Welcome to LiverConnect

June 11, 2019

The presentation will begin shortly.

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Access Number: *7886274#

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Welcome to the LiverConnect

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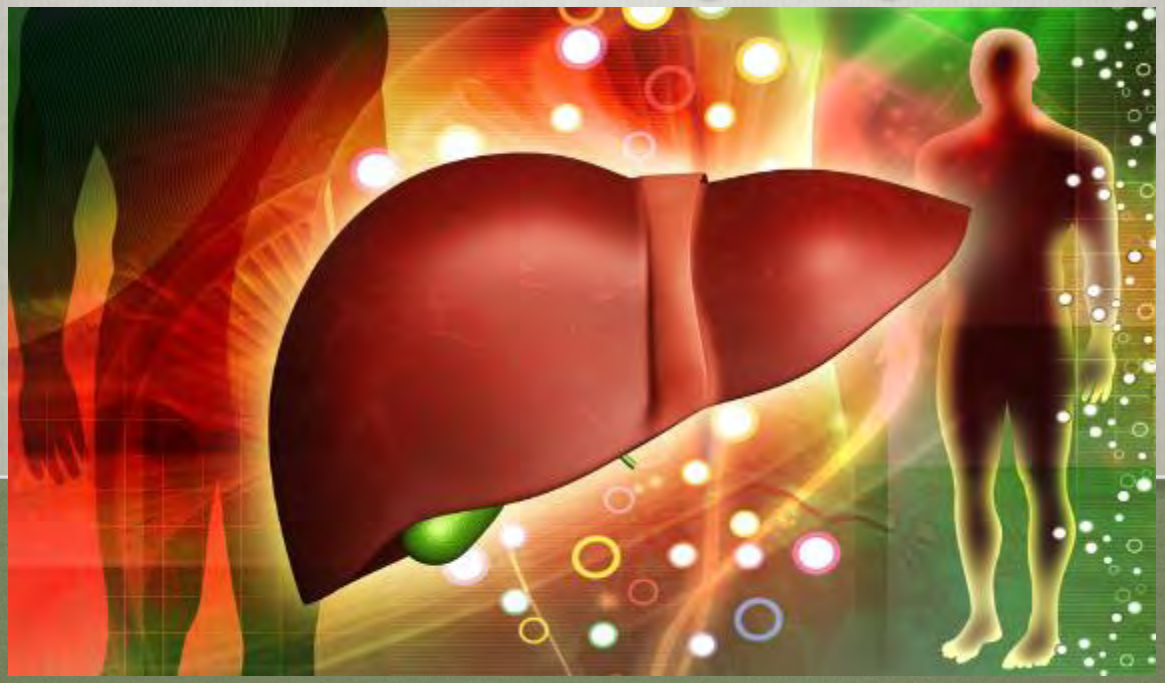
ALASKA NATIVE TRIBAL HEALTH CONSORTIUM

Drug-Induced Liver Injury



John McGilvray, B.S. Pharm, Pharm D, BCPS, FASCP

Image: drugdiscovery.com

Disclosure

I do not have (nor does any immediate family member) a vested interest in or affiliation with any corporate organization offering financial support or grant monies for this activity, or any affiliation with an organization whose philosophy could potentially bias my presentation.

Question 1

What symptoms may suggest to you that a patient is experiencing drug-induced liver injury?

Question 2

An “R” ratio of 2 or less may be suggestive of:

a) Cholestatic pattern of injury
b) Hepatocellular pattern of injury
c) Mixed hepatocellular/cholestatic injury

Question 3

Why is the diagnosis of drug-induced liver injury so challenging?

Question 4

Describe an approach to determine whether or not a patient is experiencing drug-induced liver injury?

Objectives

- To describe the importance and challenges of diagnosing drug-induced liver injury (DILI)
- To briefly discuss the incidence and pathogenesis of DILI
- To discuss how to judge the likelihood of DILI
- To evaluate case reports of DILI

Introduction

(1)

- DILI is an uncommon but **important** and **challenging** form of liver disease.
- When evaluating for new-onset liver disease, drugs, OTC substances, illicit substances, herbals, and dietary supplements should be considered as possible causes of DILI.

Image: http://www.mdwls.com/supplements.html

Why is it important to consider DILI?

