Clinicians have been trained to use statistics to identify differences and to reject apparent differences that may have occurred by chance. The objective of studies such as that by Ramond et al. is not to prove that the groups of patients are different at randomization but that they are similar. Similarity and therefore comparability are not necessarily the same as statistical nondifference. However, although it is reasonable to insist that differences at randomization should not favor the treatment effect, it is obviously unreasonable to insist that the groups should be similar to the point of near identify (i.e., a p value approaching 1). This issue may need to be addressed in a different context.

It has been suggested that steroids should be withheld in the management of patients with alcoholic hepatitis "even in desperation" (3). Ramond et al. have made another dent in that recommendation even if it is not as deep as initial inspection of the data suggests. However, they have served us well by raising another question that interaction with our statistical colleagues may be able to address.

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Editor's note: The earlier version of the next review appeared in the May issue (HEPATOLOGY 1992;15:973-974). The updated version is published below. The editor regrets the error.

HEPATITIS A – NEW INFORMATION ON AN OLD VIRUS

Rosenblum LS, Villarino ME, Nainan OV, Melish ME, Hadler SC, Pinsky PP, Jarvis WR, et al. Hepatitis A outbreak in a neonatal intensive care unit: risk factors for transmission and evidence of prolonged viral excretion among preterm infants. J Infect Dis 1991;164: 476-482.

ABSTRACT

An outbreak of hepatitis A virus (HAV) infection in a neonatal intensive care unit (NICU) provided the opportunity to examine the duration of HAV excretion in infants and the mechanisms by which HAV epidemics are propagated in NICUs. The outbreak affected 13 NICU infants (20%), 22 NICU nurses (24%), 8 other staff caring for NICU infants, and 4 household contacts; 2 seropositive infants (primary cases) received blood transfusions from a donor with HAV infection. Risk factors for infection among nurses were care for a primary infant-case (relative risk [RR], 3.2), drinking beverages in the unit (odds ratio [OR], ∞), and not wearing gloves when taping an intravenous line (OR, 13.7). Among infants, risk factors were care by a nurse who cared for a primary infant-case during the same shift (RR, 6.1). Serial stool samples from infant-cases were tested for HAV antigen (HAV-Ag) by enzyme immunoassay and HAV RNA by nucleic acid amplification using the polymerase chain reaction. Infant-cases excreted HAV-Ag (n = 2) and HAV RNA (n = 3) 4-5 months after they were identified as being infected. Breaks in infection control procedures and possibly prolonged HAV shedding in infants propagated the epidemic in a critical care setting.

COMMENTS

Hepatitis A virus (HAV) has been a known important cause of viral hepatitis since the discovery of the viral antigen in feces in 1973 (1). Despite improvements in sanitation and the strict attention paid to infection control in most neonatal intensive care units (NICUs) several large outbreaks of HAV infection have occurred in these settings during the last decade (2-5). Although HAV infection is usually spread by way of a fecal-oral route, the index case in this report and others (3, 4) was not an infected health care worker or parent but an infant who received a blood transfusion contaminated with HAV. Transmission of HAV by blood transfusion is uncommon, but donors in the prodromal phase of infection have been shown to transmit the virus by way of blood transfusion. HAV viremia is estimated to last at most 2 to 3 wk and occurs during the late incubation period of the virus. During this incubation period the donor's AST and ALT are often normal, and thus contaminated blood is not identified by AST or ALT screening (5). As expected from previous studies, there was no evidence in this report for direct maternal-fetal transmission of HAV infection (6).

Obviously, breaks occurred in infection control procedures used in NICUs because 24% of the susceptible full-time nursing personnel, 16% of the respiratory technicians and 20% of the infants became infected before the identification of the epidemic. Furthermore, two household contacts of infected nurses and two family members of infected infants also had HAV infection develop. The novel and important findings in this study were that the authors were able to identify risk factors for the subsequent infection of health care personnel and infants. Not surprisingly, those nurses who cared for one of the two primary infant cases were 3.2 times more likely to be infected than nurses who had not cared for these infants during the period of active infection. Other risk factors for HAV infection included working the night shift, those that facilitate contamination of the hands (not wearing gloves when taping intravenous lines or endotracheal tubes and having long

fingernails) and those that resulted in direct hand-to-mouth contact (smoking, drinking beverages in the unit). Surprisingly, not wearing gloves during diaper changes was not associated with a significant increased risk of infection, which has been the case with other enteric infections in day-care centers. The study does not exclude the possibility that blood-borne exposure may have played a role in the spread of the infection within the NICU because procedures that placed nurses in contact with blood and other bodily secretions also placed them at a high risk for infection, whereas diaper changing did not. The authors were able to confirm that hospital personnel did facilitate infection of other infants because care by a nurse who cared for a primary infant-case was associated with a sixfold increased risk of infection among secondary infant-cases. This report appropriately emphasizes the need for strict adherence to infection control procedures for all health care personnel.

