Hepatotoxic effect of amoxicillin/clavulanate combination in human: A review

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Abstract

Amoxicillin/clavulanate has been known as a semisynthetic penicillin/clavulanic acid antibiotic which is commonly used orally for the treatment of cutaneous and respiratory infections. It's an antibiotic that's easy to take. However, amoxicillin/clavulanate can induce a variety of side effects, including gastrointestinal, cutaneous, hematologic, and hepatic problems. In the present work, we aimed to review the possible risks of hepatotoxicity associated with amoxicillin/clavulanate using , since this combination widely administered for treatment of infections at different age stages for patients, This has been done via collecting and reading a large number of published articles and reviews to maintain our study.
It has been suggested that the clavulanic acid or the combination with amoxicillin may cause liver injury even 4 years after the 1st injury. Liver reactions fundamentally cholestatic, however, there are as well some cases with hepatocellular or the mixed cholestatic hepato-cellular hepatitis. The sequel looks to be good. Very rarely, patient died due to amoxicillin induced cholestatic hepatitis or develop a chronic liver disease with permanent abnormal liver function tests. Amoxicillin-clavulanate induced hepatotoxicity is a rare condition, and since it is a diagnostic of exclusion, it may be hard to diagnose. Amoxicillin/clavulanate is considered one of the major used antibiotics, it only causes hepatic injury in alimented number of cases. It starts to develop signs of cholestatic after six weeks of use. It causes significant hyperbilirubinemia and induce cholestatic icterus.
Liver injury may continue for four months. Treatment includes supportive. Related to the severity of cholestatic symptoms, analgesic and antiemetic medicines, along with antihistamine, cholestyramine, sertraline, or even ursodeoxycholic acid, may be used to control pruritus.

Key words: Amoxicillin/clavulanate**,** Hepatotoxicity, Cholestasis.

Abbreviations: drug induce liver injury (DILI), Alanine transaminase (ALT), amoxicillin-clavulanate (AC), Human Leukocyte Antigen (HLA).

الخلاصة:
أموكسيسيلين /كلافيولانيت هو مركب من البنسلين الصناعي والكلافيولانيت يستخدم على نطاق واسع لعلاج التهابات الجهاز التنفسي والجلد .وهو مضاد حيوي جيد التحمل عن طريق الفم .ومع ذلك ، قي بعض الاحيان ، قد يتسبب الأموكسيسيلين /كلافيولانيت في حدوث آثار جانبية ، خاصة على الجلد والجهاز الهضمي والكبد والدم .
تم اقتراح أن حمض الكلافولانيك أو الجمع مع الاموكسيسيلين يمكن أن يكون مسؤولا عن هذا التفاعل الضار .
في بعض الحالات تم تأكيد العلاقة السببية من خلال تكرار الإصابة الكبدية بعد إعادة إعطاء الدواء حتى بعد أربع سنوات من النوبة الأولى .كانت التفاعلات الكبدية يرقان صفراوي بشكل رئيسي ولكن هناك أيضًا بعض الحالات المصابة بالتهاب الكبد الصفراوي أو التهاب الكبد الصفراوي المختلط .يبدو أن النتائج جيده، حيث نادرًا ما يموت المريض بسبب التهاب الكبد الصفراوي الناجم عن الأموكسيسيلين أو الإصابة بمرض مزمن في الكبد مع استمرار اختبارات وظائف الكبد غير الطبيعية.تعد إصابة الكبد الناجمة عن الأدوية أمرًا نادر الحدوث ، ولأنه تشخيص لأستبعاد المرض ، فقد يكون من الصعب تشخيصه .لا يزال مركب الأموكسيسيلين /الكلافيولانيت أحد أكثر المضادات الحيوية شيوعًا ، إلا أنه ممكن ان يسبب تلف الكبد في نسبة صغيرة من الحالات .بدأت علامات اليرقان الصفراوي بالظهور بعد 6أسابيع من الاستخدام المتواصل للدواء .ممكن ان تستمر الاصابة الكبدية حوالي(4أشهر)حسب حالة المريض .لا يوجد علاج محدد ، العلاج يشمل العلاج الداعم ، تعويض السوائل هو نوع من العلاج الداعم ، اعتمادًا على شدة أعراض اليرقان ، يمكن استخدام الأدوية المضادة للقيء والمسكنات ، وكذلك كوليسترامين ، ومضادات الهيستامين ، وحمض أورسوديوكسيكوليك اسد ، أو حتى سيرترالين ، للسيطرة على التحسس الجلدي

