Signature Pattern
Augmentin	Cholestatic hepatitis/Cholestasis
Nitrofurantoin	Acute and chronic hepatitis
INH	Acute hepatitis
Bactrim	Cholestasis/cholestatic hepatitis
Macrolides	Cholestatic hepatitis
Levoquin	Acute hepatitis

A case report

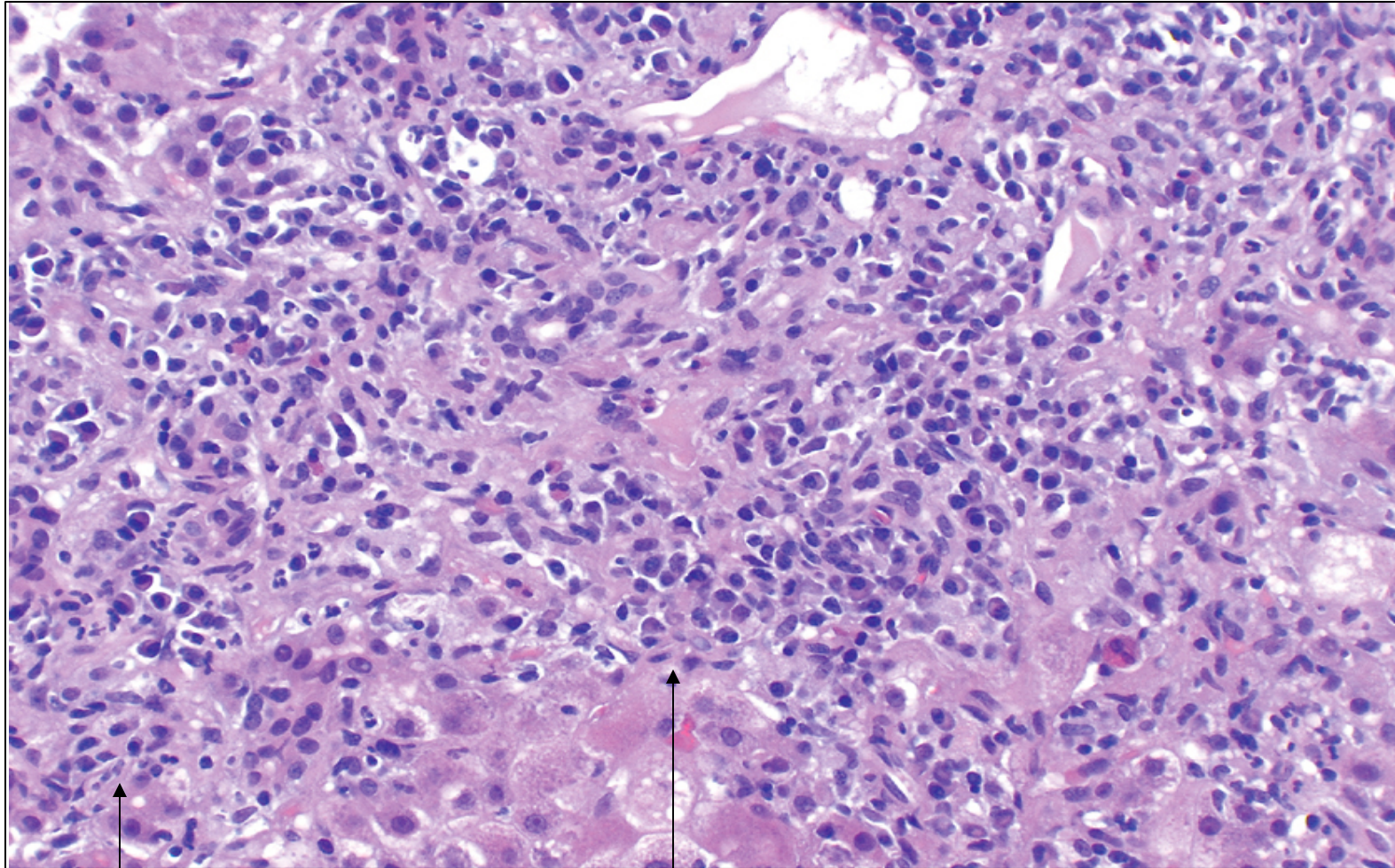
A 73 yr Japanese lady has increasing fatigue and lethargy, nausea and low grade fevers in Jan 2008. She has hyperlipidemia and a h/o vesical prolapse with UTIs for which she is on simvastatin and nitrofurantoin respectively. She has labs drawn in June and found to have elevated LFTs. Viral serologies are negative and she is told it is probably mononucleosis. She returns in July 2008 with jaundice and referred to hepatologist.

