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Review Article

Antibiotics and liver - A review of the complicated relationship

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ABSTRACT

Many antibiotics used to treat bacterial infections and to treat disorders of the liver, gallbladder and bile ducts. However, their irrational use leads to liver injury. Drug induced liver injury is the most difficult diagnosis to be established and should be differentiated from other diseases with similar conditions. Recovery occurs by withdrawal of the offending drug. Selective intestinal decontamination can be done to prevent infections resulting as a complication of cirrhosis. In children, diagnosis is challenging because of absence of specific markers. Irrational antibiotic use is the leading cause for emergence of multidrug-resistant strains of bacteria. Deriving an early and rational antibiotic therapy is essential. Antibiotics have a positive effect in diseases such as Acute on Chronic Liver Failure, cirrhosis, Portal bacteremia, etc. Short antibiotic treatment courses, early de-escalation, high doses and use of continuous or extended infusions for time-dependent antibiotics are some of the measures to help reduce resistance. The severity of injury ranges from asymptomatic to severe stage disease. In pediatric population there is varied presentation of symptoms for various antibiotic induced liver injuries and diagnosis is difficult due to age-dependent factors.

Keywords: Selective intestinal decontamination, acute on chronic liver failure, positive effects, negative effects, children, antimicrobial stewardship, antibiotic associated liver disorders.

INTRODUCTION

Bacterial infections are generally treated with antibiotics, most of which are also used to treat disorders of the liver, gallbladder and bile ducts. Irrational use of these antibiotics to treat hepatobiliary disorders, however, may lead to acute or chronic liver injury and eventually cause hepatotoxicity. Patients with hepatic diseases are prone to bacterial infections and other liver disorders and thus they should be treated appropriately. There are no specific tests to deduce the ability of the liver to metabolize or excrete antibiotics. Drug Induced Liver Injury (DILI) is the most difficult diagnosis to be established. In patients with abnormal liver function tests and normal hepatobiliary imaging, DILI should be differentiated from other diseases with similar conditions.

It can be diagnosed with the help of various factors such as thoroughly assessing the history of the

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patient's medications, performing laboratory tests, application of pharmacovigilance for excluding other diagnoses with similar symptoms, determining the agents that cause DILI, etc. Recovery occurs with the withdrawal of the offending drug. Selective intestinal decontamination (SID) is a method which can be used to prevent cirrhosis-manifested infections and also in some patients it can be used to prevent the subsequent translocation/infection with bacteria which also included death.[1] Selective intestinal decontamination (SID) consists of the administration of oral antibiotics to inhibit intestinal gram-negative flora while preserving the remaining flora, especially anaerobic bacteria that are key in preventing intestinal overgrowth and extra intestinal spread of pathogenic bacteria.

In children and adolescents, the current risk of liver injury due to antibiotics increased to threefold compared to past.[3] However, among individuals the risk differs according to the different classes of antibiotics. The drugs which are commonly associated with the liver injury in children are fluoroquinolones, sulfonamides, tetracyclines, cephalosporins, macrolides and penicillins.[3] In children diagnosing of DILI is challenging, because of the absence of specific markers.[4] The symptoms of liver injury are always nonspecific such as fatigue, nausea, vomiting or jaundice or it includes biochemical dysfunction such as elevation in Alanine transaminase (ALT), Alkaline phosphatase (ALP), or Total Bilirubin (TB).[4] Compared to adults the children's have different characteristics of DILI due to their changes in drug metabolism and their special requirements of medication.[4] The main cause of death of several patients is the presence of infection and irrational use of antibiotics. Irrational use of antibiotics is the leading cause for emergence of multidrug resistant strains of bacteria. Deriving an early and rational antibiotic therapy - prophylactic or empirical, is essential.

