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Drug induced liver injury: A comprehensive review of mechanism, different types of drugs and case reports

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Abstract

Liver is a vital organ to playing crucial role in maintaining overall health like detoxification, metabolism, bile production, and immune function, liver injury is the condition which effects the overall function in the body, it occurs due to excessive use of alcohol, continuous usage of drugs, based on the age, and hereditary, explaining about the classification of different drugs and their percentage to cause the liver injury

Drug-induced liver injury (DILI) is a significant contributor to acute liver failure, that can vary from slight increases in liver enzymes to serious hepatotoxicity. Its mechanisms are multifactorial, involving drug metabolism, immune responses, mitochondrial dysfunction, apoptosis and necropsy. Monitoring blood parameters such as SGPT, SGOT, bilirubin, and coagulation markers is essential for diagnosis and management.

This review examines DILI mechanisms associated with atorvastatin, diclofenac, doxycycline, phenytoin, and amiodarone through case reports. Atorvastatin induces hepatotoxicity in 63 years old farmer taking continuously, doxycycline induces liver injury in 28 years male he prescribed doxycycline 100 mg twice daily for 14 days he got elevation of liver enzymes, 94 years old man was suddenly fall The only new medication was topical diclofenac 1%, which he had been applying to all his joints and the lateral aspects of his legs after medical check his liver enzyme levels are elevated, Phenytoin is the choice of drug to treat epilepsy it produce hepatotoxicity in 50 years old female by prescribing and continues usage, Amiodarone is choice of drug to treat arrhythmia, which showing slight increase in liver enzymes.

Keywords: Drug -induced liver injury; Apoptosis; Necropsy; Case report

1. Introduction

1.1. Drugs Induced Liver Injury

Drug-Induced hepatotoxicity also known as Drug Induced Liver Injury (DILI), refers to an acute or chronic reaction to a synthetic or natural substance. DILI can be grouped by how it appears in the body (hepatocellular, cholestatic, or mixed), how the liver is damaged, or what a liver biopsy shows under the microscope. In United states, DILI has become the leading cause of acute liver failure and it is unpredictable, it is very hard to determine the exact incident. The majority of DILI cases show no symptoms, although jaundice is the most frequently observed sign when symptoms do occur [1].

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DILI may also occur due to several patient risk factors, including female sex, older age, and a higher body mass index (BMI) [2][3]. Over 1,000 medications and herbal compounds are known to cause hepatotoxicity, and these can be found in a searchable database called LiverTox, maintained by the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) [4][5]. Idiosyncratic cases of DILI can be triggered by:Antibiotics (45.4%): ciprofloxacin, amoxicillin-clavulanate, isoniazid, Nonsteroidal anti-inflammatory drugs (NSAIDs), Herbal and dietary supplements (16.1%)—including green tea extracts, anabolic steroids, and multi-ingredient nutritional products—are also common causes.Cardiovascular drugs (10%): statins, amiodarone, Central nervous system (CNS) agents: phenytoin, valproate, Antineoplastic drugs: tyrosine kinase inhibitors, tumor necrosis factor inhibitors, alpha inhibitors, and methotrexate [6][3].Healthcare providers must maintain a high index of suspicion for DILI, especially when prescribing high-risk drugs or managing patients on polypharmacy regimens. while DILI is a relatively rare adverse effect for most drugs, its potentially life-threatening nature demands vigilant pharmacovigilance, careful drug selection, and individualized patient management to ensure safe and effective pharmacotherapy.

2. Mechanism of Action

The DILI model consists of three main sequential steps and includes details on the intrinsic and extrinsic pathways, as well as the mechanisms of apoptosis and necrosis.

2.1. Step1: Initial Mechanisms of Toxicity

Drug metabolites may directly cause cellular stress, disrupt mitochondrial activity, or activate targeted immune responses. The cytochrome P450 (CYP450) family, which is polymorphic, plays a crucial role in generating hepatotoxic reactive metabolites through oxidative phase-I drug metabolism. However, phase II conjugation reactions can also generate hepatotoxic metabolites—such as acyl glucuronides—which are recognized contributors to drug-induced liver injury (DILI) [7][8].

