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FORUM

Blood Transfusion Services Should Have Begun Screening for Hepatitis C When an Antibody Assay First Became Available

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BACKGROUND

The risks of developing post-transfusion hepatitis (PTH) are related to the incidence of hepatotropic viral infection in the donor population and the sophistication of the epidemiological and laboratory techniques used by the transfusion services to exclude blood products liable to transmit disease. In the United States of America in the early 1960s about 50% of multiply transfused patients developed hepatitis;[1] at this time the transfusion services were reliant on 'commercial blood' obtained from a population with a bias towards lower socioeconomic groups (particularly immigrants and intravenous drug abusers).

In 1965 the hepatitis B virus was discovered. By 1970, with the elimination of commercial blood donors and the introduction of screening with crude tests for hepatitis B surface antigen (HBsAg) the incidence of PTH had been reduced to 3·7 cases/1000 units transfused.[2] During the late 1970s, however, 7–10% of blood transfusion recipients were still developing hepatitis. Serological tests for the diagnosis of hepatitis A or B infection were negative in 90% of these cases and the term 'non-A, non-B (NANB) hepatitis' was used to describe their condition.[3]

In the early 1980s it was shown that the incidence of NANB PTH could be almost halved by the exclusion of donors with antibodies to hepatitis B core (anti-HBc) or abnormal liver function tests (LFTs).[4] The presence of these surrogate markers for NANB hepatitis resulted in a loss of only 4% of the donors.[5]

In 1989 the agent responsible for most cases of NANB hepatitis (hepatitis C virus; HCV) was finally cloned and an enzyme immunoassay antibody detection system was developed using a recombinant fusion polypeptide of human superoxide dismutase and a sequence derived from a non-structural region of the virus expressed in yeast (C100).[6]

In this paper, the argument for 'Blood transfusion services should have begun screening for hepatitis C when an antibody assay first became available' will be developed by examining what is known about the serology of HCV to determine (i) how many donations would be excluded by screening for anti-C100, (ii) how many cases of PTH could be avoided by eliminating blood products positive for anti-C100 and (iii) how many cases of PTH would not be prevented by such a screening programme. An analysis of these data and our knowledge of the natural history of NANB hepatitis will permit some realistic conclusions to be drawn.

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EPIDEMIOLOGY OF ANTI-C100

How many donations would be excluded by screening for anti-C100?

Several studies have been undertaken to address this problem. A British survey[7] examined 1100 blood donations and found 6 to be anti-C100 positive (0·55%). In a Dutch study[8] 37 of 5150 (0·7%) were found to be seropositive and in Germany the seroprevalence rate varied from 0·13% (Hannover) to 0·83% (Frankfurt).[9] However, in Spain, 16 of 1044 donations (1·5%) were seropositive[10] and in Italy the seroprevalence was 0·68% in the north and 1·38% in the south.[11] Studies from America put the incidence of anti-C100 antibodies among blood donors between 0·9% and 1·4% with the greatest seroprevalence rate among black or Hispanic people.[12]

An estimate of 0·5–1% seroprevalence within the UK national blood transfusion requirement of 2·5 million blood donations[13] would result in the loss of between 12 500 and 25 000 donations. The screening would cost about £6·25 million.

How many cases of PTH could be avoided by eliminating blood products positive for anti-C100?

In the British survey,[7] only one of the six seropositive donations transmitted NANB hepatitis (17%), and this

was the only donation found to contain viral sequences detectable by polymerase chain reaction (PCR). A 17% disease transmission rate was also found in the Dutch study (6/35 anti-C100 positive donations transmitted NANB hepatitis), although the Spanish study estimated that 88% of anti-C100 positive blood was infectious (14/16 anti-C100 positive donations transmitted NANB hepatitis). Assuming a 20% infectivity rate, between 2500 and 5000 cases of PTH could be prevented each year.

How many cases of PTH would not be prevented by screening for anti-C100?

