Review Article

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Drug-Lnduced Liver Injury: Advances In Antibacterial, Antifungal And Antiviral Drugs

Shi-lu Kang[1,2#], Qian Gao[1,2#], Han-yue Ma[1,2], Yu-han Zhang[1,2] Cong Huai[*3] and Zhi-ling Li[*1,2]

[1]Department of Pharmacy, Shanghai Children's Medical Center, School of Medicine, Shanghai Jiao Tong University, Shanghai 200127, China
[2]School of Medicine,Shanghai Jiao Tong University, Shanghai 200125, China
[3]Bio-X Institutes, Shanghai Jiao Tong University
[#]These authors equally contributed to this work.

[*]**Correspondence author:**
Zhi-ling Li, Cong Huai,
Department of Pharmacy, Shanghai Children's Medical Center, School of Medicine, Shanghai Jiao Tong University, Shanghai 200127, School of Medicine,Shanghai Jiao Tong University, Shanghai 200125, Bio-X Institutes, Shanghai Jiao Tong University, China,
E-mail: lizhiling22@163.com (Z. L.); huaic@sjtu.edu.cn (H.C)

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1. Abstract

Drug-induced liver injury (DILI) is an important but rare clinical adverse event and a potential complication of many drugs, which can range from liver enzyme elevations to severe liver failure, liver transplantation even death. The severity of DILI varies from person to person, depending on the type of drug and the state of patients. Most of the drugs commonly prescribed in clinical practice today can be classified as antibacterial, antifungals, and antivirals, which generally summarize the types of drugs that cause DILI. Based on the classification of these three drugs, we summarized the literatures of various databases including Pubmed, Embase, JAMA, Web of science, ranging from 1999 to 2020, and the keywords we searched contain drug-induced liver injury, hepatotoxicity, antibiotics, antimicrobial agents antibacterials, antifungals, antivirals, and cholestasis etc., and explained the incidence, main symptoms, duration and other related indicators of DILI with representative drugs of each type. In this review, we summarized and compared the liver injury caused by different anti-infective drugs, which can guide clinicians in the treatment of patients with drug-induced liver injury complicated with infection.

2. Keywords:
Drug-Induced Liver Injury, Antimicrobial Agents, Antibacterial, Antifungals, Antivirals

3. Introduction

Drug-induced liver injury refers to disfunction or damage of liver caused by the drug usage [1]. The clinical manifestation is classified as below. [1] liver dysfunction, alanine aminotransferase (ALT) and aspartate aminotransferase (AST)elevation. [2] jaundice and cholestasis. [3] abdominal pain or discomfort. The symptoms differ individually[2,3]. Drug-induced liver injury can be classified as cholestatic type, hepatocyte injury and mixed type[4] these different types of liver injury may warrant various clinical approach and treatment.The cholestatic type is characterized by a significant and more than two-fold increase in serum alkaline phosphatase (ALP), usually accompanied by elevated bilirubin. Biopsy shows cholestasis of the canaliculi with or without portal inflammation. Hepatocyte injury is characterized by more than doubling of ALT and ALT/SAP (Serum Alkaline Phosphatase) ratio greater than 5. Hepatocyte biopsy often shows hepatocyte degeneration or necrosis, with or without inflammation. Mixed damage is a combination of the above characteristics[5]. Meanwhile, DILI can be classified as acute subacute and chronic injury in terms of the course of disease.Acute liver injury occurs within weeks after drug exposure; Subacute liver injury occurs weeks to months after drug exposure; Chronic liver injury refers to chronic progressive liver injury caused by long-term use of certain drugs, such as anti-tuberculosis drugs and anti-epileptic drugs[6].

