Drugs-induced liver injury

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Drug-induced Liver Injury

Authors: Dev Katarey\textsuperscript{1,2} (MRCP, MSc), Sumita Verma (MD, FRCP)\textsuperscript{1,2}

Affiliation:
\textsuperscript{1}\text{Department of Medicine, Brighton and Sussex Medical School, University of Sussex, Brighton, BN1 9PX}
\textsuperscript{2}\text{Department of Gastroenterology and Hepatology, Brighton and University Hospital Brighton, United Kingdom, BN2 9JA}

Correspondence to
Dr Sumita Verma
Reader in Medicine, Honorary Consultant Hepatologist
Medical School Teaching Building, Room 2.17
Brighton and Sussex Medical School
Falmer, Brighton, BN1 9PX, UK
Email: s.verma@bsms.ac.uk

Word Count:
2737
Abstract
Drug-induced liver injury (DILI) remains the most common cause of acute liver failure (ALF) in the western world. Excluding paracetamol overdose, nearly all DILI encountered in the clinical setting is idiosyncratic in nature, since affected individuals represent only a small proportion of those treated with such drugs. In many cases the mechanism for idiosyncrasy is immune mediation and is often identified by genetic risk determined by HLA variants. In the absence of diagnostic tests and/or biomarkers, the diagnosis of DILI requires a high index of suspicion after diligently excluding other causes of abnormal liver tests. Antibiotics are the class of drugs most frequently associated with idiosyncratic DILI, though recent studies indicate that herbal and dietary supplements are an increasingly recognised cause. It is imperative that upon development of DILI the culprit drug be discontinued especially in the presence of elevated transaminases (AST/ALT ≥5ULN) and/or jaundice. Risk factors for the development ALF include hepatocellular DILI and female gender, the treatment being supportive with some benefit of N-acetylcysteine in early stages. In view of the poor transplant-free survival in idiosyncratic DILI, early consideration for liver transplant is mandatory.

Keywords
Hepatotoxicity, Hepatocellular DILI, Herbal and dietary supplements, Cholestasis, Autoimmune hepatitis, Drug induced acute liver failure
Introduction
At a regulatory level drug-induced liver injury (DILI) is the commonest reason for withdrawing drugs from the market and/or issuing warnings and modification of use.\textsuperscript{1} DILI is classified as predictable and unpredictable (idiosyncratic).\textsuperscript{2} The former tends to be dose-related, has a short latency (days), is due to direct toxicity of the drug or its metabolite, and is reproducible in animal models (e.g. paracetamol overdose).\textsuperscript{3} The vast majority of DILI, however, is idiosyncratic or unpredictable – it is unexpected based on the pharmacological actions of the drug and in most cases routine animal toxicology fails to identify the risk of subsequent clinical toxicity.\textsuperscript{4} This review shall largely focus on idiosyncratic DILI.

Epidemiology
Idiosyncratic DILI is an uncommon adverse event when taking prescription or non-prescription medications. It is difficult to assess the true incidence of DILI due to different diagnostic criteria and under reporting.\textsuperscript{5} However, recent population based studies estimate the incidence to vary between 13.9-19.1 cases per 100,000 people per year\textsuperscript{5,6}.

Data from prospective DILI registries suggest that antibiotics remain the most common cause of idiosyncratic DILI. The American DILI Network (DILIN) reported antibiotics to be implicated in 45.4\% of cases.\textsuperscript{7} Other common drug classes reported by the American DILIN were herbal and dietary supplements (HDS; 16.1\% which represents a significant increase over the last 10 years), cardiovascular agents (9.8\%), central nervous system agents (9.1\%), anti-neoplastic agents (5.5\%), and analgesics (3.7\%).\textsuperscript{7} Amoxicillin-clavulanate is the most common individual drug implicated in DILI as confirmed by both European and American studies (Table 1).\textsuperscript{6-10} In some Asian countries however, HDS are implicated in >70\% of all DILI.\textsuperscript{11}

