ACG INSTITUTE RESEARCH GRANTS AND AWARDS 2022

EIGHT different award types; INCREASED Junior Faculty FUNDING;
NEW Health Equity Research Award; Med Resident and Student Awards

www.gi.org/research-awards

Grant System Opens: September 7, 2021

Deadline: December 3, 2021

Read the Grant Flyer, FAQs, or visit the webpage for the full RFAs.

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ACG INSTITUTE RESEARCH GRANTS AND AWARDS 2022

ACG INSTITUTE FOR CLINICAL RESEARCH AND EDUCATION

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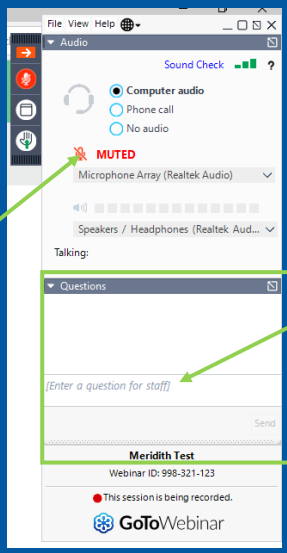
Participating in the Webinar



All attendees will be muted and will remain in Listen Only Mode.

Type your questions here so that the moderator can see them. Not all questions will be answered but we will get to as many as possible.

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How to Receive CME and MOC Points

LIVE VIRTUAL GRAND ROUNDS WEBINAR

ACG will send a link to a CME & MOC evaluation to all attendees on the live webinar.

ABIM Board Certified physicians need to complete their MOC activities by December 31, 2021 in order for the MOC points to count toward any MOC requirements that are due by the end of the year. No MOC credit may be awarded after March 1, 2022 for this activity.

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MOC QUESTION

If you plan to claim MOC Points for this activity, you will be asked to: Please list specific changes you will make in your practice as a result of the information you received from this activity.

Include specific strategies or changes that you plan to implement.
THESE ANSWERS WILL BE REVIEWED.

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ACG Virtual Grand Rounds

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Week 40, 2021
ACG Clinical Guideline: Management of Upper GI Bleeding and Bleeding Ulcers
Loren A. Laine, MD, FACG
October 14, 2021 at Noon Eastern

Week 41, 2021
Identifying and Eliminating Racism in Science and Healthcare: Historical Perspective and Current Opportunities
Darrell M. Gray, II, MD, MPH, FACG
November 4, 2021 at Noon Eastern

Visit **gi.org/ACGVGR** to Register

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Disclosures:

Speaker:
Haripriya Maddur, MD
Dr. Maddur, faculty for this educational event, has no relevant financial relationship(s) with ineligible companies to disclose.

Moderator:
Naga P. Chalasani, MD, FACG
Consultant: AbbVie, Altimmune, Foresite Labs, Galectin, Genentech, Madrigal, ObsEva, Siemens, Zydus; Grant Support: DSM, Exact Sciences, Intercept.

*All of the relevant financial relationships listed for these individuals have been mitigated

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ACG CLINICAL GUIDELINE: DIAGNOSIS AND MANAGEMENT OF IDIOSYNCRATIC DRUG-INDUCED LIVER INJURY

HARIPRIYA MADDUR, MD

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878 CLINICAL GUIDELINES

CME

ACG Clinical Guideline: Diagnosis and Management of Idiosyncratic Drug-Induced Liver Injury

Naga P. Chalasani, MD, FACG[1], Haripriya Maddur, MD[2], Mark W. Russo, MD, MPH, FACG[3], Robert J. Wong, MD, MS, FACG (GRADE Methodologist)[4] and K. Rajender Reddy, MD, FACG[5], on behalf of the Practice Parameters Committee of the American College of Gastroenterology

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BACKGROUND

- Drug induced liver injury (DILI) culprit for 3-10% of cases of acute liver injury
- Common cause for a medication to be abandoned during drug development
- Herbal and dietary supplements often culprit
- May result in ALF

Slide courtesy of Naga Chalasani MD

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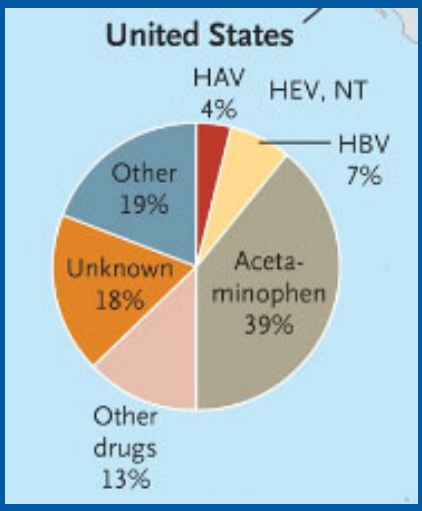
ACUTE LIVER FAILURE FROM DILI

11% of adult ALF pts had DILI

- **47% due to antibiotics, esp. TB drugs**
- **Transplant-free survival: 27%**
- **Transplant: 42%**
- **Overall survival: 66%**



