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Blood transfusion and hepatitis viruses

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Transmission of hepatitis viruses has been recognised as an undesirable effect of blood transfusion since the 1940s, when large outbreaks occurred following inoculation with a yellow fever vaccine which contained pooled human plasma. Further reports followed of jaundice occurring several months after transfusions with blood or plasma.[1] It was also noted in studies in the UK that the incidence of icteric hepatitis increased relative to the number of units transfused.[2]

After the discovery of the Australia antigen in 1965, its recognition as a marker of hepatitis B virus (HBV) infection and its association with post-transfusion hepatitis (PTH), the subsequent introduction of screening tests for this antigen in the early 1970s led to a marked decrease in the incidence of PTH. However, despite increasingly sensitive testing methods for hepatitis B surface antigen (HBsAg), as it subsequently became designated, viral hepatitis was still considered the commonest lethal complication of blood transfusion.[2] It was clear that there were still a number of cases of PTH that were due neither to hepatitis A virus nor to HBV, and the term 'non-A, non-B hepatitis' (NANBH) was coined.

The introduction of molecular techniques enabled clones to be derived from the genome of an agent associated with transfusion-transmitted NANBH,[3] and the proteins derived from these clones were then used to develop an enzyme-linked immunosorbent assay (ELISA)[4] to detect antibodies to this virus, now termed hepatitis C virus (HCV). This ELISA is now used in most developed countries to screen for HCV antibodies.

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Current status of hepatitis testing

HBV

All transfusion services in South Africa currently screen for HBsAg with ELISA kits. These tests have a high sensitivity and specificity, but it is well recognised that current methods for HBsAg detection are not yet sensitive enough to detect all potentially infectious units of blood or possible cases of hepatitis, although the risk of PTH is still very low.

For this reason the transfusion services also have stringent exclusion criteria and all persons with a history of hepatitis after the age of 10 - 12 years are either permanently excluded from donation or deferred for 12 months after recovering from the illness. Also, all donors who have had contact with a person suffering from hepatitis are excluded from donation for 6 months.

Should a donor sample be found reactive for HBsAg, a confirmatory test with a neutralisation technique is performed. If this is positive the donor is considered HBsAg positive and the unit is discarded. The donor is then informed by letter of the result of the test and advised to consult a physician.

The overall prevalence of HBsAg among apparently healthy donors in South Africa is currently approximately 0,5%, although this ranges from approximately 0,1% in white donors to 4 - 5% in black donors. New donors also have a higher prevalence than regular donors.

The prevalence of transfusion-related HBV infections is not known since a proper prospective study would be required. However, in the Western Cape we are aware of only 3 cases of proven transfusion-transmitted HBV infections during the past decade. In the context of the infusion of approximately 150 000 blood component transfusions each year in the Western Cape, the risk of HBV infection from transfusion remains very low.

HCV

Despite the introduction of HBsAg tests, cases of PTH continued to occur; in the USA the incidence was as high as 10% in the early 1980s,[5] although it varied widely in different parts of the world and clearly was also related directly to the number of units infused. The true extent of PTH in a given population can only be measured by careful follow-up of transfused recipients over several months. This is because the vast majority of cases of PTH (particularly NANBH) are asymptomatic and initially can only be detected by the serial measurement of liver enzyme levels, especially alanine aminotransferase (ALT), in the recipient following transfusion.

In the absence of a specific test, blood transfusion services in the USA and in some European countries began screening donations for surrogate markers of NANBH, namely elevated levels of ALT and for antibodies to HBV core antigen (anti-HBc). Based on a retrospective analysis from a study of blood donors and patients with PTH at the National Institute of Health, a reduction of 30 - 50% was predicted for the incidence of NANBH following introduction of surrogate testing, but no prospective evaluation was conducted.[6] However, a decline in PTH in the USA was noted before the introduction of surrogate marker tests for NANBH, and was probably due to stricter donor selection and screening procedures introduced to prevent HIV transmission.[7] Although some countries, including the USA, have continued to screen for anti-HBc and ALT levels, there remains some controversy whether this is truly efficacious and cost-effective in the light of improved anti-HCV tests. Anti-HBc tests may also be useful in identifying units infectious for HBV with sub-detectable levels of HBsAg, especially precore-defective HBV mutants.[8] However, in countries of high endemicity for HBV (such as South Africa) where many donors may be positive for anti-HBc, it would be difficult to discard all anti-HBc positive units because this would strain the blood resources. A survey of 300 donors in Natal in 1987 revealed anti-HBc-positive rates ranging from approximately 4% in whites to approximately 30% in black donors (C. Prior — unpublished data).

With the cloning of nucleic acid sequences from an RNA virus putatively responsible for most NANBH infections and the development of an assay for anti-HCV,[3,4] screening for anti-HCV is now routine in most countries and is part of the screening process in all blood transfusion services in South Africa. The first-generation tests had rather poor positive predictivity values for HCV infection in populations with a low prevalence of HCV. Although the second-generation tests are an improvement, specificity remains a problem, with a relatively large number of false positives in low prevalence populations. However, as the tests are refined, fewer false positives are likely.

