Topic review - A patient with impaired liver function

Dr. Karen Hin Kwan Luk
18/1/2018
Case

• M/69
• PMH:
  1. Diabetes
  2. Hypertension
  3. Hyperlipidaemia
  4. Paroxysmal supraventricular tachycardia
  5. Cerebral vascular accident
History

• All along stable, received follow-ups in QEH SOPD for suboptimal diabetes control

• Prior to his follow up in June,
History

• Clinically admitted for further management
  – Hepatitis A / B / C / E –ve
  – ANA –ve, anti-dsDNA –ve, ANCA –ve, ENA -ve
  – Anti-SM –ve, AMA –ve, anti-LKM -ve
  – Ig pattern normal
  – Ceruloplasmin normal

• Ultrasound abdomen: normal
Drug history

- Zocor since 2012 with no recent increase in dosage
- Over-the-counter health supplement for better glucose control
- Health supplement sent for toxicology
Toxicology report

Findings:
The plant identity could not be reliably confirmed solely with the present seed specimen. No chemical analysis would be performed on the specimen.

Interpretative comment:
"向天果" usually refer to the seed of the fruit (sky fruit) of Mahogany tree (Swietenia macrophylla) and is commonly used as folk medicine in India, some African and Asian countries. However, the active constituents of the plant are uncertain and there is very limited human data on its toxicological profile.

Whether the clinical presentation of the patient was related to "向天果" intake remains inconclusive and requires further clinical correlation and exclusion of other causes.
Patient was discharged home and closely monitored in outpatient clinic.
2 weeks later...

<table>
<thead>
<tr>
<th>Most recent from the left Hospital Code</th>
<th>Page 1 of 3</th>
<th>Return to list view</th>
<th>Show Request Date</th>
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</table>

| Sodium | 145↑ | --- | 139 | 141 | 141 | --- | --- |
| Potassium | 3.8 | --- | 3.9 | 4.6 | 3.5 | --- | --- |
| Urea | 3.6 | --- | 4.3 | 3.4 | 7.0 | --- | --- |
| Creatinine | 89 | --- | 85 | 91 | 80 | --- | --- |
| eGFR(MDRD) | --- | --- | --- | >60 | --- | --- | --- |
| Protein, Total | 66 | --- | 65↓ | 66 | --- | 65↓ | 65↓ |
| Albumin | 38 | --- | 38 | 39 | --- | 38 | 37 |
| Globulin | 28 | --- | 27 | 27 | --- | 27 | 28 |
| Bilirubin, Total | 15 | --- | 17 | 13 | --- | 12 | 10 |
| Alkaline Phosphatase, Total | 85 | --- | 87 | 89 | --- | 77 | 71 |
| Alanine Aminotransferase | 788↑ | --- | 698↑ | 628↑ | --- | 597↑ | 624↑ |
| Aspartate Aminotransferase | 514↑ | --- | 459↑ | 348↑ | --- | 265↑ | 285↑ |
| Gamma-glutamyl transferase | 57 | --- | 50 | 46 | --- | --- | 38 |
| Calcium | 2.19 | --- | --- | --- | --- | --- | --- |
Thorough history revealed...

- History of insulin use with laser 2005 to one eye
- Hx of SVT (precipitated by trauma)

- Comes alone
- Walks unaided

C/O occ. palpitation
- Good drug compliance
- Fair exercise compliance

BP 122/70 P 70
H'tix 8.4 2hrpp

L/RFT normal
HbA1c 9.2↑↑

Plan of Management:
- + Betaloc 25mg bd po
- Increase diamicron
- Advice HBGM
A case of Betaloc induced liver injury?
Drug-induced liver injury
Drug-induced liver injury

• Drug-induced liver injury (DILI) can develop following the use of prescription drugs, over-the-counter medications, herbs and dietary supplements.

• It accounts for 10% of all cases of acute hepatitis.