According to general statistics, the overall incidence of DILI is about 14-19 cases per 100,000 people [7], and the incidence varies in different countries. The most common cause is the using of anti-infective drugs[8]. Psychotropic drugs and non-steroidal anti-inflammatory drugs are also the most common causes, accounting for 22.5% and 10%, respectively[8]. The frequency of DILI caused by Traditional Chinese medicine and dietary supplements is increasing year by year[4]. Based on Chinese population Most of the anti-infective drugs are antibacterial, and DILI caused by antifungal drugs accounts for 2.9% of all drug-induced liver injury[9]. Drugs damage the liver mainly by inducing mitochondrial dysfunction, inhibition of liver transporters or formation of reactive metabolites (RM)

[10]. Drugs cause mitotic toxicity and damage the liver by inhibiting mitochondrial fatty acid oxidation, inhibiting or uncoupling oxidative phosphorylation (OXPHOS), and enhancing mitochondrial membrane permeability, and causing cell death ulteriorly[11]. Liver transporters play key roles in healthy liver, and any transportation-based disruption of the transport process may lead to liver injury[12]. Efflux transporters, such as multidrug resistant proteins (MRPs) and p-glycoproteins (P-GP), can remove toxins and other exogenous substances, including some drugs and drug conjugates). Uptake transporters, such as organic ion transport polypeptides (OATPs), assist in the absorption of sugars, peptides and other nutrients[15]. Some drugs including statins, are OATP substrates. They rely on these transporters to transport themselves into cells for their effects[16,17]. Other transporters, such as bile salt output pump (BSEP), export bile acids and assist in enterohepatic circulation, participating in key steps of bile secretion [18]. Although essential for many liver functions, some bile acids can be toxic at higher concentrations. Therefore, since some liver transporters are responsible for maintaining the proper balance of bile acids in the liver, inhibition of these transporters may lead to cholestasis and DILI.

The common pathway of drug metabolism is to transform the drug into one or more benign metabolites which are more soluble and then remove them. There are two approaches. The first is oxidative metabolism or combined metabolism, or both. A second possible pathway produces electrophilic RM [19, 20], which reacts with endogenous circulating nucleophile cells such as glutathione (GSH)[21]. In the presence of binding enzymes such as glutathione S-transferase (GST).This detoxification process usually produces a water-soluble benign binding metabolite that is more easily eliminated. Alternatively, RM may react with endogenous nucleophilic proteins to form macromolecular adduct, hydrogen electron groups, and oxygen radicals that disrupt normal organ function and may cause liver damage. Since most metabolism occurs in the liver, it is closely associated with RM - mediated toxicity. Drugs are represented by acetaminophen, which is converted to phenol-glucuronic acid metabolites (and phenol sulfate) and eliminated at normal doses. At higher doses, CYP450-mediated oxidation produces iminoquinone, which can react with GSH or bind to endogenous proteins, sometimes causing liver damage [22].

4. Antibacterials

4.1.Antibiotic:

The hepatotoxicity of most antibiotics is specific, so antibiotics-induced liver injury can be divided into a variety of mechanisms and manifestations, including hepatocyte injury, cholestasis, mixed hepatocyte/cholestatic injury. Hepatotoxicity induced by antibiotics is the most significant in DILI reportedin various countries. In general, antibiotics-associated hepatotoxicity is mild and self-limited; Most cases recover after withdrawing the drug. However, it may occasionally present as a serious life-threatening condition or may develop to a systemic chronic disease with high morbidity. This review summarizes reports of hepatotoxicity associated with major antimicrobial agents and, if possible, identifies potential risk factors and management strategies to assist clinical practice. The diagnosis of antibiotics-induced liver injury is also a problem because the infection itself leads to abnormal liver injury-related biochemical parameters and is an important cofactor of drug hepatotoxicity. Immune-mediated damage may result from liver inflammation associated with viral or bacterial infection, as well as a response to antibiotics metabolism. Some antibiotics may act synergistically with lipopolysaccharide induced inflammatory cytokine signaling to cause hepatocyte death.

4.2. Levofloxacin

Levofloxacin is a fluoroquinolone antibiotic, and about 5% of patients have slightly elevated serum ALT and AST levels during short-term administration. Side effects of levofloxacin on the liver are usually asymptomatic, self-limited and rarely require dose adjustment. Patients with mild symptoms usually recover quickly and completely within 4 to 8 weeks of discontinuing the drug, but relapse is more likely due to re-use. In a small number of cases, acute liver failure has been associated with quinolones. In some cases, chronic jaundice, cholestasis and biliary disappearance syndrome were observed. The characteristics of rapid onset and severe course of disease indicate that hypersensitivity symptoms may occur. Although it has not been confirmed yet, the similarity of clinical symptoms and incubation period of liver injury suggests that there may be cross-reactivity between levofloxacin and fluoroquinolones. Therefore, patients are advised to avoid re-taking levofloxacin and other fluoroquinolones in the future.

