Journal Watch

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1. Plasma ammonia levels predict hospitalization with liver-related complications and mortality in clinically stable outpatients with cirrhosis. Tranah TH, Ballester MP, Carbonell-Asins JA et al. J Hepatol 2022;77(6):1554–1563

Various noninvasive modalities or scoring systems for the evaluation of patients with cirrhosis, and prediction of survival are either limited by interobserver subjectivity, are unable to review the complete aspects of the pathophysiology, or are expensive. It is known that high levels of ammonia, a gut-derived neurotoxin, has a great contribution to the development of hepatic encephalopathy (HE), hepatic cell injury, and immune dysfunction. This prospective observational study dissects the hypothesis that high serum ammonia is utilized as a prognostic biomarker for HE and other liver-related complications. It can also be used as a marker for mortality in stable patients with cirrhosis. The principal aim of this study was to ascertain whether high serum ammonia level is related to the likelihood of hospitalization and the development of various liver-related complications such as over HE, variceal bleeding, bacterial infection, ascites, or mortality. A total of 754 adult outpatients who had decompensated or compensated cirrhosis, but were clinically stable, were included in the study. The most common etiologies were alcohol, nonalcoholic fatty liver disease (NAFLD), and viral hepatitis. Baseline serum ammonia was measured and patients were followed up until study closure, liver transplantation, or death. During follow-up, liver-related complications were seen in 35% of patients with infections (16%) being the most common complication. Amongst the causes of deaths, unknown cause (36%), deaths due to complications of cirrhosis or acute-on-chronic liver failure (35%), infection (28%), hepatocellular carcinoma (10%), other malignancy (12%) and other non-liver related conditions (12%) were observed. The association of raised serum ammonia and disease ETI Hepatocellular carcinoma ology was most marked in patients with NAFLD-induced cirrhosis (p = 0.002) and the association was higher in a patient with an advanced stage of cirrhosis. Hyperammonemia was observed to be an independent predictor for hospitalization with liver-related complications, over HE, variceal bleeding, ascites, bacterial infections, and mortality. The area under the receiver operating characteristics of ammonia level for hospitalization at 3 and 6 months and, at 5 years due to liver-related complications were 73.2, 74.9, and 74.4%, respectively. It was found that serum ammonia >1.4 upper limit of normal (ULN) was the right cutoff which can predict the risk of hospitalization for liver-related complications. This study also derived a predictive model using random forest plots which could demonstrate the superiority of the serum ammonia level in predicting the risk of hospitalization as compared to the established predictive models such as the Model for End-Stage Liver Disease and Child–Pugh scores. However, the effect of lowering serum ammonia on the prognosis was not evaluated in this study.

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2. Exotic viral hepatitis: A review on epidemiology, pathogenesis, and treatment. van Leeuwen LPM, de Jong W, Doornekamp L et al. Exotic viral hepatitis: A review on epidemiology, pathogenesis, and treatment. J Hepatol. 2022;77(5):1431–1443

Exotic viruses are viruses whose prevalence is seen in specific geographical areas and they lead to the involvement of the liver and cause hepatitis. The most notorious of these viruses of a special group is the viral hemorrhagic fever (VHF) virus. This group is important as we still don't have specific preventive or therapeutic measures available for them, they can lead to severe outbreaks and can spread to non-endemic areas by international travel. They can range from asymptomatic self-limiting infections to severe febrile hemorrhagic conditions. This review provides a comprehensive detail of these VHF viruses that can affect the liver.

Crimean Congo hemorrhagic fever virus (CCHFV)—this causes Crimean and Congo fever and is endemic across Africa, Asia, and Southern Europe where the Hyalomma tick, its vector is commonly found. There are four phases of the infection: the incubation phase (1–7 days); the prehemorrhagic phase (1–7 days) characterized by "flu-like symptoms"; the hemorrhagic phase (1–3 days) characterized by bleeding manifestations. For the majority of patients, death ensues in 2 weeks of this phase [case fatality rate (CFR): 5–40%] with severe liver necrosis leading to multiorgan failure, acute liver failure (ALF), and shock, and convalescence phase. Diagnosis can be reliably made by reverse transcription polymerase chain reaction (RT-PCR), and in less severely ill patients by CCHFV-specific antibodies. Treatment is supportive and the only effective prevention is to avoid tick bites.

- Dengue: This virus is a non-hepatotropic virus but commonly affects the liver. In humans, dengue occurs by transmission of the virus by *Aedes* spp. mosquitoes and is more prevalent in tropical and subtropical countries. There is no cross-immunity among the four known serotypes, therefore reinfection is possible. Humans are the major reservoir for the virus, and

