

# A brief on tuberculosis and hepatitis in the Pacific

RAUL RUDOY, M.D., M.P.H. \*

## Tuberculosis

It was just a few years ago that the western countries considered tuberculosis (TB) a conquered disease and a problem of mostly underdeveloped areas of the world. In 1993 there was a 18% increase in the number of TB cases reported in the United States with an estimated total prevalence of more than 60,000 cases<sup>1</sup>. The resurgence of this disease in the U.S. parallels both the increase in HIV infected patients and the disruption of the basic social structures of the U.S. population which has resulted in an increase in poverty, overcrowding and inability to access medical care<sup>2</sup>. In addition the magnitude of the problems has increased due to the recent emergence of TB strains that are resistant to antituberculous drugs and with the outbreaks of TB reported in institutions that provide health care<sup>3</sup>.

Known populations at risk for TB are those that fulfill the requirements of overcrowding, malnutrition and decreased immunological defenses. Individuals in correctional institutions, homeless shelters and long term care facilities have traditionally been recognized as being affected with TB in a higher proportion than the general population. To the above, we need to add individuals with increased risk of exposure to TB, such as health workers caring for patients with TB, factory workers exposed to co-workers with high incidence of active disease<sup>4</sup> and individuals living in a highly endemic area. The rate of tuberculosis in CNMI is approximately ten times higher than in the U.S., but it is similar to that reported from other Pacific Rim areas. One third of patients were ethnic Micronesian and the rest were from the Philippines, China and Korea. It is implicitly understood that the majority of

patients were migrant workers originating from rural areas of their native countries. The answer to the question of imported infection versus recent infection or reactivation needs to be looked at with great detail because the preventive measures that need to be applied are very different. Reduction of the rates of TB due mostly to importation of this disease can be accomplished by stringent immigration procedures that will require adequate clearance for TB before arriving to the CNMI.

The possibility of disease reactivation in the recent immigrants to the CNMI should also be considered. A series of immune mechanisms are put in place after becoming infected with the TB bacillus, most of them related to cell mediated immunity and it is the formation of granulomas without active disease that gives the latency properties to TB. Approximately 10% of the population with latent TB will eventually develop active disease<sup>5</sup> and the risk of developing active disease is greatest during the first two years after infection.

**“ TB is not a disease of the past, it is the leading single infectious disease cause of death among adults. It kills more than 3 million people a year, a number that is higher than the combined deaths due to AIDS, malaria and other tropical diseases. ”**

Epidemiological evaluation of recently acquired infection requires looking into the socioeconomical conditions of those infected, including their working places and an analysis of their immune status, particularly HIV testing<sup>6</sup>. The reported low incidence of resistant TB bacillus to common antituberculosis drugs is of particular interest especially when one considers the countries of origin of the infected non-Micronesian population where the frequency of multiresistant TB is high<sup>7</sup>. One of the major promoters of drug resistance is poor compliance with therapy. It is highly laudable and very encouraging to see the efforts made by the CNMI medical staff to introduce measures that will increase compliance rates. Rewarding those taking their medications and direct treatment observation are probably the best non-restrictive medication strategies to increase compliance rates.

TB is not a disease of the past, it is the leading single infectious disease cause of death among adults. It kills more than 3 million people a year, a number that is higher than the combined deaths due to AIDS, malaria and other tropical diseases. It is estimated that one third of the world population

\* Professor of Pediatrics and Chief, John A. Burns School of Medicine, University of Hawaii.

has been infected with the TB bacillus. The prospect of eradicating TB are quite limited and the facility of world travel makes this epidemic more than just a local problem. The prevention of TB starts with a decrease in the amount of exposure of the non-infected population. Prospective case findings with early identification

of infected patients, adequate treatment regimens and programs that assure compliance are important factors that need to be utilized in controlling this worldwide danger.

### Hepatitis

The last ten years have provided us with a wealth of information regarding the etiologic agents responsible for viral hepatitis (Table 1). Hepatitis virus A, B, C, D and E all have in common the capability to produce liver disease even when they greatly differ in their molecular structure and in the type of induced clinical manifestations.

