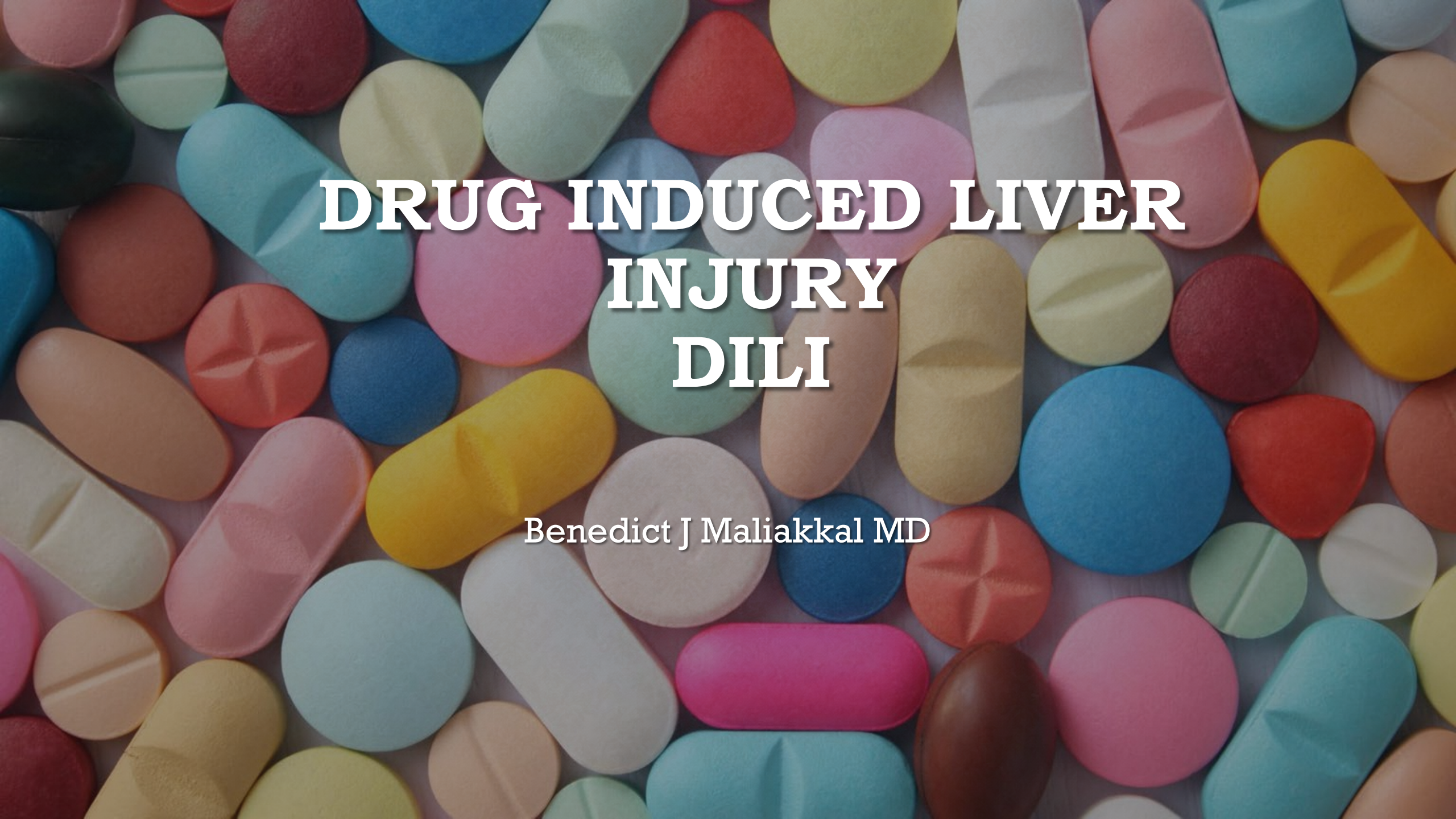


DRUG INDUCED LIVER INJURY
DILI

Benedict J Maliakkal MD

I have no financial or other disclosures to declare related to this talk

“If you don’t know where you are going, any road will take you there.”

Lewis Carroll,
Alice in Wonderland

DILI –Objectives

- Introduction to DILI
  - Definition, Incidence, societal impact
  - Types- Direct vs Idiosyncratic
  - Patterns of DILI
  - Commonly used drugs causing idiosyncratic DILI
- Clinical cases of DILI
  - Direct injury-Acetaminophen, Mushroom
  - Idiosyncratic injury- Hepatocellular/Cholestatic
- Diagnosis
  - Exclude other causes and Causality assessment
- Management
  - General care
  - Specific measures
- Genetics
- Special situations
  - Herbal / dietary supplement Liver injury
  - Immune Checkpoint Inhibitor hepatitis

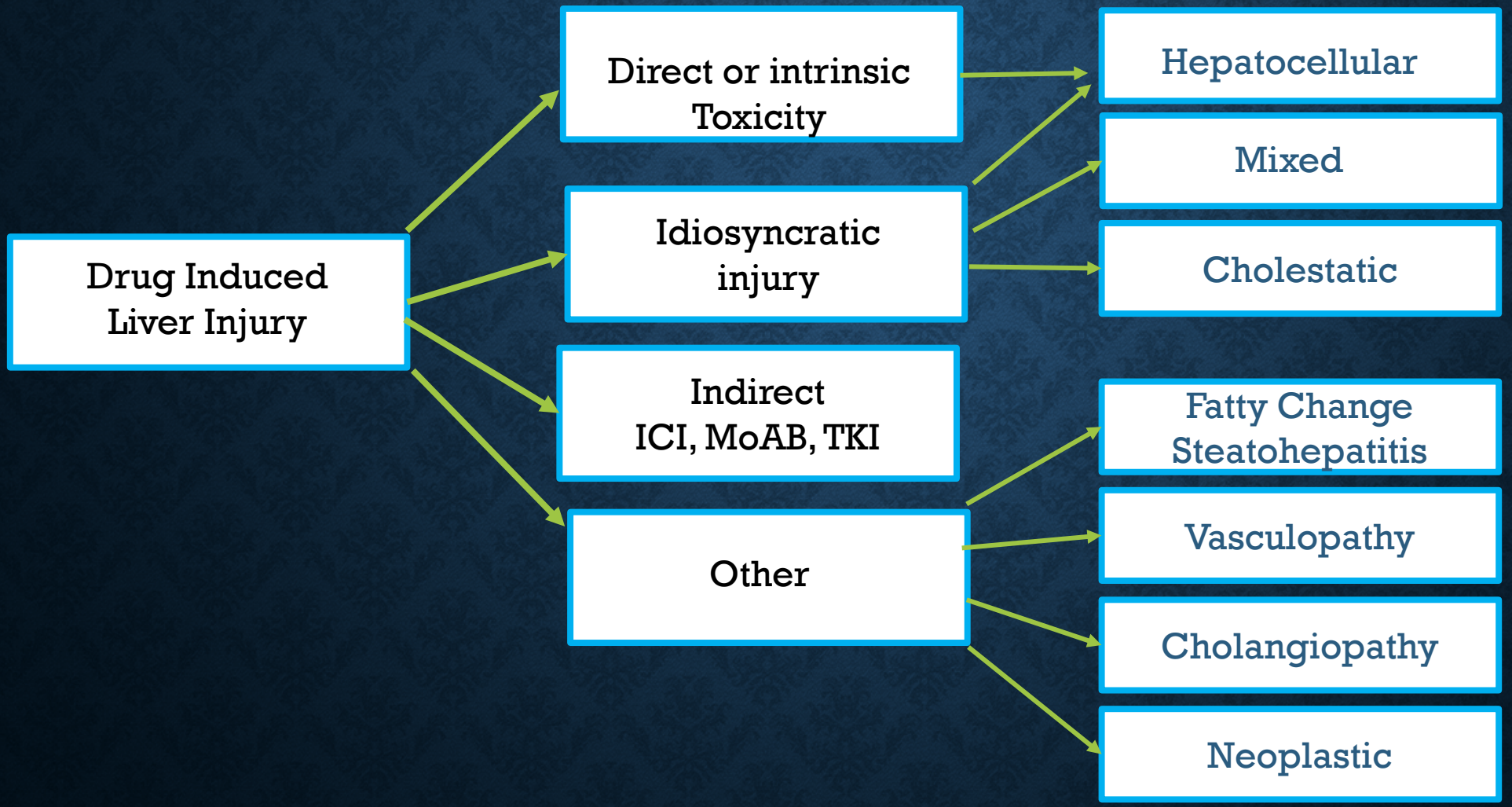
DILI – Definition, incidence

- Definition: DILI is defined as hepatotoxicity resulting from the exposure of a person to a medication/chemical or from one of its metabolites. It can mimic all other types of liver diseases

- Incidence: In United States the estimated incidence of DILI is 20/100,000 or about 65,000/yr
  - 30% of these have jaundice at presentation (22,000/yr)
  - ~10% of those with jaundice develop acute liver failure (2200/yr)
  - DILI is the most common cause of Acute Liver failure (ALF) 50-60% of total ALF
  - Of about 1000 prescription drugs, ~500 or 50% have at least one DILI reported

1) Hepatology 2002; 36:451-455 2) Gastroenterology 2013; 144:1419-1425 3) NEJM 2019; 381:264-273 4) FDA Guidance for industry July 2009)

DILI – Classification based on Mechanism



Modified from Hosack,T. Ther Adv Gastroenterol 2023 Vol 16: 1-13

DILI-DIRECT VS IDIOSYNCRATIC

DIRECT

Acetaminophen, Mushroom (Amanita)

- Intrinsic hepatotoxicity present
- DILI occurs in all patients with ↑ dose
- Degree of Injury is dose related
- Latency is short and predictable
- Liver injury is similar in all patients
- Can predict DILI with animal models

IDIOSYNCRATIC

Amox-Clav, Nitrofurantoin, Green Tea

- No intrinsic hepatotoxicity
- Only a few patients develop liver injury
- No clear DILI relationship to dose*
- Latency is variable, unpredictable
- Liver injury is variable in patients
- Not predictable using animal models