Only 63% of the PTH cases in the Dutch study and 56% in the Spanish study would have been prevented by eliminating anti-C100 positive blood. The problem with the anti-C100 assay is that seroconversion following HCV exposure may be delayed for many months (in some cases patients never seroconvert) and that some patients may lose antibodies several years after seroconversion.[12,14]

NATURAL HISTORY OF NANB HEPATITIS

A considerable amount is already known about this condition in the context of PTH. In 1982 it was shown that about 50% of cases of PTH progress to chronic liver disease[15] and serological studies have shown that anti-C100 develops after about 24 weeks in those who develop chronic liver disease and in only half of the patients who develop an acute resolving disease.[14] The liver histology from 13 of the cases in the 1982 study showed chronic persistent hepatitis (CPH) in 1 case, chronic lobular hepatitis (CLH) in 2 cases and chronic active hepatitis (CAH) in 10 cases (5 of these progressed to cirrhosis).

A more recent histopathological study of chronic NANB PTH showed that 29% of patients normalised their liver biochemistry after 3 years, 55% had CPH and 16% had CAH progressing to cirrhosis.[16] In one study of haemophiliacs with chronic liver disease 58% had CPH, 26% had CAH and 11% had cirrhosis[17] and in another study, 48% had CPH, 22% had CAH and 17% developed cirrhosis.[18] A worrying aspect of the former study was the demonstration of progression on successive biopsies from CPH to CAH and cirrhosis.

In addition to the terminal complications of cirrhosis and portal hypertension (oesophageal varices, hepatic encephalopathy and bacterial peritonitis) a clear risk for the development of hepatocellular carcinoma (HCC) has been identified. A study from Spain showed that 75% of the HCC cases were anti-C100 positive[19] and a study from Italy showed that 65% of HCC cases were anti-C100 positive.[20] Even in a population of black people where HBV infection is the major cause of HCC there has been evidence of tumour development independent of HBV infection and related to HCV as judged by anti-C100 antibodies.[21]

CONCLUSION

The introduction of an HCV screening programme for blood products using the anti-C100 assay would cost about £6·25 million/year, would result in the loss of 12 500–25 000 donations/year and prevent between 2500 and 5000 cases of PTH/year. Between 1250 and 2500 cases of chronic liver disease (CLD)/year and 250–500 cases of cirrhosis/year could be prevented, but a similar number of cases would still occur because of the 50% sensitivity of the test.

Patients with CLD will consume NHS resources as they develop the complications of portal hypertension; the cost of 250 liver transplants is about £8·75 million. It would seem to us therefore that there are financial as well as ethical considerations in HCV screening. Clinicians tend to underestimate the magnitude of the problem as 75% of PTH cases are anicteric;[22] if we are not doing everything possible to prevent NANB PTH we may find ourselves in a difficult situation when the first group of cirrhotics in the anti-C100 era become litigious.

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Against the proposition: J. A. J. Barbara

In 1989 a clone coding for part of the agent responsible for causing parenteral non-A, non-B hepatitis was isolated.[1] Subsequently, an assay for the detection of antibodies to this agent (termed hepatitis C virus; HCV) was described.[2] Inevitably, calls rapidly arose for the introduction of this assay for mandatory testing of blood donations prior to their release for transfusion. However, several reasons can be advanced to justify a cautious attitude to the introduction of such testing. As with any consideration of pre-transfusion screening for a given microbial agent, a clear understanding of the local conditions and epidemiology of the agent are essential before sensible estimates of the cost-effectiveness of screening can be made. In this context, some of the following arguments will draw heavily on UK experience. Nevertheless, most aspects have a far wider relevance.

ASSOCIATION OF CHRONIC LIVER DISEASE WITH A HISTORY OF TRANSFUSIONS

One single crucial factor in any decision concerning the introduction of a new (and in this case, very expensive) pre-transfusion screening test for blood donations must be examined: in the absence of screening, can significant transfusion-transmitted disease be associated with the agent in question? This is often the factor that is most obviously prone to geographical variation. Although the data relating chronic liver disease (CLD) to transfusion history are very sparse, striking differences are apparent between different countries. In a study in Japan[3] reported in 1982 the frequency of a history of previous transfusion in patients with chronic hepatitis, cirrhosis and hepatocellular carcinoma of the non-A, non-B hepatitis (NANBH) type was 42·8%, 37·1% and 15·1% respectively. These high figures suggested an aetiological connection between transfusion and chronic liver disease. In striking contrast to this report, the situation in the UK was recently reported by Wood *et al.*[4] Patients with CLD were matched for age and sex with other patients in the same hospital and no significant association between CLD and a history of transfusion was demonstrated. The only factor associated with CLD (once alcohol was excluded) was residence for more than a year in the Middle or Far East, in males.

