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EULAR CERTIFICATION COURSE IN RHEUMATIC DISEASES
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DRUG INDUCED HEPATOTOXICITY

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OUTLINE

- Definition
- Epidemiology
- Mechanism of DILI
- Types of drug reactions
- Risk factors
- Genetic risk factors
- Clinical features
- Diagnosis
- Role of liver biopsy
- Prevention
- Management
- Key points

DEFINITION

"Any liver injury caused by medication or herbal supplements that has led to biochemical abnormalities or liver dysfunction with the exclusion of other causes."

It may be of 2 types -

- Dose dependent - eg. aspirin, acetaminophen
- Idiosyncratic

EPIDEMIOLOGY

Greater than 1000 medications have been implicated in DILI, most commonly antibiotics & acetaminophen

Most cases of acute liver failure are due to DILI

Most of the cases of DILI are attributed to a single prescription drug

However, up to 18% have been the result of multiple agents

Dietary supplements have been linked to DILI in 7-9% of cases

BMC Clinical Pharmacology

BioMed Central

Research article

Open Access

Evaluation of the prevalence and economic burden of adverse drug reactions presenting to the medical emergency department of a tertiary referral centre: a prospective study

KJ Patel, MS Kedia, D Bajpai, SS Mehta, NA Kshirsagar and NJ Gogtay*

Background: Adverse drug reactions (ADRs) are now recognized as an important cause of hospital admissions, with a proportion ranging from 0.9–7.9%. They also constitute a significant economic burden. We thus aimed at determining the prevalence and the economic burden of ADRs presenting to Medical Emergency Department (ED) of a tertiary referral center in India

Methods: A prospective, observational study of adult patients carried out over a 6 week period in 2005. The prevalence of ADRs, their economic burden from the hospital perspective, severity, and preventability were assessed using standard criteria.

Results: A total 6899 patients presented during the study period. Of these, 2046 were admitted for various reasons. A total of 265/6899 patients had ADRs (3.84 %). A total of 141/265 was admitted due to ADsR, and thus ADRs as a cause of admissions were 6.89% of total admissions. A majority (74.71%) were found to be of moderate severity. The most common ADRs were anti-tubercular drug induced hepatotoxicity, warfarin toxicity and chloroquine induced gastritis. The median duration of hospitalization was 5 days [95% CI 5.37, 7.11], and the average hospitalization cost incurred per patient was INR 6197/- (USD 150). Of total ADRs, 59.62% (158/265) were found to be either definitely or potentially avoidable.

Conclusion: The study shows that ADRs leading to hospitalization are frequent and constitute a significant economic burden. Training of patients and prescribers may lead to a reduction in hospitalization due to avoidable ADRs and thus lessen their economic burden.

Patel et al BMC Clinical Pharmacology

Adverse drug reactions among inpatients in a north Indian referral hospital

R. UPPAL, R. JHAJ, S. MALHOTRA

Natl Med J India 2000;13:16–18

TABLE I. Adverse reactions reported from April 1994 to March 1997

Adverse reaction	n (%)
Skin and appendages	123 (38.8)
Skin rashes (maculopapular, urticarial, etc.)	92
Steven–Johnson syndrome*	18
Toxic epidermal necrolysis*	6
Alopecia	7
Gastrointestinal system	90 (28.4)
Nausea, vomiting	49
Diarrhoea	10
Gastritis	5
Perforation of ulcers*	2
Hepatitis	23
Raised serum amylase	1
Nervous system	23 (7.3)
Extrapyramidal symptoms	7
Cerebellar dysfunction	4
Hepatic encephalopathy*	4
Others	8
Haematological	28 (8.8)
Bleeding abnormalities*	10
Blood dyscrasias*	18
Respiratory system	6 (1.9)
Renal impairment	5 (1.6)
Musculoskeletal system	3 (0.4)
Osteoporosis, gouty arthritis, myopathy	1 each
Special senses	3 (1.0)
Endocrine	2 (0.6)
Cushing's syndrome*	1
Oligomenorrhoea	1
*Cardiovascular system**	5 (1.6)
Miscellaneous, chills/rigors	15 (4.7)
Anaphylaxis*	7
Others	7
Total	317

* serious/life-threatening disorders

Uppal et al Natl Med J India

PHARMACOEPIDEMIOLOGY AND DRUG SAFETY (in press)
Published online in Wiley InterScience (www.interscience.wiley.com). **DOI**: 10.1002/pds.871

ORIGINAL REPORT

Adverse drug reactions in a South Indian hospital—their severity and cost involved†

M. Ramesh*, Jayesh Pandit and G. Parthasarathi

Department of Pharmacy Practice, JSS College of Pharmacy, Mysore, India

SUMMARY

Purpose The study was aimed to assess the pattern of occurrence of adverse drug reactions (ADRs) in the local population, severity of reported ADRs and additional financial resource utilisation associated with ADRs.