Idiosyncratic = The unique way an individual's body responds (to / metabolizes a drug or a chemical)

DILI- Direct Toxicity- Prototype-Acetaminophen

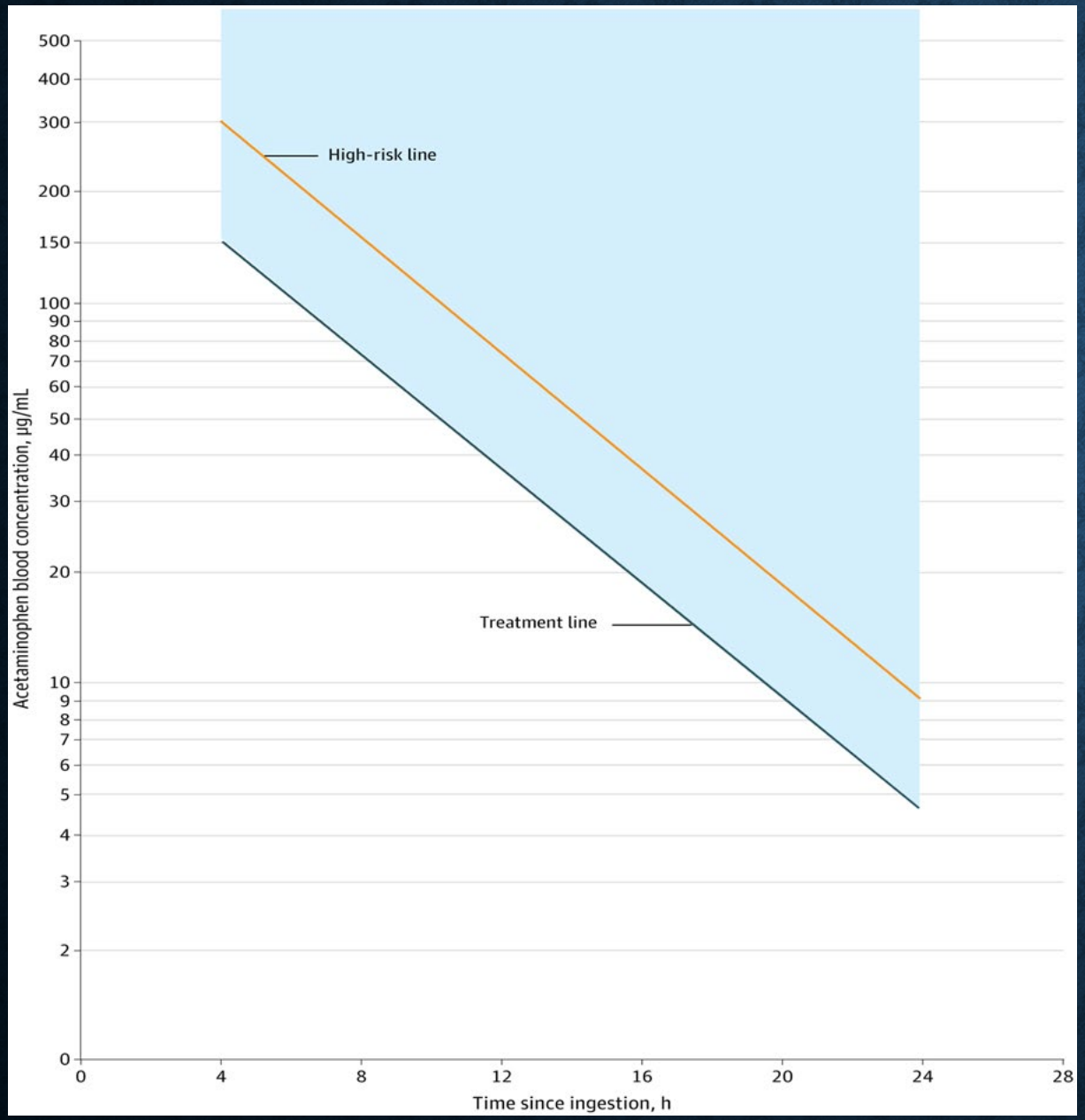
20 Year male took 20 Tablets of Tylenol along with some Benadryl at 10 PM, after he had a fight with his girlfriend

The next day 10 AM his girlfriend called the patient and when the no response, she went to his apartment and found him somnolent and called 911 and he was brought to the ER

Drowsy but arousable, VSS. Labs: ALT 340 AST 280, T Bili 1.0, INR 1.2. Tylenol level 90µgm/mL. Other liver testing and imaging were negative

Started on IV N-acetyl Cysteine in the ER and continued as inpatient.

Liver tests peaked at 36 hrs post admission with ALT 1840 AST 1620 T Bili 1.8 INR 2.0 and then normalized over the next 2 days



Rumack-Matthew Normogram-1975- 50th Anniversary

Useful for single ingestions of Acetaminophen regular. 4-24 hr post Ingestion

Unreliable when sustained release multiple ingestions, co-ingestions with antidiarrheals/opiates

Repeat Acetaminophen level 6-12 hr after admission to make sure it is undetectable.
If not consider activated charcoal PO

Death can occur from
1. Delay in starting NAC
2. Stopping NAC prematurely

Make sure to continue NAC till stopping criteria are met- Acetaminophen serum level <10µgm/mL
INR <2.0 (improving), ALT/AST 50% below peak and Patient looks clinically improved

Rumack BH, Matthew H. Acetaminophen poisoning and toxicity. *Pediatrics*. 1975;55(6):871-876

Idiosyncratic DILI- Prototype Amoxicillin-Clavulanate

70 yr male with history of HTN on Amlodipine for many years developed acute Sinusitis and was prescribed Augmentin (Amox-Clav) for 14 days. His sinusitis resolved

One week after completion, he developed whole body pruritus and his urine turned yellow

Seen in clinic- jaundice and excoriations from scratching. No features of chronic liver disease. No Hx of alcohol/ OTC/ other medications

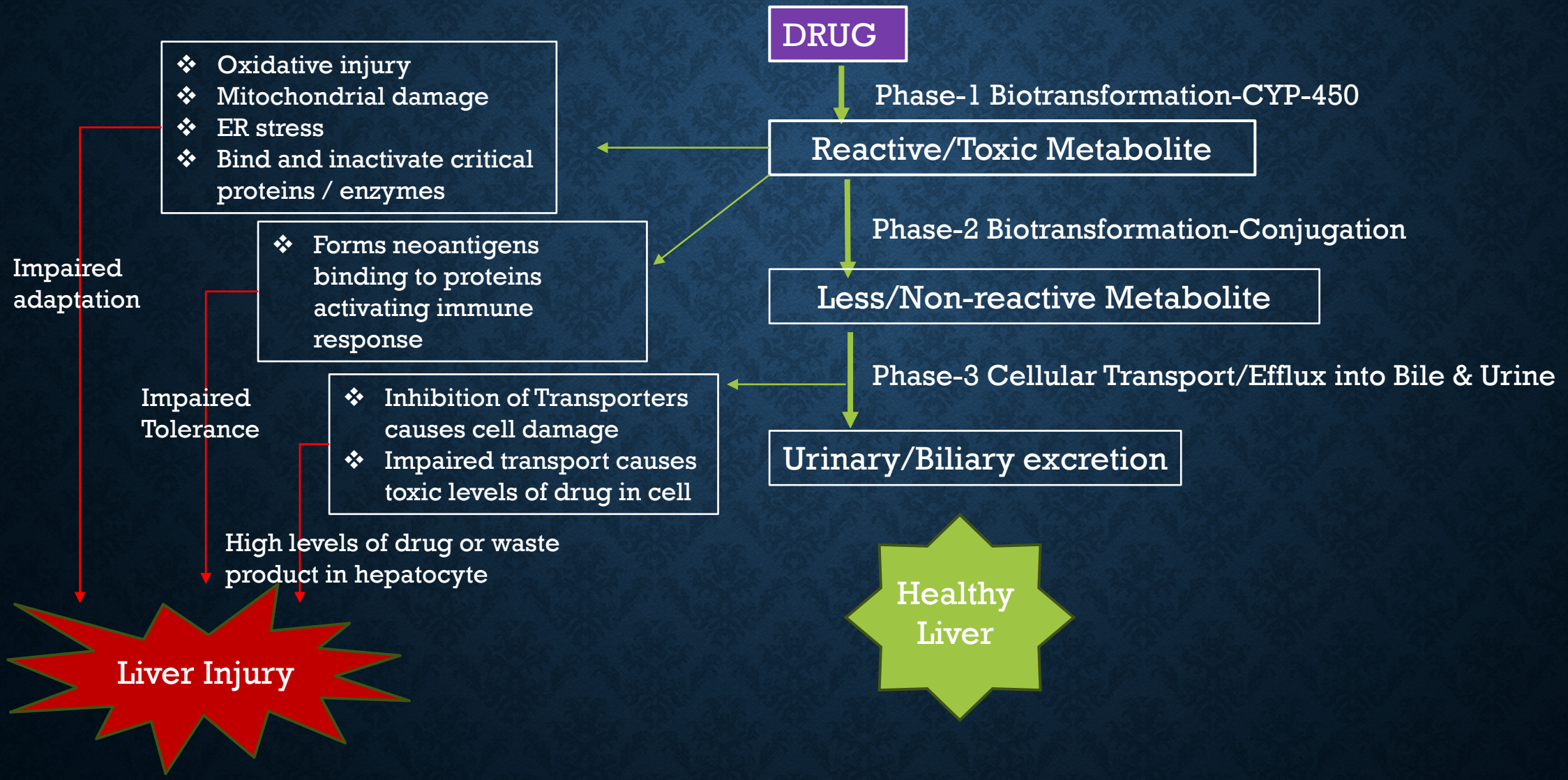
Labs: ALT 160 AST 124 Alk Phos 910, T. Bili 12.4 D. Bili 10.2. INR 1.1. CBC normal

Additional Testing: US of liver, MRI MRCP, Viral and Autoimmune serologies, Ferritin all normal

