Debate: Drug-Induced Liver Disease (DILI) in the West – Current Status

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Dhaka, November, 24th, 2016
East & West: depends on the viewpoint

⇒ My personal background: East (Germany)
⇒ Germany (reunified): now in the West
⇒ Thank you for the invitation to the East
Drug - induced liver injury (DILI): Outline

1. Introduction, Definition, Challenges
   - Definition and clinical importance
   - Epidemiology in the West
   - Usual suspects and new kids on the block: which drugs

2. Pathophysiology

3. Clinical management
   - Diagnosis & treatment, guideline recommendations

4. Reporting of DILI & prognosis: the western approach

5. Future developments and open questions
   - Current and future research activities

6. Summary & Conclusion
   - DILI in East & West: common viewpoints and differences
DILI: Definition and clinical importance

Adverse drug reaction manifesting in liver damage following intake of prescription drugs, over the counter treatments, herbals, dietary suppl.

- Drug-induced liver injury is a major reason for acute liver failure, drug withdrawal during treatment and boxed warnings in the western world
- Frequently responsible for non-approval of drugs and withdrawal of new drugs from the market
- Major concern for drug developers, regulators and clinicians
- Manifests in a very small subset of the population
- No clear dose relationship - therefore termed an idiosyncratic event

- Multifactorial, compound - dependent mechanisms and host-specific factors involved
- Prediction in preclinical test systems is very challenging

Funk & Roth Arch Toxicol 2016 in press
Problem 1: DIVERSITY of Reactions

- >1000 hepatotoxic drugs incl. “lifestyle drugs”, herbals, dietary supplements
- Genetic and (social) variance in humans – diversity in phenotypes
- Frequently - DILI reaction is delayed (drug is already discontinued)

⇒ Challenge for the physician taking patient’s history
⇒ Cooperation of the patient needed

Problem 2: genetic DIVERSITY in humans

⇒ Both are unpredictable

(From Yang et al. Nature Gen 2010)
DILI in the World of Hepatology

- 13% of cases with acute liver failure in the USA
- Development to cirrhosis: rare event

Chalasani et al. Gastroenterology 2008
**DILI: How frequent is the problem?**

**Epidemiology in the West**

- DILI is a rare clinical event; however, the incidence is rising in Western countries (14-19/100,000/yr.) – it’s not quantity
- ~5% of icterus cases, 10% of hepatitis cases
- 20-55% of ALF cases (40% Acetaminophen, 15% idiosyncratic),
- <1% of chronic hepatitis and liver cirrhosis

Because of under-reporting, the frequency of DILI is often underestimated

Over the past few years herbal and dietary supplements have been identified as causative agents of hepatotoxicity

DILI: Risk factors

- Multiple risk factors: mostly not well defined
  - Age (children more resistant than adults?, elderly – polypharmacy)
  - Sex (f : m = 2 : 1 for immunoallergic type of DILI)
  - Genetic determinants of drug metabolism & inflammation control (Cytochrome P450 variants, Bile transporter variants [MDR3, OATP, FXR, PPARα], HLA alleles for drug induced AIH?)
  - Rechallenge (You never know…)
  - Body-weight (e.g. Obesity: Tamoxifen)
  - Fasting (e.g. Acetaminophen)
  - Alcohol consumption (toxic dose threshold ↓ )
  - Enzyme - inducing agents (Rifampin, Phenytoin)
  - Renal and other organic diseases (accumulation, concomitant medication)

- Not much evidence that preexisting liver disease has higher incidence, but it’s always important to consider

- No difference between orally or iv. administrated drugs

Pretherapy risk assessment remains rudimentary at this time

Björnsson, Sem Liver Dis 2014
DILI: Variety of drugs and clinical course

- A variety of drugs prescribed for virtually all medical indications
- Broad spectrum of toxic liver disease ranging from mild, unspecific alternations of liver function parameters to acute liver failure
- Most relevant drugs: anti-infectives, systemic hormonal preparations, immune-suppressants, drugs for the treatment of metabolic, cardiovascular, musculoskeletal and nervous system disorders
- Results from DILIN prospective study:

  | Single prescription drug | 62 % |
  | Herbal & dietary supplements | 16 % |
  | Multiple drugs | 22 % |