Table 1: Types of antibiotics used in liver disease [5]

Types of antibiotics used in liver diseases
1. Penicillin G 2. Alpha-phenoxy-penicillins A. Phenoxymethyl B. Phenoxyethyl (phenethicillin) C. Phenoxybenzyl (phenbenicillin) 3. Beta Lactamase-Resistant Penicillins A. Methicillin B. Oxacillin C. Cloxacillin D. Nafcillin 4. Broad-Spectrum Penicillins A. Ampicillin B. Hetacillin C. Carbenicillin 5. Cephalosporins A. Cephalothin B. Cephaloridine 6. Streptomycin and Dihydrostreptomycin 7. Tetracyclines A. Chlortetracycline B. Oxytetracycline C. Tetracycline D. Demethylchlortetracycline E. Methacycline F. Doxycycline 8. Chloramphenicol 9. Macrolides A. Erythromycin B. Oleandomycin and triacetyl oleandomycin 10. Lincomycin 11. Novobiocin 12. Kanamycin-Neomycin-Paromomycin Group A. Kanamycin

B. Neomycin
C. Paromomycin
13. Polymyxin - Colistin Group
14. Vancomycin
15. Nitrofurantoin
16. Sulfonamides
17. Amphotericin B

DISCUSSION

In diagnosing antibiotic caused liver injury, removing the other causes of DILI, relation between drug taking and onset of injury shall help but to conclude the diagnosis is presumptive.
Several reports have been published stating that there occurs delayed hepatic injury after the course of therapy, which further makes it difficult for diagnosing DILI.

Positive Effects of Antibiotics in Liver: Bacterial infections most commonly occur in patients with Acute-on-Chronic Liver Failure (ACLF) and an early identification and precise antibiotic therapy helps in reducing mortality rates. Positive values of infection predictors such as C-reactive protein and procalcitonin show the need for immediate treatment. Multidrug resistance is to be assessed after 48 hours. [6]

The incidence of bacterial infections gradually increases with the development of ACLF. In ACLF patients, Bacterial peritonitis is one of the most common infections arises which varies from 21.1 to 34.5%, which may be associated with the risk of developing irreversible renal failure and hepatorenal syndrome. The second most common infection is pneumonia which accounts for 23.7%, and its frequency varies 7.7 to 45.0%. The least common infection is bloodstream infection which accounts for 3.1%. [7]

The incidence of bacterial infection decreases with the cirrhotic patient who are receiving antibiotic prophylaxis than the patient who are not receiving antibiotics prophylaxis.[9] In patients who are not receiving antibiotic prophylaxis, the recurrence of spontaneous bacterial peritonitis is extremely high. The incidence of in-hospital infection decreased from 45% to 14% by using antibiotic as prophylaxis. While the antibiotics as prophylaxis is used, it reduces the re-bleeding rate within 7 days.

Other complications such as recurrent variceal bleeding, hepatorenal syndrome, death and other bacterial infection in the cirrhotic patient can be prevented by the use of antibiotics. Incidence of hepatorenal syndrome (HRS), a major complication of cirrhosis, is higher and it is treated with human albumin and cefotaxime. This use has resulted in decreased incidence of the syndrome, reduced in-hospital and 3 month mortality.[6] Another complication of cirrhosis is variceal bleeding which is more susceptible for concomitant infections. Several studies show that antibiotics, especially fluoroquinolones, co-amoxiclav and third generation cephalosporins reduce early rebleeding and mortality, but have a very little effect on long term survival. For all variceal hemorrhage, The British Society of Gastroenterology guidelines suggest the use of prophylactic antibiotics.

Portal bacteremia occurs when there is a transmucosal bacterial translocation due to inflammatory processes involving the gut or when there is an alteration in its integrity. Liver abscess also occurs due to retrograde infections. For these types of infections, prolonged duration with systemic targeted antibiotics remains as the ration therapy. Antibiotics are also used in the treatment of primary biliary cirrhosis, markers of cholestasis and pruritus.

However, the increasingly irrational use of standard empirical antibiotics has caused a rise in resistance to these antibiotics which will lead to the decreased effectiveness of prophylactic antibiotics. Hence, it is of prime importance to rationally treat the infections and thus prevent the development of resistance.

The optimizing of the dose and dosage of antibiotic regimen should be done within the first 48 to 72 hours after diagnosing the infection and its severity. This will help greatly in minimizing the resistance patterns.

Short antibiotic treatment courses, early de-escalation, high doses and use of continuous or extended infusions for time-dependent antibiotics are some of the measures to help reduce resistance.[9] The differences in published data on different antibiotics causing DILI may be attributed to the differing local antibiotic strategies and the availability of different antibiotics across regions.

