

CORRESPONDENCE



Hepatitis A Vaccine versus Immune Globulin for Postexposure Prophylaxis

TO THE EDITOR: Victor et al. (Oct. 25 issue)¹ report on their study of hepatitis A vaccine as compared with immune globulin for postexposure prophylaxis. I applaud the recommendation for the postexposure use of hepatitis A vaccine to provide long-term protection. However, I am concerned that the statistical criteria used for determining substantial inferiority detract from the study findings, which indicate a 30% higher rate of hepatitis A after exposure in the group receiving vaccine. The findings support the biologically plausible position that the administration of immediately available antibodies through immune globulin has a time-dependent advantage over the delayed development of vaccine-generated antibodies. Although the statistical findings allow the rejection of the null hypothesis, they cannot be used to conclude that the difference demonstrated is not real. Data provided in the text and tables indicate that in the vaccine group there were more cases of hepatitis A, more severe symptoms, higher alanine aminotransferase levels, more cases with viral RNA, and more cases occurring in the second week after exposure. These findings are consistent with current knowledge of passive versus active immunity. An alternative recommendation should be considered: the use of both immune globulin and vaccine for postexposure situations.

Thomas G. Betz, M.D., M.P.H.

Texas Department of State Health Services
Austin, TX 78756
tom.betz@dshs.state.tx.us

1. Victor JC, Monto AS, Surdina TY, et al. Hepatitis A vaccine versus immune globulin for postexposure prophylaxis. *N Engl J Med* 2007;357:1685-94.

TO THE EDITOR: Victor et al. conclude that immune globulin is not inferior to vaccination for postexposure prophylaxis against hepatitis A. The

study was conducted in a developing country, and the conclusion may not be applicable to developed countries. For instance, the seroprevalence rate for hepatitis A is nearly zero in children in Taiwan.¹ An outbreak of hepatitis A in such a population may affect older persons, who are at risk for severe and even fatal infections.² The study by Victor et al. showed that recipients of immune globulin had lower average peak alanine aminotransferase levels than did vaccine recipients. This protective effect should be taken into consideration in developed countries. Furthermore, the study excluded 3110 study subjects because they were immune or already IgM-positive at enrollment. In the real world, we cannot check for hepatitis A antibody in all exposed persons. It would be interesting to know whether immune globulin can modify the disease severity in these seropositive persons.

Ping-Ing Lee, M.D.

National Taiwan University Hospital
Taipei 10002, Taiwan
pinging@ntu.edu.tw

1. Tzen KT, Chang MH, Tsen YJ, Lee CY, Chen DS. Hepatitis A virus infection in Taipei City in 1989. *J Formos Med Assoc* 1991; 90:138-40.
2. Kyrklagkitis I, Cramp ME, Smith H, Portmann B, O'Grady J.

THIS WEEK'S LETTERS

531 Hepatitis A Vaccine versus Immune Globulin for Postexposure Prophylaxis

532 Children and the Quality of Ambulatory Care

533 Hair Loss in Women

534 Osteoarthritis of the Hip

535 More on HIV-Associated Kaposi's Sarcoma

536 Fluorodeoxyglucose PET in Relapsing Polychondritis

Acute hepatitis A virus infection: a review of prognostic factors from 25 years experience in a tertiary referral center. *Hepatogastroenterology* 2002;49:524-8.

THE AUTHOR REPLIES: In response to Betz: although the relative risk indicated an approximately 30% higher risk among recipients of vaccine than among recipients of immune globulin, absolute risks were low, and absolute risk differences were never greater than 1.5%. Still, in our report, my colleagues and I draw attention to the potential relevance of these differences for persons who are likely to have severe illness if infected with the hepatitis A virus. Indeed, the Advisory Committee on Immunization Practices considered these small differences when updating recommendations for postexposure prophylaxis.¹

Several of Betz's characterizations of our findings merit clarification. It is arguable whether the proportions of vaccine recipients and immune-globulin recipients with detectable hepatitis A virus RNA (62% and 56%, respectively; $P=0.761$) are different; they might equally well be considered equivalent. As we noted, the study was not designed to measure disease severity. Furthermore, alanine aminotransferase levels should be interpreted with caution, since measurements were performed once at nonstandardized time points during the course of the illness; in addition, differences were limited to levels among children. Finally, although in the modified intention-to-treat population, the relative risk with vaccine as compared with immune globulin was lower in the first week after exposure than in the second week, in the per-protocol population, it was higher in the first week after exposure than in the second week (1.73 vs. 1.30).

Betz's statement that "immune globulin has a time-dependent advantage over the delayed development of vaccine-generated antibodies" appears to be based on the assumption that hepatitis A vaccine used after exposure operates solely through antibody-dependent mechanisms. However, antibody-independent T-cell effects may be important, and vaccination after exposure might modulate an already initiated immune response in participants with incubating hepatitis A virus — something immune globulin is unlikely to do.

Unlike Lee, we believe that our study results are applicable to persons in developed countries. Our analyses of relative efficacy were conducted among only those persons found to have been susceptible at the time of receipt of vaccine or immune globulin, precisely so that conclusions would be applicable to susceptible persons in any population. Moreover, the generalizability of the results is supported by studies of the transmission dynamics of hepatitis A virus in the population, conducted before implementation of the trial.^{2,3}

John C. Victor, Ph.D., M.P.H.

Program for Appropriate Technology in Health
Seattle, WA 98107
cvictor@path.org

1. Update: prevention of hepatitis A after exposure to hepatitis A virus and in international travelers: updated recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR Morb Mortal Wkly Rep* 2007;56:1080-4.
2. Victor JC, Surdina TY, Suleimenova SZ, Favorov MO, Bell BP, Monto AS. Person-to-person transmission of hepatitis A virus in an urban area of intermediate endemicity: implications for vaccination strategies. *Am J Epidemiol* 2006;163:204-10.
3. *Idem*. The increasing prominence of household transmission of hepatitis A in an area undergoing a shift in endemicity. *Epidemiol Infect* 2006;134:492-7.

Children and the Quality of Ambulatory Care

TO THE EDITOR: Mangione-Smith et al. (Oct. 11 issue)¹ report that children receive only 46.5% of recommended health care. Is our goal 100% adherence to these recommendations? What are barriers to improvement?

Hayward commented, regarding performance-measure adherence for adults, "It sounds terrible . . . that 50% of recommended care is not received, but . . . mandating adherence to these recommendations is not necessarily in the best interest of patients or society. . . . At the heart

of this problem is our wish to keep efforts at quality improvement and cost containment separate."² Benefits from guidelines are not necessarily additive,^{3,4} since there are usually costs and sometimes unintended consequences.⁵

Although many believe that children, with their developmental needs and relative dependence, deserve unlimited health care resources, such resources do not appear to be available currently. Choices are necessary. For example, should we give priority to hospitalizing young febrile