• It is the most frequently cited reason for withdrawal of medications from the market.
Risk factors

- Adults are at higher risk than children
- Women may be more susceptible than men, in part due to smaller size
- Alcohol abuse
- Malnutrition
Classification of DILI

• Clinical presentation
  – Hepatocellular injury
  – Cholestatic injury
  – Mixed injury

• Mechanism of hepatotoxicity
  – Predictable
  – Idiosyncratic

• Histological findings
  – Hepatitis
  – Cholestasis
  – Steatosis
### Classification of DILI

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#### Classifications of drug-induced liver injury

<table>
<thead>
<tr>
<th>Type of classification</th>
<th>Examples</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical laboratory</td>
<td>Hepatocellular</td>
</tr>
<tr>
<td></td>
<td>Cholestatic</td>
</tr>
<tr>
<td></td>
<td>Mixed hepatocellular/cholestatic</td>
</tr>
<tr>
<td>Mechanism of hepatotoxicity</td>
<td>Direct hepatotoxicity</td>
</tr>
<tr>
<td></td>
<td>Idiosyncratic</td>
</tr>
<tr>
<td></td>
<td>Immune-mediated</td>
</tr>
<tr>
<td></td>
<td>Metabolic</td>
</tr>
<tr>
<td>Histologic findings</td>
<td>Cellular necrosis or apoptosis</td>
</tr>
<tr>
<td></td>
<td>Cholestasis</td>
</tr>
<tr>
<td></td>
<td>Steatosis</td>
</tr>
<tr>
<td></td>
<td>Fibrosis</td>
</tr>
<tr>
<td></td>
<td>Phospholipidosis</td>
</tr>
<tr>
<td></td>
<td>Granulomatous</td>
</tr>
<tr>
<td></td>
<td>Sinusoidal obstruction syndrome</td>
</tr>
</tbody>
</table>

Graphic 74021 Version 2.0
Classification of DILI

• Clinical presentation
  – Hepatocellular injury
  – Cholestatic injury
  – Mixed injury

• Mechanism of hepatotoxicity
  – Predictable
  – Idiosyncratic

• Histological findings
  – Hepatitis
  – Cholestasis
  – Steatosis
Clinical presentation

Type of injury often reflected by the pattern of liver function tests:

1. Hepatocellular injury:
   - Disproportionate elevation in serum aminotransferases compared with the alkaline phosphatase
   - Serum bilirubin may be elevated
   - Tests of synthetic function may be abnormal

2. Cholestatic injury:
   - Disproportionate elevation in alkaline phosphatase compared with serum aminotransferases
   - Serum bilirubin may be elevated
   - Tests of synthetic function may be abnormal

Chronicity

1. Acute: <3 months
2. Chronic: >3 months
Classification of DILI

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• Histological findings
  – Hepatitis
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  – Steatosis
Mechanism of hepatotoxicity

• Dose-dependent, predictable fashion
• Unpredictable fashion (idiosyncratic)
  – Immune-mediated
  – Metabolic
Classification of DILI

• Clinical presentation
  – Hepatocellular injury
  – Cholestatic injury
  – Mixed injury

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  – Predictable
  – Idiosyncratic

• Histological findings
  – Hepatitis
  – Cholestasis
  – Steatosis
Histology

- Acute and chronic hepatocellular injury
- Acute and chronic cholestasis
- Steatosis and steatohepatitis
- Granulomas
- Signs of hepatic venous outflow obstruction
- Sinusoidal obstruction syndrome
- Phospholipidosis
- Pelliosis hepatitis
Clinical manifestations

• Acute presentations:
  – Asymptomatic liver function abnormalities
  – Cholestasis with pruritus
  – Jaundice
  – Acute liver failure

• Chronic presentation:
  – Can resemble other causes of chronic liver disease
    e.g. autoimmune hepatitis or alcoholic liver disease
Interpretation of liver function tests

• Cholestatic injury:
  – Elevated alkaline phosphatase (ALP) >2 times upper limit of normal and / or
  – Alanine aminotransferase (ALT) / ALP ratio <2

• Mixed injury:
  – 5> ALT/ALP ratio >2

• Hepatocellular injury:
  – ALT/ALP ratio >5

• Hy’s Law: Presence of jaundice (bilirubin >2 times upper limit of normal) in association with elevation in aminotransferases >3 times upper limit of normal is associated with a worse prognosis
Signs and symptoms

• Asymptomatic
• Malaise, low-grade fever, anorexia, nausea, vomiting, right upper quadrant pain, jaundice, acholic stools and dark urine
• Chronic DILI may develop significant fibrosis or cirrhosis
• Signs and symptoms of a hypersensitivity reaction such as fever and rash may be present
Diagnosis

