Drug induced liver injury

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Introduction

- DILI accounts for 10 % of all cases of acute hepatitis.
- Common reason for failure of pharmaceuticals during drug development, most frequently cited reason for withdrawal of approved medications from the market.
- Most common cause of acute liver failure in the US.
- The wide range of presentations and culprit agents and lack of objective diagnostic tests make its diagnosis and management particularly difficult.

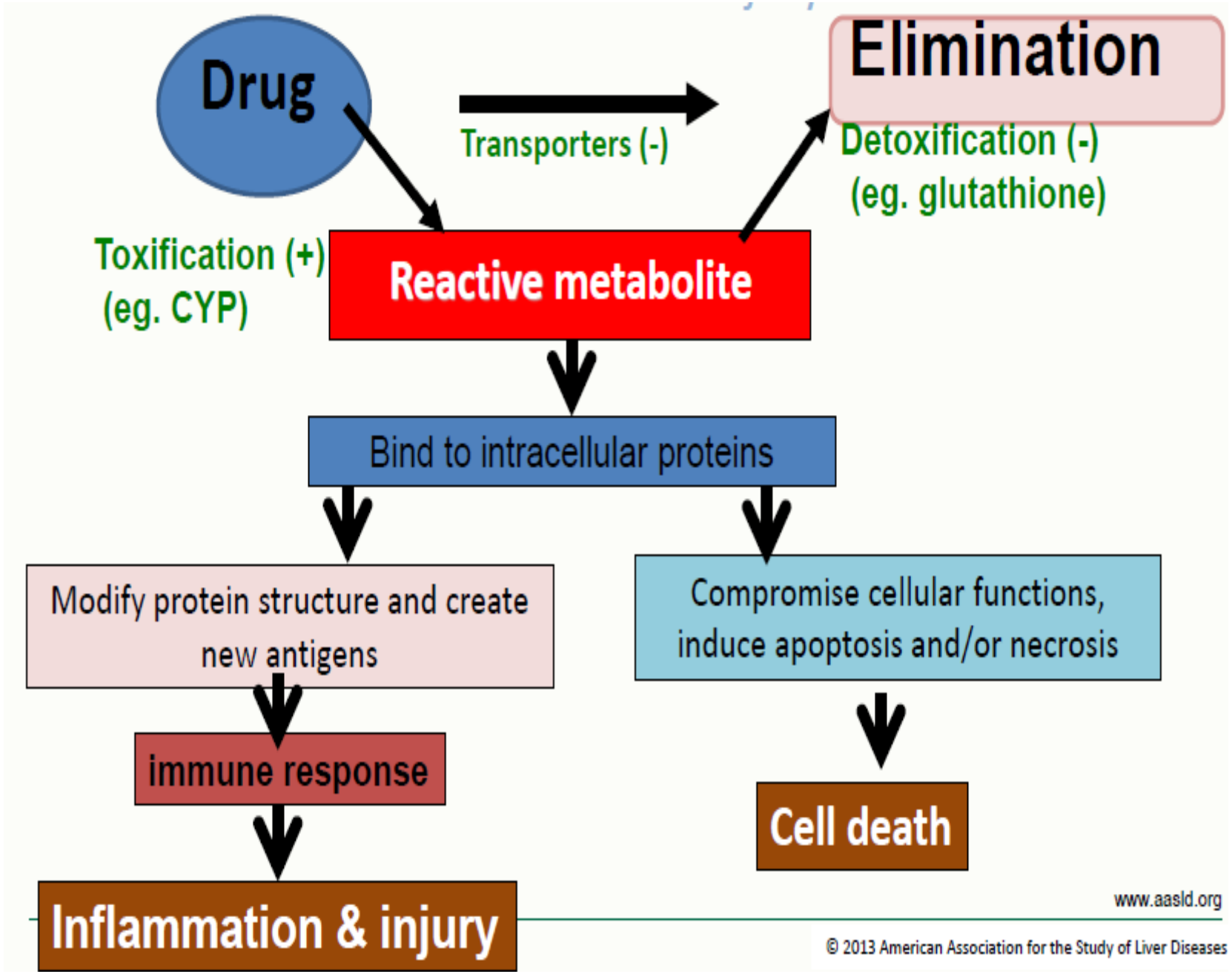
Types

Acute DILI

- Intrinsic DILI tends to affect all individuals to varying degrees (predictable), typically dose dependent (e.g. paracetamol).
- Idiosyncratic DILI tends to affect only rare susceptible individuals, less dose dependent and more varied in latency, presentation, and course.
  - *Immunoallergic* e.g. phenytoin
  - *Metabolic-idiosyncratic* e.g. INH

Chronic DILI

- Failure of return of liver enzymes or bilirubin to pre-DILI baseline, and / or other signs or symptoms of ongoing liver disease (e.g., ascites, encephalopathy) 6 months after DILI onset.


