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An Overview of Drug-Induced Liver Disease

Jiwon Kim, PharmD

Assistant Professor of Clinical Pharmacy

University of Southern California School of Pharmacy, USC University Hospital
Los Angeles, California

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Drug-induced liver disease (DILD), a potential complication with some medications, is a common cause of hepatic injury that accounts for approximately one half of all acute liver failure cases in the United States.¹ More than 1,000 drugs, ranging from NSAIDs to valproic acid, have been implicated in drug-induced liver injuries, rendering the treatment of DILD an important but challenging task for health care professionals. Recent data have shown that liver disease represents a larger percentage of adverse drug reactions than previously reported and that the incidence and severity of drug-induced liver injury is underestimated among the general population.²

Drug-induced hepatic damage is the most frequent reason that new therapeutic agents are not approved by the FDA and is the most common adverse drug reaction leading to the withdrawal of a drug from the market. For example, ximelagatran, a promising oral anticoagulation medication, was denied FDA approval in September 2004 due to several cases of hepatotoxicity, including three liver injury-associated deaths.³ This article provides an overview of the different forms of drug-induced liver injury, as well as the risk factors and mechanisms involved in drug-induced hepatotoxicity.

Epidemiology

Incidence of DILD appears to be increasing, which reflects the growing number of new therapeutic agents introduced over the past several decades. Available epidemiologic data have reported low incidence of DILD with commonly used agents (table 1).⁴ NSAIDs and amoxicillin/ clavulanate have been associated with hepatotoxicity in one to 10 cases per 100,000 population, and in one to five cases per million, respectively. However, isoniazid-associated liver dysfunction may occur in as many as 100 cases per 100,000 population, and the increase of alanine aminotransferase (ALT) or aspartate aminotransferase (AST) associated with protease inhibitor therapy has been reported to be over 9%.⁵

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Table 1	
Drugs that Cause Acute Liver Failure in Liver Transplant Patients	
Incidence	Drugs
Frequent (≥ 10%)	Isoniazid, propylthiouracil, phenytoin, valproic acid
Infrequent (2% to 9%)	Nitrofurantoin, ketoconazole, disulfiram, sulfasalazine, methyldopa, nefazodone, labetalol
Rare (≤ 1%)	Amoxicillin/clavulanate, bromfenac, bupropion, carbamazepine, ibuprofen, itraconazole, lisinopril, 6-mercaptopurine, naproxen, paroxetine, pemoline, simvastatin, trimethoprim/ sulfisoxazole, zafirlukast
<i>Note: Drugs other than acetaminophen are listed.</i>	

Drug-induced liver injury is the most frequent cause of acute liver failure and accounts for 15% of all liver transplantations in the U.S.⁶ In addition, the disease accounts for about 2% of hospitalized patients with jaundice and 25% of active chronic hepatitis. A population-based study in France from 1997 to 2000 reported that the incidence of drug-induced hepatotoxicity was 13.9 cases per 100,000 patients per year, and the drugs most often responsible for hepatic damage were antimicrobials, psychotropic agents, lipid-lowering agents, and NSAIDs.⁷ These data demonstrated that observed incidence of DILD was 16 times greater than typically reported in postmarketing surveillance, indicating an underreporting of drug-associated adverse events. Data on the epidemiology of DILD from the national European registry showed a near doubling of reported cases of drug-induced hepatotoxicity from 1968–1978 to the following decade, 1978–1987.⁸

Risk Factors

Numerous factors such as age, sex, genetic predisposition, and degree of alcohol consumption appear to increase the susceptibility of DILD in a variety of therapeutic agents. Although patients with mild to moderate chronic liver disease do not appear to be at increased risk for idiosyncratic hepatic injury from therapeutic compounds, certain drugs, including methotrexate, tolcapone, niacin, and pemoline, should be used with caution in these patients, since they may have altered metabolism of these agents and may be at increased risk for liver injury.