When mitochondria are initially affected, parent drugs or their reactive metabolites can interfere with the mitochondrial respiratory chain by uncoupling or inhibiting it, resulting in reduced ATP production and elevated reactive oxygen species (ROS). They may also impair β-oxidation—leading to lipid accumulation and steatosis, as seen with the buildup of amiodarone inside mitochondria—cause damage to mitochondrial DNA or hinder its replication, and Directly induce mitochondrial permeability transition (MPT), characterized by the opening of the MPT pore within the inner mitochondrial membrane. It's probable that there's a specific point of injury necessary for liver damage to take place. This threshold involves a decline in mitochondrial electron transport beyond a certain level, alongside an increase in cytosolic reactive oxygen species (ROS) and JNK activation that exceeds another critical level [9].

2.2. Step: 2 Both direct mechanisms and death receptor-mediated pathways can induce mitochondrial permeability transition

Secondly, initial stress within the cell or specific immune responses can initiate mitochondrial permeability transition (MPT). When the mitochondria are not directly harmed by the initial trigger, MPT may still occur through one of two mechanisms: either due to significant internal cell stress (the intrinsic pathway) or through activation of death receptors caused by lower levels of stress or immune activity (the extrinsic pathway) [10].

In the intrinsic pathway, intense intracellular stress activates the endoplasmic reticulum pathway, causes lysosomal permeabilization, or triggers c-jun N-terminal kinase (JNK) [11] [12] [13] [14]. This causes pro-apoptotic proteins to activate while preventing the action of anti-apoptotic proteins from the Bcl-2 family, ultimately leading to mitochondrial permeability transition (MPT).

In the extrinsic pathway, mild initial damage can worsen if inflammatory responses—triggered by slight stress or other influences—alter the activity of the innate immune system. Normally, this system maintains a balance between cytokines that either promote (like IL-12) or reduce (such as IL-4, IL-10, IL-13, and MCP-1) tissue injury. However, when this balance is disrupted, liver cells become more sensitiveto damaging molecules like tumor necrosis factor alpha (TNFα), Fas ligand (FasL), and interferon gamma (IFNγ). This is especially important because the liver, being the body's main detoxifying organ, is constantly subjected to stress that can activate TNFα and FasL. If the initial trigger involves a targeted immune response, antigen presentation via MHC molecules leads to the release of TNFα and FasL by Kupffer cells (liver macrophages) and cytotoxic T cells [14].

2.3. Step: 3 Apoptosis and Necrosis

Third, when mitochondrial function and energy production are compromised, cells may undergo either apoptosis or necrosis. In the case of apoptosis, cytochrome c is released into the cytosol, where it binds to the scaffold protein Apaf-1 and pro-caspase-9, assembling into a multiprotein complex called the apoptosome. This structure then initiates the activation of pro-caspase-9. This process requires ATP and can only occur if mitochondrial permeability transition (MPT) does not simultaneously affect all mitochondria. If some mitochondria remain intact and continue to produce ATP, activated pro-caspase 9, along with other pro-apoptotic mitochondrial proteins, subsequently activate executioner caspase 3. Caspase 3 then cleaves specific cellular proteins and further activates pro-caspases 6, 7, and 2, each of which targets specific proteins. These events ultimately lead to programmed apoptotic cell death, characterized by cytoplasmic and nuclear condensation and fragmentation, without loss of membrane integrity. [15].

Necrosis, in contrast, occurs when the initial cellular injury is so intense that mitochondrial permeability transition (MPT) rapidly affects all mitochondria, or when other mechanisms cause a swift and profound reduction of mitochondrial ATP, constructively blocking the apoptotic pathway. This form of cell death is often observed with hepatotoxins that impose substantial cellular stress. Furthermore, when ATP levels are insufficient, the activation of the extrinsic pathway can also result in necrotic cell death. Necrosis is marked by cellular swelling and membrane rupture, which compromise normal cell function. The ensuing cell lysis initiates an inflammatory response, including the release of cytokines that can worsen the initial damage by sensitizing surrounding hepatocytes and contributing to further tissue injury [16].

To diagnosis the hepatotoxicity in patient they are several blood parameters are tested some of the parameters are under below such as SGOT, SGPT, albumin test etc., along with their normal ranges.