Hepatitis A virus is transmitted mostly by the fecal oral route and the infection is usually asymptomatic particularly in children. Adults tend to have clinical manifestations such as nausea, vomiting, diarrhea and jaundice. The disease is self limiting and symptoms disappear by the end of the second or third week of illness. A small percentage of adults can experience recrudescence of symptoms with manifestations of cholestatic jaundice and marked pruritus which may last for several weeks. Hepatitis A virus produces only acute disease and the patients are only contagious during the acute phase of the illness.

Prevention of Hepatitis A should start with improvement in sanitation and with a reduction of crowded conditions particularly those involving fecal incontinent children. Immunoglobulin can be utilized for primary preventions or post exposure prophylaxis. Early administration of Gamma Globulin, up to two weeks after exposure, will result in 85% reduction in post exposure disease. The recently available Hepatitis A vaccine is a more permanent way to provide prevention. The vaccine produces adequate antibody levels in 99% of those individuals receiving two doses<sup>8</sup>.

Hepatitis C virus is characterized by producing a mild or usually asymptomatic infection. The infection is acquired mostly by the parenteral route and rarely sexual or perinatal

Virus	Classification	Mode of transmission	Incubation period (days)	Chronic stage
HAV	Picornavirus	Fecal Oral	15 - 50	No
HBV	Hepadnavirus	Parenteral Sexual Perinatal	60 - 180	Yes
HCV	Flavivirus	Parenteral Sexual Perinatal	15 - 160	Yes
HDV	Unclassified	Parenteral Sexual Perinatal	21 - 120	Yes
HEV	Calicivirus	Fecal Oral	21 - 63	No

transmission occurs. The risk of perinatal transmission seems to be directly correlated with the level of maternal viremia and those mothers with titers greater than 107 viral units/ml will transmit the disease to approximately 50% of their infants<sup>9</sup>. Epidemiological data exists implicating sexual transmission of Hepatitis C even when the virus has

not been detected in saliva, semen or vaginal secretions.

The natural history of Hepatitis C has not been completely elucidated but approximately 50% of the infected individuals will develop chronic disease and a certain percentage of them will eventually develop Hepatocellular Carcinoma. The mechanism by which Hepatitis C virus induces cancer is not completely known but it seems to occur more frequently in patients with evidence of previous liver disease<sup>10</sup>.

Control measures against Hepatitis C are very few. At this time a vaccine is not available. Serum gamma globulin does not contain an adequate amount of neutralizing antibodies against HCV and treatment of chronically infected individuals with Interferon alpha - 2b have resulted in improvement in only approximately 50% of individuals<sup>11</sup>. Avoidance of contaminated needles and rigid screening of materials administered parenterally will result in a decrease in the number of cases.

Hepatitis E virus, the most recently described viral agent capable of producing Hepatitis, is endemic in China, India and Africa<sup>12</sup>. Transmission is mostly through the ingestion of food or liquids contaminated with fecal material and rarely from person to person. Most epidemics have been associated with weather changes that promote an increase in the rate of rainfall. Hepatitis E is an acute self limited disease without a chronic stage. Prevention consists mostly in providing improvements in sanitation and to avoid eating foods or liquids that may be contaminated.

Currently Hepatitis B is one of the worldwide leading causes of death due to an infectious agent<sup>13</sup>. There is pronounced geographical variation in the incidence of Hepatitis B and liver cancer: the incidence is low in Western countries and high in South East Asia, Africa, and the Pacific Islands<sup>14</sup>. The current article by Mahoney *et al* in this issue of the PHD reflects the interest and great efforts in preventing Hepatitis B and it also makes us urgently aware of the high number of cases of Hepatitis B in the Micronesian population.

It is extremely alarming to see that, before the immunization campaign against Hepatitis B was implemented, 75% of 8 year olds in Chuuk had evidence of prior infection with Hepatitis B Virus and that 14% were chronic carriers. The vaccine against Hepatitis B is highly effective and this is once more demonstrated in the article by Mahoney et al where past vaccination studies demonstrated a considerable reduction in cases of Hep B infection and particularly in the number of chronic carriers.