Most hepatic adverse effects associated with drugs occur in adults rather than children. In the adult population, persons older than 40 years are at increased risk for DILD. This may be due to increased frequency of drug exposure, multiple drug therapy, and age-related changes in drug metabolism. Reports indicate that drug-induced liver injury occurs at a higher rate in patients older than 50 years and that drug-associated jaundice occurs in up to 20% of the geriatric population.⁹ In general, female gender has been associated with an increased risk of hepatic dysfunction due to drugs, especially from agents such as nitrofurantoin, methyldopa, and sulfonamides.^{10,11}

A familial predisposition to drug-induced hepatic injury is rare but has been reported with drugs such as phenytoin.¹² Genetic factors in affected individuals may decrease the ability to metabolize or eliminate drugs or may decrease the ability to modulate the immune response to drugs or metabolites. Chronic, excessive ingestion of alcohol may also increase the risk of hepatotoxicity from

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drugs such as acetaminophen by lowering the glutathione store and inhibiting clearance of toxic metabolites. Alcohol may also predispose many drugs to hepatotoxicity. Such agents include acetaminophen, isoniazid, methotrexate, and vitamin A.

Pathophysiology

A principal function of the liver is the biotransformation of nonpolar substances to polar compounds that can be excreted in urine or bile. The enzymes that catalyze the biotransformation are usually found in hepatocytes, and many of the substrates and the metabolites of biotransformation reactions are toxic. Subsequently, the liver is often the primary site of exposure to these toxins, and hepatic injury occurs frequently.

Phase I of the biotransformation is the oxidative pathway in which the compound undergoes oxidation to a more polar substance, which is mediated by cytochrome P-450 (CYP450) enzymes. This process is followed by the phase II reaction, in which esterification of metabolites forms sulfates and glucuronides, adding highly polar groups to the metabolized compound. Although other metabolic pathways exist in drug metabolism, the primary metabolic pathways for most drugs involve CYP450 and subsequent esterification. Hepatocellular necrosis occurs through a process in which high-energy metabolites formed by CYP450 activation bind to cellular membranes or DNA and disrupt cell function. The best understood example of this process is acetaminophen-induced liver toxicity. Although safe in recommended doses, large amounts of acetaminophen cause cellular necrosis.

CYP450 enzymes consist of more than 30 different enzymes that demonstrate interindividual variation in activity and are susceptible to induction and inhibition by a number of substrates. This results in several drug interactions and an increased risk of drug-induced liver injury. Individual variation in drug response may also be due to enzyme polymorphism, in which certain individuals lack the liver enzyme necessary for the metabolism of offending drugs that are associated with liver injury.

Alteration in immune response is another mechanism through which hepatocellular necrosis occurs. Studies suggest that a highly reactive intermediate formed by CYP450 metabolism covalently binds to the enzyme itself and evokes an immune response directed against newly formed metabolite-enzyme compounds.¹³ Inflammation and neutrophil-mediated hepatic injury may occur through another form of immune response involving cytokines (e.g., interferon, interleukin, tumor necrosis factor).¹⁴

In phase II conjugation reactions, the binding of glutathione, glucuronate, or sulfate to metabolites produces nontoxic substances that are readily excreted through bile or urine. Glutathione conjugation is one of the most important defenses against hepatocellular injury. Glutathione protects cellular enzymes and membranes from toxic metabolites. Inadequate stores of these binding substances can compromise efficient detoxification of reactive metabolites, and the subsequent inability to detoxify toxic substances can result in liver injury. The rate-limiting factor for glutathione synthesis is the intracellular concentration of cysteine, which is often supplied in the form of N-acetylcysteine and replenishes glutathione in acute acetaminophen toxicity.

Classification of Hepatotoxic Drug Reactions

Intrinsic (predictable) and idiosyncratic (unpredictable) drug reactions can produce liver injury. Most drugs involved in hepatotoxicity belong to the idiosyncratic group. In most patients, intrinsic agents produce liver injury in a dose-related manner when the toxic amount of drug is ingested. The hepatic injury can be due to direct hepatic necrosis, cholestatic injuries, or both. Hepatotoxicity may be the result of the drug itself or, more frequently, a result of the toxic effects of its metabolites. Dose-dependent hepatotoxins are listed in table 2. Among the listed drugs, acetaminophen is the most frequent hepatotoxic agent and can cause extensive

hepatic necrosis with as little as 10 to 12 grams. Acetaminophen overdose is the most common cause of acute liver failure and death associated with liver injury in the U.S.¹⁵

