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DRUG INDUCED LIVER DISORDER

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Abstract:

One of the most difficult adverse medication reactions seen in clinical practice is drug-induced liver injury (DILI), which is a significant contributor to liver-related morbidity. It happens when drugs, nutritional supplements, herbal products, or hazardous substances cause liver damage via immune-mediated or direct cellular toxicity. The clinical range of DILI includes acute liver failure necessitating liver transplantation as well as modest, asymptomatic increase of liver enzymes. The prevalence of DILI is rising worldwide because to the growing use of prescription pharmaceuticals, over-the-counter treatments, and herbal supplements. Numerous processes, including as oxidative stress, mitochondrial dysfunction, immunological activation, apoptosis, and altered bile acid transport, are involved in the pathophysiology of DILI. Susceptibility is influenced by both host-related and drug-related factors, including age, sex, alcohol intake, and genetic polymorphisms. Among the most commonly implicated compounds include antibiotics, antitubercular agents, nonsteroidal anti-inflammatory drugs, antiepileptic pharmaceuticals, and herbal treatments. Fatigue, nausea, jaundice, pruritus, stomach discomfort, and hepatic encephalopathy are among the many possible clinical symptoms. The diagnosis is primarily dependent on clinical history, test results, exclusion of alternate etiologies, and causality evaluation techniques because there is no particular diagnostic biomarker. The cornerstone of management continues to be the prompt identification and cessation of the offending substance. Reducing the frequency and severity of DILI requires increased knowledge, cautious monitoring, pharmacovigilance, and sensible prescribing practices.

Keywords: Drug-induced liver injury, hepatotoxicity, liver failure, oxidative stress, cytochrome P450, hepatocellular injury, pharmacovigilance

1. INTRODUCTION

Hepatic damage caused by exposure to prescription and over-the-counter pharmaceuticals, herbal remedies, nutritional supplements, and environmental pollutants is known as drug-induced liver injury (DILI). Due to its substantial correlation with morbidity, mortality, and drug withdrawal from the pharmaceutical market, it is regarded as one of the most severe adverse drug responses. As the primary organ in charge of xenobiotic metabolism and detoxification, the liver is especially vulnerable to toxic damage. Reactive intermediates that might cause direct hepatocyte damage or trigger immune-mediated inflammatory reactions may be produced during drug metabolism.Globally, DILI is becoming a more significant clinical and public health issue. Although the true frequency is probably underestimated due to underreporting and diagnostic challenges, the incidence of DILI is estimated to be between 14 and 19 cases per 100,000 people annually. DILI is a major cause of medication withdrawal during clinical trials and post-marketing surveillance, and it is one of the main causes of acute liver failure in many countries. Hepatotoxic responses are often linked to antibiotics, antitubercular medications, antiepileptics, and nonsteroidal anti-inflammatory medications. As DILI's clinical signs frequently mimic those of viral hepatitis, autoimmune hepatitis, alcoholic liver disease, and

metabolic liver disorders, diagnosing it can be extremely difficult. As of right now, DILI cannot be accurately confirmed by a single diagnostic biomarker. Clinical suspicion, a thorough medication history, the temporal correlation between drug use and the beginning of liver damage, the exclusion of competing causes, and organized causality evaluation instruments like the Roussel Uclaf Causality evaluation Method (RUCAM) are all important factors in the diagnosis process. Improving clinical outcomes and preventing the development of severe liver injury need early detection and prompt removal of the offending substance [1-3].

2.CLASSIFICATION OF DRUG-INDUCED LIVER INJURY:-

The cause of injury, clinical presentation, and biochemical pattern of liver abnormalities are often used to classify drug-induced liver injury.

2.1 Intrinsic DILI:-

Intrinsic DILI is dose-dependent and predictable. It can be replicated experimentally and typically happens soon after exposure to a toxic dose of a substance. Reactive metabolites' direct harmful effects on hepatocytes induce this type of liver damage. The typical example of intrinsic DILI is hepatotoxicity caused by paracetamol. Hepatocellular necrosis, glutathione depletion, and oxidative stress are caused by an overabundance of the poisonous metabolite N-acetyl-p-benzoquinone imine (NAPQI).

2.2 Idiosyncratic DILI:-

Idiosyncratic DILI is unpredictable and only affects those who are vulnerable. In contrast to intrinsic DILI, it may manifest weeks or months after medication exposure and is not evidently dose dependent. Susceptibility is influenced by environmental factors, immunological dysregulation, and genetic predisposition. Immune-mediated and metabolic idiosyncratic reactions are further classified. Fever, rash, eosinophilia, and the development of autoantibodies are frequently linked to immune-mediated damage.