Bernal NEJM 2014, Reuben Hepatology 2010, Squires J Peds 2006
Slide courtesy of Naga Chalasani MD

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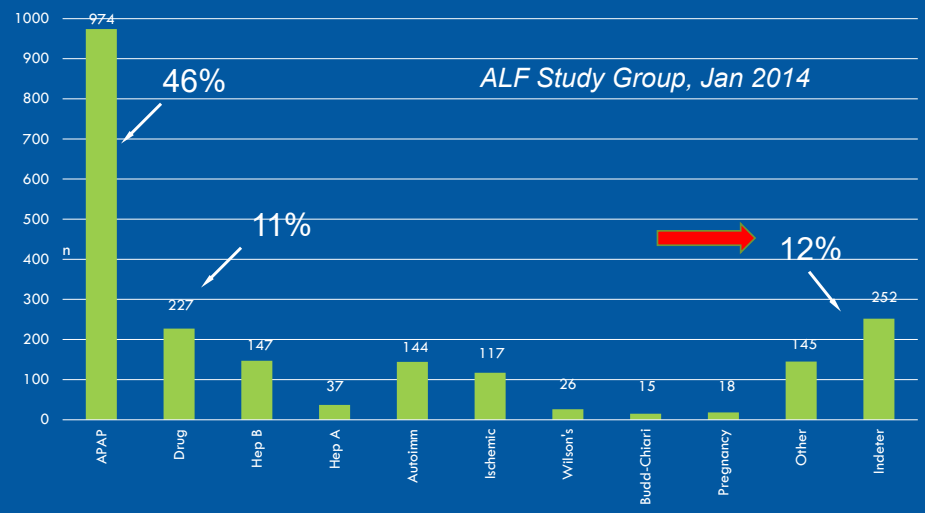
Etiology of Acute Liver Failure in the US

Adult Registry (n = 2,102)



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TOP 10 THERAPEUTIC CLASSES AND INDIVIDUAL AGENTS TO CAUSE DILI IN THE USA (N=899)

	Therapeutic Class	n
1	Antimicrobials	408
2	Herbal and dietary	145
3	CVS agent	88
4	CNS agents	82
5	Anti-neoplastics	49
6	Analgesics	33
7	Immunomodulatory	27
8	Endocrine	20
9	Rheumatologic	13
10	Gastrointestinal	12

	Individual agent	n
1	Amox-Clavulanate	91
2	INH	48
3	Nitrofurantoin	42
4	TMP/SMX (Bactrim)	31
5	Minocycline	28
6	Cefazolin	20
7	Azithromycin	18
8	Ciprofloxacin	16
9	Levofloxacin	13
10	Diclofenac	12

Slide courtesy of Naga Chalasani MD

Chalasani N, et al for the US DILIN. Gastroenterology 2015

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Table 6. Most common or well-described drug-induced liver injury agents and the patterns of their liver injury

	Latency[a]	Typical pattern of injury/identifying features
Antibiotics		
Amoxicillin/clavulanate	Short to moderate	Cholestatic injury, but can be hepatocellular; drug-induced liver injury onset is frequently detected after drug cessation
Isoniazid	Moderate to long	Acute hepatocellular injury similar to acute viral hepatitis
Trimethoprim/sulfamethoxazole	Short to moderate	Cholestatic injury, but can be hepatocellular; often with immunoallergic features (e.g., fever, rash, and eosinophilia)
Fluoroquinolones	Short	Variable—hepatocellular, cholestatic, or mixed in relatively similar proportions
Macrolides	Short	Hepatocellular, but can be cholestatic
Nitrofurantoin		Hepatocellular
Acute form (rare)	Short	Typically hepatocellular; often resembles idiopathic autoimmune hepatitis
Chronic form	Moderate to long (months–years)	Hepatocellular
Minocycline	Moderate to long	Hepatocellular and often resembles autoimmune hepatitis
Antiepileptics		
Phenytoin	Short to moderate	Hepatocellular, mixed, or cholestatic often with immune-allergic features (e.g., fever, rash, and eosinophilia) (anticonvulsant hypersensitivity syndrome)
Carbamazepine	Moderate	Hepatocellular, mixed, or cholestatic often with immune-allergic features (anticonvulsant hypersensitivity syndrome)
Lamotrigine	Moderate	Hepatocellular often with immune-allergic features (anticonvulsant hypersensitivity syndrome)
Valproate		
Hyperammonemia	Moderate to long	Elevated blood ammonia and encephalopathy
Hepatocellular	Moderate to long	Hepatocellular