4.3 rifampin

Rifampicin belongs to macrolide antibiotics, which has antibacterial activity against many kinds of bacteria, among which the inhibition effect on Mycobacterium tuberculosis is the best, and it is clinically used for the treatment of tuberculosis. Meanwhile, rifampicin is also a potent inducer of many liver enzymes (including drug metabolism enzymes CYP 1A2, 2C9, 2C19 and 3A4), meaning that the administration of rifampicin can affect the metabolic processes of many other drugs. Therefore, oral contraceptives, anticoagulants, cyclosporine, benzodiazepines and other drugs should be carefully selected and monitored in time. Patients with existing liver disease and cirrhosis are particularly prone to jaundice when treated with rifampicin, but since rifampicin is often used in combination with isoniazid and pyrazinamide (known hepatotoxic agents), it is difficult to attribute the associated liver damage to a single agent. The mechanism of hepatotoxicity induced by rifampicin is currently unknown, but based on the majority of its metabolism through the liver and its ability to induce many liver enzymes, liver injury induced by rifampicin may be due to fact that specific metabolites may directly produce toxicity or induce immune responses[23].

4.4. Minocycline

Minocycline belongs to tetracycline antibiotics, with good absorption and tissue penetration, which can be used to treat a variety of bacterial infections and acne. It is widely used and often prescribed in clinical prescriptions. Minocycline can cause a syndrome similar with acute hepatitis, usually within one to three months of taking the drug, or latent chronic hepatitis in the case of prolonged treatment. In many cases of

minocycline - induced acute hepatitis, symptoms usually appear weeks or months after treatment. Elevated enzyme levels usually show hepatocyte damage, similar to viral hepatitis. Common symptoms of immune hypersensitivity are fever, rash, and eosinophilia.

4.5. Sulfonamides

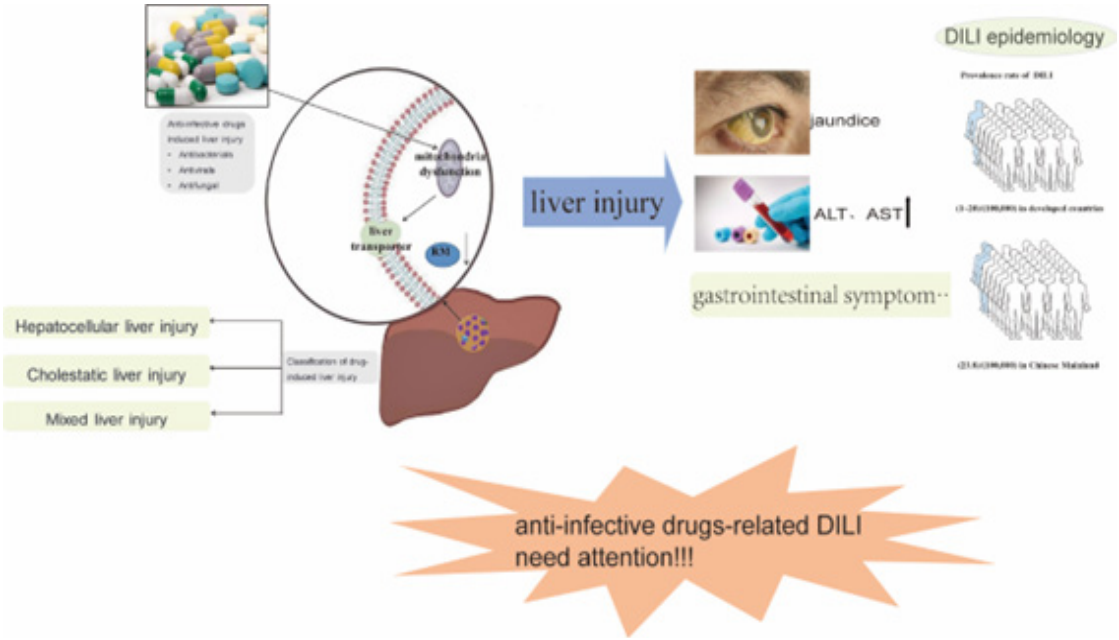
Sulfa drugs mainly include sulfasalazine, trimethoprim sulfamethoxazole, dapsone, compound sulfamethoxazole and so on. The sulfonamides are thought to be involved in the hypersensitive part of the reaction. In the GPRD (General Practice Research Database) analysis, sulfasalazine was one of the most hepatotoxic drugs, with an incidence of nearly 1 in 1000. Trimethoprim sulfamethoxazole usually causes cholestasis or mixed lesions within a few days of initiation of treatment and may have prominent hypersensitivity. Dapsone and cotrimoxazole can cause typical heterogenous liver injury, characterized by hypersensitivity. Typical clinical symptoms are sudden onset of fever and rash, followed by jaundice, eosinophils and lymphocytosis, which can be seen on biochemical tests several days or weeks after the beginning of drug therapy. Most patients recover quickly within two to eight weeks after stopping the drug. In rare cases, liver damage caused by dapsone and cotrimoxazole can lead to acute liver failure.

