ANTIMICROBIALS & HEPATOTOXICITY:

Antimicrobials include antibacterial, antiviral, antifungal, antiparasitic drugs commonly used against microbiome in routine pediatric practice. Most of the drugs are metabolized in liver. Drugs are hepato-toxic in a dose dependent or display idiosyncratic reactions. Idiosyncratic hepato-toxicity is unpredictable. Dose dependent hepatotoxicity is predictable and can be monitored safely. Some of the antimicrobial drugs interfere with metabolism of other drugs causing toxicity. Hence drugs interactions are to be kept in mind before combing antimicrobial drugs with other inducers or inhibitors.

This article grossly review commonly used antimicrobials and their hepato-toxicity potentials and their implication in routine clinical practice.

ANTI-HIV drugs & Hepatotoxicity:

Hepatotoxicity due to HAART is commonly seen in 30% of patients.**1**
Hepatotoxicity caused by HAART is usually acute, often asymptomatic, and is self-limited.**2**
Common risk factors for hepatotoxicity include viral hepatitis ,coinfection with hepatitis C or hepatitis B, advanced liver disease, and transaminitis before the start of HAART.**3**

Didanosine and stavudine are have been reported to cause potentially fatal, hepatic steatosis and lactic acidosis.**4,5** 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.**6**

The incidence transaminitis because of ritonavir is between 5% --30% .It starts between 2 and 6 months following drug initiation. Drugs metabolized by CYP3A or induce CYP3A are responsible for drug toxicity in association with protease inhibitors **7**
Prolonged exposure to didanosine play a pathogenic role in development of portal Hypertension , and removal of the drug can result in clinical or laboratory improvement **8**

ANTIBIOTICS & Hepatotoxicity:

Most hepatotoxicity due to antibiotics is idiosyncratic and unpredictable difficult to monitor clinically or biochemically .

AMOXCILLIN HEPATOTOXICITY:
Amoxicillin induced hepatotoxicity is reported in 17 in 100,000 cases.**9**Hepatotoxicity can occur from a period of few days to 6 weeks. **Cholestasis** is the most common pattern of presentation. Hepatoxicity is usually mild and self-limiting. Abnormal liver enzymes resolves within 12 weeks in most cases with discontinuation of the drug.

AMPICILLIN HEPATOTOXICITY:
Ampicillin is rarely associated with hepatotoxicity.

CARBENCILLIN HEPATOTOXICITY:
Carbenicillin is associated with hepatotoxicity.
The most common pattern is primary **Hepatocellular injury.**

FLUCOXACILLIN HEPATOTOXICITY:

Flucloxacillin, oxacillin, cloxacillin, and dicloxacillin are known to cause hepatotoxicity,**10,11,12** The predominant histopathology is **cholestatic hepatitis** .
Flucloxacillin-induced hepatotoxicity may result in vanishing bile duct syndrome or biliary cirrhosis. Onset of symptoms typically occurs 1 to 3 weeks after initiation of therapy**13**

CEPHALOSPORIN HEPATOTOXICITY:
Cephalosporins rarely cause idiosyncratic hepatotoxicity.**14**

MACROLIDE HEPATOTOXICITY:

Erythromycin estolate is the one of the most common macrolide causing hepatotoxicity. 3.6 cases per 100,000 is the prevalence **15** Symptoms occur 3 to 4 weeks after the initial course of therapy, and within 2 to 3 days during a subsequent course of erythromycin if restarted.
The pattern of injury is **cholestatic**.**16**
Erythromycin-induced hepatotoxicity is usually reversible with drug discontinuation within 2 to 5 weeks, it may persist for 3 to 6 months. Erythromycin is not usually associated with severe fatal liver injury

CIPROFLOXACIN GROUP HEPATOTOXICITY:

Ciprofloxacin, levofloxacin, ofloxacin, and norfloxacin less likely to cause hepatotoxicity .Ciprofloxacin hepatotoxicity manifest within 3 weeks of start of antibiotic .**17**

TETRACYCLIN HEPATOTOXICITY:
Tetracyclines can cause microvesicular steatosis. Children are generally less susceptible.**18**
Tetracyclines cause disruption of fatty acid oxidation and induce fat accumulation in liver.

SULFONAMIDE HEPATOTOXICITY:
Sulfamethoxazole, trimethoprim–sulfamethoxazole and sulfasalazine can cause hepatotoxicity. Hepatotoxicity is seen within 5 to 14 days after starting treatment. Slow acetylators of drug seem to be at higher risk for such hepatotoxicity.**19** hepatotoxicity is generally mild and is reversible. Cholestasis may persist for 6 to 8 months.

NITROFURANTOIN HEPATOTOXICITY:
Acute form of liver injury is more common than the chronic liver disease in nitrofurantoin induced hepatotoxicity . **Acute cholestasis** is seen after 6 weeks of treatment, whereas chronic hepatitis occurs after at least 6 months. Both forms of Hepatotoxicity are seen with Nitrofurantoin.Prevalance is 3 to 20 per 1,000 cases.**20** This is one of the antimicrobial where **Rechallenge** should not be attempted.

