HEPATITIS A AND B SUPERIMPOSED ON CHRONIC LIVER DISEASE: VACCINE-PREVENTABLE DISEASES

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ABSTRACT

A number of studies have demonstrated that the acquisition of hepatitis A or hepatitis B in patients with chronic liver disease is associated with high rates of morbidity and mortality. Superimposition of acute hepatitis A in patients with chronic hepatitis C has been associated with a particularly high mortality rate, and chronic hepatitis B virus coinfection with hepatitis C virus is associated with an accelerated progression of chronic liver disease to cirrhosis, decompensated liver disease and hepatocellular carcinoma. With the availability of vaccines against hepatitis B and hepatitis A since 1981 and 1995, respectively, these are vaccine-preventable diseases. Studies have confirmed that hepatitis A and hepatitis B vaccines are safe and immunogenic in patients with mild to moderate chronic liver disease. However, hepatitis A and B vaccination is less effective in patients with advanced liver disease and after liver transplantation. These observations have led to the recommendation that patients undergo hepatitis A and B vaccination early in the natural history of their chronic liver disease. Vaccination rates are low in clinical practice, and public health and educational programs are needed to overcome barriers to facilitate timely implementation of these recommendations.

Introduction

The literature documenting that hepatitis A and hepatitis B superimposed on chronic liver disease (CLD) is associated with high rates of morbidity and mortality has been reviewed (1–6). There is ample evidence that hepatitis A and B vaccination is safe and immunogenic in patients with mild to moderate CLD, although vaccination is less effective in those with decompensated cirrhosis or after liver transplantation (4–6). These observations have led to vaccine recommendations in patients with CLD that include hepatitis A and B vaccine in

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addition to pneumococcal and influenza vaccines (7–11). In spite of these official recommendations, most patients are not protected against one or more of these vaccine-preventable diseases (12). The outcomes of hepatitis A and B in patients with CLD and results of hepatitis vaccination of this population are reviewed.

Hepatitis A in Patients with Chronic Liver Disease

Hepatitis A is one of the most common infectious diseases worldwide, with approximately 1.4 million clinical cases of hepatitis. In the United States, hepatitis A accounts for approximately half of all reported cases of acute viral hepatitis, with approximately 61,000 cases reported in 2003 (7,13). Hepatitis A has been shown to have a substantial economic burden in industrialized countries, e.g., annual costs in the United States exceeded $480 million in 1997 (14). Recent studies show that the incidence of hepatitis A virus (HAV) infection has declined, especially in younger individuals, which is attributable to implementation of hepatitis A immunization policies as well as advances in environmental hygiene (15,16). Thus, there is the emergence of a new cohort of younger persons without antibody to HAV (anti-HAV) who are at risk for HAV infection. Older adults, foreign-born individuals, African Americans as well as persons with CLD are more likely to have had prior hepatitis A and have protective immunity with detectable anti-HAV (17). Acute hepatitis A is usually asymptomatic in younger children, but the majority of older children and adults have a symptomatic illness with jaundice (18). HAV infection is usually a self-limited illness with recovery within 2 months, but approximately 100 persons die of fulminant hepatitis each year in the United States. The case-fatality rate of hepatitis A is highest in adults older than 50 years of age (1.8%, versus 0.3% across all ages) and, as will be reviewed, patients with CLD (1–6). Thus, as hepatitis A becomes less common, the burden of new infections is shifting from children to adults, who have a higher frequency of clinically severe hepatitis, including fulminant disease.

Data available from a large outbreak of acute hepatitis A in Shanghai in 1988 and from cases of hepatitis A reported to the Centers for Disease Control and Prevention (CDC) between 1983 and 1988 demonstrated that HAV infection was more severe in patients with preexisting CLD (1,19,20). Acute hepatitis A superimposed on chronic hepatitis B virus (HBV) infection was associated with a 5.6-fold and 29-fold increased risk of death, respectively, in the Shanghai outbreak and the CDC analysis of reported cases (19,20). In addition, there was