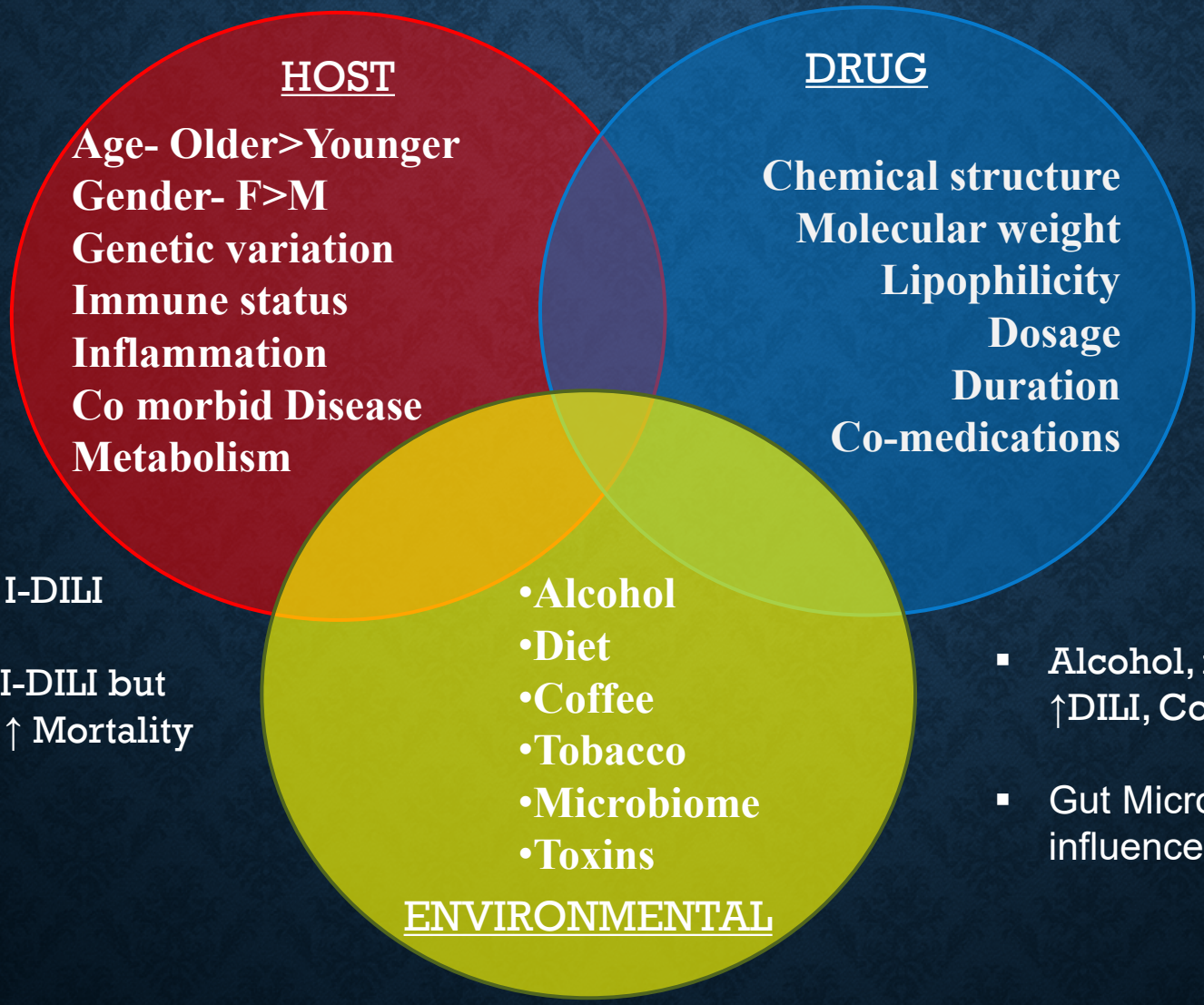
Patient started on Ursodiol 500 mg BID + Cholestyramine 4 gm TID + Hydroxyzine 25 mg TID PRN

Symptoms and Liver tests resolved slowly but completely over the next 4 months

Pathogenetic Mechanisms in DILI



DILI- Interplay of Factors associated with liver damage



- Lipophilicity and Dosage ≥100 mg/day ↑ I-DILI
- Co-medications can ↑I-DILI by altering metabolism

- Liver Inflammation ↑ I-DILI
- Cirrhosis does not ↑ I-DILI but can cause ACLF and ↑ Mortality

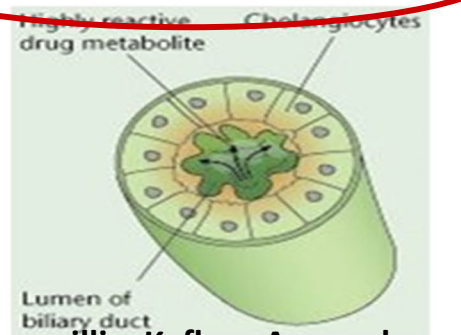
- Alcohol, malnutrition may ↑DILI, Coffee↓
- Gut Microbiome may influence ICI GI/Liver injury

Mechanisms of drug-induced liver disease

induction of apoptosis/Necrosis

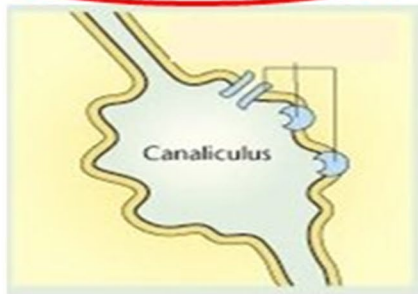
Acetaminophen, Amanita Phalloides

direct toxicity to cholangiocytes

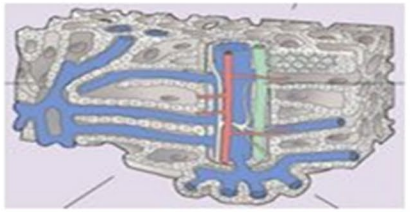


Flucloxacillin Keflex, Amox-clav

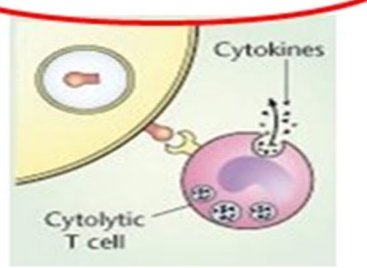
interference with transporters



Bosentan, Anabolic steroids, cyclosporine



immune-mediated



Sulfa, Allopurinol
Nitrofurantoin

mitochondrial injury

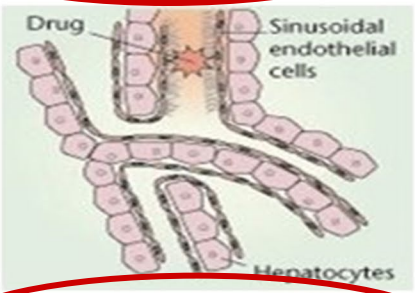
DDI, fialuridine, linezolid, VPA

direct toxicity to hepatocytes

INH , Diclofenac

sinusoidal obstruction syndrome

Busulfan/Myelotarg



NRH: Aza/ Oxaliplatin
Peliosis: AZT

TOP 5 Causes of I-DILI Varies With Country

USA (N = 899)	CHINA (N =29478)	INDIA (N = 1288)
Antimicrobials 45.3%	Herbal/Dietary 27%	Anti TB meds (46.4%)
Herbal/Dietary (17%)	Anti TB meds 22%	Herbal/Dietary (13.9%)
Cardiovascular (9.7%)	Anti-neoplastic 8.3%	Epilepsy/Psych (8.1%)
Epilepsy/Psych (9%)	Antimicrobials 6%	Antimicrobials (6.5%)
Anti-neoplastic (5.4%)	Epilepsy/Psych 5%	NSAIDs (2.6%)

Chalasani N et al. Gastroenterol 2015 Shen T et al. Gastroenterol 2019 Devarbhavi H et.al. JCEH 2021

DILI – Societal impact

- Over 50% of ALF due to DILI in United states is from Tylenol or generic Acetaminophen. Majority of these are people attempting suicide

- DILI is the most common cause of aborted drug development
- It is the single most frequent cause for safety related drug withdrawals FDA approval

- DILI increases the cost of drug development

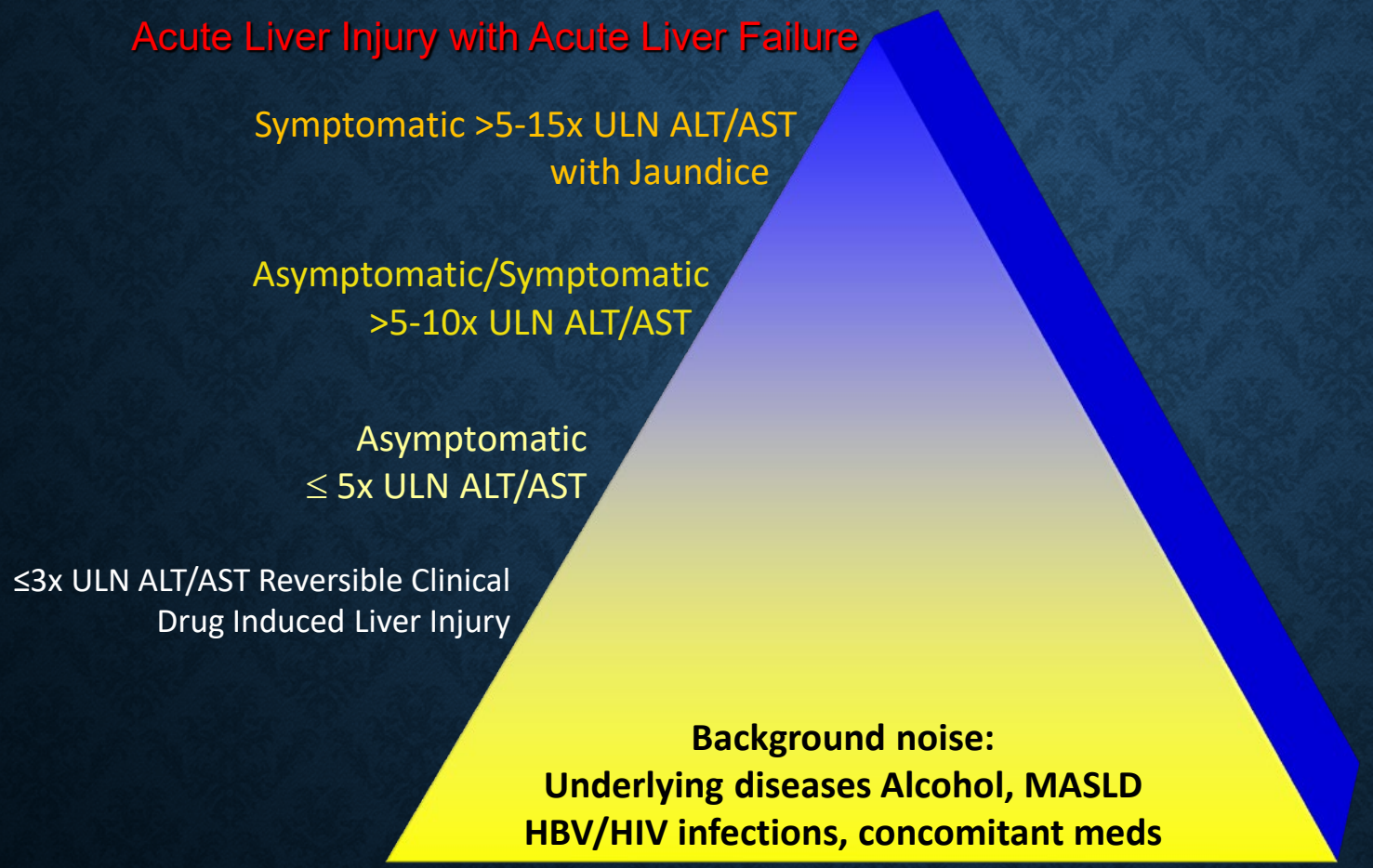
- DILI causes Litigation- Lawyers are the only folks who profit !