(1)

- If not addressed, DILI can be severe and even fatal
- Even with underlying liver conditions such at Hepatitis B or C, DILI can occur and should be considered
- DILI is a growing concern because of the increasing number of drugs on the market

Image: http://www.medindia.net/news/how-the-immune-system-induces-liver-damage-during-hepatitis-127612-1.htm

DILI Epidemiology

(2)

- Estimated Annual incidence ranges from:
  - 10 to 15 per 10,000 to 100,000 persons exposed to prescription medications
- Accounts for approximately 10% of all cases of acute hepatitis
- Most common cause of acute liver failure in the U.S. and most frequently cited reason for medication withdrawal from the marketplace

True Incidence of DILI

(3)

- Difficult to accurately determine because:
  - Unknown denominator of persons taking a drug
  - Lack of objective test to diagnose DILI
  - Lack of consensus on what liver abnormalities constitute DILI
  - Difficulty determining causality of a single drug for those on multiple medications
  - Lack of systematic reporting

Why is DILI so challenging?

(1)

- Growing number of medications available
- Clinical presentation and patterns of liver injury can mimic almost any form of liver disease
- There are no lab markers or clinical indicators to definitively diagnose DILI, so it is a diagnosis of exclusion
- Information on DILI is dispersed throughout varied disciplines in the literature and while some tertiary sources try to consolidate information on DILI, those sources may become outdated

Risk Factors: An Imperfect Science

(3, 8)

- Drug dose, drug lipophilicity, extent of hepatic metabolism
- Age (differs among drugs)
  - Isoniazid
  - Valproate
- Sex (Possibly; may be drug-specific)
  - Females have shown a higher risk from
    - Nitrofurantoin, erythromycin, flucloxacillin, minocycline, and isoniazid
- Alcohol use

Image: alcoholdeliverygrimsby.com

Risk Factors: An Imperfect Science

(8)

- Underlying diseases
  - Components of metabolic syndrome should be considered risk factors for the occurrence and the degree of drug-associated fatty liver disease in patients treated with tamoxifen and methotrexate (EASL Guidelines)
  - Chronic hepatitis B and C can be considered risk factors for DILI from anti-HIV and anti-tuberculosis therapy (EASL Guidelines)
- Concomitant drugs
- Race

Differences Between DILI in African-Americans and Caucasians

(4)

Top 3 Medications Causing DILI	
African American	**Caucasians**
1. Trimethoprim-Sulfamethoxazole	1. Amoxicillin-clavulanate
2. Isoniazid	2. Nitrofurantoin
3. Phenytoin	3. Anabolic steroids

Risk Factors: An Imperfect Science

(3)

- Genetic variations
  - Genetic basis for DILI from flucloxacillin has been established
  - Some variants have been shown to be associated with diclofenac hepatotoxiciy
  - N-Acetyltransferase 2 polymorphism appear to predispose to hepatotoxicity from sulfonamides and isoniazid

Image: Genetics and Society: A Course for Educators | Courserawww.coursera.org

HLA Risk Alleles and DILI Susceptibility

(6)

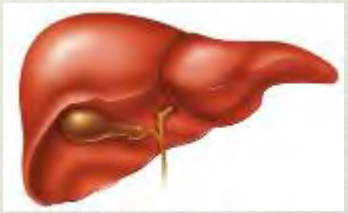
- Anti-TB drugs (isoniazid, rifampicin, pyrazinamide) in Indian populations
- Amoxicillin-clavulanate, multiple HLAs in Caucasian populations
- Ticlopidine, multiple HLAs in Japanese populations
- Others

Pathophysiology

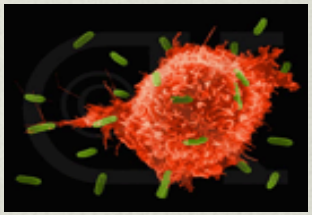
(7)

Offending drug or metabolites

Often from phase I metabolism but may be from phase II



Cell stress



Mitochondrial damage and/or specific immune reactions

Images:
www.crossfitpeoria.com, www.sccollege.edu, www.sciencedaily.com, www.sabiosciences.com/pathwaysonline/20090608.php

Proposed Pathogenesis for Idiosyncratic DILI

(6)

Selected Drugs Associated with Intrinsic vs. Idiosyncratic DILI

(8)

Intrinsic

- Acetaminophen
- Amiodarone
- Anabolic steroids
- Cholestyramine
- Cyclosporin
- HAART drugs
- Valproic acid
- Others

Idiosyncratic

- Allopurinol
- Amiodarone
- Amoxicillin-clavulanate
- Isoniazid
- Ketoconazole
- Minocycline
- Nirofurantoin
- Phenytoin
- Sulfonamides
- Others

DILI from Dietary and Herbal Supplements

(5)

