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IN SCIENCE AND TECHNOLOGY

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How to face a DILI suspicion.

A clinical algorithm for diagnostic approach

PRO-EURO DILI NETWORK
Prospective European Drug-induced Liver Injury Network

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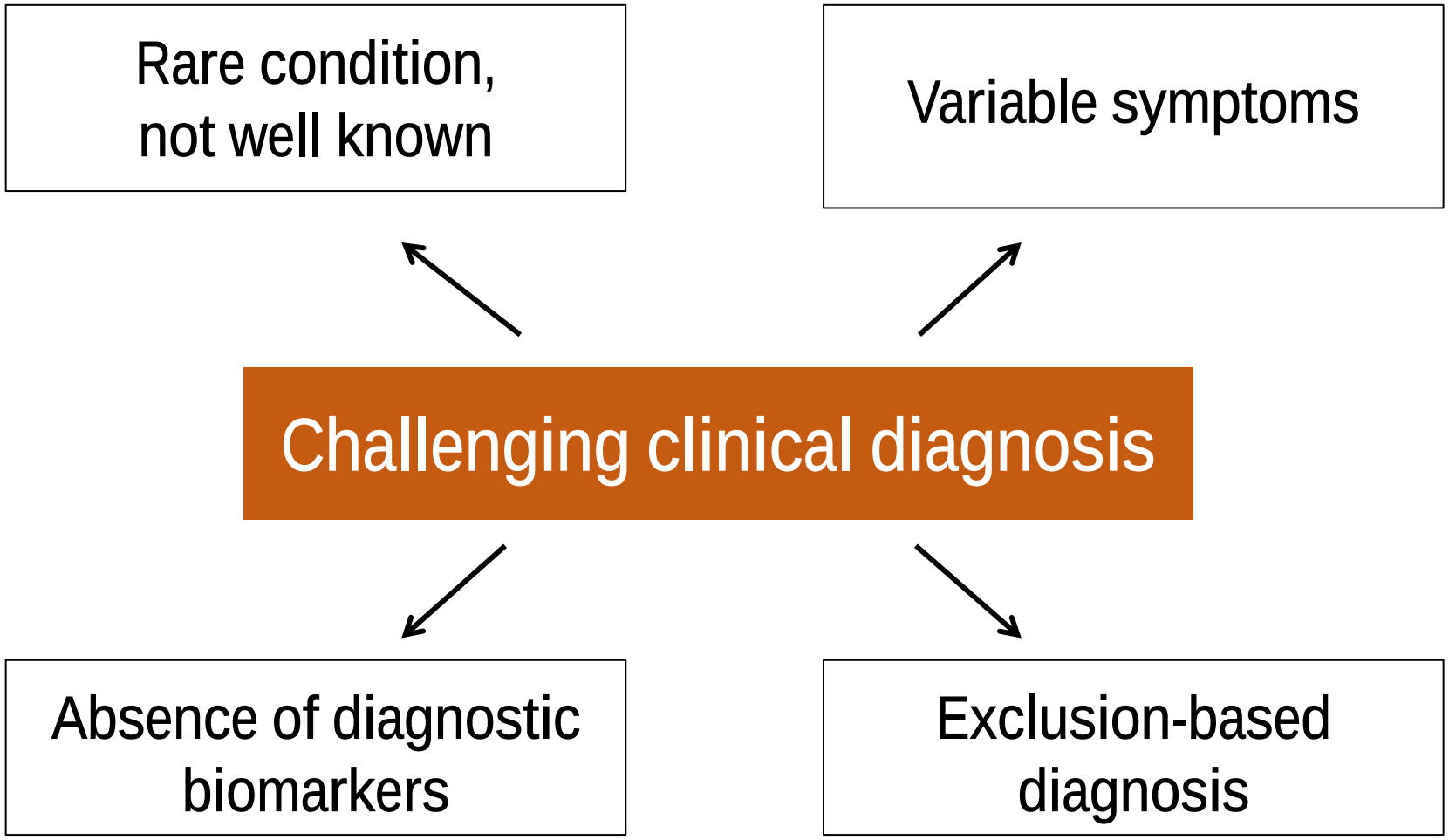
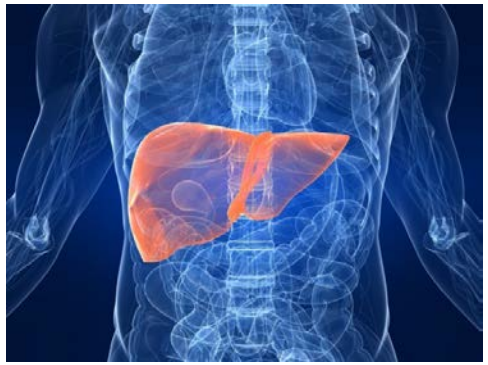