Drug
Transporters (-)
Elimination
Detoxification (-)
(eg. glutathione)
Toxification (+)
(eg. CYP)
Reactive metabolite
Bind to intracellular proteins
Modify protein structure and create new antigens
Compromise cellular functions, induce apoptosis and/or necrosis
immune response
Cell death
Inflammation & injury
www.aasld.org
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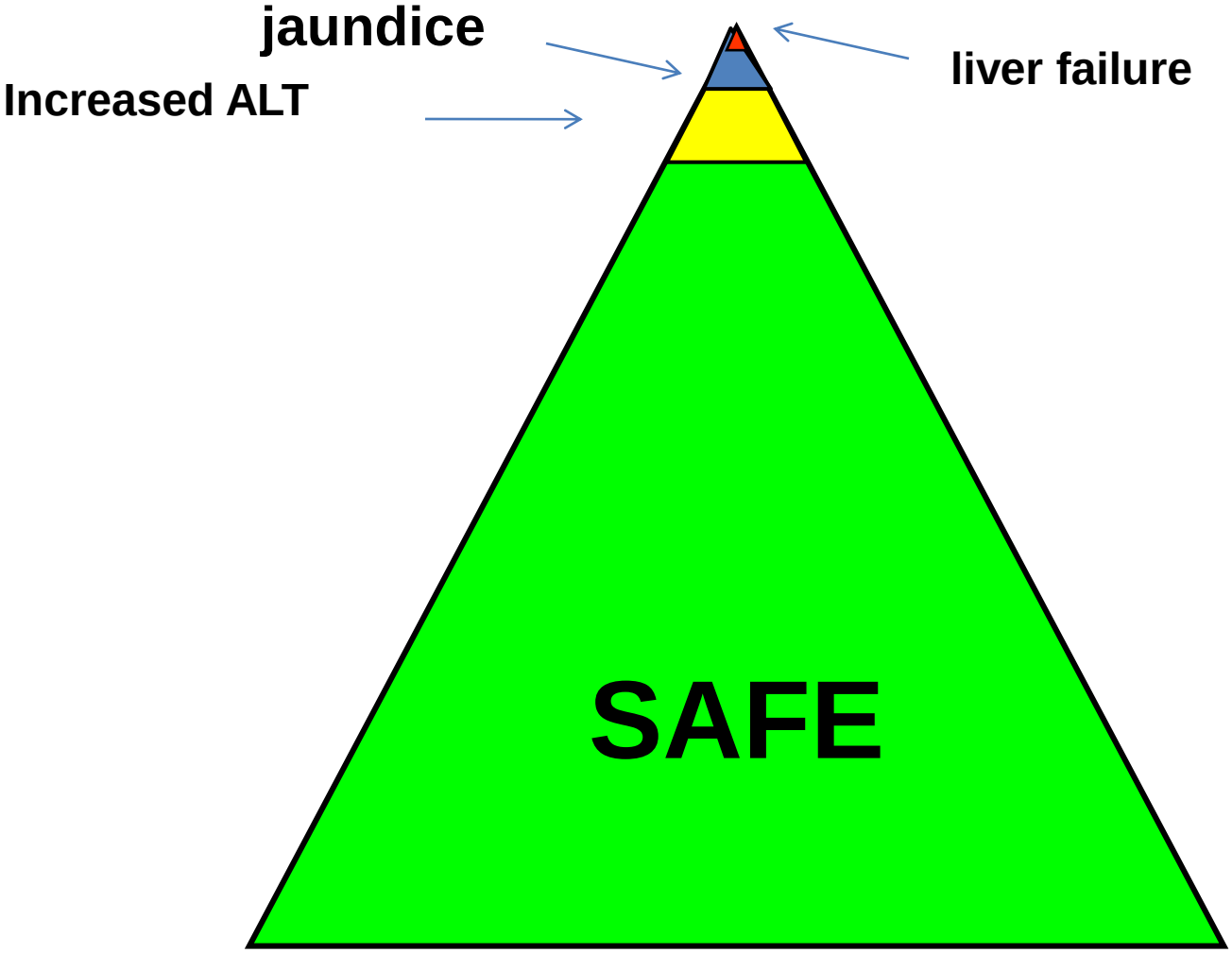


Concept of idiosyncratic hepatocellular injury

Risk factors

- Drug-related (e.g. dose, metabolic profile, concomitant medications)
- Host-related (e.g. genetics, age, gender, alcohol intake, nutritional status, co-morbidities including underlying liver disease).