- Idiosyncratic DILI (I-DILI) is here to stay, and we need to be vigilant
  - i) Mild liver enzyme elevations from drug does not correlate with severe liver injury
  - ii) < 5-10,000 people are exposed to drug during development
  - iii) incidence of serious DILI is 1:10,000 to 1:100,000 for most drugs

  Hence, we will continue to see serious liver injuries from newer FDA approved drugs

1) Hepatology 2002; 36:451-455 2) Gastroenterology 2013; 144:1419-1425 3) NEJM 2019; 381:264-273 4) FDA Guidance for industry July 2009)

DILI- Clinical Hepatotoxicity Spectrum



i) Watkins PB. Tox Path 2005;33:1-5 ii) Sarda P. IJMR 2009;129:64-7

DILI- Clinical Diagnosis of the type of Liver injury

- DILI can present with a very heterogeneous phenotype and Liver biopsy is often not done or available
- Qualification of liver injury for practical and scientific purposes is made by liver biochemistry- Requires the presence of one of the following minimal criteria:

  ALT ≥5x ULN or ALP ≥2x ULN or ALT ≥3x ULN + TBL >2x ULN.
  With or without constitutional symptoms

  Then the Pattern of liver injury is classified according to

  R = (ALT/ULN) ÷ (ALP/ULN)

  R≥5 = Hepatocellular injury
  R≤2 = Cholestatic injury
  2>R<5 = Mixed Hepatocellular+ Cholestatic injury.

Aithal GP, et al. Clin Pharmacol Ther 2011;89:806-15. EASL CPG DILI. J Hepatol 2019;70:1222-61

DILI AND HY'S LAW

- Hy's Law- In the late 1960s, **Hyman Zimmerman** discovered that Jaundice + drug-induced hepatocellular injury (no cholestasis) was associated with a 10–50% fatality rate from liver failure without Liver Transplantation.

Zimmerman HJ. Hepatotoxicity: the adverse effects of drugs and other chemicals on the liver. 2nd ed. Philadelphia: Lippincott Williams & Wilkins, 1999

✓ FDA uses the Temple's variation of 'Hy's Law cases' in drug development:

ALT >3x ULN + T. Bilirubin >2x ULN without significant ↑ALP (<2xULN)

Temple R. Hy's law: predicting serious hepatotoxicity. Pharmacoepidemiol Drug Saf 2006;15:241-3.

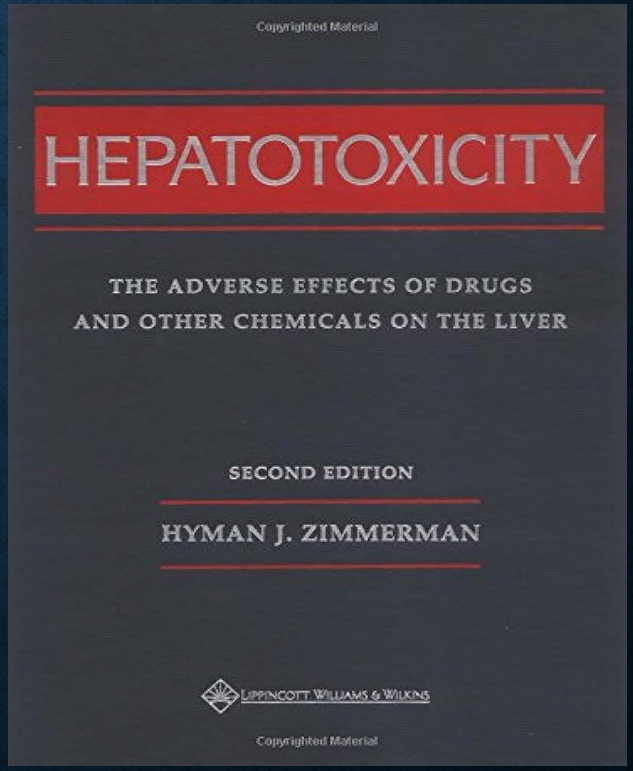
✓ **Spanish DILI registry modification of Hy's Law:**

✓ New R= [(ALT or AST*/ULN) ÷ (ALP/ULN)] >5 + T. Bilirubin >2 ULN

Mercedes Robles-Diaz. Gastroenterology:. 2014 Jul;147(1):109-118

The Father of DILI

Prof. Hyman Zimmerman MD



DILI- Unique Signature helps in making Diagnosis

- A combination of Chronological (latency), Biochemical, Clinical (immunoallergic) and Histologic features form what is termed a drug's signature of toxicity.

- This can be very useful for ruling in / out DILI from a specific drug

- Caveats:

  'Most drugs that cause DILI have signatures……it's just that sometimes the signatures are illegible.' -Willis Maddrey

  'Some drugs have multiple signatures'

Navarro V and Senior J. . 2006 Feb 16;354(7):731-9
Maddrey W: Dig Dis 2015;33:472-476

DILI Phenotype: DRESS Syndrome

Unique Signature of certain drugs:

Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS):

Rash, Fever, adenopathy, Eosinophilia, Elevated liver enzymes+ jaundice and can have multisystem manifestations with 10% mortality mostly from acute liver failure.

Prolonged Systemic Steroids / Immunosuppressants, ICU or burn unit care needed
Plasma exchange and IVIG can be beneficial

Many drugs can cause DRESS
-Carbamazepine, Phenytoin, Lamotrigine
-Dapsone (and other Sulfonamides including TMP-SMX)
-Nevirapine, Abacavir
-Allopurinol, Febuxostat
-Vancomycin, Minocycline

Devarbhavi H et al. Drug-induced liver injury with hypersensitivity features has a better outcome: a single-center experience of 39 children and adolescents. Hepatology 2011;54:1344-50.

DILI-Causality Assessment

Ascertaining whether a patient's elevated liver enzymes and functions are related to a particular drug is called causality assessment.

It is made after ruling out non-drug causes → reviewing all the medications that the patient is on currently and within several weeks previously and then based on multiple criteria, adjudicating the most likely drug that caused the liver injury

It was reliant on expert opinion for many years- But there were few real experts in the world.

Roussel Uclaf Causality Assessment Method or RUCAM was Launched in 1993 and partially based on the results of an international consensus meeting organized under the auspices of the Council of International Organizations of Medical Sciences (CIOMS)

RUCAM is a cumbersome instrument using 7 criteria – Time of onset, course, risk factors, concomitant drugs, presence or absence of non-drug causes, known information about drug causing DILI and changes in liver enzymes after administration of the suspected drug

Modified / simplified RUCAM and RECAM (Revised Electronic Causality Assessment Method) are used now

DILI Causality Assessment - mostly for Clinical trials/ publications

VARIABLES	Modified RUCAM	RECAM
Chronology (latency)		
1a. Drug start to injury onset	**+1 to +2**	**- 6 to +4**
1b. Drug d/c to onset	**+1**	**- 6 to 0**
Dechallenge- Improvement after stopping	**Hepatocellular** **-2 to +3** **Chol/Mix:** **0 to +2**	**- 6 to +4**
Competing cause of liver injury Serologic, molecular, and radiologic testing	**- 3 to +2**	**- 6 to 0**
Rechallenge	**0 to +3**	**0 or +6**
Prior reports	**0 to +2**	**0 to +3**
Risk factors	**0 to +1**	**NA**
Other medications	**- 3 to 0**	**NA**
DILI likelihood	**Modifed RUCAM**	**RECAM**
Definite	**>9**	**>8**
Probable	**6 to 8**	**4 to 7**
Possible	**3 to 5**	**-3 to +3**
Unlikely	**1 to 2**	**< -4**
Excluded	**0**	

Diagnosis of DILI is a Clinical Diagnosis mostly based on history of a recent Drug exposure. After exclusion of other liver diseases

Expert Opinion from local Hepatologist very helpful

Algorithm for I-DILI Management

Suspected Idiosyncratic DILI

Start w/u for other / competing etiologies

Hold potential DILI/ non-critical medications

- Thorough history from patient/ family/ friends- Alcohol and drugs/Herbal
- Comorbidity review- Heart Failure/ Sepsis/Rhabdomyolysis
- Viral hep serologies A/B/C and E /PCR, Autoimmune serologies, Ceruloplasmin.
- Good abdominal Imaging- Triphasic CT best if possible- look at blood vessels, liver size/morphology, features of portal htn