Rare condition, not well known
Variable symptoms
Challenging clinical diagnosis
Absence of diagnostic biomarkers
Exclusion-based diagnosis



DILI presentation

3.9-6.7%

Robles-Díaz *et al*, Gastroenterology, 2014

Chalasani *et al*, Gastroenterology, 2015

Death / Tx

Acute liver failure

Serious injury, hospitalization

Detectable slight liver functional loss

Just enzyme elevations, mostly adaptation

Patent tolerate exposure – no adverse effects occur

DILI diagnosis

Prompt recognition of DILI is important as continued medication after DILI onset increases the risk of :

- severe liver injury
- chronic liver injury

A correct diagnosis can:

- avoid delays in subsequent treatments
- detect early hepatotoxicity signals in marketed drugs
- prevent inadvertant reexposure to the causative agent

Some patients leave the hospital with a diagnosis of hepatitis of unknwon ethiology. If they are DILI patients: risk reeposure

Definite DILI diagnosis

- A definite DILI diagnosis is rarely made in clinical practice
- Rapid development of hepatitis after overdose exposure to agents capable of inducing intrinsic (type A) liver injury

  - paracetamol

  - aspirin
  - mushroom intoxication (e.g. *Amanita phalloides*)

  - industrial compounds (e.g. carbon tetrachloride)

- Close relationship between severity of liver injury and compound plasma level

Difficulties in diagnosing idiosyncratic DILI

- Lack of specific biomarker or clinical tests to ascertain a diagnosis
- Treated disease itself may be associated with liver abnormalities
- Presence of underlying chronic liver disease
- Atypical presentation: autoimmune hepatitis-like features, chronic liver injury
- Multiple drug treatments prior to DILI onset
- Self-treatment with over-the-counter medications, herbal remedies and dietary supplements