  - Antimicrobials 45 %
    - Cardiovascular 10 %
    - CNS agents 9 %
    - Anti-neoplastic drugs 5 %

  Chalasani et al. Gastroenterology 2015

Natural history:

- ~1 in 10 DILI patients die or undergo LTx. within 6 months of DILI onset
- ~1 in 5 DILI patients have residual liver injury at 6 month after onset
  - generally mild
  - cholestatic

Fontana et al. Gastroenterology 2014
DILI: Most critical compounds

- Certain agents are particularly noteworthy for DILI risk

- Usual suspects:
  - Antibiotics: Amoxicillin-clavulanate continues to be the most commonly implicated agent occurring in ~1 out of 2,300 users
  - Statines (rare, overestimated, but well documented)
  - NSAID (e.g. Diclofenac)

- New kids on the block:
  - TNF-α Blockers: Infliximab
  - Immunosuppressants (Azathioprine)
  - DILI associated with the use of herbal medicines seems to be increasing

- Open questions (relevant safety signals):
  - NOACs (novel oral anticoagulants, e.g. rivaroxaban and dabigatran)
    ⇒ DILI  
  - Tyrosine Kinase Inhibitors (Imatinib, erlotinib, sorafenib, sunitinib)
    ⇒ DILI  
    (Karczmarek-Borowska & Salek-Zan 2015)
  - Checkpoint inhibitors (Ipilimumab, pembrolizumab, nivolumab)
    ⇒ Autoimmune hepatitis  
    (Abdel-Wahab et al. PLoS ONE, 2016)
Approaches to organize current knowledge

- Approaches to organize drugs into categories (based on published cases)

- Recent German case controls study identified some drugs which completely unexpected showed DILI e.g. Biperiden, mesalazine, ramipril etc.  *(Douros et al. Br J Clin Pharm 2014)*

<table>
<thead>
<tr>
<th>Drug No.</th>
<th>Ingredient</th>
<th>No. of Cases</th>
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<tbody>
<tr>
<td>1</td>
<td>Alopérol</td>
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<tr>
<td>2</td>
<td>Amiodaron</td>
<td>&gt;100</td>
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<td>3</td>
<td>Anidronic steroids*</td>
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<td>Atorvastatin</td>
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<tr>
<td>5</td>
<td>Azathioprine/Gold products*</td>
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<tr>
<td>6</td>
<td>Azathioprine/Metapropazine</td>
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<tr>
<td>7</td>
<td>Benzylpenicilin</td>
<td>&gt;100</td>
</tr>
<tr>
<td>8</td>
<td>Chloramphenicol</td>
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<tr>
<td>10</td>
<td>Cisplatin with Antioxidin</td>
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<tr>
<td>11</td>
<td>Dapson</td>
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<td>23</td>
<td>Hydroxychloroquine</td>
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<td>Nifuroxazone/Epafuroxazone</td>
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<td>Oxyphenbutazone/Propyphenbutazone</td>
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<td>38</td>
<td>Pyramamide</td>
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<td>39</td>
<td>Quinidoxine</td>
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<td>40</td>
<td>Rizatriptan</td>
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<td>41</td>
<td>Sulfinpyrazone</td>
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<tr>
<td>42</td>
<td>Sulfinpyrazone with TMP</td>
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<tr>
<td>43</td>
<td>Sulfinpyrazone</td>
<td>&gt;100</td>
</tr>
</tbody>
</table>
Editorial

DOI: 10.1111/j.1478-3231.2010.02445.x

The dark side of sports: using steroids may harm your liver

Substances: Danazole, Methandrostenolone, Methyltestosterone, Oxymetholone, Stanazole
Liver disease

Brain disease = encephalopathy (section enlarged)

Fitness and Doping: A slippery slope

CLINICAL STUDIES

Anabolic-androgenic steroids: a possible new risk factor of toxicant-associated fatty liver disease

Paulo A. Schwingel1,2, Helma P. Cotrim1, Bernardo R. Salles1, Carlos E. Almeida1, Crimério R. dos Santos Jr2, Bruno Nache1, Antonio R. Andrade1 and Cláudio C. Zoppi2

- Case control study: anabolic androgenic steroids: n=95; no AAS n=85
- Non-professional bodybuilding (>2 yrs.)
- Abdominal ultrasound and labs
- Steatosis hepatis and/or Δ aminotransferases
- C2H5OH, other drugs, other liver disease excluded
- Results: all subjects asymptomatic, however:
  TASH criteria positive in 12.6% (AAS+) vs. 2.4% (AAS-) OR: 6.0

Σ: AAS – New risk factor for TASH
Western (Ancient Greek) view: Tale of Prometheus

Mythology

Prometheus JACOB JORDAENS, 1640 – Oil on canvas

Reality

Normalization

Tolerance, no adverse effects occur

Reversibility

Mild elevation of transaminasis, adaptation

Damage, detectable functional loss

Regeneration

Serious injury, hospitalization

Reversibility?

