UNIT NO. 6

HEPATITIS A AND B PREVENTION

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ABSTRACT

Hepatitis A occurs worldwide as an endemic disease. In developing countries, there is a high incidence of infection. In developed countries, Hepatitis A seroprevalence has decreased due to increasing household income and education, and improvements in sanitation, hygiene and water quality. It is estimated that around 2 billion individuals worldwide have evidence of present or past infection with Hepatitis B virus (HBV). Of these approximately 350 million are chronic carriers of the virus, and between 15% and 25% of them will die as a result of HBV. Most of the infections are acquired at birth, or during early childhood when the risk of chronic infection is greatest. The lifetime risk of HBV infection is greater than 60%. There are no specific antiviral drugs against Hepatitis A or Hepatitis B. Therefore preventive measures remain the most important strategy for the control of Hepatitis A and Hepatitis B. Widespread immunization programmes against HBV, which have been implemented in more than 100 countries, have dramatically reduced the occurrence of chronic HBV infection and hepatocellular carcinoma. Three highly immunogenic purified, effective and safe formaldehyde-inactived, whole particle hepatitis A virus (HAV) vaccines: Havrix (Glaxo SmithKline), Vaqta (Merck) and Avaxim (Aventis Pasteur) are approved for use in Singapore. In 1992, the World Health Organisation recommended the integration of vaccination against hepatitis B in the EPI. As of 2003, 151 countries had incorporated the hepatitis B vaccines into their routine mass infant immunisation programmes. Combination vaccine has been of particular benefit to those who are at risk of infection with both viruses. Issues in Hepatitis A immunisation are: whether there is a need for a booster; the lower immune response to HAV is lower in HBV carrier children; drug users are unaware of the need for immunisation. Issues in Hepatitis B immunisation are: HBV nonresponders; the importance of HBV escape mutants; and the roles of new mixed particle HBV vaccines.

EPIDEMIOLOGY

Hepatitis A

Hepatitis A occurs worldwide as an endemic disease. In developing countries (Africa, Asia, and Central and South America), there is a high incidence of infection. In developed countries (Japan, Australia, New Zealand, Canada, the United States and most European nations), Hepatitis A seroprevalence has decreased due to increasing household income and education, and improvements in sanitation, hygiene and water quality[1].

Typically, in developing countries, cases of acute Hepatitis A are seen in older children and adults who are in contact with children. Hepatitis A in adults from developed countries is associated with travel to areas of high endemicity. Food- and water-associated outbreaks have also been reported[2,3].

The most common known sources of infection are fecal – oral transmission among family members and friends, through person-to-person contact or through the ingestion of contaminated food or water.

Hepatitis B

It is estimated that around 2 billion individuals worldwide have evidence of present or past infection with Hepatitis B virus (HBV)[4]. Of these approximately 350 million are chronic carriers of the virus, and between 15% and 25% of them will die as a result of HBV[5].

Areas of high prevalence HBV include sub-Saharan Africa, aboriginal Australia, the East Mediterranean, Southeast Asia, South America, the Pacific Islands (excluding Japan) and the Inuit communities of Canada. It is expected more than 8% of the population in these areas are positive to Hepatitis B surface antigen (HBsAg)[6]. Most of the infections are acquired at birth, or during early childhood when the risk of chronic infection is greatest. The lifetime risk of HBV infection is greater than 60%.

GENERAL PREVENTIVE MEASURES

Hepatitis A

There are no specific antiviral drugs against Hepatitis A. Therefore preventive measures remain the most important strategy for the control of Hepatitis A. These include:

- Providing education on good sanitation and personal hygiene, especially hand-washing.
- Adequate and clean water supplies and proper waste disposal.
- Vaccination against Hepatitis A for patients at risk, e.g. travellers visiting areas where the disease is common.
- Travellers to developing countries should be advised to eat only properly cooked food and be careful of uncooked vegetables and shellfish.

Hepatitis B

Widespread immunization programmes against HBV, which have been implemented in more than 100 countries, have dramatically reduced the occurrence of chronic HBV infection and hepatocellular carcinoma[7]. Successful vaccination efforts have resulted in higher proportions of

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vaccination and prenatal screening. Screening of blood and blood products with serologic tests to detect HBV, Hepatitis C virus, human immunodeficiency virus have dramatically reduced the transmission of these viruses through transfusions. Improved disposal of needles and other sharp and new devices designed to reduce the risk of needlestick injuries have diminished exposures in medical settings.

Young adults (18 to 39 years of age) are at increased risk of HBV infection due to greater likelihood of multiple sex partners, illicit injection of drugs and other high-risk behaviours[8]. The avoidance of high-risk behaviours is an effective preventive measure in this age group.