DILI includes the whole spectrum from asymptomatic elevation in liver tests to acute liver failure (ALF). In fact, DILI remains the most common cause of ALF in the United Kingdom (UK)\textsuperscript{12} and United States.\textsuperscript{13} Specifically, in the UK, paracetamol overdose causes approximately 57\% of all ALF with non-paracetamol drugs accounting for a further 11\%.\textsuperscript{12} In idiosyncratic DILI approximately 4\% progress to ALF, risk factors
being female gender (70%) and hepatocellular DILI (80%).\(^8\) The drugs most commonly implicated with ALF include anti-tuberculosis therapies (ATT), HDS, sulpha-containing drugs, nitrofurantoin, phenytoin, sodium valproate, flutamide and amoxicillin-clavulanate.\(^8,14\)

### Types of DILI

Idiosyncratic DILI can be classified according to the pattern of liver tests observed – hepatocellular, cholestatic, or mixed. This classification was first established by the Council for International Organizations of Medical Sciences (CIOMS)\(^15\) and has recently been modified by the US FDA Drug Hepatotoxicity Steering Committee.\(^16\) Hepatocellular DILI is characterised by an alanine aminotransferase (ALT) ≥3x upper limit of normal (ULN) and ALT/ alkaline phosphatase (ALP) ratio ≥5; cholestatic DILI by an (ALP) ≥2xULN and ALT/ALP ratio of ≤2; and mixed DILI with ALT ≥3xULN, ALP ≥2xULN and ALT/ALP ratio <5 but >2. Individual drugs have dispositions toward a characteristic clinical signature, however exceptions do occur. For example, amoxicillin-clavulanate usually results in a cholestatic injury but less frequently has also been associated with ALF.\(^17,18\)

Another way to classify idiosyncratic DILI is immune-mediated (allergic) or non-immune mediated (non-allergic).\(^19\) If immune-mediated, the latency is shorter (one to six weeks) compared to non-immune mediated reactions (one month to one year).\(^1,20\) However exceptions do occur with immune reactions appearing after a very long latency with drugs such as nitrofurantoin\(^21\) or even after drug cessation (e.g. sulfonamides, erythromycin, and amoxicillin-clavulanate).\(^20\) Immune-mediated idiosyncratic reactions can be characterized by presence of fever, rash, eosinophilia, autoantibodies (such as antinuclear and anti smooth muscle antibodies), and Stevens-Johnson syndrome (SJS). Non-immune mediated reactions lack the aforementioned characteristics and importantly, as described, tend to have a long latency period (one month to one year).\(^1,4,20\)

Other forms of DILI include steatohepatitis (amiodarone, tamoxifen, methotrexate),\(^22\) neoplasms [hepatic adenomas due to androgenic anabolic steroids (AAS)],\(^23\) and vascular (nodular regenerating hyperplasia due to azathioprine).\(^24\)
Pathogenesis
The pathogenesis of idiosyncratic DILI remains unknown but is most likely due to a complex interplay between drug (e.g. dose, duration of therapy, hepatic metabolism, lipophilicity) and host factors (e.g. age, gender, genetic polymorphisms). The drug may form a reactive metabolite that triggers DILI or may form covalent adducts with tissue proteins eliciting an immune response and subsequent DILI.25,26

Risk factors
Multiple factors have been found to be associated with an increased susceptibility to idiosyncratic DILI. The American DILIN found a higher prevalence of DILI in women (59% vs. 41%),7 though this was not corroborated by the Spanish DILI registry (49% vs. 51%).8 Potential reasons for increased female susceptibility to DILI include differences in various aspects of drug pharmacokinetics or pharmacodynamics; hormonal effects or interactions with immunomodulating agents or signaling molecules; and differences in the adverse response of the immune system to some drugs, reactive drug metabolites, or drug-protein adducts.27 It is consistently observed, however, that women tend to be younger and develop hepatocellular DILI whereas men tend to be older and develop cholestatic DILI.7,28