Acute liver failure

Progression?

Symptoms

Complications, Death, LTx.

Fulminant liver necrosis

It is not that easy...

Injury & liver regeneration in DILI
**DILI: Pathophysiology**

- Obligate vs. idiosyncratic type

<table>
<thead>
<tr>
<th>Latency</th>
<th>Dose</th>
<th>Hyper-sensitivity*</th>
<th>Comment</th>
<th>Example</th>
</tr>
</thead>
<tbody>
<tr>
<td>Obligate/ intrinsic type</td>
<td>Short (hrs-days)</td>
<td>+ (strong)</td>
<td>Decreasing incidence toxic-metabolic injury</td>
<td>Acetaminophen, Asparaginase, Aspirin</td>
</tr>
<tr>
<td>Idiosyncratic type</td>
<td>Variable</td>
<td>+</td>
<td>Unpredictable, based on pharmacol. properties, Majority of cases</td>
<td></td>
</tr>
<tr>
<td>Allergic-immunologic</td>
<td>1-6 weeks</td>
<td>-</td>
<td>+</td>
<td>ANA, SMAb, IgG + Extrahepatic features &lt; 1 case/10.000</td>
</tr>
<tr>
<td>Metabolic</td>
<td>1-6 months</td>
<td>-</td>
<td>-</td>
<td>1-50 cases/10.000 Interaction with other agents: alcohol, other drugs (e.g. rifampicin)</td>
</tr>
</tbody>
</table>

*Eosinophilia, fever, rash, reactive metabolite syndrome

- Profiles (phenotypes): Hepatocellular ⇔ Mixed ⇔ Cholestatic

**Hepatocellular Prevalent**

- ALT/AP > 5

**Cholestatic Prevalent**

- ALT/AP < 2

**Mixed**

- 2 < ALT/AP > 5

**Examples**

- Hepatocellular (Elevated ALT)
  - Acarbose
  - Acetaminophen
  - Allopurinol
  - Amiodarone
  - Baclofen
  - Bupropion
  - Fluoxetine
  - HAART drugs
  - Herbs: kava kava and germander
  - Isoniazid
  - Ketocazole
  - Lisinopril
  - Losartan
  - Methotrexate
  - NSAIDs
  - Omeprazole

- Mixed (Elevated ALP + Elevated ALT)
  - Amitriptyline
  - Azathioprine
  - Capttopril
  - Carbamazepine
  - Clindamycin
  - Cypromethadine
  - Enalapril
  - Flutamide
  - Nitrofurantoïn
  - Phenobarbital
  - Phenytin
  - Sulfonamides
  - Trazodone
  - Trimethoprim–sulfamethoxazole
  - Verapamil

- Cholestatic (Elevated ALP + TBL)
  - Amoxicillin–clavulanic acid
  - Anabolic steroids
  - Chlorpromazine
  - Clopidogrel
  - Oral contraceptives
  - Erythromycins
  - Estrogens
  - Isrebarson
  - Mirtazapine
  - Phenothiazines
  - Terbinafine
  - Tricyclics

*Funk & Roth, Arch Toxicol 2016*

Mechanisms of liver injury: mimics any liver pathology

- Hepatic injury occurs in pattern specific to the affected cell organelle (disruption of membrane integrity, impaired biliary transport, apoptosis, necrosis, oxidative stress & GSH depletion, DNA binding, impaired β-oxidation, cytokine induced immune response etc.)