In the USA the majority of HBV infections occur amongst adolescents and adults. In the Pacific, the prevalence of Hepatitis B increases with age and reaches a peak in young adults, suggesting that the primary infection occurs mostly during early infancy and childhood and that Hepatitis B endemicity is maintained by both vertical transmission, from mother to the newborn infant, and by horizontal transmission between children. Mother to child transmission during pregnancy is rare because HBV rarely crosses the placenta and maternal transmission occurs mostly during the perinatal period. The presence or absence of Hepatitis E antigen in maternal blood determines the rate of transmission. Mothers with positive E antigen will transmit the infection to 90% of their infants and those with absent E antigen will transmit the disease to 20% of their newborns. The acquisition of Hepatitis B during the neonatal period predisposes to chronicity and approximately 90% of these newborns infected will become chronic carriers and 25% of them will develop degenerative liver disease. Molecular studies in pediatric patients with chronic Hepatitis B and liver cancer have demonstrated that the HBV is able to integrate viral DNA into the hosts' cells chromosomal DNA and that the translation products of the HBV genome are expressed in hepatic tumor cells. These findings have promoted the hypothesis that HBV can inject functioning genetic material into the host cells of pediatric patients and act as an oncogene. This will also explain the difficulty in eliminating the chronic stage.

Prior evidence of horizontal transmission have been described between preschool age children in Japan and school age children in New Zealand and more recently in Honolulu<sup>15</sup>. Mahoney et al demonstrated that this is also found in Micronesian children where the rate of infection increased rapidly between the ages of 1 and 10 years. The knowledge of the prevalence rate of HBV infection in a community and the demographic factors of the patients infected have important implications in HBV prevention policies. In the Pacific, where acquisition of the disease occurs mostly during the neonatal period or during early childhood, resources should be allocated to provide preventive measures for that group<sup>16</sup>. Immunization programs focused on providing Hepatitis B vaccine to all newborns and school age children will provide protection to groups who have increased risk of developing chronic disease. The excellent long term immunity provided by the vaccine will in addition prevent disease acquisition during adulthood and will consequently decrease the risk of hepatocarcinoma in the Pacific population.

## References

1. Centers for Disease Control and Prevention. *Core Curriculum on Tuberculosis, 3rd Edition*. Atlanta: U.S. Department of Health and Human Services, Public Health Service, 1994.
2. Centers for Disease Control and Prevention. Tuberculosis control among the homeless population. *MMWR*, 1987; 36: 257-9.
3. Centers for Disease Control and Prevention. Prevention and control of tuberculosis in facilities providing long term care to the elderly. *MMWR*, 1990; 39: 7-10.
4. Haley C, McDonald R, Rossi L, et al. Tuberculosis epidemic among hospital personnel. *INF Control Hospital Epidemiology*, 1989; 10: 204-10.
5. Rieder HL, et al. Epidemiology of tuberculosis in the United States. *Epidemiological Reviews*, 1989; 16: 79-98.
6. Selwyn PA, et al. A prospective study of the risk of tuberculosis among intravenous drug users with human immunodeficiency virus. *N Engl J Med*, 1989; 320: 545-556.
7. Centers for Disease Control and Prevention. Tuberculosis in Philippine national World War II veterans immigrating to Hawaii, 1992-1993. *MMWR*, 1993; 42: 656-663.
8. Marwick C. Hepatitis A vaccine set for 2 years old to adults. *JAMA*, 1995; 273: 906-907.
9. Ohto H, Terazawas, Sasaki, et al: Transmission of Hepatitis C virus from mother to infants. *N Engl J Med*, 1994; 330: 744-750.
10. Simonetti RG, Camma C, Fiarello F, et al. Hepatitis C virus infection as a risk factor for hepatocellular carcinoma in patients with Cirrhosis. *Ann Intern Med*, 1992; 116: 97-102.
11. Clement MG, Cogic M, Lau ME, et al: Effect of iron overload on the response to recombinant interferon alpha treatment in transfusion dependent patients with thalassemia major and chronic Hepatitis C. *J Pediatr*, 1994; 125: 123-128.
12. Purdy MA, Krawczynki K. Hepatitis E. *Gastroenterol Clin North Am*, 1994; 23: 537-546.
13. WHO Executive Summary: The World Health Report 1996. Fighting Disease, Fostering Development Geneva. WHO; 1996.
14. Shapiro CN, Margolis HS. Hepatitis B epidemiology and prevention. *Epidemiol Rev*, 1990; 12: 221-227.
15. Pon E, Ren H, Margolis H, et al. Hepatitis B virus infections in Honolulu students. *Pediatrics*, 1993; 92: 574-578.
16. Manea SJ, Iohp K. *The Hepatitis B immunization campaign for children in the Federated States of Micronesia*. Public Health Report, 1997; 107: 556-61. □