Elderly patients have almost a three-fold increase in the incidence of DILI as shown in the study from Iceland.6 This was attributed to the increased prescription rate of drugs in the elderly.6 In general, higher drug dose and longer duration of therapy has also been implicated in poorer outcomes.28-30 In the Spanish Registry, 77% of patients with idiosyncratic DILI received medications with daily doses ≥50mg.28 Ninety percent of patients with serious DILI needing a liver transplant and reported to the Swedish Adverse Drug Reactions Advisory Committee were consuming ≥50mg/day of the drug.29 A longer duration of drug therapy (135 ± 31 days vs. 53 ± 3 days, p<0.0001) has been associated with a higher liver-related morbidity and mortality.31
It remains controversial as to whether pre-existing liver disease increases susceptibility to idiosyncratic DILI. In the American DILIN 10% had pre-existing liver disease mostly due to hepatitis C and non-alcoholic fatty liver disease (NAFLD). This group was characterised by more severe liver injury, and higher overall mortality (16% vs. 5.2%, p<0.001) though similar liver related mortality (57% vs. 46%, p=0.5). The higher overall mortality in those with pre-existing liver disease may have been due to significantly higher prevalence of comorbidity, specifically diabetes mellitus (38% vs. 23%, p=0.004). Additionally, alcohol excess and/or risk factors for NAFLD increase susceptibility to methotrexate toxicity by 3-4 fold. Furthermore, some studies have shown that patients with chronic hepatitis B or C could have a three-fold increased risk of abnormal liver tests after receiving ATT. Nonetheless, the interpretation of liver injury in patients with chronic hepatitis B and C receiving ATT remains unclear – is it the ATT, reactivation/flare of the virus, or improved immune system function due to control of the tuberculosis infection leading to attack on the virus?

Genetic factors also increase susceptibility to DILI. For example, HLA B*5701 confers an 80-fold increased risk to flucloxacillin induced DILI, whereas the absence of this genotype has an 88% negative predictive value for flucloxacillin-related DILI.

In Case 1 (fig 1) we present a patient who could be considered to have flucloxacillin hepatotoxicity. However, unusual features were the young age, short duration of drug use and near normal gamma-glutamyl transferase (γGT) despite significant hyperbilirubinaemia. A more detailed history revealed the use of the dietary supplement Massdrol (which is an AAS) prior to ingestion of flucloxacillin. A subsequent liver biopsy revealed bland cholestasis characteristic of AAS hepatotoxicity (fig 2). His HLA genotype was B12/B42. HLA B*5701, which confers susceptibility to flucloxacillin-related hepatotoxicity, was not identified.

**Natural History of DILI, and Hy’s Law**

In the American DILIN, the presentation of DILI was with jaundice in 70% of cases. Most recovered after drug withdrawal, however 17% progressed to chronic DILI (defined as abnormal liver tests for longer than six months) and 10% needed a liver transplant and/or died. Mortality increased to 44% in the presence of SJS.
Compared to those with cholestatic DILI, those with hepatocellular DILI were more likely to require a liver transplant (6.2% vs. 2.9%, p<0.001) and have fatal injury (9% vs. 4%, p<0.001). Furthermore, use of non-body building HDS was associated with a significantly higher need for liver transplant compared to conventional drugs (13% vs. 3%, p<0.05). Worryingly, 7% of cases were attributed to HDS during the first two years of the American DILI registry compared to 20% ten years later. The American Acute Liver Failure Study Group (ALFSG) also recently reported that prevalence of DILI-ALF/acute liver injury cases due to HDS increased from 1998-2007 to 2007-2015 (12.4 vs. 21.1%, p=0.047). The HDS group had higher transplantation rates (56% vs. 32%, P<0.005), and a lower transplant-free survival (17% vs. 34%, p=0.044).

Specifically in hepatocellular DILI, a serum bilirubin ≥3xULN in the absence of biliary obstruction or Gilbert’s syndrome is associated with a mortality of approximately 10% (range 5-50%). This is also known as Hy’s law, in recognition of the pioneering work done by Hyman Zimmerman – an American Hepatologist. Hy’s law has now been confirmed by European and American prospective DILI registries. Hy’s law has also been adopted by the FDA as a predictor of severe DILI during clinical trials, though in the interest of patient safety the FDA has lowered the hyperbilirubinaemia required to ≥2xULN (“modified Hy’s Law”). The FDA states that “finding one Hy’s law case in the clinical trial database is worrisome; finding two is considered highly predictive that the drug has the potential to cause severe DILI when given to a larger population”.