Clinical chemistry criteria for DILI

- **ALT ≥** 5 xULN
- **ALP ≥** 2 xULN
- **ALT ≥** 3 xULN

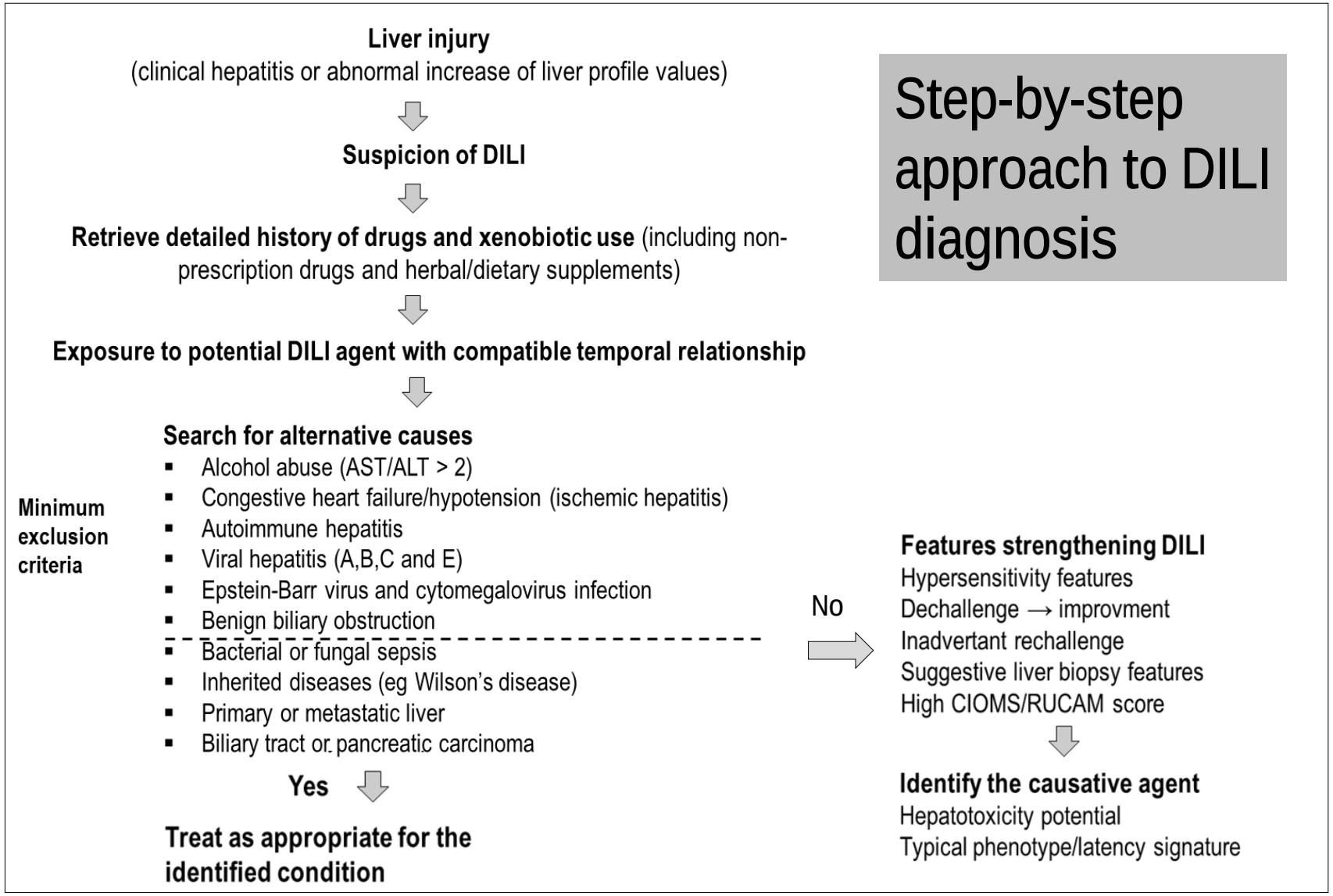
  \+

  TBL > 2 xULN

In case of abnormal liver biochemistry prior to DILI onset, ULN should be replaced by the mean baseline values obtained prior to exposure to the causative drug.

Aithal *et al*, Clin Pharmacol Ther, 2011

Step-by-step approach to DILI diagnosis



García-Cortés *et al*, J Hepatol, 2011

Pharmaceutical history

- Detailed history of drug intake in the last 6 months prior to symptoms initiation

- Not only prescription drugs, but remind patient to also reveal any recent use of:

  - over-the counter medications
  - herbal and dietary supplements
  - recreational drugs

…..which the patient may not always consider as ‘medication

Compatible temporal relationship

- Establish that the **DILI symptoms occurred after drug intake** and not to confuse with those symptoms that form part of the condition that required the treatment
- The usual **time from drug intake to DILI onset can vary**, but is often somewhat consistent for a specific drug
- Most DILI cases occur **within 3 months** from drug treatment initiation
- **Shorter latency** (often days) may occur if the patient experience a second DILI episode from the same drug (**reexposition**)

Compatible temporal relationship

- Although most DILI episodes **start while the patient is still taking the drug**
- Some drugs can produce DILI with **delayed onset:** DILI symptoms start after drug treatment has finished
- Amoxicillin-clavulanate typically induces liver injury several weeks after drug cesation

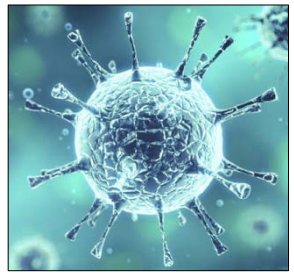
Compatible temporal relationship

- In DILI patients on **multiple drug treatments** attention should be paid to the **last introduced drug**, which is usually the responsible drug

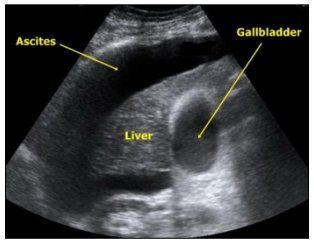
- However, when a drug with known hepatotoxic potential has been taken before the last introduced medication we should consider the **combination of the two drugs** and possible **pharmacokinetic interactions**

Exclusion of alternative causes

DILI is an exclusion based-diagnosis

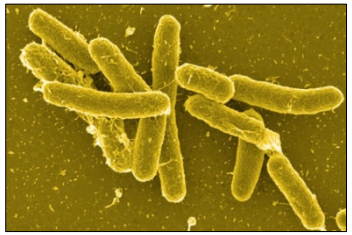


- HAV, HBV, HCV, HEV, EBV, CMV serology → **viral hepatitis**
- Autoantibodies (ANA, ASMA, AMA, LKM-1) → **autoimmune hepatitis, PBC**
- Congestive heart failure, hypotension → **ischemic hepatitis**