Competing Causes excluded or not playing a major role? → No- Treat other cause

Yes

I-DILI diagnosed

Monitor/Supportive Care
Specific treatment / Steroid trial (if appropriate)
Refer to Specialist/Liver Transplant center early if features of ALF
-Jaundice + INR>1.5 or Hepatic encephalopathy

- 10-15% of those with acute DILI will have chronic DILI-poorly researched
- Autoimmune DILI does not require long term Immunosuppression

Chalasani et al: Am J Gastro 2021May1;116(5)878-898. Andrade et al Nat Rev Dis Primers 2019 Aug 22:5(1)58

Very Few Specific Treatments for DILI

- N-Acetyl Cysteine (NAC) –
  - Tylenol (Acetaminophen) -50 years now since first reported use
  - ALF from DILI- with low grade (New Haven 1-2 grade) Hepatic Encephalopathy
- L-Carnitine for DILI from or OD of Valproic Acid
- Cholestyramine for leflunomide DILI or OD (break enterohepatic cycling)
- Steroids:
  - AIH-DILI - 1mg/kg/day Methylprednisolone
  - ICI-DILI - 1 mg/kg/dayMethylprednisolone
  - Hypersensitivity DILI/ DRESS syndrome- Higher dose steroids may be used
- UDCA (and ? Fibrate) for cholestasis
- ? Indocyanine green for Mushroom (Amanita) poisoning
  Nature Communications. 2023 May 16; 14(1):2241

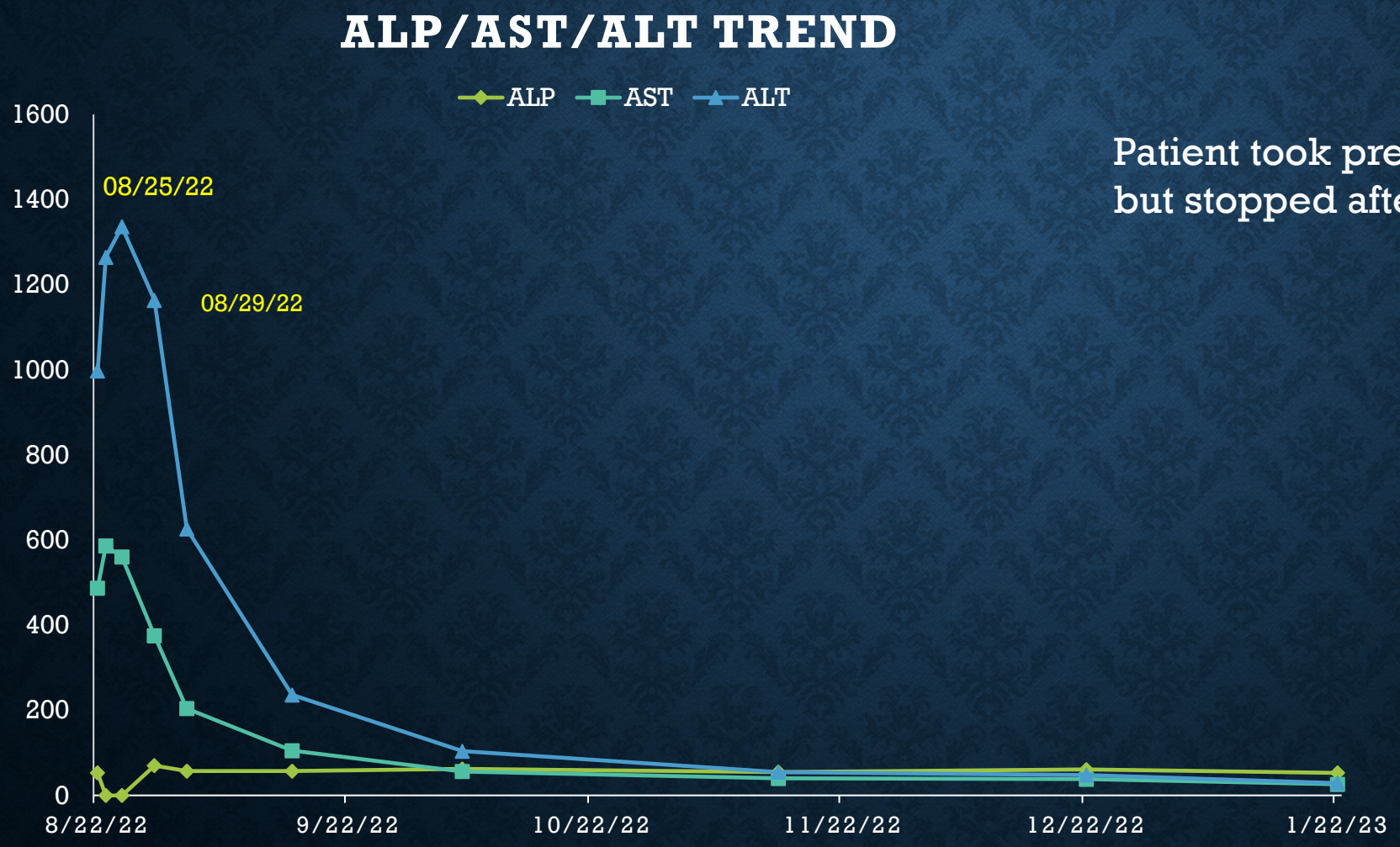
Lee W et al. Gastroenterol 2009;137:856. Prakash A et al. Drugs 1999;58:1137 Lheureux PE etal. Clin Toxicol (Phila). 2009 :47(2):101-11

DILI RELATED TO HERBAL AND DIETARY SUPPLEMENTS (HDS)

DILI from HDS

- A 50-year-old female Pediatrician with a past medical history of Hashimoto thyroiditis, presented with mild abdominal discomfort of two weeks duration. 3-4/10 in severity, located in the right upper quadrant & epigastrium region, non-radiating, with no known aggravating or relieving factors.
- Associated generalized fatigue, loss of appetite, nausea, and rare vomiting.
- 4 – 5 weeks prior to presentation, the patient started taking HistaEze which contains 900 mg of Tinospora Cordifolia extract (stem)/Giloy supplement for immune support against Covid-19 infection.
- Active medications include Synthroid, progesterone, estradiol patch, and the herbal supplement.
- Patient was seen by PCP on 8/22/22 and she had labs repeated which showed continued mild increase in transaminases despite stopping the Herbal supplement on 8/23/22 and on 08/25/22 when I saw her in the clinic

TINOSPORA CORDIFOLIA (GUDUCHI/GILOY) INDUCED LIVER INJURY:



Patient took prednisone 30 mg QD x 4 days but stopped after 08/29/22

DILI from Herbal and Dietary supplements (HDS)

- HDS used widely by healthy people as well as those with ailments due to:
  - Perception that "natural" medications are safer
  - Unhappy with cost / side effects of conventional medicine
- 40% of US population and those who attend liver clinics have used an HDS in the past year
- HDS use is highest among Asians, highly educated, younger, women and the more well off
- Even among Clinicians, the use of HDS mirrors the population at large
- 40+ Billion Dollar industry. Protected from pre-market evaluation by 1994 Congressional action.
- Accounts for 25-30% of DILI and 15-20% of DILI induced ALF in US

Hepatology:2017;65:363-373, Liver Txp: 2022; 28 (2) 169-179 Nature:2018; 561:448-50

DILI: Why do people use HDS that cause liver injury?

- Younger :
  - Weight loss- Garcinia Cambogia, Green Tea extract, Herbalife (Green tea +Ephedra) Hydroxycut, Ma Huang (Ephedra spp)
  - Muscle building/Improve virility: Anabolic steroids , Horny Goat Weed (Epimedium)
  - Depression/anxiety/ Energy: Kava Kava, Khat
  - GI problems: Turmeric, Iberogast, Rikkunshito
- Older:
  - Insomnia: Valerian root, Kava Kava, Skullcap
  - Health maintenance: Improve Immunity/memory, Adapt to Stress- Guduchi/Giloy (Tinospora Cardifolium), Ashwagandha, Turmeric, Reishi mushroom (Ganoderma lucidum), aloe vera (Aloe barbadensis), and Siberian ginseng (Eleutherococcus senticosus)
  - Menopausal issues: Black Cohosh,

.

Victor Navarro et Al- Hepatol Commun. 2019 Jun; 3(6): 792–794.

Difficulty in making a clear diagnosis of Herbal DILI

a) 40% patients will not volunteer that they are taking Herbal/Dietary supplements
b) Most herbs / natural medications have 5-10 or more ingredients, and each herb has multiple compounds- Causality determination becomes difficult
c) Different parts of the same plant -may have different drug compounds and at different concentrations One part may be beneficial and another part Toxic!
d) Sub- species can be toxic - Cinnamon Ceylon *Cinnamomum zeylanicum* vs Cinnamon Cassia *Cinnamomum aromaticum*. Cassia has high levels of Coumarin-can be hepatotoxic
e) 51% supplements were found to be mislabeled in a recent study- chemical contents did not match the label

Navarro V et al: *Hepatology Communications* 3(6):p 792-794, June 2019

f) Herbal supplements may have prescription drugs like Statin/ Diazepam etc. added for effect!

Unlike allopathic medications which are regulated/ approved by the FDA, Herbal and dietary supplements are considered as food additives and not regulated/ standardized
User Beware!