Serum glutamate oxaloacetate transaminase (SGOT) test: Serum glutamate oxaloacetate transaminase is an enzyme which is released from liver, heart, kidney, muscle or brain cell when these are damaged. Its normal serum value is up to 46 IU/L at 37°C [17]. The levels of this enzyme are elevated by 10 to 200 times in patients with acute hepatic necrosis, viral hepatitis, carbon tetrachloride (CCl_4) toxicity, and drug-induced liver injury.

- Serum Glutamate Pyruvate Transaminase (SGPT) Test: Serum Glutamate Pyruvate Transaminase is an enzyme which is released damaged liver cells. The normal serum level of SGPT is up to 49 IU/L at 37°C. SGPT levels are significantly elevated in patients with viral hepatitis and hepatic necrosis. [18].
- Serum Alkaline Phosphatase Test: Alkaline phosphatase is an enzyme found in the liver, and its levels increase in response to bile flow obstruction, liver injury, or certain cancers [19]. Normal serum alkaline phosphatase values range from 25 IU/dL to 85 IU/dL, but levels are elevated in bone diseases, hepatobiliary conditions, and during pregnancy. [20].
- Serum Total Protein and Albumin Test: When monitored on a routine basis, total protein levels in the blood are generally expected to stay between 5.5 and 8.0 grams per deciliter. In cases of extensive liver damage, the level of blood plasma proteins decreases. Albumin is an enzyme, which is synthesized in the liver, is 3.5 g/dL to 5.0 g/dL Chronic hepatic dysfunction commonly results in reduced serum albumin concentrations due to diminished synthetic capacity of the liver. [21].
- Serum Total and Direct Bilirubin Test: Approximately 7.5 g of hemoglobin is catabolized daily, resulting in the production of 250 mg of bilirubin. The serum concentration of conjugated bilirubin in adults normally approximates 0.25 mg/dL, with total bilirubin ranging from 0.2 to 1.2 mg/dL, reflecting both direct and indirect fractions. Bilirubin levels increase in conditions such as biliary excretion obstruction, hemolysis, and disorders affecting hepatic bilirubin uptake and conjugation, such as Gilbert's disease [18].
- Urine Bilirubin: Hepatobiliary disease indicates presence of bilirubin in the urine. Unconjugated bilirubin is tightly bound to albumin, preventing it from being filtered by the glomerulus, and thus it is not found in the urine. Therefore, measurable levels of conjugated bilirubin in serum are typically associated with hepatobiliary diseases [22].
- Urobilinogen: An increase in urobilinogen levels in urine is a sensitive indicator of hepatocellular dysfunction and serves as a useful marker for alcoholic liver damage, well-compensated cirrhosis, or liver malignancy. Urobilinogen levels may rise early in viral hepatitis and can significantly increase in cases of hemolysis. [22].
- Serum Lipid Profile Test:Hepatic toxicants can disrupt the synthesis and metabolism of triglycerides, cholesterol, and lipoproteins, thereby impairing cellular function. The liver synthesizes cholesterol and bile salts, so hepatic intoxication can lead to a reduction in their levels. 200 mg/dl is the normal cholesterol range. HDL and LDL are also important to analysis. Fatty liver (hepatic steatosis) is frequently associated with elevated serum triglyceride levels, typically exceeding the normal threshold of 150 mg/dL. [23].

- Lactic Dehydrogenase (LDH) Test:LDH reference values can vary between laboratories and are typically higher in childhood. In most laboratories, normal levels range from 45 U/L to 90 U/L, with an upper limit of approximately 200 U/L for adults. When tissues containing LDH are damaged, elevated levels of the enzyme are released into the bloodstream. LDH levels are also raised in liver diseases, heart attacks, certain anemias, excessive cell destruction, fractures, trauma, muscle damage, and shock [23].
- Bromosulphthaline Clearance Test:Bromosulphthaline is a dye which is cleared from the blood by the liver through mechanism of bilirubin binding, conjugation, and excretion. BSP retention was measured 45 minutes after IV injection to assess hepatic excretory function. Although the test is less commonly used today due to the availability of enzyme-based diagnostics, it remains valuable for diagnosing Dubin-Johnson syndrome [24,20].
- Superoxide Dismutase (SOD): SOD converts superoxide (O_2^-) into H_2O_2 and O_2, making it a central player in the body's antioxidant defense system [25]. This process, known as dismutation, takes one reactant and turns it into two different products. By facilitating this conversion, superoxide dismutase effectively helps to eliminate superoxide radicals from the body, contributing to overall cellular protection.