• Thorough history taking:
  – Retrieval of patient’s complete drug history including over-the-counter medications, natural/herbal remedies and illicit drugs
  – Time of exposure, especially important to clarify if there were non-specific symptoms
  – Duration of therapy: many drugs have somewhat consistent latency periods
    • Intrinsic hepatotoxins can produce liver damage in a few hours after exposure
    • Idiosyncratic DILI often requires between 1 week and 3 months
    • Allergic hepatotoxicity occurs within 5 weeks from exposure
    • Time to onset >3 months can be seen with compounds that act via a non-allergic mechanism
    • Symptoms may arise rapidly in patients sensitized from a previous exposure
Diagnosis

• Blood tests to exclude other causes of hepatitis
• Imaging to rule out biliary obstruction in cases of cholestasis
• Once alternative causes of hepatitis are excluded with positive history of drug exposure, liver biopsy is typically not required
• Liver biopsy considered in cases where the diagnosis remains uncertain or if there is evidence of chronic liver disease
<table>
<thead>
<tr>
<th>Test</th>
<th>Condition</th>
<th>Commentary</th>
</tr>
</thead>
<tbody>
<tr>
<td>Viral serology (HAV, HBV, HCV, HEV, CMV, EBV)</td>
<td>Viral hepatitis</td>
<td>Less frequent in older patients, especially hepatitis A; search for epidemiological risk factors</td>
</tr>
<tr>
<td>Bacterial serology (Salmonella, Campylobacter, Listeria, Coxiella)</td>
<td>Bacterial hepatitis</td>
<td>Often with persistent fever and/or diarrhea</td>
</tr>
<tr>
<td>Syphilis serology</td>
<td>Secondary syphilis</td>
<td>Disproportionately high serum ALP levels</td>
</tr>
<tr>
<td>Autoantibodies (AMA, ANA, p-ANCA, ASMA, and anti-LKM-1)</td>
<td>Autoimmune hepatitis, primary biliary cirrhosis</td>
<td>Predominantly in women, ambiguous course following dechallenge; search for other autoimmunity features</td>
</tr>
<tr>
<td>AST/ALT ratio &gt;2</td>
<td>Alcoholic hepatitis</td>
<td>Alcohol abuse; moderate increase in serum aminotransferases despite severity at presentation</td>
</tr>
<tr>
<td>Ceruloplasmin, urine copper</td>
<td>Wilson disease</td>
<td>Patients &lt;40 years</td>
</tr>
<tr>
<td>Alpha-1-antitrypsin</td>
<td>Alpha-1-antitrypsin deficiency</td>
<td>Pulmonary disease</td>
</tr>
<tr>
<td>Transferrin saturation</td>
<td>Hemochromatosis</td>
<td>Anicteric hepatocellular damage; mostly seen in middle-aged men and older women</td>
</tr>
<tr>
<td>Enhanced echotexture of the liver</td>
<td>Nonalcoholic steatohepatitis</td>
<td>Anicteric hepatocellular damage; obesity, metabolic syndrome</td>
</tr>
<tr>
<td>Serum aminotransferase levels markedly high</td>
<td>Ischemic hepatitis</td>
<td>Disproportionately high AST levels, hypotension, shock, recent surgery, heart failure, antecedent vascular disease, elderly</td>
</tr>
<tr>
<td>Dilated bile ducts by imaging techniques (AU, CT, MRCP, and ERCP)</td>
<td>Biliary obstruction</td>
<td>Colicky abdominal pain, cholestatic/mixed pattern</td>
</tr>
</tbody>
</table>
Assessing causality

• Difficult as there are no specific biomarkers or characteristic histological features that reliably identify a drug as the culprit

• Key elements for attributing liver injury to a drug include:
  – Drug exposure preceded the onset of liver injury (although the latent period is highly variable)
  – Underlying liver disease excluded
  – Stopping the drug with resulting improvement of liver injury
  – Rapid and severe recurrence in repeated exposure to the drug

• Another supporting factor: hepatic injury in exposure of drug in other patients
Course after drug withdrawal