•**LABS:** AST: 750 IU/L, ALT: 990 IU/L, Alk Phos: 116 IU/L, Bili: 14 mg/dl, INR: 1.5, ANA: 1: 160, AMA: negative, Viral serologies negative

How to approach problem

- What is the nature of liver injury?
 - hepatocellular
 - cholestatic
 - mixed
- How severe is it?
 - mild
 - moderate
 - severe
- What could it be?
 - R/O other causes keeping DILI in mind
- What is the first thing to do?
 - stop the drug (simvastatin and nitrofurantoin)

Liver biopsy: chronic hepatitis



Piecemeal necrosis

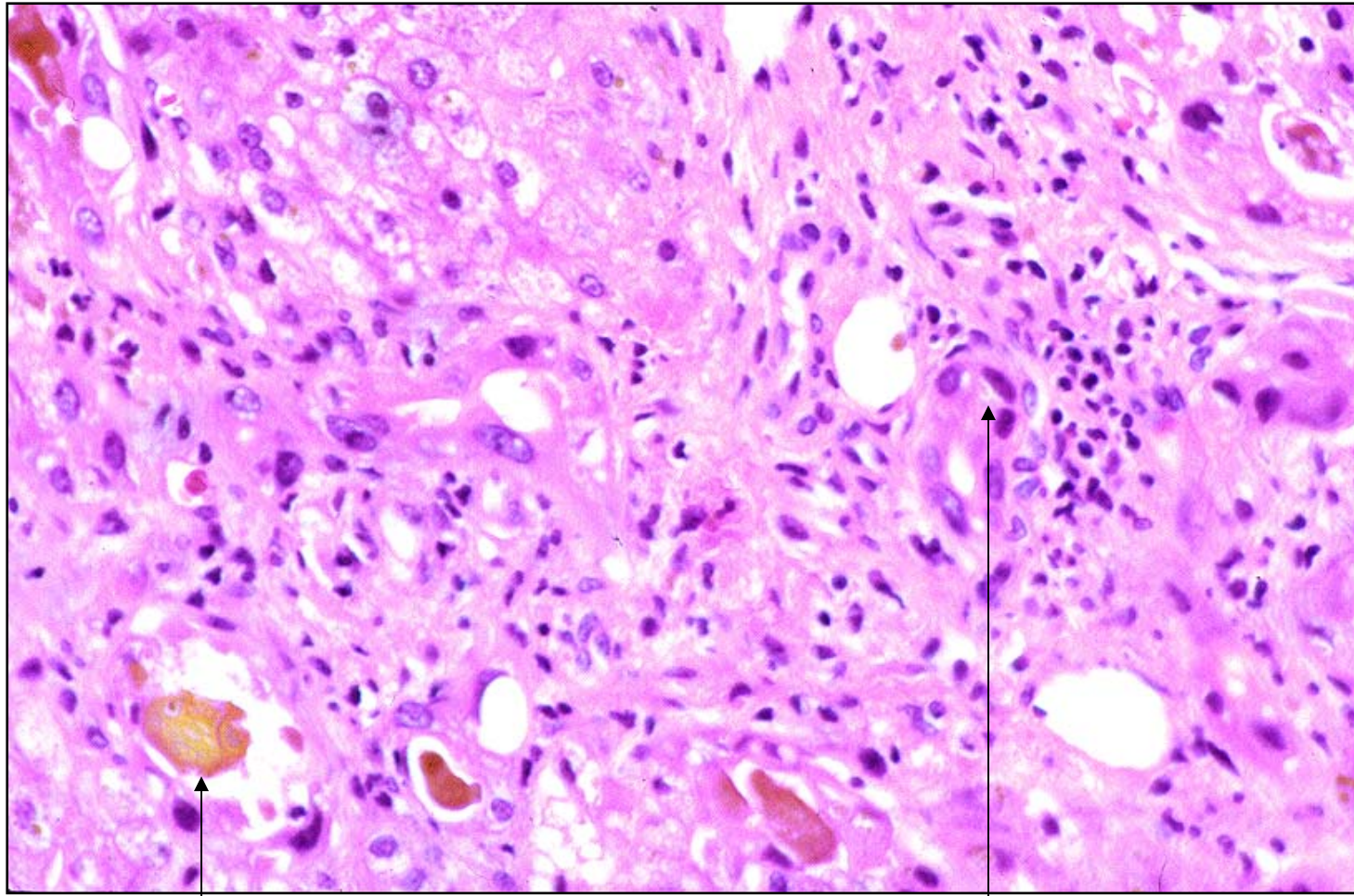
Interface hepatitis

Management

- When in doubt- STOP THE DRUG!!!
 - ALT > 10x normal
 - rise in conjugated bili or INR
- Steroids: usually used when an autoimmune profile is present. Patient started on 60 mg Prednisone and 50 mg Azathioprine