4.6. Amoxicillin clavulanate

Amoxicillin-clavulanate was the single agent most commonly associated with liver damage in most DILI studies. Intravenous administration of amoxicillin-clavulanate may increase the risk because intravenous administration can significantly alter the pharmacokinetics of a drug. However, data on hepatotoxicity associated with this route of administration are limited. Liver injury caused by amoxicillin clavulanate is usually a type of delayed cholestasis or mixed liver injury, with an average incubation period of 16-30 days[7]. A study by the Spanish Hepatotoxicity Registry showed that hepatocellular type predominated in young patients, while cholestasis/mixed type was associated with older patients[7].

Table1. Antibiotics-related DILI

DILI caused by antibiotics is a common adverse event, especially in patients with long-term, high doses of drugs or individuals with a high genetic predisposition[6]. If abnormal symptoms such as jaundice, ALT and AST elevation occur after the use of antibiotics, the dose should be



Graphical Abstract: An overview of DILI mechanism

4.7. Antifungals

In recent years, with the prevalence of AIDS, the popularization of tumor radiotherapy and chemotherapy, the abuse of antibiotics, hormones, immunosuppressants, the wide application of organ transplantation and interventional therapy, fungal infection rate is increasing[24, 25]. Antifungal liver injury is also becoming more common in clinical practice, with the increasing number of 3% of DILI events[25]. According to the instructions of antifungal drugs included in, the types of antifungal drugs with adverse reactions related to hepatotoxicity in clinical use can be retrieved: echinocandins, polyene antibiotics (amphotericin, etc.), Allyamine, (Terbinafine, etc.), azole, and antimetabolitas (flucytosine, etc.). The specific information of liver damage caused by them can be seen in Table 1[11]. In the literature summarizing the incidence of hepatotoxicity of antifungal drugs, of the 1964 cases of DILI caused by antifungal drugs, about 50% were caused by azole antifungal drugs[12]. Azole antifungals are synthetic broad spectrum antifungals, including imidazole and triazole. Triazole antifungal include ketoconazole, miconazole, econazole, clotrimazole, etc. Due to their high oral toxicity, imidazolesare currently used for topical treatment of superficial fungal infections and candida infections of the skin and mucosa. Triazole includes itraconazole, fluconazole and so on, which can be used as the first choice in the treatment of deep fungal infection.

reduced or replaced with another antibiotic in time.

The liver injury caused by triazole antifungal drugs mainly included hepatocyte injury and cholestasis, which showed typical characteristics of drug-induced liver injury. In the early stage, patients may have fatigue, loss of appetite, vomiting, abdominal distension, diarrhea and other digestive tract symptoms. Some patients also have symptoms such as rash, fever, itchy skin and muscle pain in limbs. This is followed by jaundice and mild to moderate pain in the liver. Serum alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), total bilirubin (TBil), serum γ -glutamyl transpeptidase (GGT) and other indicators were abnormally elevated.Peripheral blood eosinophils were more than 6% and pseudonuclear cells were increased.If further examination of liver tissue, liver tissue lesions can be found, such as swelling of liver cells, cholestasis of liver cells and capillary bile duct areas, inflammatory cell infiltration and other phenomena. After discontinuation of the drug, the symptoms of liver injury will be significantly relieved or disappear[13].