Predicting those who are likely to develop ALF in idiosyncratic DILI is difficult, and even the application of Hy’s law provides a specificity of only 44-67% and sensitivity of 83-90%. In an attempt to improve this the Spanish DILIN developed a composite score to predict ALF: AST ≥17.3xULN; total bilirubin ≥6.6xULN, AST:ALT ≥1.5xULN. These criteria are able to determine progression to ALF with a specificity of 82% and sensitivity of 80%. This composite score, however, needs to be validated in additional prospective studies.

**Diagnosis**
Since there are no diagnostic tests or biomarkers for idiosyncratic DILI, its diagnosis is made after stringently excluding other causes of liver disease, assessing the temporal association between use of drug and abnormal liver tests, looking for a characteristic clinical drug signature, and assessing improvement in liver tests upon drug withdrawal. Drug re-challenge is rarely indicated and cannot be advocated on ethical grounds. Nonetheless, one situation where a re-challenge may be justifiable is in the treatment of tuberculosis, however, this must only be done after carefully weighing the risks and benefits and in close liaison with a Hepatologist. Finally, various causality assessment tools exist for DILI of which the Roussell Uclaf Causality Assessment Method (RUCAM) is the most utilised though it is far from perfect.

Liver biopsy can be helpful in certain situations, particularly to exclude other causes of liver disease (e.g. alcohol, NAFLD). It also has a role if “drug-induced” autoimmune hepatitis (AIH) is suspected and needs differentiating from idiosyncratic DILI. Portal and intra-acinar plasma cells, rosette formation, and emperipolysis are histological features that favour AIH (p<0.02), whereas portal neutrophils and intracellular (hepatocellular) cholestasis are more prevalent in DILI (p<0.02; Table 2). This differentiation is nonetheless based on retrospective data and in the real world differentiating “drug-induced AIH” from idiosyncratic DILI maybe far more difficult.

In Case 2 (fig 1), a subsequent liver biopsy confirmed cirrhosis with lymphoplasmacytic portal inflammation and interface hepatitis. This was suggestive of AIH. While statins have been associated with DILI including “drug-induced” AIH, it would have been very unusual for the statin to result in cirrhosis, that too within a year. This patient most likely had an underlying propensity to develop idiopathic AIH and the statin either unmasked or triggered this, or was an innocent bystander. She was treated with corticosteroids and azathioprine with good response.

**Management of DILI**

Prompt cessation of the culprit drug as soon as DILI is suspected is of paramount importance. There are also therapies for specific causes of DILI; for example, N-acetylcysteine (NAC) for paracetamol overdose and L-carnitine for valproic acid
Corticosteroid therapy in DILI has a limited role, being reserved for those with immune-mediated DILI or “drug-induced” AIH. The former may only need a short course of steroids, whereas the latter, which is often indistinguishable from idiopathic AIH, often requires prolonged courses of steroids and/or additional immunosuppression. As already stated, not infrequently, differentiating DILI from “drug-induced” AIH can be difficult, and in such situations after careful assessment of risks benefits a trial of corticosteroids may be warranted. Though ursodeoxycholic acid is often used in cholestatic DILI, this remains non-evidenced based.

**Acute Liver Failure**

Case 3 (fig 1) presents a patient who has developed ALF. Pegylated interferon alpha use has not been associated with ALF. Hepatitis B and C flares were excluded by negative polymerase chain reaction; therefore, the most likely cause was clarithromycin-induced ALF. Clarithromycin has been associated with cholestatic DILI particularly in the elderly and ALF has been reported. This patient was urgently listed for a liver transplant but unfortunately developed progressive cerebral oedema and died before he could be transplanted.

Spontaneous survival with ALF secondary to idiosyncratic DILI (non-paracetamol) is poor with only 27.1% of patients alive at three weeks, in contrast to paracetamol-induced ALF where spontaneous survival is 64-66%. Therefore it is crucial that, especially in idiosyncratic DILI, early discussion with a tertiary liver centre takes place at the first hint of ALF (worsening jaundice, coagulopathy [INR >1.5] or development of hepatic encephalopathy [HE]). With transplantation the overall survival increases to 66.2% which demonstrates the necessity to rapidly identify those with ALF due to idiosyncratic DILI. The King’s College criteria are most commonly used to prioritise patients with paracetamol and idiosyncratic DILI for liver transplant.