Patient improved with resolution of jaundice over next 4 months and AST, ALT down to 50-100 IU/L. In Dec 2008, pruritus returned and labs showed: Bili: 4 mg/dl, AST: 50 IU/L, ALT: 96 IU/L, Alk Phos: 460 IU/L

Follow up liver biopsy: autoimmune cholangitis



bilirubinostasis

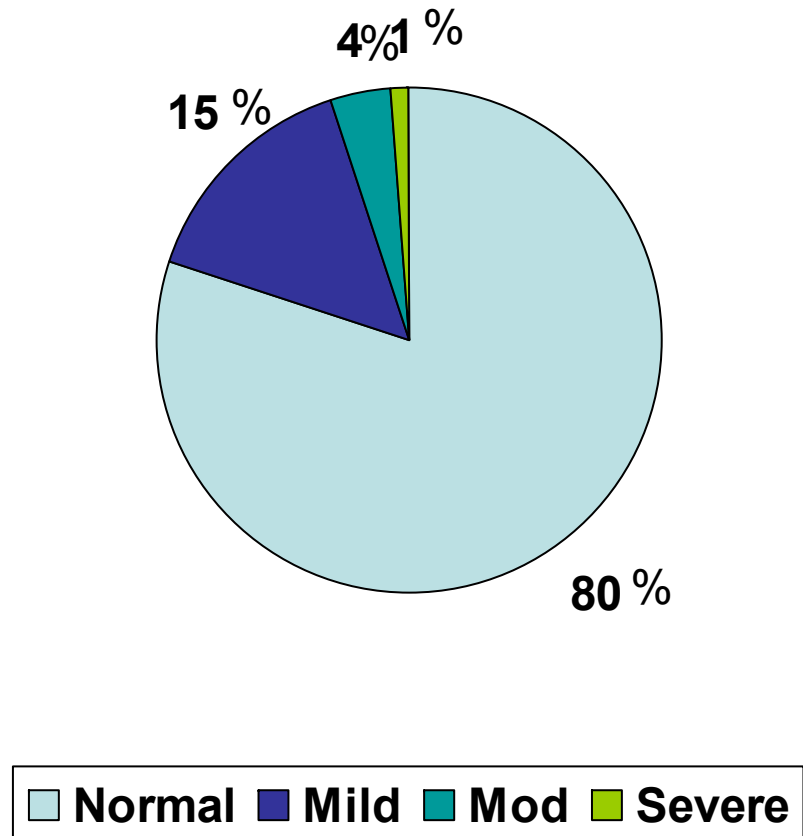
Bile duct injury

Severe Nitrofurantoin hepatotoxicity

- **Prevalence:** 0.02-0.003%
- **Time course:** weeks to years after starting drug..rarely after discontinuation
- **LFT pattern:** Hepatocellular or mixed
- **Biopsy:** Acute or chronic hepatitis, granulomas etc
- **Other clues:** female predominant, ANA +
- **Rx:** steroids for severe disease, stop drug, **NEVER RECHALLENGE**

INH Hepatotoxicity

- **Time course:** 50% within first 3 months
- **LFT pattern:** hepatocellular
- **Biopsy:** Hepatitis
- **Course:**
 - 10-20 % get ALT elevation
 - 1-2% have severe injury
 - 0.1-0.2 % will die
- **Rx:** STOP DRUG