• Rapid improvement after the withdrawal of a drug speaks in favour of a toxic aetiology
• In hepatocellular injury, the role of a drug is strongly supported by a decrease of at least 50% in liver enzyme values in the first 8 days after discontinuation
• Though less conclusive, similar decrease in liver enzymes within 30 days is also supportive
• Cholestatic and mixed types of injuries are generally considered to require a longer time for improvement, up to 6 months or more
A number of scales have been developed that attempt to codify causality of drug toxicity into objective criteria. Examples include the CIOMS Roussel-Uclaf Causality Assessment Method (RUCAM) scale and the Maria & Victorino (M&V) clinical scale. None of these scales are used routinely in clinical practice. The Drug-Induced Liver Injury Network (DILIN) developed the DILIN Causality Scoring System to adjudicate the causality of drug-induced injury. DILIN scale is not a clinically viable option for assessing causality as it relies on expert opinion.
<table>
<thead>
<tr>
<th>Components</th>
<th>RUCAM Scale [52]</th>
<th>DILIN Structured Expert Opinion Method [51]</th>
</tr>
</thead>
<tbody>
<tr>
<td>From drug intake to onset</td>
<td>+1 to +2</td>
<td>Evidence for causality is highly unlikely based on available information</td>
</tr>
<tr>
<td>From drug withdrawal to onset</td>
<td>0 to +1</td>
<td>Causality is not supported by <em>preponderance of evidence,</em> but the possibility cannot be definitely excluded</td>
</tr>
<tr>
<td>Course of the reaction</td>
<td>−2 to +3</td>
<td>Causality is supported by <em>preponderance of evidence</em> implicating the drug, but the evidence cannot be considered definite or highly likely</td>
</tr>
<tr>
<td>Risk factors</td>
<td>0 to +2</td>
<td>Evidence for causality is <em>clear and convincing</em> but not definite</td>
</tr>
<tr>
<td>Concomitant drug(s)</td>
<td>−3 to 0</td>
<td>Liver injury is typical for the drug (<em>signature</em> or pattern of injury, timing of onset, recovery). Evidence for causality is <em>beyond reasonable doubt.</em></td>
</tr>
<tr>
<td>Exclusion of nondrug causes</td>
<td>−3 to +2</td>
<td></td>
</tr>
<tr>
<td>Previous information on hepatotoxicity</td>
<td>0 to +2</td>
<td></td>
</tr>
<tr>
<td>Rechallenge</td>
<td>−2 to +3</td>
<td></td>
</tr>
</tbody>
</table>

**Implementation**

- Single user/rater
- Respond to specific questions based on patient data, clinical information and previously reported drug information
- Add up points for each question to obtain a total score
- Three independent reviewers
- All hepatologists with DILI evaluation experiences
- Assess clinical report form + clinical narrative
- Voting by full causality committee if disagreement among reviewers

**Scoring**

<table>
<thead>
<tr>
<th>RUCAM Score</th>
<th>DILIN Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;1, excluded</td>
<td>5, unlikely (&lt;25%)</td>
</tr>
<tr>
<td>1–2, unlikely</td>
<td>4, possible (25–49%)</td>
</tr>
<tr>
<td>3–5, possible</td>
<td>3, probable (50–74%)</td>
</tr>
<tr>
<td>6–8, probable</td>
<td>2, highly likely (75–95%)</td>
</tr>
<tr>
<td>&gt;8, highly probable</td>
<td>1, definite (&gt;95%)</td>
</tr>
</tbody>
</table>

RUCAM, Roussel Uclaf Causality Assessment Method; DILI, drug-induced liver injury; DILIN, Drug-Induced Liver Injury Network.
RUCAM score for this case

1. Determine the R ratio:
   \[ R = \frac{\text{ALT}}{\text{ALT ULN}} \div \frac{\text{ALP}}{\text{ALP ULN}} = \frac{532}{40} \div \frac{89}{119} = 17.8 \]
   (>5: hepatocellular injury)
2. Time of onset >90 days = 1 point
3. Course: ALT decreases by 50% within 30 days = 2 points
4. Risk factors: >55 years old = 1 point
5. Concomitant drugs: sky fruit = -1 point
6. Non drug causes: none = 2 point
7. Previous information on hepatotoxicity: cases of liver injury from the agent have been published = 1 point

Total: 6 points, probable DILI
Response to drug readministration

• The most definitive way to confirm a drug’s implication is by drug rechallenge reproducing similar symptoms
• A positive response is defined as doubling of ALT and ALP values for hepatocellular and cholestatic injuries respectively
• However rechallenge is rarely performed clinically due to ethical considerations
• In hepatocellular type of injury associated with hypersensitivity features, provoked reaction is often more severe than the initial DILI
Management