a 23-fold increased risk of death in the CDC study in patients with acute hepatitis A superimposed on miscellaneous types of CLD. A matched case-control study using mortality files from the National Center for Health Statistics confirmed the association between fatal hepatitis A and underlying CLD (21). In this study, investigators compared the prevalence of CLD in subjects whose immediate cause of death was listed by ICD-9 codes as hepatitis A (n = 1429) versus two controls groups whose immediate cause of death was listed as gastrointestinal hemorrhage (n = 2376) or biliary-pancreatic disease (n = 2477). The percent of subjects dying secondary to hepatitis A and having a secondary diagnosis of CLD was 63%, versus 8% and 11% with a diagnosis of CLD in the two control groups of gastrointestinal hemorrhage and biliary-pancreatic disease (21). A prospective 7-year study from Italy demonstrated a remarkably high incidence of acute liver failure (41%) and death (35%) in patients with acute hepatitis A and preexisting chronic hepatitis C virus (HCV) infection (22). In contrast to the Shanghai and CDC studies cited above, this prospective study did not show higher mortality of acute hepatitis A in patients with chronic hepatitis B, although 1 of 10 patients had a complicated course with a peak serum bilirubin of 28 mg/dL. This study requires confirmation, because two large reviews of fulminant hepatitis A in tertiary care centers did not reveal a large number of cases with underlying chronic hepatitis C (23,24). However, in support of the studies described above, Almasio and Amoroso (3) reviewed the clinical course of acute hepatitis A in patients with CLD reported in 18 papers in the literature and noted that the mortality rate ranged from 0 to 100% but was generally high.

Hepatitis B in Patients with Chronic Liver Disease

It is estimated that worldwide at least 350 million people are chronically infected with HBV (25). Although the prevalence of HBV infection in the United States is lower than in many other countries, an estimated 1.25 million individuals are chronically infected with HBV, which is likely an underestimate (26). The published literature regarding the outcome of HBV infection in patients with CLD has primarily addressed the impact of chronic hepatitis B superimposed on chronic HCV or hepatitis D virus (HDV) infection, rather than the outcome of acute hepatitis B in patients with CLD (4–6). The studies of acute hepatitis B in patients with CLD are limited to a few case series (4–6), but one well-conducted study showed that patients with acute hepatitis B and underlying chronic hepatitis C had a more severe course,

including fulminant hepatitis (27). On the other hand, HBV and HCV coinfection appears to be clearly associated with a higher rate of morbidity and mortality than either infection alone (4–6). Studies of patients with HBV and HCV coinfection have uniformly shown more severe laboratory abnormalities, higher rates of cirrhosis, greater likelihood of the development of complications of cirrhosis, and a higher incidence of hepatocellular carcinoma.

Vaccination Against Hepatitis A in Patients with Chronic Liver Disease

The CDC recommends that all patients with CLD undergo hepatitis A vaccination (7). Several trials have demonstrated the safety and immunogenicity of HAV vaccination in these patients (28–30), and thus provide support for this CDC recommendation. In the largest of these studies, which was a multicenter, international study of 475 subjects, the safety and immunogenicity of hepatitis A vaccine (Havrix®, SmithKline Beecham Biologicals, Philadelphia, PA) was compared in patients with miscellaneous CLD to the response in healthy controls (28). Patients with chronic hepatitis B, chronic hepatitis C, and miscellaneous CLD and no clinical or biochemical evidence of advanced liver disease were vaccinated with two doses of hepatitis A vaccine. One month after the second booster injection, there was no significant difference in seroconversion rates between healthy subjects (98%) and the three groups of patients with CLD (94% to 98%) (Table 1). The geometric mean titers of anti-HAV were significantly lower in all disease groups compared with controls, but still well above the seroprotective titer of 10 mIU/mL. Hepatitis A vaccine was also well

TABLE 1
Seroconversion rates and geometric mean titers at month 7 after two doses of HAV vaccine

	No.*	SC (%)	GMT
Healthy adults	167	98.2	1,315
Chronic hepatitis B	44	97.7	749†
Chronic hepatitis C	87	94.3	467†
Other chronic liver disease	63	95.2	562†

SC = seroconversion rate, i.e., seropositive for anti-HAV with titer >33 mIU/mL.

GMT = geometric mean titer of anti-HAV in mIU/mL at month 7 (after injections at month 0 and 6).

* Number of subjects having both injections at month 0 and 6 and returning at month 7 for measurement of anti-HAV.

† Significant difference compared with healthy adults, but still well above the seroprotective level of 10 mIU/mL.

From: Keeffe et al. (28)

tolerated with no serious adverse effects or increase in serum alanine aminotransferase levels. Two smaller studies of hepatitis A vaccine in patients with chronic HBV or HCV infection showed seroconversion rates similar to healthy controls but lower anti-HAV geometric mean titers (29,30). In the Taiwanese study of 60 patients, the seroconversion rate was 100% and the geometric mean titer of anti-HAV was 1309 mIU/mL (29). In the study from China of 65 patients with chronic HBV infection versus 28 healthy controls, the seroconversion rates were 80% and 89%, respectively, in patients versus controls, and geometric mean titers of anti-HAV were 123 versus 250 mIU/mL, respectively (30). Hepatitis A vaccine has also been shown to be safe and highly immunogenic in two studies of children with CLD (31,32).