Table 2	
Drugs with Dose-Dependent Hepatotoxicity	
Drugs	Hepatotoxicity
Acetaminophen	Hepatocellular necrosis due to single toxic dose or total dose over time
Amiodarone	Chronic steatosis due to total dose over time
Bromfenac	Toxicity after extended administration
Cyclosporine	Cholestasis with toxic blood levels
Methotrexate	Elevated aminotransferase and fibrosis after single or large total dose
Niacin	Vascular injury after large doses
Oral contraceptives	Hepatic tumor after prolonged administration
Tetracycline	Steatosis after large total dose and renal dysfunction

Idiosyncratic drug reactions occur in from one in 1,000 to one in 50,000 patients. These reactions are not due to the drug itself, since most people can tolerate the drug. Rather, unique patient characteristics, including genetic predisposition and a lack of enzymes required for the metabolism of certain drugs, may increase the risk of these adverse drug reactions. Idiosyncratic reactions occur in relatively small numbers. As a result, some drugs known to cause hepatic injury continue to be used, since the drug's benefit outweighs its risk. For example, isoniazid is implicated in about 15% to 20% of cases in which individuals develop increased transaminases after receiving the drug as a single agent for tuberculosis prophylaxis.¹⁶ Of these individuals, an estimated one in 1,000 may develop severe hepatic necrosis. NSAIDs, including cyclooxygenase-2 inhibitors, are also commonly associated with idiosyncratic liver injury.¹⁷

Most idiosyncratic drug reactions are caused by hypersensitivity reactions and can result in damage to hepatocytes in the liver. The hepatic injury occurs within one to five weeks after initiation of drug therapy and is often accompanied by systemic characteristics of allergic drug reactions, such as rash and fever.¹⁰ Signs of hepatic injury reappear with subsequent administration of the same drug with only one or two doses. Examples of agents in which idiosyncratic drug reactions through hypersensitivity mechanism can occur include methyldopa, phenytoin, chlorpromazine, and erythromycin (table 3). Idiosyncratic drug reactions can also be caused by toxic drug metabolites. This form of drug reaction usually develops one week to 12 months after initiation of drug therapy and is usually not accompanied by systemic features of allergic reaction.¹⁰ Since the adverse effect is presumed to be the result of an accumulation of toxic metabolites, rechallenge requires administration of the drug that lasts from days to weeks for reproduction of

the hepatic injury.

Table 3 Idiosyncratic Drug Reactions and Forms of Liver Injuries	
Drugs	Forms of Liver Injuries
Isoniazid, trazodone, diclofenac, nefazodone, venlafaxine, lovastatin	Hepatocellular necrosis
Chlorpromazine, estrogen, erythromycin, and other macrolides	Cholestasis
Phenytoin, sulfamethoxazole	Immunoallergic reaction
Diltiazem, sulfonamides, quinidine	Granulomatous hepatitis
Didanosine, tetracycline, valproic acid	Acute steatosis
Nitrofurantoin, methyldopa, lovastatin, minocycline	Autoimmune hepatitis
Methotrexate	Fibrosis
Oral contraceptives, anabolic steroids	Hepatic tumor
Amoxicillin/clavulanate, carbamazepine, cyclosporine, methimazole	Mixed hepatocellular/cholestatic injury

Clinical Spectrum of Drug-Induced Liver Disease

Most drugs associated with liver injury involve direct hepatocyte necrosis. However, some drugs cause cholestasis without significant hepatocyte damage or cause mixed injury, in which both hepatocellular and cholestatic damage occur. While in many drugs any of these three patterns may occur, most agents have a unique pattern of hepatotoxicity in the time of onset, frequency, and type of hepatic injury observed. In addition, several other types of injury including steatosis, fibrosis, and immunologic damage can occur with drug use.

