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Review Article

Current Challenges in Hepatitis C

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Abstract

Hepatitis C is a significant global problem with a wide-ranging personal, social and economic impact. The virus can silently attack the liver for decades before the illness becomes obvious, often as cirrhosis, liver cancer or liver failure.[1] Hepatitis C virus (HCV) is emerging as one of the major health problems in Bangladesh.

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Epidemiology

Globally, an estimated 170 million people, approximately 3% of the world's population, are infected with the HCV (WHO, 1999), with 3 to 4 million peoples being newly infected each year.[1] In Bangladesh, prevalence of HCV infection 2.4% (WHO, 1999).[2] There are significant geographical variations, and significant demographical variations within the same geographic region, in the HCV prevalence. Hepatitis C is serious threat for South East Asia region. HCV is not tested for in this region, not least because it would add to the costs. In the unscreened blood in this region the seroprevalence of hepatitis B is 0.06 - 8.5% and of hepatitis C is 1.2-3%, according to WHO.[3] Egypt has a very high prevalence of HCV and a high morbidity and mortality from chronic liver disease, cirrhosis, and hepatocellular carcinoma. Approximately 20% of Egyptian blood donors are anti-HCV positive.[3] In Bangladesh, HCV seropositivity among professional blood donors is 1.2% while in the voluntary donors is nil.[4] In another study, anti-HCV was positive in 1.7% in acute viral hepatitis, 5.5% in sub-acute hepatic failure, 6.8% in post transfusion hepatitis, 24.1% of chronic liver disease, 9.6% cases hepatocellular carcinoma.[5] HCV antibody among clinically jaundiced patients was 2.5%[6], healthy married woman 0.9%[7], injectable and non-injectable drug users 24.8% and 5.8% respectively.[8] In a recent study 12.5% thalassaemic children was found to have HCV antibody while the age matched controls had only 0.9%.[9] As most of our blood centres do not screen blood for anti-HCV antibody, it is speculated that among these recipients, a large number may develop chronic HCV infection and its sequele by the next few years.

Virology

The hepatitis C virus is an enveloped RNA virus with a diameter of about 50nm, classified as a separate genus (Hepacivirus) within the flaviridae family which appears to have a narrow host range. Humans and chimpanzees are the only known species susceptible to infection, with both species developing similar disease. HCV is highly heterogenous. HCV is clustered into several distinct genotype, eleven HCV genotypes with more than eighty subtypes have been identified throughout the world, which may be important in determining the severity of the disease and the response to treatment. Almost one thousand quasi subtypes of the HCV genotypes have been

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theorized to exist.[1] Moreover, such heterogeneity hinders the development of vaccines, since vaccine antigens from multiple serotypes will probably be necessary for global protection.[10] In Bangladesh, the predominant genotype of HCV is found to be 1b.[11]

Mode of Transmission

HCV is spread primarily by direct contact with the contaminated blood or plasma derivatives, contaminated needles and syringes are most important vehicles of spread especially among the injecting drug users. Transmission by household contact and sexual activity appears to be low. Only a small portion of HCV infection is transmitted at birth from mother to child. About 5 out of every 100 infants born to HCV infected woman become infected at the time of birth. Other modes of transmission such as social, cultural, and behavioral practices using percutaneous procedures (e.g. ear and body piercing, circumcision, tattooing) can occur if inadequately sterilized equipment is used. HCV is not spread by sneezing, hugging, coughing, food or water sharing eating utensils or causal contact.[10]

Pathogenesis

HCV infects hepatocytes. It is still unclear whether the liver damage associated with HCV infection is the result of a direct cytopathic effect or is caused by a host immune-mediated cytolytic response. Both processes are probably involved in causing hepatic damage, chronic hepatitis C is characterized by portal inflammation typically periportal hepatocellular necrosis, and fibrosis.[10]

Clinical features

A) Acute HCV infection

The incubation period for acute hepatitis C averages 6 to 10 weeks. Most persons who develop acute hepatitis C have no symptoms. The onset of disease is usually insidious, with anorexia, vague abdominal discomfort, nausea and vomiting, fever and fatigue, progressing to jaundice in about 25% of patients, less frequent than hepatitis B. Rapid, fulminant liver failure associated with HCV infection is a rare event. Probably as many as 70-90% of infected people fail to clear the virus during the acute phase of the disease and become chronic carriers.[10]

B) Chronic HCV infection and consequences

An important clinical feature of infection with HCV is the high rate of chronic hepatitis and slowly progressive lifelong infection, which may lead to cirrhosis and liver failure in about 10-20% of persons with chronic hepatitis C. HCV-associated cirrhosis leads to liver failure and death in about 20-25% of cirrhotic cases. HCV-associated cirrhosis now represents a leading indication for liver transplantation. Chronic HCV infection appears to be associated with the development of hepatocellular carcinoma (HCC) in 1-5% of persons with chronic hepatitis C. Development of HCC is rare in persons with chronic hepatitis C who do not have cirrhosis. Chronic infection is often not symptomatic, until evidence of liver failure becomes clinically apparent. The rate of progression to cirrhosis is usually slow, with 20 or more years elapsing between infection and the development of serious complications. Even in the asymptomatic carrier, a decrease in quality of life has been reported. Histopathology grade and stage of liver damage is not reflected by serum ALT/AST levels or serological status.[10]