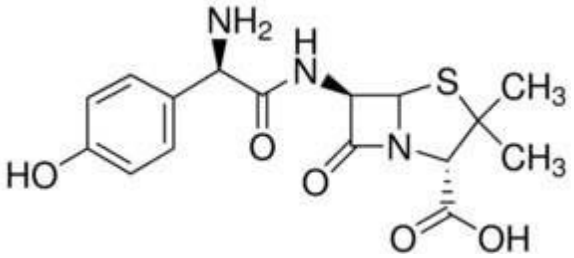
1. Introduction

Amoxicillin and Clavulanic acid (Co-Amoxicillin):

Amoxicillin is a broad spectrum, semi-synthetic βlactam effective against a wide range of the gram-positive and few of gram-negative organisms [1]. Because of the wide range of clinical applications, a complex mechanism of resistance has evolved, rendering penicillin inactive against the production of β-lactamase. This was thought to be the first stage in staphylococcal penicillin resistance [2]. In 1965, the number of clinical isolates producing β-lactamases had skyrocketed, owing to the ability of plasmids to transfer the genetic code for β-lactamase production from bacteria. Because of the plasmid-associated β-lactamase passage, resistance might spread quickly and even be passed between different genera and species of bacteria [3]. Beecham Research Laboratories (BRL) has recently begun research to overcome the problem of β-lactamase resistance [4].
Clavulanic acid's β-lactam ring binds to bacterial β-lactamase permanently, thus it from deactivating β-lactam antibiotics [5]. Amoxicillin was chosen as the antibiotic to mix with clavulanic acid because of its excellent oral absorption and broad-spectrum antimicrobial activity. Amoxicillin/clavulanate combination maintains amoxicillin activity against *streptococci, pneumococci*, as well as activity against *β-lactamase* producing *staphylococci, Escherichia coli, Moraxella catarrhalis*, and *Haemophilus influenzae*, and extends amoxicillin activity against *Klebsiella spp.* and *Bacteroides fragilis*. It has been illustrated that combination of amoxicillin and clavulanic acid extended the antibiotic's spectrum of activity. They have a crucial and distinctive function in treatment of various community-acquired diseases, which include the respiratory tract infections (RTIs) [2].

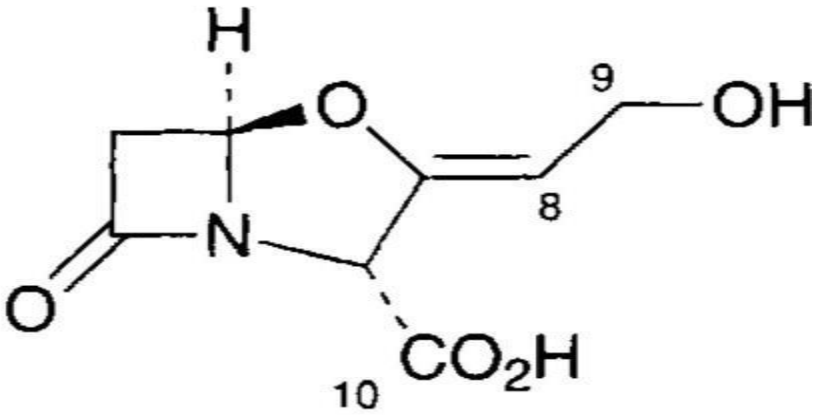
Structure of amoxicillin –clavulanic acid:

Amoxicillin can be defined as an ampicillin derivative (a semisynthetic amino penicillin) which differ from the original drug only through the hydroxylation of phenyl's side chain [6].Chemically amoxicillin is (2S,5R 6R)-6-[[(2R)-2Amino-2- (4-hydroxyphenyl) acetyl]amino]-3,3-di-methyl-7oxo-4-thia-1- azabicyclo heptane-2-carboxylicacid (Fig. 1).