Methods This was a prospective, spontaneous reporting study conducted over a period of 7 months by clinical pharmacists. The WHO definition of an ADR was adopted. Each ADR was assessed for its causality by using the WHO Probability Scale. The severity of each reported ADR was assessed using the criterion developed by Hartwig *et al.* The average cost incurred in treating the ADRs was calculated.

Results A total of 270 suspected ADRs were reported and evaluated from 164 patients. A total of 3.7% of the hospitalised patients experienced an ADR, 0.7% of the admissions were due to ADRs and 1.8% had a fatal ADR. The gastrointestinal system (36.3%) was most commonly involved with an ADR. The drug class most commonly implicated with ADRs was cardiovascular (18.3%). Majority (47%) of the reactions were 'moderate' in severity. The total cost incurred in managing all the reported ADRs was Rs 76 564 (US$ 1595) with an average cost of Rs 690 (US$ 15) per ADR.

Conclusion Detection and prevention of ADRs at the earliest is very important as they can cause not only morbidity and mortality but also involve high health care cost in their management. Well-trained pharmacists in the area of ADR detection, reporting and monitoring could prove as an asset in providing better patient care.

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KEY WORDS — adverse drug reactions; pharmacist; hospitalised patients; spontaneous reporting; severity; cost

Ramesh et al Pharmacoepidemiology and drug safety

Acute hepatic failure in India: A perspective from the East

SUBRAT K ACHARYA, SUBRAT K PANDA, ALKA SAXENA AND S DATTA GUPTA

Journal of Gastroenterology and Hepatology (2000) **15**, 473–479

Table 2 Differences in aetiology of AHF in various geographical areas

	India	USA	UK	France
Viral (%)	95	60	30	50–60
Major cause	HEV/HBV	Cryptogenic	Non-A, Non-B	HBV/HAV
Drugs (%)	4.5	30–35	60	15–20
Major cause	INH/Rifampicin	Paracetamol	Paracetamol	NSAID/Paracetamol
Other	0.5	5	10	10–15

AHF, acute hepatic failure; HEV, hepatitis E virus; HBV, hepatitis B virus; HAV, hepatitis A virus; INH, isoniazid; NSAID, non-steroidal anti-inflammatory drugs.

Table 3 Causes of acute hepatic failure in India

Authors	Year	No. cases	Percentage aetiologies							
			HAV	HBV	HCV	HDV	HEV	Mixed infection	Non A–E	Drugs
Acharya *et al.* (see text)	1999	458	4	11	4	0	23	6	47	5
Khuroo *et al.*[22]	1997	119	3	15	3	3	38	NR	39	1
Jaiswal *et al.*[20]	1996	95	4	27	2	5	41	4	15	0

NR, Not reported; HAV, hepatitis A virus; HBV, hepatitis B virus; HCV, hepatitis C virus; HDV, hepatitis D virus; HEV, hepatitis E virus; Non A–E, non-A, non-E, viruses.

S K Acharya et al. Journal of gastroenterology and hepatology.

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Abstract

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Am J Gastroenterol. 2010 Nov;105(11):2396-404. doi: 10.1038/ajg.2010.287. Epub 2010 Jul 20.

Single-center experience with drug-induced liver injury from India: causes, outcome, prognosis, and predictors of mortality.

Devarbhavi H[1], Dierkhising R, Kremers WK, Sandeep MS, Karanth D, Adarsh CK.

Author information

Abstract

OBJECTIVES: Although drug-induced liver injury (DILI) is rare, it may result in significant morbidity or death. The causes and outcome vary according to regions, with acetaminophen and complementary medicines common in the West and the Far East, respectively. This study evaluates the causes, outcomes, predictors, and models for 90-day mortality from DILI from India.

METHODS: Consecutive patients with DILI from 1997 to 2008 based on International Consensus Criteria from a medical college hospital setting were studied.