- Injured hepatocytes attract inflammatory cells and activate macrophages

- Cellular injury results in liver pathology resembling any liver disease:
  - Asymptomatic elevation of liver enzymes *(many drugs)*
  - ALF *(toxic: Acetaminophen, allergic: Halothane)*
  - Hepatitis *(toxic: INH, allergic: Nitrofurantoin)*
  - Cholestasis *(e.g. Amoxiclav)*
  - Steatohepatitis *(e.g. Valproic acid)*
  - Granulomes *(e.g. Allopurinol, carbamazepine)*
  - Fibrosis, Cirrhosis *(e.g. MTX)*
  - Vascular lesions, VOD *(e.g. Mitomycin, Azathioprine)*
  - Nodular regenerative hyperplasia *(e.g. Busulfan)*
  - Tumor development *(e.g. oral contraceptives)*
DILI: Clinical management

- Rare condition
  - Not well known
- Variable symptoms
- Absence of diagnostic biomarkers
- Exclusion-based diagnosis

- Thorough and extensive drug history
- Rechallenge with the suspected drug may be diagnostic, however should be avoided for safety reasons (it is unethical unless drug is essential in life-threatening disorders, e.g. tuberculosis)
- Limited therapeutic options
Diagnostic work-up according to ACG Guidelines

Suspect DILI

Drug history, record start and stop dates

Search databases e.g. LiverTox

Abnormal liver enzymes

Thorough history & physical
Complete review of medications and herbals and dietary supplements

Calculate R value*

\[ R \text{ value} = \frac{\text{Serum (ALT/ALT ULN)}}{\text{(Alk P/Alk P ULN)}} \]

- \( R \text{ value} \geq 5 \) (Hepatocellular)
- \( 2 < R \text{ value} < 5 \) (Mixed)
- \( R \text{ value} \leq 2 \) (Cholestatic)

Exclude alternative causes

Determine: Pattern of liver injury

Rule out: viral hepatitis, AIH
New pitfall: rising incidence of Hepatitis E in the West

Rule out: benign/ malignant biliary obstruction, PBC, PSC

Key questions for the DILI consultation

- Is it hepatitis (in the largest sense - hepatocyte injury)?
- Is it drug-induced? Have we excluded non-drug causes?
  - Exclude all other possibilities (viral hepatitis, alcohol, gall-stones etc.) as thoroughly as possible
  - Drug (or drugs), toxin or herbal or dietary supplement with an appropriate time frame
- Which drug is implicated?
- How sure are we that this is the agent?

- Consider latency (delay of symptoms)
- Usefulness of diagnostic scores: practicability questionable

**RUCAM (Roussel Uclaf causality assessment method)**
- Developed more than 20 years ago, classic causality assessment scoring system
- These steps mimic the approach of the experienced clinician in assessing likelihood
- Temporal relationship, course after cessation of drug, risk factors, concomitant drugs, previous information concerning the drug, search for nondrug causes (viral hepatitis), response to rechallenge (usually not available)
Is the internet helpful?

- Internet: huge variety of information; source of drugs, food, herbals, dietary supplements for everybody
  ⇒ sometimes confusing & hazardous

- Useful tools for medical professionals
  ⇒ RUCAM score as a diagnostic tool ([http://farmacologiaclinica.info](http://farmacologiaclinica.info))

  Information on the documented hepatotoxicity of drugs
Arguments pro and contra liver biopsy

- Used for differential diagnosis and prognosis
- Assessment: acute ⇔ chronic
- Technical considerations: - Which needle?
  - Which approach?
  - Blind, US/CT-guided?
- Role of liver biopsy in diagnosis: controversial

Pros:
- liver biopsy part of guideline recommendations
- generally safe procedure
- 65% concordance of histologic and clin. diagnosis (Suzuki et al. Hepatology 2011)
- evaluating severity of injury - prognosis

Cons:
- 80-90% of DILI cases resolve spontaneously (Strassburg ea. Verdauungskr 2009)
- clinical measures (Hy’s rule) robust tool to evaluate cause and prognosis
- no specific histologic phenotype
- limited therapeutic options vs. risk of invasive procedure (infect, blood loss)
- possible discordance between histologic and clinical diagnosis

⇒ Guideline: a liver biopsy may be considered...certain situations

Minocycline, nitrofurantoine, anti-TNFα, quinolones, diclofenac, methyldopa ⇒ corticosteroids as therapeutic option!

(3) When to consider a liver biopsy?

(a) A liver biopsy should be considered if autoimmune hepatitis remains a competing etiology and if immunosuppressive therapy is contemplated (Strong recommendation, low level of evidence).