(Figure 1). Structure of amoxicillin [7]**.**

Streptomyces clavuligerus produces clavulanic acid, a natural β-lactamase inhibitor. It is made up of a β-lactam ring with sulfur of penicillin thiazolidine ring substituted by oxygen for forming an oxazolidine ring, as shown in figure [2]. Chemically,(2R,5R)- 3-(2-hydroxy-ethylidene)-7-oxo-4oxa-1-azabicyclo-heptane-2-carboxylic acid.



(Figure 2). Structure of clavulanic acid [8].

Pharmacokinetics:

1. Absorption:

It has been demonstrated that when the clavulanic acid and amoxicillin are given together, the pharmacokinetics of the two medicines are identical to when they are given separately. Amoxicillin is readily absorbed from gastro-intestinal tract after administering amoxicillin/clavulanic acid. The presence of stomach acid has no impact on amoxicillin-clavulanate absorption.

The relative bioavailability related to clavulanic acid was reduced in one research when an oral dose of amoxicillin/clavulanic acid was administered (30 or 150) mins after the start of consumption of a high-fat meal. After oral administration, the two components attain maximum plasma concentrations in approximately 1 hr, and such quantities are proportionate to the dose administered [9].

2. Distribution:

Clavulanic acid and Amoxicillin successfully disperse the majority of body tissues and extra-cellular fluids, such as the middle ear mucosa and effusions in the children. Even though cerebrospinal fluid concentrations and bronchial secretions are minimal, tissue and body fluid distribution regarding the two components is typically sufficient to achieve antibacterial levels. Although both components cross the placenta, just a little portion of each makes it into breast milk [10] [11].

3. Protein binding:

It has been reported that amoxicillin is not very protein-bound; clavulanic acid was reported to be about 25% bound to human serum, while amoxicillin is only about 18% bound. [11].

4. Metabolism and excretion:

Amoxicillin is weakly digested by the liver (30%), and (50-80) % of an oral dose is eliminated intact in urine within 6 hrs. Clavulanic acid undergoes more extensive metabolism (decatboxylation and hydrolysis), with the kidneys excreting just 20-60% of the unaltered substance. Clavulanic acid is excreted largely via glomerular filtration, whereas amoxicillin is primarily excreted via renal tubular secretion. The typical elimination half-lives of clavulanic acid and amoxicillin in healthy adult subjects are both around 1 hr, and the mean total clearance of both is around 25 L/h. Renal impairment lowers amoxicillin clearance and, to a lesser extent, clavulanic acid clearance, requiring dosage adjustments or longer dose intervals. Since haemodialysis eliminates the two components, adequate dosage replacement is essential after each session [11].

6. Mechanism of Action:

Amoxicillin can be defined as β-lactam antibiotic that has a wide range of the action which was created from penicillin. It's a bactericidal medication that prevents bacteria from forming the peptidoglycan layer of their cell walls, killing them.The cell wall's outermost layer is crucial for the cell's structural integritycell. The facilitation of D-D transpeptidases is required for peptidoglycans formation a penicillin-binding protein (PBP) of a specific type Amoxicillin functions via interacting with PBP. Inhibiting peptidoglycan synthesis, which disrupts the cell's structure.The bacteria is destroyed, or lysed, as a result of thebacteria's adherence to the cell wall [12].