DILI Association with HLA Haplotypes

DRUG	HLA Allele/s	Population Studied	Freq. of Allele in Pop	Odds of Toxicity	P value
Allopurinol	*A*34:02* *B*53:01* *B*58:01*	USA	0.2% 0.6%, 1.2%	Unknown	0.001 0.035 0.008
Amox-Clav	*A*02:01* *DRB1*15:01*	Europe Europe	47% 26%	2.3 2.8	$1.8x10^{-10}$ $3.5x10^{-11}$
Dapsone	*B*13:01*	India	6%	NA	NA
Fenofibrate	*A*33:01*	European	1%	58.7	$3.2x10^{-7}$
Green Tea	*B*35:01*	USA	11%	Not calculated	$9.7x10^{-19}$
Infliximab	*B*39:01*	European	2%	43.6 (2.8-inf)	0.001
Nitrofurantoin	*DRB1*11:04*	European	4%	5.1	$2.3x10^{-5}$
Minocycline	*B*35:02*	European	6%	29.6 (7.8-89.8)	$2.57x10^{-8}$
Terbinafine	*A*33:01*	European	1%	40.5 (12.5-131.4)	$6.7x10^{-10}$
TMP-SMX	*B*14:01-C*08:02*	European	2%	8.7 (3.2-19.5)	$2.3x10^{-4}$

Modified from Ann K Daly, CTS Volume16, Issue 1: January 2023, Pages 37-42

DILI with no HLA Association

Some Commonly used drugs

Isoniazid (Anti-TB)
Diclofenac, Nimesulide (NSAIDs)-Mitochondrial injury
Azathioprine, Thioguanine
Ciprofloxacin and other fluoroquinolones
Atorvastatin and other statins
Interferon Beta- immune mediated

In these DILI- Metabolic pathways and non- HLA dependent immune mechanisms are likely involved

Modified from Ann K Daly, CTS Volume16, Issue 1: January 2023, Pages 37-42

Clinical application of Genetic testing to avoid DILI

Theoretically, it is possible to decrease DILI by avoiding prescription of drugs when specific HLA alleles/SNPs of enzymes in the metabolic pathway of a drug are present.

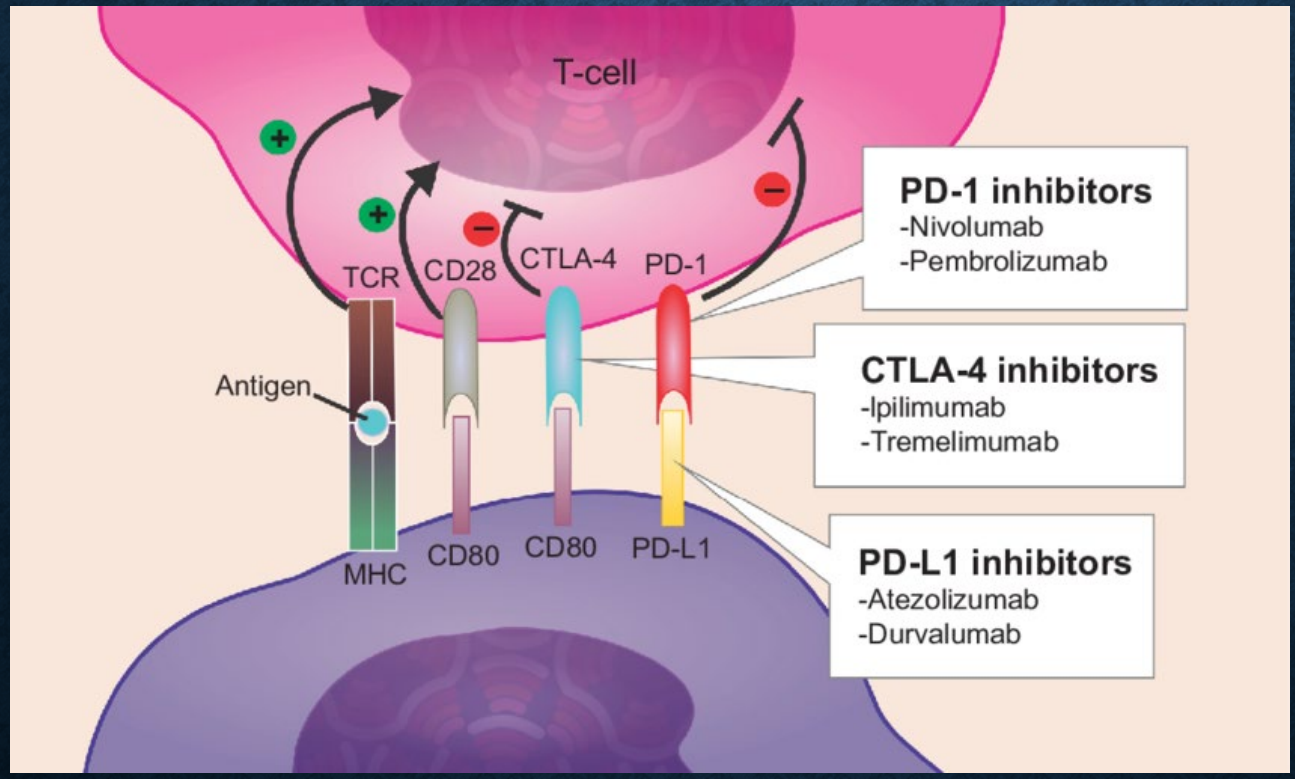
However today, this can be potentially done only for a few medications and at a high cost.

In years to come, it is possible that all will have a genetic profile stored and when a drug is prescribed, a computer can alert the physician/pharmacist and propose alternatives

Also, it may be possible in the future that Genomics/Metabolomics/Deep learning/AI can be used to screen drugs in development for increased risk of ADRs/DILI in the general population

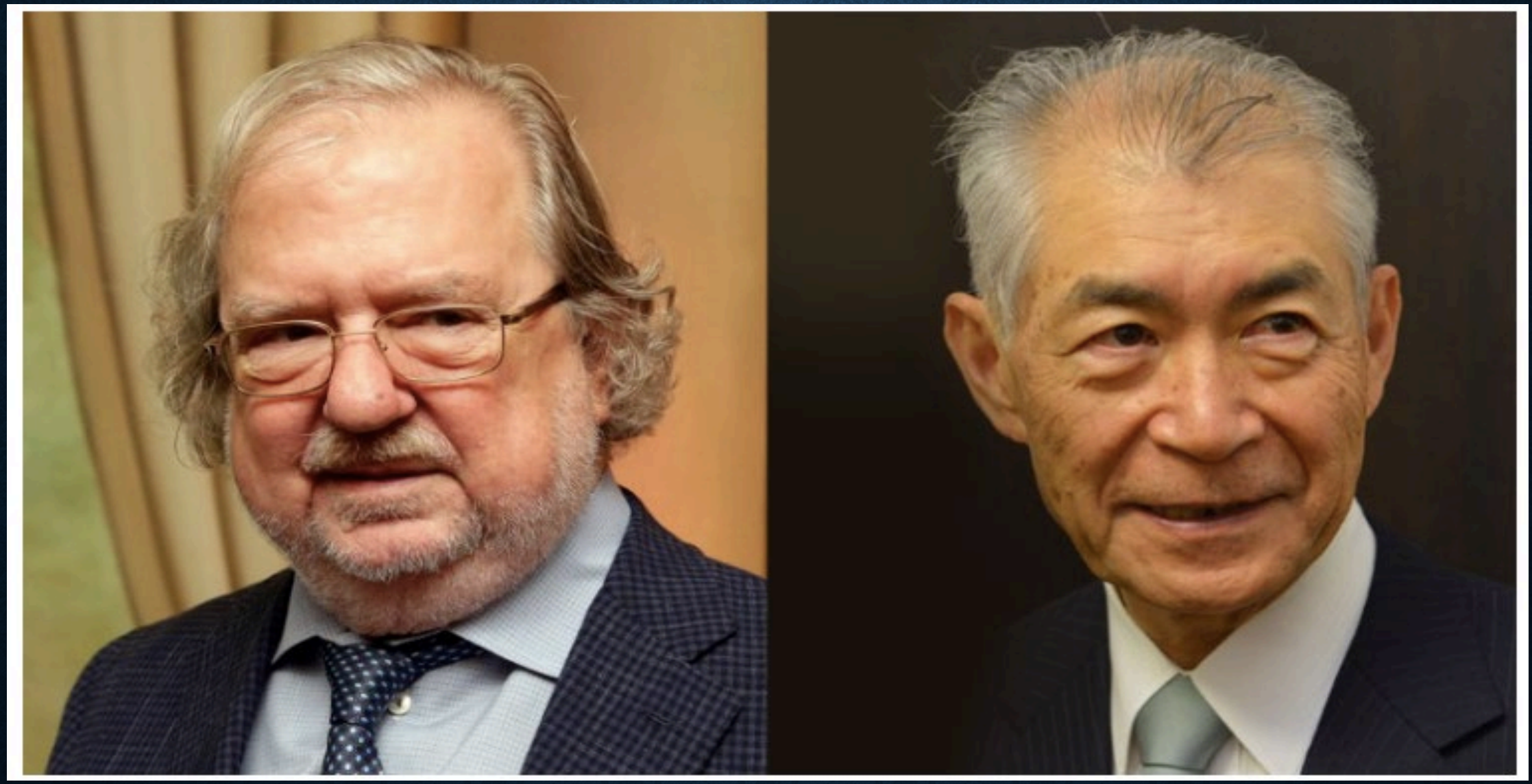
DILI caused by immune- check point inhibitors

What are immune Checkpoints ?
Dampening mechanism to decrease collateral damage and autoimmunity from excessive immune activation (of T cells) . There are positive and negative checkpoints