3. Case reports

There are different types of drugs are available in the market, each type of drug has differently used to treat the disease or disorder, but they produce adverse effect along with cure, now a days continues usage of drugs they produce hepatotoxicity is the major adverse effect, now I am trying to explain some of most commonly used drugs such as atorvastatin, diclofenac, doxycycline, phenytoin and amiIdorane with their mechanism of action to produce hepatotoxicity along with their case reports how it effect on the patent to cause the hepatotoxicity.

3.1. Atorvastatin

Atorvastatin is a potent and orally available drug, which inhibit the hepatic 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase, the key enzyme responsible for cholesterol synthesis. It is effectively lowers the LDL concentrations and total serum concentration.The suggested dosage varies between 10 and 80 mg taken once daily, based on individual tolerability and lipid levels.

3.1.1. Mechanism of Action:

It is mainly metabolized in the liver through the action of CYP 3A4 and it is eliminated via bile. Elevated ALT levels can occur due to intermediate drug metabolism, including drug-drug, drug-food, and drug-herbal interactions with substances like itraconazole, verapamil, grapefruit juice, cyclosporine, fibrates, and niacin. Several case reports have demonstrated hepatotoxicity associated with atorvastatin use.

3.1.2. Case Report

A 63-year-old man who works as a farmerwas taken to the hospital after feelingchest pain for eight hours. Over two years prior, he underwent thoracoscopic radical resection for esophageal carcinoma under general anesthesia, followed by two courses of gimeracil and oteracil potassium capsules. Regular follow-up appointments showed no abnormalities in electrocardiograms or physical examinations, such as blood pressure, respiratory rate, or temperature. Chest CT scans revealed postoperative changes in the esophagus, an arcuate gas shadow near thse heart (suspected pneumomediastinum), in the anterior segment of the right upper lobe aDiagnostic imaging shows minor pericardial fluid accumulation and non-uniform pulmonary infiltrates, consistent with a patchy radiographic pattern.

After relevant examinations, the patient was treated with piperacillin sodium and tazobactam sodium (4.5 g every 8 hours intravenously), along with pain management, phlegm reduction, infection control, and increased oxygen inhalation. Anacute lacunar infarctneartheright ventricular anterior horn andmild white matter ischemiawere identified oncranial MRI performed on the second day of hospitalization. By the third day, pericardial effusion had increased, and the patient was infected with Rothiamucilaginosa, Veillonellasulfamethoxazole, and *Candida albicans*. Antibiotics were adjusted to cefoperazonesulbactam (2 g every 8 hours), tigecycline injection (50 mg every 12 hours), and fluconazole injection (400 mg daily).On the fourth day, following a neurology consultation, antiplatelet therapy with clopidogrel tablets and lipid-lowering therapy with atorvastatin (20 mg at night) were initiated. However, five days after admission, laboratory tests revealed abnormal liver enzymes.Because certain medications, including tigecycline and atorvastatin, might harm the liver, they were stopped, and treatment to protect the liver was started.After about a week of care, the liver test results went back to normal, and theinfection was under control. Atorvastatin was resumed on the 15th day. Sixteen hours later, the patient developed severe nausea, vomiting with gastric contents, and shortness of breath, ultimately leading to fatal hepatic failure following atorvastatin administration. [26].

3.2. Diclofenac

Diclofenac is a NSAIDS. Its hepatotoxicity is low but their wide spread usage and easy acquisition become a real; problem, additionally other factors also contribute like interaction with other drug age gender and hormonal factors

3.2.1. Mechanism of Action

Cytochrome P450 (CYP) is the primary enzymatic system responsible for oxidizing lipophilic substances, and it often works alongside other CYP enzymes to deactivate these molecules. However, when biologically active drug intermediates produced during Phase I metabolism (toxifying phase) generate reactive radical species and are not neutralized by Phase II reactions—such as conjugation with glucuronic acid, sulfuric acid, acetylation, or glutathione coupling—they can cause damage to proteins or nucleic acids [2]. When enzymatic capacity is exceeded or inadequate, drug elimination is compromised. Reactiveintermediates formed during Phase I metabolism can initiate immune-mediated responses targeting both the parent compound and transporter proteins, which may result in neoantigen generationandautoimmune hepatic injury. [27].There were no signs suggesting a loss of consciousness prior to the fall. His family noted a decline in appetite and decreased oral intake over the preceding day. His medical history included arthritis

3.2.2. Case Report

A 94-year-old male was brought to the hospital after being discovered on the floor approximately one hour after an unwitnessed and Paget's disease of bone.