- Abdominal imaging test → **biliary obstruction**
- Alcohol intake → **alcoholic hepatitis.** AST/ALT >2
- Transferrine saturation → **haemochromatosis**

- Ceruloplasmin → **Wilson's disease**
- Alfa-1 antitrypsin → **A1AT deficiency**

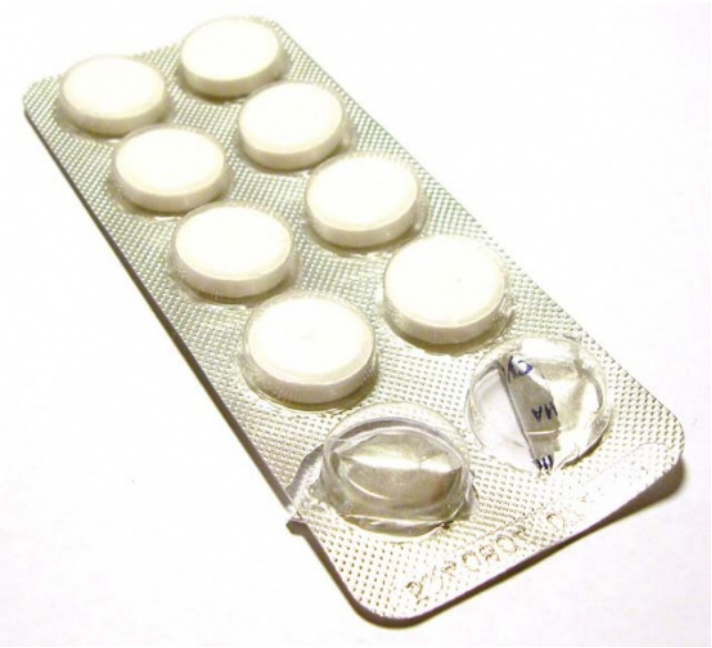


- *Salmonella, Campylobacter, Listeria, Coxiella* serology → **bacterial hepatitis**

Features strengthening a DILI diagnosis

Presence of hypersensitivity features

- skin rash
- fever
- peripheral eosinophilia
- lymphopenia
- arthralgia



Only present in ~25% of DILI cases
(Andrade et al, Gastroenterology, 2005)

Features strengthening a DILI diagnosis

Improvement of liver damage after drug cessation

Another scenes are also possible in DILI:

- Some DILI cases can continue to produce liver profile elevations after drug cessation before improving or in some cases progress to acute liver failure resulting in death or liver transplantation

- Spontaneous improvement despite drug continuation (‘adaptation’) occurs with some drugs, such as isoniazid

- Majority of DILI cases return to normal liver profile values ≤ 1 year from DILI onset, but a small proportion require >1 year (chronic DILI) Medina-Caliz et al (*J Hepatol, 2016*) found that 92% of 298 DILI patients resolved within a year and 8% were chronic

Features strengthening a DILI diagnosis

Positive rechallenge

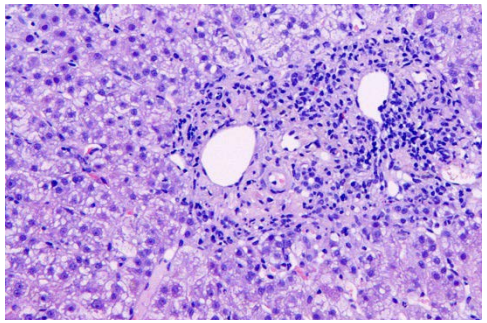
- Drug rechallenge is the **'proof'** of DILI, but is **not performed for diagnostic purposes** due to risk of a new severe episode

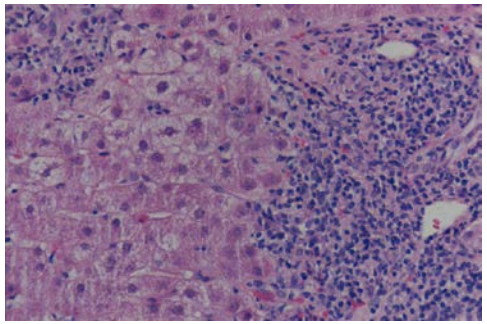
- **Inadvertent rechallenge** may occur due to **lack of information**. Always **enquire about previous use** of suspected causative agents

