International Journal of Science and Research (IJSR)
ISSN (Online): 2319-7064
Index Copernicus Value (2015): 78.96 | Impact Factor (2015): 6.391

Hepatitis B- An Emerging Global Health Problem

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Abstract: ***Viral hepatitis today is a major global health threat, in particular hepatitis B if unchecked can turn into an epidemic. Hepatitis B infection is particularly important in the Asian- Pacific region with the majority of infections being acquired perinatally or in early childhood.Concurrent infections with hepatitis B, hepatitis C and HIV viruses may occur and complicate the natural course of chronic hepatitis B virus (c/c HBV) infection. Despite recent advances in the treatment of c/c HBV infections, the results of treatment are still unsatisfactory. The development of new drugs and new strategies especially combination or sequential antiviral therapy is the highest priority in improving the outcomes of treatment. This article explores the prevalence of hepatitis B world wide with a focus on India, the different modes of transmission, diagnosis, treatment and prevention. In addition it also looks upon the recent WHO guidelines targeted towards a comprehensive approach to the prevention of hepatitis B.***

Keywords: Silent epidemic, Prevention, Treatment, WHO Guidelines, Hepatocellular carcinoma

1. Introduction

Viral hepatitis is an inflammation of the liver caused by one of the five hepatitis viruses, referred to as types **A, B, C, D** and **E**. While all of these viruses cause liver disease, they vary significantly in terms of epidemiology, natural history, prevention, diagnosis and treatment.

Viral hepatitis is now a global public health problem affecting millions of people every year, causing disability and death. Approximately 10 lakh people die each year (~ 2.7% of all deaths) from causes related to viral hepatitis, most commonly liver disease, including liver cancer[1].

Although the burden of disease is very high, the problem has not been addressed in a serious way for many reasons, including the relatively recent discovery of the causative viruses, the mostly silent or benign nature of the disease in its early stages, and the insidious way in which it causes chronic liver disease. Decades – long delay between infection and the expression of chronic liver disease or liver cancer make it difficult to link these diseases to earlier HBV or HCV infections. All these factors have resulted in "the silent epidemic" we are experiencing today.

This article focuses on Hepatitis B infection since it is a major global health problem and the most serious type of viral hepatitis.

Hepatitis B

Hepatitis B is a potentially life threatening liver infection caused by the hepatitis B virus. This virus can cause an acute illness with symptoms that last several weeks, including jaundice, extreme fatigue, nausea, vomiting and abdominal pain. It can also cause chronic liver disease and puts people at high risk of death from cirrhosis of the liver and liver cancer. It is a major infectious occupational hazard of health workers.

The likelihood that infection with the hepatitis B virus becomes chronic depends upon the age at which a person becomes infected. Young children who become infected with the hepatitis B virus are the most likely to develop chronic infections. 25% of adults who become chronically infected during childhood die from hepatitis B- related liver cancer or cirrhosis. 90% of healthy adults who are infected with the hepatitis B virus will recover and be completely rid of the virus within six months.

2. Prevalence

HBV infection has a worldwide distribution. It is estimated that two billion people have been infected with the hepatitis B virus and more than 240 million have chronic liver infections[2]. About 6 lakh people die every year due to the acute or chronic consequences of hepatitis B[3]. About 350-400 million people are chronic HBsAg carriers. Host and viral factors, as well as coinfection with other viruses, in particular hepatitis C, hepatitis D or HIV virus together with other co-morbidities including alcohol abuse and obesity, can affect the natural course of HBV infection [4,5].The prevalence of HBeAg – negative form of the disease has been increasing over the last decade as a result of ageing of the HBV – infected population and predominance of specific HBV genotypes[6].

The endemicity of hepatitis B is described by the prevalence of HBsAg in the general population of a defined geographical area. HBs Ag prevalences of ≥ 8% are typical of highly endemic areas, prevalences of 2-7% are found in areas of intermediate endemicity, whereas in areas with low endemicity <2% of the population is HBsAg positive. Population movements and migration are currently changing the prevalence and incidence of the disease in several low endemic countries in Europe and elsewhere[7,8].

Disease burden in India

India is at the intermediate endemic level of hepatitis B, with HBsAg prevalence between 2% and 10%. The prevalence does not seem to vary significantly by region in the country. The number of HBsAg carriers in India has been estimated to be over 40 million. Of the 25 million infants born every year, 1 million run the life time risk of developing chronic HBV infection. Estimates indicate that annually over 1 lakh Indians die due to illnesses related to HBV infection[9].

Transmission

Hepatitis B virus is transmitted between people by direct blood – to – blood contact or semen and vaginal fluid of an infected person. The virus is 50 to 100 times more infectious than HIV virus. It can survive outside the body for at least seven days. During this time, the virus can still cause infection if it enters the body of a person who is not protected by the vaccine. The incubation period of the Hepatitis B virus is 90 days on average, but can vary from 30 to 180 days.