•OncoTargets and Therapy -December 2016, 10:21-30

2018 Nobel prize in Medicine



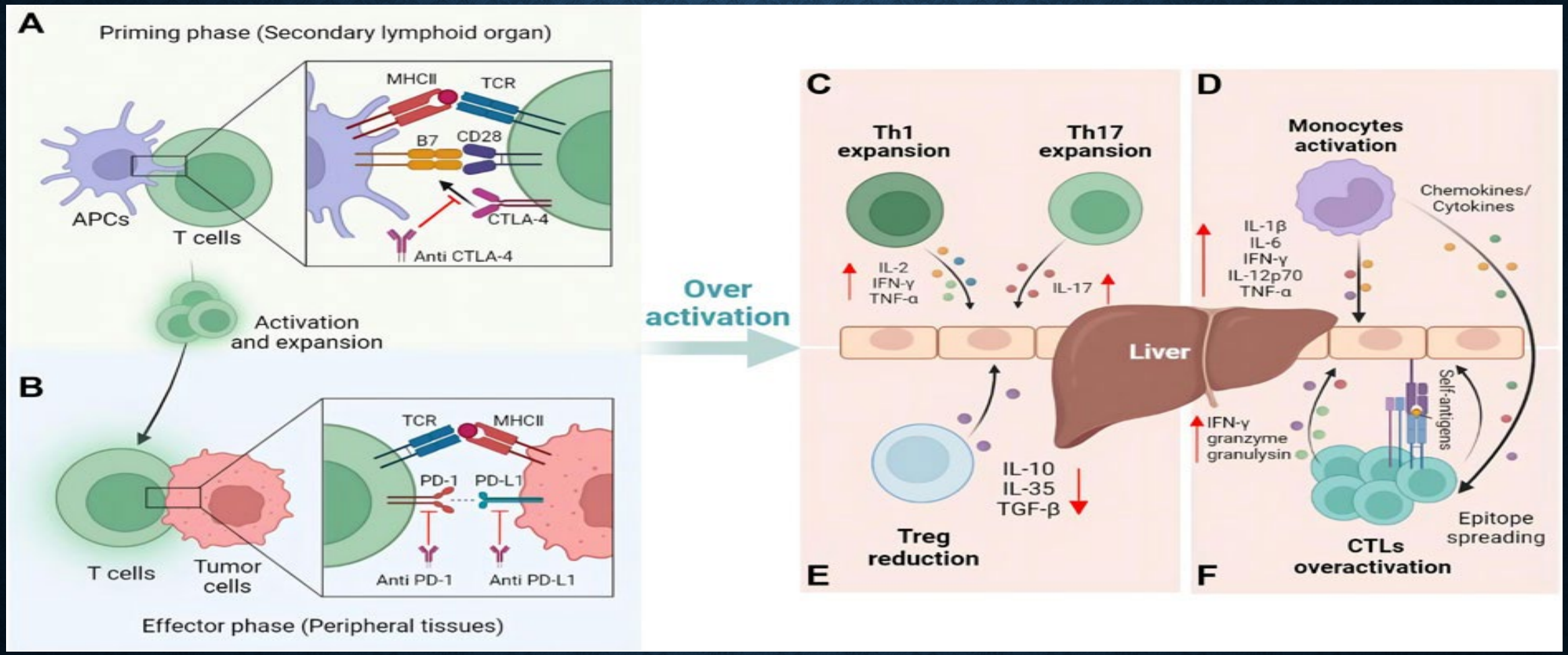
James Allison, UT MD Anderson Cancer Center

Tasuku Honjo, Kyoto University in Japan

Known Immune- check point inhibitors

Checkpoint Receptor	Checkpoint Ligand	Regulation
CTLA-4 (CD152)	B7-1 (CD80) and B7-2 (CD86)	Negative
PD-1 (CD279)	PDL-1 (CD274) and PDL-2 (CD273)	Negative
LAG-3 (CD223) and KIR (CD158)	MHC class II	Negative
TIM-3	Galectin	Negative
TIGIT	Poliovirus receptor (CD155)	Negative
4-1BB (CD137)	4-1BBL (CD137L)	Positive
GITR (CD357)	GITRL	Positive

Mechanisms of T cells activation and Auto-immune hepatitis caused by ICIs.



(A) Blockade of CTLA-4 activates T cells at the priming phase. **(B)** Further anti-tumor effect induced by the blockade of PD-1 and PD-L1 during the effector phase.

When there is break in tolerance, immune cells such as **(C)** ↑T-helper cells, **(D)** Monocyte activation, **(E)** ↓T-reg cells, and **(F)** ↑ Cytotoxic T cells are involved in the pathophysiology of ICI hepatitis.

Frontiers in Pharmacology. 2023 Jan 9;13:1077468.

CURRENTLY AVAILABLE CHECK POINT INHIBITORS

PD-1 Inhibitors

Pembrolizumab (Keytruda)HCC
Nivolumab (Opdivo)HCC
Cemiplimab (Libtayo)

PD-L1 Inhibitors

Atezolizumab (Tecentriq)HCC
Avelumab (Bavencio)
Durvalumab (Imfinzi)HCC

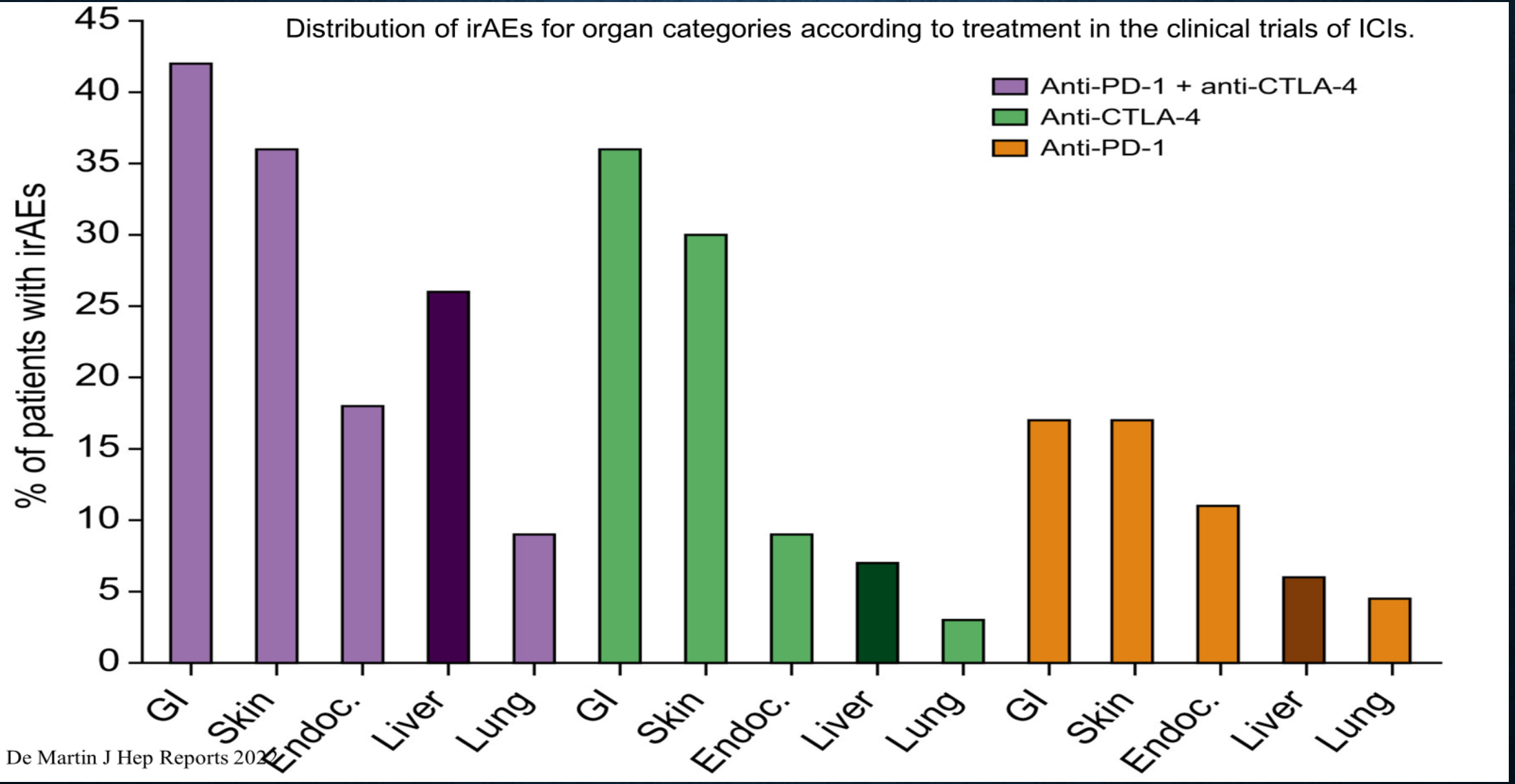
CTLA-4 inhibitors

- **Ipilimumab(Yervoy)HCC**
- **Tremelimumab (Imjuno)HCC**

LAG-3 inhibitors

- **Relatlimab**
- **Opdualag**
  Relatlimab + Nivolumab

Autoimmune Adverse Events from ICI Inhibitors



Incidence and Risk factors for ICI Hepatitis

ICI Hepatitis Incidence:

PD-1 and PD-L1 inhibitors have lower incidence (2-10%) Compared to CTLA-4 inhibitors

Combination of CTLA-4 +PD-1/PD-L1 have the highest incidence 10-20%

Combined Chemo/RT + ICI increases benefit but may also slightly increase hepatitis risk

Fulminant ICI hepatitis is rare- 0.1-0.2%

Host factors affecting ICI hepatitis:

Age <65 yrs, H/o autoimmune disease

Prior ICI hepatitis

Underlying liver disease/HCC

Gut Microbiome may affect efficacy as well as incidence of ICI autoimmune disease

No known pre-Rx predictive biomarkers for ICI- both for efficacy and risk

Front. Pharmacol. 2023 Jan 09-13:1077468.
Ann Int Med 2018, 168:121-130

ICI Hepatitis: Presentation, Diagnosis

Initial Presentation:

- 75-80%-Asymptomatic and Diagnosed with Lab monitoring
- 20-25% have symptoms- Anorexia, N/V, Abd Pain
- Only 0.2% present with fulminant liver failure

Labs:

- Most patients present with ↑ Liver tests about 1-3 months after start of ICI- after 1-3 doses
- CTLA-4 onset quicker -median 3-4 weeks (1-2 doses), PD-1/PD-L1 ~12-16 weeks (3-4 doses)
- Mostly Hepatocellular injury with >50% with ↑Bili, mixed pattern 20%. Pure cholestasis rare
- Auto-Antibody tests rarely positive- not useful for diagnosis

Imaging:

- Often normal in non-severe hepatic injury
- In severe hepatitis-
  Hepatomegaly, Periportal edema, GB wall edema, perihepatic ascites, reactive adenopathy
- Rarely Sclerosing cholangitis features of bile ducts

Liver Biopsy:

- Done rarely- Pan-lobular Hepatitis with few plasma cells, increased CD8 >>CD4 T cells

Dx of ICI Hepatitis is a Diagnosis of Exclusion just like other DILI
Best to have Baseline history/ labs/ imaging before initiating ICI

ICI Hepatitis: Monitoring and Diagnosis

The AGA, NCCN and ASCO have issued Guidelines for management of ICI Hepatitis.

