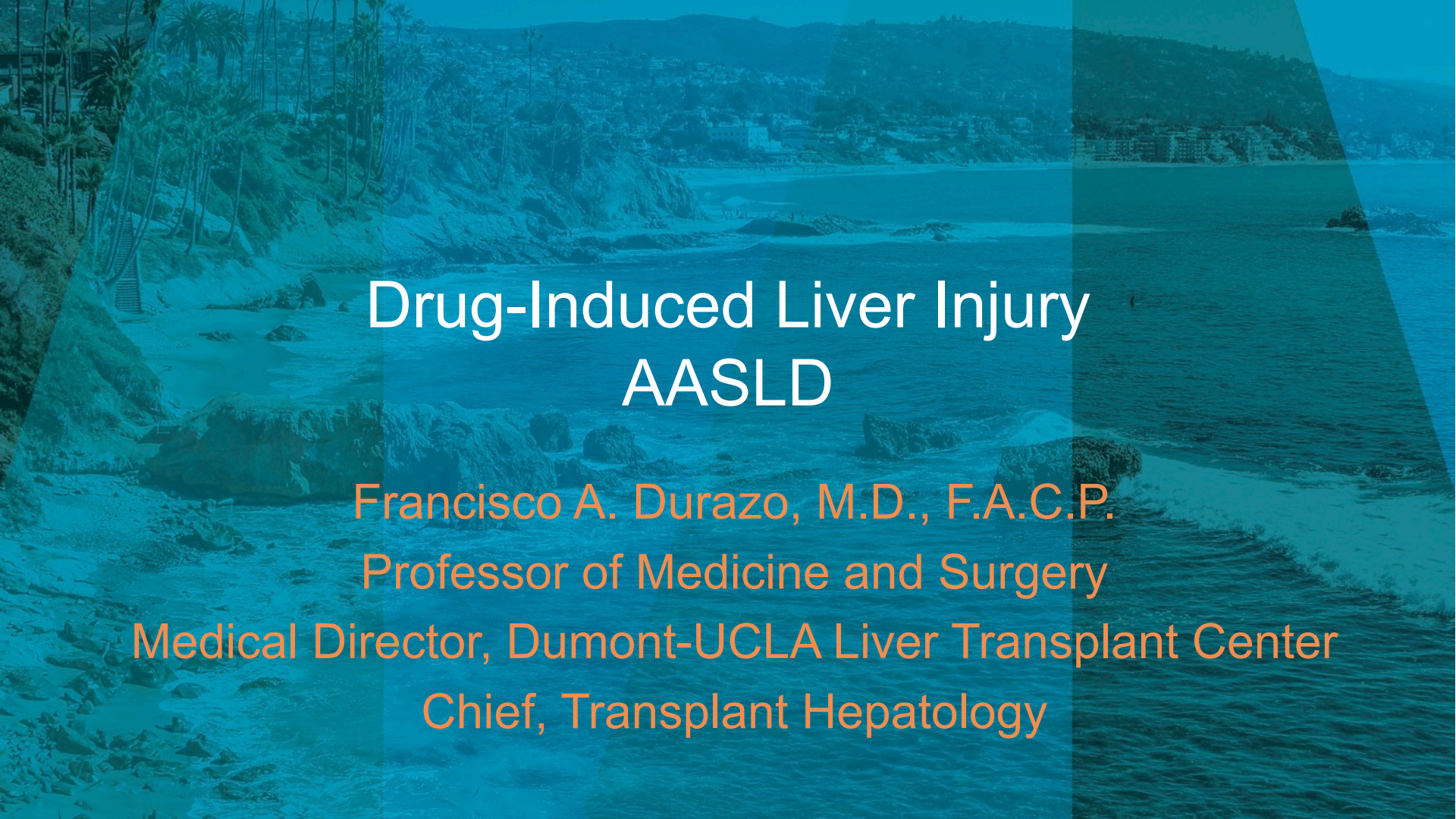

Drug-Induced Liver Injury
AASLD

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DILI/HILI

- Causes 0.1 to 3% of hospital admissions[1]
- 600 liver transplantations / year in US[1]
- Most common cause of acute liver failure in US, with acetaminophen the top contributor[2]
- Caused by many commonly prescribed drugs[4] & over the counter medications, herbs, supplements, illicit drugs
- Hepatotoxicity → Single most common adverse drug reaction leading to drug withdrawal or refusal of approval by FDA

[1]Dig Dis Sci 2007;52:2463-71.
[2]Ostapowicz GM. et al. Ann Intern Med 2002;137:947–954.
[3]Kaplowitz N. Nat Rev Drug Discov 2005;4:489–499.
[4]Suzuki A et al. Drug Safety 2010; 33: 503-522

Intrinsic vs. Idiosyncratic DILI

Intrinsic

Direct Toxicity

- predictable
- dose-related
- similar in *animals*
- high incidence
- short latency (hrs)
- mortality high

Idiosyncratic

- unpredictable
- not dose-related
- not seen in animals
- low incidence, rare
- variable latency
- mortality variable