Four months earlier, he began using topical diclofenac 1%, which he had been applying to multiple joints and along the outer parts of his legs. Thedaily amount applied gradually increased, eventually reaching approximately 50 grams per day, equivalent to half a tube.The patient's regular medications included:Acetaminophen 650 mg, Aspirin 81 mg, Atorvastatin 10 mg, Metoprolol succinate 25 mg, Ibuprofen 200 mg once daily

At presentation, his vital signs were stable. Laboratory tests revealed mild anemia and elevated liver enzymes, including AST and ALT. He was discharged with instructions to discontinue potentially hepatotoxic medications, including diclofenac, acetaminophen, ibuprofen, and atorvastatin. At a follow-up visit three weeks later, his liver function tests had returned to normal, with the exception of a persistently elevated alkaline phosphatase (ALP).

3.2.3. Conclusion

Hepatotoxicity associated with diclofenac was indicated by a moderate increase in liver enzyme levels, which fully normalized after the medication was discontinued. [28].

3.3. Doxycycline

Antibiotics are among the most common cause of drug induced liver injury worldwide, Doxycycline is a broad-spectrum antibiotic that belongs to the tetracycline family and is usually prescribed for the treatment of acute bronchitis, community acquired pneumonia, Helicobacter pyloric infection, Lyme disease and some sexually transmitted disease.

3.3.1. Mechanism of Action

It is highly lipophilic allow doxycycline to cross multiple membrane to reach target molecule, tetracycline acts as cationic coordination complexes to cross the OMpf and ompcporin channel in gram- bacteria. Tetracyclines like doxycycline stop bacteria from growing—not by killing them directly, but by blocking their ability to make proteins. This happens when the drug attaches to the 30S unit of the bacterial ribosome, interfering with the translation process.

3.3.2. Case report

A 28-year-old male farmer from a rural area arrived at the emergency department with a one-day history of nausea, vomiting, and fatigue. He reported no abdominal pain, hematemesis, or fever. Six days earlier, he had been diagnosed with early localized Lyme disease following a normal complete blood count (CBC), comprehensive metabolic panel (CMP), and liver function tests. He had been prescribed doxycycline 100 mg twice daily for 14 days but stopped the medication after five days due to nausea. The patient denied alcohol use, smoking, or a history of sexually transmitted infections. Upon admission, his CBC showed elevation, and liver enzymes, including AST and ALT, were elevated as well. Over the next 48 hours, his symptoms of nausea and vomiting were managed with intravenous promethazine. After 72 hours, he was discharged with a prescription for oral amoxicillin to complete a 14-day course of treatment, which he tolerated without issues. One month later, his liver enzymes had returned to baseline levels.[29].

3.3.3. Conclusion

This case suggests doxycycline-induced liver injury, evidenced by elevated liver enzymes and gastrointestinal symptoms that resolved after stopping the drug. Supportive care and switching to amoxicillin led to full recovery, confirmed by normal liver function one month later. Early recognition and drug withdrawal were key to the patient's recovery.

3.4. Phenytoin

Phenytoin is also Known as Diphenylhydantoin, it is a potent anticonvulsant drug used to treat and prevent generally grandma seizures, complex partial seizures and status epilepticus

3.4.1. Mechanism of Action

Phenytoin helpscalm overactive nervesbyblocking certain sodium channelsand keeping them turned off for longer. It works in both thebrain and the heart.

3.4.2. Case report

A 50-year-old African American woman with a 35-year history of schizoaffective disorder, bipolar type, has experienced numerous, occasionally extended hospitalizations at a state psychiatric institution. She also has a seizure disorder that has been well-managed with phenytoin since her initial recorded seizure in late June 2011.. Before starting phenytoin, she had no known history of elevated liver enzymesAfter beginning phenytoin treatment in 2011, she has experienced consistent increases in liver enzymes, with AST and ALT levels rising to 94 U/L and 139 U/L, respectively, and occasional elevations in alkaline phosphatase.While receiving phenytoin treatment, her ammonia levels have fluctuated between 49 and 73 mcg/dL.. Two weeks after discontinuing phenytoin, her liver enzymes normalized, with AST at 22 U/L, ALT at 19 U/L, and alkaline phosphatase at 96 U/L, and they have remained within normal limits since then.

