EDITORIAL

ACUTE HEPATITIS IN CHILDREN

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Hepatitis is the process of inflammation and/or necrosis of liver tissue that can be caused by infection, drugs, toxins, metabolic disorders, and autoimmune disorders.[1] Hepatitis in children is still a major health problem in developed and developing countries. The main aetiology of hepatitis is a viral infection of hepatotropic (liver is the main target organ) and non-hepatotropic (systemic attack and liver organ). Currently, hepatotropic viruses that are the main causes of acute infections have been found, namely A, B, C, D, E, and G. B viruses are DNA viruses. At the same time, the other types are RNA viruses. In addition to hepatotropic viruses (herpes simplex virus (HSV), cytomegalovirus (CMV), Epstein-Barr virus (EBV), varicella-zoster virus, rubella, HIV, adeno, entero, arbo, parvo) can give symptoms of hepatitis.[2,3] About 10-15% of cases of acute hepatitis are unknown, including mysterious acute hepatitis (unknown hepatitis), which is currently rife in several countries, including Indonesia. WHO stated that from an extraordinary event, unknown hepatitis was found to be involved in Adenovirus type 41 as SARS-CoV-2 co-infection.[4]

Viral hepatitis (HAV) is the most common cause of acute viral hepatitis in children in endemic areas such as Africa, South America, Central Asia and Southeast Asia. The problem of HAV is mainly found in Indonesia, a developing country with poor sanitation because transmission of this virus is transmitted through the faecal-oral route.[5] HAV infection is a self-limiting disease that provides lifelong immunity, making fulminant and chronic infections rare. Hepatitis B virus (HBV), hepatitis C virus (HCV) and hepatitis D virus (HDV) can cause chronic hepatitis or chronic hepatitis carrier status, which can lead to complications of cirrhosis or hepatocellular carcinoma.[2] Hepatitis D virus (HDV) is known as a delta agent, which is a virus that cannot produce a covering protein, and the outside of this virus is covered by a surface antigen from HBV (HBsAg/hepatitis B surface antigen). This results in coinfection with HBV or superinfection in chronic HBsAg carriers.[7]

The most significant risk factors for HBV and HCV are transmitted through blood or body fluids (parenteral), injection drug use, blood transfusion and vertical transmission (intrauterine/ perinatal infection). In contrast, horizontal transmission occurs due to close contact.[1] The magnitude of the risk of vertical transmission of HBV is largely determined by the serological status of the mother. Suppose the mother's HBsAg and Initial Hepatitis B Antigen (HBeAg) are positive. In that case, the risk of transmission reaches 90%, while if only HBeAg is positive, the risk of vertical transmission is lower at 10%.[8] HEV infection can occur after travelling to endemic areas. Hepatitis G virus (HGV) is commonly found in people infected with HIV.[2]

All hepatotropic viruses give almost the same clinical symptoms, ranging from asymptomatic, classic forms to fulminant hepatitis that can cause death. Most children infected with HAV, HBV, and HCV have non-specific asymptomatic or mild symptoms without jaundice. Discomfort in the upper right abdomen, fever (usually <39^{o}C), cold, headache, flu-like symptoms, nasal discharge, sore throat and cough. In this phase, the urine color becomes dark; the stools are paler, the aminotransferases are elevated, and mild hepatomegaly and splenomegaly are present. Extrahepatic manifestations such as arthralgia, arthritis, rash, thrombocytopenia, glomerulonephritis, or papular acrodermatitis (Gianotti-Crosti syndrome) may occur early in the disease. The prevalence of HAV in Indonesia ranges from 35% at the age of 5 years to 60-90% in children aged <6 years.[6] In acute HBV infection, the appearance of symptoms increases with age. Symptoms appear in 1% of infants aged

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<12 months to reach 30-50% in children aged> 5 years.[9]

The most common signs and symptoms of liver disease are jaundice and hepatomegaly. Jaundice or yellow color of the skin, sclera and mucous membranes occurs due to an increase in indirect and direct bilirubin. Indirect bilirubin increases due to the hemolysis process in infectious conditions and disturbances in the uptake and conjugation of indirect bilirubin due to liver cell damage. Direct bilirubin is increased due to impaired transport of conjugated bilirubin.[10] Prodromal symptoms in children may disappear in the icteric phase.

The biochemical profile of acute hepatitis may reveal elevated alanine aminotransferase (ALT) and aspartate aminotransferase (AST), reflecting parenchymal inflammation. Alkaline phosphatase and total and conjugated bilirubin indicate the degree of cholestasis due to hepatocellular and bile duct damage. Prothrombin time is a good predictor of hepatocellular damage and the progression of fulminant liver failure. Resolution of hyperbilirubinemia and normalization of transaminases takes 6-8 weeks.[7] The diagnosis of acute HAV infection is confirmed by serological examination of anti-HAV IgM antibodies accompanied by the absence or low levels of IgG antibodies for HAV.[1] The presence of HBsAg indicates acute or chronic HBV infection. Maternal HBsAg status should always be determined when diagnosing HBV infection in children younger than one year because vertical transmission may occur.[8] Serum blood tests in acute HBV will show positive HBeAg levels. The presence of HBsAg and HBeAg that persists when antibodies to the e antigen (anti-HBe) are not found indicates a high risk of transmission because viral replication occurs. The loss of HBsAg from serum before the window phase, and the subsequent appearance of antibodies to surface antigens (anti-HBs), indicates lifelong immunity and is a marker of immunization. Antibodies to the core antigen (anti-HBc) are useful markers for recognizing HBV infection during the window phase (when HBsAg has disappeared but before the appearance of anti-HBs). In addition, anti-HBe is useful for predicting low levels of infectivity during the carrier phase.[11] Seroconversion after HCV infection can occur six months after infection. An ELISA (enzyme-linked immunosorbent assay) result that is positive for HCV should be confirmed by a recombinant immunoblot assay that is more specific and can detect antibodies to multiple HCV antigens. Detection of HCV RNA by polymerase chain reaction (PCR) is a sensitive marker for active infection, and the results of this examination can be positive three days after inoculation.[3]