Diagnosis of DILI/HILI

- Diagnosis of exclusion

- History and Physical → Symptoms, medication exposure, supplement use, OTC meds, onset and course of liver test abnormalities

- NIDDK and National Library of Medicine → LIVERTOX http://www.livertox.nih.gov

Causality Assessment

- CIOMS/RUCAM
- Naranjo/ADR
- French Pharmacovigilance Method
- Maria & Victorino
- Japanese RUCAM
- Expert opinion

Testing for Hepatitis C Virus RNA is Recommended in Patients with Suspected Drug Induced Liver Injury #491

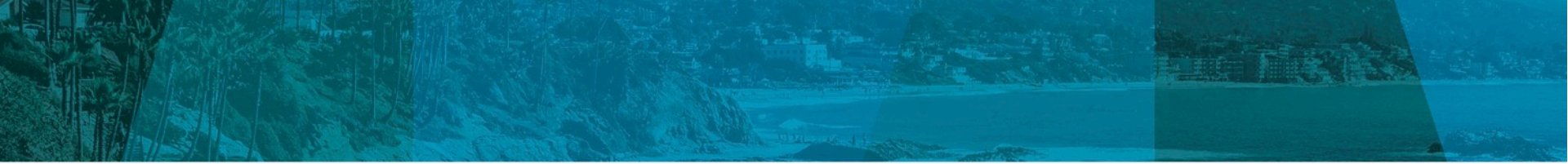
Ahmad J, Reddy R, Tillman H, Chalasani N, Hayashi P, Fontana R, Navarro V, Stolz A, Barnhart H, Cloherty G, Hoofnagle J DILIN

Aim: Review the diagnosis, testing and presentation of acute HCV in patients initially thought to have DILI enrolled in the DILIN prospective study

Methods: From 9/4 to 10/16 1734 pts. enrolled. 1518 completed 6 months follow up and causality adjudication

Causality adjudication: Expert opinion using 5-point scale: 1-definite, 2-highly likely, 3-probable, 4-possible, 5-unlikely

104 had HCV infection 10 HCV RNA alone,
16 anti-HCV alone,
78 both



Results: Acute HCV (23), chronic HCV (56), resolved HCV (13), false positive (2) or inconclusive (10)

Acute HCV cases: 9 ♀ and 14 ♂, age 20-83

Median ALT 1448 U/L (range 458-3501) , Alk phos 232 IU/L (range 92-551)
bilirubin 10.8 (range 1.1-23)

Adjudication 6 months later:

- 19 were judged as HCV not DILI (10 unlikely 9 possible)
- 4 DILI (1 highly likely, 3 probable)
- 7 pts were HCV RNA negative at presentation and later became HVC RNA positive
- 18 hospitalized, 1 patient died (unrelated to HCV)
- 11 pts with a 6 month follow up: 6 cleared HCV, 5 had persistence of HCV
  (2 achieved SVR after treatment)

Conclusion: 23/1518 (1.5%) cases of suspected DILI were actually due to HCV infection. Patients were misdiagnosed due to lack of HCV RNA testing.
Exclusion of acute HCV requires HCV RNA in patients with suspected DILI.

Immunosuppressive Therapy Using Prednisone and Azathioprine Promoted Disease Remission in Patients with Drug-Induced Liver Injury, Whose Liver Biopsy Showing Bridging or Multi-acinus necrosis #790

Wang Y, Wang Q, Tian Q, Ou X,Zhao X, Wang T

Background: Preliminary data showed that DILI patients with bridging or multi-acinus necrosis on biopsy progressed into cirrhosis rapidly

Aim: Efficacy of prednisone (PRD) and azathioprine (AZA) combination therapy in treating these patients

Methods: - Retrospective screen of DILI pts. Who had a liver biopsy

- 57/148 DILI patients with bridging or multi-acinus necrosis on liver biopsy and without typical features of autoimmune hepatitis (lymphoplasmacytic interface hepatitis, plasma cell infiltration and ↑IgG) →

- IST (10) vs. control group (47)

Results:

	IST	Controls	
Peak ALT	863 (369-1035) U/L	800 (500- 1183) U/L	P= 0.801
Peak AST	737 (325-1323) U/L	640 (363-1048) U/L	P= 0.706
Bilirubin	4.5 (1.1-10.4) mg/L	4.9 (2.0-9.7) mg/L	P= 0.748
Globilin	35 (32.5-37.2) g/L	32.9 (28.5-36.5) g/L	P= 0.173
IgG	1986 (1525-2018)	1610 (1290-1870) mg/dL	P= 0.097
HAI score	10 (8.8-12.4)	9.4 (7.1-11)	P= 0.409

F/U 13 mo (8.5-24)

Normal ALT and AST

at 3 mo	70%	17%	P= 0.001
at 9 mo	100%	59.5%	P= 0.014

Drugs/Supplements: Herbs 63.1%, Antimicrobial agents 12.3%, Statins 7%, Dietary supplements 5.3%

Conclusion: Prednisone + azathioprine increase ALT normalization hence prevent the chronicity in DILI patients with severe necroinflammatory activity

Comments:

a) Exclusion of AIH
b) No randomization
c) Serologies
d) No distinction between cholestatic and hepatocellular DILI
e) How long were they treated for?