Kopanoff et al, Am Rev Resp Dis, 1978, 117:991-1001
Nolan et al, JAMA, 1999, 281:1014-1018

How to manage TB after hepatotoxicity

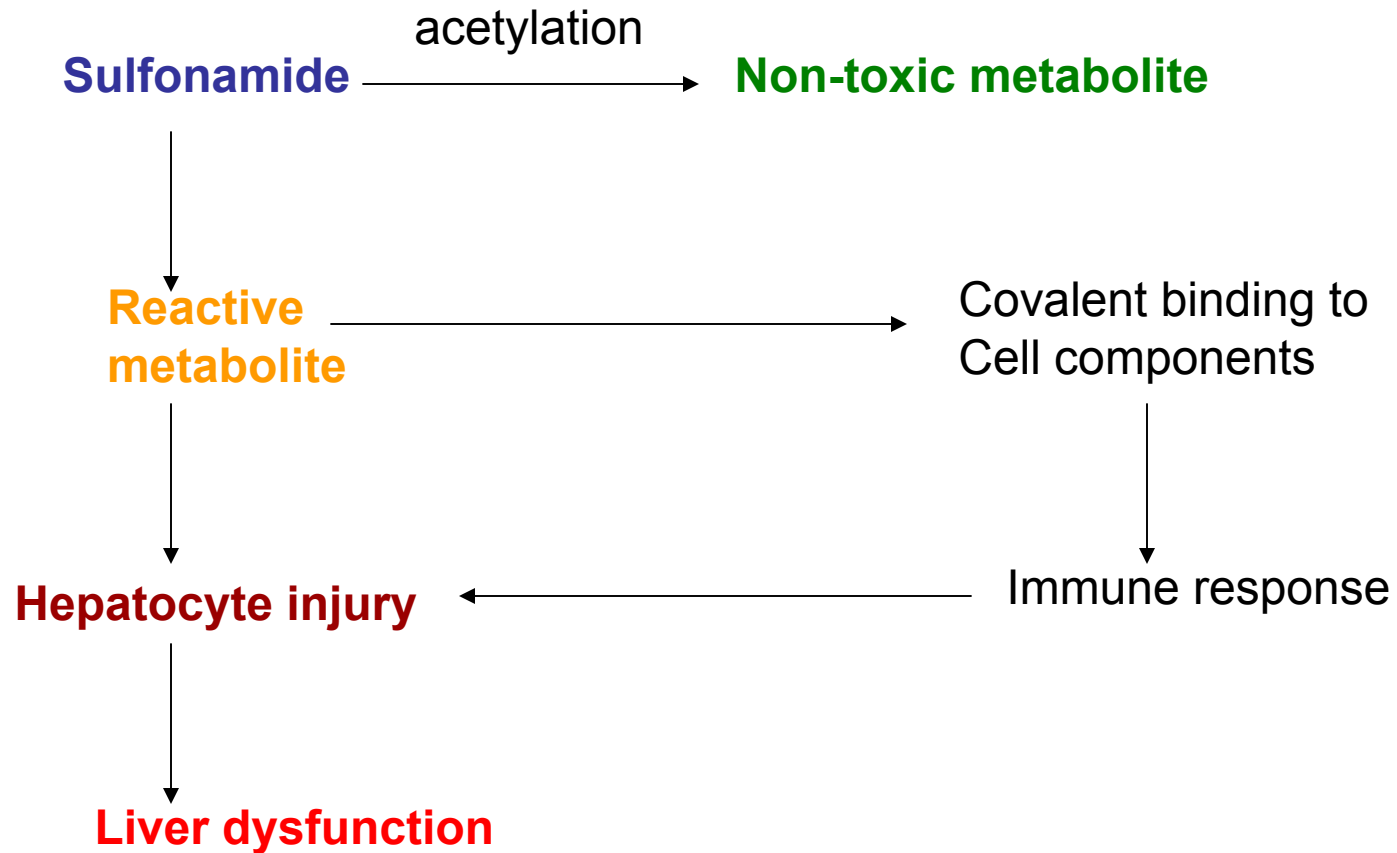
- **Step 1:** Stop all potentially offending drugs
- **Step 2:** May use non-hepatotoxic drugs e.g. Streptomycin, Ethambutol, Cipro etc
- **Rechallenge** has been performed safely in several studies
 - start with INH (50-100-200-300 mg/day) increasing at 3-5 day intervals
 - After 1 wk on full dose INH, start PZA
 - Add Rifampin after 1 wk on INH+PZA
 - Check LFTS very frequently during rechallenge q 2-3 days