In determining the aetiology of liver disease, age plays an important role. Hepatitis-like symptoms are found in neonates with physiologic jaundice, neonatal hepatitis, hemolytic disease, and sepsis. In addition, metabolic disorders (fructosemia, tyrosinemia, alpha-1 antitrypsin deficiency) and anatomic abnormalities (biliary atresia, choledochal duct cysts). Symptoms are the same in infants and children suffering from malaria, leptospirosis, brucellosis, severe infection in malignancy, gallstones and hemolytic-uremic syndrome. Reye's syndrome can mimic fulminant liver failure. Other causes of acute liver disease in childhood are drug use (isoniazid, phenytoin, valproic acid, carbamazepine, oral contraceptives, acetaminophen), parenteral nutrition, toxins (ethanol, poisonous mushrooms), Wilson's disease, metabolic diseases (galactosemia, tyrosinemia), mitochondrial disorders), a-antitrypsin deficiency, tumors, shock, anoxia, autoimmune hepatitis, hemophagocytic syndrome and graft-versus-host disease. Patients with cholecystitis, cholangitis and choledocholithiasis may experience symptoms of acute hepatitis and jaundice.[2]

Management of acute hepatitis is symptomatic and supportive, including adequate rest, hydration and nutrition. Hospitalization is indicated for children with severe vomiting and dehydration, prolonged prothrombin time, or signs of hepatic encephalopathy. If the diagnosis of viral hepatitis has been established, it is necessary to prevent the transmission of the disease. In HAV, hygiene monitoring includes hand washing and disposal of feces, contaminated diapers or clothing, needles and other items contaminated with blood. Treatment of chronic HBV and HCV infection is growing, and new antiviral drugs are being discovered. The decision to administer therapy is based on the patient's age, viral genotype, and degree of viral infection.[2,6,12]

Most cases of viral hepatitis recover

without specific therapy. The most severe complication is fulminant hepatitis, occurring in 0.1% of cases. HAV and HEV only cause acute infection. However, HBV, HCV and HDV can persist into chronic infection with chronic inflammation, fibrosis and cirrhosis and the associated risk of hepatocellular carcinoma. [13] In children who receive HBV from vertical transmission, 90% will develop a persistent infection.

Prevention of hepatitis is prioritized for children in high endemic areas. Improving good environmental hygiene will significantly reduce the risk of faecal-oral transmission of HAV. There are two forms of HAV immunization, passive immunization with immunoglobulin (IG) for children under 12 months of age and active immunization with inactivated vaccines, which is recommended for all children starting at 12 months. Unvaccinated families and contacts with people with HAV infection should be given post-exposure prophylaxis immediately and within two weeks of the last exposure. Travellers aged 12 years and over who have not been vaccinated and will travel to endemic areas must get the HAV vaccine given before the time of departure.[2,14]

Routine vaccination also effectively reduces the incidence of HBV infection in children. The Indonesian Pediatric Association (IDAI) recommended the HBV vaccine as a routine immunization for all infants starting at birth and for all children and adolescents up to the age of 18 who have not been previously immunized. The HBV vaccine is also recommended as a pre-exposure vaccination if there is an increased risk of sexual, percutaneous, or mucosal exposure to HBV, as well as in people with chronic liver disease, human immunodeficiency virus (HIV) infection, and travellers visiting areas where HBV infection is endemic. Prenatal HBsAg screening is routinely recommended for all pregnant women. Infants born to HBsAg positive mothers should receive HBV vaccination and hepatitis B immunoglobulin (0.5 mL) within 12 hours of delivery. Infants born to mothers with unknown HBsAg status should receive the vaccine within 12 hours of delivery. The combination of HBIG and vaccination is 99% effective in preventing vertical HBV transmission. Vaccination without HBIG can prevent 75% of cases with perinatal HBV transmission and approximately 95% of children with symptomatic HBV infection cases.[15] Post-exposure prophylaxis for people who are not vaccinated with HBIG and vaccine is recommended in the event of needle sticks with blood from patients with HBsAg positive and for sexual contact, sharing needles, or victims of sexual violence by HBsAg-positive perpetrators. Screening of blood donors significantly reduces the risk of blood-borne transmission.[7] HBV immunization also prevents HDV infection because replication occurs when infected with HBV. Unlike HAV and HBV, where immunoglobulins play an important role in prevention, HCV, HEV and HGV have not found an effective type of immunoglobulin.[16]

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