Clavulanic acid is a β-lactamase inhibitor commonly utilized with the amoxicillin in order to broaden the antibiotic's spectrum and combat the resistance. It has no anti-bacterial activities of its own and rather works by preventing bacteria from breaking down β-lactams. Many bacteria have evolved resistance to common betalactam antimicrobials throughout time by producing enzymes referred to as β-lactamases. Those enzymes are targeting and hydrolyzing β-lactam ring, which is essential for penicillinlike antimicrobials to function. As shown in (Figure 3), clavulanic acid stops this breakdown through binding and deactivating β-lactamases, restoring amoxicillin's antibacterial effects [13]·

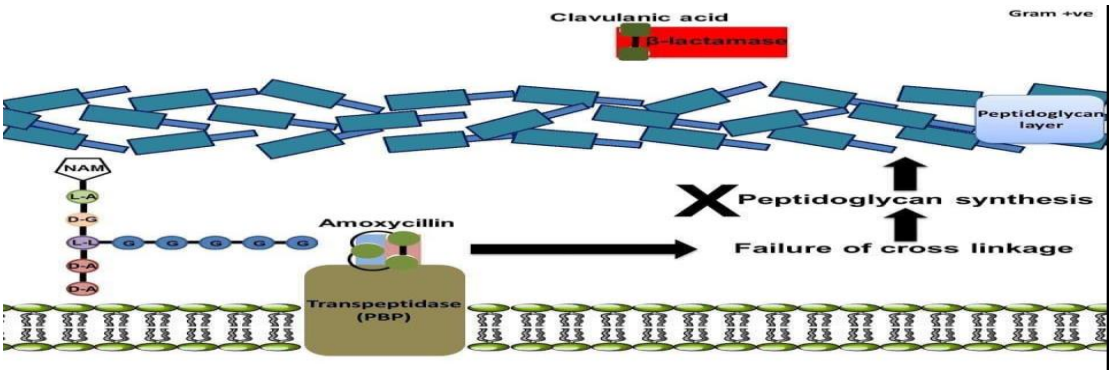


Figure (3). Amoxicillin-clavulanate mechanism of action [14]**.**

Mechanism of amoxicillin/clavulanate induce liver injury:

Amoxicillin/clavulanate-induced liver injury is more than amoxicillin-induced liver injury alone, and while it can produce any type of drug induce liver injury (DILI), cholestasis is the most common symptom. Moreover, hepatotoxicity caused by amoxicillin-clavulanic acid was mostly cholestatic, but hepatocellular and mixed cholestatic hepatocellular damage have also been reported. Hepatotoxicity caused by amoxicillin/clavulanate has a relatively moderate natural history. After an average of 11.5 weeks, self-limited normalization of liver biochemistries was observed in nearly all of the 208 instances studied [15].

1. Cytotoxicity

One of the key processes that might cause acute or chronic liver injury is cytotoxicity. Several variables, including oxidative stress, can produce cytotoxicity. Changes in antioxidant enzyme expression, as well as the creation or breakdown of the cellular thiols.
Protein oxidation ,and lipid peroxidation are both good cellular oxidation indicators. Disruption of thiol production or oxidation of cellular thiols, on the other hand, is extremely harmful.Glutathione (GSH) oxidation could as well be one of the contributing factors to the cellular toxicity.Cell death, either apoptosis or necrosis, may occur as a result of cytotoxicity [16].

Apoptosis:

Apoptosis is a cell death type that involves activating the caspase pathways (extrinsic orintrinsic). The extrinsic caspase pathways are frequently activated by chemicals and medications, resulting in an increase in caspase 8 and later caspase 3 activity, as seen in figure (4). Other drugs cause an increase in the cleavage of poly (adenosine diphosphate-ADP-ribose) polymerase (PARP), which is followed by caspase-independent apoptosis [17].