Acute hepatocellular injury: Acute hepatic injury due to drugs may be hepatocellular, cholestatic, or a combination of the two. Hepatocellular reactions are the most common types of DILD and represent up to 90% of cases.¹⁸ Drug-induced hepatocellular injury includes hepatic necrosis and steatosis, which can affect significant portions of the liver. Agents reported to cause hepatocellular necrosis include acetaminophen, methyldopa, valproic acid, trazodone, nefazodone, venlafaxine, and lovastatin.¹⁰ Nefazodone was removed from the European market after numerous cases of hepatotoxicity, including fulminant liver failure and subsequent liver transplantation, were reported.¹⁹

The injury is characterized by marked elevations (eight to 500 times the upper normal limit) in ALT and AST with variable elevation in bilirubin. Alkaline phosphatase value remains normal or only slightly elevated. These biochemical

patterns resemble those of acute viral hepatitis and are often referred to as toxic hepatitis. The AST-to-ALT ratio is important in assessing hepatic injury from drugs. In alcoholic liver disease, including severe cases, the AST is always two to three times higher than the ALT but remains less than 300 IU, while the ALT is almost always less than 100 IU.²⁰ In contrast, with most drugs causing acute hepatocellular necrosis, upper limits of these enzymes do not exist. Immense elevations in hepatic enzymes (5,000 to 10,000 IU) are most likely to be associated with acetaminophen or other chemical toxins and are unusual with other causes of liver disease, including acute viral hepatitis.

Clinical features of acute hepatocellular necrosis include fatigue, anorexia, nausea, and jaundice. When hepatocellular necrosis is accompanied by jaundice, prognosis is remarkably worse, with reported fatality rates of 10% or greater.²⁰ As hepatocellular necrosis progresses, clinical characteristics of acute liver failure such as jaundice, coagulopathy, ascites, hepatic encephalopathy, and death may occur. Several other drugs implicated in acute fulminant liver failure through the hepatocellular necrosis process are listed in table 4.

Table 4 Drugs Known to Cause Hepatocellular Necrosis	
Drug Class	Drugs
Antimicrobials	Sulfonamides, dapsone, ketoconazole, isoniazid, rifampin, pyrazinamide
Anticonvulsants	Phenytoin, valproic acid, carbamazepine, felbamate
NSAIDs and analgesics	Acetaminophen, piroxicam, diclofenac, sulindac, etodolac, bromfenac
Miscellaneous	Labetalol, flutamide, disulfiram, propylthiouracil, pemoline, nefazodone

Steatosis, another type of acute drug-induced liver toxicity, is a condition in which the hepatocytes are filled with droplets of fat and can be present in a microvesicular or macrovesicular pattern. In cases of acute steatosis associated with drug use, a microvesicular pattern is present, in which hepatocytes contain numerous small fat vesicles distributed uniformly throughout the cytoplasm without displacing the nucleus. Acute steatosis due to drugs can cause enlargement of the liver and may also result in irreversible cell damage.¹⁰ Results of liver function tests may remain normal or elevated, although not as high as those reported with hepatocellular necrosis. Drugs associated with acute steatosis include valproic acid, tetracycline, and aspirin.¹⁸ This form of drug-induced hepatitis is often asymptomatic, and manifestations of clinical features such as malaise, diarrhea, fever, jaundice, ascites, or edema indicate irreversible damage and poor prognosis.

Acute cholestatic injury: Cholestasis is a condition in which reduced secretion or obstruction of the biliary tree results in a reduction of bile flow. Cholestasis is characterized by elevations in alkaline phosphatase, gamma glutamyltranspeptidase, and other indicators of bile duct injury. In most cases of drug-associated cholestasis, symptoms of acute liver disease subside once the offending agent is withdrawn. Clinical manifestations include jaundice, pruritus, anorexia, malaise, pale stools, dark urine, and fatigue. Amoxicillin/clavulanate is one of the most frequent causes of acute cholestatic injury that can resemble biliary obstruction.²⁰ Other drugs associated with acute cholestasis include chlorpromazine, anabolic steroids, and oral contraceptives (table 5). Drug-induced

cholestasis requires a longer time to resolve than hepatocellular drug reactions but usually has a good prognosis, with jaundice resolving within several months.