Diagnosis

Diagnostic tests for HCV are used to prevent infection through screening of donor blood and plasma, to establish the clinical diagnosis and to make better decisions regarding medical management of a patient.[1,10,12]

1. Enzyme immunoassays (EIA) - In screening and preliminary diagnosis of HCV infection in high-risk patients.
2. Recombinant immunoblot assay (RIBA) - To resolve false - positive EIA results in asymptomatic patients, and in low-risk populations such as blood donors where false - positive EIA results are most likely to occur.[1]
3. HCV RNA test - (Polymerase chain reaction or PCR, branched DNA assay) - To confirm diagnosis as well as assessing the effectiveness of antiviral therapy. A positive result indicates the presence of active infection and a potential for spread of the infection and or / the development of chronic liver disease.

4. Liver function tests - ALT, AST.

5. Liver biopsy - is used to confirm diagnosis, assess disease severity, assess therapeutic effectiveness and to evaluate possible concomitant disease processes.[1]

Treatment

The goals of therapy for chronic HCV infection are to eradicate the virus, slow or reverse disease progression, improve hepatic histology, reduce the risk of HCC, and improve health-related quality of life (QoL).[1]

The European Association for the Study of the Liver (EASL) and the National Institute of Health (NIH) guidelines[13] recommended that patients with detectable serum HCV RNA combined with moderate or severe necro-inflammation and / or fibrosis should be treated. These guidelines currently suggest that in treatment naïve patients, interferon (IFN) plus Ribavirin (RBV) combination therapy should be the first line of treatment unless otherwise contraindicated. The recommendations of the French consensus conference on hepatitis C held in Paris in February 2002 have recently been published and take into account the use of pegylated IFNs in the management strategy for HCV-infected patients in France.[14] Pegylated IFN/RBV combination therapy has been recommended for patients who are naïve to treatment and have no contraindication to IFN or RBV and patients who have relapsed after, or not responded to, IFN monotherapy. In light of data from the clinical trials of Pegasys® [Peg-interferon alfa-2a (40KD)] plus RBV, it was further recommended that treatment duration should be based on HCV genotype. Patients infected with genotype 1 HCV should be treated for 48 weeks, patients infected with HCV genotype 2 or 3 should receive 24 weeks treatment. Patients infected with HCV genotype 4 are regarded as having a more difficult to treat infection and a 48 weeks treatment period was proposed, depending on individual risk benefit ratio. The same regimen was recommended for patient infected with HCV genotype 5 or 6.[15] The recommended dose of PEG-IFN-α2a is 180μg/week and of Ribavirin 800mg/day for genotype 2 and 3 and 1000-1200mg/day for genotype 1 and 4.[16]

Treatment of chronic hepatitis C (CHC) for 12 months with IFN monotherapy results in sustained virological response (SVR) of 15 to 20%. PEG-INF (Pegasys®) plus RBV yields a 78% sustained virological response (SVR). Even in the most difficult-to-treat patients, with genotype 1, the Pegasys® combination achieved a 51% SVR.[17,18] The overall response to combination therapy is 61%, irrespective of genotype. In addition, weekly therapeutic dosing improves treatment convenience and the QoL experience of the patients. The major types of side effects of combination treatment include fatigue, influenza-like symptoms, gastrointestinal disturbances, neuro-psychiatric symptoms, and hematological abnormalities.[19] These side effects may be treatment limiting and require dose reduction or drug discontinuation.[1] Pegylated interferons have significantly improved pharmacokinetics[20,21] resulting in improved antiviral efficacy, which also has the potential to alter the side effect profile.

Prevention

At present there is no vaccine against HCV and no effective post-exposure prophylaxis. Research is in progress but the high mutability of the HCV genome complicates vaccine development.[22] In the absence of a vaccine, all precautions to prevent infection must be taken including screening and testing of blood, plasma, organ, tissue, and semen donors. Virus inactivation of plasma derived products. Implementation and maintenance of infection control practices in health care setting, including appropriate sterilization of medical and dental equipment. Promotion of behavior change among the general public and health care workers to reduce overuse of injections and to use safe injection practices, and risk reduction counseling for persons with high-risk drug and sexual practices.

Conclusion

In conclusion, the ideal therapy for patients with chronic hepatitis C would be highly effective, orally bio-available, suitable for the majority of

patients, without major side effects, and cost effective. As there is no effective vaccine till today, personal protection, safe transfusion of blood and blood products, safe disposal of hospital bio-waste and use of disposable and auto-disabled syringes would be the best option for a country like Bangladesh.

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