In contrast to the good results of HAV vaccine in patients with mild or moderate CLD, the immunogenicity of HAV vaccine in patients with advanced CLD and in immunosuppressed patients after liver transplantation is poor (4–6). Seroconversion rates in patients with decompensated cirrhosis are particularly poor (0 to 66%), and geometric mean titers of anti-HAV are low (0 to 103 mIU/mL) (33–36). Thus, published literature supports the recommendation that HAV vaccine be administered early in the natural history of CLD when immunogenicity rates are high. In addition, HAV vaccination has been shown to be cost-effective in patients with CLD (37,38).

Vaccination Against Hepatitis B in Patients with Chronic Liver Disease

Similar to the results with hepatitis A vaccine, vaccination of patients with mild to moderate CLD is associated with good immunogenicity, but patients with advanced liver disease have lower seroconversion rates to hepatitis B vaccine (4–6). The anti-HBs seroconversion rate is as high as 93% to 100% in patients with mild alcoholic liver disease, but averages 50% overall (range, 18% to 75%) in patients who have alcoholic cirrhosis (4–6). Recent evidence suggests that higher and more frequent doses of hepatitis B vaccine may achieve better results in some patient populations with CLD. In one study using Engerix-B® (SmithKline Beecham Biologicals, Philadelphia, PA), a standard dose and schedule of 20 μg at month 0, 1 and 6 was compared with a high-dose, accelerated regimen using 40 μg at month 0, 1, 2 and 6 (39). The high-dose, accelerated regimen achieved higher seroconversion rates (75% vs 46%) and geometric mean titers of anti-HBs (76.4 vs. 39.4 mIU/mL). In contrast to alcoholic liver disease, patients with mild or moderate chronic hepatitis C have better immu-

nogenicity to hepatitis B vaccine, with seroconversion rates ranging from 69% to 100% (Table 2) (40–43). However, a high-dose, short interval schedule of Engerix-B® at month 0, 1 and 2 did not result in higher seroconversion rates in comparison to previous reports using a standard dose and injection regimen (43).

In patients with advanced CLD, the seroconversion rates are low (range, 16% to 62%), as are the anti-HBs geometric mean titers (4–6). The results of hepatitis B vaccination are also poor in liver transplant recipients, with one study showing that only 40% of 140 recipients vaccinated with a higher dose of Engerix-B (40 μg) developed an anti-HBs titer >10 mIU/mL (44). Patients with chronic renal failure undergoing maintenance hemodialysis also have a poor response to HBV vaccination, and the CDC recommends the use of a double-dose HBV vaccine (40 μg) in these subjects, as well as other immunosuppressed patients, based on studies showing better efficacy than with use of the standard dose of vaccine (20 μg) (8,45). This recommendation may also be appropriate for patients with end-stage liver disease and liver transplant recipients, although the study of Idilman et al (43) did not appear to support this approach.

In summary, as with hepatitis A vaccination of patients with CLD, the published literature supports the recommendation that HBV vaccine be administered early in the natural history of CLD when immunogenicity rates are high. The most cost-effective strategy in patients with CLD is to prescreen for evidence of current or prior HBV infection, using HBsAg, anti-HBc and anti-HBs, rather than empirically vaccinate these individuals (17,45). Patients with an isolated detectable anti-HBc without HBsAg or anti-HBs are generally thought to have a false positive anti-HBc, immunity to hepatitis B without detectable anti-HBs, or, in a small percent of patients, "occult HBV infection" (17). Individuals with an isolated anti-HBc can either be vaccinated in a

TABLE 2
Hepatitis B vaccination of patients with chronic hepatitis C.

Author (Ref)	No.	Dose (μg)	SC (%)	GMT
Keeffe (40)	31	20*	100	1260
Lee (41)	26	20*	89	360
Wiedmann (42)	59	10*	69	NA‡
Idilman (43)	152	40†	72	NA‡

SC = seroconversion rate, i.e., seropositive for anti-HBs with titer >10 mIU/mL.
GMT = geometric mean titer.
* Standard injection schedule at month 0, 1 and 6.
† High-dose, accelerated schedule at month 0, 1 and 2.
‡ Not available.

standard fashion, or given one injection of HBV vaccine with measurement of quantitative anti-HBs one month later; if the titer is >10 mIU/mL, then no further vaccination is needed, while those with titers <10 mIU/mL should undergo the complete vaccine series (17). Postvaccination testing for anti-HBs in patients with chronic liver disease, particularly those with more advanced disease, may be helpful to distinguish responders (anti-HBs >10 mIU/mL) from nonresponders (no detectable antibody) and hyporesponders (anti-HBs detectable but <10 mIU/mL). However, how to respond to postvaccination testing is uncertain, as there are no data on the immunogenicity of additional injections in patients with CLD who are initial nonresponders.