• Primary treatment is the withdrawal of offending drug
• Very few specific therapies are shown to be beneficial except:
  – N-acetylcysteine for Paracetamol toxicity
  – L-carnitine for Valproic acid overdose
• Glucocorticoids are of unproven benefits although a role may exist:
  – In patients with hypersensitivity reactions who develop progressive cholestasis despite drug withdrawal
  – Biopsy features resembling autoimmune hepatitis
  – Patients with extrahepatic manifestations of a hypersensitivity reaction
• Bile acid sequestrant may improve pruritus in cholestatic injury
Management

- Serial biochemical measurements until liver function tests return to normal
- Patients with evidence of acute liver failure should be transferred to a transplant centre
Prognosis – acute liver injury

- Majority will experience complete recovery once the offending medication is stopped
- Jaundice can take weeks to months to resolve
- Poor prognostic factors:
  - Bilirubin >2 times upper limit of normal and ALT >3 times upper limit of normal. Mortality rate as high as 14% and 80% if acute liver failure develops
  - Acute liver failure due to antiepileptics in children
  - Acute liver failure due to Paracetamol requiring haemodialysis
  - Elevated serum creatinine
  - Presence of pre-existing liver disease
- Overall prognosis of purely cholestatic injury is better than that for hepatocellular injury
Prognosis – chronic liver injury

• Chronic injury generally resolves upon discontinuation of offending drug
• Cholestasis may take months to resolve
• Gradual progression to cirrhosis can be seen without manifestation of clinical illness
Reported hepatotoxicity of beta blockers - Labetalol

Case Report

Hepatocellular Necrosis Associated With Labetalol

R. Craig Long, MD, PharmD; Marion R. Wofford, MD, MPH; Kimberly G. Harkins, MD; Deborah S. Minor, PharmD
Reported hepatotoxicity of beta blockers - Labetalol

• 51-year-old African American female presented with hypertension on Diltiazem
• Started on Labetalol 200mg BD and Diltiazem was discontinued
• After 8 weeks, her blood pressure remained high
• Hydrochlorothiazide 25mg daily was added and Labetalol was increased to 300mg TDS
• 4 weeks later, she developed jaundice, nausea, abdominal pain, fatigue and tea-coloured urine
• On examination blood pressure >300/130mmHg and her liver enzymes were elevated
  – ALT 1102, AST 757, total bilirubin 7
• Viral hepatitis markers / autoimmune markers / iron profile / copper, ceruloplasmin were normal
• Ultrasound of the liver and gallbladder showed no evidence of obstruction
• Hydrochlorthiazide was initially suspected to be the culprit of the liver toxicity due to the temporal relationship hence was discontinued
• Her blood pressure and liver function improved
• 1 week after, she reported weakness, malaise and decreased appetite
• Blood pressure was 220/110mmHg
• Liver function tests:
  – Total bilirubin 24mg/dL, ALT 4026 IU/L, AST 5753 IU/L, INR 2
• She was admitted to the hospital and all anti-hypertensives stopped
• Liver biopsy was performed:
  – Hepatitis with bridging necrosis with no areas of collagenation
• Her liver function improved gradually
• Nevertheless, she developed subfulminant liver failure, hepatic encephalopathy and hepatorenal syndrome
• She underwent liver transplantation
Other reports on Labetalol

• First published report was by Douglas and associates in 1989
• 11 reports of labetalol-induced liver injury were written by Clark and colleagues in 1990
Reported hepatotoxicity of beta blockers - Propranolol

- Mild to moderate elevations in serum aminotransferase levels in <2% of patients
- Usually transient and asymptomatic
- Impaired liver function resolves even with continuation of the drug
Reported hepatotoxicity of beta blockers - Atenolol