There is a need to create more awareness of HBV infection in the general population as even physicians do not realize the extent of the global threat that HBV poses to health.

ISSUES ON IMMUNISATION AGAINST HEPATITIS A AND HEPATITIS B

Hepatitis A Vaccine

Three highly immunogenic purified, effective and safe formaldehyde-inactived, whole particle hepatitis A virus (HAV) vaccines: Havrix (Glaxo SmithKline), Vaqta (Merck) and Avaxim (Aventis Pasteur) are approved for use in Singapore. At this point in time, Havrix is not approved for use in children younger than 1 year while Vaqta is not approved for children younger than 2 years. The induction of neutralizing antibodies and specific memory B cells are believed to be responsible for protection provided by HAV vaccines.

The HAV vaccine must be given in 2 doses, 6-12 months apart, for full protection. Studies have shown that 95% of patients who received the vaccines seroconverted one month after the first vaccination and 100% did so after the second. The duration of protection have been shown to persist beyond 10 years in healthy individuals.

Pre-exposure immunoprophylaxis with HAV vaccine has been recommended by the Advisory Committee on Immunization Practices (ACIP) for specific groups at high risk for HAV exposure[7]. These include children who live in countries with average annual hepatitis A rates of 20/100,000 or greater, travellers or those working in countries where HAV infection is endermic, men who have sex with men, users of illicit drugs, individuals who work with HAV in laboratories or with HAV-infected non-human primates, recipients of solvent/detergent treated with clothing factor concentrates and individuals with chronic liver disease.

Hepatitis A Vaccine: Challenges and Controversies

A single-dose may be enough

A single dose of HAV appears to provide anti-HAV adequate to ensure protection for at least 1 year in about 95% of vaccines[10]. It is possible that a single-dose vaccine would be sufficient to provide prolonged protection due to presence of memory B cells rather than the currently recommended two-dose schedule. Since no data are available, the two-dose regimen should be followed.

Anti-HAV immune response lower in HBV carriers

The anti-HAV immune response to inactivated HAV vaccine among Chinese carriers of HBV appears to be lower than in non-carrier children but the differences were not statistically significant through 5 years of follow-up and all vaccinees had detectable anti-HAV at year 5[11]. Seroprotection against HAV in children with chronic hepatitis C infection have also been reported[12].

Drug users are unaware of need for immunisation

Few studies of HAV vaccine use in drug users are available[13]. HAV vaccine is currently recommended in drug users because of the very high prevalence of hepatitis C virus in this population. Unfortunately, many such high-risk individuals who are unidentified are unaware of their risk of infection and unaware of the availability of vaccine.

Hepatitis B Vaccine

In 1992, the World Health Organisation recommended the integration of vaccination against hepatitis B in the EPI. As of 2003, 151 countries had incorporated the hepatitis B vaccines into their routine mass infant immunisation programmes[14].

Hepatitis B virus (HBV) vaccines are produced with the use of yeast and recombinant techniques to generate the hepatitis B surface antigen (HBsAg) protein. These vaccines induce immunity by stimulating the endogenous production of neutralising antibody to HBsAg (anti-HBs) which is responsible for immunity. Anti-HBs of 10 mIU/ml or higher are thought to be seroprotective. The current HBV vaccines are given intramuscularly in three doses; with the second dose given one month after the first dose and the third dose given six months after the first dose.

The vaccines are close to 95% effective in preventing HBV infection or clinical hepatitis B. The duration of protection against infection due to vaccine-induced immunity appears to be prolonged, regardless of the fact that over time levels of anti-HBs can fall below the seroprotective threshold and became undetectable (waning antibody levels). Immunologic memory appears to be responsible for the persistence of immunity.

The precise duration of protection afforded by HBV vaccine remains uncertain. The duration of immune memory is certainly over 10 years in healthy young people, has been reported to be as long as 15 years in children vaccinated at age 16 months.

Hepatitis B Vaccines: Challenges and Controversies

Management of HBV Vaccine Non-responders

Genetically determined non-responsiveness has been documented and is believed to reflect the absence of a dominant immune response gene that mediates the production of anti-HBs.

The post-vaccination anti HBs antibody level should be determined one to three months after the last dose of HBV vaccine in persons with risk factors for a lack of response (including an age greater than 30 years, obesity or immunodeficiency) or those at high risk for exposure to blood or bodily fluids. Such non-responders should be re-vaccinated with three additional doses of vaccines if they are at high risk. Seroprotective level can be reached in 50% to 60% of recipients. Those in whom anti-HBs levels are undetectable or below 10 mIU/ml threshold after the 2 vaccine series are not likely to benefit from another vaccine series or switching to another recombinant vaccine. Whether re-vaccination with currently novel vaccines or the use of more potent adjuvants can circumvent non-responsiveness remains to be determined[15].