3. Diagnosis

Laboratory diagnosis of hepatitis B infection depends on the detection of hepatitis B surface antigen (HBsAg). A positive test for HBsAg indicates that the person has an active infection.

Other commonly used tests:

Testing for antibodies to HBsAg – a positive test indicates that the person has either recovered from an acute infection and cleared the virus, or has received a hepatitis B vaccine. The person is immune to future hepatitis B infection and is no longer contagious.

Testing for antibodies to the hepatitis B core antigen – a positive test indicates that the person has had a recent infection or an infection in the past.

4. Treatment

Acute Hepatitis B

Treatment is aimed at maintaining comfort and adequate nutritional balance, including replacement of fluids lost from vomiting and diarrhoea. More than 95-99% of adults with acute HBV infection will recover spontaneously and seroconvert to anti-HBs without antiviral therapy[10].

Patients with fulminant or severe hepatitis must be evaluated for liver transplantation. These patients may benefit from NA (nucleoside/nucleotide analogues) treatment. Some case reports support such a strategy mainly with lamivudine[11].

The duration of treatment is not established. However, continuation of antiviral therapy for at least three months after seroconversion to anti-HBs is recommended. Sometimes, the distinction between true severe acute hepatitis B and reactivation of CHB may be difficult and may require liver biopsy. However, NA treatment is the treatment of choice in both cases.

Chronic Hepatitis B

People with chronic hepatitis B can be treated with drugs, including interferon and antiviral agents. Two different types of drugs can be used – conventional or pegylated interferon alpha (IFN or Peg-IFN) and nucleoside/nucleotide analogues referred to collectively as NAs[12].

NAs for HBV therapy can be classified into nucleosides (lamivudine, telbivudine, emtricitabine, entecavir) and nucleotides (adefovir and tenofovir). Entecavir and tenofovir are potent HBV inhibitors with a high barrier to resistance. Thus, they can be confidently used as first- line monotherapies[13].

The other three NAs may only be used in the treatment of CHB if more potent drugs with high barrier to resistance are not available. Immunomodulatory agents (IFN, Peg IFN and thymosin α_1) have dual actions: enhancing host immune system and modest antiviral action.

Health care workers

Health care workers require antiviral therapy even if they do not fulfil the typical indications for treatment to reduce direct transmission to patients during exposure prone procedures. Health care workers, including surgeons, gynaecologists and dentists who are HBsAg positive with HBV DNA $\geq$ 2000 IU/ml should be treated with a potent antiviral agent with a high barrier to resistance (entecavir or tenofovir) to reduce levels of HBV DNA ideally to undetectable or at least to < 2000 IU/ml before resuming exposure prone procedures.

5. Prevention

The hepatitis B vaccine is the mainstay of hepatitis B prevention. WHO recommends that all infants receive the hepatitis B vaccine. The vaccine has an outstanding record of safety and effectiveness.

Recombinant hepatitis B vaccine introduced in 1986 has gradually replaced the plasma-derived hepatitis B vaccine. A new recombinant hepatitis B vaccine that is intended for adult patients with renal insufficiency uses alum and lipid A as adjuvants[14].

Hepatitis B vaccine is available as monovalent formulations or in fixed combination with other vaccines, including DTP, haemophilus influenza type b, hepatitis A and inactivated polio. When immunizing against HBV at birth, only monovalent hepatitis B vaccine should be used. Internationally marketed hepatitis B vaccines are considered immunologically comparable and can be used interchangeably.

Effectiveness of vaccination

A recent meta-analysis of randomized controlled trials of hepatitis B vaccine administered at birth found that immunized infants born to mothers infected with hepatitis B were 3.5 times less likely to become infected with HBV[15].

The protective efficacy of hepatitis B vaccination is related to the induction of anti-HBs antibodies, but also involves the induction of memory T-cells. An anti-HBS concentration of 10 mIU/ml measured 1-3 months after administration of the last dose of the primary vaccination series is considered a reliable marker of protection against infection. The primary 3 dose vaccine series induces protective antibody concentrations in >95% of healthy infants, children and young adults[16]. After the age of 40 years, antibody response rates decline gradually[17]. Individuals who do not respond to a primary 3-dose series with anti-HBs concentrations of $\geq$ 10mIU/ml, respond to a 3-dose revaccination series.

Dose and administration of vaccines
The recommended dose varies by product and with the age of the recipient. The dose for infants and children (aged ≤ 15 years) is half the recommended adult dose. The hepatitis B vaccine does not interfere with the immune response to any other vaccine and vice-versa. However, unless formulated as fixed combinations, hepatitis B vaccine and other vaccines administered during the same visit should be given at different injection sites.

Vaccination schedules
The primary hepatitis B immunization series conventionally consists of 3 doses of vaccine (1 monovalent birth dose followed by 2 monovalent or combined vaccine doses). However, 4 doses may be given for programmatic reasons (eg:- 1 monovalent birth-dose followed by 3 monovalent or combined vaccine doses), administered according to the schedules of national routine immunization programmes.