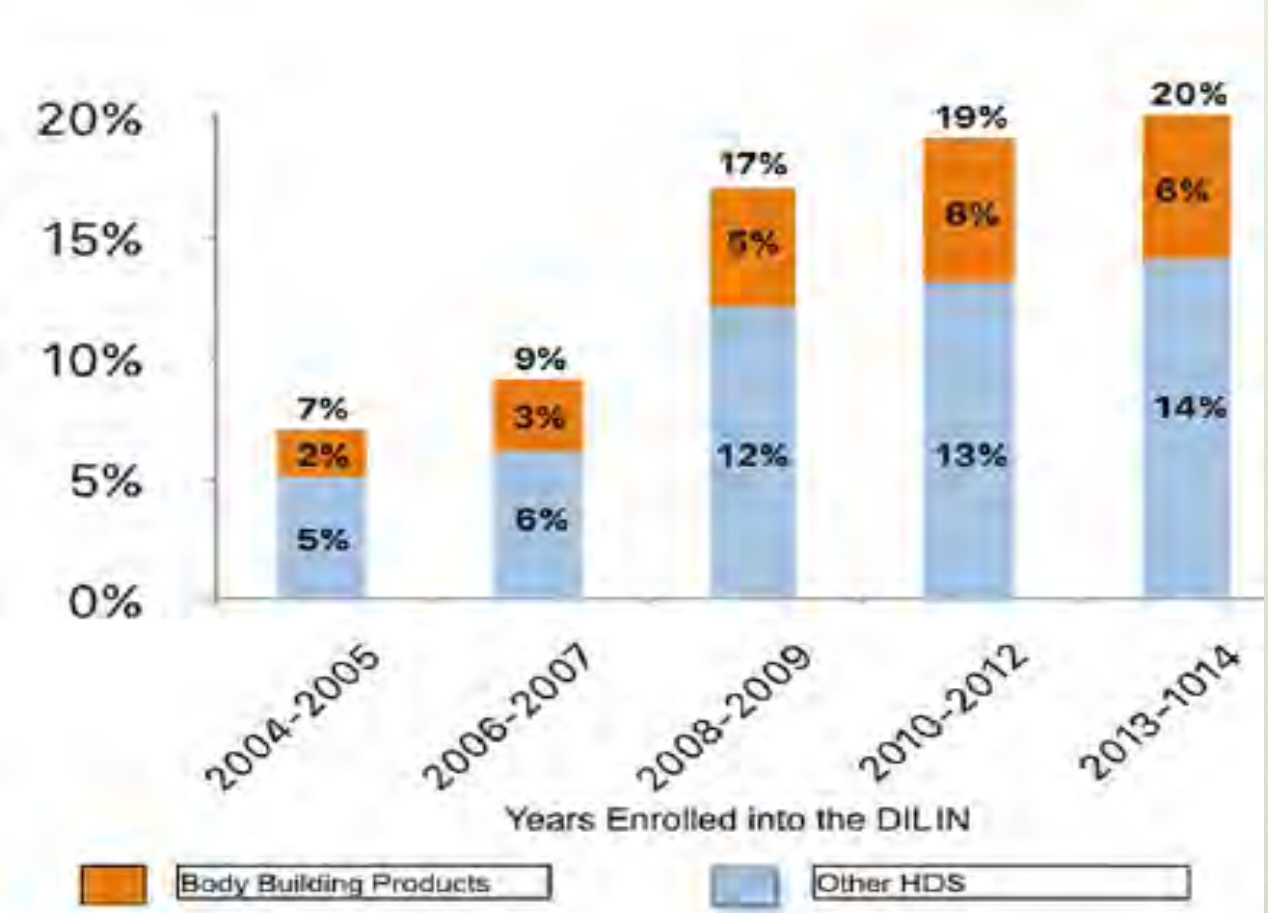


FIG. 1. Proportion of DILIN Cases due to HDS.

What if you suspect a drug may be causing liver injury?

Image: www.npr.org

Causality Instruments

(1)

- RUCAM Scale
- Maria & Victorino (M&V) Scale
- Naranjo Scale

The most commonly used method adjudicate causality, however, is “expert opinion”.