Dossing et al, Tuberc Lung Dis, 1996, 134:666-668

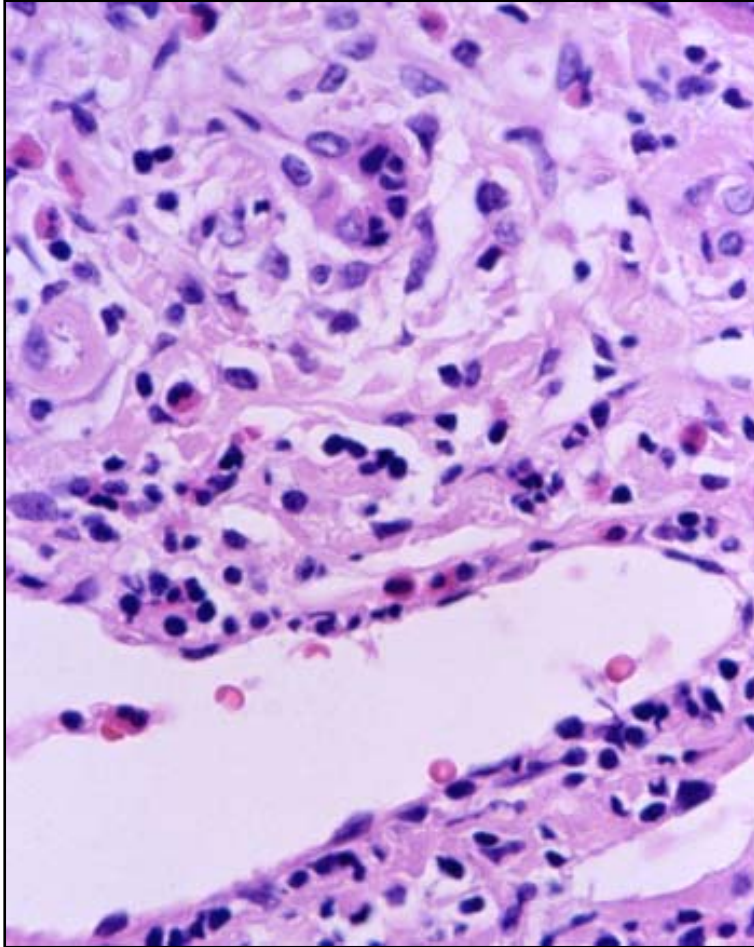
Ansari et al, Ind J Chest Dis All Sci, 1991, 33:133-138

Tandon et al, Drug-induced liver Dis, Eds Kaplowitz

Sulfonamide Hepatotoxicity



Bactrim Hepatotoxicity



- HIV infected patients are very susceptible (20%)
- Fairly common in transplant population
- **Time course:** weeks of starting
- **LFT pattern:** Mixed or hepatocellular
- **Biopsy:** cholestasis or cholestatic hepatitis
- **Course:** usually resolves but bile duct injury may last a long time

