Editorial

Transfusion Associated Hepatitis: The Indian Scenario

Transfusion associated hepatitis (TAH), developing as a consequence of transfusing infected blood or blood products, affects every sphere of medicine. Initially, the illness often remains subclinical but could later manifest as liver disease and even primary hepatocellular carcinoma. While the risks are more for the transfusion recipients, they are also substantial for those who are constantly exposed to blood, such as health care workers. The problem of TAH assumes greater significance, due to the recent discoveries of hepatitis C (HCV), hepatitis G (HGV), and mutant forms of hepatitis B viruses(l).

Hepatitis was the first viral disease recognized to be transmissible by blood transfusion in 1943(2). Recognition of this route provided insight for the detection and management of other transfusion transmitted infections. The major problem in dealing with transfusion associated hepatitis (TAH) is its lack of single etiology. While a virus was known to be a cause of 'serum hepatitis' and a transfusion hazard even in 1950s, a serological marker for hepatitis B was identified only in 1965(3). The availability of testing for hepatitis B surface antigen (HBsAg) brought a significant decline in the incidence of TAH(4). By 1975, it was well known that most cases of TAH were due to non-A, non-B (NANB) hepatitis viruses. It was not until 15 years after the recognition of NANB hepatitis, that molecular biology techniques permitted the identification of hepatitis C virus (HCV) as the predominant cause of TAH(5).

Hepatitis B is a major public health problem in India(6). The average HBsAg positivity rate in the adult healthy donor population in the country is around 4.7%, amounting to about 43 million HBV carriers in the country. In most communities, the carrier pool is formed early in childhood by means of vertical/perinatal transmission (chronicity rate of such infection being >90%) or horizontal transmission (chronicity rate in young, preschool age being 20% to 50%). However, the most important route of transmission among adults is parenteral exposure(6).

Clinical Features

Transfusion associated hepatitis needs to be suspected when a transfusion recipient (or exposure through parenteral or other invasive routes), has two elevated readings of alanine transaminase (ALT) at least 5 days apart, 14 to 180 days after the transfusion or interventional episode. There should also be no other obvious cause for the hepatitic illness *(e.g.,* pre-existing liver disease, alcohol, anesthesia, congestive failure or drugs). Most of the episodes of TAH, whether due to HBV or HCV are asymptomatic. The illness may evolve through prodrome to an acute hepatitis stage or rarely, fulminant phase or progress insidiously to a stage of chronic hepatitis and its attendant sequelae of cirrhosis and hepatocellular carcinoma. Most of the clinical features of HBV or HCV sporadic infection (including extrahepatic manifestations) can occur in post-transfusion hepatitis.

Transfusion Associated Hepatitis Due to HBV (TAH-B)

As mentioned previously, parenteral

exposure is a definite risk factor for infection with HBV. The study by Patwari *et al.(7)* showed a higher incidence of HBV carrier state in transfusion recipients than in the general population (12.3% *vs* 3.6%, $p < 0.001$). The authors found an incidence of TAH-B to be 11%. In another study, of multiply transfused cardiac surgery patients(8), despite adequate screening, about 20% of all cases of TAH (the overall incidence of TAH being 7%) were due to HBV. HBV carrier state in hemodialysis patients has been reported to be as igh as 42%(9).

In the pediatric age group, much of the data has emerged from studies on thalassemics and hemophiliacs. Whole blood and plasma derivatives (factors VIII, IX, XIII and C-l inactivator) are potent sources of TAH. This is because the donor plasma may be infected with undetectable levels of a virus and when this plasma is pooled (generally > 10^3 donor units), the infectivity of the final product is compounded. Indeed, 2% to 10% of hemophiliacs are identified to be HBsAg carriers with an additional 75% having evidence of past infection (anti-HBc+ or anti-HBs+)(10,ll). A study from eastern India showed serological evidence of HBV infection in hemophiliacs to be 24%(12). Similarly, a study from Bombay showed HBsAg positivity in 45% of multiply transfused thalassemics(13).