Acute Liver Injury due to Immunotherapy for Metastatic Cancer: a new Challenge

De Martin E, Roche B, Samuel D, Michot J, Champlat S, Marabelle A, Papouin B, Guettier C et al

Aim: Characterize acute hepatitis associated with antibodies blocking immune checkpoint programmed cell death (PD1)/programmed cell death ligand 1 (PD-L1) and cytotoxic T-lymphocyte antigen 4 (CTLA4) used for metastatic cancer

Methods: 19/1425 pts. (1.3%) treated with immunotherapy and referred to the liver unit with grade 3-4 hepatitis (3 pts. excluded)

Results: 16 pts. were evaluated, ♀ 56%, median age 63 (33-84)

9 pts. (56%) → anti PD1/PD-L1 7 pts. (44%) → anti-CTLA4

Time between initiation of therapy and hepatitis → 5 weeks (1-49)

Median number of injections → 2 (1-36)

Peak: AST 399 (117-2289), ALT 416 (266-3137), bilirubin 18 (6-324)

+ ANA → 50% + SMA → 19%

RUCAM → 14 (87.5%) highly probable 2 (12.5%) probable

Histology:

Anti-CTLA4 → granulomas, severe lobular necrotico-inflammatory activity and central vein endothelithis, lymphocytic cholangitis

Anti PD1/PD-L1 → Lobular hepatitis, moderate portal activity and lymphocytic cholangitis

8 (50%) improved either spontaneously or with steroids 8(50%) treated with steroids with the addition of another immunosuppressive drug

3(16%) immunotherapy was safely reintroduced

Conclusions: Acute hepatitis due to immunotherapy for metastatic cancer is rare (1.3%) and mostly not severe. Histology can distinguish between anti-PD1/PD-L1 and anti-CTLA4

The Frequency of Herbal and Dietary Supplement Mislabelling: Experience of the Drug Induced Liver Disease Network #264

Navarro V, Khan I, Avula B, Verma M

Aim: To analyze the contents and determine the frequency of HDS mislabeling in samples collected by the DILIN prospective study

Methods: 3/2003 and 3/2016 341 cases of DILI due to HDS, 203 underwent chemical analysis

with standard liquid chromatography-mass spectroscopy with electrospray ionization source and compared with the ingredients listed on the product labels

Mislabeling = If the chemical analysis did not confirm the ingredients listed on the label

Results: 90/203 (44%) had labels that accurately reflected their contents

Mislabeling rates based on the composition of the product

- Steroidal 80%
- Vitamins 54%
- Botanical ingredients 48%

Mislabeling based on the purported use

- Bodybuilding 79%
- Weight loss 72%
- Energy boosters 60%
- General health/Well-being 51%

Similar rates of mislabeling in 166 HGS products judged to be responsible for liver injury by DILIN investigators through a structured causality assessment process

Conclusions: HDS mislabeling is common, occurring in over half the products collected by the DILIN. Products used for bodybuilding and weight loss have the highest rates of mislabeling

Development of Hepatic Steatosis After Chemotherapy for Non-Hodgkin Lymphoma #799

Ben-Yakob G, Alao H, Haydek J, SamalaVenkata V, Fryzek N, Rotman Y

Fat accumulation can occur as a consequence of drug toxicity

Aim: Describe the incidence and risk factors for de-novo steatosis in subjects undergoing chemotherapy for non-Hodgkin lymphoma

Methods: Retrospective, case-control study of pts treated at the NIH Center for NHL. CT of the abdomen done at baseline and every 3-6 months intervals. Cases were matched 1:1 to controls by age, gender and ethnicity

Results: 277 pts treated, median follow up 53 months

Steatosis at baseline 6 (2%) De novo steatosis 25 (9%)

Steatosis during chemotherapy 2 (8%)

Steatosis during the first 18 months post-treatment

Steatosis within the first 36 months 20 (80%)

Steatosis cases had a BMI higher at baseline, more likely to have DM (4% vs. 0%), HTN (14% vs 11%) and hyperlipidemia (18% vs 7%)

BMI did not change during chemotherapy in cases or controls

From the end of chemotherapy to the development of steatosis BMI increased 2.5±1 kg/m² in cases vs. 0.8±1.5 kg/m² in controls (p=0.04)

Liver enzymes and clinical outcomes were the same for cases and controls

Weight change in the first 6 months after chemotherapy: Cases 6.5±5.7 kg increase vs 2.8±6.4 kg in the rest of the cohort (p=0.008)

>3% weight gain in the first 6 months after chemotherapy predicted development of steatosis with 87% sensitivity and 44% specificity

Conclusion: Recovery period from NHL chemotherapy is a hot spot for development of fatty liver, which seems to be driven by post-treatment weight gain. Subject who gain >3% weight in the first 6 months post chemotherapy are especially at risk