Carr et al, AIDS 1993; 7:1532-1523

Altraif et al, Am J Gastroenterol, 1994, 89:1230-1234

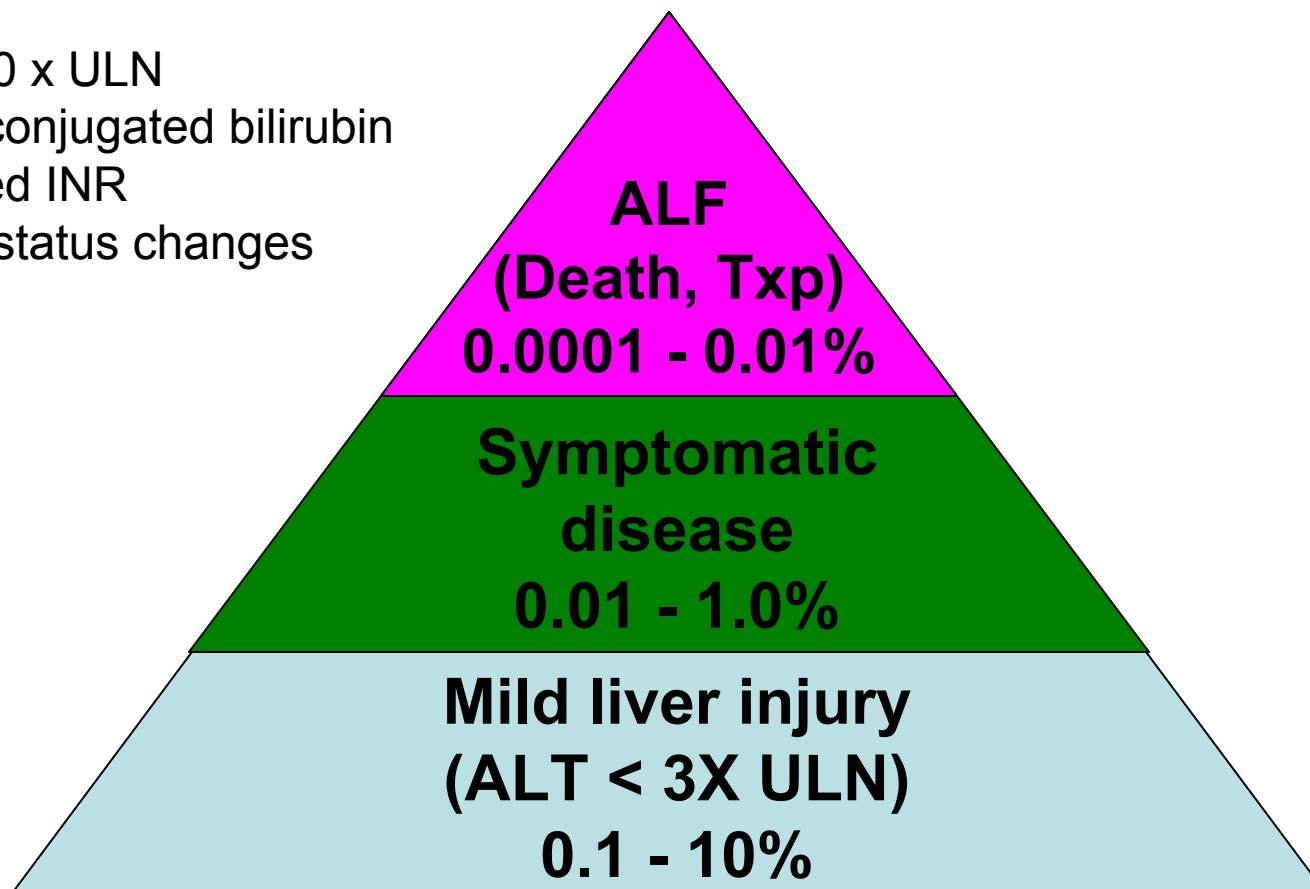
General principles of evaluation

- Have a high index of suspicion
- Ask the following questions:
 - is hepatotoxicity present?
 - how severe is it?
 - which drugs can be implicated?
 - is it dose-dependent or idiosyncratic?
 - is it due to a drug-interaction?
- **EARLY DISCONTINUATION IS THE KEY**

Spectrum of clinical severity of DILI (Hy's rule)

Severe:

- ALT > 10 x ULN
- Rise in conjugated bilirubin
- Increased INR
- mental status changes



Causality assessment of DILI



Definite

Highly probable

Probable

Possible

Unlikely

Excluded / other

Roussel Uclaf Causality Assessment Method (RUCAM) '89

- Temporal relationship (0 to 2)
- Course (-2 to 3)
- Risk factors (0 to 2)
- Concomitant drug (0 to -3)
- Non-drug causes (-3 to 2)
- Prior reports/ information (0 to 2)
- Re-challenge (-2 to 3)

Score (-8 to 14)

Highly probable >8
Probable 6-8

Possible 3-5 Excluded ≤0
Unlikely 1-2

www.fda.gov/medwatch

Summary

- Know the side effect profile and toxicity signature of drugs that you prescribe
- Have a high index of suspicion
- Don't forget other drugs and other causes of liver dysfunction which must be tested for.
- If other causes are absent and the signature fits, it is highly likely to be iatrogenic toxicity
- Assess severity early
- Stop offending drug ASAP
- Refer to Transplant program for all severe toxicity