RESULTS: Of the 313 patients, 58% were males. Leading causes were a combination of four anti-tuberculous drugs (ATDs) (58%), anti-epileptics (11%), olanzapine (5.4%), and dapsone (5.4%). The overall 90-day mortality of 17.3% was significantly higher for ATD hepatitis (21.5%) vs. those without (11.4%) (P=0.02). The highest mortality was for leflunomide (75%). Seventy-eight percent of patients received more than one drug. Fulminant hepatic failure developed more commonly in females than in males (23% vs. 17%). Of the 66% of cases with jaundice and/or icterus, mortality was 26%. Multivariable models for mortality using a combination of encephalopathy, ascites, and bilirubin, or a combination of albumin, prothrombin time, and white blood cell count yielded a C-statistic of at least 0.86 by recursive partitioning and 0.92 by logistic regression. Model for end stage liver disease (MELD) scores of 38 and 46 yield probabilities of death of 0.90 (confidence interval (CI): 0.71-0.97) and 0.99 (CI: 0.90-1.00), respectively.

CONCLUSIONS: DILI results in significant overall mortality (17.3%). ATDs, anti-convulsants, sulphonamides, and olanzapine are the leading causes of DILI. Although common in males, more females developed fulminant hepatic failure. High-MELD score or a combination of ascites, encephalopathy, high bilirubin, prothrombin time, and leukocyte count are predictive of mortality.

PMID: 20648003 [PubMed - indexed for MEDLINE]

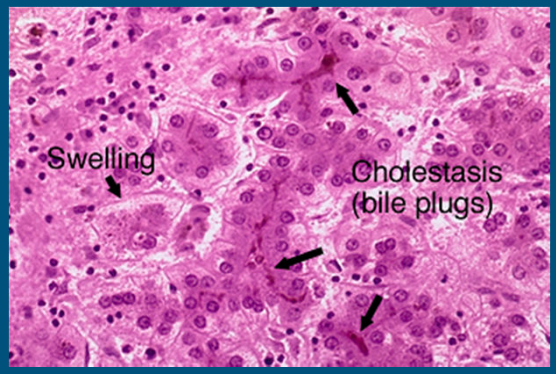
MECHANISM OF DILI

- Hepatic metabolism
  - Drugs with > 50% hepatic metabolism conveyed a significant risk of ALT increases, liver failure & mortality related to DILI
- Hypersensitivity/allergic reactions
- Autoimmunity
- Veno occlusive disease
- Idiosyncratic reactions

MECHANISM OF DILI - NEWER INSIGHTS

- Related to mitochondrial injury
- Emerging role of superoxide dismutase & glutathione peroxidase
- Effect of polymerase ɣ on cellular proliferation and non apoptotic cell death

DRUG INDUCED CHOLESTASIS



Acute drug induced cholestasis is defined as

- an elevation of ALP at least 2 times the upper limit of normal (ULN) or
- an ALT/ALP ratio of < 2, with both ALT and ALP greater than the ULN.

Cholestatic liver injury is defined by isolated elevation of alkaline phosphatase, which is released by damaged cholangiocytes, thus suggesting injury to the bile ducts

CHOLESTATIC DILI

(ALP >2 ULN or ALP/ALT <2 with both ALP and ALT >1 ULN)

1. **Antibiotics**: amoxicillin-clavulanic acid, erythromycin, trimethoprim-sulfamethoxazole
2. **Anti-inflammatory medications**: sulindac
3. **Cardiac medications**: clopidogrel, ACE inhibitors
4. **Neurologic/psychiatric medications**: carbamazepine, chlorpromazine, tricyclic antidepressants
5. **Other**: azathioprine, anabolic steroids, oral contraceptives

DRUG INDUCED HEPATOCELLULAR INJURY

Hepatocellular injury is defined as ALT elevation of at least 5 times ULN in combination with a bilirubin elevation of at least 2 times ULN

Such a presentation occurs more commonly

Drug induced hepatocellular injury has been correlated with worse outcome

HEPATOCELLULAR DILI

(ALT > 5 X ULN and Bilirubin > 2 X ULN)