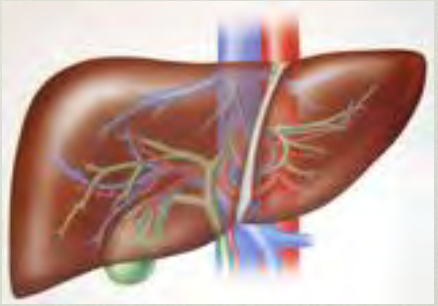
Judging the Likelihood of Drug-Induced Liver Injury

Image: www.richardtimothy.com

Judging the Likelihood of DILI

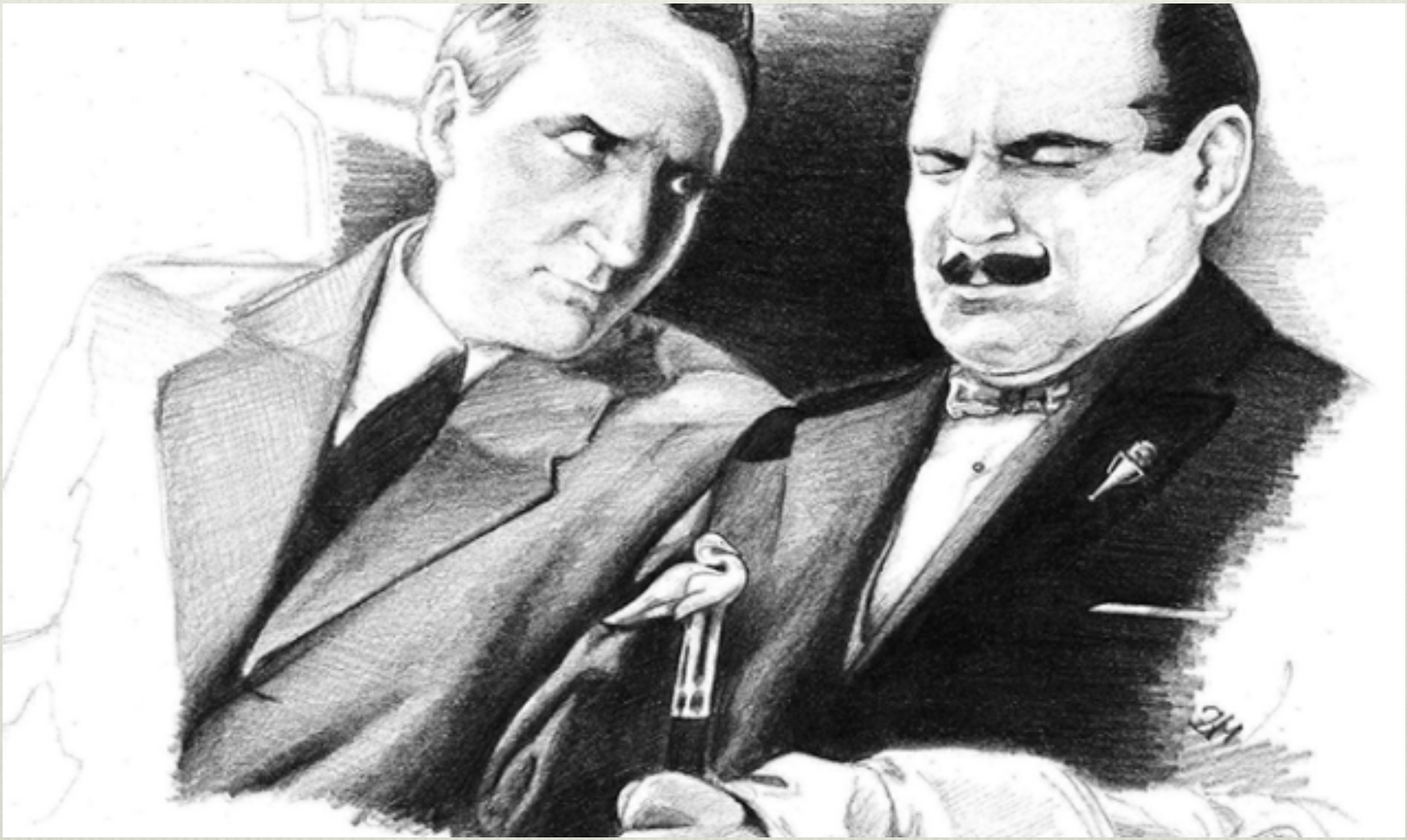
(1)

- Time to onset (after starting the drug)
- Time to recovery (after stopping drug)
- Clinical pattern (injury pattern & clinical phenotype)
- Exclusion of other causes
- Known cause (drug) of liver injury
- Response to re-exposure