Application of Immunization Recommendations in Patients with Chronic Liver Disease

There are a number of obstacles to the application of the vaccination recommendations of the CDC for patients with chronic liver disease in practice (12,46,47). Testing for HAV and HBV antibodies and hepatitis A and B vaccination rates are low in most clinical practice settings (12,46). In one survey of 693 patients seen in primary care versus specialist settings, vaccination rates were overall low, but more patients seeing specialists had completed hepatitis A (28% versus 5%) and hepatitis B (29% versus 14%) vaccination (12). Coverage was higher in centers with a policy of vaccinating on-site rather than referred to alternative vaccination sites, such as from a specialist back to a primary care provider. In another study of 1,193 patients with chronic hepatitis C at two Veterans Affairs medical centers in New York, testing for anti-HAV was performed on 53.6% of subjects (46). Only 94 of 1,193 patients (7.9%) received HAV vaccine, including 26.8% of 317 susceptible patients, 0.9% of 323 patients who were already immune, and 1.1% of 553 subjects who were never tested for anti-HAV. Three of the unvaccinated patients developed acute hepatitis A, and one of them died of fulminant hepatitis. Thus, both of these studies demonstrate that the majority of patients with CLD are not protected against vaccine-preventable diseases.

A number of obstacles in practice interfere with the implementation of standard hepatitis A and B vaccination recommendations in patients with CLD (47). Many private insurance carriers and governmental health programs do not cover the costs of hepatitis A and B vaccination. For many patients, particularly the uninsured, the costs of these vaccines are prohibitive. There are also problems with patients' compliance with the number of visits required for initial evaluation

with prevaccination testing and then administration of the two to five vaccine injections, depending upon the regimen employed and whether hepatitis A or B vaccine or both vaccines are required. A combined hepatitis A and hepatitis B vaccine (Twinrix®, SmithKline Beecham Biologicals, Philadelphia, PA) has been shown to be safe and immunogenic in patients with CLD and has the feature of convenience for those requiring both hepatitis A and B vaccine—only three injections of the combined vaccine are required versus five injections if both hepatitis A and hepatitis B vaccines are administered (48). Patients with CLD need to be counseled about the potential health risks should they acquire hepatitis A or B and the need to comply with standard vaccination recommendations.

Summary

A large body of literature indicates that acute hepatitis A, and possibly acute hepatitis B, superimposed on CLD is associated with more severe liver disease and a higher fatality rate (1–6). Chronic HBV and chronic HCV coinfection are associated with more severe laboratory abnormalities, worse histologic disease, more complications of cirrhosis, and a higher incidence of hepatocellular carcinoma (4–6). Hepatitis A and B vaccination is safe, well tolerated and has high seroconversion rates in patients with mild to moderate CLD, but has reduced efficacy in advanced liver disease and after liver transplantation. A combined hepatitis A and hepatitis B vaccine is safe and immunogenic in patients with CLD and has the added feature of convenience (48). Patients with CLD should undergo hepatitis A and B vaccination early in the natural history of their liver disease when immunogenicity rates are high.

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DISCUSSION

Mackowiak, Baltimore: That was terrific, Emmet. Thank you. A cautionary comment, and then a question. I was the Epidemic Intelligence Officer in Louisiana in the early '70's at the time of a terrific flood which required opening both of the New Orleans spillways and resulted in oyster growing areas on both sides of the Mississippi being contaminated with Mississippi River water. We learned a number of things as a result of the massive outbreak of oyster-associated hepatitis A that followed. One was that the oyster growing areas in Louisiana are located in pristine waters and not likely contaminated unless you have a major disaster such as the one just recently occurring in New Orleans. Secondly, the procedures used to tell whether or not oyster growing beds are safe monitor the water and the oysters for fecal coliforms. And thirdly, oysters handle viruses very differently from bacteria; viruses such as hepatitis A may remain in green glands, which by the way, are oysters' version of a liver, indefinitely. And so I would be concerned that we are on the verge of another major oyster-associated hepatitis A outbreak related to contamination of Louisiana oyster-growing areas with Mississippi River sewage. My question is, has there been any evidence of such yet. And secondly, I have followed the techniques used to monitor oyster-growing areas sort of loosely since the 70s and wonder if there have been any developments beyond the use of fecal coliforms to certify oyster beds safe for harvesting.