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Analgesics		
Nonsteroidal anti-inflammatory agents	Moderate to long	Hepatocellular injury
Diclofenac		Hepatocellular injury with autoimmune features
Immune modulators		
Interferon-beta	Moderate to long	Hepatocellular
Interferon-alpha	Moderate	Hepatocellular, autoimmune hepatitis–like
Anti-TNF agents	Moderate to long	Hepatocellular. Can have autoimmune hepatitis features
Azathioprine	Moderate to long	Cholestatic or hepatocellular, but can present with portal hypertension (veno-occlusive disease and nodular regenerative hyperplasia)
Immune-checkpoint inhibitors		
Ipilimumab (CTLA-4 inhibitor) Nivolumab, pembrolizumab, and cemiplimab (PD-1 inhibitors) Atezolizumab, avelumab, and durvalumab (PDL-1 inhibitors)	Under 12 wk	Initially mixed pattern, but evolves primarily into hepatocellular pattern, without significant autoantibodies
Miscellaneous		
Methotrexate (oral)	Long	Fatty liver, fibrosis
Allopurinol	Short to moderate	Hepatocellular or mixed. Often with immune-allergic features. Granulomas often present on biopsy
Amiodarone (oral)	Moderate to long	Hepatocellular, mixed, or cholestatic. Macrovesicular steatosis and steatohepatitis on biopsy
Androgen-containing steroids	Moderate to long	Cholestatic. Can present with peliosis hepatis, nodular regenerative hyperplasia, or hepatocellular carcinoma
Inhaled anesthetics	Short	Hepatocellular. May have immune-allergic features +/− fever
Sulfasalazine	Short to moderate	Mixed, hepatocellular, or cholestatic. Often with immunoallergic features
Proton pump inhibitors	Short	Hepatocellular; very rare

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HERBAL AND DIETARY SUPPLEMENTS

- **Increasingly used in the US**
- **Increasing implicated as causing liver injury**
- **Body building supplements and weight loss supplements**
- **Body building agents – Cholestatic patterns**
- **Weight loss supplements - hepatocellular injury**

Slide courtesy of Naga Chalasani MD

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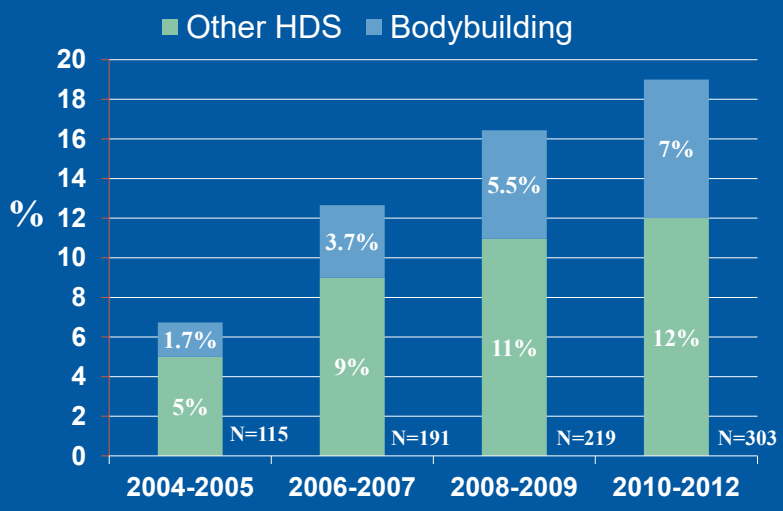
TEMPORAL TRENDS IN HDS HEPATOTOXICITY



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HDS DILI OUTCOMES

	Body building agents (n=45)	Non-body building agents (n=85)	DILI due to conventional agents (n=709)	P-value
Hospitalization (%)	71	68	58	0.07
OLT	0	13	3	<0.001
Death	0	4	7	
Severe/fatal DILIN severity score	13	35	26	0.02

Navarro V, for the US DILIN. Hepatology 2014

Slide courtesy of Naga Chalasani MD

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CLINICAL CHEMISTRY CRITERIA FOR DILI

- **Any one of the following**
  - ≥ 5 ULN of ALT
  - ≥ 2 ULN of Alk P (of liver origin)
  - ≥ 3 ULN of ALT + ≥ 2 ULN of Total bilirubin
- **In the absence of a competing etiology**

Aithal GP, et al. Clin Pharmacol Therapeutics 2011

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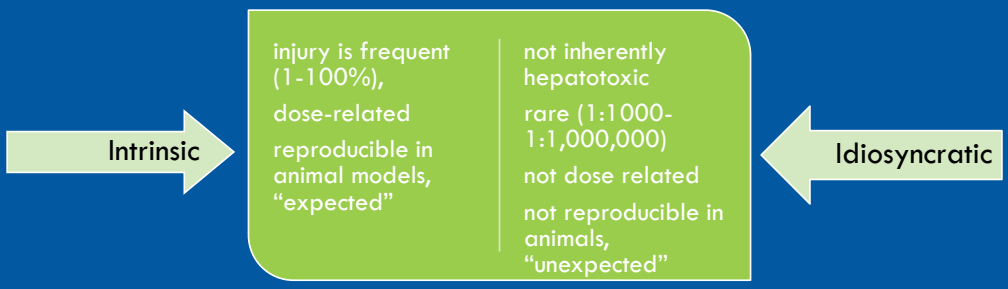
DRUG INDUCED LIVER INJURY