1. **Antibiotics**: ciprofloxacin, nitrofurantoin, tetracycline, trimethoprim-sulfamethoxazole
2. **Antidepressants**: bupropion fluoxetine, paroxetine
3. **Anti-inflammatory medications**: acetaminophen, bromfenac, diclofenac, ibuprofen, naproxen
4. **Cardiac medications**: amiodarone, lisinopril, statins
5. **Neurologic/psychiatric medications**: methyldopa, nefazodone, risperidone, sertraline, trazodone, valproic acid
6. **Other**: acarbose, amatoxin, allopurinol, cimetidine, ketoconazole, halothane, isoniazid, omeprazole, protease inhibitors, pyrazinamide, quinidine, rifampin, troglitazone

DRUG INDUCED MIXED INJURY

Elements of both hepatocellular and cholestatic injury

Increases in ALT, ALP, bilirubin

MIXED DILI
(ALT >5 ULN or Bilirubin >2 ULN and ALP >2 ULN or ALP/ALT <2 with both ALP and ALT >1 ULN)

1. **Antibiotics**: clindamycin, sulfonamides
2. **Cardiac medications**: ACE inhibitors, statins
3. **Neurologic/psychiatric medications**: phenytoin, amitriptyline
4. **Other**: azathioprine, protease inhibitors reverse transcriptase inhibitors

VENO OCCLUSIVE DISEASE LEADING TO PORTAL HYPERTENSION

1. **Antineoplastic agents**: busulfan, cyclophosphamide
2. **Environmental exposures**: arsenic, vinyl chloride, thorium dioxide
3. **Other**: Vitamin A

➢Manifestations include ascites, varices, and hepatic encephalopathy

PATTERN OF LIVER BIOCHEMISTRY

The pattern of liver injury is defined by R value, [where R = (ALT/ULN)/(ALP/ULN)]

Hepatocellular pattern: R > or = 5,

Mixed pattern: R >2 and <5,

Cholestatic pattern: R < or = 2

RISK FACTORS FOR DILI

- Age - old and young
- Obesity
- Pregnancy
- Alcohol consumption (acetaminophen, INH, nicotinamide & methotrexate)
- Genetic polymorphisms (i.e. HLA-B*5701)

RISK FACTORS FOR DILI

Gender - Male in younger patients, females in older patients

History of chronic liver disease (if aspirin, methotrexate, INH, antiretroviral drugs)

Dose and duration of treatment

Coincidental metabolic disorders and exposure to other drugs/environmental agents

DRUG	PROPOSED MECHANISM/GENETIC RISK FACTOR
AMOXYCILLIN CLAVULANATE	HLA Class II SNP rs 9274407
ANTITUBERCULOSIS DRUGS	NAT 2 POLYMORPHISM CYP2E1 POLYMORPHISM DRUG TRANSPORTER GENES (ABCB1, SLCO1B1, ABCC2 UGTA1 POLYMORPHISM PREGNANE X RECEPTOR (PXR)
FLUCLOXACILLIN	PXR POLYMORPHISM (rs 3814055;C-25385 T) HLA B*5701
ISONIAZID	Bcl-2 DOWNREGULATION CYP2E1 POLYMORPHISM NAT 2 POLYMORPHISM

Nutritional status

- Fasting predisposes to acetaminophen hepatotoxicity
- Malnutrition also increases the risk and severity of hepatotoxicity from drugs used to treat tuberculosis
- Overnutrition (obesity) increases the risk of halothane hepatitis
- Increased risk of NASH and hepatic fibrosis among those taking methotrexate, estrogens, tamoxifen, corticosteroids

Past history

Instances of cross reactivity to similar agents are reported with

- haloalkane anesthetics (eg halothane, enflurane, isoflurane)
- INH and pyrazinamide
- Sulfonamides and some COX 2 inhibitors
- Some NSAIDs and macrolide antibiotics

Any history of previous adverse drug reaction increases the risk of DILI to other agents

Previous reaction to the same drug is the single most important factor predisposing to unusual severity of drug induced hepatitis (eg acute liver failure, chronic liver disease)

Other medical disorders

Renal failure - methotrexate induced hepatic fibrosis, tetracycline induced fatty liver

Renal/solid organ transplantation - hepatic vascular injury with azathioprine

Use of cancer chemotherapeutic agents in BMT/radiotherapy - VOD/SOS

RA & SLE - salicylate hepatotoxicity & sulfasalazine induced hepatitis

HIV/AIDS & SLE - drug reactions to sulfonamides

Familial clustering...