➢ There is no evidence to suggest that these variables represent major risk factors for all-cause DILI.

Clinical Presentation

- Clinical presentation of DILI varies widely from an asymptomatic rise in liver enzymes to acute liver failure.
- Nonspecific symptoms such as anorexia, nausea, and vomiting, right upper quadrant pain, skin rash, dark urine ,pale stool or itching.
- A patient with severe or chronic DILI might suffer decompensation with jaundice, ascites, or encephalopathy.

Terminology

- Latency
- Wash-out, resolution, or de-challenge
- Rechallenge
- Hy's law
- *R –value*
- RUCAM score

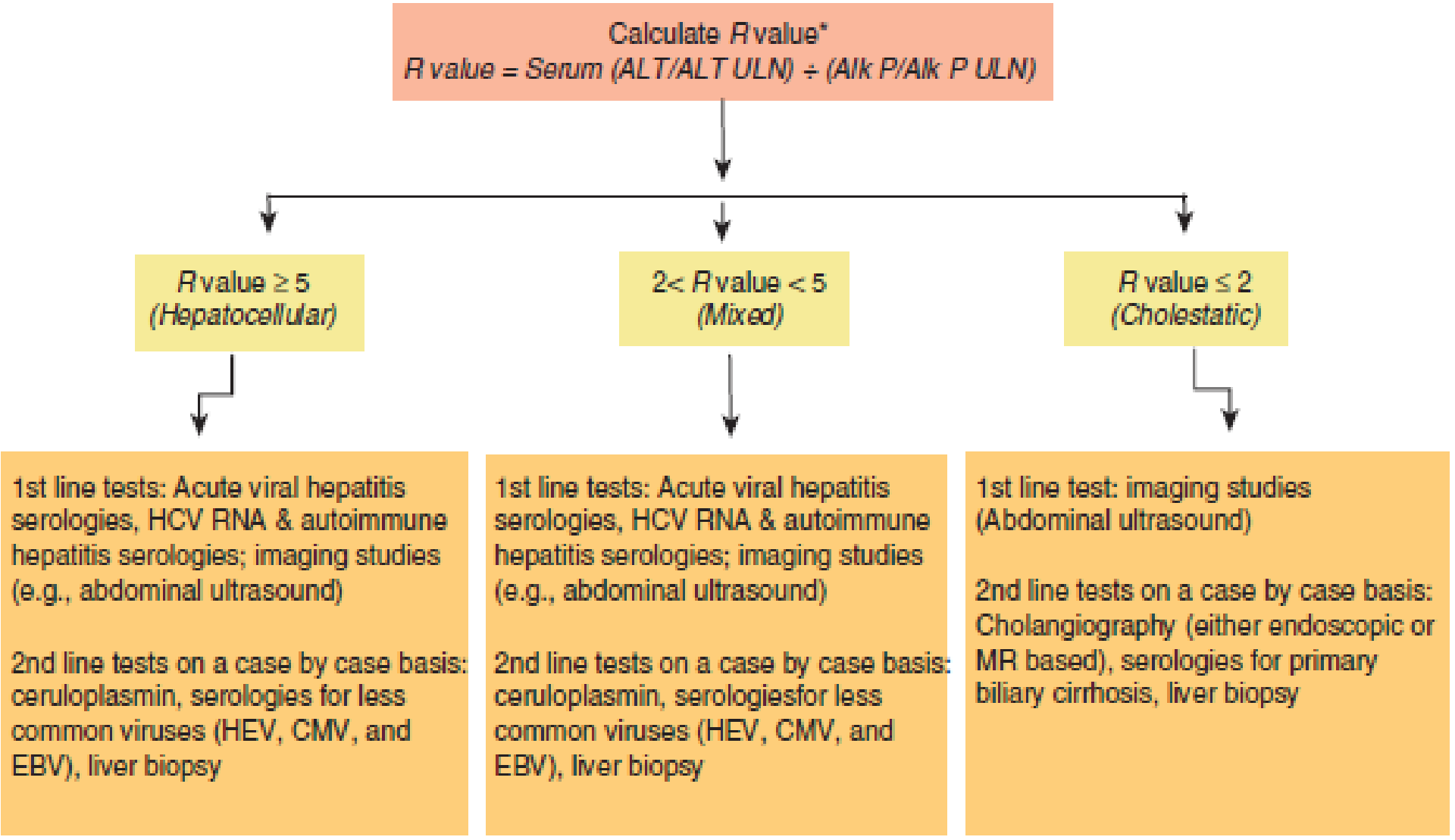
DIAGNOSIS OF DILI

- No specific or diagnostic clinical presentation, laboratory test, or histologic pattern to aid in the diagnosis of DILI.
- High index of suspicion.
- It is a diagnosis of exclusion.