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INTRINSIC HEPATOTOXICITY

- Expected outcome, dose related
  - Acetaminophen
  - Aspirin
  - Niacin
  - Many antineoplastic agents
- Serum enzyme elevations
- Acute hepatic necrosis
- Sinusoidal obstruction syndrome
- Lactic acidosis, steatosis and hepatic dysfunction
- Nodular regenerative hyperplasia

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IDIOSYNCRATIC HEPATOXICITY

- Unexpected outcome, rare, and generally not-dose related
  - Isoniazid
  - Troglitazone
  - Amoxicillin/Clavulanic acid
  - Minocycline
  - Diclofenac
- Idiosyncrasy: immunologic or metabolic
- Phenotypes, acute hepatitis, cholestatic hepatitis, bland cholestasis, nonalcoholic fatty liver
- Etiology, generally unknown
- Challenge to clinical and basic research

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INDIRECT HEPATOXICITY

- A third form of hepatotoxicity
- The medication induces a liver disease or alters a predicting condition.
  - Reactivation of hepatitis B
  - Worsening or flare of hepatitis C
  - Triggering of autoimmune liver disease
  - Exacerbation of NASH or ASH (weight gain)
- Phenotypes: acute hepatitis, acute liver failure, chronic hepatitis, cirrhosis, fatty liver
- Often can be predicted and prevented or avoided

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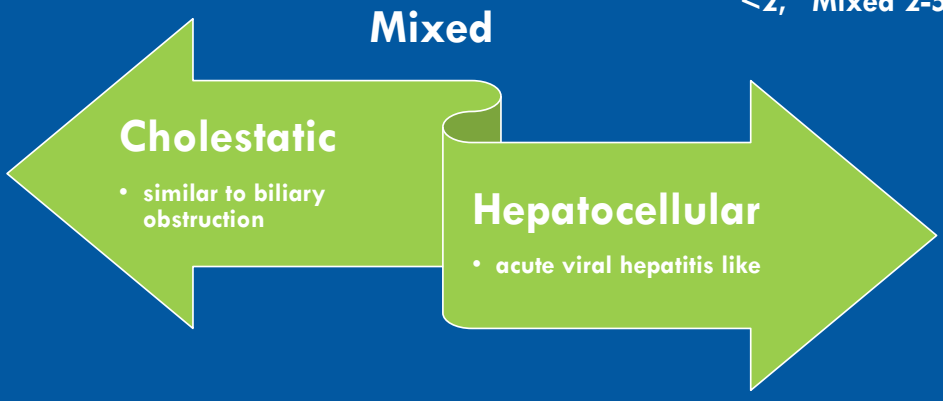
PATTERNS OF INJURY

R ratio: ALT/Alk P [expressed as x ULN]

HC >5, Cholestatic
<2, Mixed 2-5



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CAUSALITY IN DRUG INDUCED LIVER INJURY

- **DILI is a diagnosis of exclusion**
- Compatible history; no specific tests to prove causality
- Negative tests for hepatitis A, B, C and E
- Absence of heavy alcohol use, shock, autoimmunity
- Imaging studies of liver and biliary tree
- Special attention to exacerbation of underlying liver disease such as fatty liver, Hep C, Hep B, or Primary Sclerosing Cholangitis

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FROM THE GUIDELINES..

Table 1. Summary and strength of recommendations
1. In individuals with suspected hepatocellular or mixed DILI:
(a) Acute viral hepatitis (A, B, and C) and autoimmune hepatitis should be excluded with standard serologies and HCV RNA testing (strong recommendation, very low quality of evidence).
(b) Anti-HEV IgM testing may be considered in selected patients where there is heightened clinical suspicion (e.g. recent travel in an endemic area, DILI phenotype is atypical, or there is no readily identifiable culprit agent). However, it should be noted that the performance of the currently available commercial tests is not clear (conditional recommendation, very low quality of evidence).
(c) We recommend testing for acute CMV, acute EBV, or acute HSV infection be undertaken if classical viral hepatitis has been excluded or clinical features such as atypical lymphocytosis and lymphadenopathy suggest such causes (strong recommendation, very low quality of evidence).
(d) We recommend evaluation for Wilson disease and Budd-Chiari syndrome when clinically appropriate (strong recommendation, very low quality of evidence).
2. In individuals with suspected cholestatic DILI:
(a) We recommend abdominal imaging (ultrasound, computed tomography scan, and MRI) should be performed in all instances to exclude biliary tract pathology and infiltrative processes (strong recommendation, low quality of evidence).
(b) We recommend limiting serological testing for primary biliary cholangitis to those with no evidence of obvious biliary tract pathology on abdominal imaging (strong recommendation, low quality of evidence).
(c) We suggest limiting endoscopic retrograde cholangiography to instances where routine imaging including MRI or endoscopic ultrasound is unable to exclude impacted common bile duct stones, primary sclerosing cholangitis, or pancreaticobiliary malignancy (conditional recommendation, very low quality of evidence).