Negative effects of antibiotics in liver: The clinical features of antibiotic-associated liver disorders encompass the characteristics exhibited by liver damage which includes antibiotic induced cytotoxic injury, cholestatic injury, mixed cytotoxic and cholestatic injury, steatosis, chronic active hepatitis, and cirrhosis. Also, certain antibacterials

may present with more than one of the above-mentioned injuries. [2]

Increased level of transaminases is associated with hepatocellular injury or cytotoxic injury. Viral hepatitis makes it difficult to differentiate drug induced cytotoxic injury and necrosis. Serum bilirubin abnormality and coagulation disorder correlates with damaged liver. The severity of injury ranges from asymptomatic to severe stage disease.[2]

Selective impairment of the hepatocyte's ability to secrete bile, with or without hepatic-canalicular inflammation is due to cholestatic injury; but this also makes it difficult to differentiate between intrahepatic cholestasis from other etiologies.

In many cases the antibiotic-induced cytotoxic and cholestatic injury cannot be distinguished from one another so it is classified as mixed. In this condition, patients exhibit moderate abnormalities of both serum aminotransferase and alkaline phosphatase. Sometimes the features may resemble hepatitis.

The characteristics of a progressive necro-inflammatory process involving a syndrome of portal inflammation, periportal necrosis and fibrosis is exhibited by chronic active hepatitis. Sometimes prolonged exposure to the causative agent will result in Macronodular cirrhosis.[2]

Non-hepatic side effects include the inhibition of hepatic biosynthesis of Vitamin K dependent clotting factors by some beta-lactam antibiotics such as cephalosporins. Hyperbilirubinemia is another metabolic effect wherein there is inhibition of bilirubin transport and conjugation.

In children: In the pediatric population there is a varied presentation of liver injury for each antibiotic and pediatricians should be conscious of the effects of these drugs on the liver of children and the potential risks involved with their use even if it is for a short course. [3]

Diagnosing liver injury in children is more complicated due to the age-dependent maturation of CYP450 enzymes, which are involved in the metabolism of drugs.

CONCLUSION

The liver and antibiotics share a complicated relationship. That is, antibiotics are required for the treatment of various infections but still they tend to cause damage to the liver. They are the leading cause for DILI and yet they are generally prescribed for the treatment of infections resulting from liver injury. Thus, antibiotics have both positive and negative effects on the liver. Furthermore, medical practitioners and patients can be educated on the rational use of antibiotics. More research and precise guidelines on antibiotic usage are required to reduce the emergence of multidrug resistant bacterial strains in every health care sites. Antimicrobial stewardship programs can be implemented in hospitals to help in logical prescribing of antibiotics.

Early de-escalation also helps to prevent antibiotic misuse. Non-Antibiotic prophylactic methods can also be followed to reduce the risk of resistance and overuse and further investigations are recommended.

More interest is to be taken by pediatricians to antibiotic induced liver injury since antibiotics are widely used in the pediatric population. Also, they should look into the measures that can be taken to prevent these events.

Furthermore, studies are required in large amounts to assess the mechanism of DILI due to antibiotics, its risk factors and outcomes in patients and the methods that can be used to diagnose, treat and prevent injury.

SUMMARY

This article summarizes the effect of antibiotics in liver. The positive effects of antibiotics lie in its use with different diagnoses such as ACLF, bacterial peritonitis, bacterial infection with cirrhosis and complications of cirrhosis. Whereas the negative effect of antibiotics includes different types of injury such as antibiotic induced cytotoxic injury, cholestatic injury, mixed cytotoxic and cholestatic injury, steatosis, chronic active hepatitis, and cirrhosis, each type of injury exhibit different clinical characteristics. In pediatric population there will be varied presentation of symptoms for each antibiotic and the diagnosis also is tedious due to age-dependent factors. Thus, it clearly states that the effect of antibiotics will vary among different age category. This article also states it is important to educate various medical practitioners and physician in the use of various antibiotics in different diseases and also conducting programs such as antimicrobial stewardship programs in a larger scale gives more precise guidelines in the rational use of antibiotics.

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