Hepatitis A: Clinical Manifestations and Management

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**Abstract**
Due to improved living conditions and subsequent changes in hepatitis A epidemiology, the disease burden of hepatitis A is increasing in many regions. Recently, Korea has faced a large, community-wide outbreak of hepatitis A, which has prompted a vaccination program. The clinical spectrum of hepatitis A virus infection ranges from asymptomatic infection to fulminant hepatitis. Clinical manifestations depend on the age of the host: less than 30\% of infected young children are symptomatic, while about 80\% of infected adults manifest severe hepatitis with remarkably elevated serum aminotransferases. Fulminant hepatitis is rare, with a reported incidence from 0.015 to 0.5\%. Atypical manifestations include relapsing hepatitis and prolonged cholestasis, and complicated cases with acute kidney injury have been reported. Extrahepatic manifestations, such as autoimmune hemolytic anemia, aplastic anemia, pure red cell aplasia, pleural or pericardial effusion, acute reactive arthritis, acute pancreatitis, acalculous cholecystitis, mononeuritis, and Guillain-Barré syndrome, have been rarely reported. Management of hepatitis A includes general supportive care, and critical decisions regarding liver transplantation await further studies on prognostic predictors. Fundamental management of hepatitis A is active vaccination. However, a vaccination program should be adapted to the regional situation, according to differing epidemiology and disease burden.

**Introduction**
Hepatitis A virus (HAV), a positive-strand RNA virus, is stable at moderate temperature and low pH, allowing the virus to survive in the environment and be transmitted by the fecal-oral route \cite{1}. Although a highly effective and safe vaccine for hepatitis A was developed in the early 1990s, HAV is still an important etiology of acute viral hepatitis worldwide. Clinical manifestations of hepatitis A depend on the age of the host: less than 30\% of infected young children showed symptomatic hepatitis, while about 80\% of infected adults manifest as severe acute hepatitis with remarkably elevated serum aminotransferases \cite{2}.

According to changes in socioeconomic status and improved living conditions, many developing countries are experiencing an epidemiological shift of HAV infection, which has resulted in the development of many cases of adult hepatitis A. Recently, Korea has faced a large community-wide outbreak of hepatitis A, with a relative shortage of vaccine \cite{3}. The vaccination program for hep-
Hepatitis A virus infects the liver and can cause a range of symptoms, from mild to severe. The acute phase of the disease is characterized by fatigue, malaise, nausea, vomiting, and jaundice. In the chronic phase, patients may experience fatigue, anorexia, nausea, and jaundice. Some patients may develop additional symptoms such as arthritis, skin rash, and muscle pain. The disease can progress to fulminant hepatitis, which is characterized by severe liver damage, encephalopathy, and coagulopathy. In this case, the mortality rate is high, and urgent liver transplantation may be necessary. Other complications include hemolytic anemia, jaundice, and pruritus. The diagnosis of hepatitis A is based on the detection of the hepatitis A virus in the patient’s blood or the identification of specific antibodies in the patient’s serum. The treatment of hepatitis A is generally supportive and includes fluids,休息, and avoidance of alcohol and artificial sweeteners. The natural course of hepatitis A is usually self-limiting, and the majority of patients recover within a few weeks. However, in some cases, the disease may progress to chronic hepatitis A, which is characterized by persistent liver inflammation and fibrosis. This can lead to irreversible damage to the liver and an increased risk of liver cancer. The prevention of hepatitis A is crucial, as there is no specific antiviral therapy for the treatment of chronic hepatitis A. Therefore, vaccination is the primary prevention strategy, and the hepatitis A vaccine is recommended for all individuals aged 2 years and older who are at risk of exposure to the virus. The vaccine is highly effective in preventing hepatitis A infection and can be used to prevent outbreaks in populations at high risk of exposure. Overall, hepatitis A is a preventable disease, and the implementation of vaccination programs can significantly reduce the burden of this disease on public health.
anemia, aplastic anemia, pure red cell aplasia, pleural or pericardial effusion, acute reactive arthritis, acute pancreatitis and neurologic complications, such as mononeuritis, mononeuritis multiplex and Guillain-Barré syndrome [9]. Acalculous cholecystitis may often be complicated, as illustrated by an edematous gallbladder on radiological images and compatible clinical findings, many of which manifest transiently with spontaneous recovery.

Fulminant Hepatitis A

Fulminant hepatitis is a rare complication of hepatitis A, with a reported incidence from 0.015 to 0.5% of hepatitis A cases. In one study, low serum HAV RNA levels and high bilirubin levels were significantly associated with fulminant hepatitis, which suggests that HAV-related liver failure is due to a vigorous host immune response with a marked reduction in viral load, rather than a direct viral effect [12].

Fujiwara et al. [13] reported that viral strains isolated from fulminant hepatitis showed relatively few nucleotide substitutions in the 5’ noncoding region when compared with a considerable sequence variation in virus strains from nonfulminant hepatitis. Therefore, nucleotide variations in the central portion of the 5’ noncoding region of HAV may influence the severity of hepatitis A [13]. However, a recent study from India reported no evidence of HAV genome variation according to the severity of hepatitis, which warrants further study on the existence of HAV mutations associated with disease severity [14].

Risk for acute liver failure is high among older adults with underlying chronic liver disease. LT may be necessary; however, HAV-related fulminant hepatitis resolves spontaneously more frequently than fulminant hepatitis of other etiologies. Therefore, the decision to transplant or not to transplant is not an easy one. The US Acute Liver Failure Study Group reported that a prognostic index consisting of 4 presenting features (serum alanine aminotransferase <2,600 IU/l, creatinine >2.0 mg/dl, intubation, pressors) predicted the likelihood of LT or mortality, which was better than MELD or the King’s College criteria [12].