Images: www.idownloadblog.com, trialx.com

Scene of the Crime



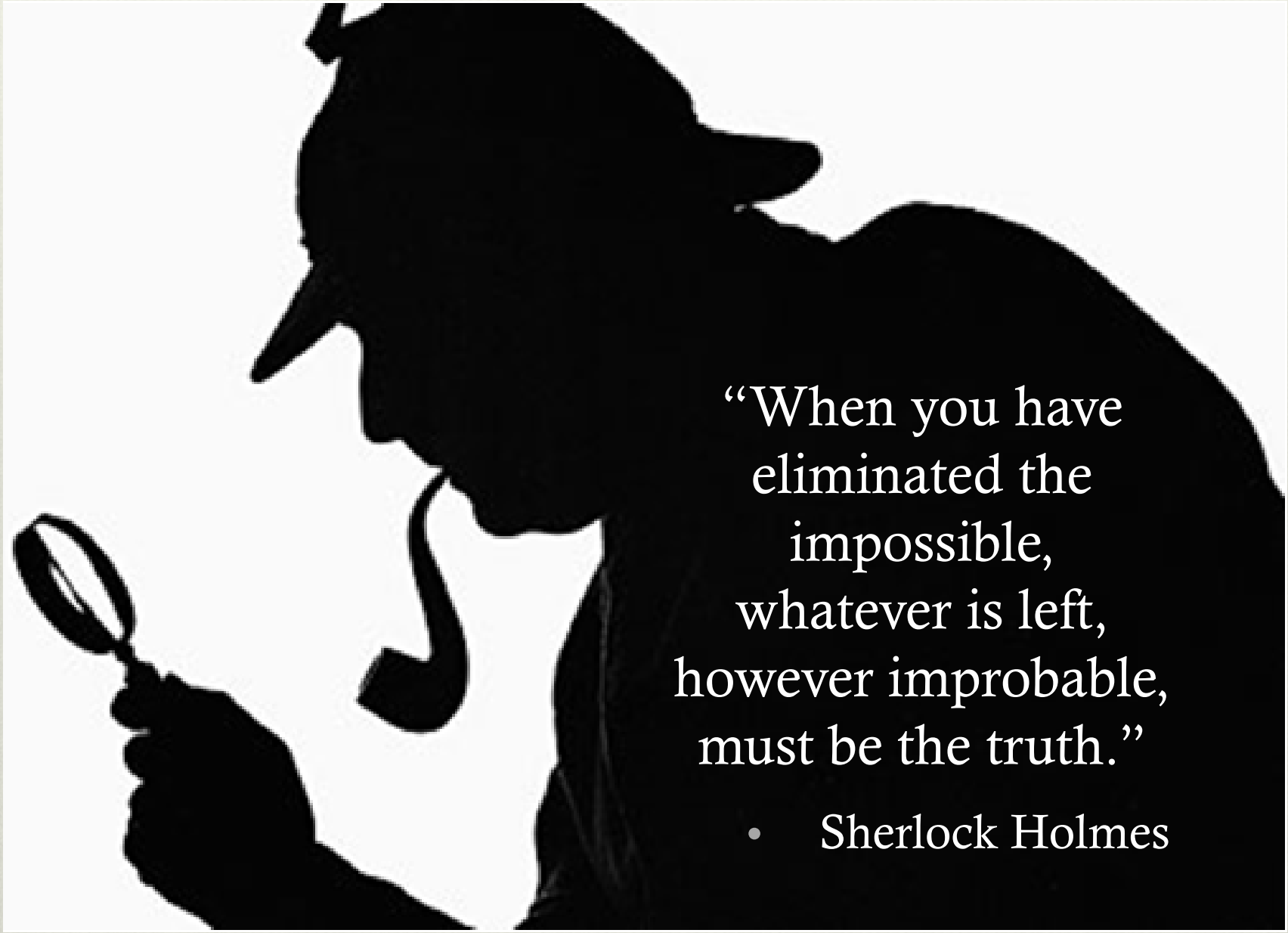


Image: www.zumahousing.com

“911, what is your emergency?”

- What tipped you off that a crime has occurred?:

- AST, ALT, bilirubin, Alk Phos, INR, albumin
- Clinical presentation:
  - Fatigue, nausea, poor appetite, dark urine, jaundice, easy bruising

A Crime (DILI) Occurs

(9)

- Was the drug in the "right place at the right time?" Does the drug have an alibi?
- Does the drug have a "prior record?"
- Are the characteristics of the crime consistent with the known signature, or modus operandi of the suspected drug?
- Are there other suspects (e.g. other possible competing causes of liver injury)?
- Is the clinical course of the reaction consistent with DILI? What's the tempo of a dechallenge? Rechallenge is generally not recommended for diagnostic purposes.