overpopulation, climate change, international travel, and poor vector control facilitate the spread of the virus. Almost 80% of infections are asymptomatic and only 5% of symptomatic cases might need hospitalization. The incubation period is 4–7 days after which the patient may experience retro-orbital pain, headache, arthralgia, myalgia, or maculopapular rash. In dengue hemorrhagic fever (DHF) and dengue shock syndrome (DSS), which are the severe forms of dengue, severe plasma leakage, resulting in shock or fluid accumulation associated with respiratory distress, severe bleeding, and multi-organ failure may be seen. About 60–90% of patients with DHF and DSS can have liver involvement and can have hepatomegaly, jaundice, or a rise in aspartate aminotransferase (AST) and alanine aminotransferase (ALT) to >3 times the ULN. About 4–15% can have transaminases >10 times ULN and 0.5% may land into ALF leading to mortality. For diagnosis, RT-PCR is the most sensitive, and other methods like enzyme-linked immunosorbent assay (ELISA) or antigen-based rapid tests can be utilized to detect the non-structural-1 dengue antigen. Treatment is fluid therapy and supportive. For endemic regions, Dengvaxia (age: 9–16 years) and EMEA (age: 6–45 years) have been approved and are indicated only for those who already had laboratory-confirmed dengue infection in the past.

- Ebola: *Zaire ebolavirus*, one of the six known Ebola virus species, is the causative agent for most human infections, mainly in central and West Africa. Fruit bats are considered probable natural reservoirs and in humans, the spread of the virus is *via* person-to-person contact, directly or through body fluids. The incubation period is 6–21 days. Clinical features mainly comprise initial fever (90%), myalgia, and asthenia; later after a week, there is the development of symptoms, such as vomiting and diarrhea leading to dehydration. In the third phase, AST and ALT are elevated (>5 ULN) and multi-organ failure can occur with 50% mortality. Diagnosis can be done by molecular testing or RT-PCR which is the gold standard. Treatment is mainly supportive, however, two monoclonal antibodies Inmazeb and Ebanga have also been approved. Two vaccines have been approved; Ervebo a live-attenuated vector vaccine (efficacy: 97.5%) and Zabdeno-and-Mvabea.
- Hantavirus: It leads to hemorrhagic fever with renal syndrome (HFRS) mainly in Eurasia and hantavirus cardiopulmonary syndrome seen in North and South America. HFRS caused by *Seoul orthohantavirus* (SEOV) is the only hantavirus that presents as hepatitis. Rodents, which are chronically infected, act as reservoirs, and the virus is transmitted to humans by the inhalation of aerosolized excreta which contains the virus, and also, probably *via* rat bites or exposure to laboratory rats. Patients may present with fever, renal failure, hemorrhage, and elevated liver enzymes but ALF has not been reported. SEOV can be detected within 8–10 days after onset by PCR. ELISA detecting hantavirus-specific immunoglobulin (Ig)M and/or IgG serum antibodies is also an important tool. Treatment is symptomatic and supportive. Some suggest ribavirin may reduce the severity but the evidence is low. Prevention is by minimizing contact with rodents in endemic areas.
- Lassa virus: It is the causative agent of Lassa fever seen endemically in West Africa (CFR: 15–20%) and Europe (CFR: 35%). The only reservoir host is the African multimammate rat. The incubation period is 1–3 weeks. Most of the patients have mild or subclinical disease with vomiting, abdominal pain, pharyngitis, and headache. Progression is seen after 7 days when typical facial edema, neurological manifestations, and hemorrhage may be seen. This stage has CFR between 38 and 52%. Later in the next stage after 2 weeks death may occur due to shock, and respiratory distress with or without hemoptysis. Recovery is characterized by long-term psychiatric manifestations, deafness, or hair loss. Hepatitis and elevated enzymes are also reported. Diagnosis can be done by the presence of anti-Lassa IgM and/or IgG antibodies and PCR. Early treatment with ribavirin is beneficial and is also used for post-exposure prophylaxis.
- Rift Valley fever virus (RVFV): It is seen endemically in several African countries and Arabian Peninsula. It predominantly infects domestic livestock with a high degree of mortality and is transmitted by *Aedes* and *Culex* mosquitoes. Humans are infected *via* mosquito bite or *via* contact with infected tissue or fluids of animals and present as incapacitating febrile illness and myalgia. Later patients can develop ocular disease, meningoencephalitis, or hemorrhagic fever. Residual neurological deficits or permanent loss of vision can be seen. Liver involvement can present as jaundice, hemorrhagic disease, AST, and ALT elevation (>10 times ULN) with high mortality (50%). diagnosis can be done by PCR during the acute stage when the viral load is high. RVF IgM-antibodies can be detected after 4 days using ELISA. The gold standard for serological testing is virus neutralization assay. Treatment is predominantly supportive, however, the role of ribavirin and favipiravir seems to be promising. Prevention of outbreaks can be done by vaccinations of the livestock.
- Yellow fever virus (YFV): It is transmitted by the bite of *A. aegypti* and is endemic in subtropical regions of Africa and South America. After 3–6 days of the incubation period, the patient presents with flu-like symptoms which are followed by remission after 3–5 days. In a few, it may progress to jaundice and ALF along with multi-organ failure. Diagnosis is done by the presence of anti-YFV antibodies using IgM-ELISA or for better accuracy, quantitative PCR. Treatment is supportive care. Roles of ribavirin, sofosbuvir, and corticosteroids are under studies. The vaccine available for yellow fever is very effective.