Anti-HCV screening is also very expensive and this has certainly affected its introduction in developing countries. Modifications such as pooling samples to decrease costs have been proposed, with apparently satisfactory results among Egyptian donors using Abbott second-generation assays,[9] but we have been unable to reproduce their results using the same test system (A. Bird, B. Gibbs — unpublished data). However, other test systems may yield more satisfactory results and are currently being evaluated in this respect. An alternative cost-saving approach is to screen out the donor base initially and then repeat anti-HCV testing on a rotational basis on repeat donations (e.g. every third - fifth donation), since it has been shown that HCV seroconversion rates in donors are extremely low (J. Barbara, P. Coghlan — personal communication).

The donor population in South Africa has a relatively low prevalence of HCV positivity at approximately 0,3 - 0,4% although, as in HBV infection, there are geographical and racial differences in prevalence. These figures are comparable to the prevalence of < 1% in most developed countries, with the exception of Japan where HCV prevalence among donors is around 1 - 2% and where PTH was common prior to HCV screening.[7] Risk factors for HCV infection among anti-HCV positive donors followed up in the Western Cape are not clearly established, with more than 50% of infected donors having no apparent source of infection. This is in contrast to studies in the USA where approximately 40% of infections are associated with intravenous drug abuse.[10]

There has been only one prospective study of PTH in South Africa of which we are aware, in which 68 cardiothoracic surgery patients who received on average 6 red cell units each were followed up.[11] Only 1 patient (1,4%) contracted NANBH based on serial measurements of ALT. With the advent of anti-HCV screening, one would predict

that the current prevalence of PTH would be well below this rate. Indeed, based on the USA experience, the current risk for PTH is approximately 3 per 10 000 units transfused[6] and since we have similar prevalence rates among our donors, it is likely that the risk in South Africa is similar. It is also important to bear in mind that recent studies with long-term follow-up indicate that post-transfusion HCV infection has a negligible effect on morbidity and mortality.[12]

The current practice therefore is to screen all donors for HCV antibodies. Should the test be repeatedly reactive, the unit will be discarded and the donor informed by letter of the results and advised to consult a physician for further testing and clinical follow-up. Should further clinical and laboratory follow-up suggest a false positive result we would accept the donor back, but only if the screening test and currently available confirmatory tests are non-reactive 6 months after the initial screen. However, as indicated in the article by Voigt and Smuts in this issue (pp 535-548), confirmatory testing is a problem and ideally all donors with positive tests should be confirmed as truly infected by sensitive viral detection methods such as polymerase chain reaction (PCR) techniques. This is relatively time-consuming and expensive, but recent sensitive recombinant immunoblot assays (RIBAs) appear to correlate reasonably well with PCR technology, particularly if the antibodies show reactivity with either C33C and C22 antigens.[13] Reactivity with C100 and/or 5-1-1 antigens correlates poorly with PCR positivity and is regarded as indeterminate.[11]

Clearly, the present anti-HCV tests are still overly sensitive and not sufficiently specific in terms of diagnosing individual patients. Nevertheless, in the context of screening blood donors, erring on the side of sensitivity is preferable. Unfortunately this leads to the unnecessary exclusion of some donors and uncertainty as to whether some are truly infected. This must, however, be balanced against the maintainance of a safe blood supply and the likelihood that more specific, yet sensitive, tests for HCV infection will be developed during the next few years.

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Liver transplantation for viral hepatitis — which patients will benefit?

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Liver transplantation constitutes a significant part of the hepatologist's armamentarium and has become the treatment of choice for most patients with chronic end-stage liver disease. The results continue to improve and many centres are now able to achieve 1-year survival figures in excess of 90% in selected patients. The surgical techiques involved in liver transplantation and the immunosuppressive protocols used postoperatively have been standardised.[1] In contrast, the indications for and contraindications to liver transplantation continue to be modified. Large numbers of patients have undergone liver transplantation in recent years and analyses of large series of patients have made it possible to determine more accurately the outcome of liver transplantation in specific hepatic disease processes. As a result, subsets of patients who are more likely to survive long term have been identified. This is particularly true of patients with viral hepatitis.

Hepatitis B

Liver transplantation in HBsAg-positive patients remains controversial.[1] For many years a carrier state of HBsAg was regarded as a contraindication to transplantation.[1] After transplantation patients with hepatitis B are at high risk of becoming reinfected with the virus which caused the original disease, and once reinfection occurs it almost invariably leads to chronicity and recurrence of the chronic active hepatitis.[1] Thus patients who are HBsAg positive have a significantly worse prognosis after transplantation than patients who are HBsAg negative.[1]

The ethical dilemma is compounded by the magnitude of the epidemiological problem. In HBV endemic areas, such as southern Africa, HBsAg-positive patients constitute a large, if not the largest, proportion of disorders causing end-stage liver disease. Exclusion of patients who are HBsAg-positive from transplant waiting lists would deprive many young patients, who are in the most productive years of life and otherwise ideal transplant candidates, from the only option available to them. Thus identification of subsets of patients with hepatitis B who have a better outcome or the introduction of measures to improve the outcome after liver transplantation would have important implications locally.

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