The Situation in Korea

Recently, Korea has faced a large community-wide outbreak of hepatitis A. According to the sentinel cases reported to the Korea Centers for Disease Control and Prevention, the total number of cases of hepatitis A has increased remarkably in the past 4 years. Our study of 109 cases of hepatitis A showed a mean age of 29 years, and males comprised 59% of the total. The mean hospital admission period was 6.7 days, which suggests a high medicosocial cost [15].

The number of cases of fulminant hepatitis A requiring LT has also increased in Korea. Results from one study showed that among 35 cases of fulminant hepatitis, 57% survived without LT, 6% died without LT, 29% survived after LT and 9% died after LT. By multiple logistic regression analysis, the independent prognostic factor for spontaneous survival was the degree of hepatic encephalopathy [16]. An interesting case of recurrent hepatitis A after LT for fulminant hepatitis A in transplanted liver has been reported [17].

Pregnancy

Hepatitis A during pregnancy is associated with high risk of maternal complications and preterm labor, despite the relatively mild features of the disease. Significant associations were observed between preterm labor and the presence of both fever and hypoalbuminemia, and hepatitis cases were clustered in the third trimester [18]. There was no evidence of mother-child transmission of hepatitis A virus infection, and hepatitis cases were clustered in the third trimester [18]. Therefore, HAV serology and maternal vaccination during pregnancy evaluation should be considered in areas where susceptible adult populations exist.

Management of Hepatitis A

General Supportive Management

There is no specific management for hepatitis A. Supportive care includes adequate hydration, nutritional support, use of antiemetics for severe vomiting, and use of antipyretics for high fever. Cases complicated by fulminant hepatic failure, hepatic encephalopathy, and low factor V level were marginally related to a history of acetaminophen intake (p = 0.07), although it was not an independent factor for the development of fulminant hepatitis by multivariate analysis [12]. Therefore, acetaminophen administration for control of high fever should be cautious during the symptomatic period of acute hepatitis.

Hemolysis can be precipitated by hepatitis A, particularly in patients with glucose-6-phosphate dehydrogenase deficiency [19]. Moreover, red cell survival can be shortened. Considering that acute kidney injury or hemolytic anemia may complicate hepatitis A, regular renal

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function testing along with complete blood analysis should be performed, with availability of hemodialysis, due to the fact that about half of hepatitis A cases with acute kidney injury need hemodialysis.

In the case of a cholestatic variant of hepatitis A, corticosteroids have been tried in the past; however, persistent elevation of aminotransferase levels and viral excretion with progressive hepatic fibrosis in one patient treated with corticosteroids were reported. Therefore, corticosteroid treatment should be used with caution [9].

**Vaccination**

Fundamental management of hepatitis A includes active and passive immunoprophylaxis. The 4 inactivated hepatitis A vaccines available worldwide are safe and effective. A single dose provides excellent short-term protection for up to 2 years in young adults, and the second dose is important for long-term protection [20]. Recommended target populations for the hepatitis A vaccine include persons at increased risk of acquiring infection or of having poor prognosis after infection, such as travelers to high endemic areas, patients with underlying chronic liver disease, hemophiliacs, intravenous drug users and men who have sex with men.

According to several reports, hepatitis A in patients with chronic liver disease has a less favorable course, although not all reported series showed concordantly poor prognosis [21]. However, considering the remarkably high levels of aminotransferase during acute hepatitis A infection in adults, patients with underlying chronic liver disease, particularly those with limited liver function, cannot tolerate such acute, vigorous liver injury. Therefore, vaccination should be offered to patients with chronic liver disease regardless of the etiology.

A vaccination program should be suited to the regional situation, taking into account differing epidemiologies and disease burdens [22]. Among the areas experiencing an epidemiological shift in hepatitis A from high to intermediate endemicity, a universal toddler-only vaccination program in Israel demonstrated high effectiveness, challenging the need for catch-up vaccination programs [23]. Therefore, to reduce morbidity and mortality caused by the recent epidemic of hepatitis A among young adults in Korea, universal vaccination of young children should be implemented as soon as possible. Catch-up vaccination of young adults and adolescents with a single-dose vaccination [24] should also be considered, due to the current vaccine shortage in Korea.

For post-exposure prophylaxis, the classical method was to administer immunoglobulin within 14 days after exposure. However, on the basis of encouraging results from randomized trials comparing the effect of immunoglobulin and hepatitis A vaccine after exposure, the use of hepatitis A vaccine has been preferred over immunoglobulin since 2007. Vaccine as post-exposure prophylaxis provides several advantages over immunoglobulin, including long-term protection, easy administration, and more abundant supply [25].

**Conclusion**

HAV remains an important cause of hepatitis outbreak, as do fatal cases of fulminant hepatitis requiring urgent LT. According to changes in HAV epidemiology, the disease burden of hepatitis A has increased in many regions, including Korea, because hepatitis A shows more severe clinical manifestations in adults than in children. Atypical features of hepatitis A include recurrent hepatitis, prolonged cholestasis, acute kidney injury, hemolytic anemia and other extrahepatic manifestations. Management of hepatitis A includes general supportive care and critical decisions regarding LT. Fundamental management of hepatitis A includes active vaccination, and the vaccination program should be suited to the regional situation, according to differing epidemiologies and disease burdens.

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**Disclosure Statement**

The authors declare that there is no conflict of interest regarding this study.
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