Table2. Antifungals-related DILI

DILI caused by antifungals is a rare and severe adverse event[26, 27] If liver dysfunction occurs during antifungal therapy, the doctor should adjust the treatment plan in time according to the situation of the patient's liver function.

4.8. Antivirals

Due to the complexity of antiviral therapy, liver injury caused by antiviral drugs is difficult to determine. In the course of treatment, some chronic viral infections may cause liver damage. Antiviral drugs are often used in combination, so it is impossible to determine whether specific liver damage is related to a specific drug. Differences in individual nutritional status and susceptibility to enzyme changes are factors that increase the difficulty in determining hepatotoxic drugs[28]. Table 3 summarizes the clinical manifestations and severe ALT elevation rates of three types of antiretroviral drugs in hepatotoxicity. The clinical manifestations and mechanisms of hepatotoxicity of some drugs are described below.

4.9. Nucleoside reverse transcriptase inhibitors (NRTI)

During antiretroviral therapy, the incidence of hepatotoxicity is between 3% and 18%. During the use of NRTI, about 5%-10% of patients showed hepatotoxicity[29]. Such drugs include stavudine, zalcitabine, didanosine, lamivudine, zidovudine, abacavir, emtricitabine and Tenofovir. NRTI can inhibit mitochondrial DNA polymerase -γ[30] and make cells change from aerobic respiration to anaerobic respiration, resulting in a large amount of lactic acid which can lead to hyperlactemia. Hyperlactic acidosis may present as an asymptomatic to potentially fatal lactic acidosis syndrome. Stavudine, zalcitabine and didanosine had highest incidence of lactic acid poisoning in these drugs and it`s the same as mitochondrial toxicity degree, which are zalcitabine, didanosine, stavudine, lamivudine, zidovudine, abacavir from heavy to light for tashi he marina, dano sheen, stavudine, lamivudine and zidovudine, abacavir[22]. NRTI may cause hepatic steatosis. In the case of liver transaminase elevation as the standard, the incidence is 5-15%[31].Patients may present with hepatomegaly, nausea, ascites, edema, dyspnea, myopathy and encephalopathy. Histology of the liver reveals microvesicles or bullae steatosis, with little necrosis but no inflammation. NRTI can also cause non-cirrhotic portal hypertension, with a prevalence rate of 1%[32]. Portal hypertension, including esophageal varices, life-threatening gastrointestinal bleeding, ascites, and splenomegaly. Liver tissue presentation may vary, with nodular regenerative hyperplasia, hepatic portal sclerosis, periportal fibrosis, and occlusive portal vein lesions. HIV infection is often associated with hepatitis VIRUS HBV and HCV infection, and the combined use of NRTI and anti-hepatitis virus drugs will increase hepatotoxicity[33].

4.10. Non-nucleoside reverse transcriptase inhibitors (NNRTI)

NNRTI mainly includes nevirapine, efavirenz and delavirdine. Liver injury caused by nevirapine usually presents as allergic toxic hepatitis. Patients may present with elevated transaminases, in addition to physical symptoms such as rash, eosinophilia, lymphadenopathy, interstitial nephritis, and pneumonia; High ALT levels, advanced fibrosis, and prolonged treatment were associated with severe hepatotoxicity of nevirapine. Studies have shown that hepatotoxicity of nevirapine is correlated with specific genes, and individuals carrying HLA DRB1*0101 gene are more likely to suffer liver injury after taking this drug[34]. The incidence of liver injury of nevirapine was higher than that of efavirenz. The frequency of DILI in patients taking efavirenz was 1%-8%, while the frequency of DILI in patients taking nevirapine ranged from 4%-18% [32].