Table 5	
Drugs Known to Cause Cholestasis	
Drug Class	Drugs
Antimicrobials	Ampicillin, amoxicillin/clavulanate, clindamycin, erythromycin, tetracycline, trimethoprim-sulfamethoxazole
Psychotropics	Chlorpromazine, amitriptyline, barbiturates, carbamazepine, haloperidol, imipramine
Miscellaneous	Azathioprine, ibuprofen, cimetidine, prochlorperazine, ticlopidine, estradiol

Acute mixed injury: Drug-induced injury in mixed form can be either primarily hepatocellular with cholestatic features or primarily cholestatic with characteristics of hepatocellular necrosis. With this injury, AST and ALT levels are elevated, usually more than eight times the upper normal limit. Alkaline phosphatase also increases to more than three times the upper normal limit. Jaundice and clinical features resembling cholestasis are commonly present. The prognosis is generally good, and fulminant hepatitis is rarely seen with mixed injury. The main drugs associated with mixed injury include tricyclic antidepressants, NSAIDs, macrolides, nitrofurantoin, sulindac, sulfonamides, amoxicillin/clavulanate, cyclosporine, methimazole, and carbamazepine.¹⁰

Chronic hepatitis: Drug-induced chronic hepatitis affects more females than males and is usually accompanied by serologic autoimmune markers.^{10,18} Drugs associated with drug-induced chronic hepatitis include dantrolene, diclofenac, methyldopa, minocycline, nitrofurantoin, and sulfonamides. Drug-induced liver damage occurs after drug administration for a prolonged period and beyond the initial liver insult. In patients with chronic hepatitis due to drug therapy accompanied by serologic markers of autoimmune disease, the majority of these patients (>90%) are women. In contrast, drugs such as lisinopril and trazodone are implicated in drug-induced chronic hepatitis without the serologic markers of autoimmune disease. Agents such as acetaminophen, aspirin, and dantrolene produce chronic hepatitis through toxic effects of the drugs, rather than through chronic inflammation of the hepatocytes. Clinical presentation of drug-induced chronic hepatitis has characteristics of both acute and chronic hepatic injury, such as enlarged liver, splenomegaly, and ascites. Jaundice, anorexia, and fatigue are also common. Results of liver function tests are usually elevated, and coagulopathy is often present. Withdrawal of the responsible agent may lead to improvement and complete resolution of chronic hepatitis within weeks. However, continued therapy with these agents may lead to cirrhosis, fulminant hepatic failure, and death.

Chronic steatosis: In contrast to acute steatosis associated with therapeutic agents, chronic steatosis has a minimal number of clinical manifestations. A macrovesicular pattern, in which a single large vacuole of fat fills the hepatocyte and displaces the nucleus to the periphery, is seen in this form of steatosis. Enlargement of the liver is the primary clinical feature of this form of chronic fatty degeneration and often results from the prolonged use of drugs such as glucocorticoids, methotrexate, amiodarone, and tamoxifen. Some chronic steatosis is benign, whereas methotrexate-induced steatosis can progress to cirrhosis. In addition, valproic acid has been associated with fatty degeneration that can result in chronic liver failure and severe hepatic necrosis.¹⁰

Other forms of drug-induced liver injury: Other types of drug-induced reactions that result in liver injury include granulomatous hepatitis, vascular injury, and hepatic tumor. Clinical characteristics of granulomatous reactions include fever, malaise, headache, and myalgia manifesting 10 days to four months after the initiation of drug therapy, with splenomegaly presenting in up to 15% of cases.¹⁰ Up to 60 medications have been associated with hepatic granulomas. In the vascular injury type of hepatotoxicity, hepatic vein thrombosis and hepatic venous occlusion can occur from drug therapy. Clinical symptoms of hepatic vein thrombosis include hepatomegaly, abdominal pain, ascites, and jaundice. Although rare, this type of liver injury has been associated with oral contraceptives.²¹ Hepatic venous occlusion also causes similar clinical presentation and has been associated with chemotherapeutic agents such as etoposide, vincristine, vinblastine, azathioprine, cyclophosphamide, methotrexate, and mitomycin.²² Drug-induced liver tumors rarely occur but are clearly associated with oral contraceptives and anabolic steroids. Incidence of oral contraceptive-induced hepatic tumors is estimated to be between three and four cases per 100,000 exposed women annually.²³

Herbal Medication–Induced Liver Injury

As herbal remedies continue to gain popularity, an increasing number of hepatic injuries due to herbal drugs are being reported. Liver injuries from herbal remedies range from mild and self-limiting to life-threatening conditions such as liver failure. The spectrum of herbal remedy–induced liver disease encompasses all forms of hepatic injuries, including minor elevation in liver function test results, acute and chronic hepatitis, steatosis, cholestasis, hepatic necrosis, hepatic fibrosis, veno-occlusive disease, and acute liver failure.²⁴ While these agents are readily available, they are not subject to rigorous testing or regulation, and a standardized manufacturing process does not exist. Consequently, safety information on these products is not available to the public. Potential health risks are increased with widespread use of these agents.

