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# Research Progress on Drug-induced Liver Injury in Children

**Jing Feng, Yanping Shi***

Shaanxi University of Chinese Medicine, Xianyang 712046, Shaanxi, China
**Correspondence Author*

**Abstract:** ***Drug-induced liver injury (DILI) is one of the most common and serious adverse drug reactions in clinical practice, with insidious onset, loss of appetite as the main clinical manifestation, and no specific detection index. Therefore, doctors should be alert to the potential damage to liver function of children taking drugs, pay attention to the emergence of drug liver injury, once found, stop the drug in time and give hepatoprotective symptomatic treatment. The purpose of this paper is to study the epidemiology, pathogenesis, clinical manifestations and staging, and current status of diagnosis and treatment of drug-induced liver injury, with a view to enhancing clinicians' understanding of DILI in children.***

**Keywords:** Children, Drug liver injury, Clinical**.**

## 1. Introduction

Drug-induced liver injury (DILI) refers to liver injury secondary to drug use, caused by drugs and/or drug metabolites, and is often caused by the moderate or excessive intake of various types of prescription and over-the-counter drugs, herbal medicines, and dietary additives [1]. As a special group, children's physiological functions are not yet perfect and their immunity is poor, so the clinical characteristics and diagnosis and treatment of DILI in children are quite different from those in adults. Drug induced liver injury (DILI), as one of the most common and serious adverse reactions, poses a serious threat to children's health and is increasingly receiving clinical attention. The research progress of DILI in children is summarized as follows.

## 2. Epidemiology

Drug-induced liver injury (DILI) is a very common clinical liver disease, and in severe cases, it can lead to acute liver failure (ALF) or even death. In our hepatology study, the annual incidence of DILI in the general population is 22-24/10, 000 people [1], which is only lower than fatty liver disease and viral hepatitis. The incidence in the pediatric population is unknown, and a retrospective study in China in 2022 [2] reported that DILI cases accounted for 0.248% of the hospitalized patients in the same period, whereas DILI cases in children under 18 years of age accounted for 4.29%. In some western countries, the incidence of drug-induced liver injury (DILI) is 14-19/100, 000 people [3], with DILI in children accounting for about 10% of all cases [4], and DILI is even the most important cause of acute liver injury, accounting for about 15%, except for ischemic hepatitis. This shows that DILI in China is significantly higher than in some western countries. There are more than 1, 000 drugs known to have hepatotoxic effects, involving Western drugs, Chinese herbs, etc. [5]. In China, the main drugs that cause DILI include herbal medicines and dietary supplements as well as anti-tuberculosis drugs. Among the major drugs causing DILI in children are antibacterials, antipyretics and analgesics, and anti-tuberculosis drugs. In western countries, 53% of DILI cases are caused by prescription drugs (36% by antibiotics), while 43% are caused by herbs (e.g., He Shou Wu, Lei Gong Teng, Uva Ursi, Tu San Qi, etc.) and dietary supplements (e.g., Vitamin B, Calcium Mineral, etc.) [6].