Duration of protection and need for booster injections
The higher the peak anti-HBS concentrations following immunization, the longer it usually takes for antibody levels to decline to ≤ 10mIU/ml[18]. A number of long term follow-up studies from various epidemiological settings have confirmed that HBsAg carrier status or clinical HBV disease rarely occurs among successfully vaccinated individuals even when the anti-HBS concentrations decline to ≤ 10mIU/ml over time[19]. Even an absent anamnestic response following booster vaccination may not necessarily signify susceptibility to HBV in such individuals[20]. Although knowledge about the duration of protection against infection and disease following hepatitis B vaccination is still incomplete, there is no compelling evidence for recommending administering a booster dose of hepatitis B vaccine in routine immunization programmes.

Contraindications
Hepatitis B vaccine is contraindicated only for individuals with a history of allergic reactions to any of the vaccine components. Neither pregnancy nor lactation are contraindications for use of this vaccine.

Prevaccination and postvaccination testing
Prevaccination serological testing is not recommended as routine practice. However, where laboratory facilities are available, serological screeing may reduce the number of unnecessary vaccinations of people who are already immune to HBV infection. Prevaccination testing can be done with a single test (anti HBc) or with a panel of tests (e.g anti Hbs and HbsAg).
Routine post vaccination testing for immunity is not necessary, but it is recommended for high risk individuals whose subsequent clinical management depends on knowledge of their immune status.

The groups to be considered for post vaccination testing are:
A] people at risk of occupationally acquired infection.
B] infants born to HBSAg positive mothers
C] chronic haemodialysis patients, people infected with HIV and other immunocompromised people .
D] sex partners or needle sharing partners of people who are HbsAg positive.
Testing should be done 1-2 months after administration of the last dose of the vaccine series using a method that allows for determination of a protective concentration of anti HBs (≥10 mIU/ml).

For people who have been vaccinated previously or whose vaccination status is unknown, interpreting anti HBs results can be problematic. Vaccine responders may remain protected even when anti HBs concentrations are no longer detectable. Positive anti HBs results occurring in people who did not complete a vaccine series might not imply that they have long term protection against infection[21].

Passive immunization against Hepatitis B:
Temporary immunity may be obtained by administering Hepatitis B immunoglobulin[HBIG] for post exposure prophylaxis. As a rule, HBIG should be used as an adjunct to hepatitis B vaccine. Improved protection has been demonstrated in neonates immunized with hepatitis B vaccine and HBIG when compared with hepatitis B vaccine alone[15]. However owing to concerns related to supply, safety and cost, the use of HBIG is not feasible in most settings.

WHO response:
In 2010, the World Health Assembly adopted resolution WHA 63,18 which calls for a comprehensive approach to the prevention of viral hepatitis. In line with WHA 63.18, the WHO secretariat established a global hepatitis programme within its department of Pandemic and Epidemic diseases, with focal points in the six regional offices to implement the resolution and attain the goals outlined in this framework. Since 2011, World hepatitis day has been celebrated annually on the 28th of July.

6. Current Global Achievements

- As of 2009, 179 countries world wide have included the HBV vaccine in their infant immunization programs.
- WHO's advice, guidance and technical support are assisting countries in ensuring the safety, quality and availability of blood and blood products to meet the needs of all patients requiring blood transfusion.
- WHO has developed tools to assess injection practices and assist countries to develop injection safety strategies.
- WHO has defined care components for infection prevention and control programmes.
- Persons with active chronic HBV and HIV infections can now benefit from new treatment with antiretroviral drugs, which are recommended in the WHO guidelines.

7. Remaining Challenges

1) Lack of adequate knowledge and awareness among the general population as well as health professionals is a major challenge.
2) Most countries lack adequate surveillance systems to enable them to take evidence – based policy decisions.
3) Global HBV vaccine coverage is currently below 90% of the global target[22].
4) Implementation of standard precautions is still a challenge in many health care settings[23].

5) Among health professionals, an additional challenge is the need to strengthen competencies for diagnosis, treatment, care and follow up of people with viral hepatitis.

8. Conclusion

Hepatitis B is a viral infection that attacks the liver and can cause both acute and chronic disease. 2 billion people worldwide have been infected with the virus and about 6 lakh people die every year due to the consequences of hepatitis B[24].

Hepatitis B is preventable with the currently available safe and effective vaccine. Our understanding of the natural history of HBV infection and the potential for therapy of the resultant disease is continuously improving. Despite the increasing knowledge, areas of uncertainity exist and therefore clinicians, patients and public health authorities must continue to make choices on the basis of the evolving evidence.

To make prevention, care and treatment available to those who need it will require an immense effort on the part of all stakeholders: They will need to increase awareness, mobilize resources and apply lessons learned from other health areas. Implementing this framework of action and translating it into national strategic plans will contribute to major and sustained improvements in health.

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