3.4.3. Conclusion

A 50-year-old woman with a long-standing seizure disorder managed with phenytoin developed mild to moderate liver enzyme elevations during treatment, which returned to normal levels only after the medication was stopped [30].

3.5. Amiodarone

Amiodarone is a commonly used antiarrhythmic drug, primarily prescribed for supraventricular tachycardia, such as atrial fibrillation, and for preventing ventricular tachycardia in high-risk patients. The most commonly observed adverse effects associated with amiodarone use are thyroid abnormalities, hepatic and pulmonary toxicity, as well as the development of corneal microdeposits [31] [32].

3.5.1. Mechanism of Action

Amiodarone can harm the liver by damaging the protective fat layers in liver cells and interfering withsmall parts of the cell that help with energy and waste removal (mitochondria and lysosomes). It is a strong inhibitor of phospholipase A, which leads to the accumulation of lipid-rich material in lysosomes. The injury pattern suggests mitochondrial damage, resulting in microvascular fat accumulation, ballooning degeneration, fibrosis, and Mallory body formation.

3.5.2. Case Report

A 79-year-old Lebanese man presented to the Emergency Department with progressively worsening epigastric pain over the course of a month. The pain was crampy, intermittent, and worsened with exertion, becoming predominantly localized to the epigastric region a few days before his visit. He denied chest pain, sweating, nausea, vomiting, or diarrhea. His medical history included hypertension, dyslipidemia, alcohol-related fatty liver disease, depression, and irritable bowel syndrome. His medications included daily venlafaxine 75 mg, moxonidine 0.3 mg, atorvastatin 10 mg, aspirin 100 mg, and mebeverine hydrochloride 200 mg, which he had been taking for months without any changes. He reported drinking 1-2 alcoholic beverages daily but denied smoking or using illicit drugs. His surgical history was limited to a sternotomy due to a gunshot wound. Laboratory tests showed normal CBC and cardiac enzymes, but mildly elevated liver function tests (LFTs), attributed to his alcohol-related fatty liver. His electrolytes were normal. An ECG revealed atrial fibrillation, and an echocardiogram showed a normal ejection fraction. IV amiodarone was administered to control his rhythm, starting with a loading dose of 150 mg, followed by 200 mg every 12 hours. After 2 days, routine lab tests revealed significant increases in LFTs, creatinine, and blood urea nitrogen. Amiodarone was withdrawn after reaching a cumulative dose of 950 mg within 48 hours. Subsequent monitoring showed restoration of hepatic and renal

function within the next 48–72 hours post-discontinuation. His LFTs returned to baseline after 10 days of discontinuation, and he was eventually discharged.

3.5.3. Conclusion

Intravenous amiodarone–related acute liver failure is a rare complication, especially when it occurs in conjunction with acute kidney injury. It typically develops within the first 24 hours of administration, and while the exact mechanism of toxicity remains unclear, it may be linked to ischemic hepatopathy or a reaction to excipients like polysorbate 80 [33].

4. Conclusion

Drug-Induced Liver Injury (DILI) is a major clinical concern due to its unpredictable nature, wide range of causes, and potential for severe liver damage. The liver's key role in drug metabolism makes it highly susceptible to toxic effects from medications, supplements, and chemicals. DILI is the leading cause of acute liver failure in the U.S., often presenting with vague symptoms like jaundice. It typically involves three steps: formation of reactive metabolites, mitochondrial dysfunction, and eventual cell death (apoptosis or necrosis). Lab markers such as SGOT, SGPT, bilirubin, and ALP help in diagnosis and monitoring. Case reports involving drugs like atorvastatin, diclofenac, and amiodarone show that DILI can occur via different mechanisms and is often idiosyncratic. Early drug discontinuation usually improves outcomes. Risk factors like age, comorbidities, and alcohol use increase susceptibility, and re-exposure to the same drug can lead to severe or fatal reactions.

Compliance with ethical standards

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