Before ICI is given:

Baseline Liver tests and Viral Hepatitis Serologies/PCR

Education about Autoimmune issues including Hepatitis and to report ASAP if issues develop

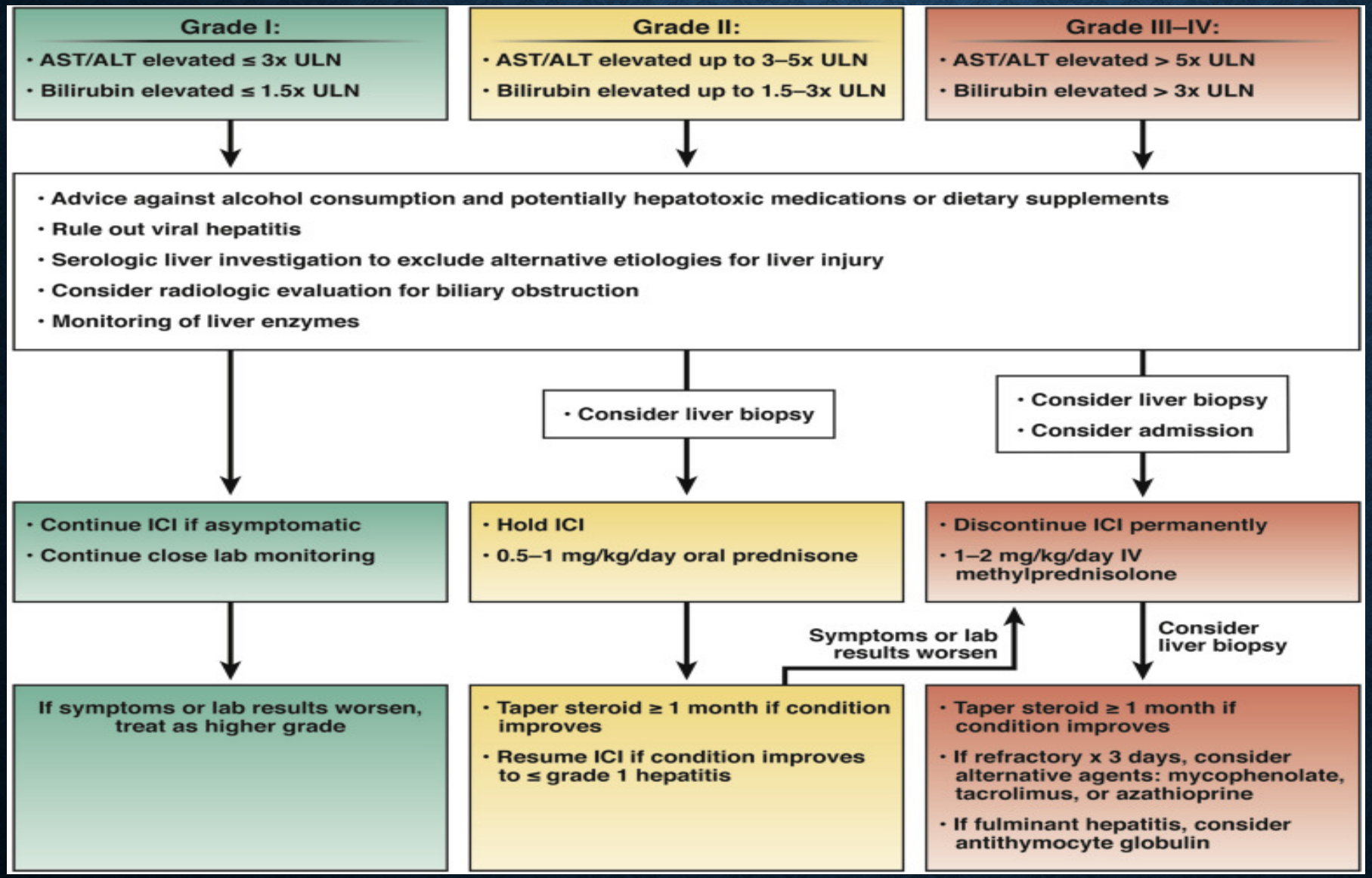
Review Labs prior to each dosing (Standard dosing Q 3 weekly for current ICI's)

When Hepatitis Develops:

ICI Hepatitis is a diagnosis of exclusion just like other DILI- other possible causes should be excluded

As patients are immunosuppressed, consider additional testing for CMV/HSV/VZV/EBV and HEV

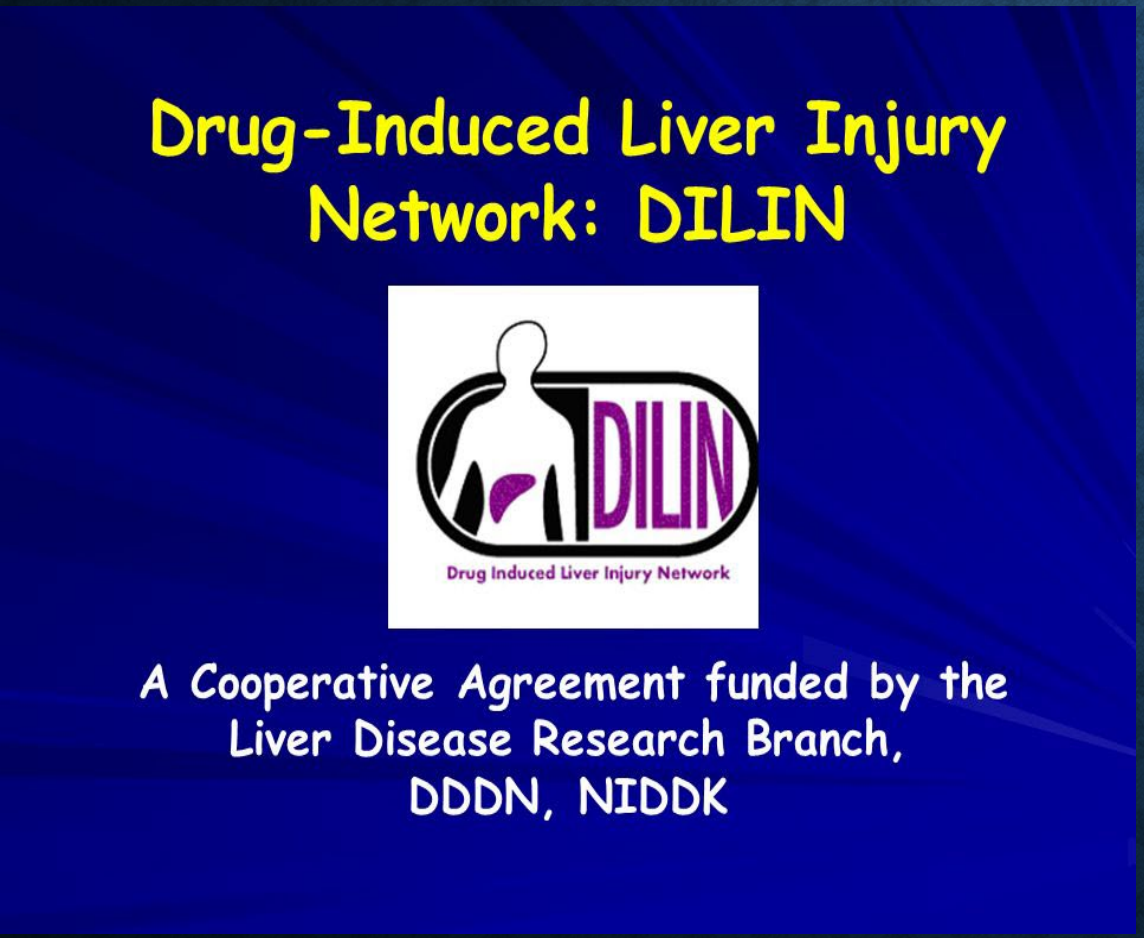
Grading and Management of ICI Hepatitis



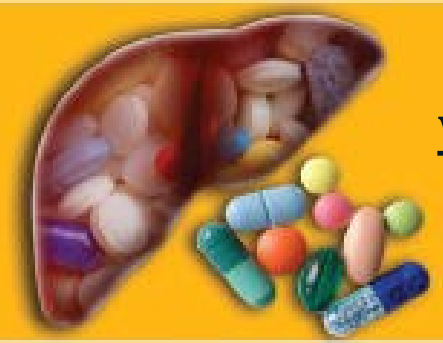
- Liver Biopsy can be avoided in a Majority. Useful in atypical presentation/ response
- Methylprednisolone dose max: 1mg/Kg/day
- 10% Steroid Refractory, MMF works in 80%
- CSA, Tacrolimus can be used in refractory ICI H
- Tolicizumab (anti-IL6) Thymoglobulin, Plasmapheresis used in Fulminant liver failure

CLINICAL PRACTICE UPDATE-DOUGAN ET AL GASTROENTEROLOGY VOLUME 160, ISSUE 4, P1384-1393, MARCH 2021

DILIN has contributed to our knowledge of all aspects of DILI
Mastermind of Dr. Jay Hoofnagle @ NIH



- Registry established in 2003 and is going strong, expanding
- Identifies clinical risk factors, mechanism of injury
- Stores blood/ urine/tissue samples and can do genetic and other testing
- Does clinical trials for Rx of DILI
- Follow up- outcomes short and long term
- Many Major publications
- Helps in Pharmacovigilance



www.livertox.nih.gov

LiverTox

Clinical and Research Information on Drug-Induced Liver Injury

The Liver Disease Research Branch of the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) and the National Library of Medicine (NLM) created the ***LiverTox*** website

LiverTox is a website with comprehensive and evidence-based information on drug, dietary supplement and herbal-induced liver injury that is freely accessible to physicians, researchers and the public.

The website is particularly designed for use by physicians and health care professionals who might rarely see patients with drug-induced liver injury, including family practitioners, internists, pediatricians, psychiatrists, surgeons, specialists and subspecialists in all areas of medicine.

The website is also helpful to hepatologists by providing complete and accurate information about the clinical features of liver injury for each medication along with complete and annotated references.

Finally, LiverTox will be helpful to patients seeking information on liver injury due to drugs.


Thank you!