Although all of the infected infants in the study were asymptomatic, impaired clearance of the organism from infected infants was investigated by the authors as a possibility for the large size of the outbreak. Within 3 wk after the onset of symptoms, adults infected with HAV are no longer infectious and cease to excrete fecal HAV antigen (7). Although HAV infection in children is much more likely to be asymptomatic than in adults, few fecal excretion studies of HAV antigen have been performed in children. One study showed that during the second week of illness children (46%) were more likely to have detectable fecal viral antigen than adults (14%), suggesting that children do indeed harbor the virus for a longer period of time. However, this study was not extended for a greater length of time (8). In this study, three infected infants were observed for more than 2 mo, and fecal excretion of HAV antigen continued for 1 to 4 mo longer than expected. The authors correctly concluded that this prolonged excretion of the virus probably worsened the HAV outbreak. One might question whether the neonatal immune response was brisk enough to clear the virus promptly. Despite the fact that the cellular and humoral immune responses of neonates are blunted, all 11 infected babies had anti-HAV IgM develop within 8 wk of exposure, which is similar to the timing of antibody development in adults. Although development of anti-HAV antibodies is associated with HAV immunity in adults, the role of the cell-mediated immune response in clearing the initial infection in children and adults remains to be explained (9). No doubt future studies will be conducted on the role of the cell-mediated immune response to HAV infection not only in clearance of the virus but also its possible effect on determining the severity of infection.

As has been the case with other viral infections such as hepatitis B, more sensitive methods of viral detection have better defined the period of infectivity. The polymerase chain reaction (PCR) is currently the most sensitive assay for the detection of viral RNA or DNA. In this study the authors extracted fecal RNA and reverse transcribed the HAV RNA to form a complementary DNA strand that was subsequently amplified. PCR has been used in the past to amplify HAV RNA and sequence the produced complementary DNA to identify different HAV genotypes in different parts of the world (10). Consistent with the sensitivity of the technique, the authors were able to detect HAV RNA by PCR for 1 to 2 mo longer than they were able to detect HAV antigen. Although it remains unclear whether the detection of HAV RNA in the absence of HAV antigen represents true infectious virus, one infant in this study continued to excrete HAV RNA for 6 mo after the onset of infection without detectable HAV antigen in the stool. This infant was the probable source of HAV infection for a nurse at least 5 mo after the infant had been identified as being infected. At that time the infant's stools were positive for HAV RNA and negative for HAV antigen, suggesting that HAV RNA detection by PCR represents true infectivity. Unfortunately, the authors were unable to collect stool from the infected nurse to amplify and sequence the HAV RNA in her stools and compare it with that of the infected infant to determine whether the infant was the true source of infection. This report does, however, raise several important clinical questions that can be answered with further studies using PCR technology. These questions are as follows: (a) because PCR is much more sensitive than any previous method for the detection of HAV, what is the actual length of time for HAV fecal shedding? (b) does the detection of HAV RNA without antigen represent true infectivity? (c) is there prolonged shedding of infectious virus in neonates and older children? (d) because the study suggests prolonged shedding in neonates, does this extend to other immunocompromised hosts as well? and (e) although only one HAV serotype exists, can PCR be used to identify HAV genotypes responsible for more severe or prolonged infections? PCR has proven to be an important tool for the detection of HBV DNA, for the identification of HCV RNA, and now will undoubtedly be used to further our understanding of hepatitis A as well.

Finally, this paper raises the question as to what else can be done to prevent these epidemics from recurring other than taking the usual measures to tighten infection control procedures. The answer seems to lie in the development of an HAV vaccine. Significant progress has occurred in this area during the last several years (11). HAV is a positive-stranded RNA virus with a genomic organization that makes it similar to poliovirus and other picornaviruses. It is therefore hoped that the lessons learned from the use of the live-attenuated and inactivated polio vaccines will be helpful in the development and administration of the candidate HAV vaccines (12). Occurrence of only one HAV serotype as opposed to the three serotypes found with polio should make immunization achievable. The successful use of immune serum globulin (ISG) to prevent exposed persons from acquiring HAV infection indicates that induction of anti-HAV antibody alone will protect against the disease. The recent ability to grow large quantities of virus in tissue culture has been an important first step in vaccine development. Currently

being studied are inactivated vaccines given by injection that appear to give anti-HAV antibody levels similar to that seen 1 wk after the administration of a single injection of immune serum globulin (13, 14). Lifelong immunity is anticipated because of the titers induced by the administration of booster doses. Vaccines have been tested in children and adults, and the side effects appear to be minimal, with only a few reports of mild injection-site tenderness. If the experiences from the polio vaccines are applicable to HAV, then it is likely that, although an HAV-inactivated vaccine will protect against the development of hepatitis, it will not prevent subsequent gut infection as would a live-attenuated vaccine. Outbreaks of paralytic polio have been reported in countries that exclusively use the inactivated vaccine, and it has been shown in these cases that fully immunized children harbored the virus in their gut and contributed to the spread of the epidemic to unimmunized contacts. Although attenuated strains of HAV have been developed and tested successfully in primates (15) and human volunteers (16), their widespread use is much more problematic because live viral excretion may exist in vaccinees that may pose a threat to immunocompromised contacts. Furthermore, the possibility of spontaneous mutations of the live-attenuated virus in vaccinees and their contacts that could restore viral virulence cannot be easily excluded. PCR technology will have an enormous impact in this area to determine the rate of spontaneous mutation and also to determine the length of fecal viral excretion. It is therefore likely that the first commercially available vaccines will contain inactivated virus. These will appear, it is hoped, within the next 2 to 3 yr. With the knowledge gained from polio vaccinations and from future HAV studies, we should also look forward to the eventual development of a safe, live-attenuated HAV vaccine.

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