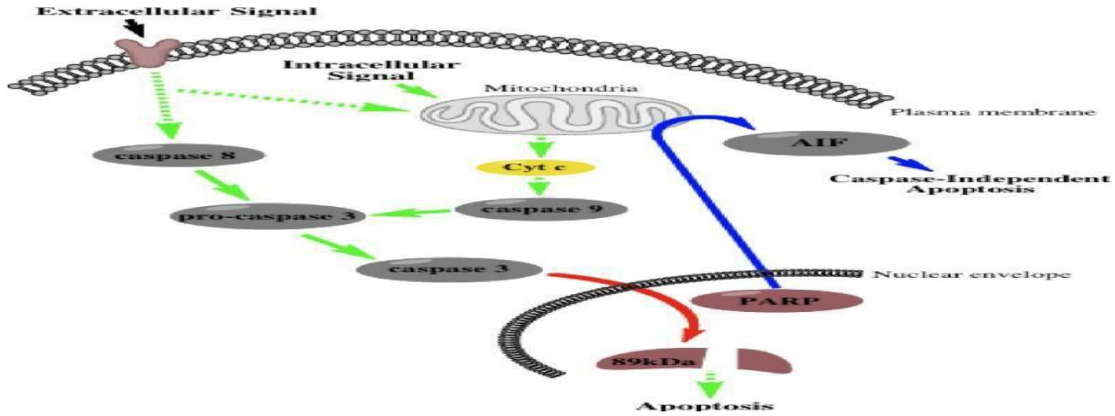


Figure (4). Apoptotic mechanism [17].

Necrosis:

Necrosis, on the other hand, is a type of cell injury that leads to autolysis, which causes cells in the live tissues to prematurely die. Hepatic necrosis is thought to be caused by an overabundance of or improperly controlled apoptosis on a cellular level. Furthermore, excessive mitochondrial malfunction or lysosomal permeabilization might lead to cell death (through apoptosis or necrosis) [18].

However, hepatocyte regeneration after necrotic and apoptotic cell death may obscure DILI [19] diagnosis [20]. The most prevalent type of necrosis caused by medicines is zonal necrosis. In this casethe injury is generally localized to a single zone of the body due to a specific pathological conditiones lobule of the liver that produces a high amount of Alanine transaminase (ALT). The disruption of liver function eventually leads to acute liver failure [21].

2. Endoplasmic reticulum (ER) stress

In eukaryotic cells, the ER is an organelle. Many biological functions rely on it, including protein synthesis, assembly, folding, trafficking, and so onafter modulation Furthermore, it ensures that both secretory and membrane quality is maintained proteins, lipid syntheses, and intra-cellular calcium hemostasis control ER anxiety is a serious conditionAlthough existing data primarily comes from other sources, liver injury is an attractive area of researchsystems that are being tested Unfolded proteins are in an unbalanced state in the strained ERand mature proteins,triggering a cascade of compensatory responses that are referred as "Unfolded protein response" is a term used to describe how a protein reacts [22].

Inositol-requiring enzyme 1 (IRE1), activating transcription factor 6 (ATF-6), and protein kinase RNA-activated (PKR)-like ER kinase. Prior to the apoptotic cell death and the depletionof the glutathione (GSH), ER stress may occur. Excessive and persistent ER stress eventually leads to cell death via apoptosis or necrosis. ER stress, on the other hand, can occur as a result of a series of events, like the depletion of the GSH and increased of oxidative stress [23].

3. Mitochondrial dysfunction

Mitochondria represent the most critical organelles for the intra-cellular energy production. They play a role in numerous metabolic activities, such as cellular respiration. Those organelles have been considered to be well-organized, have a high metabolic capacity, and communicate via a number of signaling pathways. Also, mitochondria are either indirectly or directly engaged in initiation of intracellular stress cascades, necrosis, and apoptosis, or death receptor-mediated path-ways [24]. High intra-cellular reactive oxygen species (ROS) levels, along with lipid peroxidation, GSH depletion, respiratory complex changes, and protein oxidation/alkylation, are all connected to mitochondrial dysfunction. Those events could be the cause of a variety of chronic liver disorders, including DILI [25]. In addition the generation of reactive metabolites after bio-transformation of a medicine employing Phase I or II enzymes may result in hepatitis through the direct toxicity or the immunological reactions. Due to such processes, the mitochondrial membrane may be damaged [26]. As explained in figure 5.