Atenolol Hepatotoxicity: Report of a Complicated Case

Jérôme Dumortier, Olivier Guillaud, Aurore Gouraud, Gabriella Pittau, Thierry Vial, Olivier Boillot, and Jean-Yves Scoazec
• 57-year-old female presented with liver failure and life-threatening cholestasis and chronic ascites
• On Atenolol for 3 years for hypertension
• Extensive investigations performed were unable to reveal the cause of her liver disease
• Liver transplant was performed in Nov 2006
• Histology showed macronodular cirrhosis with mild inflammatory activity; mild to moderate inflammatory infiltrates containing lymphocytes and occasional plasma cells; unusually high numbers of piecemeal necrosis
• 4 months later, liver function was normal and Atenolol was reintroduced due to the recurrence of hypertension
• 1 month later, patient presented with deranged liver function again:
  – AST 351 IU/L, ALT 789 IU/L, ALP 278 IU/L, GGT 244 IU/L, total bilirubin 2.3, INR 1
• Other causes of liver impairment were excluded. Doppler ultrasound was normal.
First post liver transplant liver biopsy

- First post liver transplant biopsy was performed in Apr 2007

- Histology
  - A combination of portal and centrilobular inflammatory lesions.
  - Inflammatory infiltrates were mild to moderate in portal spaces, contained scattered eosinophils and were associated with focal epithelial biliary lesions and focal endothelialitis.
  - Centrilobular areas: lesions were severe; large areas of confluent hepatocellular necrosis surrounded by an inflammatory infiltrate containing lymphocytes and plasma cells
  - Scattered figures of hepatocellular necrosis were observed

- Pathological diagnosis of suspected acute rejection was doubtful by the pattern and intensity of centrilobular lesions
• Nevertheless, patient was treated as acute rejection and steroids were started
• Improvement in liver function was seen afterwards
Second post transplant liver biopsy

• Second liver biopsy 2 weeks later
• Histology showed:
  – Complete disappearance of portal inflammatory lesions
  – Persistence and even increase of centrilobular lesions
  – Large areas of confluent necrosis in centrilobular areas surrounded by inflammatory cells
• Toxic hepatitis was suspected and Atenololol was stopped Apr 2007
• In Jun 2007, liver function was normal again
Control liver biopsy

• Control liver biopsy 7 months later
  – Disappearance of centrilobular lesions
  – No fibrosis
  – Only small foci of pigmented macrophages around the centrilobular veins
Reported hepatotoxicity of beta blockers - Atenolol

• Associated with mild to moderate elevations of serum aminotransferases in 1%-2% of patients
• Elevations are usually asymptomatic and transient
• Few instances of clinically apparent, acute liver injury attributable to atenolol have been reported
• Onset of injury has been reported to be within 1 to 4 weeks
• Pattern: hepatocellular or mixed in nature
As for our patient

- Betaloc was stopped immediately after the second admission

- His latest liver function is normal
Use of beta-blockers in liver cirrhosis

- Non-selective beta blockers (NSBBs) has been the cornerstone in the treatment of portal hypertension.
- The potential benefits of early initiation of NSBBs have gone beyond mere prevention of variceal bleeding.
- Potential detrimental effects of its use in patients with advanced disease has continuously evolved.
- NSBBs decrease portal venous inflow through a decrease in cardiac output and through splanchnic vasoconstriction.
Use of beta-blockers in liver cirrhosis

• In patients with advanced cirrhosis, current guidelines recommend titration to maximum tolerated dose, commonly titrated to target HR 50-55 bpm.

• In patients with refractory ascites, NSBBs were in the past thought to theoretically precipitate the decrease in cardiac output and lead to renal dysfunction and death and maybe higher mortality.

• Subsequent studies show that NSBBs do not increase mortality or can actually improve survival.
Use of beta-blockers in liver cirrhosis

- In patients with higher MELD and lower mean arterial pressure, the probability of survival was not different between those who continue and discontinue NSBBs
- Chosen NSBBs should be constantly reevaluated by assessing systemic haemodynamics, as dose adjustments might be necessary due to liver disease progression or circulatory stress
Take home message

• Diagnosis of DILI requires high index of suspicion with thorough history taking
• Key elements for attributing liver injury to a drug include:
  – Drug exposure preceded the onset of liver injury (although the latent period is highly variable)
  – Underlying liver diseases excluded
  – Stopping the drug with resulting improvement of liver injury
  – Rapid and severe recurrence in repeated exposure to the drug
• Causality assessment by scoring system not usually used clinically
• Prompt withdrawal of the culprit agent remains the cornerstone of treatment
• Liver biopsy is not necessary for the diagnosis of DILI
• Use of NSBBs in liver cirrhosis has not been shown to increase mortality with careful titration of dosage
References