2.3 Biochemical Pattern-Based Classification:-

DILI is categorized as hepatocellular, cholestatic, and mixed types based on abnormalities in liver enzymes.

Hepatocellular Damage-

Hepatocellular necrosis and increased alanine aminotransferase (ALT) levels are the main characteristics of this pattern. Acute liver failure may develop from severe hepatocellular damage.

Cholestatic Injury-

Cholestatic DILI is associated with increased alkaline phosphatase (ALP) levels, impaired bile flow, jaundice, and pruritus.

Mixed Pattern-

Mixed liver injury demonstrates features of both hepatocellular and cholestatic damage and is frequently associated with several antibiotics and antiepileptic drugs [4-5].

MECHANISM OF DRUG-INDUCED LIVER INJURY:-

Hepatocyte dysfunction and death are caused by a variety of cellular and molecular processes in the complicated pathophysiology of DILI.

3.1 Oxidative Stress-

An important factor in the development of DILI is oxidative stress. Reactive oxygen species are produced during hepatic metabolism, which causes DNA damage, protein alteration, and lipid peroxidation. Hepatocytes eventually undergo apoptosis or necrosis as a result of excessive oxidative stress upsetting cellular balance.

3.2 Mitochondrial Impairment-

By preventing oxidative phosphorylation and ATP generation, a number of hepatotoxic medications damage mitochondrial function. Reactive oxygen species build up and cellular energy reserves are depleted as a result of mitochondrial damage. Hepatocyte apoptosis and serious liver damage can be brought on by persistent mitochondrial malfunction.

3.3 Hepatotoxicity Mediated by Immunity-

Antigenic complexes that trigger immunological responses can be formed when drug metabolites attach to liver proteins. Hepatocellular inflammation and tissue damage are caused by activated T cells and inflammatory cytokines. Fever, skin rash, and eosinophilia are examples of systemic hypersensitivity symptoms that frequently accompany immune-mediated DILI.

3.4 Cytochrome P450-Induced Damage-

Many medications are metabolized by cytochrome P450 enzymes. Some drugs are bioactivated into hazardous intermediates that might cause hepatocellular damage. Individual susceptibility to DILI may be greatly impacted by changes in CYP enzyme activity.

3.5 Mechanisms of Cholestasis-

Toxic bile acids build up intra hepatically as a result of certain medications' disruption of bile acid transport and secretion. Hepatocyte destruction, inflammation, and cholestasis are all brought on by this process. Chlorpromazine and amoxicillin-clavulanate are frequently linked to cholestatic liver damage [6-8].

RISK FACTORS:-

Susceptibility to DILI is influenced by a number of host-related and drug-related factors.

1.Age-

Growing older is linked to decreased hepatic blood flow, decreased metabolic capacity, and increased polypharmacy, all of which raise the risk of hepatotoxicity.

2.Gender-

In addition to having a higher risk of acute liver failure and severe liver injury, females seem to be more vulnerable to some types of DILI.

3.Genetic Factors-

Susceptibility to idiosyncratic DILI is greatly influenced by genetic variants including cytochrome P450 enzymes, drug transporters, and human leukocyte antigens.

4.Drinking Alcohol-

Long-term alcohol consumption raises the risk of liver damage by depleting hepatic glutathione stores and producing more harmful metabolites.

5.Previously Diagnosed Liver Disease-

Severe hepatotoxic reactions are more likely to occur in patients with cirrhosis, fatty liver disease, viral hepatitis, or chronic liver problems.

6.Polypharmacy-

Drug interactions and the build-up of hepatotoxic metabolites are more likely when many drugs are taken concurrently [9-10].

CAUSATIVE DRUGS:

DILI has been linked to a variety of drugs and natural remedies.

1.Antibiotics-

One of the most frequent causes of DILI in the globe is antibiotics. Hepatotoxic responses are often linked to amoxicillin-clavulanate, isoniazid, rifampicin, nitrofurantoin, and erythromycin.

2.Antitubercular Medications-

Hepatotoxicity is primarily caused by isoniazid, rifampicin, and pyrazinamide, especially in individuals undergoing combination therapy for tuberculosis.

3.Nonsteroidal anti-inflammatory medications-

Through oxidative stress and immune-mediated pathways, NSAIDs like diclofenac and Nimesulide may cause hepatocellular or mixed liver injury.

4.Antiepileptic Medications-

Phenytoin, carbamazepine, and valproic acid are frequently linked to severe hepatotoxicity and hypersensitivity responses.

5.Paracetamol-

In many nations, the most common cause of abrupt liver failure is still paracetamol overdose. Excessive NAPQI accumulation results in hepatocyte necrosis and toxicity.

