Hepatitis A and hepatitis B vaccination of patients with chronic liver disease

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Introduction

Highly efficacious vaccines to prevent hepatitis A and hepatitis B are available, and recently interest has focused on whether patients with chronic liver disease should receive them. Important considerations in determining if hepatitis vaccination of patients with chronic liver disease is indicated include the severity of outcomes of viral hepatitis and the performance of the vaccines in these patients. This paper will review the literature and summarize available data regarding these issues.

Hepatitis A in patients with chronic liver disease

Data from several sources suggest that patients with chronic liver disease who develop hepatitis A may be at increased risk of fulminant hepatitis. Among hepatitis A cases reported to the Centers for Disease Control and Prevention's (CDC) National Notifiable Diseases Surveillance System in the United States, the case fatality ratio increased with increasing age, from 1.6/1000 reported cases among children 5-14 years old to 17.5/1000 among persons > 49 years (1). Notably, 28% of the U.S. hepatitis A fatalities reported between 1983-1987 had chronic liver disease, chiefly nonalcoholic cirrhosis (2). An association between death from fulminant hepatitis A and chronic liver disease was demonstrated in a recent study based on death certificate data from the U.S. National Center for Health Statistics Multiple Cause of Mortality files from 1981-1997 (3). In this case-control study, 63% of hepatitis A deaths included mention of chronic liver disease on the death certificate, compared with 8%-11% of deaths in two control groups of persons dying of other gastrointestinal-related causes (odds ratios 13.9 and 22.8 for the comparisons with the two control groups).

Case series that have examined the outcome of hepatitis A among patients with chronic hepatitis C have yielded conflicting results. Results of a prospective case series of 595 patients from Italy and San Marino indicated that patients with chronic hepatitis C who developed hepatitis A were at high risk of death from fulminant hepatitis (4). Seven (41%) of the 17 patients with chronic hepatitis C who developed hepatitis A during the 7 year study period had a fulminant course, and six, who had chronic active hepatitis, died. However, several retrospective case series, primarily from Italy and other European countries, failed to demonstrate a similar association (5-9). For example, no deaths occurred among the more than 6000 hepatitis A cases reported from 1992-1996 through the SEIEVA surveillance system for acute viral hepatitis in Italy (5). Included among these hepatitis A cases were 179 persons with chronic hepatitis B virus (HBV) or hepatitis C virus (HCV) infection.

Similarly, some studies of patients with chronic hepatitis B suggest an increased risk of a fulminant course with hepatitis A while others have not (10-13). During a common source hepatitis A outbreak in Shanghai involving over 310,000 cases, 15 (32%) of the 47 deaths occurred among persons with chronic HBV infection, and the case fatality ratio was 5.6 times higher for these cases compared to cases without chronic infection (14). Among reported hepatitis A deaths in the United States, 7% have evidence of chronic HBV infection (2). However, chronic hepatitis B or chronic HBV infection was not associated with fulminant hepatitis A in other case series and case reports (11-13,15).

These studies of the outcome of hepatitis A among patients with chronic liver disease suffer from a number of methodologic problems that limit their comparability and generalizability. Most suffer from the limitations inherent in case series, and many studies of patients with chronic viral hepatitis did not distinguish between chronic infection and chronic hepatitis. Nonetheless, evidence of an increased risk of death with hepatitis A emerges from analyses of surveillance and death certificate data and from case series. In the United States, the CDC and a National Institutes of Health (NIH) Consensus Conference recommend hepatitis A vaccination for patients with chronic liver disease (1,16). In other countries, whether to routinely vaccinate depends on a number of considerations including the risk of acquiring hepatitis A, the magnitude of the increased risk of death, and the cost of vaccination.

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Hepatitis A vaccine in patients with chronic liver disease

There have been a number of studies of hepatitis A vaccine in patients with chronic liver disease. The frequency of local reactions appears to be similar to that observed in other vaccinated populations, but a larger proportion (20-25%) of vaccinated patients reported mild general symptoms compared to healthy vaccinated adults (17-19). Malaise was the most frequently reported symptom, and was also higher among patients receiving hepatitis B vaccine. Hepatitis A vaccine has no effect on hepatocellular status : patients had stable liver enzyme levels and disease exacerbations were not observed.

Immunogenicity studies have demonstrated high seroconversion rates among adults and children with chronic liver disease (Table 1) (17-22). However, in studies that included a control group, the final geometric mean antibody concentration (GMC) of patients with chronic liver disease was lower than that of healthy adults (19,20). Based on limited data, patients with end stage liver disease and those who have undergone orthotopic liver transplantation (OLT) appear to respond less well to hepatitis A vaccine (Table 1) (21,22). In one study of eight patients who had undergone liver transplantation 1-56 months previously, none responded to hepatitis A vaccination (21).