ANTITUBERCULAR DRUGS & HEPATOTOXICITY:

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.**21**
Patients with INH induced mild transaminitis , continuation of isoniazid is well tolerated and their aminotransferase Levels return to normal due to a hepatic adaptation response **22**

0.1% to 2.0% of patients will develop significant clinical hepatitis.**22**Combination of isoniazid with other antituberculin drugs including rifampin and pyrazinamide increases the likelihood of toxicity. **23** Clinical hepatitis with isoniazid alone was found to be 0.6%.**25** Isoniazid in combination 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 when isoniazid and rifampin regimens are used together is a 2.5%. **23**slow acetylators being more susceptible to isoniazid-dependent liver injury**24**

Hepatotoxicity associated with **rifampin** is comparatively less than with isoniazid use. The usual histological pattern is **cholestasis**. Rifampicin is a competitive inhibitor of bile salt uptake and bile salt export pump.

An antituberculous regimen with pyrazinamide is more commonly associated with hepatotoxicity when given with rifampin or isoniazid.

ANTIFUNGALS HEPATOTOXICITY

Antifungals ,itraconazole, flucytosine, and terbinafine are commonly associated with hepatotoxicity
Ketoconazole is the most common antifungal associated with liver injury. Hepatotoxicity is usually self-limited and liver enzymes return to normal after drug discontinuation.

What we can monitor while using antimicrobial?

The parameters we can monitor are either clinical, biochemical or Lab drug levels. Clinical monitoring parameters include proper history taking, judgment of the clinical situation, and correlation with the clinical event. For example appearance of skin rash secondary to antibiotic is difficult to attribute to the antibiotic if rash appeared before hand unless know prior exposure to the similar drug, which has cross-sensitized the patient for this adverse event.

Similarly, the physical examination is extremely helpful in most of these cases. Urticarial rash may be strongly suggestive of drug allergy. Nonurticarial erythematous rash is often not attributed to antimicrobial drug.

Biochemical investigation may point towards the etiology of the adverse drug reaction but it may be difficult for attribute specifically to the drug always. Hence **combination of clinical, biochemical, lab drug levels** are useful in considering the adverse antimicrobial reaction while using antibiotics.

Antimicrobials can cause sideeffects mediated by a variety of mechanisms,not all can be assessed. While some in vivo sensitivity test may help us with risk of anaphylaxis while RAST specific IgE using a radioallergosorbent Test may be in vitro test recommended. The use of in vitro assessments for antimicrobial allergy like penicillin allergy is less specific than skin testing but is reasonably sensitive, notably when combined with a rechallenge following a negative in vitro test.**25**

Whether an adverse event is possible, probable, or definite hepatotoxicity or adverse effect can also be judged by Naranjo score, a score derived from an algorithm developed by Naranjo and colleagues for the assessment of possible adverse reactions **26**

The Naranjo scale. Possible scores range from >9 (definite ADR), 5–8 (probable ADR), 1–4 (possible ADR) or 0 or below (doubtful ADR)

Question	Yes	No	Do Not Know
Are there previous conclusive reports on this reaction?	1	0	0
Did the adverse event appear after the drug was given?	2	−1	0
Did the adverse event improve after the drug was stopped or a specific antagonist was given?	1	0	0
Did the adverse event appear when the drug was readministered?	2	−1	0
Are there alternate causes that could have caused the adverse event?	−1	2	0
Did the reaction reappear when a placebo was given?	−1	1	0
Was the drug detected in any body fluid in toxic concentrations?	1	0	0
Was the reaction more severe when the dose was increased or less severe when the dose was decreased?	1	0	0
Did the patient have a similar reaction to the same or similar drugs in a previous exposure?	1	0	0
Was the adverse event confirmed by any objective evidence?	1	0	0

Data from Naranjo CA, Busto U, Sellers EM, et al. A method for estimating the probability of adverse drug reactions. Clin Pharmacol Ther 1981;30:239–45.

Therapeutic Ranges of antibiotics Used in Critical Care**27**

Drug	Therapeutic Range
Amikacin	Trough < 5 µg/mL
	Peak < 30 µg/mL
Cyclosporine	Whole blood, 150 ng/mL
Digoxin	0.50-2.0 ng/mL
Gentamicin *	Trough < 2 µg/mL
	Peak < 10 µg/mL
Lidocaine	1.5-5 µg/mL
Phenytoin	10-20 µg/mL
Quinidine	2-5 µg/mL
Theophylline	10-20 µg/mL
Tobramycin *	Trough < 2 µg/mL
	Peak < 10 µg/mL
Vancomycin †	Trough < 5 µg/mL
	Peak < 30 µg/mL

* Once daily aminoglycoside dosing may result in different therapeutic ranges.

† Vancomycin concentrations are currently focusing on higher peak concentrations, and practice varies considerably between sites.

Hence till **Pharmacogenomics (personalized medicine)** is well developed in the course we have to keep a watch on clinical, biochemical, lab values, scoring system in combination while using these antibiotics with best results.

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