## 3. Sensibility and Pathogenesis

The pathogenesis of DILI has not been clearly elucidated, and it is currently believed that a combination of factors contributes to DILI. the first is the direct hepatotoxicity of the drug. The liver is the most important metabolizing and detoxifying organ in the body, and is highly susceptible to the effects of various drugs and metabolites. Excessive intake of drugs and metabolites, decreased detoxification function of the liver, decreased drug clearance rate and thus accumulation of drugs in the body, the toxicity of the drug will directly cause hepatocellular injury or even necrosis. The second is specific hepatotoxicity. It is mainly immune-related damage, also known as indirect damage. Through the activation of humoral immunity to complete the immune response, resulting in liver cell damage. Representative drugs include amoxicillin clavulanate potassium, cephalosporins, isoniazid and so on. The third is mitochondrial damage. This is the main cause of hepatocellular necrosis type DILI. Drug stress causes mitochondrial dysfunction, which damages the body's own circulatory processes, leading to triacylglycerol deposition and an increase in lactic acid, resulting in hepatocellular steatosis. The fourth is the inflammatory response. Relevant damage molecules hidden in the external environment are released and activate receptors on immune cells during tissue injury, resulting in an immune response, such as the production of pro-inflammatory factors and the localization of damaged cells. It has been suggested [5] that hepatocyte injury and apoptosis occur due to oxidative reactions triggered by the active components of drug metabolites, which induce organelle stress and activation of stress kinases. In conclusion, current research progress suggests that DILI is an active process in which drug metabolism or mitochondrial dysfunction after drug administration induces cellular stress, which activates the cell death pathway and immune response, and ultimately leads to hepatocyte death [5]. Foreign studies have also focused on the role of immune cells, immune cell and hepatocyte interactions [8], with a view to further elucidating the pathogenesis of DILI and providing potential therapeutic targets.

## 4. Clinical Manifestations

The most common clinical manifestations in children with DILI are loss of appetite, which accounts for more than 50% of cases [9-11], and gastrointestinal symptoms (malaise, abdominal distension, vomiting, discomfort in the liver area, jaundice, etc.). Some children also have yellow urine, white clay-like stools, itchy skin, etc., and in severe cases, acute liver failure (ALF) may occur. Children with DILI may also have allergic reactions such as liver injury, fever, skin lesions, enlarged lymph nodes, and eosinophilia, but the proportion is relatively low [12]. The clinical presentation of DILI lacks specificity, and it is easily associated with other liver diseases such as autoimmune hepatitis DILI is easily confused with other liver diseases such as autoimmune hepatitis, viral hepatitis, steatohepatitis, and primary biliary cholangitis.

## 5. Diagnosis of DILI

Due to the lack of specific diagnostic markers, the diagnosis of DILI still adopts an exclusive strategy. A clear history of drug use, the relationship between the suspected drug and liver damage, the recurrence of the disease after drug cessation, relevant pathologic examinations, and the exclusion of other etiologic factors are needed to make the diagnosis. Together with the different physiological and pathological characteristics of children, this makes the diagnosis of DILI in children more difficult and should be carefully recognized clinically.

First of all a clear history of drug use is necessary before diagnosing DILI in children. In China, the top 5 etiologies causing DILI in children are antibiotics, traditional Chinese medicines, antipyretic and analgesic drugs, antitumor drugs, and antituberculosis drugs, accounting for 34.4%, 20.1%, 15.9%, 10.7%, and 7.0% respectively [13]. When a history of suspected liver damage medication is suspected, the association between the suspected medication and liver damage needs to be evaluated. the RUCAM Causality Assessment Method (the Roussel Uclaf Causality Assessment Method) is widely used, highly accurate, and supported by a large body of evidence-based medicine [14]. However, RUCAM is not accurate enough for the diagnosis of DILI in children due to the fact that children are still in the process of growth and developmental changes and the physiological characteristics of children. China's guidelines for the diagnosis and treatment of drug-induced liver injury [15] suggest that there are chemical thresholds for the diagnosis of DILI (see Table 1). In addition, whether the liver injury stops or continues after stopping the drug also contributes to the diagnosis of DILI. Secondly, other etiologies causing liver damage, such as autoimmune liver disease, need to be excluded. Although laboratory tests have no specific advantage, ultrasound and liver biopsy can still be used to identify liver injury caused by other hepatobiliary diseases. A prospective study showed [16] that liver biopsy changed 38% of DILI patients from undetermined to highly determined, suggesting that liver biopsy plays an important value in the differential diagnosis of DILI. In general, patients with DILI have a complex and varied pattern of pathological injury and lack of characteristic pathological changes, which usually include infiltration of inflammatory cells (eosinophils, lymphocytes, etc.), cellular swelling, cellular ballooning, hepatocellular pitting necrosis, interfacial hepatitis, steatosis, and cholestasis [17, 18]. The biomarkers currently used in clinical practice include total bilirubin (TBiL), alanine aminotransferase (ALT) aspartate aminotransferase (AST), alkaline phosphatase (ALP), and direct bilirubin (DBil). Recent studies have found [19, 20] serum glutamate dehydrogenase, mitochondrial DNA, microRNA-122, high mobility group B1, keratin 18, glutathione S-transferase, and macrophage colony-stimulating factor receptor 1 to be helpful in early assessment of the risk of developing DILI. However, the above latest markers are still in the research stage and their clinical value needs to be further explored.