Chalasani et al. Am J Gastro 2014
Therapy: Practice points

- Therapeutic options for DILI are very limited
- However: neither frustration nor over-activity are justified

First of all: Stop the offending drug!
Avoid other hepatotoxic drugs!
iv.-N-acetylcysteine not only for acetaminophen (Lee et al. Gastroenterology, 2009)
Corticosteroids:
  - Drug induced autoimmune-like hepatits: 20-40 mg/d 6 months (Minocycline, anti-TNF, quinolones, diclofenac, methyldopa etc.)
  - granulomatous hepatitis (Allopurinol)
  - hypersensitivity syndrome, signs of vasculitis
  - Open questions: Who? (ANA+/SmAb+), based on liver biopsy
    How? Dose and duration unclear

Pruritus:
  - Step up: UDCA, cholestyramine, rifampicin (Cave: toxicity)
  - Drugs with CNS activity: naltrexone, sertraline
  - Ultraviolet B phototherapy (Decock et al. J Hepatol 2012)

Rifampicin (PXR agonist, 300 mg/d) for persistant hepatocellular secretory failure - experimental, improved biliary excretion (Van Dijk et al. Liver Int 2014)
Acetaminophen/ Amanita (death cap) intoxication: special recommendations (e.g. Penicillin G and silibinin [silymarin/milk thistle]) (see: AASLD guideline 2011)
**DILI: Liver transplantation**

- Indication for liver Tx. has to be considered in case of ALF due to DILI (poor prognosis)
- Important: Early recognition and referral of ALF
- **Key observations:** Coagulopathy? Encephalopathy?
- Ethical considerations: not everywhere accepted
- Problems in the West: organ shortage and allocation
- Technical aspects: no difference to other indications (orthotopic LTx.)
- Overall very good prognosis: 5 years survival: ~70%
- No significant difference between acetaminophen toxicity or other causes of DILI

Russo et al. Liver Tranplant 2004

Mindikoglu et al. Liver Transplant 2009

Chalasani et al. Am J Gastro 2014
DILI: (Bio-)Artificial liver support

- Several devices
- Promising, but experimental
- Bridging to LTX.

Case report:
- 52-yr. old woman, 3 weeks history of jaundice, pruritus and malaise after 3 months of treatment with rofecoxib (25 mg/day, for osteoarthritis)
- Patient’s medical history: hypertension, aortic valve replacement (1981), no allergy or alcohol
- Long-standing medication: phenprocoumon, HCT, metoprolol, quinalapril, estrogen for postmenopausal disorders
- Mixed cholestatic hepatitis liver failure
- Successful treatment with MARS (improved pruritus, lowering of surrogate parameters: bilirubin, bile acids

Σ: Currently artificial liver support therapies have not shown convincing evidence for DILI treatment ⇒ remains investigational

Rofecoxib-induced cholestatic hepatitis: treatment with molecular adsorbent recycling system (MARS)

Fig. 1. Time course of total bilirubin and bile acids levels (normal range: < 6 μmol/l) during three MARS treatments (arrows). Marked clinical improvement and relief of pruritus of the patient accompanied decreasing levels of parameters.

Huster et al. J. Hepatol 2002
DILI: Reporting

- DILI is underreported condition
- Reliable epidemiologic data require a reliable diagnosis
- Prospective population-based studies are necessary for more objective estimation of DILI incidence
- Recently, nationwide and international efforts such as the DILI Network (USA), Latin DILI Network (Latin America) or the ProEuroDILI Registry (EU) have been established to compile and analyze large cohorts of retrospectively and prospectively identified cases of DILI
- Results: encouraging – better overview – comparison – learn from others