Halothane, oral corticosteroids cholestasis, valproic acid and phenytoin reactions are those for which more than one case has occurred in the same family

There are strong associations between human leukocyte antigens (HLA) and cholestatic drug reactions to amoxicillin clavulanate and tiotropinin

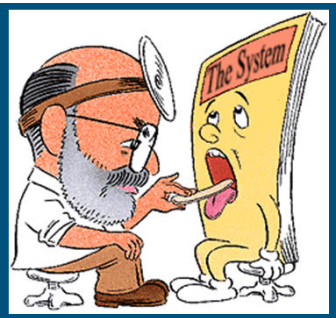
Phenytoin is an example of reactive metabolite syndrome (RMS)

CLINICAL FEATURES

Drugs have become the great mimickers of "natural" liver diseases

- nonspecific abnormalities of liver tests
- cholestasis
- acute hepatitis
- acute liver failure
- hepatic sinusoidal/venous outflow obstruction syndromes
- nodular regenerative hyperplasia
- chronic hepatitis resembling autoimmune hepatitis
- hepatic fibrosis
- NASH
- cirrhosis
- benign/malignant liver tumors

DIAGNOSIS



Thorough & complete history including information from pharmacy records

Diagnosis is always presumptive as it is based on logistic approach

“Causality assessment” -

a. determine whether link between drug ingestion & liver injury (ADR, liver histology) is plausible

b. exclude other disorders

DIAGNOSIS

The correct diagnosis is facilitated by identifying

specific risk factors for hepatotoxicity eg prolonged fasting, chronic excessive alcohol intake by a person regularly taking acetaminophen

the presence of extrahepatic features of drug hypersensitivity

clinicopathologic syndrome associated with a particular drug

- However, the absence of the “drug signature” should not be used to exonerate a given drug as the cause of liver injury
- Certain criteria used as tools to assist in clinical diagnosis of DILI

DIAGNOSTIC CRITERIA FOR DILI

Hy's Law: AST and/or ALT > 3 X ULN without initial ALP > 2 X ULN and no other causes of liver disease

Roussel Uclaf Causality Assessment Method (RUCAM): Risk factors, temporal relationship, exclusion of other causes, concomitant therapy, extrahepatic manifestations, prior reports of hepatotoxicity, rechallenge results

DDW - J: Temporal relationship, eosinophilia, positive lymphocyte stimulation test

Clinical diagnostic scale (M & V scale): Temporal relationship, exclusion of other causes, prior reports of hepatotoxicity, rechallenge results

LIMITATIONS OF DIAGNOSTIC TOOLS

Hy's law is not as sensitive as other parameters as it does not consider the temporal relationships

RUCAM - can specifically associate liver injury to a particular medication, it is complicated to administer, and rechallenging patients is rare. Thus modification to this scale has been proposed. A summed score of -10 to 14

Best modification is Digestive disease week - Japan (DDW-J) scale - higher sensitivity and lower specificity than the original scale

M&V scale - less predictive

Drug induced liver disease is a diagnosis of exclusion: consider the following

Hepatitis viruses

Other infectious agents - Epstein Barr virus, cytomegalovirus, human immunodeficiency virus, herpes simplex virus, coxiella burnetti

Autoimmune hepatitis: antinuclear antibodies, smooth muscle antibodies, liver/kidney microsomal antibodies, immunoglobulin G levels

Acute biliary obstruction, exclude cholangitis

Metabolic disorders: Wilson disease, alpha 1 antitrypsin deficiency, risk factors for nonalcoholic fatty liver disease/nonalcoholic steatohepatitis

Drug induced liver disease is a diagnosis of exclusion: consider the following

- Vascular disorders of liver
- Alcohol
- Bacterial infection
- Hepatic metastases
- Systemic malignancy or lymphoma

ROLE OF LIVER BIOPSY

Excluding other hepatobiliary disorders

Most strongly indicated when the cause of liver disease remains in doubt

there may be ambiguous evidence of autoimmunity or

the pattern of reaction may be very unusual or

the pattern of reaction may not be previously reported for the drug in question

persistence of abnormal liver biochemistries

in case of continued use and contemplated rechallenge

HISTOLOGICAL CHANGES INDICATING DILI

- Zonal lesions, including necrosis and/or steatosis
- Microvesicular steatosis (often results from mitochondrial injury)
- Necrotic lesions of disproportionate severity of the clinical picture
- Mixed hepatitis and cholestasis
- Destructive bile duct lesions