While these observations obviously support the value of reduction of transfusion-associated NANBH in Japan, transfusion cannot be demonstrated to be a risk factor for CLD in the limited UK studies to date. The reasons for these geographical variations are likely to be complex but an obvious parameter to investigate is the extent of post-transfusion hepatitis (PTH) in the different locations.

POST-TRANSFUSION HEPATITIS

The rates of PTH in Japan and the UK mirror the extent of the association between CLD and a history of transfusion; while PTH rates in Japan are high, they are very low in the UK. The only large scale prospective study in the UK with access to the latest serological techniques for diagnosing infections with hepatitis B virus and HCV has been undertaken in North London.[5] In nearly 400 transfusion recipients completing full follow-up (as in the Transfusion-Transmitted Viruses Study (TTVS) in the USA[6]), only 2 patients (0·5%) showed alanine aminotransferase (ALT) elevations consistent with NANBH. Furthermore, in only 1 of these 2 patients (0·25% of recipients), was NANBH associated with HCV seroconversion and the involvement of a seropositive donor, with infectivity confirmed by the polymerase chain reaction (PCR).

HOW DOES HCV SEROLOGY CORRELATE WITH PTH?

The relationship of HCV serology with cases of PTH has been extensively reviewed.[7,8] The predictive value of the first-generation assays for anti-HCV in relation to PTH appears to increase in areas with high rates of PTH. For

example, in a study in Barcelona[9] which recorded a post-transfusion NANBH rate of 9·6%, the predictive value of a seropositive donor transmitting HCV or NANBH was 88% since 14 of 16 seropositive donations were transfused to patients who subsequently developed NANBH and seroconverted for HCV. On the other hand, of 25 patients developing PTH, only 14 (56%) had received seropositive units. In marked contrast to the Spanish report, in our North London study[5] only 1 of 7 (14%) anti-HCV seropositive blood donations, transmitted HCV-associated NANBH. This figure is similar to the 16% value reported earlier[10] in a Dutch prospective study of PTH.

The association between PTH and HCV seroconversion discussed above for the Spanish study provides another way of examining the value of HCV screening. Alter *et al.*[11] found HCV seroconversion in all of 15 patients with post-transfusion NANBH. However, these patients were highly selected cases of typical NANBH. When samples from all patients with NANBH defined by TTVS criteria were studied for HCV seroconversion, the association became less obvious. Thus, in the study of Alter *et al.*, only 60% of the less well-defined cases of NANBH which eventually resolved, showed anti-HCV seroconversion.[11] Similarly, the figure from serological analysis of stored samples from the TTVS study was 56%;[6] from the Dutch[10] study, 67%; from the North London[5] study, 50% and from a French[12] study, 67%.

HCV SEROPREVALENCE IN BLOOD DONORS

Studies of seroprevalence in blood donors using first-generation assays for anti-HCV, so far unconfirmed by the recently available supplementary tests, reveal a range between 0·2% and 2% in most developed countries.[13] Surprisingly, the seroprevalence in, for example, Japan (1·5%) is not markedly different from countries such as the UK (0·3–0·7%) although the rates of PTH differ enormously. This may reflect variations in HCV strains which could result in less effective detection of seropositivity by the first-generation assays in certain areas. Seroprevalence studies in different countries using second generation assays will soon be forthcoming and may clarify the situation.

ASSAYS FOR ANTI-HCV

The first-generation assays for anti-HCV employed solely the C-100-3 antigen derived from a non-structural region of the virus. Antibody responses to this protein may be more likely to reflect chronic rather than short-term acute infection with the agent. These assays suffered from the following disadvantages.