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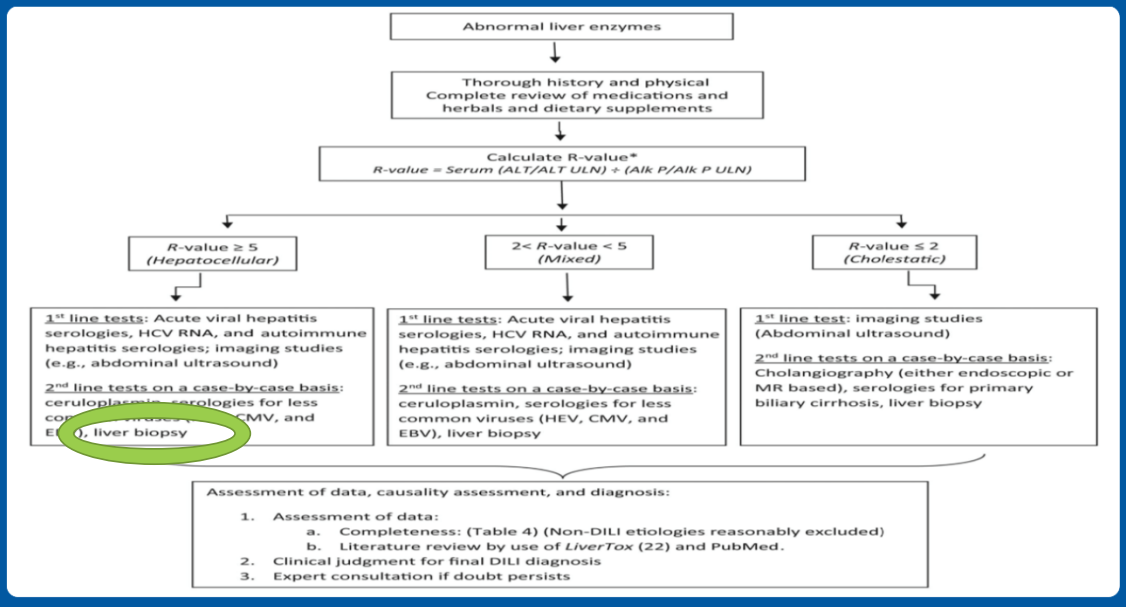

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THE ROLE OF LIVER BIOPSY?

3. When to consider a liver biopsy?
(a) We recommend performing a liver biopsy if autoimmune hepatitis remains a competing etiology and if immunosuppressive therapy is contemplated (strong recommendation, low quality of evidence).
(b) We suggest performing a liver biopsy if there is unrelenting rise in liver biochemistries or signs of worsening liver function despite stopping the suspected offending agent (conditional recommendation, very low quality of evidence).
(c) We suggest performing a liver biopsy if peak ALT level has not fallen by >50% at 30–60 d after onset in cases of hepatocellular DILI or if peak Alk P has not fallen by >50% at 180 d in cases of cholestatic DILI despite stopping the suspected offending agent (conditional recommendation, very low quality of evidence).
(d) We suggest performing a liver biopsy in cases of DILI where continued use or re-exposure to the implicated agent is contemplated (conditional recommendation, very low quality of evidence).
(e) We suggest considering a liver biopsy if liver biochemistry abnormalities persist beyond 180 d, especially if associated with symptoms (e.g., itching) or signs (e.g., jaundice and hepatomegaly), to evaluate for the presence of chronic liver diseases and chronic DILI (conditional recommendation, very low quality of evidence).

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ARE THERE SPECIFIC RISK FACTORS?

Table 4. Variables that may predispose individuals to idiosyncratic drug-induced liver injury

Host factors	Environmental factors	Drug-related factors
Age	Smoking	Daily dose
Sex	Alcohol consumption	Metabolic profile (lipophilicity and reactive metabolites)
Pregnancy	Infection and inflammatory episodes	Class effect and cross-sensitization
Malnutrition		Drug interactions and polypharmacy
Obesity		
Diabetes mellitus		
Comorbidities including underlying liver disease		

s for therapy

Key concepts

1. Although a number of host, environmental, and compound-specific risk factors have been described in the literature, there is no evidence to suggest that these variables represent major risk factors for all-cause DILI.
2. Certain variables such as age, sex, and alcohol consumption may increase risk of DILI in a drug-specific fashion.

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PROGNOSTICATION AND RECHALLENGE

4. We suggest using a prognostic model consisting of MELD, Charlson comorbidity index, and serum albumin in clinical practice for predicting 6-month mortality in individuals presenting with suspected DILI. A web-based DILI mortality calculator is available at http://gihep.com/calculators/hepatology/dili-cam/ (conditional recommendation, low quality of evidence).

5. We strongly recommend against re-exposure to a drug thought likely to have caused hepatotoxicity, especially if the initial liver injury was associated with significant aminotransferase elevation (e.g., >5xULN, Hy's law, or jaundice). An exception to this recommendation is in cases of life-threatening situations where there is no suitable alternative (strong recommendation, low quality of evidence).

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TREATMENT??