Testing patients before vaccination for evidence of immunity may be cost-effective. Factors to consider include the prevalence of immunity among patients with chronic liver disease and the costs associated with testing and vaccination. Based on age alone, a considerable proportion of patients with chronic liver disease can be expected to be immune. In one case series from the United States, the prevalence of immunity was 36-76% (21,23). Postvaccination testing generally is not indicated because commercially-available assays are not sensitive enough to detect low, but protective, antibody levels induced by vaccination. In addition, there are no data regarding response to additional vaccine doses.

Hepatitis B in patients with chronic liver disease

In determining if hepatitis B vaccination of patients with chronic liver disease is indicated, the outcomes of acute hepatitis B and of chronic HBV infection among patients with chronic liver disease need to be considered. However, without an appropriate control group, interpretation of the findings of retrospective studies and case series is difficult because of shared risk factors for HBV and HCV infection such as injecting drug use and blood transfusions and the lack of a serologic test to distinguish acute from chronic HCV infection.

Few data exist to suggest that patients with chronic liver disease who develop hepatitis B are more likely to have a fulminant course. Among the numerous published case reports and investigations of clusters of fulminant hepatitis B, few have involved patients with chronic liver disease (24-26). The few case series in which patients were tested for anti-HCV lacked appropriate control groups, making it difficult to interpret the findings (27-29). Among reported hepatitis B cases ascertained through acute disease surveillance, the case fatality ratio is higher for older persons but the prevalence of chronic liver disease has not been investigated (30).

Many studies of the outcome of chronic liver disease in patients coinfected with HBV and HCV suffer from methodologic problems such as no or inappropriate comparison groups and laboratory methods that are poorly explained or outdated (31-33). In a large retrospective chart review of over 6,000 French patients with HCV-related liver disease, the presence of biopsy-proven cirrhosis was associated with HBsAg positivity in multivariate analysis, but the effect was small in comparison to other cofactors such as alcohol consumption (34). Two studies of the histologic features of biopsies of patients with infections with a single virus compared to those with infections with multiple viruses reached opposite conclusions. In a large retrospective study from Italy, there was no difference in the severity of the histologic pattern among patients infected with single compared to multiple viruses (35). In contrast, in a small study from Australia, the biopsies of nineteen patients coinfected with HBV and HCV showed more severe disease compared to those age-matched controls infected with HCV alone (36). Several studies suggest that inapparent coinfection with HBV may be associated with more severe disease (37,38).

Some case-control studies of hepatocellular carcinoma (HCC) have found an association with concurrent infection with HBV and HCV, while others have failed to find such an effect (39-42). However, prospective

Table 1. — **Immunogenicity of hepatitis A vaccine in patients with chronic liver disease**

Author (reference)	Patient group	Age (years)	No.	% Positive	Final GMC* (mIU/mL)
Keefe (19)	Chronic liver disease	20-70	220	94	467-749
Lee (18)	Primarily hepatitis B	17-47	60	100	1309
Nebbia (17)	Hepatitis B	2-15	33	100	3776.8
Mendenhall (20)	Cirrhosis	?	16	100	1129
Dumot (21)	End stage disease ; Transplant	32-70	24	29	35
Arslan (22)	Transplant	20-71	28	26	?

*Geometric mean concentration.

studies among patients with chronic liver disease and cirrhosis consistently indicate higher rates of HCC among patients with HBV and HCV coinfection. (43,44).

Thus, studies of the outcome of acute hepatitis B among patients with chronic liver disease provide little evidence for an increased risk of acute liver failure. Results of studies of the effect of coinfection on the natural history of chronic liver disease are inconsistent, with the strongest evidence pointing to a possible synergistic effect of concurrent infection with HBV and HCV on the risk of developing HCC. In the United States, the ACIP recommends hepatitis B vaccination only for those chronic liver disease patients who report a recognized risk factor, because the majority of adults with acute HBV infection report such exposures (30). However, the recent NIH consensus conference recommended hepatitis B vaccination for all patients with chronic liver disease (16).