HISTOLOGICAL CHANGES INDICATING DILI

- Prominent neutrophils and (in later stages) eosinophils (>25%)
- Granulomas
- Vascularity of hepatic tumors - sinusoidal dilatation, peliosis
- Vascular lesions
- Florid steatohepatitis - resembles alcohol related steatohepatitis more than typical “primary” nonalcoholic steatohepatitis

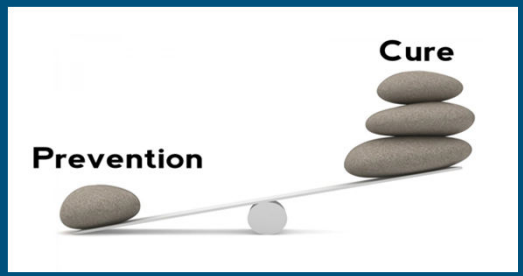
PREVENTION

Appropriate use of drugs (nonpharmacologic approaches, optimal choice of agents, avoiding polypharmacy where possible, avoiding excessive dosage)

Restricted availability and blister packaging of OTC medications

Physician and public education about possible drug side effects and about how to recognize and what to do about them

Monitoring for adverse drug reactions



PREVENTION

LFT monitoring - agents for which LFT monitoring is strongly endorsed eg methotrexate, INH, etretinate and other synthetic retinoids, ketoconazole, anti cancer drugs and prolonged therapy with minocycline

Drug should be stopped if ALT > 5 X ULN

but any abnormality of serum bilirubin/albumin/prothrombin time & the presence of any symptoms are clear indication to stop therapy

MANAGEMENT

Most important - early recognition & discontinuation of putative agent

At each visit patients should be warned to report any untoward new symptoms

With possible ADR, physicians should immediately check LFT to document hepatotoxicity

Most ADR will resolve spontaneously, rapidly & completely

Drugs with prolonged half life are associated with protracted hepatic ADR

eg Amiodarone, etretinate, ketoconazole & hypervitaminosis A

MANAGEMENT

Aspiration of stomach contents to remove unabsorbed drug - acetaminophen, metals & and toxic mushrooms

Use of charcoal/resins/osmotic cathartics unlikely to be effective

Chelating resins, hemodialysis, forced diuresis - not effective for most hepatotoxins

MANAGEMENT

Largely supportive, except when acetaminophen/Amanita mushroom poisoning is suspected for which antitoxins are available

Testing of drug levels may be indicated in dose dependant hepatotoxicity

Hospitalization in case of severe reactions - repeated vomiting, deepening jaundice & development of laboratory/clinical features of liver failure

Early transfer to a liver transplant unit before the worsening (bleeding, HRS, hepatic encephalopathy) of the patients

ROLE OF CORTICOSTEROIDS

- DILI associated with vasculitis (eg allopurinol, sulfonamides)
- Some cases of drug induced chronic hepatitis
- When D/D between AIH & drug induced chronic hepatitis remains in doubt
- “Steroid whitewash” - short course of corticosteroids to hasten recovery in persons with prolonged drug induced cholestasis

A pragmatic approach is to observe the course for 3-6 weeks after stopping the drug (unless there is evidence of further deterioration), reserving corticosteroids for cases in which there is failure to show clinical or biochemical improvement

ROLE OF UDCA

- UDCA used with success in patients presenting with cholestatic liver injury attributed to amoxycillin-clavulanate, flucloxacillin, flutamide, cyclosporin
- Dose of ursodeoxycholic acid (15 mg/kg body weight)
- During prolonged cholestatic reactions fat soluble vitamin deficiency should be corrected
- Treat pruritus: consider emollients, diphenhydramine, bile acid resins, selective norepinephrine reuptake inhibitors

MANAGEMENT- ACETAMINOPHEN POISONING

Administer N Acetylcysteine if elevated AST or ALT or detectable serum acetaminophen levels, consider IV administration if presentation is > 10 hours after ingestion or if vomiting precludes oral administration

Continual observation and psychiatry consult if intentional overdose suspected

MANAGEMENT - MUSHROOM POISONING

Administer silibinin

Administer high dose Penicillin G

Consider administering N acetylcysteine or cimetidine

PREDICTING DILI

As of now, ALT remains the gold standard to predict DILI

However, ALT is not the ideal biomarker as it merely reflects injury after it has happened

A truly predictive biomarker identifies at risk patients prior to the initiation of potentially hepatotoxic drug therapy (eg. HLA B*5701 & abacavir)

