Monitoring of drugs causing hepatotoxicity:

drugs causing drug-induced hepatotoxicity include antibiotics, lipid lowering agents, oral hypoglycemics, psychotropics, antiretrovirals, acetaminophen, and complementary and alternative medications. Drug-induced hepatotoxicity is underreported. Liver toxicity is the most common form of adverse drug reaction resulting in delays and stoping of drug development or withdrawal from the market. Development of jaundice in combination with elevated aminotransferases in patients with DILI is associated with an estimated mortality rate of 10%.1Drug-induced hepatotoxicity can manifest as either direct or idiosyncratic reactions. Direct hepatotoxicity is generally dose dependent. Idiosyncratic reactions are manifested after a delay or latency period ranging from 5 to 90 days after drug ingestion.2

Direct or dose-dependent hepatotoxicity is reproducible and often has a predictable course. The period of time between initiation of a drug and hepatotoxicity is usually consistent from person to person for each drug. The dosage required to produce liver injury is also consistent from person to person. Drug-induced hepatotoxicity can present as a hepatocellular, cholestatic, or mixed picture. Most drug-induced hepatotoxicity is idiosyncratic and unpredictable rather than directly hepatotoxic. Idiosyncratic reactions can be divided into 2 main categories: metabolic or immunologic. Metabolic reactions may result from a specific genetic polymorphism resulting in the formation of a toxic metabolite. The reaction caused by a specific genetic polymorphism is not reproducible from person to person. 3Immunologic reactions are hypersensitivity reactions to a specific drug. The immunologic response is often due to
a drug–protein adduct in the liver. The reaction includes a delayed response and laboratory evidence of immunologic alterations. These hypersensitivities have featuresincluding mild fever, eosinophilia, atypical lymphocytosis, and liver infiltrates.4The most definitive confirmation of a hypersensitivity reaction is a rapid positive rechallenge. This approach is not recommended and is rarely, if ever, justified.5

Hepatotoxic Drugs and monitoring:

Statins:6
→no evidence that monitoring liver enzymes reduces the rate of hepatotoxicity
with statins.
→liver enzymes checked before initiation of statin therapy

Anti HIV :

-→Hepatotoxicity due to HAART is common, with up to 30% of patients .7Hepatotoxicity caused by HAART is usually acute, often asymptomatic, and self-limited.8
→risk factors for hepatotoxicity include viral hepatitis coinfection with hepatitis C or hepatitis B, advanced liver disease, and elevated transaminases before the start of HAART.9
-→Didanosine and stavudine are have been reported to cause a rare, but potentially fatal, hepatic steatosis and lactic acidosis.10, 11

-→Monitoring of liver enzymes for the first 18 weeks of therapy with nevirapine is recommended. Hepatic failure/hepatitis can be associated with signs of hypersensitivity including rash, fever, and eosinophilia.12
-→incidence of liver enzyme elevation with ritonavir is between 5% and 30% ,onset between 2 and 6 months following drug initiation.
-→drugs metabolized by CYP3A or induce CYP3A expression are affected by con-current use with Protease inhibitors,like INH and rifampicin. PIs are pregnane and xenobiotic receptor (PXR) ligands that induce CYP3A
expression, are metabolized by CYP3A, and following metabolism can become mechanism-based inhibitors of CYP3A13
-→Prolonged exposure to didanosine may play a pathogenic role in development of portal Hypertension , and removal of the drug can result in clinical laboratory improvement 14

Antibacterial:
→Most hepatotoxicity-related antimicrobial use is idiosyncratic;
→amoxcillin induced hepatotoxicity: 17 in 100,000 cases.15Hepatotoxicity occurs at variable period of few days to as much as 6 weeks. Cholestasis is the most common pattern of presentation of hepatotoxicity, usually mild and self-limited with abnormal liver enzymes resolving within 12 weeks.
-→Ampicillin is rarely associated with hepatotoxicity,
-→Carbenicillin has caused hepatotoxicity primary Hepatocellular type of injury