Time to Onset

(1)

- Typically between 5 days and 3 months (with exceptions)
- 24 to 72 hours onset can occur with hypersensitivity reactions
  - e.g., sulfonamides, macrolide antibiotics
- 3 to 12 months onset can occur with some drugs
  - e.g., isoniazid, flutamide
- Can occur after years of use with some drugs
  - e.g., minocycline, amiodarone, nitrofurantoin

Time to Recovery

(1)

- The time from stopping the suspected drug to full recovery from liver injury
- DILI usually starts to resolve within a few days to a week of discontinuation
- In most cases, the injury does not fully resolve for several weeks or months

Image: mombizcoach.com

Clinical Pattern

(1)

- Injury Pattern
  - Hepatocellular injury
  - Cholestatic injury
  - Mixed Hepatocellular-cholestatic injury
- Clinical phenotype

How do you know what pattern of injury you suspect?

Image: www.funwallz.com

Injury Pattern & "R" Ratio

(1)

- The R ratio is a ratio of ALT to Alk. Phosphatase (both expressed as multiples of the upper limit of normal range). The R ratio helps determine the pattern of injury.
  - R ratio of **2 or less** is used to define a **cholestatic pattern** of injury but may not always be accurate. This pattern resembles bile duct obstruction.
  - R ratio of **between 2 and 5** is used to define a **mixed pattern** of injury
  - R ratio of **5 or greater** is used to define a **hepatocellular pattern** of injury but may not always be accurate

“R” Ratio (example)

- ALT → 638 (Normal 10-40)
  - 638 ÷ 40 = **16**
- Alk. Phos. → 199 (Normal 42-128)
  - 199 ÷ 128 = **1.55**
- R ratio = **16 ÷ 1.55** = 10.3

Drug Examples & Injury Patterns

(1)

- Cholestatic injury
  - Amoxicillin-clavulanate, ciprofloxacin, and sulfonylureas
- Mixed hepatocellular-cholestatic injury
  - Sulfonamides, phenytoin, and enalapril
- Hepatocellular injury
  - Isoniazid, green tea, nitrofurantoin, and methyldopa

Clinical Phenotype

(1)

- Livertox lists about 16 “phenotypes” that overlap to some degree with the pattern of injury.
- Examples include acute hepatitis, acute hepatic necrosis, cholestatic hepatitis, mixed hepatitis, serum enzyme elevations without jaundice, nonalcoholic fatty liver, and others.
- Moreover, characteristic features or outcomes are often assigned to each phenotype such as:
  - Immunoallergic features
  - Autoimmune features
  - Acute liver failure
  - Vanishing bile duct syndrome
  - Cirrhosis

Always consider:

(1)

- Exclusion of other diagnoses
  - Acute viral hepatitis
  - Gall stone disease with biliary obstruction
  - Acute fatty liver
  - Chronic hepatitis and cirrhosis
  - Others
- Is the drug a known cause of liver injury?
  - LiverTox website (livertox.nih.gov)

Exclusion of other diagnoses

(1)

- **A careful history,** focusing on:
  - Risk factors for viral hepatitis
  - Alcohol use
  - Weight gain
  - History of autoimmune disease
  - History of cardiac failure, shock, or septicemia
  - History of all drug intake, including time of starting and stopping prescription and nonprescription (over-the-counter) drugs and herbals within the previous 3 months

Exclusion of other diagnoses

(1)

- **Laboratory test results** (and diagnoses to exclude):
  - IgM anti-HAV (hepatitis A)
  - HBsAg or IgM anti-HBc or both (hepatitis B)
  - Anti-HCV or HCV RNA or both (hepatitis C)
  - Antinuclear antibody (ANA) and globulin levels (autoimmune hepatitis)
  - Ultrasound or other radiological visualization of gallbladder and biliary system (gallstones and obstructive jaundice), and
    - Ultrasound characterization of liver quality (alcoholic and nonalcoholic fatty liver disease)

Exclusion of other diagnoses (1)

In some instances, more uncommon forms of liver disease must be ruled out.

DILI can mimic virtually any form of liver disease.

Known Cause of Liver Injury

(1)

- The Livertox website helps provide a brief description of the hepatotoxicity risk (with features) of many commonly used medications.
- Some of the drugs are rated on a likelihood scale defined by how well described and well reported, characteristic signature known, and number of case reports conclude causative likelihood.