Research in proteomics, metabolomics, transcriptomics & pharmacogenomics may find clues in accurate prediction of DILI

Genetic predispositions recently identified for flucloxacillin and lumiracoxib

KEY POINTS

- Greater than 1000 medications have been implicated in DILI
- Greater than 1 in 100 hospitalized patients are diagnosed with DILI
- DILI is responsible for greater than 50% of cases of fulminant hepatic failure
- Drug induced hepatocellular injury carries a worse prognosis than cholestatic jaundice
- Management includes withdrawing the offending drug, administering proven antidotes when appropriate, symptomatic treatment, and monitoring of biochemical tests

KEY POINTS

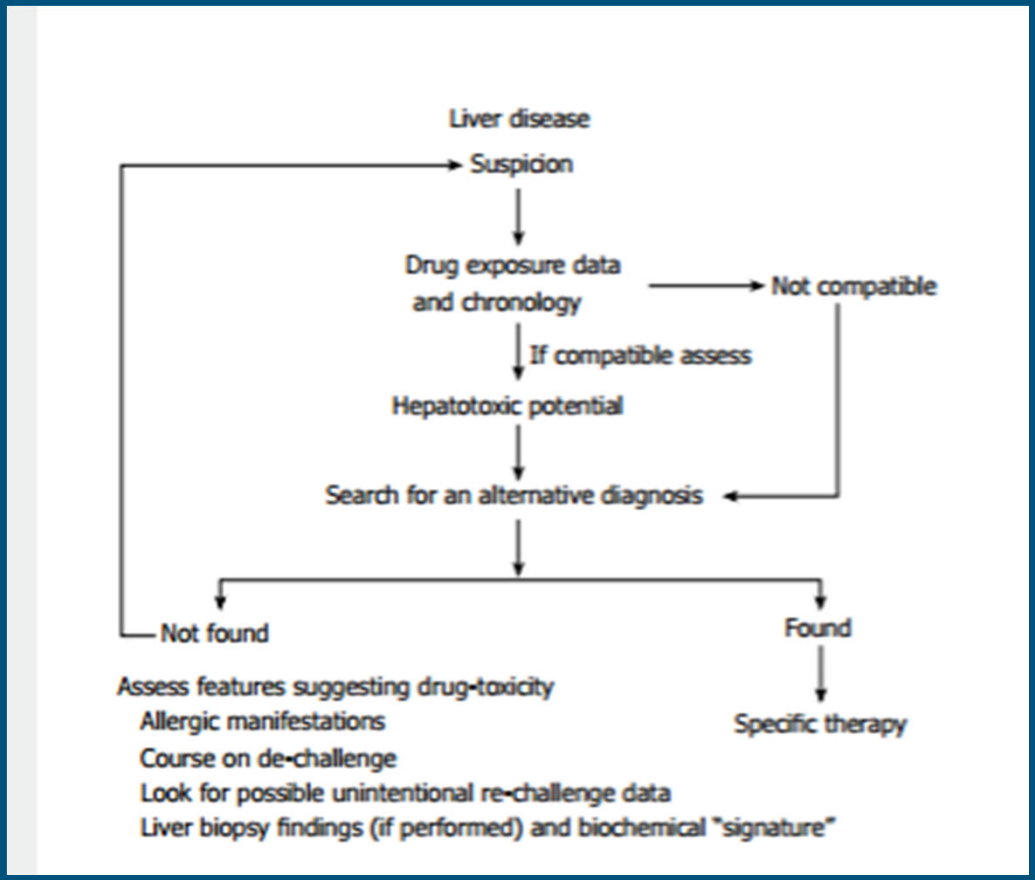
Early recognition of DILI and subsequent referral and transfer to a transplant center can be life saving.

In most cases, biochemical resolution of DILI occurs within 60 days

Hepatotoxicity remains an important cause of drugs withdrawn from market

Proteomics, metabolomics, transcriptomics and pharmacogenomics may help in the accurate prediction of DILI in future

KEY POINTS


Liver disease
Suspicion
Drug exposure data and chronology
Not compatible
If compatible assess
Hepatotoxic potential
Search for an alternative diagnosis
Not found
Found
Assess features suggesting drug-toxicity
Allergic manifestations
Course on de-challenge
Look for possible unintentional re-challenge data
Liver biopsy findings (if performed) and biochemical "signature"
Specific therapy

THANKS