In a recently concluded study on thalassemic children from our own center(14), 54 (72%). of the 75 patients were shown to have present or past evidence of HBV infection (9 patients HBsAg and HBV DNA positive by dot hybridisation and PCR; others positive for HBsAg or more commonly IgG anti-HBc or anti-HBs). The incidence of dual infection (HBV and HCV) was 53%. In the presence of coinfection with HCV, HBV infection was rarely showing serological evidence of replication Interestingly, none of the patients was symptomatic and ALT was elevated in 51% of cases only. Liver biopsies were not done in these patients, though there is evidence from literature to suggest that 58% of thalassemics may have histological evidence of chronic liver disease(15).

The risk of TAH due to Hepatitis Delta Virus (HDV) is about 30 times less than with HBV. The chances of HDV infection are' remote if the donor blood has been properly screened for HBsAg and anti-HBc. The prevalence of serological markers for HDV is 13% in multi-transfused hemophiliacs(16).

Transfusion Associated Hepatitis Due to HCV (TAH-C)

As highlighted earlier, it was known in late 1970s that most of TAH was due to NANBH agent. With the discovery of HCV, more than 85% of these cases could be attributed to this agent. Before the discovery of HCV, in early 1980s, ALT and anti-HBc were used as 'surrogate markers' for the detection of NANBH(17,18). Testing for these two parameters decreased the incidence of NANBH related TAH by 3-4 folds. Indeed, after tests for HCV serology became available, 40%-50%, of patients with abnormal parameters (ALT and/or anti HBc) were found to be anti-HCV positive. The use of first generation enzyme immunoassays (EIAs) for HCV saw a reduction in HCV related TAH by 80% and the second generation EIAs, a reduction by 90%.

The prevalence of HCV infection in the western countries ranges from 0.4% to 5%. No detailed epidemiological studies are available from India but in a recent study from our center, 1.73% of 2,000 healthy, voluntary donors reporting to the blood bank were anti-HCV positive. The seroprevalence of HCV markers in children with thalassemia is as high as 60%(19), in

hemophilia, 98%(20) and in children undergoing hemodialysis, 15-20%.

In the study on thalassemic children from our center(14) 51 (68%) of the 75 children had anti-HCV positivity by the third generation EIA. As already mentioned, the incidence of dual HBV and HCV infection was 53%. Among these, 11 of the 40 patients tested were HCV RNA positive by RT-PCR. The occurrence of infection with HBV or HCV was more common in children more than 5 years of age (98%) vis-a-vis those less than 5 years (67%). This was largely due to the greater number of blood units transfused in the former group. Also, serum ferritin levels were found to be significantly higher in infected children than in controls. Since high hepatic iron favors viral replication, and also is a negative factor for response to interferon therapy, chronicity of infection is more likely to occur in these patients. Lai *et al*.(19) showed that among thalassemic patients acquiring HCV through transfusion, resolution of infection is seen in 20% cases, recurrent or chronic hepatitis in 80% and cirrhosis in 11%. Hepatitis G is a newly discovered blood borne virus which is also transmitted by blood and blood products(21). It is not certain whether it causes liver disease of any consequence(22).

With approximately 3 million units transfused every year, it is estimated that nearly 53,000 new cases of TAH are added every year in India(23).

Prevention of Transfusion Associated Hepatitis

TAH is a largely preventable disease. The basic step is to encourage voluntary blood donation system. In our country, 58% of donations are of replacement type and 39%, voluntary. In Japan, a mere change from paid donor system in 1963-64 to voluntary donation in 1968-72, decreased the incidence of TAH from 51% to 16%. Those found unsafe for blood donation should be deferred from doing so for adequate periods of time depending on their infectivity and clearance of infection.