6.Dietary and Herbal Supplements-

Due to contamination, adulteration, and lack of standardization , herbal goods such as green tea extract, kava, turmeric supplements, and traditional herbal treatments are becoming more widely acknowledged as significant sources of liver damage [11-13].

3.CLINICAL PRESENTATION:-

DILI can present with a wide variety of clinical symptoms, from fulminant liver failure to asymptomatic biochemical abnormalities.

1.Early Signs-

Fatigue, anorexia, nausea, vomiting, malaise, and stomach pain are among the initial symptoms, which are typically nonspecific.

2.Hepatocellular Presentation-

Jaundice, black urine, right upper quadrant pain, and noticeably increased serum transaminases are common symptoms in patients with hepatic damage.

3.Cholestatic Presentation-

Jaundice, pruritus, pale stools, and increased alkaline phosphatase levels are frequent symptoms of cholestatic DILI.

4.Features of Hypersensitivity-

Fever, rash, eosinophilia, lymphadenopathy, and systemic inflammatory symptoms can all be linked to immune-mediated DILI.

5.Serious Liver Damage-

Coagulopathy, hepatic encephalopathy, multiorgan failure, and death are possible outcomes of severe cases. Due to irreparable liver disease, some individuals could need a liver transplant [14]

Diagnosis of Drug-Induced Liver Injury (DILI)

Drug-induced liver injury (DILI) is a liver disorder caused by prescription drugs, over-the-counter medications, herbal products, or dietary supplements. It is considered one of the most difficult liver diseases to diagnose because there is no single specific biomarker for confirmation. Therefore, DILI is primarily a diagnosis of exclusion, meaning other possible causes of liver injury must first be ruled out.

The diagnosis begins with a detailed medication history. Clinicians should assess all recently used drugs, herbal preparations, supplements, and alternative medicines. The temporal relationship between drug exposure and onset of symptoms is extremely important. Most cases develop within days to months after exposure to the offending agent. Common symptoms include fatigue, nausea, jaundice, abdominal pain, pruritus, and dark urine, although some patients remain asymptomatic with only elevated liver enzymes.

Laboratory investigations play a major role in diagnosis. Liver function tests such as alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), bilirubin, albumin, and prothrombin time are evaluated. Based on enzyme elevation patterns, DILI is classified into hepatocellular, cholestatic, or mixed injury. The R ratio is commonly used for this classification.

$$R = \frac{ALT/ULN_{ALT}}{ALP/ULN_{ALP}}$$

An R value ≥5 indicates hepatocellular injury, ≤2 indicates cholestatic injury, and values between 2 and 5 indicate mixed injury. Viral hepatitis, autoimmune hepatitis, alcoholic liver disease, metabolic liver disorders, and biliary obstruction should be excluded through appropriate laboratory and imaging studies.

Causality assessment tools are frequently used to strengthen the diagnosis. The Roussel Uclaf Causality Assessment Method (RUCAM) is the most widely accepted scoring system. It evaluates factors such as timing of drug administration, improvement after withdrawal, exclusion of alternative causes, previous reports of hepatotoxicity, and response to re-exposure.

Imaging studies including ultrasonography, CT scan, or MRI may help exclude biliary obstruction or structural liver disease. Liver biopsy is not routinely required but may be considered in uncertain cases, persistent liver injury, or suspected autoimmune-like hepatitis. Histopathological findings may reveal hepatocellular necrosis, cholestasis, granulomas, steatosis, or fibrosis depending on the causative drug and pattern of injury.

Early recognition is critical because delayed diagnosis may lead to acute liver failure, chronic liver disease, or death. Therefore, prompt identification and withdrawal of the offending drug remain essential components of diagnosis and management [15-17]

Management and Treatment of Drug-Induced Liver Injury

The cornerstone of DILI management is immediate discontinuation of the suspected offending drug. Early withdrawal significantly improves prognosis and reduces the risk of progression to severe liver injury or acute liver failure. Re-exposure to the causative drug is generally avoided because recurrence may be more severe and potentially fatal.

Most patients improve with supportive care alone. Treatment mainly focuses on monitoring liver function, maintaining hydration and nutrition, and controlling symptoms such as nausea, vomiting, and pruritus. Patients with mild disease are often managed conservatively with regular follow-up and liver enzyme monitoring.