4.11. Protease inhibitors (PIs)

PIs include indinavir, nelfinavir, amprenavir, ritonavir, saquinavir, lopinavir/ritonavir, fosamprenavir, atazanavir, tipranavir, darunavir. Ritonavir in high dose may have the highest probability of liver injury among these drugs, with the incidence of severe hepatotoxicity of 3-9%, while toxicity can be avoided in low dose[22]. It has been reported that 6-25% of patients taking indinavir develop hyperbilirubinemia and generally do not show clinical symptoms, but jaundice may occur occasionally[35]. Indinavir competitively inhibits uridine diphosphate (UDP) -glucuronyl transferase (UGT), and UGT1A1*28 can increase the severity of its induced hyperbilirubinemia in Caucasian patient populations[22]. UGT1A1*6 has been proved to be associated with hyperbilirubinemia induced by indinavir treatment in Thai patients[36]. Hyperbilirubinemia also occurs in patients taking atazanavir, whose mechanism is similar to that of indinavir[32]. Tipranavir, a newer drug commonly used in combination with ritonavir, has been associated with severe hepatotoxicity and a black-box warning was issued in 2006 warning of the risk of hepatitis and liver decompensation in people taking tipranavir and ritonavir, especially in patients with co-infection with hepatitis B or C.

Table3. Antivirals-related DILI

Antivirals mainly include antiretroviral drugs, anti-hepatitis B virus drugs and anti-hepatitis C virus drugs, which may lead to elevation of liver enzyme levels, hepatitis and even liver necrosis[37].Therefore, for patients using such drugs, especially those with abnormal liver function,

it is necessary to monitor liver function closely and use drugs rationally under the guidance of doctors.

5. Discussion

The severity of drug-induced liver injury varies from person to person, depending on the type of drug and the patient itself, such as drug dose, lipophilic, metabolic activity; Race, age, sex, genetic susceptibility and drug combination were all factors affecting drug-induced liver injury. Most patients can recover completely, but some patients may develop acute liver failure (ALF), requiring liver transplantation or even leading to death1. Hy's Rule believes that the co-occurrence of liver injury and jaundice caused by a drug is associated with poor prognosis, and the mortality rate is 10-50%[38]. Regarding drugs causing DILI, a large-scale, multi-center, retrospective study in China included a total of 25 927 patients with DILI from 308 hospitals from 2012 to 2014.Traditional Chinese medicine or HDS(26.81%), anti-tuberculosis drugs (21.99%), anti-tumor drugs or immunomodulators (8.34%) were the main causes of DILI in China[39]. In addition, the study also found that 13% of patients had chronic DILI, and 23.38% of patients had basic liver diseases such as viral hepatitis and fatty liver at the time of DILI, and these patients had more severe liver injury and a higher risk of liver failure and death.

At present, human beings mainly establish preclinical drug DILI risk prediction model, and conduct cell experiments and animal experiments on model cells - cancer cells. In the future, induced pluripotent stem cells (IPSCs) and larger organoids significantly improve genomic stability compared to cancer cells, and advances in bioprinting methods are expected to improve reproducibility[21]. High-throughput imaging analysis and fibroomics techniques can identify intracellular components such as nuclear and mitochondrial morphology, oxidative stress, and other endpoints associated with DILI[33,40] . The fusion of various technologies in microfluidic, cell biology, micromachining and microengineering can create microfluidic cell culture chips, or "organs on chips"[32]. Liver microarrays have been used to evaluate several known DILI mechanisms, including mitotic toxicity and RM-induced toxicity[41]. Another important possibility is integration with other organs on the chip to simulate the results of tissue-tissue, organ-organ interactions. One example demonstrates the integration of liver and kidney chips to study primary and secondary toxicity and drug-drug interaction effects[42]. Further complexity and multi-organ integration are being developed towards "body-on-chip" platforms[36]. It is possible to simulate human tissue more closely than simple cells and animals, and it is easier to observe DILI before clinical trials, avoiding the loss and injury caused by further clinical trials. Through large data of known human adverse reaction of drugs and is considered a safe test and retrospective analysis, determine the process of drug metabolism, liver transporter, reactive metabolites, mark the liver damage related genes of specific drugs, metabolism of types and characteristics, to establish digital model to simulate the human body, clinical prediction DILI is a development direction in the future. It may become a reality for clinicians to prescribe medicine by inputting the patient's chief complaint, age, sex, height, weight, race, history of drug allergies, genetic loci and reviewing the type and dosage of drugs recommended by the model.