Sensitive tests like third generation EIA (sensitivity to the order of 0.2-0.5 ng/ml) should be used for the detection of HBsAg. In India, less than 5% of blood banks use such techniques for donor screening. Sometimes, anti-HBc might be the lone marker of HBV infection. Therefore, some people have suggested that donors having high titres (> 1:64) of anti-HBc or negative for anti-HBs (but positive for anti HBc) should not be accepted(24). This however, may lead to lot of wastage of donor units.

As already highlighted, the era of use of surrogate markers to detect HCV has passed. At least the second generation EIA (and cross checked by RIBA II or III) should be used to detect anti-HCV. Using an extremely economical technique of passive hemagglutination (PHA) to detect anti-HCV, the Japanese Red Cross has reduced the incidence of HCV related TAH to zero(25). Another alternative to screening for viruses is development of techniques for viral inactivation. The solvent detergent technique for inactivation of HBV and HCV is arguably the best. The technique is extremely efficient and the risk for transmission of HBV or HCV is 1 in 10^{13} and 1 in 10^{6}, respectively. For -pooled products therefore, there is a theoretical risk of infection. In a study by the National Institute of Biological Standards and Controls, U.K. 5 out of 95 plasma pools tested were positive for HCV RNA by RT PCR(26) (all were anti-HCV negative). As of now, this technique can't be recommended for routine screening. New methods of viral inativation under exploration include use of short wave-length ultraviolet light (UVC) with or without anti-oxidants(27).

Inspite of rapid advances in the field of serological testing and viral inactivation techniques, some amount of risk of infection is always there. For HBV at least, there is an extremely immunogenic and efficacious vaccine available. Till such time that the use of this vaccine is incorporated into the Extended Programme for Immunization (EPI), at least the high risk group children (hemophiliacs, hemodialysis patients, thalassemics, *etc)* should be electively vaccinated. For HCV, the development of vaccine is still a remote goal because of the inherent nature of the virus to mutate quickly and repeatedly and its existence in blood as 'quasispecies'.

it is reasonable to suggest that with our current abilities to screen for HBV and HCV along with inactivation protocols for pooled plasma fractions, we would be able to eliminate the risk of TAH to a very large extent. However, to achieve this goal an important issue needs to be addressed; the cost for providing 'safe blood'. A rational, cost-effective approach for screening needs to be evolved for every country with achievable and affordable risk reduction goals. In a recently held conference, the "Indian Association for the Study of Liver (INASL)" recommended the following guidelines(28).

1. All blood donations should necessarily be voluntary and non-remunerated.
2. Autologus blood transfusion and use of blood components rather than whole blood should be encouraged.
3. Screening in the blood banks should be mandatory and legally binding for HBsAg (EIA), anti-HCV (EIA-3), HIV I and II, malaria and syphilis. Rationale for anti-HBc testing should be assessed for developing countries like India.
4. Internal and external quality control for serological screening at regional and national level should be ensured.
5. HBV DNA and HCV RNA testing is not currently recommended for blood banks. These tests should be used at present, for research work and for assuring therapeutic response to antiviral agents.
6. Certain low-priced techniques such as, passive hemagglutination (PHA) and gelatin particle agglutination (PA), which have been found to be very successful in Japan, need to be evaluated in the developing countries, and if found satisfactory, should be adopted.
7. Vaccination for hepatitis B before an elective interventional procedure of surgery is strongly recommended and should be universally practised.
8. Interferon therapy for chronic hepatitis B is effective and is strongly recommended. The success of interferon therapy is limited in chronic hepatitis C.
9. There is a need for donor awareness program and donor deferral practice to be developed in developing countries like India.
10. Starting of recipient surveillance programs (follow-up) after transfusion, in every country, would help assess the efficacy of donor screening programs of the blood banks.
11. Centralization and reorganization of blood bank services is necessary. Quality assurance and auditing of transfusion services should be routine and mandatory.
12. Setting up of a consultative group comprising of personnel from trans-

fusion medicine, laboratory medicine, hepatology and general public (recipients) is recommended.

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