**Table 1:** Chemical thresholds for the diagnosis of DILI in the 2023 guidelines for the diagnosis and management of drug-induced liver injury

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|---|
| (i) ALT ≥5× upper limit of normal (ULN) |
| (ii) ALP ≥ 2×ULN (especially when accompanied by elevated GGT or when primary pathologic changes in bone are excluded) |
| (iii) ALT≥3×ULN and TBil≥2×ULN. |

Note: One of the above conditions must be met.

## 6. Treatment of DILI

Domestic and international guidelines recognize that the first and foremost measure for the treatment of DILI is to discontinue drugs suspected of causing liver damage in a timely manner and to avoid using other drugs with potential liver damage, which is also the basic principle of treatment. About 95% of DILI patients have improvement or even cure after stopping the drugs [21]. In order to avoid unnecessary drug discontinuation, guidelines such as those of China and the European Society of Hepatology jointly provide reference standards (see Table 2). Secondly, hepatoprotective therapy is added on the basis of drug discontinuation according to the level of liver function, and commonly used drugs include glycyrrhizic acid preparation [22], silymarin, adenosylmethionine [23], xiyanping injection [24], reduced glutathione [25], dicyclomine [26], ursodeoxycholic acid [27] and so on. In addition, specialized antidotes can be used for specific drugs, such as N-acetylcysteine to relieve the hepatotoxicity of acetaminophen, levocarnitine to ameliorate the hepatotoxicity of valproate, and kaulethylene amine to attenuate the hepatotoxicity of leflunomide. The use of glucocorticosteroids is currently controversial and lacks evidence-based medical support, and it is not recommended as a routine treatment option for DILI in the Chinese 2023 guidelines for the diagnosis and treatment of drug-induced liver injury. In the course of treatment, the occurrence of ALF should also be monitored, and timely liver transplantation is the most effective approach for certain children with DILI who progress rapidly to liver failure, such as hepatic encephalopathy and untreatable coagulation disorders. Survival after liver transplantation is high, 60%-90% [28].

**Table 2:** Reference criteria provided by China and European Society of Hepatology and other guidelines [29]

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|---|
| (i) Serum ALT or AST > 8 times normal value |
| (ii) ALT or AST >5 times normal value |
| (iii) ALT or AST >3 times the normal value and TBil >2 times the normal value or INR >1.5 |
| (iv) ALT or AST >3 times the normal value, accompanied by fatigue and gastrointestinal symptoms that progressively worsen, and/or eosinophilia. |

## 7. Summary

In summary, the incidence of DILI is increasing year by year and has become a global public health problem. the pathogenesis of DILI is unclear, there is no specific diagnostic index or marker, it is difficult to differentiate it from other diseases, and it is only found in routine examination and is difficult to be treated. Once a diagnosis is made, the primary treatment is to discontinue the suspected drug and to give hepatoprotective therapy. However, DILI in children has not been systematically emphasized and is still based on adult criteria, and more clinical and experimental research needs to be invested in this special group of children. It is expected that more prospective biomarkers and biochemical diagnostic thresholds for DILI in line with the age-dependent trend of children can be explored to assist in the diagnosis, so that children's own diagnostic and treatment system can be established as soon as possible, and clinical pediatricians can be guided to more accurately recognize and treat DILI in children.

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