6. We recommend promptly stopping suspected agent(s) in individuals with suspected DILI, especially when liver biochemistries are rising rapidly or there is evidence of liver dysfunction (strong recommendation, low quality of evidence).
7. Although no definitive therapies are available either for idiosyncratic DILI with or without ALF, we suggest consideration of NAC treatment in adults with early stage ALF, given its good safety profile and some evidence for efficacy in early coma stage patients (conditional recommendation, low quality of evidence).
8. We suggest against using NAC for children with severe DILI leading to ALF (conditional recommendation, low quality of evidence).
9. There are no well-conducted studies to either recommend or refute corticosteroid therapy in patients with DILI. However, they may be considered in a subset of patients with DILI exhibiting AIH-like features (conditional recommendation, low quality of evidence).

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AUTOIMMUNE LIKE DILI

- Clinical syndrome with high resemblance to autoimmune hepatitis
- Nitrofurantoin and minocycline are prototypes but many others can also do this (TNFα antagonists, statins, α-methyl dopa)
- Long latency and presence of autoantibodies
- Identification is critically important
- Steroid therapy

Slide Courtesy of Naga Chalasani MD

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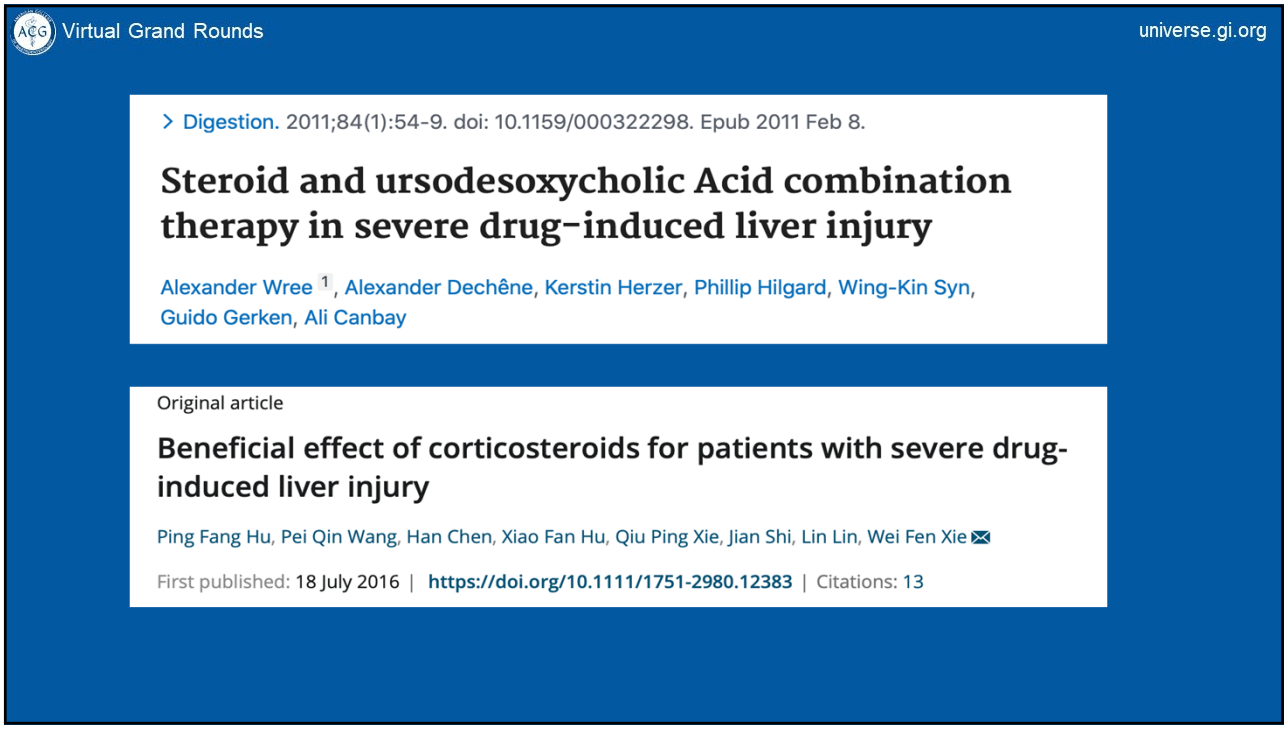
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Digestion. 2011;84(1):54-9. doi: 10.1159/000322298. Epub 2011 Feb 8.
Steroid and ursodesoxycholic Acid combination therapy in severe drug-induced liver injury
Alexander Wree [1], Alexander Dechêne, Kerstin Herzer, Phillip Hilgard, Wing-Kin Syn, Guido Gerken, Ali Canbay
Original article
Beneficial effect of corticosteroids for patients with severe drug-induced liver injury
Ping Fang Hu, Pei Qin Wang, Han Chen, Xiao Fan Hu, Qiu Ping Xie, Jian Shi, Lin Lin, Wei Fen Xie
First published: 18 July 2016 | https://doi.org/10.1111/1751-2980.12383 | Citations: 13