Case Reports

Image: exchanges.wiley.com

Case Report #1

(10)

- 47 y/o woman with left frontal astrocytoma
- Admitted to hospital for a syncopal episode & control of seizures
- Medications:
  - Phenobarbital
  - Levetiracetam
  - Valproate
- While hospitalized, was started on irradiation for her brain tumor

Case Report #1

(10)

- After 1 month in hospital:
  - Seizures reasonably well-controlled
  - Developed unexplained somnolence & confusion
  - Liver tests were normal
  - Ammonia levels were markedly elevated

Case Report 1: Valproate

(10)

Days after starting	Days after stopping	ALT (U/L)	Alk P (U/L)	Bilirubin (mg/dL)	Ammonia (umol/L)	Other
0		Valproate	started:	500mg	daily	
60		15	50	0.4		Hospital admission
80		15	58	0.2		
90	0	28	59	0.1	286	
91	1				362	Valproate stopped
92	2				70	
93	3				36	
96	6	74	74	0.1	20	
103	13	90	155	0.3	37	
Normal	Values =	<42	<115	<1.2		

Key Points

(10)

- **Medication:** Valproate 500mg/day
- **Pattern:** (R=not applicable)
- **Severity:** 1+ (no jaundice)
- **Latency:** 3 months
- **Recovery:** 4 days
- **Other meds:** Phenobarbital, levetiracetam, promethazine (all were continued)

Scene of the Crime: Case #1

(9)

- Was the drug in the "right place at the right time?" Does the drug have an alibi?
- Does the drug have a "prior record?"
- Are the characteristics of the crime consistent with the known signature, or modus operandi of the suspected drug?
- Are there other suspects (e.g. other possible competing causes of liver injury)?
- Is the clinical course of the reaction consistent with DILI? What's the tempo of a dechallenge? Rechallenge is generally not recommended for diagnostic purposes, analogous to letting the criminal go free to see if he commits the crime again.

Valproic Acid

(10)

- 3 clinically distinguishable forms of DILI (besides simple aminotransferase elevations) can occur with valproate:
  1. Hyperammonemia with minimal or no evidence of liver injury
  2. Acute hepatocellular injury with jaundice
  3. A Reye-like syndrome in children who develop fever and lethargy followed by confusion, stupor and coma w/raised ammonia levels and marked ALT elevations but normal or minimally elevated bilirubin levels

Case Report #2

(11)

- 33 y/o woman treated with a 21-day course of Cotrimoxazole for sinusitis

- 1 day after stopping therapy she developed:
  - Macular rash
  - Fever
  - Right upper quadrant abdominal pain
  - Nausea

- 3 days later she was seen in emergency room with:
  - Fever
  - Rash
  - Systemic symptoms
  - And was admitted to hospital

Case Report #2

(11)

Time After Starting	**Time After Stopping**	**ALT (U/L)**	**Alk P (U/L)**	**Bilirubin (mg/dL)**	**Other**
25 days	4 days	981	195	0.5	**Hospitalization**
26 days	5 days	805	213	0.8	**Normal Ultrasound**
27 days	6 days	623	316	1.1	**Discharged**
5 weeks	12 days	156	386	0.6	**Asymptomatic**
6 weeks	3 weeks	49	168	0.4	
9 weeks	5 weeks	34	77	0.4	
Normal	Values =	<45	<130	<1.2	

Key Points

(11)

- **Medication:** Cotrimoxazole
- **Pattern:** Hepatocellular (R=14)
- **Severity:** 1+ (Anicteric)
- **Latency:** 3 weeks
- **Recovery:** 4 weeks
- **Other meds:** Multivitamins, ibuprofen

Scene of the Crime: Case #2

(9)

- Was the drug in the "right place at the right time?" Does the drug have an alibi?
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Cotrimoxazole

(11)

- Causes a characteristic idiosyncratic liver injury with features of drug-allergy or hypersensitivity resembling injury attributable to sulfonamides
- Typical onset is sudden development of fever & rash followed by jaundice within a few days or weeks of starting the medication
- Pattern is typically cholestatic or mixed
- In most recent case series, it's been ranked within the top 5 to 10 causes of drug-induced, idiosyncratic fulminant hepatic failure, however, most cases resolve resolve rapidly, usually within 2 to 4 weeks unless cholestasis is severe.
- It can also cause mild elevations in ALT that do not proceed to more severe liver injury or jaundice

Trimethoprim

(11)

- By itself also can cause idiosyncratic, clinically apparent acute liver injury.
- Onset is usually 2 to 12 weeks after starting med.
- Pattern is typically mixed or cholestatic
- Immunoallergic features are not common, unlike sulfamethoxazole
- Most instances of DILI from Cotrimoxazole are from the sulfa component

Case Report #3

(12)

- 52 y/o man without major medical illnesses given a 14-day course of amoxicillin-clavulanate (500mg/125mg twice daily) for upper respiratory infection.
- 1-2 months later, (for similar symptoms of fever & congestion), he was given a 2nd and 3rd 14-day course along with antihistamines and decongestants.
- 2 weeks after the 3rd course of antibiotics, developed abdominal pain, nausea, poor appetite, and itching, followed soon after by jaundice and dark urine.