Importance of HBV Escape Mutants

Breakthrough infections in immunized infants of HBV-infected mothers are not common but are of concern. Potentially responsible mechanisms are as follows:

- In utero infection established before immunization.
- Genetically controlled vaccine non-responsiveness in infant
- Breakthrough HBV escapes mutant transmission from mother to infant.
- Induction of HBV escapes mutants in infant.

These mutant HBV viruses have been reported worldwide but in low frequency. The presence of an arginine instead of a glycine at amino acid 145 in the HBsAg protein has been shown to reduce the binding of HBsAg to anti-HBs, thereby permitting the mutant to escape the normal anti-HBs protective response[16].

Incorporation of antigens from the mutant strains into HBV vaccines could be necessary.

The role of new HBV vaccines

So-called mixed particle vaccines (which contain pre-S_1, pre-S_2 and S antigens) have been studied and have to be superior to S subunit vaccines that are given in higher doses (40 mg) in persons who do not have a response to a standard series of three doses of 10 or 20 mg[17].

STATUS OF COMBINATION VACCINE AGAINST HEPATITIS A AND B

Combination vaccine has been of particular benefit to those who are at risk of infection with both viruses. In clinical studies of the combination vaccine Twinrix (GlaxoSmithKline) when given to healthy adults in a three-dose schedule, the vaccine appears to be highly immunogenic. At 4 years after the first dose, 100% of the vaccinees were anti-HAV positive and more than 95% had seroprotective levels of anti-HBs.

HEPATITIS B IMMUNE GLOBULIN

Hepatitis B immune globulin is used to prevent hepatitis B infection in persons without demonstrated immunity to HBV who have been exposed to HBV perinatally (ie infants born to HBsAg-positive mothers), by cutaneous or mucosal contact with HBsAg-positive blood or bodily fluids or by sexual contact with a person who is positive for HBsAg.

One dose of hepatitis B immune globulin is administered as soon as possible after exposure (within 24 hours after birth for perinatal exposure, within 7 days post-needlestick exposure and within 14 days after sexual exposure) along with the first dose of hepatitis B vaccine (followed by additional doses of HBV vaccine). The reported efficacy is 85-95% for prevention of newborn infection and approximately 75% for the prevention of infection after needlestick or sexual exposure[20].

CONCLUSIONS

The development of highly effective and safe inactivated HAV vaccines and highly effective and safe recombinant HsAg subunit HBV vaccines represents major advances in the control of viral hepatitis. Whether HAV or HBV vaccine provide lifelong protection remains to be determined. Potential challenges include the implementation of universal childhood immunization programmes for HAV and HBV and addressing the issue of HBV vaccine non-responsiveness and HBV escape mutants.

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TAKE HOME MESSAGES

- **Hepatitis A occurs worldwide as an endemic disease. In developed countries, Hepatitis A seroprevalence has decreased due to increasing household income and education, and improvements in sanitation, hygiene and water quality..**
- **It is estimated that around 2 billion individuals worldwide have evidence of present or past infection with Hepatitis B virus (HBV). Most of the infections are acquired at birth, or during early childhood when the risk of chronic infection is greatest. The lifetime risk of HBV infection is greater than 60%.**
- **There are no specific antiviral drugs against Hepatitis A or Hepatitis B. Preventive measures remain the most important strategy for the control of Hepatitis A and Hepatitis B.**
- **Three highly immunogenic purified, effective and safe formaldehyde-inactived, whole particle hepatitis A virus (HAV) vaccines: Havrix (Glaxo SmithKline), Vaqta (Merck) and Avaxim (Aventis Pasteur) are approved for use in Singapore.**
- **In 1992, the World Health Organisation recommended the integration of vaccination against hepatitis B in the EPI. As of 2003, 151 countries had incorporated the hepatitis B vaccines into their routine mass infant immunisation programmes.**
- **Combination vaccine has been of particular benefit to those who are at risk of infection with both viruses.**
- **Issues in Hepatitis A immunisation are: whether there is a need for a booster; the lower immune response to HAV is lower in HBV carrier children; drug users are unaware of the need for immunisation.**
- **Issues in Hepatitis B immunisation are: HBV nonresponders; the importance of HBV escape mutants; and the roles of new mixed particle HBV vaccines.**