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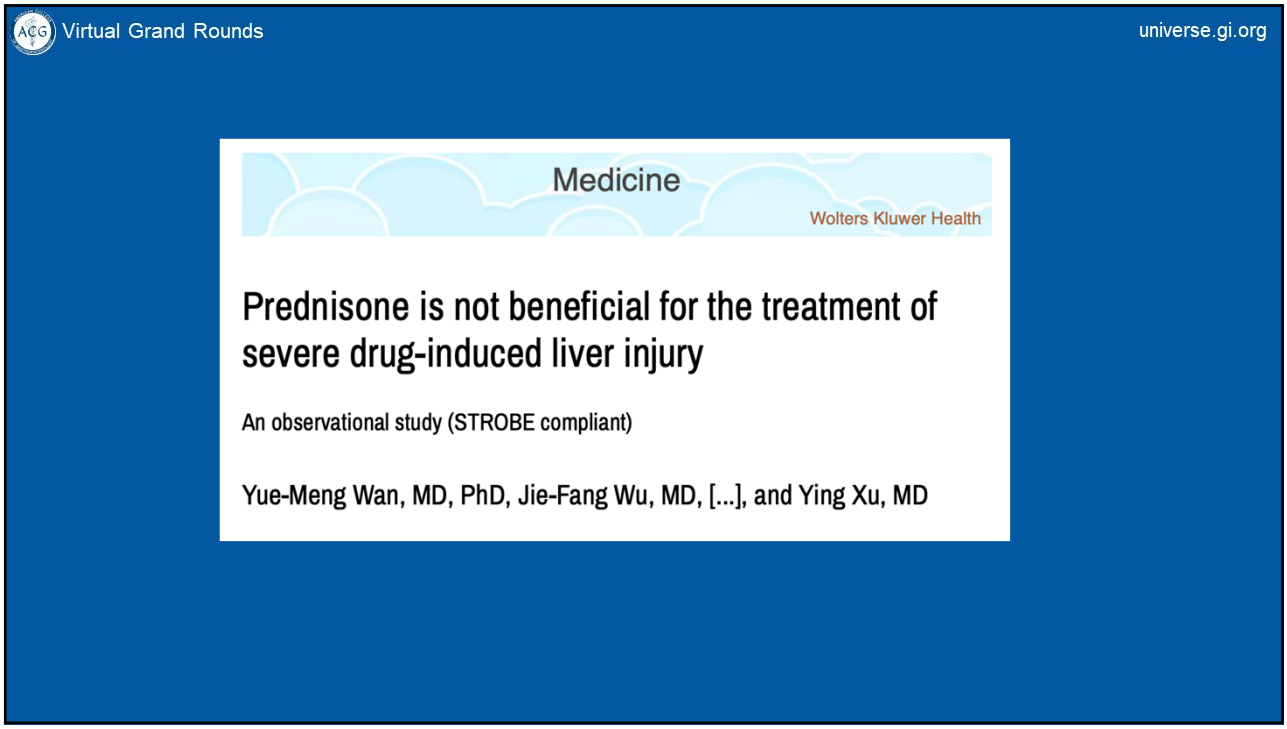
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Medicine
Wolters Kluwer Health
Prednisone is not beneficial for the treatment of severe drug-induced liver injury
An observational study (STROBE compliant)
Yue-Meng Wan, MD, PhD, Jie-Fang Wu, MD, [...], and Ying Xu, MD

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IMMUNOTHERAPY INDUCED DILI

HEPATOLOGY
AASLD
REVIEWS | HEPATOLOGY, VOL. 72, NO. 1, 2020

Hepatotoxicity From Immune Checkpoint Inhibitors: A Systematic Review and Management Recommendation

Thoetchai (Bee) Peeraphatdit [1], Jennifer Wang [1], Matthew A. Odenwald [1], Shaomin Hu [2], John Hart, [2] and Michael R. Charlton [1]

Rule out Hepatitis B reactivation

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Target	Agent
CTLA-4	Ipilimumab
PD-1	Pembrolizumab
PD-1	Nivolumab
PD-1	Cemiplimab
PD-L1	Atezolizumab
PD-L1	Avelumab
PD-L1	Durvalumab

TABLE 2. Severity Grading of ICI-Induced Hepatotoxicity According to the National Cancer Institute's CTCAE, Version 4.03

Grade	1 Mild	2 Moderate	3 Severe	4 Life-Threatening
AST (xULN)	>1-3×	>3-5×	>5-20×	>20×
ALT (xULN)	>1-3×	>3-5×	>5-20×	>20×
ALP (xULN)	>1-2.5×	>2.5-5×	>5-20×	>20×
GGT (xULN)	>1-2.5×	>2.5-5×	>5-20×	>20×
Total- bilirubin (xULN)	>1-1.5×	>1.5-3×	>3-10×	>10x

Peerphatdit, et al, Hepatotoxicity from Checkpoint Inhibitors, *Hepatology*,72, Nov, 2020