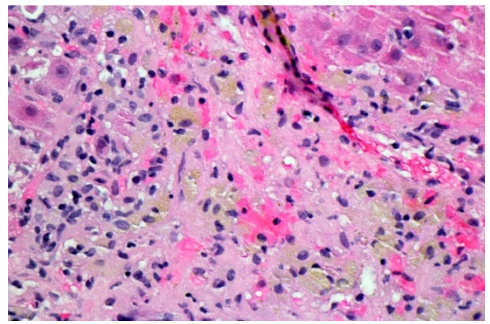
- Drug rechallenge do **not always produce a reaction similar to the first** DILI episode

Liver biopsy in DILI diagnosis

- Liver biopsy findings do not confirm DILI
- A liver biopsy in a potential DILI patients is only performed for prognostic purposes and for clarifying ambiguous cases







High CIOMS/RUCAM score

CIOMS/RUCAM scale is the **most commonly used causality assessment scale** in DILI diagnosis

A high CIOMS/RUCAM score increases the probability of a case being drug-induced, but a low score does not necessarily exclude a DILI diagnosis

….more details in later presentation

Identify the causative agent

Hepatotoxicity potential

- The hepatotoxic potential varies between drugs, with some drugs being more prone to produce DILI than others
- LiverTox (www.livertox.nlm.nih.gov) is a valuable source of information on hepatotoxic potentials of a wide range of drugs

- It also provides information about the typical pattern or signature of some drugs
- It can help us to identify the causative agent when there are more than one drug with compatible temporal relationship

Identify the causative agent

Drugs with typical phenotype/latency signature

- Amoxicillin-clavulanate: **delayed onset** after drug cessation, generally **cholestatic** type of liver injury
- Isoniazid: Onset **2 weeks – 6 months** from drug initiation; mainly **hepatocellular** type of liver injury, **mild transient transaminases elevations** occur in 10-20% of users; can induced **antinuclear antibodies**
- Nitrofurantoin: Often produced **after long term therapy** (months to years), frequent presentation of **autoimmune features**
- Anabolic Androgenic Steroids: mild increase in transaminases and very high levels of bilirubin

Clinical challenges in DILI diagnosis

- Underlying liver conditions
- Autoimmune hepatitis
- Herbal and dietary supplements

DILI in patients with underlying liver condtions

Chronic viral hepatitis

- Check potential increase in viral load
- Chronic viral hepatitis can be a risk factor for specific forms of DILI, eg HBV and anti-TBC hepatotoxicity
- Liver profile values prior to drug intake should be used instead of ULN

Cirrhosis

- Mild elevations in transaminases without meeting biochemical criteria
- Increase in bilirubin and alteration in coagulation parameters
- Many times impossible to distinguish of decompensations in cirrhotic patients

Autoimmune features

Suspected DILI cases with autoimmune features can be:

- **Idiopathic autoimmune hepatitis coinciding with drug-intake** in a patient with previously diagnosis or not
- **Drug-induced autoimmune hepatitis**
- **DILI with autoimmune hepatitis-like features**
  - Drugs known to cause autoimmune features include: nitrofurantoin, minocycine and statins (de Boer *et al*, Clin Gastroenterol Hepatol, 2016; Perdices *et a*l, Rev Esp Enferm Dig, 2014)
  - ~30% of patients in the Spanish DILI registry present positive autoantibody titres during the DILI episode
- **Important to differentiate idiopathic AIH from drug- induced AIH**
- **Most of DILI patients with autoimmune features have a spontaneus recovery**

DILI due to herbal and dietary supplements (HDS)

The use of HDS products is increasing and likewise the identification of HDS DILI cases

Difficult to determine the exact causative agent as many HDS products contain multiple compounds or are taken together with other HDS products

Lack of summary of product characteristics and detailed product informations

Many times patients do not report the use of these products

Conclusions

- The diagnosis of idiosyncratic DILI continues to be a major challenge given its heterogeneous clinical presentation and lack of specific diagnostic biomarkers
- An accurate pharmacological history and exclusion of alternative causes are of paramount importance to DILI diagnosis
- Recognition of hypersensitivity features should not be overlooked
- Liver biopsy findings do not confirm DILI; a liver biopsy in a potential DILI patients is only performed for prognostic purposes and for clarifying ambiguous cases
- Assesment scales such as CIOMS scale and the use of databases such as livertox are very useful tools in DILI diagnosis

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