1. Low predictive value in the absence of supplementary tests, which were not available until some time after the screening tests were marketed.
2. Short-lived antibody in a significant proportion of subjects; in some cases this may reflect false-positive, rather than genuine transient reactivity.
3. Long delay until seroconversion, following infection. Although normally apparent within 4–6 months, seropositivity to the C-100-3 antigen can take as long as a year to occur.[11]
4. Low titre of the anti-C-100-3 response. The highest dilution level of antibody that we have noted is in the order of 1/1000 (unpublished data). This compares with $1/10^5$ to $1/10^6$ for anti-HIV assays, for example.

In areas with low rates of PTH and little association of prior transfusion history with CLD, the unconfirmed first-generation assay did not appear appropriate for screening of routine donations. Its value lay in research into the epidemiology of HCV infection and in analysis of PTH. Subsequently, improved assays, incorporating structural as well as additional nonstructural HCV antigens in both screening and supplementary formats, have been developed. They have been reviewed in more detail elsewhere.[7] Large scale laboratory evalutions of these assays have just begun and the manufacturers' reports of their increased specificity and sensitivity suggest a significant improvement of tests for anti-HCV for screening and diagnostic purposes. Polymerase chain reaction using highly conserved noncoding regions from the 5′ terminus of the HCV genome may provide the definitive confirmatory diagnosis of viraemia[7] although the timing at which samples are taken may be crucial, as viraemia may be intermittent.[14]

COSTS AND IMPLICATIONS FOR TRANSFUSION SERVICES

The high development costs involved in the derivation of the anti-HCV assay have resulted in a very expensive test. Bulk prices for the anti-HCV assay are approximately four-fold higher than for anti-HIV assays. Furthermore, supplementary assays such as the recombinant immunoblot assay (RIBA) are ten times the price of the screening assay. Prices may be lower for assays based on synthetic antigens produced from an analysis of the HCV nucleic acid sequence, which are becoming available. However, the commercial position of such assays may be subject to patent litigation.

In the UK, the cost of the actual screening of 2·5 million donations would be considerably in excess of £5 million annually. In addition, with the first generation assays, approximately 1 in 150 donors would have required costly RIBA testing, resulting in a further expenditure of £350 000 per annum, without taking into account the even more expensive PCR testing to define infectivity. With such a high reactivity rate, mostly associated with false-positivity, the ensuing increased risk for operational errors in an already complex screening programme is considerable. Apart from the actual testing, the increased workload and costs from quarantining, referral and replacement of donations, together with counselling of confirmed seropositive donors (and possibly donors deferred because of false-positivity) are enormous. It is hoped that the second generation assays will reduce this financial burden but details are not yet known.

In areas with low associations of CLD and transfusion of blood or blood components, the question of the risk to

recipients of clotting factor concentrates may still arise. However, where effective methods of viral inactivation are in use, the risk of transmission of NANBH by fractionated blood products appears to have been eliminated[15] (although this lack of infectivity will require continual monitoring). Indeed, although the USA screens all donations for anti-HCV, it does not screen plasma destined for pooling and fractionation![16] It is also noteworthy that in the USA, the rate of PTH has been estimated to have fallen sharply[17] following exclusion of donors at risk of contracting HIV infection but prior to ALT, anti-HBc and anti-HCV screening. A similar situation pertains in Canada (S. V. Feinman, personal communication).

CONCLUSION

The reasons for not initiating anti-HCV screening in the UK as soon as tests first became available may be summarized as follows:

1. No evidence for an association of transfusion and CLD.
2. Very low rate of PTH or transfusion-transmitted HCV infection.
3. Defects of the first available assays (low predictive value in low-prevalence populations; possibility of false-negatives).
4. Absence of supplementary tests initially.
5. Enormous workload and cost implications with the risk of diversion of resources from existing screening programmes and the resulting dilution of their efficiency.

In arguing against the introduction of mass pre-transfusion screening when tests first became available, all the factors described above present an overwhelming case. Even with second generation screening and supplementary assays, the cost involved will be enormous, and the likely benefits require careful assessment. Certainly, the mechanism of funding of mass screening will be of crucial importance if resources are not to be diverted from other vital areas of health care provision, with potentially damaging effects.

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Dr J. A. J. Barbara

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