Comfrey is often ingested as an ingredient in herbal teas and belongs to species of plants that produce pyrrolizidine alkaloids, which have been recognized for more than 70 years as a cause of hepatotoxicity. The principal form of liver injury with comfrey is veno-occlusive disease, characterized by nonthrombotic occlusion of small veins within the liver lobules. Liver failure has occurred during the acute phase, with a mortality rate of up to 40%.²⁵

Jin bu huan is a traditional herbal remedy that has been used as a sedative and an analgesic. At least 10 cases of acute hepatitis have been linked to the use of Jin bu huan, with patients presenting with symptoms of fever, fatigue, nausea, pruritus, abdominal pain, jaundice, and hepatomegaly.²⁶ Symptoms resolved after the withdrawal of the agent, in most cases. Kava has been one of the most popular herbal remedies in recent years and is usually used for anxiety, insomnia, and stress. Several cases of kava-associated hepatotoxicity, including one report of hepatic failure requiring liver transplantation, have been reported. Warnings of potential health risks associated with the use of kava have been issued by the FDA.²⁷ Other herbal remedies implicated in hepatic injury include chaparral leaf, camphor, gentian, germander, and valerian.²⁸

Treatment and Prevention

The only well established treatment method to prevent drug-induced hepatitis is administering N-acetylcysteine to detoxify reactive metabolites, which can be given to patients with acetaminophen overdose. N-acetylcysteine should be given within the first 10 hours for the optimal protective effect.²⁹ In other cases of drug-associated hepatic injury, there is no specific treatment. Identifying and stopping the administration of the offending agent is the most important step in preventing the injury from progressing to life-threatening condition.

Prevention of drug-induced liver injury begins with assessing the toxicity of the drug at the preclinical stage and analyzing the safety in healthy volunteers or in patients

during the various steps of drug development. While these measures are currently used in drug development, hepatotoxicity continues to occur--although at low frequency--in susceptible patients. After the drug is marketed, prevention of hepatic injury can be accomplished by avoiding readministration of the offending drug and other drugs belonging to the same class. There are several reported cases of cross-hepatotoxicity between drugs within the same class, such as NSAIDs, macrolides, sulfonamides, tricyclic antidepressants, and pheno-thiazine derivatives.²⁰ In addition, avoiding the simultaneous administration of several drugs can also prevent drug-induced liver injury. Drugs associated with enzyme induction or inhibition can produce drug-drug interactions when administered with substrates of these reactions, which can result in hepatic injury. The elderly require a higher level of monitoring since older individuals are more susceptible to drug hepatotoxicity. Finally, follow-up liver function tests should be routinely monitored, especially for drugs with a known association to liver injury.

Role of the Pharmacist

The pharmacists involved in the direct care and monitoring of patients with DILD should be diligent in ordering and recommending baseline and follow-up liver function tests for those patients taking drugs with predictable hepatotoxicity. Pharmacists should be aware of drugs likely to cause liver injury and should educate patients on recognizing symptoms of liver damage associated with drug use. The most recent drugs that are reported to cause liver toxicities and that have been issued warnings by the FDA include Avonex (Biogen Idec), Remicade (Centocor), and Strattera (Eli Lilly). The elderly are at increased risk for hepatic injury due to age-associated changes in drug metabolism and possible multiple drug-therapy regimens. This population can benefit from the services of pharmacists who provide them with patient education and warnings about liver toxicities from medications. Information on possible adverse effects to the liver should be reinforced as often as possible. The most important role for the pharmacist in preventing DILD may be reporting drug-induced liver injuries to ongoing adverse drug reaction surveillance organizations or to the FDA. The NIH recently created the Drug-Induced Liver Injury Network to develop a standardized method of identifying and characterizing variations of DILD. Accurate assessment of adverse events and their frequency through postmarketing surveillance can help prevent future hepatic injuries.

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