Keeffe, Palo Alto: I would answer your questions in the following way. One interesting bit of information is that there is a declining incidence rate of hepatitis A in the U.S. This has been reported from a number of sources and is probably the result of two things. One factor is improved environmental hygiene, and the other factor is the impact of vaccination programs around the region, because the CDC recommends hepatitis A vaccine in all counties or states where there is a high incidence rate of hepatitis A. So we have a growing cohort of people entering early adult and middle-adult life that are now not immune to hepatitis A and are at risk. As outbreaks occur from potentially contaminated oysters, and there have been outbreaks related to other food items as well, we have an increasing proportion of the American population at risk for hepatitis A. I just learned as I was coming to this meeting the day before that the CDC is going to recommend routine hepatitis A vaccination in childhood. This will get around that problem of a growing adult population at risk for hepatitis A.

Lemon, Galveston: Emmet, that was a very nice talk. I have two questions that are related. One is whether you could speculate on the mechanisms that are in play that result in greater pathogenicity or worse clinical outcome when hepatitis A occurs in the background of chronic hepatitis or other chronic liver diseases. Is it reduced hepatic reserve or altered hepatic architecture that leads to a greater disease response, or is there an impaired immune response based on the chronic liver disease that facilitates increased replication of the invading virus? The second question, that is related to the first, is: why in hepatitis A, we find age to be very strongly correlated with severity of disease. Most severe forms of disease occur over the age of 55. So does the association of

severe disease with pre-existing chronic liver disease extend across all ages, or is it dependent upon age as well?

Keeffe: Stan, in answer to your first question, there appear to be no definitive data in terms of the potential role of impaired reserve. In the one prospective study by Dr. Vento that I quoted from the New England Journal of Medicine, all of the patients had a biopsy and many of them had mild chronic hepatitis C histologically even though they went on to high morbidity and mortality after superimposed infection with hepatitis A virus. So there's something more than hepatic reserve accounting for the adverse outcomes. Secondly, your point about increasing age is particularly relevant because most patients with chronic liver disease are middle-aged or older. Thus, age probably enters into the risk of an adverse outcome from superimposed acute hepatitis A or B. For example, in the CDC data that I analyzed, there was a much higher case-fatality rate than in the Shanghai outbreak, because the Shanghai patients were younger. So your point about the impact of age is very well taken.

Gollan, Omaha: Emmet, a related question on immunogenicity. With regard to hepatitis B vaccine, there are a small group of patients who are non-responsive to hepatitis B vaccination in the normal population; if you relate the immunogenicity between chronic liver disease or decompensated liver disease in the transplant population, they are kind of comparable. Do we have any kind of logical explanation as to this kind of lowered immunogenicity and its clinical relevance? Is it all to do with the relative state of immunosuppression?

Keeffe: John, I think it is. An appropriate comparison is the dialysis population, who are relatively immunosuppressed and known to respond poorly to standard doses of hepatitis B vaccine. So do patients with advanced chronic liver disease, especially when decompensated, have poor immune function as well? It appears they simply cannot mount an adequate antibody response to the antigenic challenge from the hepatitis A or B vaccine. These observations support an important role of immune function. The most dramatic situation is post-transplant when patients are formally immunosuppressed with drugs, and the results of vaccination are particularly poor.

Boyer, New Haven: Emmet, what do we know about the duration of protection in patients with chronic liver disease as opposed to the normal population?

Keeffe: Jim, there are no specific data regarding the duration of protection after vaccination of patients with chronic liver disease. However, geometric mean titers are fairly robust after vaccination of these patients, and extrapolating from what is known regarding long-term immunogenicity in the general population, protection is probably long-term in patients with chronic liver disease. Long-term immunity can be modeled based on antibody decline early after vaccination, but this modeling has not been formally studied in patients with chronic liver disease. My suspicion is that protection is probably good.

Gotto: New York: Very nice presentation. In the group of patients who had a mixed response to the various hepatitis B antigens, would the delta factor help in making a prediction and what is its involvement—what is its involvement in these results—the delta factor?

Keeffe: For Hepatitis D?

Gotto: Yes

Keeffe: I don't know that hepatitis D, or delta virus, plays a role. As you know, hepatitis D only occurs in patients who have underlying chronic hepatitis B. To the best of my knowledge, this was not a factor.