Hepatitis B vaccine in patients with chronic liver disease

The recombinant hepatitis B vaccines have been studied among alcoholics, patients with chronic hepatitis C, with chronic liver disease of other etiologies, and in the setting of OLT. The vaccines are safe, with local and general symptoms (primarily malaise) following vaccination reported by 7-19% and 5-19% of vaccinated patients, respectively (19,45-47). Vaccination has no effect on serum alanine aminotransferase or other liver tests, or on HCV RNA levels in patients with chronic hepatitis C (19,45-47).

A total of 70-100% of patients with chronic hepatitis C who did not have decompensated cirrhosis responded to hepatitis B vaccine with titers of > 10 mIU/mL (19,45,46,48,49). The final GMC was lower compared to healthy control subjects in one study (45) but not in others (46,49). Clinical characteristics were not associated with non-response, but in one study, women were more likely to respond than men (45,48).

In studies among alcoholics vaccinated using a variety of vaccines, vaccination schedules, and definitions of response, 49-70% of patients with minimal liver disease responded to vaccination ; response rates were lower among cirrhotic patients (47,50-53). No other predictors of vaccine response, including indicators of current alcohol consumption, were consistently identified. When measured six months after administration of the last vaccine dose, the response rate was higher among alcoholic patients who received double compared to the standard dose (75% vs. 46%) (47). This effect occurred among patients with (60% vs. 20%) and without (77% vs. 49%) cirrhosis.

Because of the possibility of acquiring hepatitis B through liver transplantation, there has been considerable interest in hepatitis B vaccination of these patients. When the standard dose was given according to an accelerated schedule of 0, 1, and 2 months, response rates among patients referred for or awaiting OLT were 16-47% (Table 2) (54,55). A similar proportion of patients responded when vaccinated on a compressed schedule at 0, 7, and 21 days (56). Only a small proportion of patients vaccinated after OLT respond ; in one study 7% of patients vaccinated a mean of 39 months after OLT responded (55). There have been no consistent associations between etiology of liver disease and likelihood of response to vaccination (55, 57-58).

Because of the poor response with the standard dosage, a double dose has been studied according to a variety of schedules (Table 2). Response rates among patients receiving three doses before transplantation were approximately 40%, and somewhat lower with fewer doses before transplantation (57-60). Additional doses given to non-responders raised the overall response rate to 50%-60% (58, 61).

Among responders, there is a rapid decline in antibody following OLT ; 37-73% lost detectable antibody when measured 6-12 months following transplantation (57,60). By two years after transplantation, only 7% had detectable antibody (57). New HBV infection following OLT has been reported among patients who responded

Table 2. — **Immunogenicity of hepatitis B vaccine in susceptible transplant patients using alternate dosages and schedules**

Author (reference)	Patient group	Dose (ug)	Schedule	Response	Comments
Chalasani (55)	Pre- (n = 57) and post- (n = 45) transplantation	20	0, 1, 2 months	16% pre- 7% post-transplant	Retrospective chart review
Kallinowski (56)	Awaiting transplant (n = 20)	20	0, 7, 21 days	36%	Final anti-HBs* titer 35 mU/mL
Clemente (61)	Awaiting transplant (n = 34)	40	0, 1, 2 months ; boosters at 3, 6 months for non-responders	65%	
Arslan (57)	Pre- and post-transplantation (n = 356)	40	0, 1, 2 months	36%	43% if completed pre-transplant
Dominguez (58)	Pre- and post-transplantation (n = 62)	40	0, 1, 2 months ; boosters at 3, 6 months for non-responders	56%	Response defined as anti-HBs* > 25 mIU/mL
Horlander (60)	Awaiting transplant (n = 140)	40	0, 1-2, 3-4 months	37%	
Loinaz (59)	Awaiting transplant (n = 140)	40	0, 1, 2 months	40%	Included patients with anti-HBc**

* antibody to hepatitis B surface antigen.
** antibody to hepatitis B core antigen.

to vaccination (59-61). However, the frequency has not been compared to unvaccinated transplant recipients.

Prevaccination testing may be cost-effective, depending on the prevalence of past infection and the cost of testing, vaccine, and an additional visit. In particular populations such as injecting drug users or older persons, the expected prevalence may be high enough to warrant testing. Post vaccination testing may be indicated because the response rate is likely to be low and additional doses could be considered for at least some populations of non-responders.

Future directions

On the horizon may be hepatitis B vaccines with improved immunogenicity including new constructs, such as the inclusion of pre S1, pre S2 proteins, and new adjuvants (62-66). Therapeutic hepatitis B vaccines for treatment of patients with chronic HBV infection are also being studied (67,68). Unfortunately, prospects for the development of an effective hepatitis C vaccine on the near future are not promising.

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