→flucloxacillin, oxacillin, cloxacillin, and dicloxacillin are known to cause hepatotoxicity, cholestatic hepatitis 17,18 ,16 Flucloxacillin-induced hepatotoxicity may occasionally result in vanishing bile duct syndrome or biliary cirrhosis. Onset of symptoms typically occurs 1 to 3 weeks after initiation of therapy19
→Cephalosporins rarely cause idiosyncratic hepatotoxicity.20
-→Erythromycin estolate is the most common macrolide causing hepatotoxicity. 3.6 cases per 100,000 21Symptoms
usually occur 3 to 4 weeks after the initial course of therapy, and within 2 to 3 days during a subsequent course of erythromycin. the pattern of injury is usually cholestatic.22Erythromycin-induced hepatotoxicity is usually reversible with drug discontinuation within 2 to 5 weeks, but rarely it may persist for 3 to 6 months. Erythromycin is not usually associated with severe fatal liver injury
-→Ciprofloxacin, levofloxacin, ofloxacin, and norfloxacin have been reported less frequently than other groups of antibiotics to cause hepatotoxicity .ciprofloxacin hepatotoxicity with 3 weeks of start.23
→Tetracyclines cause microvesicular steatosis. children are less susceptible.24Tetracyclines cause disruption
of fatty acid oxidation and induce fat accumulation in liver.
-→sulfamethoxazole, trimethoprim–sulfamethoxazole and sulfasalazine can cause hepatotoxicity;
occurring 5 to 14 days after starting treatment. Genetic polymorphisms related to N-acetyltransferase

enzyme activity play a role in susceptibility to liver injury; slow acetylators seem to be at higher risk for such hepatotoxicity.25 hepatotoxicity is mild and reversible with a few weeks after discontinuation of drug therapy,
however cholestasis may persist for 6 to 8 months.

→acute form of liver injury is more common than the chronic in nitrofurantoin induced hepatotoxicity . acute cholestasis occurs after 6 weeks of treatment, whereas chronic hepatitis occurs after at least 6 months of nitrofurantoin use. 3 to 20 per 1,000 cases.26Rechallenge with nitrofurantoin should not be attempted
-→Drug-induced hepatotoxicity caused by isoniazid is characterized by hepatocellular necrosis, Liver injury from isoniazid seems to be mediated by the toxic metabolite hydrazine and its monoacetyl derivative.27In many of
Patients with INH induced mild transaminitis , continuation of isoniazid is well tolerated and their aminotransferase
levels will return to normal or nearly normal levels, representing a hepatic adaptation response 28 0.1% to 2.0% of
patients treated with isoniazid will develop significant clinical hepatitis.28 Combination of isoniazid with other antituberculin drugs including rifampin and pyrazinamide increases the likelihood of toxicity with isoniazid. 28 clinical hepatitis with isoniazid alone was found to be 0.6%.29Isoniazid in a combination of drugs without rifampin causes clinical hepatitis 1.6% of the time. Combination antituberculous therapy with rifampin but without isoniazid has a 1.1% incidence of clinical hepatitis, and when isoniazid and rifampin regimens are used together, there is a 2.5% incidence of clinical hepatitis. 29 slow acetylators being more susceptible to isoniazid-dependent liver injury30
-→Hepatotoxicity associated with rifampin use is less frequent than with isoniazid use. The usual histologic pattern is cholestasis,as rifampicin is a competitive inhibitor of bile salt uptake and bile salt export.
-→An antituberculous regimen with pyrazinamide is more commonly associated with hepatotoxicity when given with rifampin or isoniazid.

Antifungals:
-→Antifungals such as itraconazole, flucytosine, and terbinafine are more commonly associated with hepatotoxicity
than amphotericin B.

→Ketoconazole is the most common antifungal associated with liver injury. Hepatotoxicity is usually self-limited after
drug discontinuation

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