Case Report #3

(12)

Time after starting	Time after stopping	ALT (U/L)	Alk P (U/L)	Bilirubin (mg/dL)	Other
2 weeks	0	Amoxicillin-clavulanate stopped			
4 weeks	16 days	Nausea, jaundice, arthralgia			
	16 days	879	731	3.9	Albumin 4.3 g/dL
5 weeks	3 weeks	629	503	1.7	
7 weeks	5 weeks	141	182	0.8	
10 weeks	8 weeks	90	103	0.8	
14 weeks	3 months	88	95	0.6	INR 0.9
~1 year		57	76	0.7	Albumin 4.5 g/dL
Normal Values =		<65	<126	<1.2	

Key Points

(12)

- **Medication**: Amoxicillin-clavulanate 500mg/125mg twice daily for 42 days
- **Pattern**: Mixed cholestatic-hepatocellular (R – 2.3)
- **Severity**: 2+ (jaundice, never hospitalized)
- **Latency**: 58 days, 16 days after stopping
- **Recovery**: 6 months after stopping
- **Other medications**: None

Scene of the Crime: Case #3

- Was the drug in the "right place at the right time?" Does the drug have an alibi?
- Does the drug have a "prior record?"
- Are the characteristics of the crime consistent with the known signature, or modus operandi of the suspected drug?
- Are there other suspects (e.g. other possible competing causes of liver injury)?
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Amoxicillin-clavulanate

(12)

- Currently the most common cause of clinically apparent, drug-induced acute liver injury both in the U.S. and Europe.
- Onset of injury is typically a few days to as long as 8 weeks (avg. ~3 weeks) after start of therapy & often occurs after antibiotic is completed, the delay being a few days to as long as 6 weeks.
- Pattern is typically cholestatic with marked elevations in alk. phosphatase and gamma glutamyl transpeptidase

BUT…

Amoxicillin-clavulanate

(12)

BUT…

- Aminotransferase levels, in some instances, are markedly elevated, giving a mixed OR hepatocellular pattern, particularly in younger patients with earlier onset of injury.
- In children, amox-clav. hepatotoxicity is typically anicteric and presents with nausea, vomiting and abdominal pain rather than jaundice and itching.
- The pattern of enzyme elevations is also much more likely to be hepatocellular in children, but the course of illness is typically benign.

Amoxicillin-clavulanate

(12)

- The hepatic injury is idiosyncratic and estimated to occur after ~1 in 2,500 prescriptions.
- It's more common in men than women, in the elderly, and after multiple courses.

Resources

- Livertox (livertox.nih.gov)
- Re. Herbal Supplements:
  - UpToDate. Uptodate.com. Hepatotoxicity due to herbal medications and dietary supplements
  - Natural Medicines, a combination of the databases Natural Medicines Comprehensive Database (NMCD) and Natural Standard. https://naturalmedicines.therapeuticresearch.com/
  - Navarro VJ, Khan I, Björnsson E, Seeff LB, Serrano J, Hoofnagle JH. Liver injury from herbal and dietary supplements. *Hepatology*. 2017;65(1):363–73.

Question 1

What symptoms may suggest to you that a patient is experiencing drug-induced liver injury?

Question 2

An “R” ratio of 2 or less may be suggestive of:

a) Cholestatic pattern of injury
b) Hepatocellular pattern of injury
c) Mixed hepatocellular/cholestatic injury

Question 2

An “R” ratio of 2 or less may be suggestive of:

a) Cholestatic pattern of injury
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c) Mixed hepatocellular/cholestatic injury

Question 3

Why is the diagnosis of drug-induced liver injury so challenging?

Question 4

Describe an approach to determine whether or not a patient is experiencing drug-induced liver injury?

Lastly…

Document

Document

Document!

Questions?

Image: http://forensicpsychologist.blogspot.com/2013/03/remarkable-experiment-proves-pull-of.html

References (2019 version)

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Today at noon: AK ECHO

HCV Treatment case presentations and didactic:

"HCV Elimination at a Tribal Health Facility"

https://echo.zoom.us/j/710370793

Next LiverConnect

July 9, 2019

Topic: AST and ALT are in Muscle Too!

Elizabeth Ferucci, MD

August 13, 2019

Topic: The NAFLD Epidemic

Youssef Barbour, MD

To view past presentations, visit: anthc.org/hep, click on the LiverConnect-AK ECHO link, Scroll down and select a recording to view.