Two earlier randomised controlled trials (RCT) showed no benefit of corticosteroids in ALF, and even demonstrated a poorer outcome in those with DILI. A more
recent study from the ALFSG corroborated this showing no improvement in overall survival in drug induced, indeterminate or autoimmune ALF (61% vs. 66%, p=0.41). In fact, lower survival was observed in those patients with the highest Model for End Stage Liver Disease (MELD) scores (>40) after corticosteroid therapy (30% vs. 57%, p=0.03).

NAC has a well established role in paracetamol-induced ALF though is now also recommended in selected cases of non-paracetamol ALF. A recent RCT in patients with non-paracetamol ALF from the ALFSG demonstrated similar three-week survival for patients given NAC versus placebo (70% vs. 66%, p=0.283). However, transplant-free survival was significantly better for patients who received NAC compared to placebo (40% vs. 27%, p=0.043), but this was confined to those with early HE (52% vs. 30%, p=.010); whereas those with grade 3-4 HE had no benefit with NAC (9% vs. 22%, p=0.912). DILI was the most prevalent aetiology of ALF within this study.

**Conclusion**

DILI includes the whole spectrum from asymptomatic and transient elevation in liver tests to ALF. DILI due to paracetamol overdose and idiosyncratic drug reactions remains the most common causes of ALF in the western world. DILI is a diagnosis of exclusion and there remains an urgent need to develop diagnostic biomarkers. Antimicrobials remain the most common cause of idiosyncratic DILI though recent studies show a significant increase in DILI due to herbal and dietary supplements. Hepatocellular DILI is more likely to progress too ALF compared with cholestatic or mixed DILI. The management of DILI is symptomatic with prompt cessation of the culprit drug and early referral for liver transplant upon the development of ALF especially in those with idiosyncratic DILI.
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Disclosure: The authors declare no conflicts of interest related to this manuscript
References


Common drugs implicated in idiosyncratic DILI according to studies from different countries

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Table 2: Comparison of idiosyncratic DILI, “drug-induced” autoimmune hepatitis and idiopathic autoimmune hepatitis. ⁴⁶,⁴⁷,⁴⁸,⁴⁹

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<td>Relapse on steroid withdrawal</td>
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AIH = autoimmune hepatitis.
**Case 1.**
A 33-year-old male was admitted with a two-week history of jaundice. He was prescribed a five day course of flucloxacillin three weeks ago for an ingrown toenail.

Investigations demonstrated: bilirubin 120 µmol/L (peak 614 µmol/L), AST 244 iu/L, ALT 312 iu/L, ALP 130 iu/L, γGT 72 iu/L, INR 1.0. Liver screen including viral serology and imaging were unremarkable.

**Case 2.**
A 62-year-old female was referred for abnormal liver tests: ALT 125 iu/L, ALP 245 iu/L. On examination she had stigmata of chronic liver disease, and further investigation revealed a positive anti-smooth muscle antibody and elevated immunoglobulins, specifically IgG. Imaging confirmed cirrhosis. She had commenced a statin one year ago.

**Case 3.**
A 55-year-old male, co-infected with the hepatitis B (inactive carrier) and hepatitis C virus was 4 months into a six-month course of pegylated interferon alpha and ribavirin. He was non-cirrhotic and thus far had shown an excellent response to antivirals with a normal liver panel and negative hepatitis B and C PCR. He was subsequently prescribed a seven-day course of clarithromycin for a chest infection and presented a week later with jaundiced and confusion.

Investigations demonstrated: bilirubin 350 µmol/L, ALT 2000 iu/L, INR 3.0. Liver screen including viral PCR and imaging were unremarkable.

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**Fig 1:** Three cases of DILI – what is the diagnosis and management? Each case will be discussed in the manuscript. Bilirubin range = 5-17µmol/L, AST = aspartate aminotransferase (range = 10-40 iu/L), ALT = alanine aminotransferase (range = 7-56 iu/L), ALP = alkaline phosphatase (range = 45-115 iu/L), γGT = gamma-glutamyl transferase (range = 9-48 iu/L), INR = international normalised ratio (range = 0.8-1.2), PCR = polymerase chain reaction.