First step

- Detailed history regarding the onset of symptoms, time latency ,drug dose, route of administration, duration, previous administration, and any concomitant liver diseases.
- Also ask the patient about use of herbal products, dietary supplements, over-the-counter medications and alcohol.
- History taking is greatly enhanced by knowledge of the most common and most rarely implicated DILI agents.

Second step


Calculate R value*
R value = Serum (ALT/ALT ULN) ÷ (Alk P/Alk P ULN)
R value ≥ 5
(Hepatocellular)
2< R value < 5
(Mixed)
R value ≤ 2
(Cholestatic)
1st line tests: Acute viral hepatitis serologies, HCV RNA & autoimmune hepatitis serologies; imaging studies (e.g., abdominal ultrasound)
2nd line tests on a case by case basis: ceruloplasmin, serologies for less common viruses (HEV, CMV, and EBV), liver biopsy
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1st line test: imaging studies (Abdominal ultrasound)
2nd line tests on a case by case basis: Cholangiography (either endoscopic or MR based), serologies for primary biliary cirrhosis, liver biopsy

Third step

Hepatocellular injury – RUCAM score

RUCAM Assessment	Time	Score
Time to onset of ALT>2xULN after drug start	5-90 days ≤15d after stopping	+2 +1
≥50% decrease in ALT after stopping drug	< 8 days < 30 days	+3 +2
Negative hepatitis screens and ultrasound		+2
Hepatotoxicity in product characteristics/label		+2
No concomitant medications Concomitant medications		0 -1 to -3
Positive rechallenge		+3
Alcohol or pregnancy		+1
Age > 55		+1

Scoring:
Highly probable >8
Probable 6-8
Possible 3-5
Unlikely 1-2
Excluded ≤0

Toxicologic Pathology 2005; 33: 155-164

Forth step

- ***http://www.livertox.nih.gov/***

  Free and helpful online DILI resource consisting of detailed information on more than 600 agents, and it is updated periodically.
- ***http://dilin.dcri.duke.edu/***

Fifth step

Liver biopsy is strongly recommended:-

- If autoimmune hepatitis remains a competing etiology and if immunosuppressive therapy is needed.
- If there is unrelenting rise in liver biochemistries or signs of worsening liver function despite stopping the suspected offending agent.
- In cases of DILI where continued use or re-exposure to the implicated agent is expected.

Liver biopsy may be recommended:-

- If the peak ALT level has not decreased by > 50 % at 30 – 60 days after the onset in cases of hepatocellular DILI, or if the peak ALP has not fallen by > 50 % at 180 days in cases of cholestatic DILI despite stopping the suspected offending agent.
- If liver biochemistry abnormalities persist beyond 180 days to evaluate for the presence of chronic liver diseases (CLDs) and chronic DILI.

- Histologic risk stratification is generally based on assessment of the degree of necrosis and fibrosis.
- The US DILIN recognizes 18 distinct histologic patterns.
- Histologic patterns of DILI do not perfectly correlate with the biochemical pattern of injury.
- Liver biopsy can provide prognostic information that can assist in patient management.
- The presence of hepatic eosinophils and lesser degree of necrosis have been associated with a greater likelihood of recovery.

Treatment

- The first step is to discontinue the suspected drug.
- No specific treatment. (There is exceptions)

  N -acetylcysteine in the early phases of acetaminophen toxicity.

  L-carnitine is potentially valuable in cases of valproate toxicity.
- Symptomatic treatment e.g In drug-induced cholestasis Cholestyramine may be used for pruritus. Ursodeoxycholic acid may be used.

- Glucocorticoids are of unproven benefit for most forms of drug hepatotoxicity.

They may have a role for treating patients with:-

- Hypersensitivity reactions who have progressive cholestasis despite drug withdrawal.
- Biopsy features resembling autoimmune hepatitis.
- Extrahepatic manifestations of a hypersensitivity reaction e.g. severe pulmonary involvement in patients with DRESS.

- Re-exposure of the drug is strongly discouraged especially if the initial liver injury was associated with significant aminotransferase elevation (for example, > 5xULN, Hy's law, or jaundice).

An exception to this recommendation is in cases of life-threatening situations where there is no suitable alternative.

The future

- More studies into pharmacogenomics and personalized medicine may aid in predicting which patients will go on to develop chronic drug-induced liver injury.
- New biomarkers for DILI using proteomics and micro RNA appear promising but require further study.

THANK YOU