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Reference

1. Hoofnagle, J.H. and E.S. Björnsson, Drug-induced liver injury—types and phenotypes. New England Journal of Medicine, 2019. 381(3): p. 264-273.
2. David, S. and J. Hamilton, Drug-induced Liver Injury. US gastroenterology & hepatology review, 6, 73-80. 2010.
3. Kaplowitz, N., Drug-induced liver injury. Clinical infectious diseases, 2004. 38(Supplement_2): p. S44-S48.
4. Andrade, R.J., et al., Drug-induced liver injury. Nature Reviews Disease Primers, 2019. 5(1): p. 58.
5. Brown, S.J. and P.V. Desmond. Hepatotoxicity of antimicrobial agents. in Seminars in liver disease. 2002. Copyright© 2002 by Thieme Medical Publishers, Inc., 333 Seventh Avenue, New ….
6. Park, J.H., et al., Prevalence and clinical characteristics of antibiotics associated drug induced liver injury. Annals of Translational Medicine, 2021. 9(8).
7. Björnsson, E.S., Drug-induced liver injury due to antibiotics. Scandinavian journal of gastroenterology, 2017. 52(6-7): p. 617-623.
8. Devarbhavi, H. and R.J. Andrade. Drug-induced liver injury due to antimicrobials, central nervous system agents, and nonsteroidal anti-inflammatory drugs. in Seminars in liver disease. 2014. Thieme Medical Publishers.
9. Kyriakidis, I., et al., Clinical hepatotoxicity associated with antifungal agents. Expert opinion on drug safety, 2017. 16(2): p. 149-165.
10. Will, Y. and J.A. Dykens, Mitochondrial dysfunction caused by drugs and environmental toxicants. 2018: John Wiley & Sons.
11. Will, Y. and J. Dykens, Mitochondrial toxicity assessment in industry–a decade of technology development and insight. 2014, Taylor & Francis. p. 1061-1067.
12. Hillgren, K.M., et al., Emerging transporters of clinical importance: an update from the International Transporter Consortium. Clinical Pharmacology & Therapeutics, 2013. 94(1): p. 52-63.
13. Hodges, L.M., et al., Very important pharmacogene summary: ABCB1 (MDR1, P-glycoprotein). Pharmacogenetics and genomics, 2011. 21(3): p. 152.
14. Borst, P., et al., The multidrug resistance protein family. Biochimica et Biophysica Acta (BBA)-Biomembranes, 1999. 1461(2): p. 347-357.
15. Kalliokoski, A. and M. Niemi, Impact of OATP transporters on pharmacokinetics. British journal of pharmacology, 2009. 158(3): p. 693-705.