Hospitalization is required in patients with severe jaundice, coagulopathy, encephalopathy, or signs of acute liver failure. Liver transplantation may be necessary in fulminant hepatic failure when recovery is unlikely. Prognostic indicators such as Hy's law are used to identify patients at high risk of mortality.

$$ALT > 3 \times ULN \text{ and } Total\ Bilirubin > 2 \times ULN$$

Specific antidotes are available only for selected conditions. N-acetylcysteine (NAC) is highly effective in acetaminophen-induced hepatotoxicity and may also provide benefit in some cases of non-acetaminophen acute liver failure. Corticosteroids can be considered in immune-mediated DILI or drug-induced autoimmune hepatitis, especially with checkpoint inhibitor therapies. Ursodeoxycholic acid may be used in prolonged cholestatic injury, although evidence remains limited.

Monitoring includes serial assessment of ALT, AST, bilirubin, INR, and clinical symptoms. Recovery may take weeks to months depending on severity and patient factors. Chronic DILI may develop in a small proportion of patients, particularly in cholestatic or autoimmune-like forms.

Patient education is also an important part of management. Individuals should be informed about avoiding self-medication, unnecessary herbal supplements, and previously implicated drugs. Proper pharmacovigilance and adverse drug reaction reporting systems help improve future patient safety [18-22].

Prevention of Drug-Induced Liver Injury

Prevention of DILI is essential because effective treatment options remain limited once significant liver damage occurs. Rational prescribing and careful patient monitoring are the primary preventive strategies. Physicians should

evaluate risk factors such as advanced age, female sex, alcohol use, pre-existing liver disease, polypharmacy, and genetic susceptibility before initiating potentially hepatotoxic drugs.

Baseline liver function testing is recommended before starting medications known to cause hepatotoxicity, including antitubercular drugs, antiepileptics, methotrexate, and certain anticancer agents. Periodic monitoring during therapy helps identify liver injury at an early stage before progression to severe disease.

Avoidance of unnecessary medications and irrational combinations can reduce the incidence of DILI. Patients should be advised against indiscriminate use of herbal products and dietary supplements because many are associated with hepatotoxicity and lack adequate safety evaluation. Clear labeling and public awareness programs may improve medication safety.

Pharmacogenomics is emerging as a valuable preventive strategy. Genetic screening for susceptibility markers such as specific HLA alleles may help identify high-risk individuals before drug exposure. Improved pharmacovigilance systems and adverse drug reaction databases such as LiverTox contribute significantly to early detection and prevention efforts.

Healthcare professionals should educate patients regarding early warning symptoms such as jaundice, itching, dark urine, fatigue, and abdominal pain. Prompt reporting of these symptoms can lead to earlier diagnosis and discontinuation of the offending medication [23-26].

4.Future Perspectives in Drug-Induced Liver Injury

Future research in DILI is focused on improving early diagnosis, identifying predictive biomarkers, and developing targeted therapies. One of the major challenges in DILI is the absence of highly sensitive and specific diagnostic markers. Current research is exploring genomic, proteomic, metabolomic, and microRNA-based biomarkers that may enable earlier and more accurate detection of hepatotoxicity.

Artificial intelligence and machine learning models are increasingly being used to predict hepatotoxic potential during drug development. These technologies may help reduce late-stage drug failure and improve patient safety by identifying high-risk compounds before clinical use.

Advances in pharmacogenomics may allow personalized medicine approaches in the future. Identification of genetic susceptibility factors could help clinicians individualize therapy and avoid potentially hepatotoxic drugs in vulnerable patients. Similarly, organoid models and in vitro liver cell systems are being investigated as alternatives to traditional animal testing for hepatotoxicity assessment.

International collaborative registries and databases such as LiverTox and DILIN are expected to improve understanding of epidemiology, clinical patterns, and outcomes. Future multicenter studies may establish standardized diagnostic criteria and evidence-based treatment protocols.

Research is also ongoing for targeted therapies aimed at reducing oxidative stress, mitochondrial dysfunction, and immune-mediated liver injury. These developments may eventually provide disease-specific treatment options beyond supportive care alone [27].

5.Conclusion

Drug-induced liver injury remains an important cause of acute and chronic liver disease worldwide. Its diagnosis is challenging because it lacks specific biomarkers and closely mimics other hepatic disorders. Careful clinical evaluation, exclusion of alternative causes, laboratory assessment, and causality scoring systems are essential for accurate diagnosis. Early recognition and prompt withdrawal of the offending drug are the most effective management strategies.

Although most patients recover completely with supportive care, severe cases may progress to acute liver failure requiring liver transplantation. Preventive measures such as rational drug prescribing, patient education, liver function monitoring, and pharmacovigilance are crucial for reducing disease burden. Advances in biomarker discovery, pharmacogenomics, and artificial intelligence are expected to improve diagnosis, prevention, and treatment in the future. Continued research and international collaboration will play a major role in enhancing patient safety and minimizing the impact of drug-induced liver injury.

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