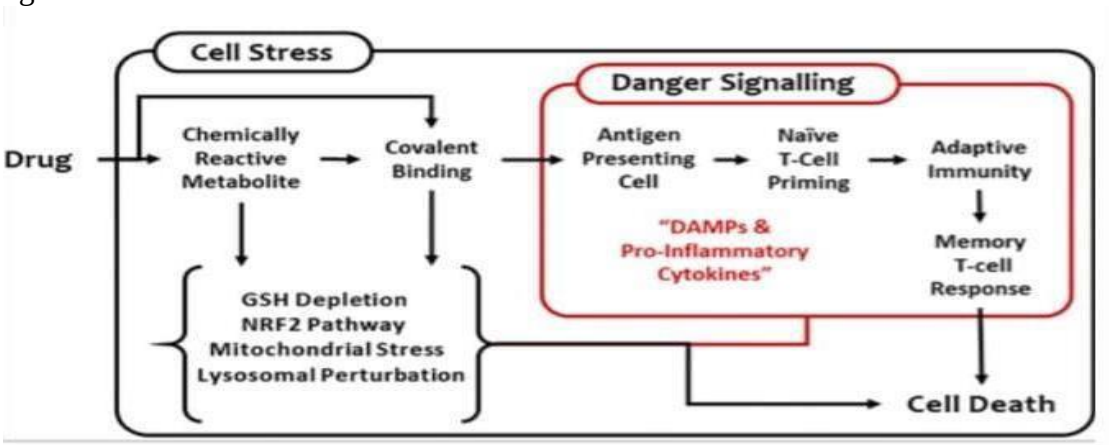


Figure (5). A diagram of path-ways leading to the cell death in the drug-induced liver injuries that result from the direct toxicity and the immune-mediated toxicity. Importantly, in a cell stress environment, danger signaling to immune system may happen [25].

3. Immune Allergic Hypothesis:

The cause of amoxicillin-clavulanate hepatotoxicity is unknown, however it is most likely caused by an immune reaction. Rash, fever, arthralgias, and eosinophilia are examples of allergic symptoms. In the vast majority of cases, zone 3 was dominantGranulomas and/or eosinophils, which are frequently related to and assumed to be indicative of immunoallergic damage, were rather common.

Recent research has revealed that amoxicillin-clavulanate (AC) and other medicines linked to immuno-allergic damage produce hepatitis, with many T cells infiltrating the portal triads, the majority of which are CD-8 cytotoxic T cells. These and other data point to an immune-mediated attack on cholangiocytes or possibly the apical pole of hepatocytes as the primary etiology of liver injury [27].

4. Genetic Cause on Chromosome 6P:

Amoxicillin-clavulanate-associated liver illness could also be caused by a connection to another gene on chromosome 6p. The "connected gene" theory could explain why, despite the fact that jaundice with co-amoxicillin medication is uncommon. Human leukocyte antigen (HLA) haplotype is common in northern Europe, accounting for up to 30% of the population. Amoxicillin-clavulanate is routinely prescribed to the general public. Moreover, the high. When compared to other HLA-related diseases, the frequency of homozygotes is uncommonillnesses, it's possible that the sickness manifests itself more commonly in those who have two(As in an autosomal recessive disease.) copies of the candidate gene more HLA class I alleles (A*3002 and B*1801) were more frequently associated with hepatocellular injury in AC-DILI cases than controls, while the presence of the human leukocyte antigen (HLA) class II DR2 haplotype (DRB1*1501- DQB1*0602) allele has been increased considerably in the cholestatic/mixed cases, according to a recent study of genotype–phenotype interaction in AC Clinical, histological, and genetic findings all point to the adaptive immune response being important in development as well as progression of DILI caused by amoxicillin-clavulanate [28].

5. Elevation of oxidative stress

In a recent study, either amoxicillin or clavulanic acid, alone or in combination, caused a significant increase ($P \leq 0.01$) in oxidative stress markers, as evidenced by increased lipid peroxidation product malondialdehyde (MDA), ROS production, and a reduction in antioxidant molecules such as reduced glutathione (GSH). Increased consumption of GSH in nonenzymatic elimination of oxygen-radicals could explain GSH depletion after administration of either amoxicillin (AMOX) or 11 clavulanic acid (CLAV) or their combination. Furthermore, in rat liver treated with either csslavulanate or amoxicillin-clavulanate, myeloperoxidase enzyme activity was enhanced, indicating increased neutrophil infiltration and activation, as shown in the histopathologic findings (figure 6). The results imply that oxidative stress reactions could be playing a role in the development of amoxicillin-clavulanate-induced liver impairment [29].