16. Shitara, Y., et al., Clinical significance of organic anion transporting polypeptides (OATPs) in drug disposition: their roles in hepatic clearance and intestinal absorption. Biopharmaceutics & drug disposition, 2013. 34(1): p. 45-78.
17. Maeda, K., Organic anion transporting polypeptide (OATP) 1B1 and OATP1B3 as important regulators of the pharmacokinetics of substrate drugs. Biological and Pharmaceutical Bulletin, 2015. 38(2): p. 155-168.
18. Cheng, Y., et al., In vitro model systems to investigate bile salt export pump (BSEP) activity and drug interactions: a review. Chemico-biological interactions, 2016. 255: p. 23-30.
19. Stachulski, A.V., et al., The generation, detection, and effects of reactive drug metabolites. Medicinal research reviews, 2013. 33(5): p. 985-1080.
20. Park, B.K., et al., Managing the challenge of chemically reactive metabolites in drug development. Nature Reviews Drug Discovery, 2011. 10(4): p. 292-306.
21. Hayes, J.D., J.U. Flanagan, and I.R. Jowsey, Glutathione transferases. Annu. Rev. Pharmacol. Toxicol., 2005. 45: p. 51-88.
22. Underhill, G.H. and S.R. Khetani, Bioengineered liver models for drug testing and cell differentiation studies. Cellular and molecular gastroenterology and hepatology, 2018. 5(3): p. 426-439. e1.
23. Acocella, G., Clinical pharmacokinetics of rifampicin. Clinical pharmacokinetics, 1978. 3: p. 108-127.
24. Waring, M.J., et al., An analysis of the attrition of drug candidates from four major pharmaceutical companies. Nature reviews Drug discovery, 2015. 14(7): p. 475-486.
25. Dykens, J.A. and Y. Will, The significance of mitochondrial toxicity testing in drug development. Drug discovery today, 2007. 12(17-18): p. 777-785.
26. Banankhah, P.S., K.A. Garnick, and D.J. Greenblatt, Ketoconazole-associated liver injury in drug-drug interaction studies in healthy volunteers. The Journal of Clinical Pharmacology, 2016. 56(10): p. 1196-1202.
27. Tverdek, F.P., D. Kofteridis, and D.P. Kontoyiannis, Antifungal agents and liver toxicity: a complex interaction. Expert Review of Anti-Infective Therapy, 2016. 14(8): p. 765-776.
28. Núñez, M., Clinical syndromes and consequences of antiretroviral-related hepatotoxicity. Hepatology, 2010. 52(3): p. 1143-1155.
29. Korenblat, K.M. and P.D. Berk, Hyperbilirubinemia in the setting of antiviral therapy. Clinical Gastroenterology and Hepatology, 2005. 3(4): p. 303-310.
30. Perronne, C., Antiviral hepatitis and antiretroviral drug interactions. Journal of hepatology, 2006. 44: p. S119-S125.
31. Han, H., et al., Antiretroviral and Anti–Hepatitis C Virus Direct-Acting Antiviral-Related Hepatotoxicity. Clinics in Liver Disease, 2013. 17(4): p. 657-670.
32. Bhatia, S.N. and D.E. Ingber, Microfluidic organs-on-chips. Nature biotechnology, 2014. 32(8): p. 760-772.
33. Garside, H., et al., Evaluation of the use of imaging parameters for the detection of compound-induced hepatotoxicity in 384-well cultures of HepG2 cells and cryopreserved primary human hepatocytes. Toxicology in Vitro, 2014. 28(2): p. 171-181.
34. Daly, A.K. and C.P. Day, Genetic association studies in drug-induced liver injury. Drug metabolism reviews, 2012. 44(1): p. 116-126.
35. Boyd, M.A., et al., Relationship between hyperbilirubinaemia and UDP-glucuronosyltransferase 1A1 (UGT1A1) polymorphism in adult HIV-infected Thai patients treated with indinavir. Pharmacogenetics and genomics, 2006. 16(5): p. 321-329.
36. Skardal, A., T. Shupe, and A. Atala, Organoid-on-a-chip and body-on-a-chip systems for drug screening and disease modeling. Drug discovery today, 2016. 21(9): p. 1399-1411.
37. Kausar, S., et al., A review: Mechanism of action of antiviral drugs. International journal of immunopathology and pharmacology, 2021. 35: p. 20587384211002621.
38. Björnsson, E.S., Drug-induced liver injury: an overview over the most critical compounds. Archives of toxicology, 2015. 89: p. 327-334.
39. Theobald, J., et al., Liver-kidney-on-chip to study toxicity of drug metabolites. ACS Biomaterials Science & Engineering, 2018. 4(1): p. 78-89.
40. Kenna, J.G. and J. Uetrecht, Do in vitro assays predict drug candidate idiosyncratic drug-induced liver injury risk? Drug Metabolism and Disposition, 2018. 46(11): p. 1658-1669.
41. Banaeiyan, A.A., et al., Design and fabrication of a scalable liver-lobule-on-a-chip microphysiological platform. Biofabrication, 2017. 9(1): p. 015014.
42. Borba-Santos, L.P., et al., Tacrolimus increases the effectiveness of itraconazole and fluconazole against Sporothrix spp. Frontiers in Microbiology, 2017. 8: p. 1759.
43. Voican, C.S., et al., Antidepressant-induced liver injury: a review for clinicians. American Journal of Psychiatry, 2014. 171(4): p. 404-415.
44. Kaliyaperumal, K., et al., Pharmacogenomics of drug-induced liver injury (DILI): molecular biology to clinical applications. Journal of hepatology, 2018. 69(4): p. 948-957.