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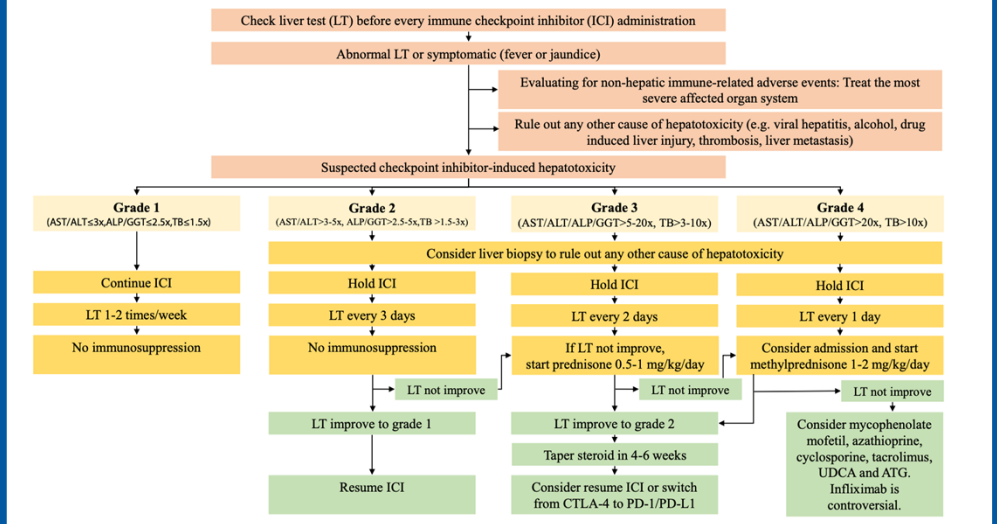

FIG. 4. Proposed management algorithm for checkpoint inhibitor–induced hepatotoxicity. Abbreviations: ALP, alkaline phosphatase; ICI, immune checkpoint inhibitors; GGT, gamma-glutamyltransferase; LT, liver test; TB, total bilirubin.

Peerphatdit, et al, Hepatotoxicity from Checkpoint Inhibitors, *Hepatology*,72, Nov, 2020

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SPECIAL POPULATIONS

1. There are no definitive data to show that underlying CLD is a major risk factor for all-cause DILI, but it may increase the risk of DILI due to selected medications. Patients with chronic HBV and HCV may be more prone to develop liver injury due to specific agents such as isoniazid and antiretrovirals and may experience more severe outcomes.
2. Individuals with underlying fatty liver disease are not at increased risk of hepatotoxicity from statins. Indications for statins should be reevaluated in patients with decompensated cirrhosis because their risk to cause rhabdomyolysis may be heightened in such patients.
3. Patients with decompensated cirrhosis who have chronic hepatitis C should avoid protease inhibitors. Obeticholic acid has been associated with hepatic decompensation in patients with PBC and Child-Pugh class B and C cirrhosis who received a higher than recommended dose.

14. As the diagnosis of DILI in patients with CLD requires a high index of suspicion, we recommend exclusion of other more common causes of acute liver injury including a flare-up of the underlying liver disease (strong recommendation, low quality of evidence).
15. The decision to use potentially hepatotoxic drugs in CLD patients should be based on the risk vs benefit of the proposed therapy on a case-by-case basis (conditional recommendation, low quality of evidence).
16. There are no data to recommend a specific liver biochemistry monitoring plan when a potential hepatotoxic agent is prescribed in individuals with known CLD. Often, information contained in the package inserts is incomplete or unhelpful. Patients should be advised to promptly report any new onset symptoms such as scleral icterus, abdominal pain/discomfort, nausea/vomiting, itching, or dark urine. In addition, it is reasonable to monitor serum liver biochemistries at 4–6 weekly intervals, especially during the initial 6 months of treatment with a potentially hepatotoxic agent (conditional recommendation, very low quality of evidence).

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SPECIAL POPULATIONS (CHILDREN)

1. Children may rarely develop DILI. Antimicrobial agents such as minocycline administered for facial acne and antiepileptic agents are the most common culprits for DILI in children in the United States.
2. Pediatric DILI may be associated with significant morbidity and mortality including requiring liver transplantation and death.
3. Minocycline DILI may have long latency (e.g., >1 year) and can present with features resembling AIH. Adolescents with presenting autoimmune such as liver disease should be carefully questioned about their minocycline use for facial acne.

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SUMMARY

- Drug induced liver injury is a diagnosis of exclusion
- Prompt recognition needed as drug cessation is mainstay of therapy
- Antimicrobial agents often culprit in addition to antimicrobial therapy
- No definitive role for steroid therapy
- Rechallenge should be avoided unless no viable alternatives
- Immunotherapy induced DILI more likely with multiple agents; management depended on severity

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Special Thanks to Naga Chalasani MD

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Questions?

Speaker:
Haripriya Maddur, MD

Moderator:
Naga P. Chalasani, MD, FACG

*All of the relevant financial relationships listed for these individuals have been mitigated

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