<table>
<thead>
<tr>
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<th>Spanish DILI Registry</th>
<th>SLATIN DILI Network</th>
<th>US DILI N</th>
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<tbody>
<tr>
<td>DILI cases</td>
<td>867</td>
<td>200</td>
<td>899</td>
</tr>
<tr>
<td>Age, mean</td>
<td>54</td>
<td>51</td>
<td>49</td>
</tr>
<tr>
<td>Female sex (%)</td>
<td>49</td>
<td>59</td>
<td>59</td>
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<tr>
<td>Jaundice (%)</td>
<td>68</td>
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<td>70</td>
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<tr>
<td>Hospitalization (%)</td>
<td>59</td>
<td>46</td>
<td>55</td>
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<tr>
<td>Type of injury</td>
<td></td>
<td></td>
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<tr>
<td>Hepatocellular</td>
<td>64</td>
<td>54</td>
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<tr>
<td>Cholestatic</td>
<td>19</td>
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<tr>
<td>Mixid</td>
<td>17</td>
<td>19</td>
<td>23</td>
</tr>
<tr>
<td>Liver related death or LTx. , n (%)</td>
<td>36 (4)</td>
<td>10 (5)</td>
<td>60 (6,6)</td>
</tr>
</tbody>
</table>

**DILI: Prognosis**

- Early recognition of drug-induced liver diseases and immediate discontinuation of the suspected drug is essential and renders a mostly good prognosis.

- Although rare, lethal outcomes are possible.

- **Hy’s rule**: DILI patients with:
  - Hepatocellular injury, AST/ALT ≥ 5 (3) ULN
  - Cholestasis, Total Bilirubin > 2 ULN

  ⇒ higher risk of a severe outcome (10%-50% ALF/LTx.)

- Results from DILI Networks:
  - ALF (independent risk factors: TBL, hepatocellular injury, AST/ALT, females):
    - Spanish DILI Registry: 916 cases ⇒ 36 (3,9%)
    - Latin American DILI Network: 213 cases ⇒ 11 (5,2%)
    - US DILIN: 899 cases ⇒ 60 (6,7%)

- Frequency of chronic DILI*: up to 18,9 % (generally mild)

Understanding the genetic basis of DILI is still in its infancy. However, increasing knowledge of pharmaco- and toxicogenetics may identify causative agents and risk factors and facilitate improved therapy and prognosis in the future. Test systems in development, that may predict DILI from *in vitro*. Resolving genetic susceptibility in DILI made some advances:

- **Established HLA associations in DILI**

<table>
<thead>
<tr>
<th>Drug</th>
<th>HLA alleles (selected)</th>
<th>Population affected</th>
<th>Hazard ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amoxicillin-clavulanic acid*</td>
<td>DQB1<em>0602 DRB1</em>1501</td>
<td>European</td>
<td>3.3–7.4</td>
</tr>
<tr>
<td>Fluoxacillin*</td>
<td>DRB1<em>5701 DRB1</em>0701</td>
<td>European</td>
<td>80.6</td>
</tr>
<tr>
<td>Isoniazid</td>
<td>DQB1*0201</td>
<td>Indian</td>
<td>1.9</td>
</tr>
<tr>
<td>Lappatinib</td>
<td>DQA1*0201</td>
<td>European</td>
<td>9.0–14.1</td>
</tr>
<tr>
<td>Nevirapine</td>
<td>DRB1*01</td>
<td>European</td>
<td>3.0</td>
</tr>
</tbody>
</table>

* Cholestatic liver injury possible.

Lammert Dig Dis 2016

Need for development of reliable Biomarkers (*Robles-Diaz et al Front Pharmacol 2016*).

Unfortunately pre-therapy risk assessment for DILI in the individual patient is currently very difficult: with increasing knowledge and improved models, cases of DILI might become predictable in future.
DILI in East & West: Similarities & Differences

- DILI and HILI (rising in the West)
- Antimicrobials, NSAID
- Cardiovascular, malignancies in focus
- Lifestyle drugs
- Reports of DILI in new developed drugs (e.g. NOACs, TKIs, Checkpoint inhibitors) should stimulate vigilance
- Approaches to organize huge data amounts in DILI registries for getting crucial information on phenotypes and prognosis
- New developments & basic research

- New drugs become available soon
- Other diseases in focus
- Variants in enzyme activity and metabolism (Cyt.P450)
- Basic principles are the same
- Isoniazid and other anti-tuberculosis drugs (East and West, but higher incidence of Tb in the East)
  ⇒ More by Dr. Deepak Amarapurkar
  Mumbai India

Summary & Conclusions

- The combination of analysis of large case databases with improved understanding of the underlying genetic and molecular bases of DILI may pave the way for better understanding, prevention and management of this serious global clinical condition
- General:
  Prevention - the best therapy
  ⇒ Use any drug with clear indication & care
Thank you!