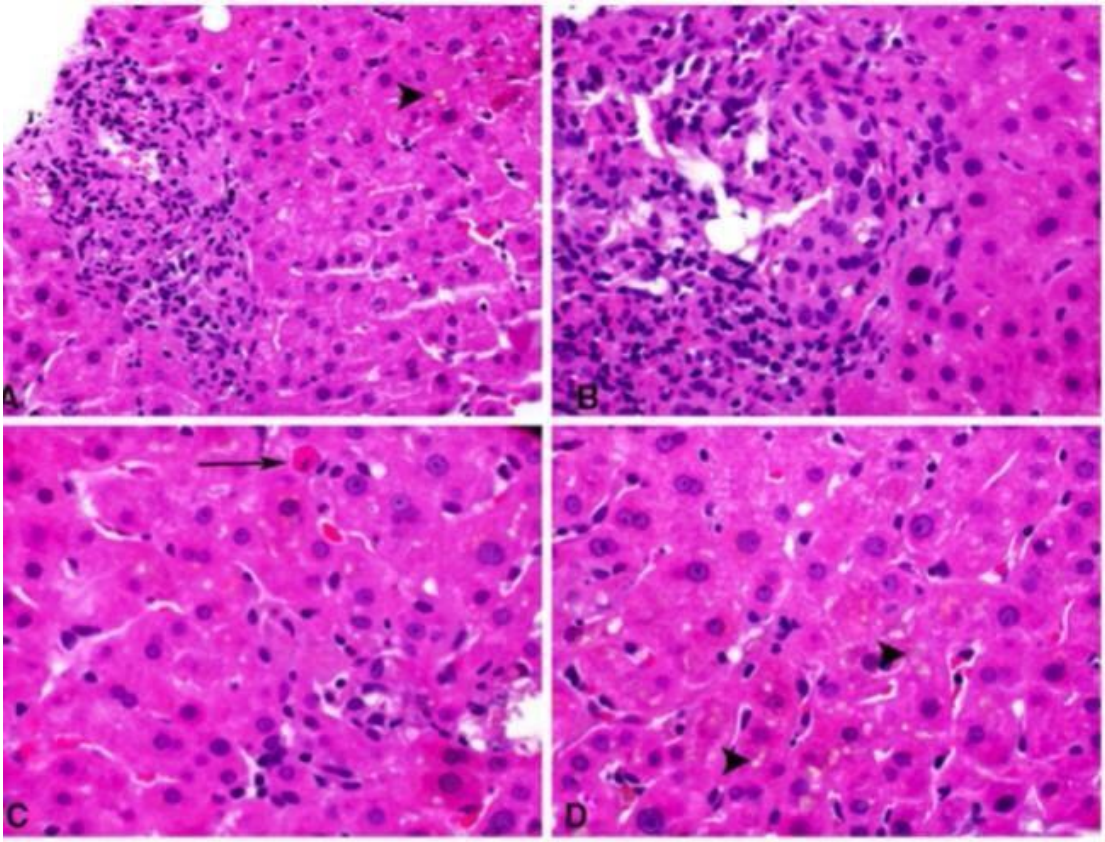


Figure (6). Histopathologic findings of cholestatic hepatitis due to amoxicillin–clavulanate [29]. (X100, H&E stain)

Signs and Symptoms of hepatotoxicity:

