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Drugs, Chemicals, Hepatotoxins: Is it the Substance or the Person?

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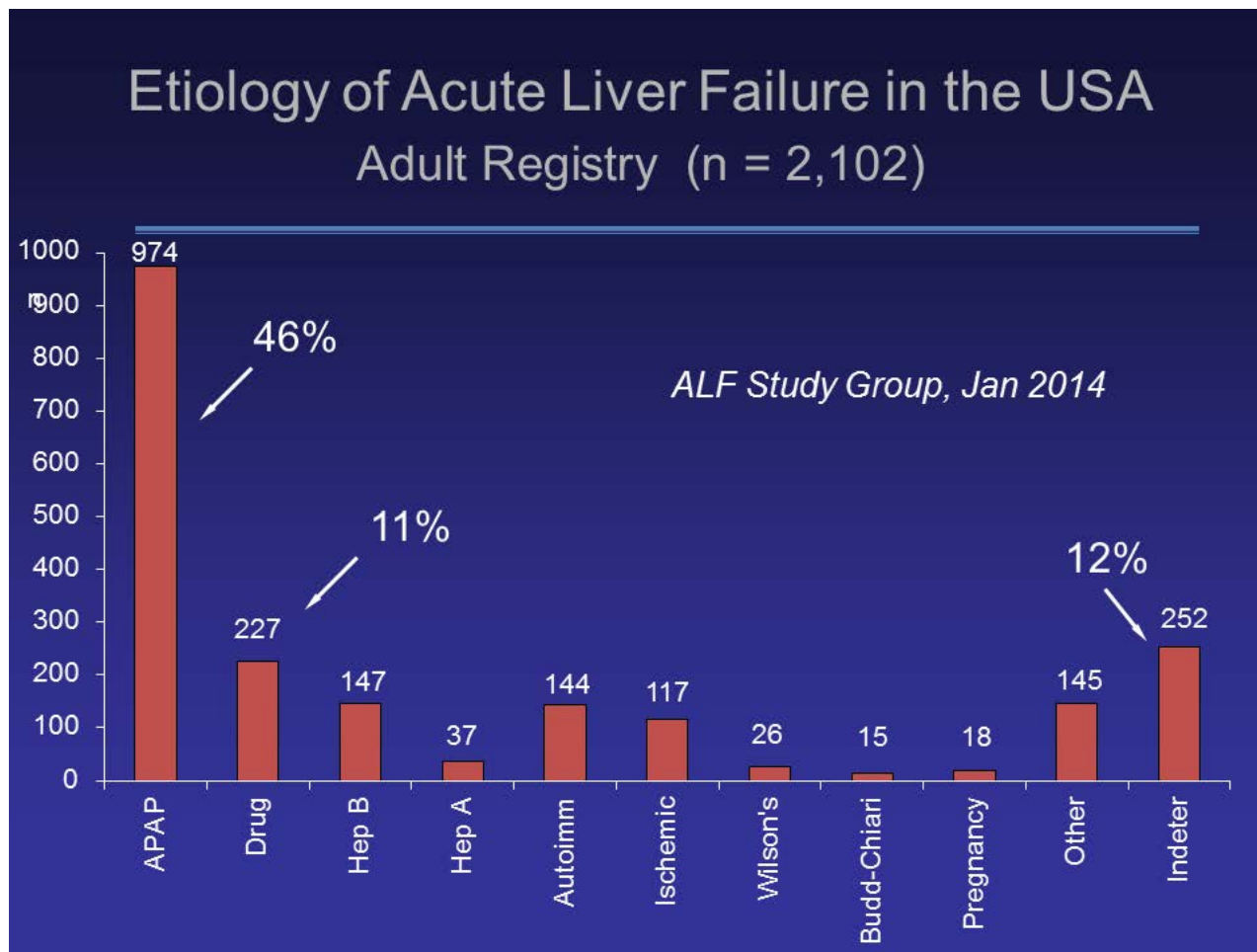


Known Facts

- DILI:
 - a major concern in medical practice and public health
 - the leading cause of acute liver failure in the world
 - major cause for drug failure in clinical trials
 - usually considered idiosyncratic
 - until 1997, it was the leading cause for withdrawal of an FDA-approved drug – **8 WDs; 4 for liver failure***
- Incidence:
 - 14-19/100,000 in general population**
 - 30-35/100,000 using EMR data*** – **under-reported?**



Data Through January 2014





Drugs Approved in 1997 and Subsequently WD for Liver Failure

Established Name Proprietary Name / Sponsor	Intended Use Toxicity	Approval Date	WD Date
Troglitazone Rezulin / ParkeDavis	Diabetes Fatal liver failure	01/29/97	05/01/02
Bromfenac Duract / Wyeth	Analgesic Fatal liver failure	07/15/97	07/03/03
Trovafloxacin Trovan / Pfizer	Antibiotic Liver Failure	12/18/97	03/09/05
Alatrofloxacin Trovan IV / Pfizer	Antibiotic Liver failure	12/19/97	03/09/05



The Fundamental Questions

- Is it a toxic drug?

OR

- An especially susceptible person?
- **How can a rare problem be the leading cause of acute liver failure, more than all diseases combined?**



Additional Facts

- The same drug may be quite safe for **most people**, but quite toxic for a few*
 - Severity
 - Consequences
 - Time course
 - Degree of causal likelihood
- The liver has an amazing capacity to recover from injury**
 - Regrows if 2/3 resected - **regenerates rapidly if hepatocytes are killed or removed**
 - Alters the activities of enzymes – **changes itself, “adapts” to injurious effects**



Problem Drugs and Individual Risk Factors

- Identification of either is always challenging!
- Dose and properties of drugs impact initial cellular damage
- Host factors drive susceptibility as well as repair
- Idiosyncrasy of the host is responsible for many of the cases of DILI after marketing*



Thoughts from Hy Zimmerman

- There are a variety of chemical agents that induce hepatotoxicity
 - inorganic
 - organic
- “Natural” substances can also be problematic
- The potential for producing injury is arranged along a **spectrum**, modified by a number of variables and involving several different mechanisms





Problem Drugs and Individual Risk Factors

- Risks in humans likely determined by multiple factors:
 - Drug properties
 - Patient attributes
 - DILI mechanisms



Drug Properties Related to DILI

- Threshold dose
- Lipophilicity
 - Affects cellular uptake
 - Affects ADMET (absorption, distribution, metabolism, excretion, and toxicity)
- Reactive metabolites
- Oxidative stress
- Mitochondrial liability



Predicting Serious Liver Injury: Challenges

- Biomarkers are not specific enough ---
- Negative rechallenge is unconvincing ---
- - - for rare events
- Positive rechallenge is powerful but dangerous
- Difficult to determine causality



As I Have Listened, I Ask, and You Should Continue to Ask...

- What makes certain people respond better to the same dose and regimen of the same drug than do others?
- What makes certain people susceptible to serious adverse effects, when most people aren't?



Listen carefully to the speakers who follow ---

- They will be touching on many of these points