Hundreds of cases of clinically obvious acute liver injury have been linked to amoxicillin-clavulanate, and such combination is now the most frequent cause of drug-induced liver disease in the majority of large case studies from the Europe and US. After the starting of treatment, the start of harm can take anywhere from some days to as long as 8 weeks (on average 3 weeks). The delay 15 can range from some days to six weeks following the completion of antibiotic course. The first case of hepatotoxicity was caused by this drug. In 1988, it was first mentioned [30]. A cholestatic pattern is typically seen with hepatic damage. Granulomatous and hepatocellular patterns are the most common, with granulomatous and hepatocellular patterns showing up on rare occasions [31]. Cholestatic symptoms and signs, on the other hand, make up the vast majority of clinical characteristics. A few of the symptoms include hyporexia, malaise, vomiting, nausea, choluria, jaundice, cutaneous acholia, and fecal acholia. Hepatomegaly can cause pruritus and, in rare cases, painful hepatomegaly. Symptoms and signs associated with hypersensitivity symptoms, like fever and skin rash, can affect up to 5% of the population [32].

Treatment

There is no specific treatment for amoxicillin/clavulanate-induced liver damage. Notably the treatment is usually supportive and symptom-based. Several hundred plants have been studied for treatment in a range of liver ailments, in addition to several synthetic chemicals. Green tea and licorice were among the 170 phytocomponents extracted from 110 plants belonging to 55 families that were found to have liver-protective properties [33].

Stopping the suspected substance is the first step in hepatotoxicity treatment. In the case when a patient's jaundice isn't severe and their prothrombin time is low or normal, and they haven't shown any indicators of coagulopathy or encephalopathy and have been ill for a long period. Medical care could simply be supportive, with the patient being monitored on an outpatient basis regularly. There is no requirement for treatment unless there are signs of impending hepatic failure or if the protein or other elements are altered. Anorexia continues and might be treated in many ways. Small meals are encouraged, as are vegetables, fruits, and dairy foods instead of meat. Even if nausea is present, carbonated beverages, hard sweets and fruit juice are often well tolerated. Physical activity must not be prohibited, yet patients should be urged to stay within the limits of fatigability. A patient with high bilirubin levels and a prothrombin time prolongation must be hospitalized to the hospital (or closely monitored as an outpatient), particularly if anorexia and nausea persist after the drug has been stopped [34]. Due to the reduced fluid intake and vomiting, patients often get dehydrated. Therefore, determining the volemic status is crucial, and if needed, it must be addressed as quickly as feasible. Cholestatic symptoms might become restrictive, prompting the prescription of analgesics, anti-emetics, and pruritus medications for symptomatic individuals. Cholestyramine is a kind of cholestyramine which is found in the body (which might provide relief through trapping components which result in itching) [35].

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Depending on the severity of symptoms and the service's expertise with the drugs, antihistamines, ursodeoxycholic acid (UDCA), and sertraline are utilized [36]. Hepatocytes' mitochondrial and plasma membranes are stabilized by ursodeoxycholic acidcan serve as an antiapoptotic agent and protect them from different external damage (Its antioxidant function is most likely to blame for this protective effect [37]. Interestingly urodeoxycholic acid was able to restore normal metabolic oxidative stress levelsindicators, ROS generation, and a normalized GSH level that all play a role in the liver of amoxicillin-clavulanate-treated individuals has an antioxidant defense mechanismUDCA is thought to have antioxidant effects. This idea is supported by a number of recent studiesMoreover, UDCA's antioxidant properties have been confirmed [38] [39].

3. Conclusion

Despite the need for more research into pathogenesis of amoxicillin/clavulanate liver injury, immunological allergy pathways are considered to be involved. The existence of eosinophils in inflammatory infiltrate, hypersensitivity symptoms including hypereosinophilia and skin rashes, and the correlation with the Human Leukocyte Antigen (HLA) all point to an immunological attack as a cause of antibiotic-induced liver injury. DILI might happen up to 90 days following the first dosage of the drug or up to 30 days after the last one. After a drug suspicion, this clinical state might take up to 6 months to completely resolve.

Although most of the cases are benign, liver failure might occur in rare cases, demanding close monitoring. The mainstays of treatment are the withdrawal of offending substance and supportive care, like fluid replacement. Analgesic and antiemetic drugs can aid with cholestatic symptoms, which might be debilitating.

Conflict of interest

The authors declare that they have no conflicts of interest.

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